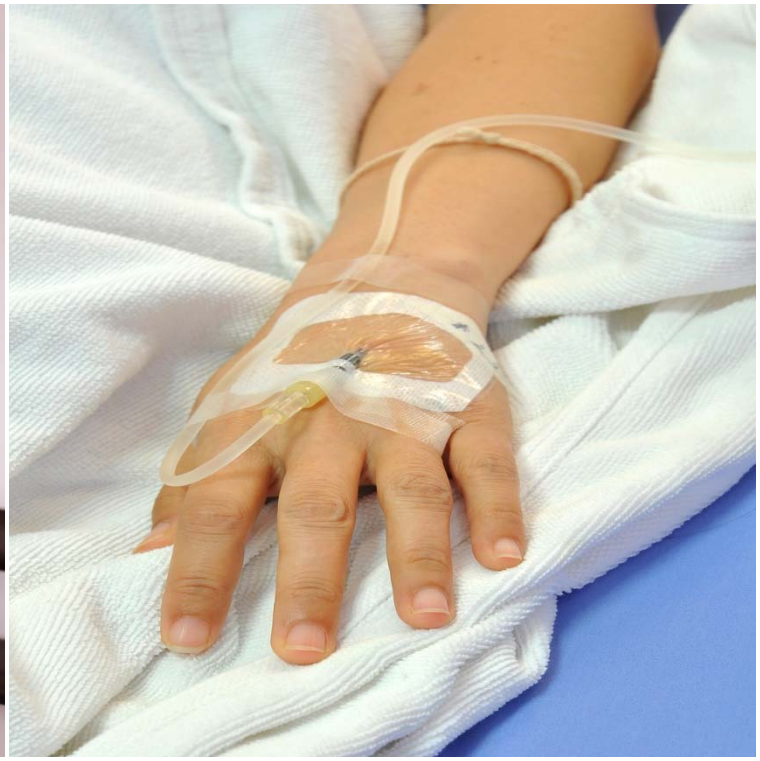
KCE REPORT 191C

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

SUPPORTIVE TREATMENT FOR CANCER

PART 2: PREVENTION AND TREATMENT OF ADVERSE EVENTS RELATED TO CHEMOTHERAPY AND RADIOTHERAPY



Belgian Health Care Knowledge Centre

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KCE REPORT 191C
GOOD CLINICAL PRACTICE

Federaal Kenniscentrum voor de Gezondheidszorg
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SUPPORTIVE TREATMENT FOR CANCER

PART 2: PREVENTION AND TREATMENT OF ADVERSE EVENTS RELATED TO CHEMOTHERAPY AND/OR RADIOTHERAPY

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COLOPHON

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FOREWORD

Sometimes the cure seems worse than the disease. Persons who are diagnosed with a malignant tumour often do not feel very sick initially or have few or no symptoms. But when radiotherapy or chemotherapy is started, they can become completely distressed. Indeed, these are often aggressive treatments that can disturb the physical equilibrium locally or generally and that can seriously affect the quality of life.

Of course, the primary focus of oncologic treatment remains to fight and eradicate the cancer if possible. The KCE has contributed his bit with numerous clinical practice guidelines. However, most of these guidelines, including the ones from abroad, usually do not address the adverse effects of the recommended treatments. Nevertheless, these are often very burdensome for the patient, and they weigh heavily in the subjective burden associated with cancer. Furthermore, these complications are often objectively serious and sometimes even life-threatening. As they are rather linked to the treatment type than to a specific cancer, they deserve a guideline in itself, useful for oncology in general.

Indeed, oncologists or other specialists, general practitioners and nurses that are involved in cancer treatment rarely have a complete picture about what is or is not effective against these side effects. Relevant studies are relatively scarce, hard to find, and not always of good quality. Researchers and the pharmaceutical industry are actually more interested in finding and testing new anticancer drugs, which in itself is of course worth to be taken to heart. However, in daily practice the clinician is constantly confronted with these adverse events and with the request to do something about them.

In this study we have attempted to separate chaff from wheat in the multitude of praised therapies and remedies. And there was a lot of chaff. But fortunately, still many grains can be collected. At first sight, these treatments do not appear to be essential, but from a patient's perspective they can hopefully make a difference and eventually contribute to render chemo- or radiotherapy bearable. This is, by all means, a goal in itself.

Raf MERTENS

Chief Executive Officer

EXECUTIVE SUMMARY

INTRODUCTION

The development of guidelines is one of the main action points of the Belgian National Cancer Plan 2008-2010 and one of the tasks of the College of Oncology. KCE collaborates with the College of Oncology and provides scientific support in the joint development of clinical practice guidelines. Until now guidelines were developed on breast cancer, colorectal cancer, testicular cancer, pancreatic cancer, upper gastrointestinal cancer and cervical cancer (www.kce.fgov.be).

Since many guidelines already now cover different aspects of supportive care, which are often not cancer type specific, it was decided to develop a separate series of reports on the supportive care of cancer patients under treatment. The following aspects are currently being covered:

- Exercise treatment during chemotherapy and/or radiotherapy (KCE report 185);
- Treatment of adverse events related to chemotherapy and/or radiotherapy (this report);
- Psychosocial support (ongoing project);
- Treatment of cancer-related pain (ongoing project).

The present report aims to formulate, on the basis of scientific evidence, recommendations relative to the prevention and treatment of adverse events of chemotherapy and/or radiotherapy. The report is intended to be used by health care professionals involved in the supportive care of cancer patients across the cancer care continuum, more specifically medical oncologists, radiation oncologists, surgeons, oncology specialists, nurses, general practitioners, etc.

METHODS

A list of adverse events of chemotherapy and/or radiotherapy and interventions to prevent or treat these adverse events were selected by health care professionals involved in the care for cancer patients and patient representatives. For each selected adverse event, the important outcomes to be considered were defined in advance. The literature search focused on the selected interventions and outcomes.

Initially, systematic reviews and meta-analyses were searched. Additional searches for randomized controlled trials (RCTs) were performed to update the selected reviews or to identify all high level evidence if no systematic review was available.

Systematic reviews and meta-analyses were searched in the following databases: OVID Medline and PreMedline, EMBASE, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) database. RCTs were searched in: Medline, EMBASE and CENTRAL. Searches were run between December 2011 and August 2012. Additionally, guideline databases and websites of international oncology guideline developers were searched for evidence-based guidelines relevant to the subject.

The AMSTAR instrument was applied for the critical appraisal of the systematic reviews. Risk of bias for the included RCTs was determined using the Cochrane Collaboration's tool for assessing risk of bias. The GRADE system was used to assign the levels of evidence and grades of recommendations.

A draft of recommendations was discussed on several occasions with a multidisciplinary panel of clinical experts and also separately with three patient representatives. Based on these face-to-face discussions, conclusions and recommendations were adapted, and where necessary, information was added to facilitate patient choice.

RESULTS

Fifteen separate searches were performed. The majority of searches yielded a limited number of RCTs per comparison and outcome. The evidence supporting the recommendations frequently was of low or very low quality (with the exception of neutropenia and nausea & vomiting).

From a patient's perspective, it is important to be fully informed about the frequency and degree of possible side effects and risks, possible alternatives and financial consequences of a proposed therapy before giving consent, as stated in the Belgian law on patients rights of 26 September 2002. Information should be correct, complete and communicated in a clear and unambiguous way. Easy access to information on preventive measures and support when problems occur should be continued throughout the entire treatment period.

The conclusions on the effectiveness of the selected interventions are presented by adverse event in the table below.

Table 1 – Overview of recommended and not recommended interventions for the prevention and treatment of adverse events related to chemotherapy and/or radiotherapy

Adverse event	Recommended	Not recommended
Prevention of oral mucositis	**Strongly recommended:** Oral cooling (ice chips) **Weakly recommended:** Sucralfate, allopurinol, benzydamine or zinc mouthwashes Honey	Chlorhexidine mouthwash Amifostine Specialized, intensified oral care protocols Palifermin Low-level laser therapy
Treatment of oral mucositis	**Weakly recommended:** Allopurinol mouthwashes Low-level laser therapy	Mouthwashes: benzydamine, sucralfate, chlorhexidine, magic mouthwash, phenylbutyrate, triclosan and sodium bicarbonate Honey Sucralfate gel
Prevention of oral candidiasis	**Weakly recommended (for high-risk patients)** First choice: fluconazole Second choice: ketoconazole, itraconazole, clotrimazole or miconazole	Amphotericin B, nystatin, chlorhexidine, thymostimulin, natamycin, norfloxacin Mouthwashes in general
Treatment of oral candidiasis	**Weakly recommended** Ketoconazole or fluconazole	Amphotericin B, nystatin
Skin problems	**Weakly recommended** Gentle skin and hair washing is allowed during radiotherapy	Neutral hydrophilic cream during radiotherapy Topical corticosteroids for radiodermatitis Honey gauze
Prevention of neuropathy ***P.S.: treatment of neuropathic pain will be addressed in a subsequent KCE report***	-	Glutamine Calcium and magnesium infusions
Prevention of neutropenia & neutropenic fever	**Strongly recommended**	G-CSF or GM-CSF as primary prophylaxis (with

Adverse event	Recommended	Not recommended
	Patients with neutropenia who are at very high risk for severe infections: prophylactic antibiotics Cancer patients with uncomplicated neutropenic fever: oral administration of antibiotics Outpatient management or early discharge policy **Weakly recommended** Patients with acute leukemia: prophylactic fluconazole or itroconazole or amphotericin B	exception for selected high risk chemotherapy schedules) Prophylactic ketoconazole or miconazole in patients with acute leukemia
Treatment of neutropenia & neutropenic fever	**Strongly recommended** Cancer patients with uncomplicated neutropenic fever: oral administration of antibiotics Outpatient management or early discharge policy **Weakly recommended** Patients with neutropenic fever and high risk for severe complications: therapeutic G-CSF or GM-CSF Patients with acute leukemia and neutropenic fever: empirical use of amphotericin B	Empirical use of voriconazole in patients with acute leukemia and neutropenic fever Routine patient isolation in a protected environment with HEPA filtration and laminar airflow
Treatment of radioproctitis	**Weakly recommended** Hyperbaric oxygen if medical treatment ineffective Endoscopic coagulation therapy for repetitive rectal bleeding Surgery if medical treatment is insufficiently effective	Oral sulfasalazine Rectal corticosteroids
Prevention of infertility	**Weakly recommended** GnRH analogues in women (depending on tumour type and patient preferences) *P.S.: All patients of reproductive age should be*	GnRH antagonists, GnRH agonists or testosterone in male patients Ovarian cryopreservation (outside the framework of clinical research)

Adverse event	Recommended	Not recommended
	informed about possible consequences of cancer treatment on fertility and should have access to all possible fertility preservation measures (such as sperm or embryo cryopreservation) before the start of cytotoxic treatment.	
Prevention of nausea & vomiting	NK1 receptor antagonist + 5- HT3 receptor antagonist + dexamethasone for highly emetogenic chemotherapy 5- HT3 receptor antagonist + dexamethasone for moderately emetogenic chemotherapy Dexamethasone for low emetogenic chemotherapy 5-HT3 antagonist + dexamethasone for patients at high risk for radiation-induced nausea and vomiting	Lorazepam or diphenhydramine as single-agent Cannabinoids
Diarrhoea	**Strongly recommended** Loperamide **Weakly recommended** Octreotide for moderate to severe diarrhoea	Prophylactic octreotide Probiotics Nutritional supplements
Prevention of cardiac toxicity due to chemotherapy	-	Dexrazoxane

G-CSF: Granulocyte Colony Stimulating Factor. GM-CSF: Granulocyte Macrophage Colony Stimulating Factor. NK1: Neurokinin 1. 5-HT3: 5-hydroxytryptamine 3.

For the following interventions, there was insufficient evidence to formulate a recommendation:

- Intra-oral fluoride releasing systems to prevent oral mucositis
- Aloe vera gel, hyaluronic acid cream, trolamine-based cream (biafine) to prevent or treat radiodermatitis
- Pre-emptive treatment with skin moisterizers, sunscreen, topical steroids and doxycycline to prevent skin toxicity during anti-EGFR treatment
- Foot soaks to prevent or treat skin toxicity
- Anti-inflammatory creams to prevent or treat skin toxicity
- Acetyl-l-carnitine to prevent neurotoxicity
- Probiotocs to treat radioproctitis
- Oral contraceptives to preserve fertility
- Somatostatin analogues other than octreotide to treat diarrhoea
- Co-enzyme q10 or amifostine to prevent cardiotoxicity

DISCUSSION AND CONCLUSION

This report is the second in a series of four, which evaluates supportive actions for patients with cancer. In this report, preventive and therapeutic interventions for a selection of adverse events related to chemo- and/or radiotherapy were evaluated. This topic is considered very relevant, since the success of cancer treatment is not only dependent on its effectiveness in terms of survival or response, but also on its effect on symptoms, daily functioning and quality of life.

It appears that many of the 'habitual' approaches to prevent or deal with side effects of cancer treatments are not underpinned by robust evidence. Fortunately, moderate or sometimes even strong evidence could be found for a number of approaches. We hope that it will offer guidance to cancer patients and their caregivers on how adverse events related to chemo- and/or radiotherapy can be prevented or treated. Wherever possible, clinical recommendations were formulated in a generic way, i.e. not focusing on a specific cancer type. The report presents several treatment options and can help to make informed treatment choices. Furthermore, the report can serve as a complementary document to cancer-specific guidelines developed by the College of Oncology in collaboration with the KCE.

Due to time constraints and faced with a wide range of possible adverse events related to chemo- and/or radiotherapy, the scope of the report needed to be narrowed. Choices were made in collaboration with health professionals involved in the care for cancer patients and with patient representatives. Consequently, the report is not comprehensive and does not discuss all treatment options for the studied adverse events.

With the exception of studies on neutropenia and nausea/vomiting, the number of RCTs for the studied interventions was disappointingly low. Furthermore, the selected trials were often poorly designed and/or not focused on patient-important outcomes, such as survival or quality of life. All this is reflected in the level of evidence as evaluated with the GRADE system, which is often low to very low.

It can be considered as a limitation that our report focused on (systematic reviews of) RCTs. For some interventions (e.g. anti-inflammatory creams to treat skin toxicity), no RCTs were identified, leading to gaps in our evidence base. An additional search for observational studies would have covered these gaps, but was not feasible within this project.

Finally, this report highlights the need for well-conducted high-quality research. It is our perception that side effects related to chemo- and or radiotherapy do not receive the scientific attention they deserve. Clearly, studies are needed to investigate interventions to prevent or treat side effects. Above this, and as important, this report should be considered an invitation for more basic research into the mechanisms of toxicity, optimized reporting of adverse events in clinical trials and post-marketing surveillance.

GENERAL RECOMMENDATIONS[a]

Recommendations for the healthcare providers

- **Cancer patients should be fully informed about the frequency and degree of possible side effects and risks, possible alternatives and financial consequences of a proposed therapy before giving consent.**
- **This information should be correct, complete and communicated in a clear and unambiguous way.**
- **Easy access to information on preventive measures and support when problems occur should be continued throughout the entire treatment period.**

Agenda for the research community

- **High-quality studies are needed to investigate interventions to prevent and treat side effects of chemotherapy and/or radiotherapy.**
- **Basic research is needed into the mechanisms of toxicity, optimized reporting of adverse events in clinical trials and post-marketing surveillance.**

[a] These recommendations are under the sole responsibility of the KCE

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
95%CI	95% Confidence Interval
ADL	Activities of Daily Living
AMH	Anti-Mullerian Hormone
APC	Argon plasma coagulation
ASCO	American Society of Clinical Oncology
BDP	beclomethasone dipropionate
BEC	Bipolar electrocoagulation
BMT	Bone marrow transplantation
Ca	Calcium
CDT	Clinical Decision Threshold
CER	Control event rate
DCC	Dutch Cochrane Centre
EGFR	Epithelial Growth Factor Receptor
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Canccer Quality of Life Questionnaire Core 30
ESMO	European Society of Medical Oncology
FDA	Food and Drug Administration
G-CSF	Granulocyte Colony Stimulating Factor
GI	Gastrointestinal
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
GnRH	Gonadotropin-Releasing Hormon
GnRH-a	Gonadotropin-Releasing Hormon analogue(s)
HR	Hazard ratio
IBDQ	Inflammatory Bowel Disease Quality of Life Index
ITT	Intention to treat
KCE	Belgian Health Care Knowledge Centre
LLL	Low-level-laser

MA	Meta-analysis
MASCC	Multinational Association of Supportive Care in Cancer
MD	Mean difference
Mg	Magnesium
MID	Minimal important difference
MMF	Mometasone furoate cream
NCI-CTC	National Cancer Institute-Common Toxicity criteria
NSAID	Non-steroidal anti-inflammatory drug
OIS	Optimal information size
OR	Odds ratio
OS	Overall Survival
PFS	Progression –Free Survival
PICO	Patients Intervention Comparator Outcome
POF	Premature Ovarian Failure
QoL	Quality of Life
RCT	Randomized controlled trial
RD	Risk difference
RR	Relative Risk
RRI	Relative risk increase
RRR	Relative risk reduction
RTOG	Radiation Therapy Oncology Group
SCCAI	Simple Clinical Colitis Activity Index
SR	Systematic review
SSRI	Selective serotonin re-uptake inhibitor
TMP-SMZ	Trimethroprim-sulfamethoxazole
vs.	versus
WHO	World Health Organisation

SCIENTIFIC REPORT

1. INTRODUCTION

The development of care pathways is one of the main items within the Belgian National Cancer Plan 2008-2010 and one of the tasks of the College of Oncology. KCE collaborates with the College of Oncology and provides scientific support in the development of clinical practice guidelines. Until now guidelines were jointly developed on breast cancer, colorectal cancer, testicular cancer, pancreatic cancer, upper gastrointestinal cancer and cervical cancer.

Since many cancer-specific guidelines also cover aspects of supportive care, which are often not specific to a certain cancer type, it was decided to develop a separate series of reports on the supportive care of adult cancer patients receiving active treatment for their cancer. The following aspects will be covered by this series: prevention and treatment of adverse events related to chemotherapy and/or radiotherapy, exercise treatment, psychosocial support, and treatment of cancer-related pain.

The present report aims to formulate, on the basis of scientific evidence, recommendations relative to the prevention and treatment of adverse events of chemotherapy and/or radiotherapy. The report is intended to be used by health care professionals involved in the supportive care of cancer patients across the cancer care continuum, more specifically medical oncologists, radiation oncologists, surgeons, oncology specialists, nurses, general practitioners, etc.

2. METHODS

2.1. Scoping

2.1.1. Methodology

On November 8th 2011, a stakeholder meeting took place at the KCE. A list of potential research questions and outcomes related to the 4 above-mentioned topics was presented to a group of experts. Based on a web-survey prior to the meeting and a face-to-face discussion during the meeting, a selection of research questions and outcomes was made. A final selection was made by the KCE and validated by the experts by email. The selected outcomes were prioritized in agreement with the consulted experts.

2.1.2. Research questions and outcomes

Eight adverse events were selected: (1) oral complications (mucositis, candidiasis), (2) neutropenia and neutropenic fever, (3) gastrointestinal complications (nausea and vomiting, diarrhoea), (4) infertility, (5) neuropathy, (6) radioproctitis, (7) skin toxicity, and (8) cardiac toxicity. Table 1 provides an overview of the (prioritized) outcomes. Only these outcomes will be reported on.

Table 1 – Prevention and treatment of adverse events of chemotherapy and radiotherapy: selected outcomes

Adverse event	Outcomes (in order of priority)
(1) Oral complications	
Oral mucositis	• Severity and duration of oral mucositis assessed using a validated scale • Incidence of oral mucositis (only for preventive interventions) • Performance status (validated scale) • Adverse effects of intervention • Quality of life (validated instrument) • Need for parenteral feeding • Progression-free survival (PFS)
Oral candidiasis	• Incidence of oral candidiasis (only for preventive interventions) • Incidence of systemic infections • Quality of life (validated instrument) • Adverse events of intervention • PFS • Death • Pain
(2) Skin toxicity	
Acute skin reactions due to radiotherapy	• Severity of acute skin reaction as assessed by validated scale • Quality of life (validated instrument) • Adverse events of intervention • PFS
Hand-foot syndrome	• Severity of symptoms as assessed by validated scale • Performance status (validated scale) • Quality of life (validated instrument) • Adverse events of intervention • PFS

Adverse event	Outcomes (in order of priority)
EGFR-related skin reactions	• Severity of symptoms as assessed by validated scale • Quality of life (validated instrument) • Adverse events of intervention • PFS
Nail toxicity	• Severity of nail toxicity as assessed by validated scale • Quality of life (validated instrument) • Adverse events of intervention • PFS
(3) Neuropathy	• Severity and duration of neuropathy assessed using a validated scale • Incidence of neuropathy (only for preventive interventions) • Functional outcomes, activities of daily living • Adverse events of intervention • Quality of life (validated instrument) • PFS
(4) Neutropenia and neutropenic fever	• Overall survival (OS) • PFS • Incidence of febrile neutropenia • Adverse events (e.g. tumour progression, myelodysplastic syndrome, antibiotic resistance) • Quality of life (validated instrument) • Need for hospitalization
(5) Radioproctitis	• Severity and duration of symptoms, assessed by validated scale • Performance status (validated scale) • Adverse events of intervention • PFS • OS • Quality of life (validated instrument)
(6) Infertility	• Pregnancy rate, life birth rate • Foetal malformation • PFS • OS • Adverse events of intervention • Premature ovarian failure
(7) Gastrointestinal complications	
Nausea and vomiting	• Severity of nausea and vomiting as assessed by validated scale • Performance status (validated scale) • Adverse events of intervention • PFS • Quality of life (validated instrument) • Need for hospitalization • OS
Diarrhoea	• Severity and duration of diarrhoea • Quality of life (validated instrument) • Adverse events of intervention • PFS • OS
(8) Cardiac toxicity	• OS • PFS • Performance status (validated scale) • Quality of life (validated instrument) • Adverse events of intervention • Measured cardiac function (ejection fraction)

For the treatment (and/or prevention) of the selected adverse events, a list of interventions was selected in agreement with the consulted experts (Table 2). The literature search focused on these interventions. Only these interventions will be reported on.

Table 2 – Prevention and treatment of adverse events of chemotherapy and radiotherapy: selected interventions

Adverse event	Interventions
(1) Oral complications	• Oral cooling/ice chips • Oral candidiasis prophylaxis with fluconazole, ketoconazole, nystatin • Mouth washes general • Mucosal coating agents, e.g. gelclair • Amifostine • Intra-oral fluoride releasing system • Basic oral care, dental care • Palifermin • Honey • Athermic laser / low-level laser
(2) Skin toxicity	• Gentle skin washing +/- soap • Neutral hydrophilic cream • Corticosteroid cream • Emollients • Topical exfoliating products (urea, salicylic acid) • Foot soaks (magnesium sulfate) • Honey • Anti-inflammatory creams
(3) Neuropathy	• Oral glutamine • Acetyl-L-carnetine • Calcium • Magnesium • Anti-convulsant drugs (e.g. gabapentin) • Tricyclic antidepressants • NSAID • SSRI • Opioids
(4) Neutropenia and neutropenic fever	• Prophylactic G-CSF / GM-CSF • Therapeutic G-CSG / GM-CSF • Prophylactic antibiotics • Prophylactic antifungals • Outpatient treatment versus hospitalisation • Nursing practices: isolation • Therapeutic antibiotics: oral versus IV
(5) Radioproctitis	• Hyperbaric oxygen • Surgery • Coagulation therapy (argon plasma) • Sulfalazine • Probiotics • Corticosteroids
(6) Infertility	• GnRH agonists women • Oral anticonception women • Hormonal interventions general women • Hormonal interventions men general • Pharmacological interventions men • Ovarian cryopreservation
(7) Gastrointestinal complications	
Nausea and vomiting	• 5-HT3 receptor antagonists • Cannabinoids • NK1 receptor antagonists general • Aprepitant • Dexamethasone • Benzodiazepines
Diarrhoea	• Somatostatin analogues general • Octreotide • Probiotics • Nutritional supplements • Loperamide
(8) Cardiac toxicity	• Dexrazoxane • Co-enzyme q10 • Amifostine

2.2. Literature search

For all research topics, the search first focused on systematic reviews, meta-analyses and evidence-based guidelines (i.e. guidelines clearly based on a systematic review of the literature). The following sources were used:

- OVID Medline and PreMedline
- EMBASE (Embase.com)
- Cochrane Database of Systematic Reviews (Wiley)
- DARE (Wiley)
- HTA database (Wiley)

Additionally, the following websites were searched for evidence-based guidelines:

Organisation	Website(s)
National Guideline Clearinghouse	http://www.guidelines.gov/
American Society of Clinical Oncology (ASCO)	http://www.asco.org/
Cancer Care Ontario	http://www.cancercare.on.ca/english/home/
Haute Autorité de Santé (HAS)	http://www.has-sante.fr/
National Health and Medical Research Council (NHMRC)	http://www.nhmrc.gov.au/
Scottish Intercollegiate Guidelines Network (SIGN)	http://www.sign.ac.uk/
New Zealand Guidelines Group (NZGG)	http://www.nzgg.org.nz/
Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC)	http://www.sor-cancer.fr/
National Institute for Health and Clinical Excellence (NICE)	http://www.nice.org.uk/

Depending on the quality and currency of the identified reviews, an additional search for randomized controlled trials (RCTs) was done. The following sources were used:

- OVID Medline and PreMedline
- EMBASE (Embase.com)
- CENTRAL (Wiley)

Detailed search strategies can be found in Appendix 1.

2.3. Selection process

A first selection of guidelines, systematic reviews and meta-analyses based on title and abstract was performed by one reviewer (LV). After this first selection, the full-text of the selected abstracts was retrieved and selected by the same reviewer. Doubtful cases were discussed with a second reviewer (JV). Before assessing the methodological quality of each review, a quick critical appraisal was performed of each full-text following the criteria mentioned above. Reviews not meeting these criteria were excluded from further review.

A similar strategy was used for RCT selection by DCC.

2.3.1. Selection criteria systematic reviews

To be finally included the systematic review had to:

- address the treatment or prevention of chemotherapy- and/or radiotherapy-related adverse events in patients receiving cancer treatment for the selected topics and interventions (for details see Table 2);
- evaluate the selected critical and important outcomes (see Table 1);
- have searched MEDLINE and at least one other electronic database;
- have indicated the date of the search;
- have included an assessment of risk of bias of each primary study which included at least the three following main items: concealment of allocation, blinded outcome assessment and completeness of follow-up (preferably summarised in a table).

2.3.2. Selection criteria randomized controlled trials

To be finally included, RCTs had to address all elements of the PICOs.

2.4. Quality appraisal

2.4.1. Systematic reviews

For the quality appraisal of systematic reviews, the AMSTAR instrument was used (see Appendix 3.1.1). Three items of this checklist were considered key for labelling a review as high quality:

- Item 3: Was a comprehensive literature search performed?
- Item 7: Was the scientific quality of the included studies assessed and documented?
- Item 9: Were the methods used to combine the findings of studies appropriate?

2.4.2. Randomized controlled trials

For the quality appraisal of RCTs, the Cochrane Collaboration's tool for assessing risk of bias [1] was used (see Appendix 3.2). Judgement of each item includes three categories: 'low risk of bias', 'high risk of bias', and 'unclear risk of bias'. For each criterion the definitions as described in the Cochrane Handbook [1] were used. If applicable, risk of bias for the items regarding detection bias and attrition bias were assessed per class of outcomes (e.g. subjective and objective outcomes). At the end, each study was labelled as low risk of bias, unclear risk of bias or high risk of bias according to the criteria described in the Cochrane Handbook [1].

2.5. Statistical analysis

When new RCTs were found in addition to an existing meta-analysis, or in case subgroup analysis was needed for certain topics, meta-analysis was performed using Review Manager version 5. If heterogeneity was present, a random-effects model was used instead of a fixed-effect model. In practice, it only concerned dichotomous variables, for which a risk ratio was calculated using the Mantel-Haenszel method. Heterogeneity was statistically assessed using the I^2 measure.

Apart from these meta-analyses, Review Manager was also used to compute the RR for individual studies in case it was lacking from the publication.

2.6. Grading of evidence

Data extraction was done by one reviewer using the standard KCE template for evidence tables (see Appendix 6).

The pooled results from included systematic reviews were extracted or newly identified RCTs were pooled if appropriate, and the quality of evidence was evaluated using GRADE methodology [2]. A level of evidence was assigned to each conclusion using the GRADE system [2] (Table 3).

GRADE for guidelines was used, meaning that the evidence across all outcomes and across studies for a particular recommendation was assessed. The following quality elements for intervention studies were evaluated: study limitations, inconsistency, indirectness, imprecision and publication bias.

As only RCTs were considered in this review, quality rating was initially considered to be of high level. The rating was then downgraded if needed based on the judgement of the different quality elements. Each quality element considered to have serious or very serious risk of bias was rated down -1 or -2 points respectively. Judgement of the overall confidence in the effect estimate was also taken into account. We considered confidence in estimates as a continuum and the final rating of confidence could differ from that suggested by each separate domain [3].

The general principles used to downgrade the quality rating are summarized in Table 4. Decisions on downgrading with -1 or -2 points were based on the judgement of the assessors. Reasons for (no) downgrading were summarized in the GRADE profiles in Appendix 4.

Since upgrading of the level of evidence is primarily relevant to observational studies and our report focused on RCTs, upgrading was not considered applicable although theoretically possible. In practice this option never occurred [4].

For each clinical question, conclusions were formulated at the level of individual treatment outcomes using standardized language (Table 5).

Table 3 – Levels of evidence according to the GRADE system

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

Table 4 – Downgrading the quality rating of evidence using GRADE

Quality element	Reasons for downgrading
Limitations [5]	For each study reporting the selected outcome, possible risk of bias introduced by lack of allocation concealment, lack of blinding, lack of intention-to-treat analysis, loss of follow-up and selective outcome reporting were assessed. Additionally, other limitations such as stopping early for benefit and use of unvalidated outcome measures were taken into consideration. Level of evidence was downgraded if studies were of sufficiently poor quality. Downgrading was omitted if studies with low risk of bias were available that lead to similar conclusions as the studies with a high risk of bias.
Inconsistency [6]	Downgrading the level of evidence for inconsistency of results was considered in the following situations: point estimates vary widely across studies, confidence intervals show minimal or no overlap, the statistical test for heterogeneity shows a low p-value or the I^2 is large. If large variability in magnitude of effect remained unexplained, the quality of evidence was rated down. If the body of evidence included only a single study, rating was downgraded with -2 points as consistency of results cannot be judged and there is no proof that results are reproducible. The only exception was the availability of one large multicentre trial without heterogeneity across sites.
Indirectness [7]	Quality rating was downgraded for indirectness in case the trial population or the applied intervention differed significantly from the population or intervention of interest. Also, the use of surrogate outcomes could lead to downgrading. A third reason for downgrading for indirectness occurred when the studied interventions were not tested in a head-to-head comparison.
Imprecision [8]	Evaluation of the imprecision of results was primarily based on examination of the 95%CI. Quality was rated down if clinical action would differ if the upper versus the lower boundary of the 95%CI represented the truth. In general, 95%CIs around relative effects were used for evaluation, except when the event rate was low in spite of a large sample size. To examine the 95%CIs, the clinical decision threshold (CDT) was defined. When the 95%CI crossed this clinical decision threshold, the quality level was rated down. A relative risk reduction (RRR) of 25% was defined as CDT by default and adapted if deemed appropriate e.g. in case of a low risk intervention. Even if 95%CIs appeared robust, level of evidence could be rated down because of fragility. To judge fragility of results, it is

Quality element	Reasons for downgrading
	suggested to calculate the number of patients needed for an adequately powered (imaginary) single trial, also called the optimal information size (OIS). If the total number of patients included in a systematic review was less than the calculated OIS, rating down for imprecision was considered. For calculations, a RRR of 25% was used, unless otherwise stated. When the OIS could not be calculated, a minimum of 300 events for binary outcomes and a minimum of 400 participants for continuous outcomes were used as a rule of thumb.
Reporting bias	Quality rating was downgraded for reporting bias if publication bias was suggested by analysis using funnel plots or searching of trial registries. Publication bias was also suspected if results came from small, positive industry-sponsored trials only.

Table 5 – Standardized language used for formulating scientific conclusions

Evidence base	Conclusion	Recommendation
High level of evidence	It is demonstrated that…	… is (not) recommended / needed / indicated / standard / should be...
Moderate level of evidence	It is plausible that…	
One study of high or moderate quality **Low or very low level of evidence**	There are indications that…	… can(not) be considered / is (not) an option.
Inconsistent evidence	There is conflicting evidence that…	
Limited evidence	There is limited evidence that…	

2.7. Formulation of recommendations

Based on the retrieved evidence, a first draft of recommendations was prepared by a small working group (LV, JV). In general, recommendations were formulated using standardized language as summarized in Table 5.

This first draft together with the evidence tables was circulated to the expert group about 2 weeks prior to the face-to-face meetings. The expert group met on two occasions to discuss the first draft (September 3rd and 24th 2012). Recommendations were changed taking into account the factors listed in Table 7. Based on the discussion meetings a second draft of recommendations was prepared and discussed with a separate panel of patient representatives (October 3rd 2012). A grade of recommendation was assigned to each recommendation using the GRADE system (Table 6 and Table 7). The final draft was once more circulated to the expert group for final approval.

Table 6 – Strength of recommendations according to the GRADE system

Grade	Definition
Strong	The desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not
Weak	The desirable effects of an intervention probably outweigh the undesirable effects, or probably do not

Table 7 – Factors that influence the strength of a recommendation

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted

2.8. Project team and involved experts

The scientific report, including the literature search, evidence report and conclusions were written by a team of 5 methodological experts. The majority of the searches were outsourced to the Dutch Cochrane Centre (lead by R.J.P.M. Scholten) and supervised by the KCE (Leen Verleye, Joan Vlayen [project leader]). The Dutch Cochrane Centres delivered the evidence reports, evidence tables, quality appraisal results, etc. However, the KCE had the final responsibility and adapted the delivered texts if deemed necessary.

To set the scope the following experts were consulted:

- Tom Boterberg (radiation oncologist)
- Fréderic Duprez (radiation oncologist)
- Johan Menten (radiation oncologist; palliative care coordinator)
- Marc Peeters (gastroenterologist; president of College of Oncology)
- Annemarie Coolbrandt (oncology nurse)
- Sophie Hanssens (oncology nurse)
- Ward Rommel (Vlaamse Liga tegen Kanker, acting as patient representative)
- Didier Vander Steichel (Fondation contre le Cancer, acting as patient representative)

All draft recommendations were discussed with the following expert team:

- Tom Boterberg (radiation oncologist)
- Fréderic Duprez (radiation oncologist)
- Johan Menten (radiation oncologist; palliative care coordinator)
- Marc Peeters (gastroenterologist; president of College of Oncology)
- Jean-Luc Canon (medical oncologist)
- Joseph Kerger (medical oncologist)
- Johan Maertens (haematologist; consulted by phone)

Conflicts of interest of the involved experts are reported in the colophon of the report.

2.9. Patient involvement

On 9 October 2012, the pre-final draft of recommendations was discussed with three patient representatives. All topics were carefully explained in non-medical language if necessary. The patient representatives were asked the following questions:

- Are there considerations from the patients' perspective that we missed in formulating our recommendations?
- Do we need to add information that allows to make clear choices when doctors discuss treatment options with patients?
- Are all recommendations relevant, or can we omit some of them?

Based on the face-to-face discussion, some recommendations were adapted to considerations from the patients' perspective. Where necessary, information was added to facilitate patient choice. Above this, some recommendations were changed from weak to strong, or vice versa.

3. EVIDENCE REPORT

3.1. Introduction

Anticancer treatments such as chemotherapy, radiotherapy and targeted treatments are frequently associated with significant side effects with potentially detrimental effects on dose and intensity of treatment, quality of life and even mortality. Toxic effects appear to be even more commun with newer antineoplastic therapy [9]. Before giving consent, patients should be fully informed about the frequency and degree of possible side effects and risks, possible alternatives and financial consequences of a proposed therapy, as stated in the Belgian law on patients rights of 26 September 2002 [10]. Information should be correct, complete and communicated in a clear and unambiguous fashion. Easy access to information on preventive measures and support when problems occur should be continued throughout the entire treatment period.

Good clinical practice

- Patients should be fully informed about possible side effects before giving consent to any anticancer treatment.
- All possible measures to prevent serious side effects of chemotherapy, radiotherapy or targeted treatments should be put in place.
- Easy acces to information on preventive measures and support should be available to the patient throughout the entire treatment period.

3.2. Oral Mucositis

Chemotherapy and radiotherapy can cause severe ulcers in the mouth, also called oral mucositis. The condition can be very painful and may be associated with difficulties in eating and drinking, poor nutrition and infections including life-threatening septicaemia. Mucositis-related morbidity can be serious and lead to treatment delay or interruption of treatment[11].

In addition to prevention and treatment of the ulcerations, attention must be given to sufficient pain relief, feeding support and possible fungal surinfections. Also, good oral hygiene is considered important to protect the mucosal barrier and avoid spreading of infections through ulcerative lesions. Furthermore, all oral lesions should be assessed for other possible causes and treated accordingly if indicated.

3.2.1. Prevention of oral mucositis

Two systematic reviews were identified that met the inclusion criteria [11, 12].

The review of Sasse et al. addressed the effect of adding amifostine to radiotherapy compared to radiotherapy alone for the prevention of oral mucositis in patients with head and neck cancer. The search date was April 2005. The overall risk of bias of this review was considered to be low.

The second review of Worthington et al. assessed the effectiveness of interventions for the prevention of oral mucositis in patients with cancer receiving radiotherapy, chemotherapy or targeted therapies. The search date was February 2011. The overall risk of bias of this review was considered to be low. The review included 131 RCTs with 10 514 randomised participants involving several different prophylactic agents. The primary outcome measure addressed in the review was the presence of mucositis (at all levels of severity). Mucositis was measured on a 0 to 4 point scale that was dichotomised as any mucositis (grade 1-4), moderate plus severe mucositis (grade 2-4) or severe mucositis (grade 3-4). Secondary outcome measures included relief of pain/use of analgesia, duration or severity of dysphagia, use of parenteral nutrition or feeding tube, treatment interruption, toxicity (nausea/vomiting/constipation/diarrhoea), toxicity (skin changes, unspecific), xerostomia, quality of life, death, weight loss/gain, caloric intake by oral nutrition, eating/drinking difficulty, overall health, recurrence of cancer.

In April 2012 an update of the literature search of Worthington et al. was performed. Eleven additional RCTs were identified [13-23].

In the next paragraphs, only the interventions that were relevant for the study questions of this guideline were described: oral cooling (ice chips), mouth washes, amifostine, oral care, palifermin, honey and laser therapy.

3.2.1.1. *Oral cooling (ice chips) versus no treatment*

Six trials included in the review of Worthington et al. [11] compared oral cooling (ice chips) with either no treatment or placebo (saline) control. The majority of included patients received chemotherapy (5-FU, metotrexate, melphalan or not specified), only in one trial some patients received whole body radiation in preparation of bone marrow transplantation. The latter was not included in the meta-analysis. A benefit was associated with the use of ice chips for all three outcome categories (any mucositis: RR = 0.74, 95%CI 0.57 to 0.95; moderate plus severe mucositis: RR = 0.53, 95%CI 0.31 to 0.91; severe mucositis: RR = 0.36, 95%CI 0.17 to 0.77). However, the authors identified substantial heterogeneity in each meta-analysis.

Through the update, one additional trial comparing oral cooling with routine care was found [19]. The trial was judged to have an unclear risk of bias. Sixty participants were included who received outpatient chemotherapy (5-fluorouracil plus leucovorin) for various cancer types. No statistically significant differences were found between the experimental and control group for the development of oral mucositis grades 1+, 2+, and 3+ on day 21 (RR = 0.61, 95%CI 0.35 to 1.06; RR = 0.42, 95%CI 0.17 to 1.04; and RR = 0.17, 95%CI 0.02 to 1.30, respectively).

The results of this study were added to the meta-analysis of Worthington et al. [11], which resulted in statistically significant effects in favour of the treatment group for all three outcome measures (any grade mucositis: RR = 0.74, 95%CI 0.57 to 0.92; moderate plus severe oral mucositis: RR = 0.51, 95%CI 0.31 to 0.84; severe oral mucositis: RR = 0.34, 95%CI 0.17 to 0.70).

No data on the effect of oral cooling on performance status, quality of life, the need for parental feeding and progression-free survival were found in the literature. Possible adverse events due to the intervention were not reported.

Conclusion

- There are indications that oral cooling prevents moderate and severe oral mucositis caused by chemotherapy (Katranci 2011, Worthington 2011; low level of evidence).

Other considerations

It is unclear if these findings can be extrapolated to patients receiving (chemo)radiotherapy for head and neck tumours in or near the oral cavity, as there is concern that the effect of oral cooling on blood supply may have an unwanted negative effect on response to treatment. The expert group advises not to use oral cooling in this group of patients.

Evidently, oral cooling should only be used in patients receiving chemotherapy known to frequently cause oral mucositis, such as anthracyclines, 5-fluorouracil and irinotecan.

From a patient perspective, oral cooling is considered a harmless intervention that, apart from preventing oral mucositis, can give comfort to patients receving chemotherapy toxic to the oral mucosa. Therefore, oral cooling should be offered to all these patients, but it can be omitted if experienced as a hassle. Based on this consideration, the recommendation was considered to be strong.

Recommendation

- Oral cooling (ice chips) should be offered to prevent oral mucositis caused by chemotherapy associated with a significant risk of mucositis (strong recommendation).

3.2.1.2. *Mouthwashes*

In the review of Worthington et al. [11] various mouthwashes (allopurinol, benzydamine, chlorhexidine and sucralfate) were studied. One review (Potting 2006) was superseded by the review of Worthington et al. and, therefore, not further processed.

Through the update, a further three trials [14, 16, 21] were identified. The results of all comparisons are separately described below.

Allopurinol versus placebo/no treatment

Four trials included in the review of Worthington et al. [11], of which two were designed as cross-over studies, compared allopurinol mouth rinse with placebo or no treatment. All trials provided data for the outcome category of any mucositis and there was no statistically significant difference between allopurinol and control (RR = 0.77; 95%CI 0.50 to 1.19). Two trials provided data for the moderate plus severe (RR = 0.66; 95%CI 0.50

to 0.86) and severe outcome categories (RR = 0.81; 95%CI 0.63 to 1.04). There was substantial heterogeneity in both meta-analyses, probably due to differences with regard to the type of tumour and cancer treatment in the trials.

Benzydamine versus placebo

Four studies included in the review of Worthington et al. [11] compared benzydamine mouthwash with placebo in 332 patients with head and neck cancer. No meta-analysis was performed. One study found a statistically significant reduction in severe mucositis (RR = 0.55; 95%CI 0.38 to 0.82) and another found a statistically significant reduction in the development of any mucositis (RR = 0.67; 95%CI 0.47 to 0.97). Two further studies used other mucositis indices to evaluate the outcome (multivariable scale: area of involvement, severity of inflammation, severity of ulceration and maximum size of ulceration each graded using a 0-3 scale; scores then combined). Both trials reported statistically significant differences in favour of benzydamine (results not quantified).

Chlorhexidine mouthwash versus placebo/no treatment

Nine trials included in the review of Worthington et al. [11], with a total of 692 participants treated with chemotherapy or radiotherapy for various cancer types, compared chlorhexidine mouthwash with either placebo or no treatment. Four trials provided data for the outcome category any mucositis, three trials for moderate plus severe mucositis, and four trials for severe mucositis. Chlorhexidine was not found to be more effective than placebo or no treatment for any of the outcomes evaluated (any mucositis: RR = 0.76; 95%CI 0.47 to 1.24; moderate plus severe mucositis: RR = 0.93; 95%CI 0.72 to 1.21; severe mucositis: RR = 0.82; 95%CI 0.54 to 1.23 respectively). There was substantial heterogeneity in the meta-analysis of any mucositis and moderate plus severe mucositis levels, which may be partly due to clinical differences between the studies in terms of the cancer type and treatment. Two further trials of the review presented data as mean mucositis scores for each group. They reported statistically significant differences in mean mucositis scores in each group which favoured chlorhexidine over placebo.

Through the update a further two trials [14, 16] were identified that studied the effectiveness of mouthwashes containing chlorhexidine.

The trial by Lanzos et al. included 36 participants that were irradiated as part of their therapy for head and neck cancer and who were randomized to either an antiseptic, non-alcohol based, mouth rinse containing chlorhexidine (CHX) and cetyl-pyridinium chloride (CPC) or a placebo mouth rinse [16] .This trial was judged to be at high risk of bias. No significant differences in change of degree of mucositis (from baseline to 4 weeks) between study groups were found (no change: RR = 2.14, 95%CI 0.50 to 9.11; increase: RR = 0.86, 95%CI 0.52 to 1.43; decrease: RR = 0.29, 95%CI 0.01 to 6.38). No adverse effects were reported in either group.

The second trial by Meca et al. included 60 participants undergoing head and neck radiotherapy, who were randomly divided into four groups [14]. Three to four weeks before radiotherapy, participants in group I-III received initial dental treatment, which consisted of extractions, restorations, scaling and dental prophylaxis. In addition, group I received chlorhexidine gluconate (0.12%) once daily during radiotherapy and for six months after, group II received sodium fluoride (0.5%, aqueous solution) daily during and after radiotherapy, and group III received sodium iodine (2% in hydrogen peroxide 10 v/v) once daily during and after radiotherapy. Oral hygiene instructions for group I, II and III were reinforced at each visit. There was no intervention for participants in group IV: they received medical treatment with no odontological assistance and received oral hygiene instructions only during and after radiotherapy. The risk of bias of this trial was judged to be unclear. In none of the intervention groups at any time point the incidence of oral mucositis differed significantly from the no treatment group (group I: immediately after radiotherapy RR = 1.11, 95%CI 0.82 to 1.49; six months after radiotherapy RR = 0.51, 95%CI 0.22 to 1.19; group II: immediately after radiotherapy RR = 1.09, 95%CI 0.80 to 1.49; six months after radiotherapy RR = 0.43, 95%CI 0.16 to 1.15; group III: immediately after radiotherapy RR = 0.94, 95%CI 0.65 to 1.37; six months after radiotherapy RR = 0.47, 95%CI 0.20 to 1.10).

Sucralfate (mouthwash and gel) versus placebo/usual care

Twelve trials included in the review of Worthington et al. [11] evaluated the use of sucralfate; ten compared sucralfate mouthwash with placebo and one compared sucralfate mouthwash with usual care. The remaining trial compared sucralfate mouthwash with placebo, but also instructed all participants to apply sucralfate gel to the skin on one side of the radiation area (resulting in possible contamination of the placebo group).

No significant difference was found between the sucralfate group and the placebo group in the proportion of patients who developed any mucositis in the three trials that reported this outcome (RR = 0.98; 95%CI 0.88 to 1.10) or in the prevention of moderate plus severe mucositis in the four trials that reported this outcome (RR = 0.75; 95%CI 0.54 to 1.04). Seven trials provided evidence that sucralfate is effective in the prevention of severe mucositis compared to placebo (RR = 0.67; 95%CI 0.48 to 0.92). A further two trials reported outcome data in a different format, but neither found a statistically significant difference between sucralfate and placebo in the prevention of mucositis. The study which compared sucralfate mouthwash with placebo, but also instructed all participants to apply sucralfate gel to the skin on one side of the radiation area also showed no significant differences for the incidence of any grade mucositis, moderate and severe mucositis and severe mucositis (RR = 1.07, 95%CI 0.96 to 1.20; RR = 1.21, 95%CI 1.00 to 1.46; RR = 1.13, 95%CI 0.89 to 1.44, respectively).

Zinc mouthwash versus placebo

One trial, identified through the update, evaluated the effectiveness of zinc mouthwash on chemotherapy-induced oral mucositis lesions [21]. The trial was considered to have an unclear risk of bias and involved 30 participants. The mean severity scores were generally lower in the zinc group compared to the controls at all four time intervals evaluated, but only the differences in weeks of 2 and 3 were statistically significant (p = 0.025) (results were not quantified). The authors concluded that zinc sulfate was found to be beneficial in reducing the severity of chemotherapy-induced mucositis, but that these results should be confirmed by additional randomized studies with larger number of patients.

Conclusions

- There are indications that allopurinol mouthwash prevents moderate and severe oral mucositis (Worthington 2011; low level of evidence).
- There is limited evidence that benzydamine mouthwash prevents oral mucositis (Worthington 2011; very low level of evidence).
- A positive effect of chlorhexidine mouthwash on the incidence of oral mucositis could neither be demonstrated nor refuted (Worthington 2011; very low level of evidence).
- There are indications that sucralfate mouthwash prevents the development of severe oral mucositis (Worthington 2011; very low level of evidence).
- There is limited evidence that Zinc mouthwash prevents oral mucositis (Medhipour 2011; very low level of evidence).

Other considerations

The use of any mouth wash, even plain water, can have a beneficial effect by the mechanical rinsing and cleaning of the oral cavity, especially in patients suffering from a dry mouth (xerostomy) as a consequence of their cancer treatment. As such, a mouth wash containing an anaesthetic (e.g. lidocaine) for pain relief only could also be considered a valuable option. As there is no strong evidence in favour of one of the suggested options, the composition of a mouthwash can be decided on taking into account patient preferences (e.g. taste), availability and cost.

Recommendations

- The use of sucralfate, allopurinol, benzydamine or zinc mouth washes can be considered to prevent oral mucositis in patients receiving chemotherapy and/or radiotherapy (weak recommendation).
- The use of chlorhexidine mouthwash is not recommended to prevent oral mucositis (weak recommendation).

3.2.1.3. Amifostine versus placebo/no treatment

Eleven trials included in the review of Worthington et al. [11] compared amifostine with no treatment or a placebo. There was a significant but

small benefit for amifostine preventing any mucositis (RR = 0.95; 95%CI 0.91 to 0.99). Six trials provided data for moderate plus severe mucositis demonstrating a benefit for amifostine compared with placebo or no treatment (RR = 0.75; 95%CI 0.58 to 0.96). However, this meta-analysis showed substantial heterogeneity. Nine trials provided data for severe mucositis and the meta-analysis showed a non-significant benefit for amifostine in the prevention of severe mucositis (RR = 0.68; 95%CI 0.45 to 1.03).

The systematic review included a further trial (at high risk of bias) which provided a graph of weekly mean mucositis scores. In the text of the results section it was indicated that there was a statistically significant difference in favour of amifostine compared to no treatment at 2 weeks. However, no overall result was reported in this paper.

In addition, a meta-analysis of the second included review of Sasse et al. [12] showed a beneficial effect of the addition of amifostine to radiotherapy compared to radiotherapy alone with respect to the occurrence of grade 3-4 mucositis (OR = 0.44; 95%CI 0.30 to 0.65). The meta-analysis included five trials, four of which were also included in the aforementioned review [11].

This review also addressed the protective effect of amifostine for other adverse effects (esophagitis, radioproctitis, xerostomia, dysphagia, pneumonitis and cystitis) and assessed treatment response and side effects of amifostine across all included RCTs. The occurrence of partial radiotherapy response did not differ significantly between the groups (9 studies; OR = 0.93; 95%CI 0.65 to 1.33), but complete response occurred more often in the group that was treated with additional amifostine (8 studies; OR = 1.81; 95%CI 1.10 to 2.96). The overall response rates did not differ significantly (OR = 1.31; 95%CI 0.90 to 1.89). Relapse rates were studied in 5 RCTs and there was no significant difference between the groups (RD = 0.00; 95%CI -0.08 to +0.07). Side effects of amifostine were nausea (7 studies; OR = 2.47; 95%CI 1.38 to 4.40), grade 3-4 emesis (5 studies; OR = 2.23; 95%CI 1.09 to 4.56) and grade 3-4 hypotension (RD = 0.03; 95%CI 0.01 to 0.05).

Conclusions

- There are indications that amifostine prevents the development of oral mucositis (Worthington 2011, Sasse 2006; very low level of evidence).
- There are indications that amifostine is associated with nausea, emesis and hypotension (Sasse 2006; very low level of evidence).

Other considerations

Despite the limited effect on the occurrence of oral mucositis overall, the risk-benefit balance does not support the use amifostine given the significant side effects and the absence of a significant effect on the incidence of severe oral mucositis.

Recommendation

- Amifostine is not recommended to prevent oral mucositis associated with chemotherapy or radiotherapy (weak recommendation).

3.2.1.4. Oral care protocol versus usual care

One study from the review [11] compared an intense oral care protocol with usual care. The study showed a small significant difference between specific oral care protocols and usual care with regard to the prevention of mucositis (RR = 0.62; 95%CI 0.43 to 0.91). A second study only included patients considered for bone marrow transplantation and was not considered for this report.

Through the update, one additional trial [13] was found which evaluated the effects of the intensive dental care protocol in preventing oral complications in acute leukemia patients. Thirty-four patients were randomly assigned to receive the intensive dental care protocol or no intervention. The intensive dental care group of patients received dental treatment and plaque and calculus removal prior to chemotherapy and supervised oral hygiene measures during chemotherapy. The control group did not receive pre-chemotherapy dental care. The trial was considered to have a high risk of bias. The results of this study showed a non-significantly lower incidence of mucositis (any grade, evaluated according to WHO classification) in the intensive dental care group of patients during the whole period of examination compared with the control

group (day 7: RR = 0.63, 95%CI 0.24 to 1.71; day 14: RR = 0.76, 95%CI 0.36 to 1.61; day 21: RR = 0.84, 95%CI 0.39 to 1.84; day 28: RR = 0.63, 95%CI 0.24 to 1.71).

Finally, in the above-mentioned study of Meca et al. [14], in none of the intervention groups at any time point the incidence of oral mucositis differed significantly from the no treatment group (group I: immediately after radiotherapy RR = 1.11, 95%CI 0.82 to 1.49; six months after radiotherapy RR = 0.51, 95%CI 0.22 to 1.19; group II: immediately after radiotherapy RR = 1.09, 95%CI 0.80 to 1.49; six months after radiotherapy RR = 0.43, 95%CI 0.16 to 1.15; group III: immediately after radiotherapy RR = 0.94, 95%CI 0.65 to 1.37; six months after radiotherapy RR = 0.47, 95%CI 0.20 to 1.10).

No meta-analysis was performed with these studies because of the important clinical heterogeneity.

Conclusions

- A positive effect of initial dental treatment combined with chlorhexidine gluconate (0.12%), sodium fluoride (0.5%) or sodium iodine (2% in hydrogen peroxide 10 v/v) on the incidence of mucositis immediately or 6 months after radiotherapy could neither be demonstrated nor refuted (Meca 2009; very low level of evidence).
- A positive effect of an oral care protocol on the development of oral mucositis could neither be demonstrated nor refuted (Worthington 2011, Djuric 2006; very low level of evidence).

Other considerations

Basic oral care and hygiene is considered good clinical practice. The effect of specialized, intensified oral care protocols will depend on the quality of basic oral care in the control group. Overall, the evidence is very limited and of poor quality.

Recommendation

- Specialized, intensified oral care protocols are not recommended in addition to basic oral care and hygiene measures. However, patients should be informed about the importance of maintaining oral hygiene during treatment (weak recommendation).

3.2.1.5. Intra-oral fluoride releasing systems

No evidence from RCTs could be found in the literature.

Conclusion

- There is no evidence from RCTs on the preventative use of intra-oral fluoride releasing systems in patients receiving chemotherapy or radiotherapy.

Recommendation

- There is insufficient evidence to recommend intra-oral fluoride releasing systems to prevent oral mucositis.

3.2.1.6. Keratinocyte growth factor (palifermin) versus placebo

Seven trials included in the review of Worthington et al. [11] compared keratinocyte growth factor with placebo. All three mucositis outcome categories showed evidence of a benefit associated with keratinocyte growth factor (RR = 0.82, 95%CI 0.71 to 0.94 for any mucositis; RR = 0.74, 95%CI 0.62 to 0.89 for moderate plus severe mucositis; and RR = 0.72, 95%CI 0.58 to 0.90 for severe mucositis). However, there was substantial heterogeneity in the any mucositis and moderate to severe mucositis outcome categories.

Through the update, two additional trials were found [18, 20].

The first trial [18] investigated whether palifermin reduces the occurrence of severe oral mucositis in patients with head and neck cancer undergoing postoperative radiochemotherapy (60-66 Gy, cisplatin). Patients were randomly assigned to receive weekly palifermin 120 µg/kg or placebo from 3 days before and continuing throughout radiochemotherapy. The trial included 186 patients and was considered to have a high risk of bias. Trained evaluators performed oral assessments twice weekly. The trail reported on the following outcomes: incidence of severe oral mucositis (WHO grades 3 to 4), median duration of severe mucositis, median time to onset of severe mucositis, incidence of supplemental nutrition and adverse events. The incidence of severe oral mucositis was significantly less in the treatment group as compared to the control group (RR = 0.76; 95%CI 0.60 to 0.97). In addition, palifermin decreased the duration of severe mucositis (median 4.5 vs. 22.0 days) and prolonged the time to develop severe mucositis (median 45 vs. 32 days). There was a non-significant difference in the incidence of supplemental nutrition between the two groups (RR = 0.98; 95%CI 0.88 to 1.09). As for the adverse events, only a slightly significant difference was found for dysphagia (RR = 1.63; 95%CI 1.01 to 2.64).

The second trial [20] evaluated the efficacy and safety of palifermin to reduce oral mucositis associated with definitive chemoradiotherapy (70 Gy of fractionated radiotherapy and cisplatin) for locally advanced head or neck cancer. The trial included 188 participants and was considered to have a low risk of bias. Patients received palifermin or placebo before starting chemoradiotherapy and then once weekly for seven weeks. The study reported on the following outcomes: incidence of severe mucositis (WHO grade 3 to 4), median duration of severe mucositis, median time to onset of severe mucositis, incidence of supplemental nutrition and adverse events. The incidence of severe mucositis was significantly lower for palifermin than for placebo (RR = 0.78; 95%CI 0.62 to 0.99). In the palifermin arm, median time to severe oral mucositis was delayed (47 versus 35 days), median duration of severe oral mucositis was shortened (5 vs 26 days). There was a non-significant difference in the incidence of supplemental nutrition between the two groups (RR = 1.21; 95%CI 0.96 to 1.53). As for the adverse events, more patients in the treatment group reported at least one adverse event as compared to the control group, although the difference was not significant (RR = 1.05; 95%CI 0.98 to 1.12). Similarly, study drug-related adverse events and the incidence of serious adverse events related to the study treatment were also more reported in the treatment group as opposed to the control arm, although not significantly in the latter case (RR = 3.19, 95%CI 1.67 to 6.10; and RR = 2.42, 95%CI 0.48 to 12.16, respectively). The most frequent study drug–related adverse events (palifermin vs. placebo) were rash (9% vs. 2%), flushing (5% vs. 0%), dysgeusia (5% vs. 1%), nausea (4% vs. 1%) and vomiting (3% vs. 1%). None of these events led to study withdrawal. There was no difference in progression-free survival between the palifermin and placebo arms (HR = 1.13; 95%CI, 0.75 to 1.71).

The results of both studies were added to the meta-analysis of the outcome 'severe mucositis' of the review [11]. The results showed a statistically significant difference in favour of the treatment group (RR = 0.74; 95%CI 0.65 to 0.85). Also the results of the two studies [18, 20] for the outcome 'Incidence of supplemental nutrition' were pooled and did not show a significant difference (RR = 1.48; 95%CI 0.85 to 2.56).

Conclusions

- There are indications that keratinocyte growth factor (Palifermin or Velafermin) prevents the development of any grade oral mucositis (Worthington 2011; low level of evidence).
- There are indications that keratinocyte growth factor (Palifermin or Velafermin) prevents the development of moderate plus severe oral mucositis (Worthington 2011; low level of evidence).
- It is plausible that keratinocyte growth factor (Palifermin or Velafermin) prevents the development of severe oral mucositis (Henke 2011; Le 2011; Worthington 2011; moderate level of evidence).
- An effect of keratinocyte growth factor (Palifermin or Velafermin) on the need for supplemental nutrition could neither be demonstrated nor refuted (Henke 2011; Le 2011; moderate level of evidence).
- There is limited evidence that palifermin is not associated with an important increase in adverse events (Le 2011; very low level of evidence).
- There is limited evidence that Palifermin has no effect on progression free survival (Le 2011; very low level of evidence).

Other considerations

Additional information on adverse events of palifermin can be found on the websites of the European Medicines Agency (EMA) and the American Food and Drug Administration (FDA). Side effects seen in more than 10% of patients include dysgeusia and hypertrophia of the oral mucosa, rash, pruritus, oedema and arthralgia. These side effects have serious effects on the quality of life of patients and limit its use. Furthermore, due to the nature of the product, there is concern that palifermin stimulates the growth of tumour cells of epithelial origin. Both agencies restrict the indication of palifermin to patients with haematological malignancies receiving myeloablative radiochemotherapy associated with a high incidence of severe mucositis and requiring autologous haematopoietic stem cell support.

Recommendation

- Palifermin is not recommended to prevent oral mucositis in patients receiving non-myeloablative chemotherapy and/or radiotherapy (strong recommendation).

3.2.1.7. Honey versus no treatment / lignocaine

Based on three trials included in the review of Worthington et al. [11], each with 40 randomised patients undergoing (chemo)radiotherapy for head and neck cancer, there is evidence that honey is associated with a moderate benefit with regard to the prevention of any mucositis (RR = 0.70; 95%CI 0.56 to 0.88), moderate to severe mucositis (RR = 0.48; 95%CI 0.31 to 0.74) and severe mucositis (RR = 0.26; 95%CI 0.13 to 0.52). However, in view of the considerable statistical heterogeneity and high risk of bias of the included trials, these results should be interpreted with caution according to the authors.

Through the update, one additional trial [15] was identified that compared honey with lignocaine. The trial included 40 participants undergoing radiotherapy for oral cancer, and was considered to have a high risk of bias. The proportion of patients with intolerable oral mucositis (mucositis grade 3 or 4, measured by the Radiation Therapy Oncology Group [RTOG] scale) was significantly lower in the honey group than in the lignocaine group (RR = 0.07; 95%CI 0.01 to 0.46). Adverse events were not reported on.

The results of this study were added to the meta-analysis of the outcome 'severe mucositis' of the review Worthington et al. [11]. The results showed a significant benefit in favour of the treatment group (RR = 0.19; 95%CI 0.10 to 0.37).

Conclusion

- There are indications that honey prevents the development of oral mucositis in patients receiving (chemo)radiation (Worthington 2011; very low level of evidence).

Other considerations

The evidence is very weak and unreliable, but as honey is considered a safe intervention, it can be considered. However, experience has shown that patients with xerostomia do not tolerate the sticky substance.

Recommendation

- The use of honey can be considered to prevent oral mucositis in patients undergoing (chemo)radiotherapy for head and neck cancer (weak recommendation).

3.2.1.8. Laser versus placebo or sham control

Five studies included in the review of Worthington et al. [11], comprising a total of 234 patients, compared laser with a sham laser placebo or no treatment. Three studies were included in the meta-analyses. There was no statistical difference in the incidence of any mucositis (3 studies; RR = 0.91; 95%CI 0.71 to 1.17) or moderate plus severe mucositis (2 studies; RR = 0.64; 95%CI 0.38 to 1.08) between the laser and control group, but there was a statistically significant reduction in the incidence of severe mucositis in the laser group compared to sham or no treatment (2 studies; RR = 0.20; 95%CI 0.06 to 0.62). There was substantial heterogeneity in both the moderate plus severe and severe outcome categories.

Through the update, three additional trials were found [17, 22, 23].

The first trial [17] evaluated the effect of low-level laser (LLL) in the prevention and treatment of mucositis in head and neck cancer patients. A

total of 70 patients were randomized into two low-level laser therapy groups: group 1 (660 nm/15 mW/3.8 J/cm2/spot size 4 mm2) or group 2 (660 nm/5 mW/ 1.3 J/cm2/spot size 4 mm2, which is considered to have minimal biological effects [sham]) starting on the first day of radiotherapy. This trial was considered to have an unclear risk of bias and reported on the mean time to development of oral mucositis and mean grade of mucositis (assessed daily and weekly using the NCI and WHO scales). The patients in group 1 took longer to present grade II and III mucositis (WHO grading) as opposed to the patients in group 2 (grade II: 13.5 days [range 6–26 days] vs. 9.8 days [range 4–14 days, p = 0.005], grade III: 23.6 days [range 11–31 days] vs. 17.1 days [range 10–31 days, p = 0.014]). In addition, group 2 also presented a higher mucositis grade than group 1 with significant differences found in weeks 2 (p = 0.019), 3 (p = 0.005) and 4 (p = 0.003) for the WHO scale and weeks 2 (p = 0.009) and 4 (p = 0.013) for the NCI scale. No significant differences were reported in weeks 6 (27 patients evaluated) and 7 (17 patients evaluated).

The second trial [22] evaluated the efficacy of LLL therapy to decrease severe oral mucositis and its effect on radiotherapy interruptions. A total of 75 patients with head and neck cancer were included who received either galliumaluminum-arsenide LLL therapy 2.5 J/cm2 or placebo laser, before each radiation fraction. The trial was considered to have a low risk of bias and reported on the oral mucositis severity. During radiotherapy, the number of patients diagnosed with grade 3 mucositis treated with LLL vs. placebo was 4 vs. 5 (week 2, RR = 0.82; 95%CI 0.24 to 2.82), 4 vs. 12 (week 4, RR = 0.34; 95%CI 0.12 to 0.97), and 8 vs. 9 (week 6, RR = 0.91; 95%CI 0.39 to 2.11), respectively. No Grade 4 mucositis was detected throughout the study period.

The third trial [23] assessed the impact of laser on the quality of life (QoL) of patients with head and neck cancer receiving radiotherapy (RT). Sixty patients were randomly assigned to laser applications or sham laser. The trial was considered to have a high risk of bias and reported on QoL (assessed using the University of Washington QoL questionnaire) and the need for feeding tube. A reduction was shown for all QoL domain scores in both groups. Pain (p = 0.03), chewing (p = 0.004), and saliva (p < .001) domains were more affected in the placebo group. Less patients in the treatment group scored a poor to very poor QoL (health related and overall QoL) after 30 RT sessions. However, the difference was not significant.

The need for feeding tubes was lower in the treatment group compared to the control group (RR 0.47 [95%CI 0.05 to 4.78]), but this difference was not significant.

The results of one study [22] could be added to the meta-analysis of the included review [11] for the outcome 'severe mucositis'. The results showed a significant difference in favour of the treatment group (RR = 0.26; 95%CI 0.12 to 0.56).

There are no data from RCTs on the effect of LLL on performance status, adverse events of the intervention and progression-free survival.

Conclusions

- There are indications that laser has no effect on the overall incidence of oral mucositis (Worthington 2011; low level of evidence).
- A positive effect of laser on the incidence of moderate to severe oral mucositis could neither be demonstrated nor refuted (Worthington 2011; very low level of evidence).
- There are indications that laser prevents the development of severe oral mucositis (Gouvea de Lima 2012; Worthington 2011; low level of evidence).
- An effect of laser on quality of life in patients with head and neck cancer undergoing radiotherapy could neither be demonstrated nor refuted (Oton-Leite 2012; very low level of evidence).
- An effect of laser on the need for feeding tube in patients with head and neck cancer undergoing radiotherapy could neither be demonstrated nor refuted (Oton-Leite 2012; very low level of evidence).

Other considerations

Overall, evidence is still limited and of low quality. Data on side effects of LLL therapy are lacking. For patients with a tumour in or near the oral cavity, it is of concern to the expert group that the effect of laser treatment on tumour cells is unknown and that long-term follow-up on oncological outcomes is not available.

The preventive use of LLL therapy is not compared with therapeutic LLL when symptoms occur in a randomized fashion. Furthermore, to reproduce the results obtained in clinical trials, LLL therapy must be performed by a skilled person.

LLL therapy is currently not reimbursed in Belgium. Financial consequences for patients should be clearly communicated in advance.

Recommendation

- Low-level laser therapy is not recommended to prevent oral mucositis in cancer patients receiving chemotherapy outside the framework of a clinical trial (weak recommendation).

3.2.2. Treatment of oral mucositis

One review was included that assessed the effectiveness of interventions for treating oral mucositis in patients with cancer receiving chemotherapy or radiotherapy or both [24]. The search date was June 2010. The overall risk of bias of this review was considered to be low.

The review included 32 RCTs with 1 505 randomised participants and evaluated 27 different interventions. Of all the interventions examined in this review, six mucositis treatments were within the scope of this report

In April 2012 an update of the literature search of Clarkson et al. [24] was performed. Three additional RCTs were identified [25-27].

3.2.2.1. Mouthwashes

Benzydamine mouthwash versus placebo

Two trials included in the review of Clarkson et al. [24] compared benzydamine mouthwash with placebo. There was no statistically significant difference between benzydamine and placebo with respect to improvement of mucositis (RR = 1.22; 95%CI 0.94 to 1.60).

Sucralfate (mouthwash and gel) versus placebo

Two trials included in the review of Clarkson et al. [24] compared sucralfate (sucralfate gel and sucralfate solution) with placebo. There was no statistically significant difference between sucralfate and placebo with respect to eradication of mucositis (RR = 1.13; 95%CI 0.66 to 1.94).

Allopurinol mouthwash versus placebo

One trial included in the review of Clarkson et al. [24] compared allopurinol mouthwash with placebo. A statistically significant benefit in favour of allopurinol for improvement in mucositis, eradication and time to heal was found (RR = 6.33; 95%CI 2.18 to 18.37; RR = 19.00; 95%CI 1.17 to 307.63, MD = -4.50; 95%CI -5.77 to -3.23 respectively).

Chlorhexidine versus salt and soda

One trial included in the review of Clarkson et al. [24] compared chlorhexidine mouthwash with salt and soda. No statistically significant differences were found for the eradication of mucositis and time to heal mucositis (days) (RR = 1.10; 95%CI 0.90 to 1.35, MD = -0.40; 95%CI -1.49 to 0.69 respectively).

'Magic' versus salt and soda

One trial included in the review of Clarkson et al. [24] compared 'magic' (lidocaine solution, diphenhydramine hydrochloride and aluminium hydroxide suspension) versus salt and soda. No statistically significant differences were found for the eradication of mucositis and time to heal mucositis (days) (RR = 0.98; 95%CI 0.78 to 1.24, MD = 0.17; 95%CI -0.97 to 1.31 respectively).

Phenylbutyrate mouthwash versus placebo

Through the update, one trial was found which evaluated the therapeutic safety and efficacy of phenylbutyrate (an antitumor histone deacetylase inhibitor and chemical chaperone) 5% mouthwash for treating oral mucositis caused by cancer therapy [27]. The trial included 36 participants who were randomized to either standard oral care plus 5 ml of either phenylbutyrate 5% mouthwash or placebo (mouthwash vehicle) four times daily. The risk of bias of this trial was considered to be unclear and the following outcomes were reported: severity of mucositis, duration of mucositis, adverse events and need of tube feeding. As for the severity of mucositis (WHO score), no significant difference was found (MD = -0.35; 95%CI -1.11 to 0.41).There was no significant difference in the percentage of patients with severe mucositis (WHO score ≥ 3) between the treatment and the control group (RR = 0.91; 95%CI 0.24 to 3.41). The median duration of severe mucositis (WHO mucositis score ≥ 3) was 2 days (range 0–56 days) in the phenylbutyrate group and 12 days (range 0–82 days) in the placebo group. The median duration of symptomatic mucositis (WHO score ≥ 2) was 16 days (range 0–70 days) in the phenylbutyrate group and 50 days (range 0–82 days) in the placebo group. The patients in the placebo group had a higher frequency of tube feeding or 'nothing per oral' because of severe mucositis than the patients in the phenylbutyrate group, although the difference was not significant (RR = 0.61; 95%CI 0.06 to 6.02). With regards to the adverse events, no significant differences between treatment and control group were observed.

Triclosan mouthwash versus sodium bicarbonate mouth rinse

Through the update, one trial was found which evaluated the effectiveness of triclosan mouth rinse compared with conventional sodium bicarbonate mouth rinse [26]. The trial included 24 participants who were allocated to either triclosan mouth rinse or sodium bicarbonate mouth rinse. The trial was considered to have a high risk of bias and the following outcomes were evaluated: severity and duration of mucositis and the food intake (change in way of feeding). No significant differences were found in the mean number of days it took for a change in the WHO grade of mucositis. A significant difference was found in the incidence of grade 4 mucositis (RR = 0.10; 95%CI 0.02 to 0.66). As for the change in food intake, a significant difference was found in the number of days it took for a change from liquid to solid (MD = -19.57; 95%CI -30.80 to -8.34), but not for solid to liquid (MD 0.00 [95%CI -3.85 to 3.85]).

Conclusions

- An effect of benzydamine mouthwashes on improvement of oral mucositis could neither be demonstrated nor refuted (Clarkson 2010; very low level of evidence).
- An effect of sucralfate mouthwash and gel on eradication of oral mucositis could neither be demonstrated nor refuted (Clarkson 2010; low of evidence).
- There are indications that allopurinol mouthwashes lead to improvement in oral mucositis (Clarkson 2010; very low level of evidence).
- There are indications that allopurinol mouthwashes have a positive effect on eradication of oral mucositis (Clarkson 2010; very low level of evidence).
- There are indications that allopurinol mouthwashes shorten the duration of oral mucositis (Clarkson 2010; very low level of evidence).
- An effect of chlorhexidine mouthwash on eradication of oral mucositis could neither be demonstrated nor refuted (Clarkson 2010; very low level of evidence).
- An effect of chlorhexidine mouthwash on time to heal oral mucositis could neither be demonstrated nor refuted (Clarkson 2010; very low level of evidence).
- An effect of 'magic' mouthwash on eradication of oral mucositis could neither be demonstrated nor refuted (Clarkson 2010; very low level of evidence).
- An effect of 'magic' mouthwash on time to heal oral mucositis could neither be demonstrated nor refuted (Clarkson 2010; very low level of evidence).
- An effect of standard oral care plus 5 mL of phenylbutyrate 5% mouthwash on severity of oral mucositis could neither be demonstrated nor refuted (Yen 2012; very low level of evidence).

- An effect of standard oral care plus 5 mL of phenylbutyrate 5% mouthwash on the incidence of at least one adverse event could neither be demonstrated nor refuted (Yen 2012; very low level of evidence).
- An effect of standard oral care plus 5 mL of phenylbutyrate 5% mouthwash on incidence of nausea/vomiting, constipation, cough, pharyngeal pain, insomnia, mild to moderate irritation, hyperpigmentation of the skin and metabolic and nutrition disorders could neither be demonstrated nor refuted (Yen 2012, very low level of evidence).
- An effect of phenylbutyrate 5% mouthwash in combination with standard oral care on the number of visits with tube feeding or 'nothing per oral' could neither be demonstrated nor refuted (Yen 2012; very low level of evidence).
- A difference in effect of triclosan mouth wash vs. sodium bicarbonate mouth rinse on the mean number of days it takes for a change of grade of oral mucositis (WHO grading) could neither be demonstrated nor refuted (Satheeskumar 2010, very low level of evidence).
- There is limited evidence that triclosan mouth wash reduces the incidence of grade 4 oral mucositis when compared to sodium bicarbonate mouth rinse (Satheeskumar 2010, very low level of evidence).
- There is limited evidence that triclosan mouth wash reduces the duration of oral mucositis when compared to sodium bicarbonate mouth rinse (Satheeskumar 2010, very low level of evidence).
- A difference in effect of triclosan mouth wash vs. sodium bicarbonate mouth rinse on the number of days it takes for a change in the way of feeding from solid to liquid could neither be demonstrated nor refuted (Satheeskumar 2010, very low level of evidence).
- There are indications that triclosan mouth wash leads to a shorter period of time to resume solid food from liquid compared to sodium bicarbonate mouth rinse (Satheeskumar 2010, very low level of evidence).

Other considerations

As for preventive use, rinsing with any mouthwash probably has a mechanical effect on the oral cavity. Due to the lack of strong evidence, no detailed advice on the preferred composition of mouth washes can be given.

Recommendations

- Allopurinol mouthwashes can be considered to treat oral mucositis due to chemo- and/or radiotherapy (weak recommendation).
- Benzydamine, sucralfate or chlorhexidine mouthwashes, magic mouthwash, phenylbutyrate mouthwash, triclosan and sodium bicarbonate mouth wash are not recommended to treat oral mucositis due to chemo- and/or radiotherapy (weak recommendation).

3.2.2.2. Honey versus placebo (golden syrup)

Through the update, one trial was found which evaluated the effect of active manuka honey on radiation-induced mucositis [25]. A total of 131 patients diagnosed with head and neck cancer who received radiotherapy to the oral cavity or oropharyngeal area were randomly allocated to manuka honey or placebo (golden syrup) 20 ml 4 times daily for 6 weeks. The trial was considered to have an unclear risk of bias and reported on the following outcomes: incidence of mucositis grade 3 (assessed according to the Radiation Therapy Oncology Group [RTOG] scale at baseline, weekly during radiotherapy, and twice weekly thereafter until the mucositis resolved), severity and duration of mucositis and the need for tube feeding.

There was no significant difference between honey and golden syrup in their effects on the incidence of grade 3 mucositis (RR = 1.07; 95%CI 0.88 to 1.29). In addition, there was no significant difference (p=0.79) in the severity or duration of mucositis in the treatment group and the control group (results not quantified). Similarly, no significant difference was found in the need for tube feeding between the two groups (RR = 1.03; 95%CI 0.64 to 1.65).

Conclusions

- An effect of manuka honey on the incidence of grade 3 mucositis in patients with head and neck cancer undergoing radiotherapy could neither be demonstrated nor refuted (Bardy 2012; very low level of evidence).
- An effect of manuka honey on the need for tube feeding in patients with head and neck cancer undergoing radiotherapy could neither be demonstrated nor refuted (Bardy 2012; very low level of evidence).
- An effect of manuka honey on the severity and duration of oral mucositis in patients with head and neck cancer undergoing radiotherapy could neither be demonstrated nor refuted (Bardy 2012; very low level of evidence).

Recommendation

- Honey is not recommended to treat oral mucositis due to chemo- and/or radiotherapy (weak recommendation).

3.2.2.3. Laser versus sham treatment

Two trials of the systematic review by Clarkson et al. [24] compared low-level laser with sham treatment in patients with mild to moderate oral mucositis. There was a statistically significant benefit for the laser with respect to therapeutic effect (mild to moderate mucositis) (RR = 5.28; 95%CI 2.30 to 12.13). Due to clinical heterogeneity the results of this meta-analysis should be interpreted with caution.

Conclusion

- There are indications that low level laser therapy is an effective treatment for oral mucositis (Clarkson 2010; very low level of evidence).

Other considerations

As stated above, data on side effects of LLL therapy are lacking. For patients with a tumour in or near the oral cavity, it is of concern to the expert group that the effect of laser treatment on tumour cells is unknown and that long-term follow-up on oncological outcomes is not available.

Furthermore, to reproduce the results obtained in clinical trials, LLL therapy must be performed by a skilled person.

Recommendation

- Low-level laser therapy can be considered to treat oral mucositis due to chemo- and/or radiotherapy. For patients with a tumour in or near the oral cavity, low-laser therapy should only be used within the framework of a clinical trial (weak recommendation).

3.2.2.4. Mucosal coating agents

One trial of the review by Clarkson et al. [24] compared sucralfate gel with placebo (this trial was already included in the meta-analyses of sucralfate). No statistically significant differences were found in the improvement of mucositis (RR = 0.93; 95%CI 0.71 to 1.24).

Conclusion

- A therapeutic effect of sucralfate gel on oral mucositis could neither be demonstrated nor refuted (Clarkson 2010; very low level of evidence).

Recommendation

- Sucralfate gel is not recommended to treat oral mucositis due to chemo- and/or radiotherapy (weak recommendation).

3.3. Oral candidiasis

Two reviews about oral candidiasis were identified that met the inclusion criteria. One review (Clarkson 2009) addressed interventions for *preventing* oral candidiasis in patients with cancer receiving chemotherapy and/or radiotherapy, the other (Worthington 2010) addressed interventions for the *treatment* of oral candidiasis in patients with cancer receiving chemotherapy or radiotherapy or both [11, 28].

3.3.1. Prevention of oral candidiasis

The search of the review of Clarkson et al. about prevention of oral candidiasis was performed in July and August 2009 [28]. The overall risk of bias of the review was judged to be low. The review included 28 trials involving 4 226 patients. Some of the included trials studied children. Patients in the included trials had different types of cancer and some underwent bone marrow transplantation. The quality of the included studies was mixed. The studied interventions were categorised according to the degree of absorption from the gastrointestinal (GI) tract: absorbed (fluconazole, ketoconazole, itraconazole), partially absorbed (clotrimazole, miconazole) or not absorbed (amphotericin B, nystatin, chlorhexidine, thymostimulin, natamycin, norfloxacin). Eleven trials included a placebo group, seven a 'no treatment' control group and one trial had a control intervention of saline rinse. Eight trials compared different agents with varying doses, frequency and duration of use. One trial compared different doses of the same test agent.

The primary outcome measure addressed in the review was absence/presence of oral candidiasis. Secondary outcome measures included: relief of pain, amount of analgesia, relief of dysphagia, incidence of systemic infection, duration of stay in hospital, cost of oral care, patient quality of life, death, use of empirical antifungal treatment, toxicity and compliance.

In April 2012 an update of the literature search of Clarkson et al. was performed. Two additional RCTs were identified [14, 29].

3.3.1.1. Oral candidiasis prophylaxis with fluconazole, ketoconazole, itraconazole, clotrimazole, miconazole, amphotericin B, nystatin, chlorhexidine, thymostimulin, natamycin and norfloxacin

In the review of Clarkson et al. results were presented according to the degree of absorption from the GI tract of the drugs [28]:

Drugs absorbed from GI tract: fluconazole, ketoconazole, itraconazole

The review included seven trials involving 1 153 patients that compared drugs absorbed from the GI tract (fluconazole, ketoconazole, itraconazole) with placebo or 'no treatment' control group. The majority of these trials included patients with haematological malignancies. The meta-analysis showed that these drugs prevented oral candidiasis (RR 0.47; 95%CI 0.29 to 0.78). There were no significant differences between drugs absorbed from the GI compared with placebo or 'no treatment' for the following outcomes: systemic fungal infection (6 studies, RR = 0.65; 95%CI 0.37 to 1.14), death (3 studies, RR = 1.44; 95%CI 0.14 to 15.43), toxicity (3 studies, RR = 1.18; 95%CI 0.84 to 1.67).

Two trials compared different drugs absorbed from the GI tract. One study compared itraconazole with fluconazole finding no evidence of a difference in presence of oral candidiasis. Another study compared ketoconazole with itraconazole also finding no difference. For none of the other outcomes (systemic fungal infection, death or toxicity) differences were found.

Eight studies compared drugs absorbed from the GI tract directly with those not absorbed. A significant benefit in using the absorbed drugs rather than those not absorbed to prevent oral candidiasis was found (RR = 0.40; 95%CI 0.21 to 0.76). For other outcomes no significant difference was found (systemic fungal infection: 8 studies, RR = 0.59; 95%CI 0.33 to 1.06; death: 3 studies, RR = 1.25; 95%CI 0.38 to 4.13; toxicity: 6 studies, RR = 0.88; 95%CI 0.33 to 2.30).

Drugs partially absorbed from GI tract: clotrimazole, miconazole

Four trials involving 292 patients compared drugs partially absorbed from the GI tract (clotrimazole, miconazole) with placebo and these drugs were found to prevent oral candidiasis (RR = 0.16; 95%CI 0.06 to 0.46).

Drugs not absorbed from GI tract: amphotericin B, nystatin, chlorhexidine, thymostimulin, natamycin, norfloxacin

Eight studies involving 382 patients compared drugs not absorbed from the GI tract (amphotericin B, nystatin, chlorhexidine, thymostimulin, natamycin, norfloxacin) with placebo or 'no treatment' control groups, and overall the drugs did not have a significant benefit in preventing oral candidiasis (RR = 0.68; 95%CI 0.46 to 1.02). There were no significant differences between drugs not absorbed from the GI compared with placebo or 'no treatment' for the following outcomes: systemic fungal infection (2 studies, RR = 0.10; 95%CI 0.01 to 1.75), death (1 study, RR = 0.16; 95%CI 0.01 to 2.95).

Three trials compared different drugs which were not absorbed from the GI tract with each other. For presence of oral candidiasis no significant difference was found (chlorhexidine versus nystatin, 1 study, RR = 0.89; 95%CI 0.36 to 2.21; chlorhexidine versus chlorhexidine plus nystatin, 1 study, RR = 1.62; 95%CI 0.64 to 4.10; nystatin versus chlorhexidine plus nystatin, 1 study, RR = 1.82; 95%CI 0.73 to 4.54; nystatin versus natamycin, 1 study, RR = 1.07; 95%CI 0.83 to 1.37; norfloxacin + amphotericin B versus amphotericin B, 1 study, RR = 0.38; 95%CI 0.15 to 1.00). One study reported the outcome systemic infection and found no significant difference for norfloxacin plus amphotericin B vs. amphotericin B (RR = 0.67; 95%CI 0.20 to 2.23). No other outcomes (death or toxicity) were reported in these studies.

Conclusions

- There are indications that fluconazole, ketoconazole or itraconazole prevent the occurrence of oral candidiasis in patients receiving chemotherapy or radiotherapy (Clarkson 2009; low level of evidence).
- An effect of prophylactic fluconazole, ketoconazole, itraconazole on the occurrence of systemic fungal infections in patients receiving chemotherapy or radiotherapy could neither be demonstrated nor refuted (Clarkson 2009; low level of evidence).
- An effect of prophylactic fluconazole, ketoconazole, itraconazole on mortality in patients receiving chemotherapy or radiotherapy could neither be demonstrated nor refuted (Clarkson 2009; very low level of evidence).
- There are indications that prophylactic fluconazole, ketoconazole, itraconazole is not associated with significant toxicity in patients receiving chemotherapy or radiotherapy (Clarkson 2009; very low level of evidence).
- There is limited evidence that prophylactic fluconazole and itraconazole are not different in terms of incidence of oral candidiasis, systemic fungal infections, mortality and toxicity (Clarkson 2009; very low level of evidence).
- There is limited evidence that prophylactic ketoconazole and itraconazole are not different in terms of incidence of oral candidiasis (Clarkson 2009; very low level of evidence).
- There are indications that drugs absorbed from the GI tract (fluconazole, ketoconazole, itraconazole) are more effective in preventing oral candidiasis compared to drugs not absorbed from the GI tract (amphotericin B, nystatin, chlorhexidine, thymostimulin, natamycin, norfloxacin) (Clarkson 2009; very low level of evidence).
- There are indications that drugs absorbed from the GI tract (fluconazole, ketoconazole, itraconazole) and drugs not absorbed from the GI tract (amphotericin B, nystatin, chlorhexidine, thymostimulin, natamycin, norfloxacin) are not significantly different in terms of the incidence of systemic fungal infections and toxicity (Clarkson 2009; very low level of evidence).
- There are indications that drugs absorbed from the GI tract (fluconazole, ketoconazole, itraconazole) and drugs not absorbed from the GI tract (amphotericin B, nystatin, chlorhexidine, thymostimulin, natamycin, norfloxacin) are not significantly different in terms of mortality (Clarkson 2009; low level of evidence).
- It is plausible that clotrimazole or miconazole prevent the occurrence of oral candidiasis in patients receiving chemotherapy or radiotherapy (Clarkson 2009; moderate level of evidence).

- There are indications that drugs not absorbed from the GI tract (amphotericin B, nystatin, chlorhexidine, thymostimulin, natamycin, norfloxacin) have no effect on the incidence of oral candidiasis, systemic fungal infections and mortality in patients receiving chemotherapy or radiotherapy (Clarkson 2009; very low level of evidence).

Other considerations

Drugs absorbed from the GI tract and drugs partially absorbed from the GI tract are not directly compared in a RCT. Analysis for the separate drugs included in the group of drugs not absorbed from the GI tract shows no effect for all drugs included. In clinical practice, fluconazole appears to be the drug of choice, based on availablilty, pharmacological characteristics and toxicity profile.

The expert group pointed out that prevention only should be considered in high-risk patients, such as patients suffering from leukemia or head and neck cancer. General use of prophylactic measures is considered not indicated, since treatment when first symptoms occur has almost immediate effect.

Recommendations

- Prophylactic use of fluconazole, ketoconazole, itraconazole, clotrimazole or miconazole can be considered to prevent oral candidiasis in patients receiving chemotherapy or radiotherapy with a high risk of causing oral candidiasis (weak recommendation).
- Drugs not absorbed from the GI tract (amphotericin B, nystatin, chlorhexidine, thymostimulin, natamycin, norfloxacin) are not recommended to prevent oral candidiasis in patients receiving chemotherapy or radiotherapy (weak recommendation).

3.3.1.2. Mouth washes general

Trials studying the use of e.g. chlorhexidine mouthwashes already included in the review by Clarkson et al. are not again discussed in this paragraph. Two RCTs were identified that studied the effects of mouth washes [14, 29].

The trial of Lanzos et al. involved 36 participants who were randomized to either an antiseptic, non-alcohol based, mouth rinse containing chlorhexidine (CHX) and cetyl-pyridinium chloride (CPC) or a placebo mouth rinse [29]. This trial was judged to be at high risk of bias. Participants were examined at three visits: baseline (start radiotherapy), 14 days and 28 days after start of radiotherapy. No differences between study groups were found as to the detection of Candida species in samples of oral mucosa and tongue. No relevant adverse effects were reported in either group.

The trial of Meca et al. involved 60 participants who were randomly divided into four groups [14]. Three to four weeks before radiotherapy, participants in group I-III received initial dental treatment, which consisted of extractions, restorations, scaling and dental prophylaxis. In addition, group I received chlorhexidine gluconate (0.12%) once daily during radiotherapy and for six months after, group II received sodium fluoride (0.5%, aqueous solution) daily during and after radiotherapy, and group III received sodium iodine (2% in hydrogen peroxide 10 v/v) once daily during and after radiotherapy. Oral hygiene instructions for group I, II and III were reinforced at each visit. There was no intervention for participants in group IV: they received medical treatment with no odontological assistance and received oral hygiene instructions only during and after radiotherapy. The risk of bias of this trial was judged to be unclear. In none of the intervention groups at any time point the incidence of oral candidiasis differed significantly from the no treatment group (group I: immediately after radiotherapy RR = 0.35, 95%CI 0.12 to 1.01; six months after radiotherapy RR = 0.13, 95%CI 0.01 to 2.22; group II: immediately after radiotherapy RR = 0.41, 95%CI 0.14 to 1.16; six months after radiotherapy RR = 0.33, 95%CI 0.04 to 2.63; group III: immediately after radiotherapy RR 0.43, 95%CI 0.17 to 1.08; six months after radiotherapy RR 0.12, 95%CI 0.01 to 2.04). Also in the between group comparisons of the active interventions no significant differences were found (group I vs. group II: immediately after radiotherapy

RR 0.85, 95%CI 0.21 to 3.38; six months after radiotherapy RR 0.30, 95%CI 0.01 to 6.62; group I vs. group III: immediately after radiotherapy RR 0.81, 95%CI 0.22 to 2.94; six months after radiotherapy RR not estimable; group II vs. group III: immediately after radiotherapy RR 0.95, 95%CI 0.27 to 3.40; six months after radiotherapy RR 3.60, 95%CI 0.16 to 79.01).

Conclusions

- An effect of chlorhexidine mouth washes on the occurrence of oral candidiasis and are not associated with significant toxicity could neither be demonstrated nor refuted (Lanzos 2011; very low level of evidence).
- An effect of dental treatment combined with mouth washes on the occurrence of oral candidiasis could neither be demonstrated nor refuted (Meca 2009; very low level of evidence).

Other considerations

As stated above, rinsing with any mouthwash probably has a mechanical effect on the oral cavity. Due to the lack of strong evidence, no detailed advice on the preferred composition of mouth washes can be given.

Recommendation

- The use of mouth washes is not recommended to prevent oral candidiasis in patients receiving chemotherapy or radiotherapy (weak recommendation).

3.3.2. Treatment of oral candidiasis

The search of the review of Worthington et al. about treatment of oral candidiasis was performed in June 2010 [30]. The overall risk of bias of the review was judged to be low. The review included ten RCTs involving 940 patients. Only one of the included RCTs was assessed to be at low risk of bias. The studied interventions were categorised according to the degree of absorption from the gastrointestinal (GI) tract: absorbed (fluconazole, ketoconazole, itraconazole), partially absorbed (clotrimazole, miconazole) or not absorbed (amphotericin B, nystatin). In two trials a comparison was made with a placebo. Two other trials compared different doses of the same drug. The majority of the included studies compared different agents with varying doses, frequency and duration of use.

The primary outcome measure addressed in the review was absence/presence of oral candidiasis. Secondary outcome measures included: relief of pain, amount of analgesia, relief of dysphagia, incidence of systemic infection, days stay in hospital, cost of oral care and patient quality of life. Apparently none of the secondary outcomes were reported in the included RCTs.

All trials reported both a clinical and microbiological outcome of oral candidiasis. For the clinical eradication of oral candidiasis one of the placebo-controlled trials found a significant benefit for ketoconazole (RR = 3.61; 95%CI 1.47 to 8.88). However, this was not found for mycological eradication. In the other placebo-controlled trial no benefit (clinical nor mycological) was demonstrated for the partially absorbed drug clotrimazole.

Three trials compared different types of absorbed drugs with each other and they failed to demonstrate a clinical benefit of one drug against another. However, for mycological eradication a statistically significant benefit was found for fluconazole over itraconazole (RR = 1.17; 95%CI 1.04 to 1.33).Three other trials compared absorbed drugs with drugs not absorbed. The meta-analysis found a clinical and mycological benefit for the absorbed drugs over the non-absorbed drugs (clinical: RR = 1.29; 95%CI fixed 1.09 to 1.52; mycological: RR = 1.82; 95%CI 1.28 to 2.57). However, there was substantial heterogeneity between the three trials with I^2 = 78% and 85%, respectively. The two trials comparing different doses of the same drug did not find any significant difference.

In April 2012 an update of the literature search of Worthington et al. was performed. No additional RCTs were identified.

Conclusions

- There is limited evidence that ketoconazole is an effective treatment for oral candidiasis in patients receiving chemotherapy or radiotherapy (Worthington 2010; very low level of evidence).
- A therapeutic effect of clotrimazole for oral candidiasis in patients receiving chemotherapy or radiotherapy could neither be demonstrated nor refuted (Worthington 2010; very low level of evidence).
- There is limited evidence that ketoconazole and fluconazole are equally effective in eradicating oral candidiasis (Worthington 2010; very low level of evidence).
- There are indications that fluconazole is a more effective treatment for oral candidiasis than itraconazole (Worthington 2010; low level of evidence).
- There are indications that drugs absorbed from the GI tract (fluconazole, ketoconazole, itraconazole) are more effective in iradicating oral candidiasis than drugs not absorbed (amphotericin B, nystatin) (Worthington 2010; very low level of evidence).

Recommendations

- Ketoconazole or fluconazole can be considered for the treatment of oral candidiasis associated with chemo- and/or radiotherapy (weak recommendation).
- Drugs not absorbed from the GI tract (amphotericin B, nystatin) are not recommended for the treatment of oral candidiasis associated with chemo- and/or radiotherapy (weak recommendation).

3.4. Skin toxicity

Skin toxicity due to cancer treatment is common and can be associated with radiotherapy, chemotherapy or targeted therapies. Symptoms include radiodermatitis, hand and foot syndrome as seen in patients treated with docetaxel or capecitabine and papulopustular eruptions associated with EGFR inhibitors. As pathophysiology, signs and proposed treatment differ, patient populations included in the trials are specified.

3.4.1. Literature review

One systematic review was identified that met the inclusion criteria [31]. The review addressed the effectiveness of aloe vera compared to any other intervention for the prevention and minimization of radiation-induced skin reactions in cancer patients.

On May 4, 2012 a literature search was performed to identify evidence on the interventions. Eighteen RCTs were identified comparing different interventions to treat or prevent treatment-related skin reactions in cancer patients [32-49].

3.4.2. Gentle skin washing

Three trials comparing different washing policies during radiotherapy were identified [32, 46, 49].

In the first trial by Campbell et al. a total of 99 patients receiving adjuvant radiotherapy to the breast or chest wall were randomized to one of three washing policies: (1) no washing, (2) washing with water alone, (3) and washing with soap and water [32]. Fifty-three of the patients were treated without the use of a bolus (a waxy tissue equivalent material placed on the skin surface to homogenize or modulate the range of the dose from external beams of radiation), and 46 patients were treated using a bolus for 10 to 15 of the 20 treatment fractions. Severity of acute skin reaction was graded according to an expansion of the EORTC/RTOG acute skin reaction scoring system (itching, erythema and desquamation). The trial was considered as having an unclear risk bias. Patients who were randomized to washing had itching scores either similar to or less than those not washing in both the no bolus and the bolus groups. Several of the comparisons at the different time points showed a statistically significant reduction in itching, although the results were not quantified.

There were minor differences between washing with water alone and washing with soap and water, with a trend favouring the latter. There was little difference in average scores for erythema between the washing groups, and a small trend for the non-washing groups to have the highest reactions. Several of the comparisons again showed a statistically significant reduction in erythema associated with washing. Patients who were washing had markedly smaller scores for desquamation than patients who were not washing, again with some comparisons reaching statistical significance.

The second trial by Roy et al. evaluated the impact of washing the breast skin with water and soap during radiotherapy on the intensity of acute skin toxicity [46]. Ninety-nine patients treated for breast cancer were randomized into two groups: (1) no washing was allowed during radiotherapy (49 patients); and (2) washing was allowed with water and soap (50 patients). Severity of acute skin reaction was recorded according to the Radiation Therapy Oncology Group (RTOG) acute skin toxicity scale. The trial was considered as having a low risk bias. There was a significant difference in the grade of toxicity in favour of the washing group. The maximal erythema score was not significantly different between the two groups, but the incidence of moist desquamation was significantly higher in the non-washing group (RR = 2.33; 95%CI 1.05 to 5.17).

The third trial by Westbury et al. assessed the effect of advice on scalp care on the local skin reaction in patients undergoing cranial radiotherapy [49]. One hundred and nine patients undergoing cranial radiotherapy were randomized into two groups: (1) advice not to wash hair during treatment; and (2) maintain normal pattern of hair washing. Severity of acute skin reaction was measured by a RTOG/EORTC acute skin reaction scoring system, skin reaction was assessed clinically using erythema/desquamation score. The trial was considered as having an unclear risk bias. There were no significant differences between scores of skin reaction in the two groups for each of the variables measured (pain, itching, erythema, desquamation).

Conclusion

- An effect of no washing on the severity of acute skin reactions during radiotherapy could neither be demonstrated nor refuted (Campbell 1992, Roy 2001, Westbury 2000; very low level evidence).

Other considerations

Although gentle washing of skin and hair is not harmful, it is important not to harm the irritated skin by the use of aggressive soaps, too frequent washing or friction by tissues.

Recommendation

- Washing of skin and hair should not be discouraged routinely to prevent acute radiodermatitis. Instead, patients should receive advice on how to wash skin and hair during radiotherapy (weak recommendation).

3.4.3. Neutral hydrophilic cream

One study comparing bepanthen cream with no topical ointment has been identified [40]. Eighty-six laryngeal and breast cancer patients were included. The cream was applied on randomly selected parts of treatment fields, and so each patient acted as his own control. The severity of acute skin reaction was assessed using a modified skin reaction grading according to EORTC/RTOG. The trial was considered as having an unclear risk of bias.

No significant differences were found for erythema grade, itching grade and desquamation grade between treated and untreated area.

Conclusion

- An effect of a neutral hydrophilic cream on the severity of acute skin reactions during radiotherapy could neither be demonstrated nor refuted (Lokkevik 1996; very low level of evidence).

Recommendation

- The use of a neutral hydrophilic cream during radiotherapy to avoid severe skin reactions is not recommended (weak recommendation).

3.4.4. Corticosteroid cream

Five trials comparing different corticosteroid creams were identified [33, 35, 43, 47, 48]. In three of these studies a comparison was made with placebo or no intervention [33, 43, 48], in the two other studies two active interventions were compared [35, 47].

The first trial by Bostrom et al. investigated the effect of mometasone furoate cream (MMF) on radiation dermatitis [33]. Fifty patients with node-negative breast cancer were randomized to receive either 0.1% MMF or emollient cream as placebo. Both groups additionally received non-blinded emollient cream daily. Severity of acute skin reaction was assessed by 'maximal assessed erythema scores' and subjective experience of burning and itching. Risk of bias for this study was judged to be low. A significant difference was found for the maximal assessed erythema scores (score 3 or higher, RR = 0.72; 95%CI 0.53 to 0.98) in favour of the treatment group. Furthermore, patients in the group receiving furoate cream experienced less itching and burning as opposed to the group treated with emollient cream, but the difference was not significant.

The second trial by Glees et al. compared two different steroid creams, 1% hydrocortisone cream and 0.05% clobetasone butyrate (Eumovate), in 54 patients undergoing radiation therapy for breast cancer [35]. The risk of bias of this trial was considered to be high. A significant difference was found for 'maximum' skin reactions assessed by the authors (RR = 0.38; 95%CI 0.19 to 0.77), but not for 'moderate or maximum' skin reaction combined (RR = 1.09; 95%CI 0.93 to 1.27). No significant differences were found for skin reactions assessed by the radiotherapist ('maximum': RR = 0.75; 95%CI 0.40 to 1.41, 'maximum and moderate' combined: RR = 0.99; 95%CI 0.74 to 1.32, 'dry': RR = 1.07; 95%CI 0.26 to 4.45, 'moist': RR = 1.07; 95%CI 0.45 to 2.55).

The third trial by Omidvari et al. investigated whether prophylactic use of topical betamethasone 0.1% can prevent acute radiation dermatitis caused by chest wall irradiation [43]. Fifty-one patients who underwent modified radical mastectomy for breast cancer and who were planned for radiotherapy, were randomly assigned to receive (1) topical betamethasone 0.1%, (2) petrolatum or (3) no intervention during radiotherapy. Severity of acute skin reaction was measured using the RTOG scoring criteria. Follow up was two weeks after the completion of radiotherapy and the risk of bias of this trial was considered to be high. The maximum observed grade of acute skin reaction was not significantly different between the three treatment arms.

The fourth trial by Schmuth et al. compared treatment with topical 0.1% methylprednisolone with 0.5% dexpanthenol in patients undergoing fractionated radiation therapy for breast cancer [47]. Twenty-three patients were randomized to one of two treatment schemes. The risk of bias of this trial was considered to be high. Nineteen of 21 evaluated patients developed clinical signs of radiation dermatitis, an incidence comparable with an non-randomized untreated control group. There were fewer patients with scores ≥4 in the methylprednisolone than in the dexpanthenol group ($p<0.05$). Comparison of mean severity scores between the treatment groups suggested a less severe clinical course in patients who received methylprednisolone than in those who received the dexpanthenol formulation, but the differences did not reach statistical significance. As for the adverse effects, no significant differences were found between the two treatment groups. In the dexpanthenol group, all dimensions of the Skindex questionnaire worsened during treatment, while in the corticosteroid group only four of seven dimensions worsened. The difference between the two treatment groups was significant for the dimension of embarrassment ($P < 0.05$) and approached significance for the dimensions of fear ($P=0.06$) and physical discomfort ($P=0.057$).

In the last trial by Shukla et al. topical beclomethasone dipropionate spray was used as prophylaxis to reduce the risk of wet desquamation of skin in the irradiated field [48]. Sixty patients with breast carcinoma and who were planned for postoperative locoregional radiotherapy were randomized into a group that used beclomethasone dipropionate spray in the irradiated axilla from day one of radiotherapy onwards and a group that was not allowed to use any topical agent in the irradiated area. Severity of acute skin reaction was evaluated. Follow up was four weeks and the risk of bias of this trial was considered to be unclear. No significant differences were found for skin erythema, dry desquamation and wet desquamation (RR =

1.31; 95%CI 0.87 to 1.97, RR = 1.67; 95%CI 0.44 to 6.36, RR = 0.36; 95%CI 0.13 to 1.01). The authors conclude that the application of topical steroid (beclomethasone dipropionate spray) during radiotherapy significantly reduces the risk of wet desquamation of the skin.

Conclusion

- An effect of topical corticosteroids on the severity of acute radiodermatitis could neither be demonstrated nor refuted (Bostrom 2001, Omidvari 2007, Shukla 2006, very low level of evidence).

Recommendation

- The use of topical corticosteroids to reduce symptoms of acute radiodermatitis is not recommended (weak recommendation).

3.4.5. Emollients

One systematic review was identified that addressed the effectiveness of Aloe vera compared to any other intervention for the prevention and minimisation of radiation-induced skin reactions in cancer patients [31]. Eight trials comparing different emollients were identified [34, 36-39, 41, 44, 45].

Aloe vera

The search date of the review by Richardson et al. was August 2004 [31]. All research studies where aloe vera gel was applied as a specific intervention for the prevention and/or treatment of radiation-induced skin reactions in cancer patients were included. The overall risk of bias of this review was considered to be low. Five RCTs were identified. None of the included studies had a low risk of bias. All trials assessed severity of acute skin reaction. Results were presented in a narrative manner. Only three studied compared aloe vera to placebo or no treatment. No difference between groups was seen in these trials. The two remaining studies compared aloe vera cream with 1% anionic phospholipid based cream and aqueous cream respectively. Both trials reported findings in favour of the control group.

Hyaluronic acid

Liguori et al. included 152 patients with either a head and neck, pelvic or breast carcinoma of any stage, and given a fractionated radiation therapy [39]. Patients were randomly allocated to either 0.2% hyaluronic acid cream or identical placebo cream. The status of the irradiated skin surface was evaluated according to the following scale: 0, normal skin; 1, light epidermal irritation (consisting of the onset of skin redness, possibly associated to slight tenderness); 2, erythema with dry desquamation; 3, exudate <50%; 4, exudate >50%; 5, ulcer. Both the patient and the physician gave a global judgment on efficacy of the treatment. Any side effect observed during study was reported. The study scored a high risk of bias. Significantly fewer patients treated with hyaluronic acid cream had a skin surface score higher than 1 from week 3 till week 7 (end of radiotherapy) and at the first two follow-up measurements. In the placebo group four adverse events were observed opposed to one in the hyaluronic acid cream group (RR = 0.23; 95%CI 0.03 to 1.99).

Kirova et al. evaluated the efficacy of hyaluronic acid compared to placebo [37]. Two-hundred breast cancer patients with grade 1–2 radio induced dermatitis during postoperative radiotherapy were randomised to receive either hyaluronic acid or a simple emollient. Severity of acute skin reaction was assessed using the RTOG scale and clinical evaluation of the erythema measured as success versus failure (defined as interruption of radiotherapy due to worsening of erythema). Quality of life was assessed with the EORTC QLQ-C30 questionnaire. The risk of bias of this trial was considered to be high. No statistically significant differences were found for the evaluation of erythema (failures: RR = 0.72; 95%CI 0.46 to 1.13). Concerning the quality of life assessment, the hyaluronic group tends to score better on quality of life items. However, no significant differences on any of the domains were found.

Trolamine based cream (Biafine)

Four RCTs compared Biafine with five other interventions:

Biafine versus Lipiderm ointments versus placebo

Fenig et al. evaluated the effects of Biafine and Lipiderm oinments in preventing radiation dermatitis [34]. Seventy-four early breast carcinoma patients who were referred for adjuvant external beam radiation were randomized to (1) Biafine, (2) Lipiderm or (3) no treatment. Severity of acute skin reaction was assessed by the RTOG scale. This trial was considered to be high risk of bias. No significant differences were found for the radiotherapist's impression of the incidence of grade 3-4 reaction between the three groups (Biafine vs. control: RR = 0.84; 95%CI 0.32 to 2.22, Lipiderm vs. control: RR = 1.88; 95%CI 0.82 to 4.31, Biafine vs. lipiderm: RR = 0.51; 95%CI 0.23 to 1.11). Similarly, no significant differences were found for the patient's and nurse's impression of the incidence of grade 3-4 reaction between the three groups.

Biafine RE cream versus Radiacare gel versus Aquaphor ointment versus placebo

Gosselin et al. evaluated the effectiveness of three commonly used skin care products for women receiving whole-breast radiation therapy against a placebo in reducing the incidence of radiation therapy-induced skin reactions prophylactically [36]. Three hundred and one women were randomized to either (1) placebo (sterile water mist), (2) Aquaphor (ointment), (3) Biafine RE (cream), or (4) RadiaCare™ (gel). Severity of acute skin reaction was measured by the RTOG questionnaire. The risk of bias of this trial was considered to be low. None of the skin care products demonstrated a statistically significant difference in minimizing the incidence of a grade 2–4 skin reaction compared to placebo.

Calendula ointment versus Biafine ointment

Pommier et al. investigated 254 women with a non-metastatic breast adenocarcinoma who were referred for radiotherapy [44]. Calendula ointment was compared to Biafine ointment. Acute dermal toxicity (evaluated according to the RTOG-scale) and allergic reactions were recorded. This study was judged to be low risk of bias. Incidence of grade 2-3 dermatitis was lower for the Calendula group than for the Biafine group: RR = 0.65; 95%CI 0.51 to 0.83. No grade 4 dermatitis was observed in either group. The incidence of allergic reactions was also lower in the Calendula group: RR = 0.11; 95%CI 0.01 to 2.07.

Avene thermal spring water anti-burning gel versus trolamine based cream (Biafine)

In the trial of Ribet et al. 69 patients with breast cancer or head and neck cancer requiring radiotherapy were randomly allocated to Avène thermal spring water anti-burning gel or trolamine based cream (Biafine®) [45]. Incidence and severity of radiation dermatitis (National Cancer Institute classification), efficacy and tolerance (both judged by investigator and patients) were determined. Risk of bias was judged to be high for this study. Incidence of radiation dermatitis on day 42 did not differ between the groups (RR = 1.01; 95%CI 0.76 to 1.34). No significant difference in severity of radiation dermatitis was found between the two groups (MD = -0.21; 95%CI -0.53 to 0.11). Judgment of efficacy by investigator corresponds with the judgment of efficacy by patients: the Avène group seems to score better than the trolamine group. The investigator judged tolerance in almost all cases as 'good' or 'very good', tolerance was judged by patients as 'very satisfied' in 74% of the Avène group compared to 50% in the trolamine group (p=0.12).

Kamillosan cream versus almond ointment

In the trial of Maiche et al. kamillosan cream was compared to almond ointment [41]. Fifty women operated for local breast cancer who were to receive radiotherapy to the scar area were included in this study. As the areas above and below the scare were randomly treated by kamillosan cream or almond ointment each patient served as her own control. Throughout the radiotherapy course the drugs were applied gently to the skin twice daily, the first application 30 min before irradiation and the second before bedtime. Outcomes reported were acute skin reaction (evaluated by using the following scale: 0 = no change, 1 = light erythema, 2 =dark erythema, 3 = moist desquamation), allergic reaction and subjective evaluation. The study was judged to be of unclear risk of bias.The authors reported no significant difference for skin reaction in kamillosan cream and almond ointment areas. An allergic reaction resembling urticaria was seen in two kamillosan cream and one almond ointment areas. Subjective symptoms like itching and pain were quite equally uncommon in the two groups, according to the authors.

Pre-emptive treatment versus reactive treatment

Lacouture et al. examined differences between pre-emptive and reactive skin treatment for specific skin toxicities in patients with metastatic colorectal cancer for any epidermal growth factor receptor (EGFR) inhibitor [38]. Ninety-five patients receiving panitumumab-containing therapy were randomly assigned to pre-emptive or reactive treatment after the first signs of skin toxicity. Pre-emptive treatment included use of skin moisturizers, sunscreen, topical steroid and doxycycline. The trial reported on the following outcomes: severity of acute skin reaction, quality of life (assessed with the Dermatology Life Quality Index (DLQI), adverse events and median progression free survival. Median follow up was 31.0 versus. 40.7 weeks and the risk of bias was considered to be high. A significant difference was found for specific ≥ grade 2 skin toxicities during the 6-week skin treatment in favour of the pre-emptive treatment (RR = 0.47; 95%CI 0.29 to 0.78). As for the adverse events, a significant difference was found for the incidence of maximum grade 3 or higher adverse events (RR = 0.75; 95%CI 0.57 to 0.98). There were no grade 5 adverse events in either treatment group. Furthermore, the results from the DLQI indicated that quality of life was less impaired in the pre-emptive group compared with the reactive group. No significant differences were found for the median progression free survival time (HR = 1.0; 95%CI 0.6 to 1.6).

Conclusions

- There are indications that aloe vera has no clinically significant effect on the severity of acute radiodermatitis (Richardson 2005; very low level of evidence).
- There is limited evidence that hyaluronic acid cream prevents moderate to severe acute radiodermatitis (Liguori 1997; very low level of evidence).
- An effect of hyaluronic acid cream on the incidence of adverse events compared with placebo could neither be demonstrated nor refuted (Liguori 1997; very low level of evidence).
- An effect of hyaluronic acid for the treatment of acute radiodermatitis could neither be demonstrated nor refuted (Kirova 2011; very low level of evidence).
- There are indications that Trolamine based cream (Biafine) has no effect on the severity of radiodermatitis (Fenig 2001, Gosselin 2010; very low level of evidence).
- An effect of lipiderm ointments on the severity of radiodermatitis could not be demonstrated nor refuted (Fenig 2001; very low level of evidence).
- An effect of radiacare gel on the severity of radiodermatitis could not be demonstrated nor refuted (Gosselin 2010; very low level of evidence).
- An effect of Aquaphor ointment on the severity of radiodermatitis could not be demonstrated nor refuted (Gosselin 2010; very low level of evidence).
- There is limited evidence that Calendula is more effective in reducing the incidence and the severity of radiodermatitis compared to Trolamine based cream (Pommier 2004; very low level of evidence).
- An effect of Avene thermal spring water anti-burning gel on the severity of radiodermatitis could not be demonstrated nor refuted (Ribet 2008; very low level of evidence).
- An effect of Kamillosan on the severity of radiodermatitis could not be demonstrated nor refuted (Maiche 1991; very low level of evidence).
- An effect of almond ointment on the severity of radiodermatitis could not be demonstrated nor refuted (Maiche 1991; very low level of evidence).
- There is limited evidence that pre-emptive treatment reduces the incidence of severe skin toxicity of EGFR inhibitors compared to treatment started at the first signs of skin toxicity (Lacouture 2010; very low level of evidence).
- There is limited evidence that pre-emptive treatment is not associated with an increase in adverse events compared to treatment started at the first signs of skin toxicity during EGFR treatment (Lacouture 2010; very low level of evidence).

Other considerations

Studies on the effect of specific products used to prevent or treat radiodermatitis have shown no clear effect or harm. However, in the experience of the expert group, it is advisable to provide long term hydration of the skin and to consider using gauses e.g. with paraffin taking into account patient preferences.

Recommendation

- The evidence is too weak to recommend one of the following interventions to prevent or treat radiodermatitis: aloe vera gel, hyaluronic acid cream, trolamine-based cream (Biafine). The evidence is too weak to recommend pre-emptive treatment with skin moisterizers, sunscreen, topical steroids and doxycycline to reduce the incidence and severity of skin toxicity during EGFR treatment (weak recommendation).

3.4.6. Topical exfoliating product

No RCTs evaluating a topical exfoliating product for radiation-induced skin reactions in cancer patients were identified.

Conclusion

- There is no evidence from RCTs to evaluate the effect of topical exfoliating products on skin toxicity due to cancer treatment.

Recommendation

- There is insufficient evidence to recommend topical exfoliating products to prevent or treat skin toxicity due to cancer treatment.

3.4.7. Foot soaks

No RCTs evaluating foot soaks for the radiation-induced skin reactions in cancer patients were identified.

Conclusion

- There is no evidence from RCTs to evaluate the effect of topical exfoliating products on skin toxicity due to cancer treatment.

Recommendation

- There is insufficient evidence to recommend foot soaks to prevent or treat skin toxicity due to cancer treatment.

3.4.8. Honey

One trial was identified in which the effect of honey was compared to conventional treatment on healing of radiotherapy-induced skin toxicity [42]. Twenty six females receiving radiotherapy to the breast or thoracic with grade 3 skin toxicities (RTOG scale) larger than 15 mm in diameter were included in this trial. Wounds were treated with either honey gauze or paraffin gauze once daily until closure of skin toxicity and patients were followed until complete healing as assessed by an independent physician. Visual Analogue Scales (VAS) were used to measure pain, itching, irritation, malodour and general satisfaction of treatment. Risk of bias for this study was judged to be high. No differences between study groups were found for time to closure of skin toxicity and time to complete healing (MD = -2.0; 95%CI -6.74 to 2.74 and MD = -1.40; 95%CI -7.36 to 4.56, respectively). A trend towards less pain, itching, irritation in the honey population was shown by the VAS results. No relevant side effects of either skin treatment were noted.

Conclusion

- A difference in effect between honey gauze and paraffin gauze on the healing of radiodermatitis could neither be demonstrated nor refuted (Moolenaar 2006; very low level of evidence).

Recommendation

- The use of honey gauze to treat radiodermatitis is not recommended (weak recommendation).

3.4.9. Anti-inflammatory creams

No RCTs evaluating anti-inflammatory creams for radiation-induced skin reactions in cancer patients were identified.

Conclusion

- There is no evidence from RCTs to evaluate the effect of anti-inflammatory creams on skin toxicity due to cancer treatment.

Recommendation

- There is insufficient evidence to recommend anti-inflammatory creams to prevent or treat skin toxicity due to cancer treatment.

3.5. Neuropathy

Several chemotherapeutic agents, such as platinum compounds, taxanes, vinca alkaloids and thalidomide, are toxic to the nervous system. The incidence of neuropathy in patients receiving chemotherapy varies from 30 to 40% depending on the type of drug, duration of administration, cumulative dose and pre-existing peripheral neuropathy and is a frequent dose-limiting event. Chemotherapy induced neuropathy is predominantly sensory. Symptoms can include tingling in the extremities, numbness, loss of vibration sense and decreased tendon reflexes [50, 51].

3.5.1. Literature review

One systematic review [52] was identified that met the inclusion criteria. The review addressed randomized controlled trials concerning the ability of any form of chemoprotective agent to prevent or limit the neurotoxicity of cisplatin (or related compounds including oxaliplatin or carboplatin). The search date was August 2010. The overall risk of bias of this review was judged to be low.

The review included 27 RCTs involving nine possible chemoprotective agents. The quality and characteristics of these RCTs were quite variable, and included different assessment methods (qualitative and subjective), different durations of follow-up, and different analyses. The primary outcome measure addressed in the review was the change in quantitative sensory testing results. Secondary outcome measures included nerve conduction study results (SNAP amplitude) and measures of neurological impairment (amongst which clinical impairment measured by neurological examination using a validated scale, functional measures of activities of daily living and information from toxicity rating scales).

On 26 March 2012 an update of the search of Albers et al. was performed by the Cochrane Neuromuscular Disease Group. Two RCTs were identified that were not yet included in the existing review [53, 54].

3.5.2. Oral glutamine

The review by Albers et al. [52] did not include RCTs investigating the effect of glutamine on neurotoxicity in patients receiving cisplatin. The review by Amara et al. [55], which was excluded, investigated oral glutamine for the prevention of peripheral neuropathy due to any chemotherapy regimen. As their search was limited to Pubmed only, an additional search in CENTRAL and EMBASE was performed with an update of the search in the three databases up to July 2012. Three RCTs were found [56-58].

Loven et al. [58] randomized 67 ovarian cancer patients scheduled for treatment with carboplatin and paclitaxel. Patients were randomized to receive either oral glutamine or a placebo during chemotherapy. Risk of bias of the trial was judged to be high. Frequency of neuropathy on electro-diagnostic tests on signs on clinical examinations were not significantly different between groups. There was a significant difference in pain symptoms (3/23 versus 9/18; p=0.011), but not in other symptoms (tingling, numbness and loss of strength). Two of the 23 glutamine patients had a severe skin rash, no other intervention related toxicity was noted.

Wang et al. [56] included 68 patients with advanced colorectal cancer planned for oxaliplatin treatment. Patients received either glutamine or no intervention. The risk of bias was judged to be high. Grade 3-4 neurotoxicity was found to be lower in the glutamine arm after 4 and 6 cycles of chemotherapy (p=0.05 and p=0.04, respectively). Also, the

interference with ADL was lower in the intervention arm (p=0.02). Patients taking glutamine needed significantly fewer dose reductions of oxaliplatin (p=0.02), but that did not result in a difference in response to chemotherapy (p=0.90) or median survival time (p=0.79). There was no significant difference in the number of non-neurological adverse events grade 3-4 between the two study arms (p=0.76).

Strasser et al. [57] randomized 52 cancer patients receiving taxanes. Risk of bias was considered to be low. Sensory neuropathy was lower in the glutamine group, compared to placebo (maltodextrin) (p=0.048).

Results could not be pooled due to heterogeneity. The effect of glutamine on quality of life was not assessed in any RCT.

Conclusions

- An effect of glutamine on the incidence and severity of neuropathy associated with chemotherapy could neither be demonstrated nor refuted (Wang 2007, Loven 2009, Strasser 2008; very low level of evidence).
- The occurrence of adverse events associated with the use of glutamine could neither be demonstrated nor refuted (Wang 2007, Loven 2009; very low level of evidence).
- There is limited evidence that glutamine is associated with less interference with ADL and has no effect on response rate to chemotherapy or median survival time (Wang 2007; very low level of evidence).

Recommendation

- Glutamine is not recommended to prevent neurotoxicity from chemotherapy (weak recommendation).

3.5.3. *Acetyl-L-carnitine*

No RCTs were identified that addressed acetyl-L-carnitine.

Conclusion

- There is no evidence from randomized controlled trials on the use acetyl-L-carnitine to prevent neurotoxicity from cancer treatment.

Recommendation

- The use of Acetyl-Lcarnitine to prevent neurotoxicity of cancer treatment is not recommended outside the context of clinical research (weak recommendation).

3.5.4. *Calcium and magnesium*

The review of Albers et al. [52] included one single placebo-controlled trial that involved calcium and magnesium infusions before and after infusion of oxaliplatin. The trial was considered to be of low risk of bias and there were 33 participants. According to the NCI-CTC the incidences of ≥ grade 1, 2, and 3 neurotoxicity were 100, 6, and 6% in the Ca/Mg group, respectively, and 94, 6, and 0% in the control group after six cycles of treatment. The difference was not significant. According to the Debiopharm Neurotoxicity Scale (DEB-NTS) the incidences of ≥ grade 1, 2, and 3 neurotoxicity were 100, 71, and 6% in the Ca/Mg group, respectively, and 94, 56, and 0% in the control group (no significant difference between the groups). The study was terminated prematurely due to treatment results that were poorer in the Ca/Mg group. This early discontinuation resulted in a small sample size and insufficient data to determine if Ca/Mg infusions had neuroprotective potential.

The search update resulted in two further trials [53, 54]. Both trials were stopped early, which was due to preliminary reports [59] that suggested that Ca/Mg decreased treatment efficacy (which data later were found to be incorrect).

The first trial published by Chay et al. evaluated the effect of 1g calcium gluconate plus 1g 15% magnesium sulphate IV [53]. This RCT included 27 patients that were treated with FOLFOX-4 or XELOX for colorectal cancer, but eight patients (four in each group) did not complete the study because

of the above mentioned premature study termination. Median follow-up was 8.7 months. The trial was considered to have an unclear risk of bias. Only 19 patients were available for analysis: nine in the Ca/Mg group and 10 in the placebo group. No significant differences between the groups with respect to the oxaliplatin-specific scale (OSS) and CTC grade for cumulative neuropathy were reported during or at the end of treatment. Subjective acute neuropathy rate was 77% in the intervention arm versus 86% in the placebo arm (p=0.6). Incidence of grade 2 neurotoxicity or greater was 33.3% in the Mg/Ca group versus 20% in the placebo group. The median time to onset of grade 1 numbness (OSS) was 18 vs. 13 weeks (log-rank test: p=0.5) and for grade 2 or 3 numbness (NCI-CTC) 18.1 vs. 19.6 weeks (log-rank test: p=0.7). There were no significant differences between the groups for recurrences.

The second trial [54] published by Grothey et al. included 104 patients who received fluorouracil, leucovorin, and oxaliplatin (FOLFOX) for colon cancer. Patients were randomly assigned to 1g calcium gluconate plus 1g magnesium sulfate pre- and post-oxaliplatin or placebo. Although 300 patients were planned, the study closed after the inclusion of 104 patients. Follow-up stopped after 127 days because of the premature study closure. The trial was considered to have a low risk of bias. Ca/Mg reduced the incidence of grade 2 or greater sensory neurotoxicity. The risk ratio based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) criteria was 0.53 (95%CI 0.29 to 0.99), and 0.55 (95%CI 0.33 to 0.92) for the OSS criteria. The onset of grade 2 or greater sensory neurotoxicity was significantly delayed in patients who received Ca/Mg. The patient reported outcomes numbness and tingling were less severe in the Ca/Mg group. There were no substantial differences in adverse effects between the groups. Hypercalcemia occurred in none and in one (2%) of the patients in the Ca/Mg and placebo groups, respectively, and hypermagnesemia occurred in seven (14%) and eight (16%) patients, respectively.

A meta-analysis (by the KCE) including the three above mentioned trials showed a RR = 0.69 (95%CI 0.40 to 1.19) for the development of grade 2 neurotoxicity or higher when receiving calcium and magnesium transfusion compared to placebo.

There are no data available on the effect of magnesium and calcium on activities of daily living, quality of life or progression-free survival.

Conclusions

- An effect of calcium and magnesium infusions on the incidence of grade 2 neurotoxicity or greater associated with oxaliplatin could neither be demonstrated nor refuted (Albers 2011, Chay 2010, Grothey 2011; low level of evidence).
- An effect of calcium and magnesium infusions on the incidence of adverse events could neither be demonstrated nor refuted (Grotey 2011; very low level of evidence).

Other considerations

Hypomagnesemia and hypocalcemia can give symptoms such as muscle cramps and irritability of the nerveus system. Evidently these conditions should be treated appropriately. The following recommendation only applies to the preventative use of Ca and Mg infusions in patients with normal blood levels of ca and Mg.

Recommendation

- Calcium and magnesium infusions should not be used to prevent neurotoxicity in patients receiving chemotherapy (weak recommendation).

3.5.5. Anti-convulsant drugs, tricyclic antidepressants, NSAIDs, SSRIs and opioids

The use of anti-convulsant drugs, tricyclic antidepressants, NSAIDs, SSRIs and opioids in the treatment of neuropathic pain will be discussed in the KCE report on the treatment of cancer-related pain.

3.6. Neutropenia and neutropenic fever

Twelve systematic reviews were included [60-71]. On 4 July 2012, updates of the searches for the various interventions were performed and five RCTs were identified that were not yet included in the existing reviews [72-76].

3.6.1. Prophylactic G-CSF / GM-CSF

Two systematic reviews and one 'special advice report' were identified that met the inclusion criteria [60, 65, 68]. The reports addressed the following comparisons: G-CSF or GM-CSF versus placebo or no prophylaxis (Bohlius 2008), prophylaxis with G(M)-CSF versus prophylaxis with antibiotics (Herbst 2009) and primary or secondary prophylaxis with filgrastim versus placebo or no filgrastim or best supportive care (including prophylactic antibiotics) (Madernas 2009). A further two RCTs that were published after 2008 and met the inclusion criteria were identified [72, 74].

3.6.1.1. Prophylaxis with G-CSF or GM-CSF versus placebo or no prophylaxis

Lymphoma

The review by Bohlius et al. included 13 RCTs with 2 607 randomised patients undergoing treatment for malignant lymphoma [60]. The search date was April 2008. The overall risk of bias of this review was judged to be low.

Compared with no prophylaxis, both G-CSF and GM-CSF did not significantly improve overall survival (RR = 0.97; 95%CI 0.87 to 1.09) or freedom from treatment failure (HR = 1.11; 95%CI 0.91 to 1.35). There was no evidence that either G-CSF or GM-CSF lowered mortality during chemotherapy (RR = 0.93; 95%CI 0.60 to 1.43). Prophylaxis significantly reduced severe neutropenia defined as absolute neutrophil count < $0.5*10^9$/litre (RR = 0.67; 95%CI 0.60 to 0.73) and febrile neutropenia (RR = 0.59; 95%CI 0.48 to 0.72). Quality of life parameters were evaluated in only one study which found no differences between the treatment groups. Adverse effects attributable to G-CSF and GM-CSF, such as bone pain (RR = 3.57; 95%CI 2.09 to 6.12), were more frequently reported in patients treated with growth factors than in the control groups. Skin rash (RR = 7.69; 95%CI 2.84 to 20.82) and injection site reactions (RR = 6.55; 95%CI 3.01 to 14.25) occurred also more frequently in the CSF groups. No significant differences were found for thromboembolic complications, myalgia and mucositis (thromboembolic complications: RR = 1.29; 95%CI 0.56 to 3.01, myalgia: RR = 0.95, 95%CI 0.60 to 1.45, mucositis: RR = 0.95; 95%CI 0.64 to 1.41).

Conclusions

- It is plausible that prophylactic G-CSF/GM-CSF reduces the incidence of severe neutropenia and febrile neutropenia in patients undergoing treatment for malignant lymphoma (Bohlius 2008; moderate level of evidence).
- It is demonstrated that prophylactic G-CSF/GM-CSF has no effect on overall survival in patients undergoing treatment for malignant lymphoma (Bohlius 2008; high level of evidence).
- There are indications that prophylactic G-CSF/GM-CSF has no effect on freedom of treatment failure in patients undergoing treatment for malignant lymphoma (Bohlius 2008; low level of evidence).
- There is limited evidence that prophylactic G-CSF/GM-CSF has no effect on quality of life in patients undergoing treatment for malignant lymphoma (Bohlius 2008; very low level of evidence).
- It is plausible that prophylactic G-CSF/GM-CSF is associated with an increase of bone pain (Bohlius 2008; moderate level of evidence), skin rash and injection site reactions in lymphoma patients. Other adverse events, such as thromboembolic events, myalgia and mucositis, are not affected by the use of prophylactic G-CSF/GM-CSF.

Other considerations

Although prophylactic use of G-CSF or GM-CSF appears to reduce the incidence of neutropenia and febrile neutropenia, there is no effect on more important outcomes such as OS, PFS and quality of life. A possible gain in morbidity and length of hospital stay will come at the cost of adverse events, mainly bone pain and acute skin reactions at the injection site. However, bone pain is easily treated with paracetamol according to the expert panel. When the risk for neutropenia is high (>20%), primary prophylaxis can be considered. This is also true for patients older than 65 years and for dose-dense chemotherapy regimens.

Overall, a policy of secondary prevention in patients who suffered from a febrile neutropenia episode may be preferable.

Recommendation

- G-CSF or GM-CSF are not routinely recommended as primary prophylactic intervention in patients undergoing treatment for malignant lymphoma, but can be considered for chemotherapy regimens associated with a high risk for neutropenia (weak recommendation).

Breast cancer

The special advice report by Madarnas et al. addressed the primary or secondary prophylaxis with filgrastim in patients with breast cancer who received chemotherapy [68]. The guideline based its recommendations mainly on three other high quality guidelines, three systematic reviews (of which two were later excluded because they did not address solely patients with breast cancer) and four RCTs. The abstracts of three unpublished RCTs were included as well. However, review of RCTs included in the SRs or guidelines shows that only two of the included RCTs compared prophylactic G-CSF with no G-CSF [77, 78]. Meta-analysis performed by KCE shows that prophylactic G-CFS reduces the incidence of febrile neutropenia (RR = 0.10; 95%CI 0.05 to 0.19).

The study by Vogel et al. reports a non-significant increase in bone pain associated with the use of G-CSF (31% versus 27%). Also, for withdrawal due to adverse events, there was no significant difference (RR = 1.11; 95%CI 0.60 to 2.04) [77].

The study by Papaldo et al. reported on 5-year OS and PFS. No significant differences were seen (80.6% versus 79.6% and 67.2% versus 72.9% (p=0.21) respectively) [78].

The two further identified RCTs compared prophylaxis with pegfilgrastim versus no G-CSF support (Brugger 2009) or placebo (Hecht 2010) [72, 74].

In the trial by Brugger et al., 59 elderly women with breast cancer who received adjuvant FEC100 (5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2 and cyclophosphamide 500 mg/m^2) were randomized to pegfilgrastim primary prophylaxis or no G-CSF in cycle 1. The risk of bias of this RCT was considered to be low. No significant differences were found for the incidence of grade 4 neutropenia in cycle 1 (RR = 1.06; 95%CI 0.79 to 1.43). The duration of grade 3–4 neutropenia was shorter with pegfilgrastim than without (1 day vs 3 days on average in cycle 1).

The study by Hecht et al. was not further discussed as the included patients were treated for colorectal cancer.

Conclusions

- There are indications that prophylactic use of G-CSF reduces the incidence of febrile neutropenia in breast cancer patients receiving chemotherapy (Vogel 2005, Papaldo 2005; low level of evidence).
- There is limited evidence that prophylactic use of G-CSF has no effect on disease-free and overall survival in breast cancer patients receiving chemotherapy (Papaldo 2005; very low level of evidence).
- There is limited evidence that prophylactic use of G-CSF has no significant effect on the incidence of bone pain and withdrawal due to adverse events in in breast cancer patients receiving chemotherapy (Vogel 2005; very low level of evidence).

Other considerations

The same considerations apply as for lymphoma patients.

Recommendation

- G-CSF or GM-CSF are not routinely recommended as primary prophylactic intervention in patients undergoing adjuvant treatment for breast cancer, but can be considered for chemotherapy regimens associated with a high risk for neutropenia (weak recommendation).

3.6.1.2. Prophylaxis with G-CSF or GM-CSF versus antibiotics

One review was identified that compared the effectiveness of G-CSF or GM-CSF with antibiotics in cancer patients receiving myeloablative chemotherapy, bone marrow or stem cell transplantation with respect to preventing fever, febrile neutropenia, infection, infection-related mortality, early mortality and improving quality of life [65]. As only patients eligible for bone marrow transplantation were included, this review is considered out of scope for this review.

3.6.2. Therapeutic G-CSF / GM-CSF

One review and one RCT were identified that met the inclusion criteria. Both compared the safety and effectiveness of G-CSF or GM-CSF combined with antibiotics to antibiotics alone [61, 73].

3.6.2.1. G-CSF or GM-CSF plus antibiotics versus antibiotics alone

The review of Clark et al. included 13 RCTs with a total of 1 518 patients [61]. The search dates depended on the database and were performed between 2000 and 2002. The overall risk of bias of this review was judged to be low.

G-CSF or GM-CSF did not significantly affect overall mortality (OR = 0.68; 95%CI 0.43 to 1.08), but reduced infection-related mortality (OR = 0.51; 95%CI 0.26 to 1.00). There was also a significant effect regarding the length of hospitalisation (HR = 0.63; 95%CI 0.49 to 0.82). The latter meta-analysis suffered from considerable heterogeneity (I^2 = 73%) due to the influence of one trial. The results remained significant when this trial was left out. There was no significant difference between the treatment groups with respect to deep vein thrombosis (OR = 2.49; 95%CI 0.72 to 8.66). For bone, joint pain and flu-like symptoms a significant difference was found favouring the control group (OR = 2.05; 95%CI 1.22 to 3.46).

The RCT of Er et al. compared adding G-CSF to antibiotic therapy versus antibiotic therapy alone in the treatment of neutropenic fever [73]. In this RCT 53 patients with 60 episodes of febrile neutropenia were included. The risk of bias of this RCT was judged to be unclear. No significant differences were found between the groups regarding the number of days of hospitalization (mean 8; range 5-17 versus mean 9; range 6-14;p=0.24) and mortality (n=1 versus n=3; p=0.49). Side effects of therapy were mild and there were no treatment-related deaths.

Conclusions

- There are indications that the addition of G-CSF or GM-CSF to antibiotic treatment of febrile neutropenia has no significant effect on overall mortality and infection-related mortality in patients receiving chemotherapy (Clark 2009; low level of evidence).
- There is limited evidence that the addition of G-CSF or GM-CSF to antibiotic treatment of febrile neutropenia shortens the length of hospital stay in patients receiving chemotherapy (Clark 2009; very low level of evidence).
- It is plausible that the addition of G-CSF or GM-CSF to antibiotic treatment of febrile neutropenia is associated with an increase in bone and joint pain and flu like symptoms (Clark 2009; moderate level of evidence).

Other considerations

Given the lack of effect on mortality and infection-related mortality, routine use of costly growth factors can not be recommended. However, in patients with a high risk for severe complications and prolonged hospital stay, the use of G-CSF or GM-CSF can be considered. High risk patients can be identified using the Multinational Association for Supportive Care in Cancer (MASCC) score [79].

Recommendation

- G-CSF or GM-CSF are not routinely recommended as treatment for febrile neutropenia in patients receiving chemotherapy, but can be considered for patients at high risk (e.g. identified using the MASCC score) for severe complications (weak recommendation).

3.6.3. Prophylactic antifungals

Three systematic reviews were identified that met the inclusion criteria [64, 66, 67]. The reviews addressed the following comparisons: antifungals versus placebo or no treatment (Gotzsche 2011a), fluconazole versus amphotericin B [66], and voriconazole versus amphotericin B [67]. No RCTs were identified that were published after the search dates of the reviews.

3.6.3.1. Antifungal agent versus placebo or no treatment

One review was identified that compared the use of prophylactic or empiric amphotericin B, fluconazole, ketoconazole, miconazole, itraconazole or voriconazole with placebo or no treatment in cancer patients with neutropenia caused by chemotherapy (with or without bone marrow transplantation) [64]. The review included 32 RCTs, of which some included

children. The search date was July 2011. The overall risk of bias of this review was judged to be low.

There was no significant difference in mortality from any cause between antifungals in general and placebo or no treatment (RR = 0.94; 95%CI 0.81 to 1.09; 26 studies, 3 902 participants). Amphotericin B, however, was the only antifungal that resulted in a significant reduction of mortality (RR = 0.69; 95%CI 0.50 to 0.96). As for the other antifungals, no significant effects were observed (fluconazole RR = 1.04; 95%CI 0.84 to 1.30, ketoconazole RR = 0.97; 95%CI 0.63 to 1.49, miconazole RR = 1.16; 95%CI 0.71 to1.87, itraconazole RR = 0.94; 95%CI 0.63 to 1.40; for voriconazole no studies were found). The incidence of invasive fungal infection significantly decreased after amphotericin B (RR = 0.41; 95%CI 0.24 to 0.73), fluconazole (RR = 0.39; 95%CI 0.27 to 0.5]) and itraconazole (RR = 0.53; 95%CI 0.29 to 0.97), but not after ketoconazole (RR = 1.32; 95%CI 0.68 to 2.54) or miconazole (RR = 0.52; 95%CI 0.20 to 1.31). Effect estimates were similar for the 13 trials that had adequate allocation concealment and were blinded. The reporting of adverse events was too variable across the trials to allow meaningful conclusions. Yet, in general many more treatment discontinuations were observed in patients receiving the study drug.

All trials investigating the effect of prophylactic or empiric amphotericin B included patients with acute leukemia or bone marrow transplantation. The use of prophylactic amphotericin B in other patient groups is not considered clinically indicated as the incidence of severe fungal infections is much lower. However, no data are available.

Subgroup analysis (by the KCE) showed a significant effect on mortality for prophylactic use in neutropenic patients (RR = 0.67; 95%CI 0.45 to 0.98), but not for the empiric use of amphotericin B in patients with neutropenic fever (RR 0.75; 95%CI 0.40 to 1.40). Incidence of invasive fungal infection is significantly reduced both with empirical treatment and prophylactic use (0.21; 95%CI 0.05 to 0.90 and RR 0.48; 95%CI 0.26 to 0.89 respectively).

For fluconazole, ketoconazole, itraconazole and miconazole trials only tested prophylactic treatment in patients with acute leukemia or bone marrow transplantation.

Conclusions

- It is plausible that prophylactic amphotericin B reduces the number of deaths and invasive fungal infections in neutropenic patients with acute leukemia or bone marrow transplantation (Gotzsche 2011; moderate level of evidence).
- An effect of empirical amphotericin B on mortality in neutropenic patients with acute leukemia or bone marrow transplantation could neither be demonstrated nor refuted (Gotzsche 2011; low level of evidence).
- There are indications that empirical amphotericin B reduces the number of invasive fungal infections in neutropenic patients with acute leukemia or bone marrow transplantation (Gotzsche 2011; very low level of evidence).
- It is plausible that prophylactic fluconazole has no effect on mortality but reduces the number of invasive fungal infections in neutropenic patients with acute leukemia or bone marrow transplantation (Gotzsche 2011; moderate level of evidence).
- It is plausible that prophylactic ketoconazole has no effect on mortality in neutropenic patients with acute leukemia or bone marrow transplantation (Gotzsche 2011; moderate level of evidence).
- An effect of ketoconazole on the number of of invasive fungal infections in neutropenic patients with acute leukemia or bone marrow transplantation could neither be demonstrated nor refuted (Gotzsche 2011; low level of evidence).
- It is plausible that prophylactic itraconazole has no effect on mortality but reduces the number of invasive fungal infections in neutropenic patients with acute leukemia (Gotzsche 2011; moderate level of evidence).
- An effect of prophylactic miconazole on mortality or the number of invasive fungal infections in neutropenic patients with acute leukemia or bone marrow transplantation could neither be demonstrated nor refuted (Gotzsche 2011; moderate level of evidence).

3.6.3.2. *Fluconazole versus amphotericin B*

One review was identified that compared fluconazole with amphotericin B in cancer patients with neutropenia caused by chemotherapy [66]. The review included 17 RCTs, amongst which also one study included children. The search date was July 2011. The overall risk of bias of this review was judged to be low.

Overall, there were no significant differences between fluconazole with amphotericin B with respect to all-cause mortality (RR = 0.88; 95%CI 0.73 to 1.05), mortality related to fungal infection (OR = 0.95; 95%CI 0.57 to 1.58), the occurrence of invasive fungal infections (RR = 0.93; 95%CI 0.72 to 1.21) and dropouts (RR = 0.76; 95%CI 0.44 to 1.29). Fluconazole resulted in less dropouts due to adverse effects (RR = 0.33; 95%CI 0.14 to 0.78). The major harms were hepatic impairment and gastrointestinal adverse effects with fluconazole and infusion-related toxicity, renal impairment and gastrointestinal adverse effects with amphotericin B. Five patients treated with amphotericin B underwent haemodialysis.

According to the authors, some of the applied methods in the various studies were unfavourable to amphotericin B and, therefore, biased in favour of fluconazole (e.g. combining results for amphotericin B with results for the inactive drug nystatin in a “polyene” group, the use of oral amphotericin B, which is poorly absorbed, amphotericin B not given under optimal circumstances).

Outcomes were calculated separately for prophylactic and empirical treatment by the KCE. The two studies with results of amphotericin B in a polyene group were excluded from the analysis. There was no significant difference in mortality or incidence of invasive fungal infections for prophylactic fluconazole versus prophylactic amphotericin B (RR = 0.96; 95%CI 0.74 to 1.23 and RR = 0.83; 95%CI 0.54 to 1.26 respectively). For empirical use, there was also no significant difference for both outcomes (RR = 0.76; 95%CI 0.56 to 1.04 and RR = 1.06; 95%CI 0.74 to 1.51 respectively).

Conclusions

- It is plausible that there is no difference in effect on mortality between prophylactic fluconazole and amphotericin B in neutropenic patients with acute leukemia or bone marrow transplantation (Johansen 2011; moderate level of evidence).
- There are indications that there is no difference in effect on the incidence of invasive fungal infections and the number of dropouts between prophylactic fluconazole and amphotericin B in neutropenic patients with acute leukemia or bone marrow transplantation. However, there are indications that fluconazole is associated with less dropouts due to adverse events (Johansen 2011; low level of evidence).
- There are indications that there is no difference in effect on mortality, the incidence of invasive fungal infections and the number of dropouts between empirical fluconazole and amphotericin B in neutropenic patients with acute leukemia or bone marrow transplantation. However, there are indications that fluconazole is associated with less dropouts due to adverse events (Johansen 2011; low level of evidence).

3.6.3.3. *Voriconazole*

One review was identified that compared voriconazole with amphotericin B in cancer patients with neutropenic fever associated with chemotherapy or bone marrow transplantation [67]. The review included two RCTs, of which one addressed the use of empirical voriconazole. The search date was November 2007. The overall risk of bias of this review was judged to be low.

The included prophylactic study included patients with leukaemia, other types of cancer, and patients who had undergone stem cell transplantation. The study was considered to be of high risk of bias as there was no concealment of allocation. There was a discrepancy between the number of patients in the report and the data provided by the manufacturer. The review authors, however, calculated the results by the use of all available data. In total 871 patients were randomized.

The RR for all-cause mortality was 1.37 (95%CI 0.96 to 1.96) and the risk difference for invasive fungal infections was 1.8% (95%CI -1.0% to 4.7%). Nephrotoxicity was observed in 29 patients receiving voriconazole and in 32 patients receiving liposomal amphotericin B. There was no significant difference between the groups with respect to discontinuing therapy due to toxic effects, but significantly more patients in the voriconazole group had to discontinue therapy due to lack of efficacy and had visual disturbances or hallucinations. Dyspnoea and serum potassium below 2.5 mmol/L occurred significantly occurred more frequently in the amphotericin B group.

Conclusion

- A difference in effect between empirical voriconazole and amphotericin B could neither be demonstrated nor refuted (Jorgensen 2009; very low level of evidence).

Other considerations

For none of the above mentioned drugs, prophylactic use was compared with empirical treatment in a clinical trial.

Side effects, route of administration and costs also have to be considered in the choice between different products. In practice, fluconazole is the drug of first choice.

Voriconazole is approved in Belgium for the treatment of serious invasive fungal infections.

Recommendations

- Prophylactic fluconazole or itroconazole or amphotericin B can be considered in patients with acute leukemia (weak recommendation).
- Prophylactic ketoconazole or miconazole should not be used in patients with acute leukemia (weak recommendation).
- Empirical use of amphotericin B can be considered in patients with acute leukemia and neutropenic fever (weak recommendation).
- Emipirical voriconazole is not recommended in patients with acute leukemia and neutropenic fever (weak recommendation).

3.6.4. Prophylactic antibiotics

One recent systematic review was identified that met the inclusion criteria. This review superseded the other identified reviews which will therefore not be further described [63]. The review addressed RCTs comparing any antibiotic prophylaxis (oral or intravenous) for bacterial infections with another antibiotic, placebo or no intervention in afebrile neutropenic cancer patients receiving chemotherapy. The search date was March 2011. The overall risk of bias of this review was judged to be low. Given the recent search date of the review, no update was performed.

The review included 109 RCTs with 13 579 participants. Amongst the included studies there were also studies addressing children and patients who underwent bone marrow transplantation. Prophylactic antibiotics were compared with any other antibiotic, placebo or no intervention.

Compared to placebo or no intervention, antibiotic prophylaxis significantly reduced the risk of death from all causes (46 studies, 5 635 participants; RR = 0.66; 95%CI 0.55 to 0.79) and the risk of infection-related death (43 studies, 5 777 participants; RR 0.61 [95%CI 0.48 to 0.77]). The estimated number needed to treat to prevent one death was 34 (all-cause mortality) and 48 (infection-related mortality). Antibiotic prophylaxis resulted in more side effects (mostly gastrointestinal, including diarrhoea and nausea) (37 studies, 5 103 participants; RR = 1.58; 95%CI 1.19 to 2.12).

For quinolones the RRs for death from all causes and infection-related death were 0.54 (95%CI 0.40 to 0.74) and 0.74 (95%CI 0.65 to 0.84), respectively; for TMP-SMZ 0.71 (95%CI 0.49 to 1.02) and 0.80 (95%CI 0.69 to 0.92), respectively; for other systemic antibiotics 0.96 (95%CI 0.65 to 1.43) and 0.94 (95%CI 0.85 to 1.04), respectively; and for non-absorbable antibiotics 0.64 (95%CI 0.44 to 0.94) and 0.88 (95%CI 0.67 to 1.16), respectively. Various sensitivity analyses did not change the results.

Quinolones scored better than TMP-SMZ with respect to side effects (RR = 0.62; 95%CI 0.43 to 0.90).

Conclusion

- It is plausible that prophylactic antibiotics reduce overall mortality in high risk chemotherapy patients (Gafter-Gvili 2012; moderate level of evidence).

Other considerations

According to the consulted experts, prophylactic antibiotics are mainly used in patients suffering from haematological cancers, who receive chemotherapy with a very high risk of developing neutropenia (e.g. neutropenia for more than 10 days, patients undergoing bone marrow transplantation). Furthermore, widespread use of prophylactic antibiotics could lead to unacceptable resistance to antibiotic treatment. Therefore, the recommendation below only applies to the above mentioned patients.

Recommendation

- Prophylactic antibiotics can be considered in selected chemotherapy patients with neutropenia who are at very high risk for severe infections (strong recommendation).

3.6.5. Therapeutic antibiotics: oral versus IV

One systematic review was identified that met the inclusion criteria [70]. The review addressed RCTs comparing oral antibiotics to intravenous antibiotics for the treatment of neutropenic cancer patients with fever. The search date was September 2007. The overall risk of bias of this review was judged to be low.

The review included 18 RCTs. The included studies addressed both children and adults. In addition, the review included studies regarding cancer patients who underwent bone marrow transplantation. The "oral antibiotics" group were given oral antibiotics immediately or after a short, predefined period of IV antibiotics. The oral antibiotics differed between studies: antipneumococcal quinolones in one study, other quinolones in seven studies. Quinolones were given in combination with ampicillin-clavulanate, ampicillin-sulbactam or penicillin V in six studies and in combination with clindamycin in one study. The antibiotics given orally were different in most studies from the drugs given intravenously. In six studies all patients were treated as outpatients, patients randomised to oral therapy were treated as outpatients while the control group was treated in hospital in three studies. In the remaining studies, all patients were treated in hospital. Inpatient versus outpatient treatment will also be addressed in section 3.6.6.

There was no significant difference in mortality from any cause or caused by the infectious episode between oral and intravenous treatment (RR = 0.95; 95%CI 0.54 to 1.68; 9 studies, including studies with children). The RR of treatment failure (defined as a composite end-point comprising one or more of the following: death; persistence, recurrence or worsening of clinical signs or symptoms of presenting infection; any addition to or modification of the assigned intervention) for 'initial oral' studies was 0.95 (95%CI 0.85 to 1.07). In adults this RR was 0.99 (95%CI 0.86 to 1.14). Adverse effects that required discontinuation of the assigned antibiotic therapy did not differ significantly between the treatment arms (RR 1.80 [95%CI 0.58 to 5.60]). When only the studies with immediate oral antibiotics were taken in consideration, the risk for adverse effects that required discontinuation was significantly higher in the oral antibiotics group (RR = 3.66; 95%CI 1.45 to 9.23). However, the absolute risk difference appears clinically not important.

The search update resulted in one further RCT [76]. The trial evaluated the effect of oral moxifloxacin compared to intravenous ceftriaxone in 96 cancer patients who received chemotherapy. The groups were similar at baseline. However, more treatment with growth factors occurred in the moxifloxacin group. Assessments were made 'at resolution of a fever episode'. The study was considered to be of high risk of bias due to lack of blinding. The study was designed as a non-inferiority study, but had to stop early due to low accrual. Furthermore, none of the patients died. The mean global quality of life score at 24 hours after the end of the treatment (which was only available for 16 patients in the ceftriaxone arm and 26 patients in the moxifloxacin arm) was 44.9 vs 46.3 (p=0.78). Toxicity requiring discontinuation of the study drug did not differ significantly between the groups (RR = 0.19; 95%CI 0.01 to 3.89). The authors reported three moderate gastrointestinal toxicities in the moxifloxacin arm and five adverse events in the ceftriaxone arm (two cases of cutaneous allergy, one of moderate cutaneous modification, and two of moderate gastrointestinal toxicity). Treatment was stopped in two cases in the ceftriaxone arm for cutaneous allergy.

Meta-analysis with inclusion of the results of Sebban et al. did not alter the conclusions (RD = 3%; 95%CI 1 to 5%).

Conclusions

- It is plausible that there is no difference of effect on mortality between IV and oral antibiotics for neutropenic fever (Vidal 2009, Sebban 2008; moderate level of evidence).
- There are indications that oral antibiotics are not associated with more adverse events requiring discontinuation of assigned treatment compared to IV antibiotics (Vidal 2009; low level of evidence).

Other considerations

Findings are supported by pharmacodynamic data of specific antibiotics, such as quinolones, but may be not generalizeble for other products. Furthermore, it was pointed out by the expert panel that only patients with uncomplicated infections are included in the clinical trials. Patients with severe symptoms or impaired GI tract function may need IV administration, although the presence of IV access is insufficient reason to avoid oral intake of antibiotics.

Recommendation

- Oral administration of antibiotics (in- or outpatient) is recommended in the treatment of uncomplicated neutropenic fever in cancer patients (strong recommendation).

3.6.6. Inpatient treatment versus outpatient treatment

One systematic review was identified that met the inclusion criteria [69]. The additional search resulted in one RCT that was not yet included in the review [75].

The review by Teuffel et al. addressed RCTs comparing any inpatient antibiotic treatment to any outpatient antibiotic treatment for the management of febrile neutropenia in cancer patients [69]. The search date of the review was February 2010. The overall risk of bias of the review was judged to be low.

The review included 4 RCTs in adults. The inpatient and outpatient treatments were intravenous (IV) antibiotics vs. IV antibiotics (1 study), IV vs. oral antibiotics (2 studies) and oral vs. oral antibiotics (1 study). The meta-analyses showed no significant differences between inpatient and outpatient management with respect to treatment failure at 30 days (RR = 0.79; 95%CI 0.52 to 1.20) or mortality (RR = 0.96; 95%CI 0.27 to 3.43). Various sensitivity analyses did not change the results qualitatively.

The RCT of Talcott et al. evaluated the effect of continued inpatient antibiotic therapy compared to early discharge with identical antibiotic treatment at home in 121 adult cancer patients with post-chemotherapy fever at presentation or by patient measurement at home, and neutropenia that persisted after at least 24-hour inpatient observation [75]. The groups were similar at baseline with respect to clinical characteristics, but not with respect to GSF use, ethnicity, and status of job / medical insurance. The study was considered to be of high risk of bias due to lack of blinding. In addition, the study was stopped early due to poor accrual. None of the patients died. Four outpatient episodes resulted in hospital readmission. Major medical complications occurred in 5 episodes in the inpatient group (8%) compared to 4 (9%) in the homecare group (RD -1% exact 95%CI -13% to 10%). With respect to quality of life (measured with various instruments), reported pain slightly increased for hospitalized patients and decreased for home care patients (change, 13.1 vs. -2.72; p=0.01). The Role Function subscale of the EORTC QLQ C-30 increased more for home care patients than for hospitalized patients (change, 0.78 vs. 0.58; p=0.05) and the Emotional Function scores declined for hospitalized patients but increased for homecare patients (change, -6.94 vs. 3.27; p=0.04). No other QLQ-C30 subscale differences were evident. No differences were observed for the Consumer Satisfaction or General Well-Being instruments.

Conclusions

- There are indications that inpatient and outpatient treatment of febrile neutropenia are equally effective in terms of treatment failure at 30 days (Teuffel 2011; low level of evidence).
- There are indications that inpatient and outpatient treatment of febrile neutropenia are equally effective in terms of mortality (Teuffel 2011; very low level of evidence).
- There is limited evidence that inpatient and outpatient treatment of febrile neutropenia are equally effective in terms of quality of life (Talcott 2011; very low level of evidence).

Recommendation

- Outpatient management or early discharge policy can be considered in the treatment of febrile neutropenia associated with chemotherapy (weak recommendation).

3.6.7. Nursing practices: protective isolation

One review of Eckmanns et al. compared the effectiveness of a protected environment with high-efficiency particulate air (HEPA) filtration with that of a non-protected area in decreasing the rates of mortality and fungal infection among patients with haematological malignancies and neutropenia or BMT and among patients undergoing bone marrow transplant for other reasons than cancer [62]. The review included 16 trials and the risk of bias was considered to be high (no formal quality assessment of included studies, however individual quality criteria are reported). As no other evidence was identified in the literature, it was decided to include this review.

No significant advantages of protected environments with HEPA filtration and laminar airflow were found in the prevention of death among patients with haematological malignancies receiving chemotherapy (2 RCTs) or BMT for any reason (4 RCTs) (RR = 0.86; 95%CI 0.65 to 1.14). Also no significant differences were found for fungal infections (RR = 0.57; 95%CI 0.13 to 2.53).

Conclusions

- An effect of isolation in a protected environment with HEPA filtration and laminar airflow on mortality in patients with haematological malignancies receiving chemotherapy or patients undergoing BMT could neither be demonstrated nor refuted (Eckmanss 2006; low level of evidence).
- There are indications that isolation in a protected environment with HEPA filtration and laminar airflow is not effective in reducing the incidence of fungal infections in patients with haematological malignancies with severe neutropenia (Eckmanss 2006; very low level of evidence).

Other considerations

According to the consulted experts, HEPA filtration is still used in patients undergoing BMT and in patients with severe neutropenia lasting for more than 10 days.

Recommendation

- Patient isolation in a protected environment with HEPA filtration and laminar airflow is not routinely recommended in patients with severe neutropenia (strong recommendation).

3.7. Radioproctitis

Radiotherapy to the pelvis, e.g. to treat cervical or prostate cancer can cause chronic damage to the rectum. Submucosal injury with ischaemia, fibrosis and ulceration can lead to symptoms such as tenesmus, urgency, either diarrhoea or constipation, anal sphincter dysfunction (affecting the control of the bowels), mucoid or bloody discharge per rectum or frank bleeding with ulceration which may perforate. Impact on quality of life can be devastating [80]. Treatment of radioproctitis depends on the dominant symptom, for example rectal bleeding, diarrhea or pain. The treatment of diarrhoea (paragraph 3.10) and pain (ongoing KCE project) will be discussed elsewhere.

3.7.1. Literature review

One systematic review was identified that met the inclusion criteria [80]. The review addressed RCTs concerning the effect of various non-surgical interventions for late radiation proctitis. The original search was performed in April 2007 and the overall risk of bias of the review was judged to be low. The review included three studies that addressed non-surgical interventions that were included in the PICO [81-83]. In January 2012, the literature search was updated starting from the search date of the review, which resulted in the inclusion of a further six RCTs. A full risk of bias assessment of both the new studies and those that were already included in the original review was performed. In addition, a full search for studies on probiotics and surgical interventions was performed in March 2012. No relevant studies were identified. However, one study concerning probiotics

was identified during the update of the literature search of Denton et al. [80] and was included.

3.7.2. Prevention of radioproctitis

3.7.2.1. Corticosteroids

Beclomethasone dipropionate enema vs. placebo

One RCT [84] was identified evaluating the efficacy of topical beclomethasone dipropionate (BDP) compared with placebo for the prevention of radiation-induced proctopathy in patients submitted to radiotherapy for prostate cancer. The trial involved 120 patients who were randomized to either a daily 3 mg BDP enema or identical-looking placebo during radiotherapy and, subsequently, two 3 mg BDP suppositories or placebo for 4 more weeks. The risk of bias of this trial was considered to be high and the trial reported on the following five outcomes: severity of symptoms, quality of life (according to the Inflammatory Bowel Disease Quality of Life Index [IBDQ]), endoscopic assessment (Vienna rectoscopy score, VRS), incidence of severe hemorrhagic proctopathy and adverse events. Three and 12 months after the end of radiotherapy, the analyses of the modified Simple Clinical Colitis Activity Index (SCCAI) did not show any difference between the two treatment arms regarding day and night stool frequency and urgency. Rate of blood in stool was lower in the intervention group (OR = 0.38; 95%CI 0.17 to 0.86). Three and 12 months after the end of radiotherapy, no differences were found between the two treatment groups based on the RTOG⁄EORTC toxicity scales. After 12 months of follow-up, the reduction of quality of life (total IBDQ scores) was significantly more pronounced for patients on placebo (p=0.034). As for the endoscopic assessment at three months after the end of radiotherapy, no difference in Vienna Rectoscopy Score was noted between the two treatment groups. However, after 12 months of follow-up, the Vienna Rectoscopy Score was significantly lower in the BDP group. During the entire period of the study, severe haemorrhagic proctopathy, defined as haemorrhagic proctopathy requiring was diagnosed in 10 patients, four in the BDP arm and six in the placebo arm (ITT OR = 0.69; 95%CI 0.18 to 2.60). No patients reported adverse events related to the study treatments. The study did not report on a possible effect of preventative local steroids on performance status, progression-free or overall survival.

Conclusions

- In patients undergoing radiation therapy to the pelvis, an effect of beclomethasone dipropionate enema on severity of radioproctitis symptoms after completion of radiotherapy could neither be demonstrated nor refuted (Fuccio 2011; very low level of evidence).
- In patients undergoing radiation therapy to the pelvis, an effect of beclomethasone dipropionate enema on the incidence of severe haemorrhagic proctopathy could neither be demonstrated nor refuted (Fuccio 2011; very low level of evidence).
- There is limited evidence that preventive topical beclomethasone dipropionate reduces the negative impact of pelvic radiotherapy on quality of life (Fuccio 2011; very low level of evidence).
- There is limited evidence that preventive topical beclomethasone dipropionate is not associated with significant side effects compared to placebo enema (Fuccio 2011; very low level of evidence).

Recommendation

- Beclomethasone dipropionate enemas are not recommended to prevent radioproctitis due to pelvic radiotherapy (weak recommendation).

3.7.2.2. Probiotics

One RCT was identified evaluating the efficacy of a high-potency probiotic preparation for the prevention of radiation-induced diarrhoea in cancer patients [85]. The trial involved 490 patients who were randomly assigned to either treatment with VSL#3 (containing *L. casei, L. plantarum, L. acidophilus, and L. delbruekii subsp. bulgaricus, B. longum, B. breve, and B. infantis, Streptococcus salivarius subsp. Thermophilus*) or a VSL#3-identical appearing placebo starting from the first day of radiation therapy until the end of the scheduled cycles of radiation therapy. The risk of bias of this trial was considered to be unclear and the trial reported on the following outcomes: incidence of radiation-induced diarrhoea, severity of

radiation-induced diarrhoea (WHO grading) and daily number of bowel movements.

More patients in the placebo group had radiation-induced enteritis and colitis compared with the VSL#3 group (51.8% vs. 31.6%; RR = 0.61; 95%CI 0.49 to 0.76). Furthermore, patients assigned to placebo suffered more severe toxicity compared with VSL#3 recipients (p<0.001; RR = 0.19; 95%CI 0.10 to 0.37). Grade 3 or 4 diarrhoea was documented in 69 of 124 (55.4%) placebo-treated patients and 8 of 77 (1.4%) VSL#3-treated patients. Fifty of 124 placebo-treated patients had grade 1 or 2 diarrhoea compared with 34 of 77 VSL#3 recipients (RR = 1.10; 95%CI 0.79 to 1.52). The mean daily number of bowel movements was 14.7 ± 6 and 5.1 ± 3 among placebo and VSL#3 recipients, respectively (p<0.05). No tumour- or treatment-related deaths or deaths from other causes were recorded in either group during the period of radiation therapy, and no cases of bacteremia, sepsis, or septic shock were reported among the VSL#3 recipients during the treatment period or during the six months beyond active treatment. No other adverse events reasonably attributable to the use of probiotics were noted.

The study did not report on performance status, quality of life or PFS.

Conclusion

- There is limited evidence that probiotics reduce the incidence and severity of radiation-induced diarrhoea in cancer patients who receive adjuvant pelvic radiation therapy (Delia 2007; very low level of evidence).

Other considerations

As probiotics are considered a cheap and harmless intervention, it can be considered if it improves quality of life during radiotherapy treatment.

Recommendation

- Probiotics can be considered to prevent radiation-induced diarrhea in patients receiving radiotherapy to the pelvis (weak recommendation).

3.7.3. Treatment of radioproctitis

3.7.3.1. Hyperbaric oxygen

Two RCTs were identified that evaluated the effect of hyperbaric oxygen for refractory radiation proctitis [86, 87].

The first trial of Clarke et al. [86] included 150 patients who were randomized to either daily hyperbaric oxygen sham treatment. The total number of sessions was 30-40. After the intervention period all patients in the sham group were crossed over to the active intervention. The trial reported on the following three outcomes: severity of symptoms (measured by the late effects normal tissue-subjective, objective, management, analytic score [SOMA-LENT]), standardized clinical assessment and change in quality of life.This trial was considered to be of high risk of bias, because 30 patients (11 and 19, respectively) were excluded from the study after randomization and no intention to treat analysis was performed. A decrease of the SOMA-LENT score was seen in both groups after completion of the initial allocation. A decrease (improvement) of 5.00 points (95%CI 3.96 to 6.03) occurred in the intervention group and a decrease of 2.61 points (95%CI 1.51 to 3.70) in the sham group. The decrease was significantly larger in the intervention group than in the sham group (p=0.0019). The proportion of responders (healed, significant improvement or modest improvement versus no improvement) in the intervention group was higher than in the sham group (88.9% vs. 62.5%, respectively; RR = 1.65, 95%CI 1.30 to 2.10). Based on a repeated measures logistic model the OR for improvement was 5.93 (95%CI from 2.04 to 17.24), of which a risk difference was derived of 0.32 (32%) resulting in a number needed to treat of 3. With respect to bowel-specific quality of life marked improvement was noted for the intervention group after treatment but not for the sham group (14% for bowel bother and 9% for bowel function vs. 5% and 6%, respectively). These differences disappeared after the crossover. No differences were observed in the general well-being assessment.

The second trial of Sidik et al. [87] included 65 patients who were randomized to either daily hyperbaric oxygen with pressure between 2-3 atmosphere absolute or no intervention. The trial reported on the following two outcomes: severity of symptoms (measured by the SOMA-LENT score) and performance status (measured by the Karnofsky score). The

trial was considered to be of high risk of bias. The ratio of acute side effects before and soon after intervention showed a significant difference in favour of the treatment group (44.12 ± 28.22 vs. 0.71 ± 30.16; p<0.001). The ratio of late side effects before and soon after intervention also showed a significant difference in favour of the treatment group (33.64 ± 57.64 vs. -19.69 ± 69.44; p=0.008). The ratio of the Karnofsky score before and after intervention was significantly different in favour of the treatment group (19.67 ± 9.64 vs. 4.53 ± 10.74; p<0.001) which remained the same for the results after 6 months of intervention (15.27 ± 14.74 vs. 2.47 ± 16.11; p=0.007).

There were no data on the effect of hyperbaric oxygen on PFS and OS.

Conclusions

- There is limited evidence that hyperbaric oxygen treatment improves the SOMA-LENT score in patients with refractory radiation proctitis (Clarke 2008; Sidik 2007; very low level of evidence).
- There is limited evidence that hyperbaric oxygen treatment for refractory radiation proctitis increases the proportion of healed or improved patients (Clarke 2008; very low level of evidence).
- There are indications that hyperbaric oxygen treatment improves quality of life in patients with refractory radiation proctitis (Clarke 2008; very low level of evidence).
- There are indications that hyperbaric oxygen treatment improves performance status in patients with radiation proctitis (Sidik 2007; very low level of evidence).

Recommendation

- Hyperbaric oxygen treatment can be considered for refractory radioproctitis, i.e. when medical treatments are exhausted (weak recommendation).

3.7.3.2. Coagulation therapy

Heater probe versus bipolar electrocoagulation probe

One RCT was identified that included 21 participants with chronic radiation proctitis resistant to one year of medical treatment. Participants were randomised to receive treatment with either a heater probe (n = 9) or a bipolar electrocoagulation probe (n = 12) [83]. The risk of bias of this trial was considered to be unclear as there was insufficient information on the methods of this trial. Follow up period was one year. Severe bleeding episodes, defined as a bleeding that provoked an unscheduled hospital assessment, occurred in 11% (1/9) of the heater probe group and in 33% (3/12) of the bipolar probe group (RR = 0.44; 95%CI 0.05 to 3.60). The mean number of severe bleeding episodes was similar in both groups (0.4 vs. 0.3). No major complications occurred.

Argon plasma coagulation versus bipolar electrocoagulation

One RCT was identified that evaluated the efficacy and safety of argon plasma coagulation (APC) and bipolar electrocoagulation (BEC) in the treatment of bleeding from chronic radioproctitis [88]. This trial involved 30 patients with recurrent rectal bleeding that had started 6 months after radiotherapy and who had at least one bleeding episode in the week before inclusion. The risk of bias of this trial was considered to be unclear as there was insufficient information on the methods of this trial.There were no significant differences between the groups with respect to rectal bleeding. Based on an intention-to-treat analysis the success rates (defined as eradication of all telangiestasias) were 12/15 (80.0%) for APC and 14/15 (93.3%) for BEC (RR = 0.86; 95%CI 0.64 to 1.14). In a per-protocol analysis, these results were 92.3% and 93.3% respectively (p=1.000). Minor complications were recorded in 5/15 in the APC group and 10/15 in the BEC group (RR = 0.50; 95%CI 0.22 to 1.11) and major hemorraghic complications in 1 and 5, respectively (RR = 0.20; 95%CI 0.03 to 1.51). No other major adverse effects, such as fistula, extensive necrosis, perforation or bowel explosion were observed. Relapse of rectal bleeding occurred in 1/12 after APC and in 2/14 after BEC (RR = 0.58; 95%CI 0.06 to 5.66).

Argon plasma coagulation, electrical power setting of 60 W versus 50 W

One RCT was identified that evaluated the efficacy and complications of argon plasma coagulation using the electrical power setting of 60 W (group A) or 50 W (group B) [89]. This trial involved 42 patients and the risk of bias of this trial was considered to be unclear as no details on the method of randomisation, allocation concealment and blinding were reported and a relatively high number of patients dropped out in Group B. In 56.5% of the patients in Group A, no rectal bleeding occurred versus 26.3% in Group B (p=0.16); RR 2.15 (95%CI 0.93 to 4.94). Minor intermittent bleeding occurred in 43.5% of the patients in Group A versus 73.7% in Group B; RR 0.59 (95%CI 0.34 to 1.01).

Conclusions

- A difference in effect on severe rectal bleeds after 1 year between coagulation therapy with a bipolar heater probe or with a bipolar electrocoagulation probe could neither be demonstrated nor refuted (Jensen 1997; very low level of evidence).
- A difference in effect on success rates between argon plasma coagulation or bipolar electrocoagulation in patients with chronic radiation coloproctopathy could neither be demonstrated nor refuted (Lenz 2010; very low level of evidence).
- There is limited evidence that argon plasma coagulation leads to less minor complications than bipolar electrocoagulation in patients with chronic radiation coloproctopathy (Lenz 2010; very low level of evidence).
- In patients with chronic radiation coloproctopathy a difference in major complications between argon plasma coagulation and bipolar electrocoagulation could neither be demonstrated nor refuted (Lenz 2010; very low level of evidence).
- In patients with chronic radiation coloproctopathy a difference in relapse of rectal bleeding between argon plasma coagulation and bipolar electrocoagulation could neither be demonstrated nor refuted (Lenz 2010; very low level of evidence).
- In patients with radiation proctitis a difference in rectal bleeding between argon plasma coagulation electrical power setting 60 W and argon plasma coagulation electrical power setting 50 W could neither be demonstrated nor refuted (Gheorghe 2003; very low level of evidence).

Other considerations

Although evidence supporting the use of endoscopic coagulation is limited, it is often the only safe option if medical treatment appears ineffective. As surgery in irradiated tissue is considered a high risk intervention, endoscopic treatment is preferred.

Recommendation

- Endoscopic coagulation therapy can be considered for repetitive rectal bleeding due to radioproctitis after pelvic radiotherapy (weak recommendation).

3.7.3.3. Sulfasalazine

One RCT was identified which included 37 patients with radiation-induced proctosigmoiditis [82]. Patients were randomized to either oral sulfasalazine 500 mg and rectal prednisolone 20 mg or oral placebo and rectal sucralfate suspension. The risk of bias of this trial was considered to be unclear as there was insufficient information on the methods of this trial.

The trial reported on the following two outcomes: changes in clinical grading and endoscopic appearance. The sulfalazine/steroid group showed less improvement compared to the sucralfate group (RR = 0.57; 95%CI 0.35 to 0.92). Eight out of 15 in the sulfasalazine/steroid group showed a clinical improvement compared to 16 out of 17 in the sucralfate group. Seven out of 15 in the sulfasalazine/steroid group showed endoscopic improvement compared to 12 out of 17 in the sucralfate group (RR = 0.66; 95%CI 0.35 to 1.23). Two patients in the sulfasalazine/steroid group did not tolerate the drugs and had to be excluded due to myalgia, nausea and headaches.

Conclusion

- There is limited evidence that oral sulfasalazine + rectal prednisolone leads to less clinical improvement than oral placebo + rectal sucralfate in patients with radioproctitis (Kochhar 1991; very low level of evidence).

Recommendation

- Oral sulfasalazine cannot be recommended as treatment of radioproctitis after radiotherapy to the pelvis (strong recommendation).

3.7.3.4. Corticosteroids

Hydrocortisone vs. betamethasone

One RCT was identified that involved 32 participants with radioproctitis who received either hydrocortisone acetate mousse or a rectally administered betamethasone enema [81]. The risk of bias of this trial was considered to be high.

Over the four weeks of treatment, the endoscopic appearance improved more in the hydrocortisone group (12 out of 16) than in the betamethasone group (5 out of 14) (RR = 2.10; 95%CI 0.98 to 4.48). Potential reasons for the difference in effect may be the more aggressive grade of disease in the betamethasone group at baseline which would have been less likely to respond to any treatment, and also the fact that the betamethasone enema was poorly tolerated in 10 out of 14 compared with 2 out of 16 in the hydrocortisone group (RR = 0.18; 95%CI 0.05 to 0.67 in favour of the hydrocortisone group). No side effects were reported.

Conclusion

- A difference in effect on endoscopic appearance between hydrocortisone acetate mousse and betamethasone lavage in patients with radioproctitis could neither be demonstrated nor refuted (Rougier 1992; very low level of evidence).

Other considerations

The study by Kochhar et al. [82] mentioned above (3.7.3.3) can also be taken into account regarding the effect of rectal prednisolon on radioproctitis.

Corticosteroids are known to be associated with serious adverse events.

Recommendation

- Rectal corticosteroids cannot be recommended as treatment of radioproctitis after radiotherapy to the pelvis (strong recommendation).

3.7.3.5. Probiotics

No RCT was identified that addressed treatments with probiotics for radioproctitis in patients with cancer.

Conclusion

- There is no evidence from randomized controlled trials on the use of probiotics to treat radioproctitis.

Recommendation

- There is insufficient evidence to recommend the use of probiotics to treat radioproctitis (weak recommendation).

3.7.3.6. Surgery

No RCT was identified that addressed surgical interventions for radioproctitis in patients with cancer.

Conclusion

- There is no evidence from randomized controlled trials on the use of surgery in the treatment of radioproctitis.

Other considerations

A full search of observational studies was not undertaken. The following principles can be considered, based on expert opinion:

- Surgery in radiated tissues is at high risk for complications and should therefore only be used if medical or endoscopic treatment is not available or response to medical or endoscopic treatment is insufficient. Morbidity of surgical intervention is high, ranging from 30% to 65%, the mortality rates in the postoperative period is reported as 6.7% to 25%.[90]
- Decisions on the timing and type of surgery need to be taken on a case by case basis and depend on the type of symptoms (e.g. for obstruction, perforation or fistulas), involvement of other parts of the bowel and extent of received radiotherapy.
- There is no consensus on the prefered procedure to be used (bypass versus resection). However, often limited surgery with diversion as symptomatic treatment is preferred.

Recommendation

- Surgery can be considered to treat radioproctitis on a case by case basis if medical treatment is ineffective (weak recommendation).

3.8. Infertility

3.8.1. Introduction

Chemotherapy and radiotherapy can have serious adverse effects on fertility in both women and men. As an increasing number of patients who are diagnosed with cancer in the reproductive age can be cured, fertility preservation has become an important issue in cancer treatment. Risk of infertility after treatment varies depending on total dose, type of agent used and age of the patient, but can be as high as 100% [91]. As damage to the reproductive system can be irreversible, patient information and access to fertility preservation before the start of gonadotoxic treatment should be routine and is considered good clinical practice.

The currently best known methods to preserve reproductive function are embryo cryopreservation in women and sperm cryopreservation in men. The field is rapidly evolving and techniques for oocyte and ovarian cryopreservation and alternative techniques for sperm collection have been developed [92]. As these techniques are not specifically studied for cancer patients and are not the subject of randomized controlled trials, they will only be briefly discussed [93].

Also, pharmacological interventions have been tested for their ability to protect ovaries and testes for damage caused by chemotherapy. The current literature search concentrated on RCTs of hormonal and pharmacological interventions. It should be noted that there are limitations in using RCTs for studying interventions regarding infertility as side-effect of gonadotoxic chemotherapy as the most important, long term outcomes are relatively infrequent and follow-up periods might not be long enough.. Recent reports consider pregnancy after cancer treatment safe, the incidence of genetic disease and cancer appears not increased in the children of cancer survivors [94, 95].

Good clinical practice

- All prepubertal patients and patients of reproductive age should be informed about possible consequences of treatment on fertility and should have access to all possible fertility preservation measures before the start of cytotoxic treatment.

3.8.2. Literature review

One systematic review was identified that met the inclusion criteria [96]. The review addressed RCTs comparing the addition of GnRH analogues to chemotherapy with chemotherapy alone in premenopausal women at risk of premature ovarian failure (POF) as a side-effect of gonadotoxic chemotherapy. The search date was January 2010. The overall risk of bias of this review was judged to be low.

On 11 April 2012 an update of the search of Bedaiwy et al. was performed. One RCT was identified that was not yet included in the existing review [97]. A second study that was included in Bedaiwy et al. as an abstract was recently published [98].

On 28 March 2012 a search for additional interventions other than GnRH agonists regarding infertility as side-effect of gonadotoxic chemotherapy was performed. One RCT was identified that met the inclusion criteria [93].

3.8.3. Addition of GnRH agonists to gonadotoxic chemotherapy

The review of Bedaiwy et al. included six RCTs [96]. Data were available for occurrence of pregnancy, proportion of women with new onset of premature ovarian failure (POF) and resumption of ovulation. All included studies defined POF as cessation of menstruation, but some studies added criteria such as increased serum follicle stimulating hormone (FSH) level. Both the incidence of women with spontaneous menstruation (OR = 3.46; 95%CI 1.13 to 10.57) and incidence of spontaneous ovulation (OR = 5.70; 95%CI 2.29 to 14.20) after treatment demonstrated a statistically significant difference in favour of the use of GnRH agonists. A beneficial effect on pregnancy rates could neither be demonstrated nor refuted (OR 0.44; 95%CI, 0.07-2.59). There were no data available for the following outcomes: incidence of women with POF after an initial normal cycle, incidence of women with regular cycles but abnormal markers of ovarian reserve and time to reestablishment of a regular menstrual cycle.

In the study of Del Mastro et al. [97] addition of triptorelin, a GnRH agonist, was compared to no additional intervention in women receiving (neo)adjuvant chemotherapy for breast cancer. Two hundred and eighty-one women were randomized. This study was considered to have a low risk of bias. The authors reported three pregnancies in the intervention group and one in the control group. The effect of the intervention on death and recurrence of disease was not statistically significant (RR = 2.32, 95%CI 0.63-8.55 and R = 0.94, 95%CI 0.46-1.92 respectively). Rates of several adverse events were reported. No statistically significant differences between groups were found (hot flushes: OR = 1.61, 95%CI 0.87 to 2.97; headache: OR = 1.42, 95%CI 0.75 to 2.72; sweating: OR = 1.76, 95%CI 0.81 to 3.80; mood modification: OR = 0.91, 95%CI 0.43 to 1.93; vaginal dryness: OR = 1.01, 95%CI 0.45 to 2.27). For the outcome 'rate of early menopause' a statistically significant difference was found, with lower rates for the intervention group (intention to treat analysis using imputed values for missing data: OR = 0.28, 95%CI 0.14 to 0.56; analysis of available cases: OR = 0.25; 95%CI 0.12 to 0.52).

Gerber et al. [98] compared the addition of goserelin to no additional intervention. Sixty-one women were randomized. This study was included as an abstract in the review of Bedaiwy et al., and was considered to have an unclear risk of bias. No difference between groups in pregnancy rate was observed (OR = 1.00; 95%CI 0.06 to 16.76). For none of the presented adverse events a statistically significant difference was found (hot flushes: OR = 2.29, 95%CI 0.80 to 6.50; mood swings: OR = 1.00, 95%CI 0.13 to 7.60; insomnia: OR = 5.80, 95%CI 0.63 to 53.01; urogenital symptoms: OR = 7.25, 95%CI 0.82 to 64.46). Outcomes related to ovarian failure were incidence of regular menses at six or twelve months after end of therapy and long term ovarian reserve and fertility, represented by levels of Anti-Müllerian Hormone (AMH). No statistically significant differences between study groups were found (regular menses six months: OR = 1.78, 95%CI 0.62 to 5.17; regular menses 12 months: OR = 1.25, 95%CI 0.34 to 4.64; AMH > 0.2 µg/L: OR = 2.00, 95%CI 0.28 to 14.20).

The results of Del Mastro et al. were added to the meta-analyses of Bedaiwy et al. The incidence of women without ovarian failure after treatment demonstrated a statistically significant difference in favour of the use of GnRH agonists (RR = 1.49; 95%CI 1.14 to 1.94). A beneficial effect on pregnancy rates could neither be demonstrated nor refuted (OR 0.83; 95%CI, 0.24 to 2.81).

Conclusions

- There are indications that the addition of a GnRH analogue to gonadotoxic chemotherapy has no effect on the incidence of future pregnancy (Bedaiwy 2011, Del Mastro 2011; low level of evidence).
- There are indications that the addition of a GnRH analogue to gonadotoxic chemotherapy increases the incidence of spontaneous ovulation (Bedaiwy 2011; very low level of evidence).
- There are indications that the addition of a GnRH analogue to gonadotoxic chemotherapy increases the incidence of spontaneous menstruation (Bedaiwy 2011, Gerber 2011, Del Mastro 2011; very low level of evidence).
- An effect of the addition of a GnRH analogue to gonadotoxic chemotherapy on long term ovarian reserve and fertility could neither be demonstrated nor refuted (Gerber 2011; very low level of evidence).

- It is unclear whether the addition of a GnRH analogue to gonadotoxic chemotherapy has any effect on death or recurrence of disease (Del Mastro 2011; very low level of evidence).
- The effect of the addition of GnRH analogues to gonadotoxic chemotherapy on adverse events, such as hot flushes, mood modification, sweating, headache, vaginal dryness, insomnia and urogenital symptoms could neither be demonstrated nor refuted (Del Mastro 2011, Gerber 2011; moderate /very low level of evidence).

Other considerations

Available evidence on the benefit of GnRH analogues during gonadotoxic chemotherapy mainly concentrates on short term outcomes such as the spontaneous resumption of ovulation or menstruation shortly after therapy, which are not good predictors of long term fertility. Furthermore, the absolute risk reduction may be insufficient to convince women to abandon cryopreservation techniques as the risk of ovarian failure after treatment remains as high as approximately 27%. Overall the observed benefits of GnRH analogues appear insufficient to balance against the disadvantages of having injections, expected menopausal symptoms and increased costs.

For premenopausal women with hormone-receptor positive breast cancer, there is concern that GnRH analogues make tumour cells less sensitive to treatment by reducing cell growth rate. Furthermore, the 2 trials in breast cancer patients did not show a significantly beneficial effect of GnRH analogues [97, 98].

For women with other cancer types other than breast cancer, GnRH analogues during chemotherapy can be considered despite limited data, taking into account patient preferences. An additional advantage can be that contraception is ensured during treatment.

Recommendation

- GnRH analogues can be considered in addition to gonadotoxic chemotherapy in order to preserve spontaneous ovulation and menstruation, taking into account tumour type and patient preferences (weak recommendation).

3.8.4. Oral contraceptives

No RCTs were identified in which oral contraceptives with chemotherapy were compared to chemotherapy alone.

One RCT was identified in which oral contraceptives were compared to GnRH analogues [93]. This study was stopped early due to slow accrual and upcoming concerns about *a priori* assumptions. Twenty-three women with biopsy-proven Hodgkin lymphoma (HL) at first diagnosis in advanced stages were randomly assigned to either oral contraceptives (OC) or GnRH analogue. Only 19 participants were evaluated (OC n=9, goserelin n=10). This trial was considered as having a high risk of bias. No woman in both groups gave birth to a child. No statistically significant differences with respect to menstrual status were found in OC group compared to goserelin group (amenorrhea: RR = 3.33, 95%CI 0.42 to 26.58; irregular menstruation: RR = 2.22, 95%CI 0.24 to 20.57; regular menstruation: RR = 0.48, 95%CI 0.17 to 1.31).

Conclusions

- An effect of the addition of oral contraceptives vs. GnRH analogues to gonadotoxic chemotherapy on pregnancy rate could neither be demonstrated nor refuted (Behringer 2009; very low level of evidence).
- An effect of the addition of oral contraceptives vs. GnRH analogues to gonadotoxic chemotherapy on the protection of the ovarian reserve and menstrual status after chemotherapy could neither be demonstrated nor refuted (Behringer 2009; very low level of evidence).

Other considerations

Available evidence is insufficient to advise on the use oral contraceptives to preserve fertility during gonadotoxic chemotherapy. However, as adequate contraception is vital during anti-cancer therapy, the use of oral contraceptives can be considered if the treated disease is not sensitive to hormones. It also prevents bleeding problems during chemotherapy, which can be an advantage in thrombocytopenic patients (next to the contraception).

Recommendation

- Oral contraceptives should not be used in addition to gonadotoxic chemotherapy in order to preserve reproductive function in female cancer patients (weak recommendation).

3.8.5. Hormonal and other pharmacological interventions in men

No RCTs were identified that addressed pharmacological interventions in men with cancer. The addition of GnRH agonists or antagonists or testosterone to gonadotoxic cancer treatment has been suggested also in men, but only minimal clinical data are available in humans [92].

Recommendation

- GnRH antagonists, GnRH agonists or testosterone should not be used in addition to gonadotoxic chemotherapy to preserve reproductive function in male cancer patients (strong recommendation).

3.8.6. Ovarian cryopreservation

No RCTs were identified that addressed ovarian cryopreservation in cancer patients. The technique is still in development and only available in very specialized centres. Recently, German authors identified 15 life births following retransplantation of ovarian tissue reported by various teams across the world [99].

Ovarian cryopreservation has several possible advantages over embryo freezing. Delay to start treatment can be kept short. Freezing of ovarian tissue is also possible in pre-pubertal girls and for women without partner. Furthermore, the ethical dilemma of freezing embryos that may never be used is avoided. On the other hand, there is concern about the possibility of retransplanting malignant cells.

Recommendation

- Ovarian cryopreservation cannot be recommended before gonadotoxic cancer treatment in female cancer patients outside the context of clinical research (weak recommendation).

3.9. Nausea and vomiting

3.9.1. Introduction

The prevention and treatment of nausea and vomiting in cancer patients receiving treatment has extensively been studied. Recent evidence-based recommendations are available based on high-quality evidence. The expert panel agreed to adopt these recommendations with slight modifications.

The evidence of cannabinoids was updated with two additional RCTs and therefore discussed separately.

3.9.2. 5-HT3 receptor antagonists, dexamethasone, benzodiazepines and NK1 receptor antagonists

Three systematic reviews were included that met the inclusion criteria [100-102]. The review of Billio et al. was already included in another review and will, therefore, not further be described.

The search date of the review of Keeley et al. was April 2008 [102]. The review addressed the anti-emetic effectiveness of various interventions in patients undergoing emetogenic chemotherapy or radiotherapy. Reported outcomes were nausea, retching, vomiting, vomitus volume, ability to remove nasogastric tube, quality of life, and adverse effects. The overall risk of bias of the review was judged to be low. Level of evidence was assessed using the GRADE methodology by the authors of the review. Their conclusions are quoted in Table 8.

The review included one systematic review that addressed the effectiveness of adding dexamethasone to other antiemetics (primarily 5-HT3 antagonists) in people receiving emetogenic chemotherapy (mainly cisplatin) for both early and advanced cancer. Dexamethasone led to significantly more absence of vomiting within 24 hours or within 1–7 days of chemotherapy (OR = 2.22; 95%CI 1.89 to 2.60 and OR = 2.04; 95%CI 1.63 to 2.56 respectively). Most studies reported mild and tolerable adverse effects, several studies reported increased hiccups or gastrointestinal symptoms with dexamethasone and one person on dexamethasone had haematemesis.

The review also included one RCT that addressed the effectiveness of dexamethasone versus placebo in people undergoing radiotherapy. All participants also received 5-HT3 antagonists. After 15 fractions of radiotherapy significant differences in favour of dexamethasone were found for complete control of emesis (23% vs. 12%; p=0.02) and average nausea scores (0.28 vs. 0.39; p <0.03). Complete control of nausea did not differ significantly (15% vs. 9%; p=0.14). With respect to adverse effects significant differences were found in favour of placebo for sleep quality (p < 0.002) and constipation (p < 0.003).

One systematic review included in Keeley et al. compared 5-HT3 antagonists with high-dose metoclopramide alone or metoclopramide at any dose in combination with dexamethasone, lorazepam or orphenadrine. The proportion of people with vomiting was significantly reduced in the 5-HT3 antagonists arm (OR = 0.60; 95%CI 0.51 to 0.70).

Two RCTs included in the review addressed the effectiveness of aprepitant versus placebo in people undergoing chemotherapy and receiving a 5-HT3 receptor antagonist plus dexamethasone. Complete response at 5 days (defined as no vomiting and no use of rescue drug treatment) occurred significantly more often in the aprepitant group (63% vs. 43%; p < 0.001). The same applies to complete response at day 1 (acute phase), days 2–5, and overall (85%, 66%, and 63% vs. 75%, 51%, and 49%; all p < 0.01). Similar rates of adverse effects were reported. No significant differences were found for asthenia/fatigue, constipation, or hiccups.

The overall conclusions of the review are summarized in Table 8.

Table 8 – Nausea & vomiting: summary of conclusions review by Keeley et al. [102]

Metoclopramide is likely to be effective for reducing episodes of vomiting in people having chemotherapy (low level of evidence).
Dexamethasone, in combination with other antiemetics, reduces acute and delayed emesis compared with placebo in people receiving emetogenic chemotherapy (high level of evidence), and it may be more effective than metoclopramide in this population (very low level of evidence).
5HT3 antagonists also reduce acute vomiting in people having chemotherapy compared with metoclopramidebased regimens, and this benefit is enhanced by the addition of dexamethasone (high level of evidence).
Cannabinoids are effective for nausea and vomiting in people receiving chemotherapy (high level of evidence), but may be associated with a high and often unacceptable burden of adverse effects (moderate level of evidence).
Adding aprepitant to a conventional antiemetic regimen of a 5HT3 antagonist plus a corticosteroid reduces treatment-related nausea and vomiting in people receiving highly emetogenic chemotherapy (moderate level of evidence).
We don't know whether antihistamines, antimuscarinics, antipsychotics, benzodiazepines, or NK1 antagonists (alone) are effective in people with cancer-related nausea and vomiting.
We don't know whether 5HT3 antagonists alone reduce nausea and vomiting in people having radiotherapy. However, adding dexamethasone to 5HT3 antagonists seems more effective than 5HT3 antagonists alone (moderate level of evidence).

An update of the ASCO guideline addressed the anti-emetic effectiveness of 5-HT3 receptor antagonists (ondansetron, granisetron, dolasetron, palonosetron, ramosetron and tropisetron), dexamethasone and NK1 receptor antagonists (aprepitant, fosaprepitant) in patients undergoing emetogenic chemotherapy or radiotherapy [100]. Primary outcomes were complete response and rates of any vomiting or nausea. The search date was December 2009. The overall risk of bias of the review was judged to be low.

The guideline addressed both chemotherapy-induced and radiotherapy-induced nausea and vomiting. The recommendations were categorized according to the intensity of the emetic effect of the applied chemotherapy or the level of risk of nausea and vomiting during radiotherapy as defined by MASCC and ESMO[103].

The guideline's recommendations are summarized in Table 9. In summary, for patients who receive any highly emetic chemotherapy agent a combination of a 5-HT3 receptor antagonist, dexamethasone, and a NK1 receptor antagonist is recommended. For moderate emetic risk regimens palonosetron is recommended, combined with dexamethasone. For low-risk agents, ASCO recommends dexamethasone before the first dose of chemotherapy. Patients undergoing high emetic risk radiation therapy should receive a 5-HT3 receptor antagonist before each fraction and for 24 hours after treatment and may receive a 5-day course of dexamethasone during fractions 1 to 5.

Table 9 – Nausea & vomiting: summary of ASCO recommendations [100]

Chemotherapy induced nausea and vomiting	
Highly emetogenic agents	The three-drug combination of an NK1 receptor antagonist (days 1-3 for aprepitant; day 1 only for fosaprepitant), a 5- HT3 receptor antagonist (day 1 only), and dexamethasone (days 1-3 or 1-4) is recommended for patients receiving highly emetogenic chemotherapy. The Update Committee also recommended reclassification of the combined AC (anthracycline and cyclophosphamide) regimen as highly emetogenic.
Moderately emetogenic Agents	The two-drug combination of palonosetron (day 1 only) and dexamethasone (days 1-3) is recommended for patients receiving moderately emetogenic chemotherapy. If palonosetron is not available, clinicians may substitute a first-generation 5-HT3 receptor antagonist, preferably granisetron or ondansetron. Limited evidence also supports adding aprepitant to the combination. Should clinicians opt to add aprepitant in patients receiving moderate-risk chemotherapy, any one of the 5-HT3 antagonists is appropriate.
Low emetogenic agents	A single 8-mg dose of dexamethasone before chemotherapy is suggested.
Minimally emetogenic Agents	No antiemetic should be administered routinely before or after chemotherapy.
Combination chemotherapy	Patients should be administered antiemetics appropriate for the component chemotherapeutic (antineoplastic) agent of greatest emetic risk. AC combinations are now classified as highly emetogenic.
Adjunctive drugs	Lorazepam or diphenhydramine are useful adjuncts to antiemetic drugs but are not recommended as single-agent antiemetics.
Complementary therapy	No published randomized controlled trial data that met inclusion criteria are currently available to support a recommendation about such therapies.
Multiday chemotherapy	It is suggested that antiemetics appropriate for the emetogenic risk class of the chemotherapy be administered for each day of the chemotherapy and for 2 days after, if appropriate. The Update Committee suggests, based on limited data, that patients receiving 5-day cisplatin regimens be treated with a 5-HT3 antagonist in combination with dexamethasone and aprepitant.
Emesis or nausea despite optimal prophylaxis	Clinicians should re-evaluate emetic risk, disease status, concurrent illnesses, and medications; ascertain that the best regimen is being administered for the emetic risk; consider adding lorazepam or alprazolam to the regimen; and consider adding olanzapine to the regimen or substituting high-dose intravenous metoclopramide for the 5-HT3 antagonist or adding a dopamine antagonist to the regimen.
Anticipatory nausea and vomiting	Use of the most active antiemetic regimens appropriate for the chemotherapy being administered to prevent acute or delayed emesis is suggested. Such regimens should be used with initial chemotherapy, rather than assessing the patient's emetic response with less effective treatment. If anticipatory emesis occurs, behavioural therapy with systematic desensitization is effective and suggested.
Radiation-induced nausea and vomiting	
High risk	On the basis of extrapolation from indirect evidence, the Update Committee recommends that all patients should receive a 5-HT3 antagonist before each fraction and for at least 24 hours after completion of radiotherapy. Patients should also receive a 5-day course of dexamethasone during fractions 1-5.
Moderate risk	The Update Committee recommends that patients receive a 5-HT3 antagonist before each fraction for the entire course of radiotherapy. Patients may be offered a short course of dexamethasone during fractions 1-5.
Low risk	The Update Committee recommends a 5-HT3 antagonist alone as either prophylaxis or rescue. For patients who experience radiation-induced nausea and vomiting while receiving rescue therapy only, prophylactic treatment should continue until radiotherapy is complete.

Minimal risk	Patients should receive rescue therapy with either a dopamine receptor antagonist or a 5-HT3 antagonist. Prophylactic antiemetics should continue throughout radiation treatment if a patient experiences radiation-induced nausea and vomiting while receiving rescue therapy.
Combined chemotherapy and radiation therapy	
	Patients should receive antiemetic prophylaxis according to the emetogenicity of chemotherapy, unless the emetic risk with the planned radiotherapy is higher.

Other considerations

- The authors of the ASCO guideline did not make recommendations about the preferred 5-HT3 receptor antagonist, except for patients who receive moderate emetic chemotherapy regimens, for which they recommend palonosetron (combined with a corticosteroid). After reviewing the supporting evidence for this recommendation, which was considered to be too weak, it was decided to not recommend in favour of one particular 5-HT3 receptor antagonist.
- At the time of the development of the ASCO guideline, no evidence was available supporting the recommendation to treat patients receiving multiday chemotherapy with a 5-HT3 antagonist in combination with dexamethasone and aprepitant. However, in the meantime, a recent RCT reported results in favour of this drug combination. Therefore, it was decided to adopt the ASCO recommendation [100].
- NB: since the ASCO recommendations were adopted, no GRADE was applied.

Recommendations

- The three-drug combination of an NK1 receptor antagonist (days 1-3 for aprepitant; day 1 only for fosaprepitant), a 5- HT3 receptor antagonist (day 1 only), and dexamethasone (days 1-3 or 1-4) is recommended for patients receiving highly emetogenic chemotherapy.
- The two-drug combination of a 5-HT3 antagonists (day 1 only) and dexamethasone (days 1-3) is recommended for patients receiving moderately emetogenic chemotherapy.
- A single 8-mg dose of dexamethasone before low emetogenic chemotherapy is suggested.
- No antiemetic should be administered routinely before or after minimally emetogenic chemotherapy.
- Patients receiving combination chemotherapy should be administered antiemetics appropriate for the component chemotherapeutic (antineoplastic) agent of greatest emetic risk.
- Lorazepam or diphenhydramine are useful adjuncts to antiemetic drugs but are not recommended as single-agent antiemetics.
- For patients receiving multiday chemotherapy, it is suggested that antiemetics appropriate for the emetogenic risk class of the chemotherapy be administered for each day of the chemotherapy and for 2 days after, if appropriate. It can be considered to treat patients receiving 5-day cisplatin regimens with a 5-HT3 antagonist in combination with dexamethasone and aprepitant.
- If emesis or nausea persist despite optimal prophylaxis, clinicians should re-evaluate emetic risk, disease status, concurrent illnesses, and medications; ascertain that the best regimen is being administered for the emetic risk; consider adding lorazepam or alprazolam to the regimen; and consider adding olanzapine to the regimen or substituting high-dose intravenous metoclopramide for the 5-HT3 antagonist or adding a dopamine antagonist to the regimen.
- Patients undergoing radiotherapy with a high risk of radiation-induced nausea and vomiting should receive a 5-HT3 antagonist before each fraction and for at least 24 hours after completion of radiotherapy. Patients should also receive a 5-day course of dexamethasone during fractions 1-5.
- A 5-HT3 antagonist is recommended before each fraction for the entire course of moderate-risk radiotherapy. Patients may be offered a short course of dexamethasone during fractions 1-5.
- A 5-HT3 antagonist alone as either prophylaxis or rescue is recommended for low-risk radiotherapy. For patients who experience radiation-induced nausea and vomiting while receiving rescue therapy only, prophylactic treatment should continue until radiotherapy is complete.
- Patients undergoing radiotherapy with a minimal risk of radiation-induced nausea and vomiting should receive rescue therapy with either a dopamine receptor antagonist or a 5-HT3 antagonist. Prophylactic antiemetics should continue throughout radiation treatment if a patient experiences radiation-induced nausea and vomiting while receiving rescue therapy.
- Patients receiving combined chemotherapy and radiotherapy should receive antiemetic prophylaxis according to the emetogenicity of chemotherapy, unless the emetic risk with the planned radiotherapy is higher.

3.9.3. Cannabinoids

Two systematic reviews were identified that met the inclusion criteria[102, 104]. A further two RCTs that were published after 2008 and met the inclusion criteria were identified[105, 106].

3.9.3.1. Canabinoids versus placebo

The review by Machado et al. evaluated interventions using *Cannabis sativa* in the treatment of nausea and vomiting in patients with any type of cancer receiving chemotherapy, tested in randomized clinical trials and compared with any type of control group [104]. The search date was December 2006. The overall risk of bias of this review was judged to be low. The two studies included in this review were also included by Keeley et al.

The review by Keeley et al. addressed the anti-emetic effectiveness of cannabinoids in patients undergoing emetogenic chemotherapy or radiotherapy. The review included one systematic review that compared cannabinoids with placebo in patients undergoing chemotherapy. Significant differences between the groups in favour of cannabinoids were found for complete control of nausea (RR = 1.21; 95%CI 1.03 to 1.42) and complete control of vomiting (RR = 1.84; 95%CI 1.42 to 2.38). Adverse effects, however, were significantly more present in the cannabinoids group: "high" sensation (RR = 10.6; 95%CI 6.86 to 16.50), drowsiness, sedation, somnolence (RR = 1.66; 95%CI 1.46 to 1.89) and withdrawal because of adverse effects (RR = 4.67; 95%CI 3.07 to 7.09). Euphoria, dizziness, dysphoria or depression, hallucination, paranoia, arterial hypertension were all significantly more frequent after cannabinoids.

The trial by Duran et al. evaluated the tolerability, preliminary efficacy, and pharmacokinetics of an acute dose titration of a whole-plant cannabis-based medicine (CBM) containing delta-9-tetrahydrocannabinol and cannabidiol, taken in conjunction with standard therapies in the control of chemotherapy-induced nausea and vomiting (CINV) [105]. The risk of bias of this trial was considered to be high. The proportion of patients showing complete response to anti-emetic therapy on day 1 was not significantly different (RD = 4.8%; 95%CI -36.7% to 42.1%), but for the overall period, complete respons was significantly more frequent in the CBM group as compared to the control group (RD = 49%; 95%CI 1% to 75%). No significant differences were found for the absence of delayed nausea (RD = 34.9% (95%CI -10.8% to 66.3%) or 'significant delayed nausea' (RD = 27.0%; 95%CI -18.0% to 59.7%). Significant differences were found for the absence of delayed emesis (RD = 49% (95%CI 1.0% to 75.0%). No differences in quality of life measurements in the two groups were found (no patients in either group scored >108 in the FLIE questionnaire). Concerning adverse events, no significant differences were found for the following end points: at least one adverse event (RD = 19%; 95%CI -23.7% to 52.4%), severe adverse events (RD = 0.03; 95%CI -0.30 to 0.36) and drug tolerance (RD = -14.3%; 95%CI -40.2% to 11.6%).

The second study by Meiri et al. compared dronabinol, ondansetron or their combination with placebo for the prevention of delayed-onset chemotherapy-induced nausea and vomiting, measured 2–5 days after moderately to highly emetogenic chemotherapy [106]. Sixty-four participants were randomized into four treatment groups. Patients received a standard prechemotherapy regimen of dexamethasone (20 mg) and ondansetron (16 mg). Patients in the three active treatments group also received 2.5 mg dronabinol. Patients in the placebo group received matching placebo for dronabinol. The risk of bias of this trial was considered to be high. Only the results of dronabinol vs. placebo will be reported here. No significant difference was found for total response to anti-emetic chemotherapy between dronabinol (54%) and placebo (20%). Nausea absence was significantly higher in the dronabinol group (71%) than in the placebo group (15%). For vomiting and/or retching, no statistically significant difference was observed among groups for mean number of episodes of vomiting and/or retching. Vomiting and/or retching were lowest in patients treated with dronabinol. Regarding the patients' wellness measured by the Eastern Cooperative Oncology Group (ECOG) performance status, the overall mean change from baseline to end point did not differ much from zero: 0.058 for dronabinol vs. 0.077 for placebo (p=0.036 in favour of placebo). Improvement from baseline in quality of life (measured by the McCorkle Symptom Distress Scale, MSDS) was observed only in patients receiving dronabinol (mean change from baseline –2.0 ± 4.2). At least one treatment emergent adverse effect occurred more frequently in the dronabinol group than in the placebo group (14/17 versus 7/14; RR = 1.65; 95%CI 0.93 to 2.91), whereas at least one serious adverse event occurred

less frequently in the dronabinol group (2/17 vs. 2/14; RR = 0.82; 95%CI 0.13 to 5.12).

The two recent RCTs were combined with two studies that were included in the meta-analysis referred to by Keeley et al. Two other trials included in that meta-analysis were not considered, since their definition of response was judged to be inappropriate[107, 108]. Results show that complete response is more frequently achieved with cannabinoids compared with placebo (4 studies, N = 264; RR = 3.11, 95%CI 1.57 to 6.18).

3.9.3.2. Cannabinoids versus other anti-emetics

In the review included by Keeley et al. cannabinoids were also compared with other anti-emetics in patients undergoing chemotherapy [102]. Significant differences between the groups in favour of cannabinoids were found for complete control of nausea (RR = 1.38; 95%CI 1.18 to 1.62) and complete control of vomiting (RR = 1.28; 95%CI 1.08 to 1.51). Adverse effects were not formally assessed for this comparison and the authors refer to the placebo-controlled studies.

Conclusions

- There are indications that cannabinoids are more effective in controlling nausea and vomiting in patients receiving chemotherapy compared to placebo (Chang 1979, Frytak 1979, Orr 1980, Chang 1981, Meiri 2007, Duran 2010; low level of evidence).
- There are indications that cannabinoids are associated with an increased frequency of adverse events leading to interruption of treatment compared to placebo (Keely 2009; low level of evidence).

Recommendation

- Cannabinoids are not recommended to treat nausea and vomiting associated with chemotherapy or radiotherapy (weak recommendation).

3.10. Diarrhoea

3.10.1. Loperamide

One RCT by Yeoh et al. was included that compared loperamide with placebo [109]. This study with a crossover design compared loperamide oxide tablets with placebo in 20 patients with persistent diarrhoea three to 22 years after therapeutic pelvic irradiation for carcinoma of the genitourinary tract. This trial was considered to have a low risk of bias. A significantly lower median number of bowel actions per week was reported for loperamide (13.5, range 6-39 vs. 19, range 9-53; p<0.001). For stool frequency per three days there was also a statistically significant difference in favour of loperamide (5, range 1-10 vs. 7, range 2-14; p<0.05). No significant adverse effects were reported.

For the direct comparison of loperamide with octreotide: see paragraph 3.10.2.

Conclusions

- There is limited evidence that loperamide is an effective treatment for persistent diarrhoea associated with pelvic radiation therapy (Yeoh 1993; very low level of evidence).
- There is limited evidence that loperamide is not associated with serious adverse events in patients who received pelvic radiotherapy (Yeoh 1993; very low level of evidence).

Other considerations

The evidence on the efficacy of loperamide for treating diarrhoea from other causes was also taken into account, although not discussed here. At present, loperamide is considered standard treatment of diarrhoea from any cause.

Recommendation

- Loperamide is recommended for the treatment of diarrhoea associated with chemotherapy or radiotherapy (strong recommendation).

3.10.2. Octreotide

3.10.2.1. Prophylactic octreotide versus placebo

Three trials were identified that evaluated the efficacy of octreotide versus placebo in the prevention of diarrhoea caused by chemotherapy, radiotherapy or both [110-112].

In thet trial by Cascinu et al., 43 patients who had already suffered from diarrhoea during a 24-hour period following a previous cisplatin administration were randomized to receive either octreotide (2 doses of 0.1 mg s.c.) or placebo during the next cisplatin course [110]. The trial was judged to have a low risk of bias and reported on the following two outcomes: incidence of diarrhoea and adverse events. Follow-up time was 24 hours after the administration of chemotherapy. A significant difference was found for the incidence of diarrhoea (defined as more than two loose bowel movements) in favour of octreotide (RR 0.06; 95%CI 0.01 to 0.42). Octreotide was well tolerated and no major side effects related to its use were observed.

The second trial by Martenson et al. evaluated the effectiveness of long-acting depot octreotide acetate for the prevention of diarrhoea during pelvic radiation therapy [111]. One hundred and twenty-five patients receiving pelvic radiation therapy were randomly allocated to receive octreotide or placebo. The trial was judged to have a high risk of bias. No significant differences were found for grade 2 or 3 diarrhoea (RR = 1.20; 95%CI 0.83 to 1.75), grade 2 or 3 abdominal cramps (RR = 0.89; 95%CI 0.48 to 1.66), mild to moderate rectal bleeding (RR = 1.20; 95%CI 0.77 to 1.88) or moderate rectal bleeding (RR = 5.08; 95%CI 0.25 to 103.71). Some patient-reported symptoms were worse in the octreotide group, including nocturnal bowel movements (p=0.004), clustering of bowel movements (p=0.004), and bleeding with bowel movements (p=0.01). The median reported quality of life score on 0-10 scale was 7.8 for patients treated with octreotide and 7.7 for patients receiving placebo (p=0.29).

The third trial by Zachariah et al. evaluated the efficacy of long-acting octreotide acetate (LAO) in preventing the onset of acute diarrhoea in patients undergoing chemoradiation therapy for rectal or anal cancer [112]. Two hundred thirty-three patients were randomized to 30 mg LAO or placebo via intramuscular injection before the start of radiation therapy. A second dose was given on day 22 (±3 days) of radiation treatment. A total of 215 patients were included in the final analysis. The trial was judged to have low risk of bias and reported on the following three outcomes: incidence of diarrhoea, adverse events and quality of life. Median follow-up time was 9.6 months. No significant differences were found for the incidence rates of grade 2–4 acute diarrhoea (RR = 0.90; 95%CI 0.67 to 1.20). For quality of life, no statistically significant difference between treatment groups was found for the proportion of patients who reported improved quality of life or bowel function at 3 months (among evaluable patients) in any of the four assessments. The authors reported several treatment-related adverse events (one severe infection and three severe hematologic adverse events in the LAO group; one severe grade 4 dehydration and four severe hematologic adverse events in the placebo group) which were nearly equally distributed between the two treatment groups. Two patients in the LAO group had severe neurological events not attributed to the treatment and one patient in the placebo group died because of multiorgan failure not attributed to the treatment.

Meta-analysis of the studies by Martenson and Zachariah performed by KCE shows a RR of 1.01 (95%CI 0.76 to 1.35) for the prevention of moderate to severe diarrhea by octreotide.

Conclusions

- There are indications that prophylactic octreotide does not reduce the incidence of moderate to severe diarrhoea in patients undergoing chemotherapy or pelvic (chemo)radiation (Martenson 2008, Zachariah 2010; low level of evidence).
- There is limited evidence that prophylactic octreotide has no effect on quality of life in patients undergoing chemotherapy or pelvic (chemo)radiation (Martenson 2008, Zachariah 2010; very low level of evidence).
- There are indications that prophylactic octreotide is not associated with an increase in severe adverse events (Casinu 1994, Zachariah 2010; low level of evidence).

Other considerations

Current available evidence is limited to patients receiving cisplatin chemotherapy or pelvic (chemo)radiotherapy.

Recommendation

- Octreotide is not recommended to prevent diarrhoea in patients treated with chemotherapy or (chemo)radiotherapy (weak recommendation).

3.10.2.2. Therapeutic octreotide versus loperamide

Two RCTs were identified that compared octreotide with loperamide[113, 114].

The first RCT by Cascinu et al. compared octreotide with loperamide in 41 patients with 5-FU induced grade 2 or 3 diarrhoea [113]. Patients with grade 4 diarrhoea were excluded; they all received intensive treatment in hospital. The risk of bias of this trial was considered to be high. After three days, diarrhoea completely resolved in 19/21 vs. 3/20 patients (RR = 6.03; 95%CI 2.11 to 17.28). Average stool frequency on day 1, 2 and 3 were 4, 3 and 0 versus 5, 5 and 5 (significance not reported). No response to treatment (requiring further hospital treatment) occurred in 1/21 vs. 10/20 patients (RR = 0.10; 95%CI 0.01 to 0.68). No side effects were observed in any treatment arm.

The second RCT by Gebbia et al. compared octreotide with loperamide for 3 days in 40 patients with WHO-grade 3-4 diarrhoea due to chemotherapy [114]. The risk of bias of this trial was considered to be high. After three days, complete resolution of loose bowel movements occurred in 16/20 vs. 6/20 patients (RR = 2.67; 95%CI 1.32 to 5.39). No response to treatment after 10 days was observed in 1/20 vs. 5/20 patients (RR = 0.20; 95%CI 0.03 to 1.56). Of the 20 patients treated with octreotide 3 experienced pain in the injection site. Of all patients 15% had mild abdominal pain.

Conclusion

- There are indications that octreotide is more effective than loperamide in treating grade 2-4 diarrhoea associated with chemotherapy (Cascinu 1993, Gebbia 1993; very low level of evidence).

Other considerations

As octreotide is a costly intervention, loperamide remains the first choice therapy for moderate to severe diarrhoea associated with chemotherapy. Octreotide can be considered if loperamide is insufficiently effective. There is no evidence on the effect of long-acting octreotide.

Recommendation

- Octreotide can be considered to treat moderate to severe chemotherapy-associated diarrhoea (weak recommendation).

3.10.3. Somatostatin analogues general

No RCTs were identified that addressed somatostatin analogues other than octreotide.

Conclusion

- There is no evidence from RCTs to support the use of somatostatin analogues other than octreotide.

Recommendation

- The use of somatostatin analogues other than octreotide to treat diarrhoea associated with chemotherapy or radiotherapy is not recommended outside the framework of clinical research (weak recommendation).

3.10.4. Probiotics

One systematic review was identified that met the inclusion criteria [115]. The review included four RCTs that compared probiotic supplementation with placebo or dietary control to prevent or treat radiation-induced diarrhoea in patients undergoing radiotherapy for pelvic or abdominal tumours. The search date was January 2009. The overall risk of bias of this review was judged to be low.

Three included RCTs with a total of 632 participants evaluated the preventive effect of probiotic supplementation. Random effects meta-analysis did not show significant differences between probiotic supplementation and control treatment (OR = 0.47; 95%CI 0.13 to 1.67) with respect to the development of radio-induced diarrhoea. However, the few available trials and the presence of significant clinical and statistical heterogeneity limited the analysis.

One included RCT with 205 participants evaluated the therapeutic effect of probiotics. No significant differences between the groups were observed (data not quantified).

No major adverse events owing to probiotic supplementation were reported in any study. On August 24, 2012 an update of the search was performed (from 2009 onwards) and no new RCTs were identified.

Conclusions

- There is limited evidence that prophylactic use of probiotics is not effective in reducing the incidence of radiation-induced diarrhoea (Fuccio 2009; very low level of evidence).
- There is limited evidence that priobiotics are not effective to treat radiation-induced diarrhoea (Fuccio 2009; very low level of evidence).
- It is plausible that the use of probiotics is not associated with major adverse events (Fuccio 2009; moderate level of evidence).

Recommendation

- Probiotics are not recommended to prevent or treat radiation induced diarrhoea (weak recommendation).

3.10.5. Nutritional supplements

One systematic review by McGough et al. was identified that met the inclusion criteria [116]. The review addressed nutritional interventions to alleviate side effects of patients with gynaecological, rectal or urological malignancy before, during or after a course of pelvic radiotherapy and 36 studies (of which 14 were RCTs) were included. The search date was May 2003. The overall risk of bias of this review was judged to be low.

Four included RCTs evaluated nutritional supplements during radiotherapy. In three studies elemental diet supplementation was evaluated. None of the results were quantified. Elemental supplementation to normal diet (providing approximately 900 kcal) showed a statistically significant decrease in the incidence and severity of acute diarrhoeal symptoms. For elemental supplementation to low roughage diet (providing 900 kcal) no significant differences in bowel symptoms were found. In a third study, also elemental supplementation to low fibre diet was evaluated. However, the effect on gastrointestinal outcomes was not assessed.

Enzyme supplementation (WOBE-MUGOS – 100 mg papain, 40 mg chymotrypsin and 40mg trypsin) was studied in another included RCT. On a non-validated diarrhoea scale 57% of the intervention and 36% of the control group were rated as having moderate or severe bowel symptoms (p=0.11).

One RCT by McGough et al. published after May 2003 was identified [117]. An elemental diet intervention (replacement of one meal per day with oral E028 formula) was compared to habitual diet for the prevention of gastrointestinal toxicity in cancer patients undergoing pelvic radiotherapy. The risk of bias was considered to be high. There were no differences in toxicity ratings between study groups (Radiation Therapy Oncology Group scale) at weeks 3, 5 or 10 (median and range: 1 (0-2) vs. 2 (0-2), 2 (0-2) vs. 2 (0-2), 0.5 (0-2) vs. 0.5 (0-2), respectively; significance not reported). Quality of life was measured with the Inflammatory Bowel Disease Questionnaire – Bowel specific sub-set (IBDQ-B) and Vaizey Incontinence Questionnaire (VIQ). Results were nearly similar in both groups (median and range at weeks 3, 5 and 10 for IBDQ-B: 57 (23-66) vs. 60 (29-70), 58 (35-67) vs. 60 (35-69), 68 (54-70) vs. 69 (34-70); VIQ: 6 (0-22) vs. 4 (0-13), 6 (0-18) vs. 4 (0-13), 1 (0-13) vs. 1.5 (0-13); significance not reported).

Conclusions

- An effect of elemental diet supplementation to normal diet on the incidence and severity of bowel symptoms in cancer patients receiving pelvic radiotherapy could neither be demonstrated nor refuted (McGough 2004, McGough 2008; very low level of evidence).
- An effect of elemental diet supplementation to normal diet on quality of life in cancer patients receiving pelvic radiotherapy could neither be demonstrated nor refuted (McGough 2008; very low level of evidence).
- An effect of elemental diet supplementation to low rouphage diet on the incidence and severity of bowel symptoms in cancer patients receiving pelvic radiotherapy could neither be demonstrated nor refuted (McCough 2004; very low level of evidence).

Recommendation

- Nutritional supplements are not recommended to prevent diarrhoea in patients undergoing pelvic radiotherapy (weak recommendation).

3.1. Cardiac toxicity

Several chemotherapeutic substances and targeted treatments are known to have a detrimental effect on cardiac function. Anthracyclines (doxorubicin, epirubicin and daunorubicin) are very effective for many cancer types, but their use is limited by a dose-dependent cardiac toxicity. Damage to the heart can be diagnosed by technical investigations only (subclinical heart failure) or by the occurrence of symptoms (clinical heart failure). Symptomatic heart failure can seriously affect exercise tolerance and daily functioning [118].

3.1.1. Literature review

One systematic review by Van Dalen et al. was identified that met the inclusion criteria [118]. The review addressed RCTs in which any cardioprotective agent was compared to no additional therapy or placebo in cancer patients (children and adults) receiving anthracyclines. The search date was November 2010. The overall risk of bias of this review was considered to be low.

The review included 18 RCTs involving eight cardioprotective interventions (N-acetylcysteine, phenethylamines, coenzymeQ10, a combination of vitamins E and C and N-acetylcysteine, L-carnitine, carvedilol, amifostine and dexrazoxane). The primary outcome measure addressed in the review was heart failure. Secondary outcome measures included potential adverse effects of cardioprotective interventions on response (defined as the number of complete and partial remissions), overall survival (OS), progression-free survival (PFS), quality of life (QoL) and toxicities other than cardiac damage (such as alopecia, nausea, vomiting, stomatitis, diarrhoea, fatigue, anaemia, leukopenia, thrombocytopenia). In April 2012, the literature search was updated starting from the search date of the review. No new RCTs were identified.

3.1.2. Dexrazoxane

Ten included trials with a total of 1619 participants evaluated the cardioprotective effects of dexrazoxane (mostly for adults with advanced breast cancer). In eight studies the control group did not receive a cardioprotective intervention (n = 535); in two studies the control group received a placebo (n = 285). Moreover, six studies included adult patients, three studies included both children and adults and one study included solely children.

Data on survival could be extracted from four trials with a total of 848 patients (adults only). As for overall survival, the meta-analysis showed no significant difference between the dexrazoxane and the control groups (HR = 1.04; 95%CI 0.88 to 1.23). No heterogeneity was detected (I^2 = 0%). For PFS the meta-analysis also showed no significant difference between the dexrazoxane and control groups (HR = 1.01; 95%CI 0.86 to 1.18). Because of unexplained heterogeneity (I^2 = 68%) a random-effects model was also used, which confirmed the findings of no significant difference between treatment groups (RR = 0.97; 95%CI 0.73 to 1.29).

Eight trials (1561 patients: adults and children) provided data on clinical heart failure. Data on combined clinical and subclinical heart failure could be extracted from five trials (643 patients). Subclinical heart failure was defined as either histological abnormalities scored by the Billingham score on endomyocardial biopsy or abnormalities in cardiac function measured by echocardiography or radionuclide ventriculography. Meta-analysis

showed a statistically significant benefit in favour of the use of dexrazoxane for the occurrence of both clinical heart failure and clinical and subclinical heart failure combined (RR = 0.18; 95%CI 0.10 to 0.32 and RR = 0.29; 95%CI 0.20 to 0.41, respectively).

Data on response rate (defined as the number of patients in complete and partial remission) could be extracted from six trials (1021 patients). The meta-analysis showed no significant difference between the treatment groups (RR = 0.89; 95%CI 0.78 to 1.02). No heterogeneity was detected (I^2 = 0%).

There was no significant difference between intervention and control group for the several tested grade 3-4 adverse events.

Quality of life and performance status were not evaluated in any of the included studies.

Conclusions

- It is plausible that dexrazoxane prevents the occurrence of clinical heart failure (Van Dalen 2011; moderate level of evidence). However, the absolute effect is less convincing (NNT = 14).
- It is plausible that dexrazoxane prevents the occurrence of clinical heart failure and subclinical heart failure combined (Van Dalen 2011; moderate level of evidence).
- It is plausible dexrazoxane has no effect on overall survival. (Van Dalen 2011; moderate level of evidence).
- There are indications that dexrazoxane has no effect on progression free survival (Van Dalen 2011; low level of evidence).
- An effect of dexrazoxane on response rate could neither be demonstrated nor refuted (Van Dalen 2011; low level of evidence).
- There are indications that dexrazoxane does not increase grade 3-4 adverse events during chemotherapy (Van Dalen 2011; low level of evidence).

Recommendation

- The use of dexrazoxane to prevent cardiac toxicity of anti-cancer treatments can not routinely be recommended (weak recommendation).

3.1.3. Co-enzyme q10

One study of the review addressed Co-enzyme q10. However, this trial is not further discussed as solely children were included.

Conclusion

- There is no evidence from randomized controlled trials on the effect of co-enzyme q10 on cardiotoxicity due to chemotherapy.

Recommendation

- The use of co-enzyme q10 to prevent cardiac toxicity of cancer treatment is not recommended outside the context of clinical research (weak recommendation).

3.1.4. Amifostine

One study of the review addressed amifostine. However, this trial is not further discussed as solely children were included.

Conclusion

- There is no evidence from randomized controlled trials on the effect of amifostine on cardiotoxicity due to chemotherapy.

Recommendation

- The use of amifostine to prevent cardiac toxicity of cancer treatment is not recommended outside the context of clinical research (weak recommendation).

4. DISCUSSION AND CONCLUSIONS

This report is the second in a series of four, which evaluates supportive actions for patients with cancer. In this report, preventive and therapeutic interventions for a selection of adverse events related to chemo- and or radiotherapy were evaluated. This topic is considered very relevant, since the success of cancer treatment is not only dependent on its effectiveness in terms of survival or response, but just as much on its effect on symptoms, daily functioning and quality of life. Even if a cancer treatment is proven to be effective, its (often chronic) toxicity should be taken into account and impact on later life should be minimized by all means. Furthermore, if a treatment-related adverse event can effectively be prevented or treated, the cancer treatment can be continued at the desired dosage and/or schedule or even intensified. There are indications that new anticancer drugs are associated with even more morbidity and treatment-related mortality [9]. It can therefore be expected that treatment-related toxicity will deserve even more attention in the future.

Due to time constraints and faced with a wide range of possible adverse events related to chemo- and/or radiotherapy, the scope of the report needed to be focused. Choices were made in collaboration with health professionals involved in the care for cancer patients and with patient representatives. Consequently, the report is not comprehensive and does not discuss all treatment options for the studied adverse events.

With the exception of neutropenia and nausea/vomiting, the number of RCTs for the studied interventions was disappointingly low. Furthermore, the selected trials were often poorly designed and/or not focused on patient-important outcomes, such as survival or quality of life. All this is reflected in the level of evidence as evaluated with the GRADE system, which is often low to very low.

It can be considered as a limitation that our report focused on (systematic reviews of) RCTs. For some interventions (e.g. surgery for radioproctitis), no RCTs were identified leading to gaps in our evidence base. An additional search for observational studies would have covered these gaps, but was not feasible within this project.

The report can be used mainly in two ways. First, it offers guidance to cancer patients and their caregivers on how adverse events related to

chemo- and or radiotherapy can be prevented or treated. Wherever possible, clinical recommendations were formulated in a generic way, i.e. not focused on a specific cancer type. The report presents several treatment options and can help making informed treatment choices. Second, the report can serve as a reference document supporting cancer-specific guidelines developed by the College of Oncology in collaboration with the KCE.

Finally, this report highlights the need for well-conducted high-quality research. It is our perception that side effects related to chemo- and or radiotherapy do not receive the scientific attention they deserve. Clearly, studies are needed to investigate interventions to prevent or treat side effects. Above this, and as important, this report should be considered an invitation for more basic research into the mechanisms of toxicity, optimized reporting of adverse events in clinical trials and post-marketing surveillance.

APPENDICES

APPENDIX 1. SEARCH SYNTAX BY DATABASE

Appendix 1.1. Systematic reviews

Table 10 – Systematic reviews: search OVID Medline

Date	**22-11-2011**
Database	Medline OVID
Search Strategy	1 exp Neoplasms/ (2327365) 2 Neoplasm Staging/ (103545) 3 cancer$.ti,ab. (863951) 4 tumor$.ti,ab. (820330) 5 tumour$.ti,ab. (175521) 6 carcinoma$.ti,ab. (407798) 7 neoplasm$.ti,ab. (85745) 8 lymphoma.ti,ab. (97206) 9 melanoma.ti,ab. (64929) 10 staging.ti,ab. (41905) 11 metastas$.ti,ab. (183033) 12 metastatic.ti,ab. (117234) 13 exp Neoplasm Metastasis/ (141345) 14 exp neoplastic processes/ (298816) 15 neoplastic process$.ti,ab. (2088) 16 non small cell.ti,ab. (23591) 17 adenocarcinoma$.ti,ab. (81736) 18 squamous cell.ti,ab. (55422) 19 nsclc.ti,ab. (12889) 20 osteosarcoma$.ti,ab. (13022) 21 phyllodes.ti,ab. (1142) 22 cystosarcoma$.ti,ab. (544) 23 fibroadenoma$.ti,ab. (2715)

24	(non adj small adj cell).ti,ab. (23591)
25	(non adj2 small adj2 cell).ti,ab. (23800)
26	(nonsmall adj2 cell).ti,ab. (1482)
27	plasmacytoma$.ti,ab. (4946)
28	myeloma.ti,ab. (31766)
29	multiple myeloma.ti,ab. (19914)
30	lymphoblastoma$.ti,ab. (259)
31	lymphocytoma$.ti,ab. (252)
32	lymphosarcoma$.ti,ab. (3572)
33	immunocytoma.ti,ab. (400)
34	sarcoma$.ti,ab. (65098)
35	hodgkin$.ti,ab. (47627)
36	(nonhodgkin$ or non hodgkin$).ti,ab. (27245)
37	or/1-36 (2667070)
38	adjuvant.mp. or Chemotherapy, Adjuvant/ or Radiotherapy, Adjuvant/ (96903)
39	Antineoplastic Combined Chemotherapy Protocols/ or Neoadjuvant Therapy/ or neoadjuvant.mp. (102112)
40	chemothera$.tw. (224749)
41	radiothera$.tw. (96469)
42	Radiotherapy/ (33141)
43	antineoplastic agents combined/ (92420)
44	combined modality therapy/ (130686)
45	chemoradi$.mp. (9590)
46	CRT.mp. (5593)
47	or/38-46 (482795)
48	meta-analysis.mp,pt. or review.pt. or search:.tw. (1837533)
49	Mucositis/dh, dt, pc, su, th [Diet Therapy, Drug Therapy, Prevention & Control, Surgery, Therapy] (237)
50	exp Stomatitis/dh, dt, pc, su, th [Diet Therapy, Drug Therapy, Prevention & Control, Surgery, Therapy] (3502)
51	exp Proctitis/dh, dt, pc, su, th [Diet Therapy, Drug Therapy, Prevention & Control, Surgery, Therapy] (958)
52	exp Taste Disorders/dh, dt, pc, su, th [Diet Therapy, Drug Therapy, Prevention & Control, Surgery, Therapy] (215)
53	Xerostomia/dh, dt, pc, su, th [Diet Therapy, Drug Therapy, Prevention & Control, Surgery, Therapy] (1055)
54	exp Lymphedema/dh, dt, nu, pc, rh, su, th [Diet Therapy, Drug Therapy, Nursing, Prevention & Control, Rehabilitation, Surgery, Therapy] (3388)
55	exp Leukopenia/dh, dt, nu, pc, su, th [Diet Therapy, Drug Therapy, Nursing, Prevention & Control, Surgery, Therapy] (6407)
56	Diarrhea/dh, dt, nu, pc, su, th [Diet Therapy, Drug Therapy, Nursing, Prevention & Control, Surgery, Therapy] (8918)
57	Constipation/dh, dt, nu, su, th [Diet Therapy, Drug Therapy, Nursing, Surgery, Therapy] (4072)
58	Vomiting/dh, nu, pc, su, th [Diet Therapy, Nursing, Prevention & Control, Surgery, Therapy] (3886)
59	Vomiting, Anticipatory/dt, nu, pc, th [Drug Therapy, Nursing, Prevention & Control, Therapy] (114)
60	Fatigue/dh, dt, nu, pc, rh, su, th [Diet Therapy, Drug Therapy, Nursing, Prevention & Control, Rehabilitation, Surgery, Therapy] (2864)
61	Anemia/dh, dt, nu, pc, su, th [Diet Therapy, Drug Therapy, Nursing, Prevention & Control, Surgery, Therapy] (9557)
62	Polyneuropathies/dh, dt, nu, pc, rh, su, th [Diet Therapy, Drug Therapy, Nursing, Prevention &

	Control, Rehabilitation, Surgery, Therapy] (757)
63	Peripheral Nervous System Diseases/dh, dt, nu, pc, rh, su, th [Diet Therapy, Drug Therapy, Nursing, Prevention & Control, Rehabilitation, Surgery, Therapy] (3611)
64	Neurotoxicity Syndromes/dh, dt, nu, pc, rh, su, th [Diet Therapy, Drug Therapy, Nursing, Prevention & Control, Rehabilitation, Surgery, Therapy] (582)
65	Cardiomyopathies/dh, dt, nu, pc, rh, su, th [Diet Therapy, Drug Therapy, Nursing, Prevention & Control, Rehabilitation, Surgery, Therapy] (4356)
66	Heart Diseases/dh, dt, nu, pc, rh, su, th [Diet Therapy, Drug Therapy, Nursing, Prevention & Control, Rehabilitation, Surgery, Therapy] (15641)
67	Opportunistic Infections/dh, dt, nu, pc, su, th [Diet Therapy, Drug Therapy, Nursing, Prevention & Control, Surgery, Therapy] (3279)
68	exp Fistula/dh, dt, nu, pc, su, th [Diet Therapy, Drug Therapy, Nursing, Prevention & Control, Surgery, Therapy] (23820)
69	exp Alopecia/dh, dt, nu, pc, rh, su, th [Diet Therapy, Drug Therapy, Nursing, Prevention & Control, Rehabilitation, Surgery, Therapy] (3155)
70	exp Dermatitis/dh, dt, nu, pc, su, th [Diet Therapy, Drug Therapy, Nursing, Prevention & Control, Surgery, Therapy] (17625)
71	Drug Hypersensitivity/dh, dt, nu, pc, su, th [Diet Therapy, Drug Therapy, Nursing, Prevention & Control, Surgery, Therapy] (2227)
72	Osteonecrosis/dt, nu, pc, su, th [Drug Therapy, Nursing, Prevention & Control, Surgery, Therapy] (1798)
73	exp Menopause/th [Therapy] (25)
74	exp Infertility/dh, dt, nu, pc, su, th [Diet Therapy, Drug Therapy, Nursing, Prevention & Control, Surgery, Therapy] (17468)
75	or/49-74 (137065)
76	37 and 47 and 48 and 75 (1870)
77	exp Antineoplastic Agents/ (744267)
78	37 and 48 and 75 and 77 (1414)
79	78 not 76 (439)
80	exp Nail Diseases/ (7318)
81	Nausea/ (11856)
82	exp Foot Dermatoses/ and exp Hand Dermatoses/ (1592)
83	80 or 81 or 82 (20486)
84	37 and 47 and 48 and 83 (357)
85	84 not (76 or 79) (175)
86	47 or 77 (1062422)
87	75 or 83 (154928)
88	37 and 48 and 86 and 87 (2553)

Table 11 – Systematic reviews: search EMBASE.com

Date	**22-11-2011**
Database	EMBASE.com
Search Strategy	'neoplasm'/exp OR 'cancer staging'/exp OR 'metastasis'/exp OR 'oncogenesis and malignant transformation'/exp OR cancer*:ab,ti OR tumor*:ab,ti OR tumour*:ab,ti OR carcinoma*:ab,ti OR neoplasm*:ab,ti OR lymphoma:ab,ti OR melanoma:ab,ti OR staging:ab,ti OR metastas*:ab,ti OR metastatic:ab,ti OR (neoplastic:ab,ti AND process*:ab,ti) OR (non:ab,ti AND small:ab,ti AND cell:ab,ti) OR adenocarcinoma*:ab,ti OR (squamous:ab,ti AND cell:ab,ti) OR nsclc:ab,ti OR osteosarcoma*:ab,ti OR phyllodes:ab,ti OR cystosarcoma*:ab,ti OR fibroadenoma*:ab,ti OR (non:ab,ti AND small:ab,ti AND next:ab,ti AND cell:ab,ti) OR (small NEAR/2 cell):ab,ti OR (nonsmall NEAR/2 cell):ab,ti OR plasmacytoma*:ab,ti OR myeloma:ab,ti OR (multiple:ab,ti AND myeloma:ab,ti) OR lymphoblastoma*:ab,ti OR lymphocytoma*:ab,ti OR lymphosarcoma*:ab,ti OR immunocytoma:ab,ti OR sarcoma*:ab,ti OR hodgkin*:ab,ti OR nonhodgkin*:ab,ti OR (non:ab,ti AND hodgkin*:ab,ti) AND ('chemotherapy'/exp OR 'radiotherapy'/exp OR 'chemoradiotherapy'/exp OR adjuvant:ab,ti OR neoadjuvant:ab,ti OR chemothera*:ab,ti OR radiothera*:ab,ti OR chemoradi*:ab,ti OR crt:ab,ti) AND ('mucosa inflammation'/exp OR 'stomatitis'/exp OR 'proctitis'/exp OR 'taste disorder'/exp OR 'xerostomia'/exp OR 'lymphedema'/exp OR 'leukopenia'/exp OR 'diarrhea'/exp OR 'constipation'/exp OR 'chemotherapy induced emesis'/exp OR 'anticipatory nausea and vomiting'/exp OR 'radiation induced emesis'/exp OR 'cancer fatigue'/exp OR 'anemia'/exp OR 'polyneuropathy'/exp OR 'peripheral neuropathy'/exp OR 'toxicity and intoxication'/exp OR 'cardiomyopathy' OR 'heart disease' OR 'opportunistic infection'/exp OR 'fistula'/exp OR 'alopecia'/exp OR 'dermatitis'/exp OR 'drug hypersensitivity'/exp OR 'bone necrosis'/exp OR 'menopause'/exp OR 'early menopause'/exp OR 'infertility'/exp OR 'nausea'/exp OR 'vomiting'/exp OR 'nail disease'/exp OR 'hand foot syndrome'/exp) AND ([cochrane review]/lim OR [meta analysis]/lim OR [systematic review]/lim) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [embase]/lim AND [2001-2012]/py

Table 12 – Systematic reviews: search Cochrane Library (1)

Date	**28-09-2011**
Database	Cochrane Library
Search Strategy	#1 MeSH descriptor: [Neoplasms] explode all trees #2 MeSH descriptor: [Neoplasm Staging] this term only #3 cancer*:ti,ab #4 tumor*:ti,ab #5 tumour*:ti,ab #6 carcinoma*:ti,ab #7 neoplasm*:ti,ab #8 lymphoma:ti,ab #9 melanoma:ti,ab #10 staging:ti,ab #11 metasta*:ti,ab #12 MeSH descriptor: [Neoplasm Metastasis] 1 tree(s) exploded #13 MeSH descriptor: [Neoplastic Processes] 1 tree(s) exploded #14 neoplastic process*:ti,ab #15 non small cell:ti,ab #16 adenocarcinoma*:ti,ab #17 squamous cell:ti,ab

#18	nsclc:ti,ab
#19	osteosarcoma*:ti,ab
#20	phyllodes:ti,ab
#21	cystosarcoma*:ti,ab
#22	fibroadenoma*:ti,ab
#23	(non next small next cell):ti,ab
#24	(nonsmall near/2 cell):ti,ab
#25	plasmacytoma*:ti,ab
#26	myeloma:ti,ab
#27	lymphoblastoma*:ti,ab
#28	lymphocytoma*:ti,ab
#29	lymphosarcoma*:ti,ab
#30	immunocytoma:ti,ab
#31	sarcoma*:ti,ab
#32	hodgkin*:ti,ab
#33	nonhodgkin*:ti,ab
#34	non hodgkin*:ti,ab
#35	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34
#36	adjuvant:ti,ab
#37	MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] 1 tree(s) exploded
#38	MeSH descriptor: [Chemotherapy, Adjuvant] 1 tree(s) exploded
#39	MeSH descriptor: [Radiotherapy] explode all trees
#40	MeSH descriptor: [Neoadjuvant Therapy] explode all trees
#41	MeSH descriptor: [Antineoplastic Agents] explode all trees
#42	MeSH descriptor: [Combined Modality Therapy] explode all trees
#43	chemothera*:ti,ab
#44	radiothera*:ti,ab
#45	chemoradi*:ti,ab
#46	CRT:ti,ab
#47	#36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46
#48	MeSH descriptor: [Mucositis] 1 tree(s) exploded
#49	MeSH descriptor: [Stomatitis] explode all trees
#50	MeSH descriptor: [Proctitis] 1 tree(s) exploded
#51	MeSH descriptor: [Taste Disorders] 1 tree(s) exploded
#52	MeSH descriptor: [Xerostomia] explode all trees
#53	MeSH descriptor: [Lymphedema] explode all trees
#54	MeSH descriptor: [Leukopenia] explode all trees

Table 13 – Systematic reviews: search Cochrane Library (2)

Date	**27-02-2012**
Database	Cochrane Library
Search Strategy	#1 MeSH descriptor: [Neoplasms] explode all trees #2 MeSH descriptor: [Neoplasm Staging] this term only #3 cancer*:ti,ab #4 tumor*:ti,ab #5 tumour*:ti,ab #6 carcinoma*:ti,ab #7 neoplasm*:ti,ab #8 lymphoma:ti,ab #9 melanoma:ti,ab #10 staging:ti,ab #11 metasta*:ti,ab #12 MeSH descriptor: [Neoplasm Metastasis] 1 tree(s) exploded #13 MeSH descriptor: [Neoplastic Processes] 1 tree(s) exploded #14 neoplastic process*:ti,ab #15 non small cell:ti,ab #16 adenocarcinoma*:ti,ab #17 squamous cell:ti,ab #18 nsclc:ti,ab #19 osteosarcoma*:ti,ab #20 phyllodes:ti,ab #21 cystosarcoma*:ti,ab #22 fibroadenoma*:ti,ab #23 (non next small next cell):ti,ab #24 (nonsmall near/2 cell):ti,ab #25 plasmacytoma*:ti,ab #26 myeloma:ti,ab #27 lymphoblastoma*:ti,ab #28 lymphocytoma*:ti,ab #29 lymphosarcoma*:ti,ab #30 immunocytoma:ti,ab #31 sarcoma*:ti,ab #32 hodgkin*:ti,ab #33 nonhodgkin*:ti,ab #34 non hodgkin*:ti,ab #35 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 #36 adjuvant:ti,ab #37 MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] 1 tree(s) exploded #38 MeSH descriptor: [Chemotherapy, Adjuvant] 1 tree(s) exploded #39 MeSH descriptor: [Radiotherapy] explode all trees #40 MeSH descriptor: [Neoadjuvant Therapy] explode all trees #41 MeSH descriptor: [Antineoplastic Agents] explode all trees #42 MeSH descriptor: [Combined Modality Therapy] explode all trees #43 chemothera*:ti,ab #44 radiothera*:ti,ab #45 chemoradi*:ti,ab #46 CRT:ti,ab #47 #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46

#48	MeSH descriptor: [Mucositis] 1 tree(s) exploded
#49	MeSH descriptor: [Stomatitis] explode all trees
#50	MeSH descriptor: [Proctitis] 1 tree(s) exploded
#51	MeSH descriptor: [Taste Disorders] 1 tree(s) exploded
#52	MeSH descriptor: [Xerostomia] explode all trees
#53	MeSH descriptor: [Lymphedema] explode all trees
#54	MeSH descriptor: [Leukopenia] explode all trees
#55	MeSH descriptor: [Thrombocytopenia] explode all trees
#56	MeSH descriptor: [Diarrhea] explode all trees
#57	MeSH descriptor: [Constipation] explode all trees
#58	MeSH descriptor: [Vomiting] this term only
#59	MeSH descriptor: [Vomiting, Anticipatory] explode all trees
#60	MeSH descriptor: [Fatigue] this term only
#61	MeSH descriptor: [Anemia] this term only
#62	MeSH descriptor: [Polyneuropathies] this term only
#63	MeSH descriptor: [Peripheral Nervous System Diseases] this term only
#64	MeSH descriptor: [Neurotoxicity Syndromes] this term only
#65	MeSH descriptor: [Cardiomyopathies] this term only
#66	MeSH descriptor: [Heart Diseases] this term only
#67	MeSH descriptor: [Opportunistic Infections] this term only
#68	MeSH descriptor: [Fistula] explode all trees
#69	MeSH descriptor: [Alopecia] 1 tree(s) exploded
#70	MeSH descriptor: [Dermatitis] explode all trees
#71	MeSH descriptor: [Drug Hypersensitivity] explode all trees
#72	MeSH descriptor: [Osteonecrosis] this term only
#73	MeSH descriptor: [Menopause] 1 tree(s) exploded
#74	MeSH descriptor: [Infertility] 1 tree(s) exploded
#75	#48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74
#76	#35 and #47 and #75
#77	MeSH descriptor: [Nausea] this term only
#78	MeSH descriptor: [Nail Diseases] explode all trees
#79	MeSH descriptor: [Foot Dermatoses] explode all trees
#80	MeSH descriptor: [Hand Dermatoses] explode all trees
#81	#79 or #80
#82	#77 or #78 or #81
#83	(#35 and #47 and #82)
#84	#83 not #76

Appendix 1.2. Oral complications

Table 14 – Oral complications: search OVID Medline

Date	**16-04-2012**
Database	Medline OVID
Search Strategy	1. exp NEOPLASMS/ 2. exp LEUKEMIA/ 3. exp LYMPHOMA/ 4. exp RADIOTHERAPY/ 5. Bone Marrow Transplantation/ 6. neoplasm$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name] 7. cancer$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name] 8. (leukaemi$ or leukemi$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name] 9. (tumour$ or tumor$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name] 10. malignan$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name] 11. neutropeni$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name] 12. carcino$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name] 13. adenocarcinoma$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name] 14. lymphoma$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name] 15. (radioth$ or radiat$ or irradiat$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name] 16. (bone adj marrow adj5 transplant$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name] 17. chemo$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name] 18. or/1-17 19. exp STOMATITIS/ 20. Candidiasis, Oral/ 21. stomatitis.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name] 22. mucositis.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name] 23. (oral and cand$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name] 24. (oral adj6 mucos$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade

	name] 25. (oral and fung$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name] 26. (mycosis or mycotic).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name] 27. or/19-26 28. 18 and 27 Cochrane / OHG Search filter for MEDLINE via OVID Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomized trials in MEDLINE: sensitivity maximising version (2009 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of The Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. 1. randomized controlled trial.pt. 2. controlled clinical trial.pt. 3. randomized.ab. 4. placebo.ab. 5. drug therapy.fs. 6. randomly.ab. 7. trial.ab. 8. groups.ab. 9. or/1-8 10. exp animals/ not humans.sh. 11. 9 not 10
Note	Search performed by Anne Littlewood, Trials Search Co-ordinator, Cochrane Oral Health Group

Table 15 – Oral complications: search OVID EMBASE

Date	**16-04-2012**
Database	EMBASE SS via OVID
Search Strategy	1. exp NEOPLASM/ 2. exp LEUKEMIA/ 3. exp LYMPHOMA/ 4. exp RADIOTHERAPY/ 5. exp bone marrow transplantation/ 6. (neoplasm$ or cancer$ or leukemi$ or leukaemi$ or tumour$ or tumor$ or malignan$ or neutropeni$ or carcino$ or adenocarcinoma$ or lymphoma$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] 7. (radioth$ or radiat$ or irradiat$ or radiochemo$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] 8. (bone marrow adj3 transplant$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] 9. chemo$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] 10. or/1-9 11. exp Stomatitis/ 12. Thrush/ 13. (stomatitis or mucositis or (oral and candid$) or (oral adj4 mucositis) or (oral and fung$) or mycosis or mycotic or thrush).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] 14. or/11-13

	15. 10 and 14 Filter for EMBASE via OVID 1. random$.ti,ab. 2. factorial$.ti,ab. 3. (crossover$ or cross over$ or cross-over$).ti,ab. 4. placebo$.ti,ab. 5. (doubl$ adj blind$).ti,ab. 6. (singl$ adj blind$).ti,ab. 7. assign$.ti,ab. 8. allocat$.ti,ab. 9. volunteer$.ti,ab. 10. CROSSOVER PROCEDURE.sh. 11. DOUBLE-BLIND PROCEDURE.sh. 12. RANDOMIZED CONTROLLED TRIAL.sh. 13. SINGLE BLIND PROCEDURE.sh. 14. or/1-13 15. ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/ 16. HUMAN/ 17. 16 and 15 18. 15 not 17 19. 14 not 18
Note	Search performed by Anne Littlewood, Trials Search Co-ordinator, Cochrane Oral Health Group

Table 16 – Oral complications: search CENTRAL

Date	**16-04-2012**
Database	CENTRAL
Search Strategy	1. Exp NEOPLASMS 2. Exp LEUKEMIA 3. Exp LYMPHOMA 4. Exp RADIOTHERAPY 5. Exp BONE MARROW TRANSPLANTATION 6. neoplasm* or cancer* or carcino* or malignan* 7. leukemi* or leukaemia* 8. tumour* or tumor* 9. neutropeni* 10. adenocarcinoma* 11. lymphoma* 12. (radioth* or radiat* or irradiat* or radiochemo*) 13. (bone next marrow next transplant*) 14. chemo* or radiochemo* 15. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14) 16. Exp STOMATITIS 17. MUCOSITIS 18. CANDIDIASIS ORAL 19. stomatitis 20. (stevens next johnson next syndrome) 21. mucositis 22. oral near cand* 23. mouth near cand* 24. oral and fung* 25. mouth and fung* 26. (mycosis or mycotic or thrush) 27. #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 28. #15 AND #27
Note	Search performed by Anne Littlewood, Trials Search Co-ordinator, Cochrane Oral Health Group

Table 17 – Oral complications: search Cochrane Oral Health Trials Register – PaPaS Trial Register

Date	**16-04-2012**
Database	Cochrane Oral Health Trials Register / PaPaS Trials Register
Search Strategy	((neoplasm* OR leukemia OR leukaemia OR leukaemia OR lymphoma* OR plasmacytoma OR "histiocytosis malignant" OR reticuloendotheliosis OR "sarcoma mast cell" OR "Letterer Siwe disease" OR "immunoproliferative small intestine disease" OR "Hodgkin disease" OR "histiocytosis malignant" OR "bone marrow transplant*" OR cancer* Or tumor* OR tumour* OR malignan* OR neutropeni* OR carcino* OR adenocarcinoma* OR radioth* OR radiat* OR radiochemo* OR irradiat* OR chemo*) AND (stomatitis OR "Stevens Johnson syndrome" OR "candidiasis oral" OR mucositis OR (oral AND (cand* OR mucos* OR fung*)) OR mycosis OR mycotic OR thrush))
Note	Search performed by Anne Littlewood, Trials Search Co-ordinator, Cochrane Oral Health Group

Appendix 1.3. Skin toxicity

Table 18 – Skin toxicity: search Medline OVID

Date	**27-4-2012**
Database	Medline OVID
Search Strategy	1. ointments.tw. 2. adjuvant.mp. or Chemotherapy, Adjuvant/ or Radiotherapy, Adjuvant/ 3. Antineoplastic Combined Chemotherapy Protocols/ or Neoadjuvant Therapy/ or neoadjuvant.mp. 4. chemothera$.tw. 5. radiothera$.tw. 6. Radiotherapy/ 7. antineoplastic agents combined/ 8. combined modality therapy/ 9. chemoradi$.mp. 10. CRT.mp. 11. exp Antineoplastic Agents/ 12. or/2-11 13. randomized controlled trial.pt. 14. controlled clinical trial.pt. 15. randomized.ab. 16. placebo.ab. 17. clinical trials as topic.sh. 18. randomly.ab. 19. trial.ti. 20. 13 or 14 or 15 or 16 or 17 or 18 or 19 21. exp animals/ not humans.sh. 22. 20 not 21 23. exp Skin Diseases/ or skin toxicity.mp. 24. 12 and 22 and 23 25. skin washing.mp. 26. "Hygiene"/ 27. "Decontamination"/ 28. hydrophilic cream.mp. or exp Ointments/ 29. exp Anti-Inflammatory Agents/ and Administration,

	Topical/ 30. Emollients/ 31. exp Chemexfoliation/ or topical exfoliating.mp. 32. foot soak$.mp. 33. Magnesium Sulfate/ and Administration, Topical/ 34. Honey/ 35. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 36. 24 and 35 37. skin.tw. 38. derma*.tw. 39. 23 or 37 or 38 40. 39 and 12 and 22 41. 35 and 40 42. washing.tw. 43. hygiene.tw. 44. decontamination.tw. 45. exp Urea/ or urea.mp. 46. salicylic acid.mp. or exp Salicylic Acid/ 47. (anti-inflammatory adj2 cream$).tw. 48. 35 or 42 or 43 or 44 or 45 or 46 or 47 49. 22 and 39 and 48 50. 49 and 12
Note	RCT filter NICE

Table 19 – Skin toxicity: search EMBASE OVID

Date	**4-5-2012**
Database	EMBASE via OVID
Search Strategy	1. exp adjuvant chemotherapy/ 2. adjuvant.tw. 3. exp antineoplastic agent/ 4. exp adjuvant therapy/ 5. neoadjuvant.tw. 6. chemothera$.tw. 7. radiothera$.tw. 8. exp radiotherapy/ 9. multimodality cancer therapy/ 10. chemoradi$.tw. 11. CRT.tw. 12. or/1-11 13. skin.tw. 14. derma*.tw. 15. exp skin disease/ 16. exp skin toxicity/ 17. skin toxicity.tw. 18. or/13-17 19. skin washing.tw. 20. exp hygiene/ 21. Decontamination.tw. 22. hydrophilic cream.tw. 23. exp ointment/ 24. exp antiinflammatory agent/ 25. exp topical drug administration/ 26. exp emollient agent/ 27. esthetic surgery/ 28. foot soak$.tw. 29. exp magnesium sulfate/ 30. exp honey/ 31. or/19-30 32. 19 or 20 or 21 or 22 or 23 or 25 or 26 or 28 or 29 or 30

	33.washing.tw. 34.hygiene.tw. 35.exp Urea/ or urea.mp. 36.salicylic acid.mp or exp Salicylic Acid/ 37.(anti-inflammatory adj2 cream$).tw. 38.32 or 33 or 34 or 35 or 36 or 37 39.12 and 18 and 38 40.limit 39 to "therapy (best balance of sensitivity and specificity)"
Note	Haynes therapy filter built into OVID

Table 20 – Skin toxicity: search CENTRAL

Date	**27-4-2012**
Database	CENTRAL
Search Strategy	The same strategy has been used as for Medline OVID, but without the RCT filter.
Note	

Appendix 1.4. Neuropathy

Table 21 – Neuropathy: search OVID medline

Date	**26-03-2012**
Database	Ovid MEDLINE(R) <1946 to March Week 2 2012>
Search Strategy	1 randomized controlled trial.pt. (321630) 2 controlled clinical trial.pt. (83679) 3 randomized.ab. (226659) 4 placebo.ab. (129223) 5 drug therapy.fs. (1511329) 6 randomly.ab. (163835) 7 trial.ab. (233719) 8 groups.ab. (1080338) 9 or/1-8 (2803360) 10 exp animals/ not humans.sh. (3683920) 11 9 not 10 (2379403) 12 cisplatin/ae, tu, to (14118) 13 cisplatin.tw. (34017) 14 cis-diamminedichloroplatinum.tw. (1966) 15 platinum compounds.tw. or platinum compounds/ae, to, tu (1314) 16 exp organoplatinum compounds/ae, to, tu (5972) 17 (oxaliplatin or carboplatin).tw. (12117) 18 or/12-17 (49164) 19 exp peripheral nervous system diseases/ci, pc (6510) 20 exp central nervous system diseases/ci, pc (85451) 21 (neuropath$ or neuro$ or nerv$).tw. (1334839) 22 or/19-21 (1397491) 23 18 and 22 (4871) 24 exp neuroprotective agents/ (55063) 25 chemoprotect$.mp. (1097)

	26 Protective Agents/ (2722) 27 neuroprotective agents/ (18205) 28 (protect$ or neuroprotect$).tw. (439292) 29 (ORG2766 or ORG 2766).tw. (216) 30 Adrenocorticotropic Hormone/ (42874) 31 (acth or corticotropin or corticotrophin or adrenocorticotropin or adrenocorticotrophin).tw. (42166) 32 glutathione/ or glutathione.tw. (86460) 33 amifostine.tw. or amifostine/ (1554) 34 exp nerve growth factors/ (33391) 35 (nerve adj3 growth adj3 factor$).tw. (14073) 36 neurotrophin 3.tw. (1953) 37 exp antidotes/ (47166) 38 antidote$.tw. (3323) 39 vitamin E.tw. or vitamin E/ (28723) 40 (alc or acetyl l carnitine).tw. (1563) 41 Acetylcarnitine/ (961) 42 or/24-41 (708355) 43 11 and 18 and 22 and 42 (255) 44 43 and 20100801:20120326.(ed). (24)

The search was an update of the search of the review of Albers (2011) and was performed by the Cochrane Neuromuscular Diseases Group.

Table 22 – Neuropathy - glutamine: search OVID medline

Date	**06-08-2012**
Database	Ovid MEDLINE(R) <1946 to March Week 2 2012>
Search Strategy	1 glutamin$.mp. (35097) 2 randomized controlled trial.pt. (333233) 3 controlled clinical trial.pt. (84755) 4 randomized.ab. (248409) 5 placebo.ab. (138066) 6 clinical trials as topic.sh. (161481) 7 randomly.ab. (182013) 8 trial.ti. (106885) 9 2 or 3 or 4 or 5 or 6 or 7 or 8 (798706) 10 exp animals/ not humans.sh. (3760079) 11 9 not 10 (738260) 12 1 and 11 (911) 13 limit 12 to yr="2008 - 2012" (230)

Table 23 – Neuropathy: search OVID EMBASE

Date	**26-03-2012**
Database	Ovid Embase <1974 to 2012 Week 12>
Search Strategy	1 crossover-procedure/ (33346) 2 double-blind procedure/ (110282) 3 randomized controlled trial/ (320882) 4 single-blind procedure/ (15595) 5 (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).tw. (1131808) 6 or/1-5 (1209480) 7 human/ (13272195) 8 6 and 7 (878656)

9 nonhuman/ or human/ (16368940)
10 6 not 9 (225888)
11 8 or 10 (1104544)
12 CISPLATIN/ae, to [Adverse Drug Reaction, Drug Toxicity] (24407)
13 cisplatin.tw. (44721)
14 cis-diamminedichloroplatinum.mp. (2219)
15 Platinum Derivative/ae, to [Adverse Drug Reaction, Drug Toxicity] (1089)
16 (platinum compound or platinum derivative).mp. (6286)
17 Platinum Complex/ae, to [Adverse Drug Reaction, Drug Toxicity] (779)
18 oxaliplatin.tw. or OXALIPLATIN/ (15401)
19 carboplatin.tw. or CARBOPLATIN/ (37050)
20 or/12-19 (99004)
21 exp Peripheral Neuropathy/ (43660)
22 (neuropath$ or neuro$ or nerv$).mp. (2593926)
23 21 or 22 (2594425)
24 20 and 23 (18426)
25 Neuroprotective Agent/ (7723)
26 Neuroprotection/ (37035)
27 (chemoprotect$ or neuroprotect$ or protect$).mp. (667912)
28 (ORG 2766 or ORG2766).mp. (455)
29 CORTICOTROPIN/ (57932)
30 (acth or corticotropin or corticotrophin or adrenocorticotropin or adrenocorticotrophin).mp. (80317)
31 GLUTATHIONE/ or Glutathione.tw. (104469)
32 amifostine.tw. or AMIFOSTINE/ (3301)
33 Nerve Growth Factor/ (19988)
34 (nerve adj growth adj factor).tw. (16036)
35 neurotrophin 3.tw. or Neurotrophin 3/ (3656)
36 antidote$.tw. or Antidote/ (7858)
37 vitamin E.tw. or Alpha Tocopherol/ (56592)
38 (ALC or acetly l carnitine).tw. (1633)
39 or/25-38 (903813)
40 11 and 20 and 24 and 39 (200)
41 40 and 201033:201212.(em). (26)
42 crossover-procedure.sh. (33346)
43 double-blind procedure.sh. (110282)
44 single-blind procedure.sh. (15595)
45 randomized controlled trial.sh. (320882)
46 (random$ or crossover$ or cross over$ or placebo$ or (doubl$ adj blind$) or allocat$).tw,ot. (873513)
47 trial.ti. (132844)
48 or/42-47 (1002662)
49 (animal/ or nonhuman/ or animal experiment/) and human/ (1165711)
50 animal/ or nonanimal/ or animal experiment/ (3360567)
51 50 not 49 (2804520)
52 48 not 51 (919835)
53 limit 52 to embase (716499)
54 53 and 20 and 24 and 39 (185)
55 54 not 40 (12)
56 54 and 41 (22)
57 55 or 56 (34)

The search was an update of the search of the review of Albers (2011) and was performed by the Cochrane Neuromuscular Diseases Group.

Table 24 – Neuropathy - glutamine: search EMBASE (Embase.com)

Date	**06-08-2012**
Database	Embase.com
Search Strategy	#1 'glutamine'/exp OR glutamin*:ab,ti #2 #1 AND ([cochrane review]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [2008-2012]/py

Table 25 – Neuropathy: search CENTRAL

Date	**26-03-2012**
Database	CENTRAL (The Cochrane Library, Issue 4, 2012).
Search Strategy	ID Search #1 (cisplatin OR cis-diaminedichloroplatinum OR platinum OR organoplatinum OR oxaliplatin OR carboplatin) #2 (therap* OR adverse OR toxic* OR neurotoxic*) #3 (#1 AND #2) #4 (neuroprotect* OR chemoprotect* OR protect* OR org2766 OR corticotrop* OR glutathione OR amifostine OR (growth NEXT factor*) OR neurotrophin3 OR neurotropin3 OR antidote* OR (vitamin NEXT E)) #5 MeSH descriptor Acetylcarnitine, this term only #6 (acetyl l carnitine) or alc #7 (#4 OR #5 OR #6) #8 (neuropath* OR nerv* OR neurotox* OR neurol*) #9 MeSH descriptor Peripheral Nervous System Diseases, this term only #10 MeSH descriptor Peripheral Nerves, this term only #11 (#8 OR #9 OR #10) #12 (#3 AND #7 AND #11)

Table 26 – Neuropathy - glutamine: search CENTRAL

Database	CENTRAL (The Cochrane Library, Issue 4, 2012).
Search Strategy	#1 glutamin*:ti,ab

Appendix 1.5. Neutropenia and neutropenic fever

Table 27 – Neutropenia: search OVID medline – G(M)CSF, prophylactic antifungals, prophylactic antibiotics and therapeutic antibiotics (oral versus IV)

Date	**05-07-2012**
Database	Medline OVID
Search Strategy	1. adjuvant.mp. or Chemotherapy, Adjuvant/ or Radiotherapy, Adjuvant/ 2. Antineoplastic Combined Chemotherapy Protocols/ or Neoadjuvant Therapy/ or neoadjuvant.mp. 3. chemothera$.tw. 4. radiothera$.tw. 5. Radiotherapy/ 6. antineoplastic agents combined/ 7. combined modality therapy/ 8. chemoradi$.mp. 9. CRT.mp. 10. exp Antineoplastic Agents/ 11. COLONY-STIMULATING FACTORS/ 12. COLONY-STIMULATING FACTORS/ 13. exp GRANULOCYTE COLONY-STIMULATING FACTOR/ 14. exp GRANULOCYTE COLONY-STIMULATING FACTOR/ 15. MACROPHAGE COLONY-STIMULATING FACTOR/ 16. MACROPHAGE COLONY-STIMULATING FACTOR/ 17. (rhg?csf$ or rhgm?csf$).tw,kf,ot.

18. (rmethug$ or rhmethug$).tw,kf,ot.
19. (rhug$ or rhugm$).tw,kf,ot.
20. (gcsf$ or g-csf$).tw,kf,ot.
21. (gm-csf$ or gmcsf$).tw,kf,ot.
22. (granulo?yt$ adj3 fa?tor$).tw,kf,ot.
23. (ma?rophag$ adj5 fa?tor$).tw,kf,ot.
24. csf.ti.
25. FILGRASTIM$.tw,hw,nm,kf.
26. NEUPOGEN$.tw,hw,nm,kf.
27. LENOGRASTIM$.tw,hw,nm,kf.
28. GRANOCYTE$.tw,hw,nm,kf.
29. EUPROTIN$.tw,hw,nm,kf.
30. PEG?FILGRASTIM$.tw,hw,nm,kf.
31. NEULASTA$.tw,hw,nm,kf.
32. LEUKINE$.tw,hw,nm,kf.
33. MOLGRAMOSTIN$.tw,hw,nm,kf.
34. Mielogen$.tw,kf,ot.
35. LEUCOMAX$.tw,hw,nm,kf.
36. or/1-10
37. or/11-35
38. neutropen*.tw.
39. exp Neutropenia/
40. 38 or 39
41. 36 and 37 and 40
42. randomized controlled trial.pt.
43. 41 and 42
44. limit 43 to yr="2008 -Current" ➔ G(M)CSF treatment neutropenia RCT
45. limit 43 to yr="2002 - 2007" ➔ G(M)CSF treatment neutropenia RCT
46. exp ANTI-BACTERIAL AGENTS/
47. (antibacterial$ or anti-bacterial$).tw,kf,ot.
48. antibio$.tw,kf,ot.
49. (antimicrobial$ or anti-microbial$).tw,kf,ot.
50. (anti-mycobacterial$ or antimycobacterial$).tw,kf,ot.
51. bacteriocid$.tw,kf,ot.
52. (selective$ adj3 decontaminat$).tw,kf,ot.
53. ANTIBIOTIC PROPHYLAXIS/
54. exp QUINOLONE/
55. fluoroquinolones$.tw,kf,ot.
56. ciprofloxa?in$.tw,kf,ot.
57. ofloxa?in$.tw,kf,ot.
58. norfloxa?in$.tw,kf,ot.
59. enoxa?in$.tw,kf,ot.
60. pefloxa?in$.tw,kf,ot.
61. exp TRIMETHOPRIM/
62. trimethoprim$.tw,kf,ot.
63. sulfamethoxazol$.tw,kf,ot.
64. trimethoprim-sulfamethoxazol$.tw,kf,ot.
65. tmp-smz$.tw,kf,ot.
66. exp POLYMYXINS/
67. colistin$.tw,kf,ot.
68. (nalidixic$ adj3 acid$).tw,kf,ot.
69. polymyxin$.tw,kf,ot.
70. AMINOGLYCOSIDES/
71. GENTAMICINS/
72. gentami?in$.tw,kf,ot.
73. exp NEBRAMYCIN/
74. tobramy?in$.tw,kf,ot.
75. NEOMYCIN/
76. neomy?in$.tw,kf,ot.
77. VANCOMYCIN/
78. vancomy?in$.tw,kf,ot.

79. ROXITHROMYCIN/
80. roxithromy?in$.tw,kf,ot.
81. RIFAMPIN/
82. (rifampin$ or rifampicin$).tw,kf,ot.
83. BETA-LACTAMS/
84. beta-lactam$.tw,kf,ot.
85. PENICILLINS/
86. peni?illin$.tw,kf,ot.
87. AMOXICILLIN/
88. amoxi?illin$.tw,kf,ot.
89. CEPHALOTHIN/
90. (cephalot?in$ or cefalot?in$).tw,kf,ot.
91. CEFTRIAXONE/
92. ceftriaxone$.tw,kf,ot.
93. TICARCILLIN/
94. ticar?illin$.tw,kf,ot.
95. framycetin$.tw,kf,ot.
96. from 43 keep 1-353
97. from 44 keep 1-50
98. from 45 keep 1-80
99. or/46-95
100. 36 and 40 and 42 and 99
101. exp Infusions, Parenteral/
102. parenteral.ti,ab.
103. exp Injections/
104. injection$.ti,ab.
105. exp Infusion Pumps/
106. infusion.ti,ab.
107. exp Infusions, Intravenous/ or exp Injections, Intravenous/
108. intravenous.ti,ab.
109. exp Administration, Oral/
110. oral.ti,ab.
111. or/101-110
112. 100 and 111
113. exp Antifungal Agents/ or exp Fluconazole/
114. fluconazol$.ti,ab.
115. fungizone.mp. or exp Amphotericin B/
116. exp Nystatin/
117. nystatin.ti,ab.
118. 113 or 114 or 115 or 116 or 117
119. 36 and 40 and 42 and 111
120. 118 and 119
121. exp Antibiotic Prophylaxis/
122. exp Chemoprevention/
123. prevent*.mp.
124. prophyla*.mp.
125. 121 or 122 or 123 or 124
126. 99 or 118
127. 36 and 40 and 99 and 111
128. ("systematic review".ti. or "meta-analysis".pt. or "meta-analysis".ti. or "systematic literature review".ti. or ("systematic review".tw. and "review".pt.) or "consensus development conference".pt. or "practice guideline".pt. or "cochrane database syst rev".jw. or "acp journal club".jw. or "health technol assess".jw. or "evid rep technol assess summ".jw. or (("evidence based".ti. or "evidence-based medicine".sh. or best practice*.ti. or "evidence synthesis".tw.) and ("review".pt. or "diseases category".sh. or "behavior and behavior mechanisms".sh. or "therapeutics".sh. or "evaluation studies".pt. or "validation studies".pt. or "guideline".pt.)) or (("systematic" or "systematically" or "critical" or "study selection" or (("predetermined" or "inclusion") and criteri*) or exclusion criteri* or "main outcome measures" or "standard of care" or "standards of care").tw. and ((survey or surveys or

	overview* or review or reviews or search* or handsearch or analysis or critique or appraisal).tw. or (reduction.tw. and (risk.sh. or risk.tw.) and (death or recurrence).tw.)) and ((literature or articles or publications or publication or bibliography or bibliographies or published or unpublished or citation or citations or database or internet or textbooks or references or scales or papers or datasets or trials or meta-analy* or (clinical and studies)).tw. or "treatment outcome".sh. or "treatment outcome".tw.))) not ((letter or "newspaper article" or comment).pt. or (animal/ not (animal/ and human/))) 129. 127 and 128 130. 36 and 40 and 118 and 125 and 128 ➔antifungal prophylaxis neutropenia systematic reviews 131. 127 and 42 132. limit 131 to yr="2005 -Current" ➔ antibiotics neutropenia RCT 133. 36 and 40 and 42 and 118 and 125 ➔antifungal prophylaxis neutropenia RCT
Note	Search for SRs and RCTs for study question re G(M)CSF, prophylactic antifungals, prophylactic antibiotics and therapeutic antibiotics (oral versus IV). SR methodological filter NICE. This is a general search strategy for neutropenic patients after either chemo- or radiotherapy. Sub questions are indicated in bold

Table 28 – Neutropenia: search EMBASE ovid - G(M)CSF, prophylactic antifungals, prophylactic antibiotics and therapeutic antibiotics (oral versus IV)

Date	**06-07-2012**
Database	Embase OVID
Search Strategy	1. exp adjuvant chemotherapy/ 2. adjuvant.tw. 3. exp antineoplastic agent/ 4. exp adjuvant therapy/ 5. neoadjuvant.tw. 6. chemothera$.tw. 7. radiothera$.tw. 8. exp radiotherapy/ 9. multimodality cancer therapy/ 10. chemoradi$.tw. 11. CRT.tw. 12. colony stimulating factor/ 13. exp granulocyte colony stimulating factor/ 14. exp recombinant granulocyte colony stimulating factor/ 15. exp granulocyte macrophage colony stimulating factor/ 16. (rhg?csf$ or rhgm?csf$).tw,ot. 17. (rmethug$ or rhmethug$).tw,ot. 18. (rhug$ or rhugm$).tw,ot. 19. (gcsf$ or g-csf$).tw,ot. 20. (gm-csf$ or gmcsf$).tw,ot. 21. (granulo?yt$ adj3 fa?tor$).tw,ot. 22. (ma?rophag$ adj5 fa?tor$).tw,ot. 23. csf.ti. 24. FILGRASTIM$.tw,hw. 25. NEUPOGEN$.tw,hw.

26. LENOGRASTIM$.tw,hw.
27. GRANOCYTE$.tw,hw.
28. EUPROTIN$.tw,hw.
29. PEG?FILGRASTIM$.tw,hw.
30. NEULASTA$.tw,hw.
31. LEUKINE$.tw,hw.
32. MOLGRAMOSTIN$.tw,hw.
33. Mielogen$.tw,ot.
34. LEUCOMAX$.tw,hw.
35. or/1-11
36. or/12-34
37. neutropen*.tw.
38. exp Neutropenia/
39. or/37-38
40. 35 and 36 and 39
41. randomized controlled trial/
42. 40 and 41
43. limit 42 to yr="2008 -Current"
44. limit 42 to yr="2002 - 2007"
45. exp antiinfective agent/
46. (antibacterial$ or anti-bacterial$).tw,ot.
47. antibio$.tw,ot.
48. (antimicrobial$ or anti-microbial$).tw,ot.
49. (anti-mycobacterial$ or antimycobacterial$).tw,ot.
50. bacteriocid$.tw,ot.
51. (selective$ adj3 decontaminat$).tw,ot.
52. exp quinolone/
53. fluoroquinolones$.tw,ot.
54. ciprofloxa?in$.tw,ot.
55. ofloxa?in$.tw,ot.
56. norfloxa?in$.tw,ot.
57. enoxa?in$.tw,ot.
58. pefloxa?in$.tw,ot.
59. exp trimethoprim/
60. trimethoprim$.tw,ot.
61. sulfamethoxazol$.tw,ot.
62. trimethoprim-sulfamethoxazol$.tw,ot.
63. tmp-smz$.tw,ot.
64. exp polymyxin/
65. colistin$.tw,ot.
66. (nalidixic$ adj3 acid$).tw,ot.
67. polymyxin$.tw,ot.
68. exp aminoglycoside/
69. exp gentamicin/
70. gentami?in$.tw,ot.
71. exp nebramycin/
72. tobramy?in$.tw,ot.
73. exp neomycin/
74. neomy?in$.tw,ot.
75. VANCOMYCIN/
76. vancomy?in$.tw,ot.
77. ROXITHROMYCIN/
78. roxithromy?in$.tw,ot.
79. RIFAMPIN/
80. (rifampin$ or rifampicin$).tw,ot.
81. exp beta lactam/
82. beta-lactam$.tw,ot.
83. exp penicillin derivative/
84. peni?illin$.tw,ot.
85. AMOXICILLIN/
86. amoxi?illin$.tw,ot.
87. exp cefalotin/

	88. (cephalot?in$ or cefalot?in$).tw,ot. 89. exp ceftriaxone/ 90. ceftriaxone$.tw,ot. 91. ticarcillin/ 92. ticar?illin$.tw,ot. 93. framycetin$.tw,ot. 94. or/45-93 95. 35 and 36 and 41 and 94 96. exp parenteral drug administration/ 97. parenteral.ti,ab. 98. exp injection/ 99. injection$.ti,ab. 100. exp infusion/ 101. infusion.ti,ab. 102. exp intravenous drug administration/ 103. intravenous.ti,ab. 104. exp oral drug administration/ 105. oral.ti,ab. 106. or/96-105 107. 94 and 106 108. exp antifungal agent/ 109. exp fluconazole/ 110. fluconazol$.ti,ab. 111. amphotericin B deoxycholate/ 112. fungizone.mp. 113. exp nystatin/ 114. nystatin.ti,ab. 115. or/108-114 116. 35 and 36 and 41 and 115 117. 115 and 116 118. exp prophylaxis/
	119. exp chemoprophylaxis/ 120. prevent*.mp. 121. prophyla*.mp. 122. or/118-121 123. 35 and 36 and 94 and 122 124. (exp Meta Analysis/ or ((meta adj analy$) or metaanalys$).tw. or (systematic adj (review$1 or overview$1)).tw. or (cancerlit or cochrane or embase or (psychlit or psyclit) or (psychinfo or psycinfo) or (cinahl or cinhal) or science citation index or bids).ab. or (reference lists or bibliograph$ or hand-search$ or manual search$ or relevant journals).ab. or ((data extraction or selection criteria).ab. and review.pt.)) not ((letter or editorial).pt. or ((animal/ not animal/) and human/)) 125. 35 and 39 and 41 and 115 and 106 126. 35 and 39 and 115 and 122 127. 126 and 124 ➔ radio/chemo + neutropenia + antifungal + prophylaxis + SR 128. 126 and 41➔ radio/chemo + neutropenia + antifungal + prophylaxis + RCT 129. 46 or 47 or 48 or 49 or 50 or 51 or 53 or 54 or 55 or 56 or 57 or 58 or 60 or 61 or 62 or 63 or 65 or 66 or 67 or 70 or 72 or 74 or 76 or 78 or 80 or 82 or 84 or 86 or 88 or 90 or 92 or 93 130. 35 and 39 and 41 and 129 and 106 ➔ radio/chemo + neutropenia + drug administration + RCT 131. 35 and 39 and 129 and 122 132. 131 and 124 133. 131 and 41 ➔ radio/chemo + neutropenia + AB + prophylaxis + RCT 134. limit 133 to yr="2005 -Current"
Note	Search for SRs and RCTs for study question re re G(M)CSF, prophylactic antifungals, prophylactic antibiotics and therapeutic antibiotics (oral versus IV).

	NICE SR filter is used. This is a general search strategy for neutropenic patients after either chemo or radiotherapy. Sub questions are indicated in bold.

Table 29 – Neutropenia: search Cochrane Database of Systematic reviews - prophylactic antifungals, prophylactic antibiotics and therapeutic antibiotics (oral versus IV)

Date	**June 28, 2012**
Database	Cochrane Database of Systematic Reviews
Search Strategy	(antifungal):ti,ab,kw or (neutropenia):ti,ab,kw
Note	Search for SRs for study question re prophylactic antifungals, prophylactic antibiotics and therapeutic antibiotics (oral versus IV)

Table 30 – Neutropenia: search Medline OVID – inpatient versus outpatient care

Date	**15-08-2012**
Database	Medline OVID
Search Strategy	1. (((agranulocytosis/ or neutropenia/ or leukopenia/) and (fever/ or "fever of unknown origin".mp.)) or (febrile adj5 (neutropen* or granulocytop* or agranulocyto* or leukocytop??ni*)).ti,ab.) and (exp Anti-Bacterial Agents/ or exp Bacterial Infections/) and (Ambulatory Care/ or Home Care Services/ or Outpatient Clinics, Hospital/ or inpatients/ or outpatients/ or "length of stay"/ or patient discharge/ or (early adj5 discharg*).ti,ab. or (domiciliary or ambulatory or inpatient* or outpatient* or "outpatient*" or admission* or admitted or home).mp 2. ((randomized controlled trial or controlled clinical trial).pt. or drug therapy.fs. or (randomized or placebo or randomly or trial or groups).ab.) not (animals/ not (humans/ and animals/)) 3. 1 and 2 4. (randomized controlled trial or controlled clinical trial).pt. not (animals/ not (humans/ and animals/)) 5. 1 and 4 6. limit 3 to yr="2010 -Current" 7. 3 not 5
Note	Search for study question re inpatient versus outpatient treatment. Cochrane highly sensitive RCT filter

Table 31 – Neutropenia: search EMBASE OVID – inpatient versus outpatient care

Date	**15-08-2012**
Database	Embase OVID
Search Strategy	1. crossover procedure/ or double-blind procedure/ or single-blind procedure/ or randomized controlled trial/ 2. (crossover$ or cross over$ or placebo$ or (doubl$ adj blind$) or allocat$).ti,ab,ot. or random$.ti,ab,ab. or trial$.ti. 3. 1 or 2 4. (Febrile Neutropenia/ or ((leukopenia/ or agranulocytosis/ or granulocytopenia/ or neutropenia/) and (fever/ or pyrexia idiopathica/)) or (febrile adj5 (neutropen* or granulocytop* or agranulocyto* or leukocytop??ni*)).ti,ab.) and (exp Antibiotic Agent/ or exp Bacterial Infection/) and (ambulatory care/ or ambulatory care nursing/ or home care/ or home intravenous therapy/ or hospital care/ or "length of stay"/ or outpatient/ or exp hospital patient/ or outpatient care/ or hospital department/ or outpatient department/ or oncology ward/ or child hospitalization/ or hospital admission/ or hospital discharge/ or hospitalization/ or hospital readmission/ or (early adj5 discharg*).ti,ab. or (domiciliary or ambulatory or inpatient* or outpatient* or "outpatient*" or admission* or admitted or home).mp.)

	5. 3 and 4 6. limit 5 to yr="2010 -Current"
Note	Search for study question re inpatient versus outpatient treatment . 2012 version of broad selection filter for identification of RCT's in Embase

Table 32 – Neutropenia: search Cochrane Database of Systematic reviews – inpatient versus outpatient care

Date	**June 28, 2012**
Database	Cochrane Database of Systematic Reviews
Search Strategy	(neutropenia outpatient):ti,ab,kw
Note	Search for SRs for study question re inpatient versus outpatient treatment

Appendix 1.6. Radioproctitis

Table 33 – Radioproctitis: search OVID Medline

Date	**10-01-2012**
Database	Ovid MEDLINE(R) <1946 to April Week 2 2012>
Search Strategy	1. exp Proctitis/ 2. (proctitis or proctitides or proctopathy or proctocolitis or proctosigmoiditis or rectitis or rectocolitis or rectocolitides or rectosigmoiditis).mp. 3. ((rect* or anus or anal or anorectal) adj5 (injur* or inflam* or diseas* or bleed* or rupture* or discharge* or pain* or discomfort* or irritat*)).mp. 4. 1 or 2 or 3 5. exp Radiotherapy/ 6. radiotherapy.fs. 7. radiation effects.fs. 8. exp Radiation Injuries/ 9. (radiotherap* or radiat* or irradiat* or radiochemo* or chemoradio*).mp. 10. 5 or 6 or 7 or 8 or 9 11. 4 and 10 12. randomized controlled trial.pt. 13. controlled clinical trial.pt. 14. randomized.ab. 15. placebo.ab. 16. drug therapy.fs. 17. randomly.ab. 18. trial.ab. 19. groups.ab. 20. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 21. 11 and 20 22. exp animals/ not humans.sh. 23. 21 not 22

Table 34 – Radioproctitis: search OVID EMBASE

Date	**10-01-2012**
Database	Ovid MEDLINE(R) <2007 to 2012 week 01>
Search Strategy	1 proctitis/ 2 (proctitis or proctitides or proctopathy or proctocolitis or proctosigmoiditis or rectitis or rectocolitis or rectocolitides or rectosigmoiditis).mp. 3 ((rect* or anus or anal or anorectal) adj5 (injur* or inflam* or diseas* or bleed* or rupture* or discharge* or pain* or discomfort* or irritat*)).mp. 4 1 or 2 or 3 5 exp radiotherapy/ 6 rt.fs. 7 exp radiation injury/ 8 radiation response/ 9 (radiotherap* or radiat* or irradiat* or radiochemo* or chemoradio*).mp. 10 5 or 6 or 7 or 8 or 9 11 4 and 10 12 crossover procedure/ 13 double-blind procedure/ 14 randomized controlled trial/ 15 single-blind procedure/ 16 random*.mp. 17 factorial*.mp. 18 (crossover* or cross over* or cross-over*).mp. 19 placebo*.mp. 20 (double* adj blind*).mp. 21 (singl* adj blind*).mp. 22 assign*.mp. 23 allocat*.mp. 24 volunteer*.mp. 25 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 26 11 and 25 27 (exp Animal/ or Nonhuman/ or exp Animal Experiment/) not Human/ 28 26 not 27

Table 35 – Radioproctitis: search CENTRAL

Date	**10-01-2012**
Database	Ovid MEDLINE(R) <Issue 4 2011>
Search Strategy	#1 MeSH descriptor Proctitis explode all trees #2 (proctitis or proctitides or proctopathy or proctocolitis or proctosigmoiditis or rectitis or rectocolitis or rectocolitides or rectosigmoiditis) #3 ((rect* or anus or anal or anorectal) near/5 (injur* or inflam* or diseas* or bleed* or rupture* or discharge* or pain* or discomfort* or irritat*)) #4 (#1 OR #2 OR #3) #5 MeSH descriptor Radiotherapy explode all trees #6 Any MeSH descriptor with qualifier: RT #7 Any MeSH descriptor with qualifier: RE #8 MeSH descriptor Radiation Injuries explode all trees #9 (radiotherap* or radiat* or irradiat* or radiochemo* or chemoradio*) #10 (#5 OR #6 OR #7 OR #8 OR #9) #11 (#4 AND #10)

Appendix 1.7. Infertility

Table 36 – Infertility: search OVID Medline GnRH analogue

Date	**11-04-2012**
Database	Ovid MEDLINE(R) <2007 to Dec week 4 2011>
Search Strategy	1 adjuvant.mp. or Chemotherapy, Adjuvant/ or Radiotherapy, Adjuvant/ (100671) 2 Antineoplastic Combined Chemotherapy Protocols/ or Neoadjuvant Therapy/ or neoadjuvant.mp. (102772) 3 chemothera$.tw. (234330) 4 radiothera$.tw. (100245) 5 Radiotherapy/ (32722) 6 antineoplastic agents combined/ (92098) 7 combined modality therapy/ (129813) 8 chemoradi$.mp. (10667) 9 CRT.mp. (6132) 10 exp Antineoplastic Agents/ (732641) 11 or/1-10 (1065824) 12 randomized controlled trial.pt. (324361) 13 controlled clinical trial.pt. (83883) 14 randomized.ab. (239836) 15 placebo.ab. (134839) 16 clinical trials as topic.sh. (159206) 17 randomly.ab. (176381) 18 trial.ti. (103208) 19 12 or 13 or 14 or 15 or 16 or 17 or 18 (778077) 20 exp animals/ not humans.sh. (3696525) 21 19 not 20 (719537) 22 Infertility, Female/ (21829) 23 infertil*.ti,ab. (37526) 24 Gonadotropin-Releasing Hormone/ (23141) 25 Gonadotropin-Releasing Hormone.mp. (26900) 26 GnRH.mp. (15993) 27 Gn-RH.mp. (373) 28 Luteinizing Hormone-Releasing Hormone.mp. (4980) 29 Luteinizing Hormone Releasing Hormone.mp. (4980) 30 LHRH.mp. (8037) 31 LH-Releasing Hormone.mp. (720) 32 LH Releasing Hormone.mp. (720) 33 LH-RH.mp. (3224) 34 GnRH-a.mp. (852) 35 (LH-FSH Releasing Hormone or LH FSH Releasing Hormone).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (27) 36 (Gonadoliberin or Gonadorelin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (286) 37 LFRH.mp. (3) 38 LHFSH Releasing Hormone.mp. (0) 39 Releasing Hormone, LHFSH.mp. (0) 40 LHFSHRH.mp. (3) 41 Luliberin.mp. (169) 42 Dirigestran.mp. (5) 43 Kryptocur.mp. (6) 44 Gonadorelin Acetate.mp. (3) 45 Gonadorelin Hydrochloride.mp. (8) 46 Cystorelin.mp. (17) 47 Factrel.mp. (9) 48 (Lupron Depot or Trelstar LA or Lupron or Lupron Depot or Lupron Depot-PED or Synarel or Zoladex or Supprelin LA or Eligard or Factrel or Lupron Depot-Gyn or Trelstar or Trelstar Depot or Vantas or Viadur).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (542) 49 22 or 23 (49442) 50 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or

	42 or 43 or 44 or 45 or 46 or 47 or 48 (34749) 51 11 and 21 and 49 and 50 (116) 52 limit 51 to yr="2010 -Current" (11)

Table 37 – Infertility: search OVID Medline other interventions for fertility preservation

Date	**28-03-2012**
Database	Ovid MEDLINE(R) <1946 to March Week 2 2012>
Search Strategy	1 adjuvant.mp. or Chemotherapy, Adjuvant/ or Radiotherapy, Adjuvant/ (100133) 2 Antineoplastic Combined Chemotherapy Protocols/ or Neoadjuvant Therapy/ or neoadjuvant.mp. (102145) 3 chemothera$.tw. (233045) 4 radiothera$.tw. (99640) 5 Radiotherapy/ (32590) 6 antineoplastic agents combined/ (91547) 7 combined modality therapy/ (129291) 8 chemoradi$.mp. (10488) 9 CRT.mp. (6076) 10 exp Antineoplastic Agents/ (729176) 11 or/1-10 (1060703) 12 randomized controlled trial.pt. (322347) 13 controlled clinical trial.pt. (83717) 14 randomized.ab. (238425) 15 placebo.ab. (134006) 16 clinical trials as topic.sh. (158452) 17 randomly.ab. (175345) 18 trial.ti. (101959) 19 12 or 13 or 14 or 15 or 16 or 17 or 18 (773422) 20 exp animals/ not humans.sh. (3683920) 21 19 not 20 (715180)
	22 infertility, Female/ or infertility/ or infertility, Male/ (45143) 23 infertil*.ti,ab. (37377) 24 ((fertility or reproduc*) adj5 (preserv* or sparing or saving)).mp. (2888) 25 prevent*.mp. (836218) 26 22 or 23 (61175) 27 25 and 26 (2650) 28 24 or 27 (5481) 29 11 and 21 and 28 (86)

Table 38 – Infertility: search OVID EMBASE GnRH analogue

Date	**11-04-2012**
Database	OVID Embase 1980 to Present
Search Strategy	1 adjuvant.ti,ab. (98627) 2 adjuvant.mp. or exp adjuvant therapy/ or exp adjuvant chemotherapy/ or exp cancer adjuvant therapy/ (150883) 3 exp antineoplastic agent/ (1193219) 4 neoadjuvant.ti,ab. (18342) 5 chemothera$.tw. (302940) 6 radiothera$.tw. (128250) 7 exp radiotherapy/ (307458) 8 antineoplastic agent/ (196758) 9 exp multimodality cancer therapy/ (57871) 10 chemoradi$.ti,ab. (15135) 11 CRT.ti,ab. (10356) 12 exp antineoplastic agent/ (1193219) 13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (1628685) 14 (Clinical trial/ or Randomized controlled trial/ or Randomization/ or Single blind procedure/ or Double

	blind procedure/ or Crossover procedure/ or Placebo/ or Randomi?ed controlled trial$.tw. or Rct.tw. or Random allocation.tw. or Randomly allocated.tw. or Allocated randomly.tw. or (allocated adj2 random).tw. or Single blind$.tw. or Double blind$.tw. or ((treble or triple) adj blind$).tw. or Placebo$.tw. or Prospective study/ or (random* adj3 trial*).ti,ab. or (randomized or placebo or randomly or trial or groups).ab.) not (Case study/ or review.pt. or Case report.tw. or Abstract report/ or letter/ or (exp animal/ not (exp animal/ and exp human/))) (2196096)
15	exp female infertility/ (32374)
16	infertil*.ti,ab. (46146)
17	Gonadotropin-Releasing Hormone/ (26706)
18	Gonadotropin-Releasing Hormone.mp. (11217)
19	GnRH.mp. (19211)
20	Gn-RH.mp. (438)
21	Luteinizing Hormone-Releasing Hormone.mp. (4874)
22	Luteinizing Hormone Releasing Hormone.mp. (4874)
23	LHRH.mp. (6896)
24	LH-Releasing Hormone.mp. (599)
25	LH Releasing Hormone.mp. (599)
26	LH-RH.mp. (3131)
27	GnRH-a.mp. (1028)
28	(LH-FSH Releasing Hormone or LH FSH Releasing Hormone).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (28)
29	(Gonadoliberin or Gonadorelin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (42618)
30	LFRH.mp. (1)
31	LHFSH Releasing Hormone.mp. (0)
32	Releasing Hormone, LHFSH.mp. (0)
33	LHFSHRH.mp. (1)
34	Luliberin.mp. (180)
35	Dirigestran.mp. (5)
36	Kryptocur.mp. (36)
37	Gonadorelin Acetate.mp. (158)
38	Gonadorelin Hydrochloride.mp. (8)
39	Cystorelin.mp. (50)
40	Factrel.mp. (137)
41	(Lupron Depot or Trelstar LA or Lupron or Lupron Depot or Lupron Depot-PED or Synarel or Zoladex or Supprelin LA or Eligard or Factrel or Lupron Depot-Gyn or Trelstar or Trelstar Depot or Vantas or Viadur).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (3515)
42	15 or 16 (66165)
43	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 (51598)
44	13 and 14 and 42 and 43 (862)
45	limit 44 to yr="2010 -Current" (112)

Table 39 – Infertility: search OVID EMBASE other interventions for fertility preservation

Date	**28-03-2012**	
Database	OVID Embase 1980 to Present	
Search Strategy	1	adjuvant.ti,ab. (98006)
	2	adjuvant.mp. or exp adjuvant therapy/ or exp adjuvant chemotherapy/ or exp cancer adjuvant therapy/ (150004)
	3	exp antineoplastic agent/ (1187031)
	4	neoadjuvant.ti,ab. (18165)
	5	chemothera$.tw. (300809)
	6	radiothera$.tw. (127628)
	7	exp radiotherapy/ (306010)
	8	antineoplastic agent/ (195948)
	9	exp multimodality cancer therapy/ (57795)
	10	chemoradi$.ti,ab. (15011)
	11	CRT.ti,ab. (10269)
	12	exp antineoplastic agent/ (1187031)
	13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (1620540)
	14	infertil*.ti,ab. (45988)
	15	infertility/ or female infertility/ or male infertility/ (62975)
	16	((fertility or reproduc*) adj5 (preserv* or sparing or saving)).mp. (4501)
	17	prevent*.mp. (1138404)
	18	14 or 15 (76223)
	19	17 and 18 (3765)
	20	16 or 19 (8175)
	21	(Clinical trial/ or Randomized controlled trial/ or Randomization/ or Single blind procedure/ or Double blind procedure/ or Crossover procedure/ or Placebo/ or Randomi?ed controlled trial$.tw. or Rct.tw. or Random allocation.tw. or Randomly allocated.tw. or Allocated randomly.tw. or (allocated adj2 random).tw. or Single blind$.tw. or Double blind$.tw. or ((treble or triple) adj blind$).tw. or Placebo$.tw. or Prospective study/ or (random* adj3 trial*).ti,ab. or (randomized or placebo or randomly or trial or groups).ab.) not (Case study/ or review.pt. or Case report.tw. or Abstract report/ or letter/ or (exp animal/ not (exp animal/ and exp human/))) (2187140)
	22	13 and 20 and 21 (410)

Table 40 – Infertility: search CENTRAL GnRH analogue

Date	**11-04-2012**	
Database	CENTRAL	
Search Strategy	#1	MeSH descriptor Chemotherapy, Adjuvant explode all trees
	#2	MeSH descriptor Radiotherapy, Adjuvant explode all trees
	#3	(adjuvant)
	#4	(#1 OR #2 OR #3)
	#5	MeSH descriptor Antineoplastic Combined Chemotherapy Protocols explode all trees
	#6	MeSH descriptor Neoadjuvant Therapy explode all trees
	#7	(neoadjuvant.)
	#8	(#5 OR #6 OR #7)
	#9	(chemothera*):ti,ab,kw or (radiothera*):ti,ab,kw
	#10	MeSH descriptor Radiotherapy explode all trees
	#11	MeSH descriptor Antineoplastic Combined Chemotherapy Protocols explode all trees
	#12	MeSH descriptor Combined Modality Therapy

	explode all trees
#13	(chemoradi*) or (CRT)
#14	MeSH descriptor Antineoplastic Agents explode all trees
#15	(#4 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)
#16	MeSH descriptor Infertility, Female explode all trees
#17	infertil*.ti,ab.
#18	Gonadotropin-Releasing Hormone:ti,ab,kw or (GnRH):ti,ab,kw or (Gn-RH):ti,ab,kw or (GnRH-a):ti,ab,kw
#19	(Luteinizing Hormone-Releasing Hormone):ti,ab,kw or (Luteinizing Hormone Releasing Hormone):ti,ab,kw or (LHRH):ti,ab,kw or (LH Releasing Hormone):ti,ab,kw or (LH-Releasing Hormone):ti,ab,kw
#20	(LH-RH):ti,ab,kw or (LH-FSH Releasing Hormone):ti,ab,kw or (LH FSH Releasing Hormone):ti,ab,kw or (Gonadoliberin):ti,ab,kw or (Gonadorelin):ti,ab,kw
#21	(LFRH):ti,ab,kw or (LHFSH Releasing Hormone):ti,ab,kw or (Releasing Hormone, LHFSH):ti,ab,kw or (LHFSHRH):ti,ab,kw or (Luliberin):ti,ab,kw
#22	(Dirigestran):ti,ab,kw or (Kryptocur):ti,ab,kw or (Gonadorelin Acetat):ti,ab,kw or (Gonadorelin Hydrochloride):ti,ab,kw or (Cystorelin):ti,ab,kw
#23	(Factrel):ti,ab,kw
#24	(Lupron Depot or Trelstar LA or Lupron or Lupron Depot or Lupron Depot-PED or Synarel or Zoladex or Supprelin LA or Eligard or Factrel or Lupron Depot-Gyn or Trelstar or Trelstar Depot or Vantas or Viadur):ti,ab,kw
#25	(#16 OR #17)
#26	(#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24)
#27	(#15 AND #25 AND #26)

Table 41 – Infertility: search CENTRAL other interventions for fertility preservation

Date	**28-03-2012**
Database	CENTRAL
Search Strategy	#1 MeSH descriptor Chemotherapy, Adjuvant explode all trees
	#2 MeSH descriptor Radiotherapy, Adjuvant explode all trees
	#3 (adjuvant)
	#4 (#1 OR #2 OR #3)
	#5 MeSH descriptor Antineoplastic Combined Chemotherapy Protocols explode all trees
	#6 MeSH descriptor Neoadjuvant Therapy explode all trees
	#7 (neoadjuvant.)
	#8 (#5 OR #6 OR #7)
	#9 (chemothera*):ti,ab,kw or (radiothera*):ti,ab,kw
	#10 MeSH descriptor Radiotherapy explode all trees
	#11 MeSH descriptor Antineoplastic Combined Chemotherapy Protocols explode all trees
	#12 MeSH descriptor Combined Modality Therapy explode all trees
	#13 (chemoradi*) or (CRT)
	#14 MeSH descriptor Antineoplastic Agents explode all trees
	#15 (#4 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)
	#16 MeSH descriptor Infertility, Female explode all trees
	#17 MeSH descriptor Infertility explode all trees

	#18 MeSH descriptor Infertility, Male explode all trees #19 infertil*.ti,ab. #20 fertil*.ti,ab. #21 (fertility preservation):ti,ab,kw #22 (#16 OR #17 OR #18 OR #19 OR #20 OR #21) #23 (#15 AND #22)

Appendix 1.8. Gastrointestinal complications

Appendix 1.8.1. Nausea & vomiting

Table 42 – Nausea & vomiting: search Medline via PubMed (benzodiazepines)

Date	**August 24, 2012**
Database	PubMed
Search Strategy	(("benzodiazepines"[MeSH Terms] OR "benzodiazepines"[All Fields]) OR ("alprazolam"[MeSH Terms] OR "alprazolam"[All Fields]) OR ("benzodiazepinones"[MeSH Terms] OR "benzodiazepinones"[All Fields]) OR ("anthramycin"[MeSH Terms] OR "anthramycin"[All Fields]) OR ("bromazepam"[MeSH Terms] OR "bromazepam"[All Fields]) OR ("clonazepam"[MeSH Terms] OR "clonazepam"[All Fields]) OR ("devazepide"[MeSH Terms] OR "devazepide"[All Fields]) OR ("diazepam"[MeSH Terms] OR "diazepam"[All Fields]) OR ("flumazenil"[MeSH Terms] OR "flumazenil"[All Fields]) OR ("flunitrazepam"[MeSH Terms] OR "flunitrazepam"[All Fields]) OR ("flurazepam"[MeSH Terms] OR "flurazepam"[All Fields]) OR ("lorazepam"[MeSH Terms] OR "lorazepam"[All Fields]) OR ("nitrazepam"[MeSH Terms] OR "nitrazepam"[All Fields]) OR ("oxazepam"[MeSH Terms] OR "oxazepam"[All Fields]) OR ("pirenzepine"[MeSH Terms] OR "pirenzepine"[All Fields]) OR ("prazepam"[MeSH Terms] OR "prazepam"[All Fields]) OR ("temazepam"[MeSH Terms] OR "temazepam"[All Fields]) OR ("chlordiazepoxide"[MeSH Terms] OR "chlordiazepoxide"[All Fields]) OR ("clorazepate dipotassium"[MeSH Terms] OR ("clorazepate"[All Fields] AND "dipotassium"[All Fields]) OR "clorazepate dipotassium"[All Fields]) OR ("estazolam"[MeSH Terms] OR "estazolam"[All Fields]) OR ("medazepam"[MeSH Terms] OR "medazepam"[All Fields]) OR ("midazolam"[MeSH Terms] OR "midazolam"[All Fields]) OR ("triazolam"[MeSH Terms] OR "triazolam"[All Fields])) AND (("drug therapy"[Subheading] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "drug therapy"[All Fields] OR "chemotherapy"[All Fields] OR "drug therapy"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "chemotherapy"[All Fields]) OR ("radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR "radiotherapy"[MeSH Terms])) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) AND (("nausea"[MeSH Terms] OR "nausea"[All Fields]) OR ("vomiting"[MeSH Terms] OR "vomiting"[All Fields])) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH Terms] AND "humans"[MeSH Terms])) AND ("2008/01/01"[PDAT] : "3000/12/31"[PDAT])
Note	Search for RCTs for study question re benzodiazepines >2008

Table 43 – Nausea & vomiting: search Medline via PubMed (cannabinoids)

Date	August 24, 2012
Database	PubMed
Search Strategy	(("cannabinoids"[MeSH Terms] OR "cannabinoids"[All Fields]) OR ("cannabidiol"[MeSH Terms] OR "cannabidiol"[All Fields]) OR ("cannabinol"[MeSH Terms] OR "cannabinol"[All Fields]) OR ("tetrahydrocannabinol"[MeSH Terms] OR "tetrahydrocannabinol"[All Fields])) AND (("nausea"[MeSH Terms] OR "nausea"[All Fields]) OR ("vomiting"[MeSH Terms] OR "vomiting"[All Fields]) OR ("nausea"[MeSH Terms] OR "nausea"[All Fields])) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH Terms] AND "humans"[MeSH Terms])) AND ("2006/01/01"[PDAT] : "3000/12/31"[PDAT])
Note	Search for RCTs for study question re cannabinoids >2006

Table 44 – Nausea & vomiting: search EMBASE

Date	August 24, 2012
Database	Embase OVID
Search Strategy	1. exp cannabinoid/ 2. cannabinoid$.ti,ab,ot. 3. exp cannabidiol/ 4. cannabidiol.ti,ab,ot. 5. exp cannabinol/ 6. cannabinol.ti,ab,ot. 7. 1 or 2 or 3 or 4 or 5 or 6 8. nausea.ti,ab,ot. 9. exp "nausea and vomiting"/ 10. vomiting.ti,ab,ot. 11. 8 or 9 or 10 12. crossover procedure/ or double-blind procedure/ or single-blind procedure/ or randomized controlled trial/ 13. (crossover$ or cross over$ or placebo$ or (doubl$ adj blind$) or allocat$).ti,ab,ot. or random$.ti,ab,ab. or trial$.ti. 14. 12 or 13 15. animal/ not human/ 16. 14 not 15 17. 7 and 11 and 16 18. limit 17 to yr="2006 -Current" 19. exp adjuvant chemotherapy/ 20. adjuvant.tw. 21. exp antineoplastic agent/ 22. exp adjuvant therapy/ 23. neoadjuvant.tw. 24. chemothera$.tw. 25. radiothera$.tw. 26. exp radiotherapy/ 27. multimodality cancer therapy/ 28. chemoradi$.tw. 29. or/19-28 30. 18 and 29 31. anthramycin.mp. or exp anthramycin/ 32. bromazepam.mp. or exp bromazepam/ 33. clonazepam.mp. or exp clonazepam/ 34. devazepide.mp. or exp devazepide/ 35. diazepam.mp. or exp diazepam/ 36. exp flumazenil/ or flumazenil.mp. 37. flunitrazepam.mp. or exp flunitrazepam/

	38. flurazepam.mp. or exp flurazepam/ 39. lorazepam.mp. or exp lorazepam/ 40. nitrazepam.mp. or exp nitrazepam/ 41. oxazepam.mp. or exp oxazepam/ 42. prazepam.mp. or exp prazepam/ 43. pirenzepine.mp. or exp pirenzepine/ 44. temazepam.mp. or exp temazepam/ 45. exp chlordiazepoxide/ or chlordiazepoxide.mp. 46. clorazepate.mp. or exp clorazepate/ 47. estazolam.mp. or exp estazolam/ 48. medazepam.mp. or exp medazepam/ 49. exp midazolam/ or midazolam.mp. 50. triazolam.mp. or exp triazolam/ 51. or/31-50 52. 11 and 16 and 29 and 51
Note	Search for RCTs for study question re cannabinoids >2006 and re benzodiazepines >2008 (time limits both applied in Reference Manager)

Appendix 1.8.2. Diarrhoea

Table 45 – Diarrhoea: search Medline OVID

Date	**August 31, 2012**
Database	Medline OVID SP
Search Strategy	1. adjuvant.mp. or Chemotherapy, Adjuvant/ or Radiotherapy, Adjuvant/ 2. Antineoplastic Combined Chemotherapy Protocols/ or Neoadjuvant Therapy/ or neoadjuvant.mp. 3. chemothera$.tw. 4. radiothera$.tw. 5. Radiotherapy/ 6. antineoplastic agents combined/ 7. combined modality therapy/ 8. chemoradi$.mp. 9. CRT.mp. 10. exp Antineoplastic Agents/ 11. or/1-10 12. randomized controlled trial.pt. 13. controlled clinical trial.pt. 14. randomized.ab. 15. placebo.ab. 16. clinical trials as topic.sh. 17. randomly.ab. 18. trial.ti. 19. 12 or 13 or 14 or 15 or 16 or 17 or 18 20. exp animals/ not humans.sh. 21. 19 not 20 22. Diarrhea/ 23. Somatostatin/ 24. Octreotide/ 25. Vitamins/ or Food, Formulated/ or Dietary

	Supplements/ or Minerals/ or Food,Fortified/ 26. Loperamide/ 27. 23 or 24 or 25 or 26 28. 11 and 21 and 22 and 27
Note	

Table 46 – Diarrhoea: search EMBASE

Date	**August 31, 2012**
Database	Embase OVID SP
Search Strategy	1. adjuvant.ti,ab. 2. adjuvant.mp. or exp adjuvant therapy/ or exp adjuvant chemotherapy/ or exp cancer adjuvant therapy/ 3. exp antineoplastic agent/ 4. neoadjuvant.ti,ab. 5. chemothera$.tw. 6. radiothera$.tw. 7. exp radiotherapy/ 8. antineoplastic agent/ 9. exp multimodality cancer therapy/ 10. chemoradi$.ti,ab. 11. CRT.ti,ab. 12. exp antineoplastic agent/ 13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 14. (Clinical trial/ or Randomized controlled trial/ or Randomization/ or Single blind procedure/ or Double blind procedure/ or Crossover procedure/ or Placebo/ or Randomi?ed controlled trial$.tw. or Rct.tw. or Random allocation.tw. or Randomly allocated.tw. or Allocated randomly.tw. or (allocated adj2 random).tw. or Single blind$.tw. or Double blind$.tw. or ((treble or triple) adj blind$).tw. or Placebo$.tw. or Prospective study/ or (random* adj3 trial*).ti,ab. or (randomized or placebo or randomly or trial or groups).ab.) not (Case study/ or review.pt. or Case report.tw. or Abstract report/ or letter/ or (exp animal/ not (exp animal/ and exp human/))) 15. 13 and 14 16. exp diarrhea/ or Diarrhea.mp. 17. exp somatostatin/ or Somatostatin.mp. 18. exp octreotide/ or Octreotide.mp. 19. exp vitamin/ 20. Vitamins$.ti,ab. 21. exp elemental diet/ 22. exp diet supplementation/ 23. exp mineral/ 24. exp loperamide/ or Loperamide.mp. 25. (crossover$ or cross over$ or placebo$ or (doubl$ adj blind$) or allocat$).ti,ab,ot. or random$.ti,ab,ab. or trial$.ti. 26. crossover procedure/ or double-blind procedure/ or single-blind procedure/ or randomized controlled trial/ 27. 25 or 26 28. 27 and 13 29. or/17-24 30. 29 and 16 31. 30 and 13 and 28 32. 30 and 13
Note	

Appendix 1.9. Cardiac toxicity

Table 47 – Cardiac toxicity: search Medline via PubMed

Date	**17-04-2012**
Database	Medline (PubMed) NB: details are shown
Search Strategy	#1 anthracyclines OR anthracyclin* OR anthracycline antibiotics OR antibiotics, anthracycline OR 4-demethoxydaunorubicin OR 4 demethoxydaunorubicin OR 4-desmethoxydaunorubicin OR 4 desmethoxydaunorubicin OR IMI 30 OR IMI30 OR IMI-30 OR idarubicin hydrochloride OR hydrochloride, idarubicin OR NSC 256439 OR NSC-256439 OR NSC256439 OR idarubicin OR idarubic* OR 4'-epiadriamycin OR 4' epiadriamycin OR 4'-epidoxorubicin OR 4' epidoxorubicin OR 4'-epi-doxorubicin OR 4' epi doxorubicin 4'-epi-adriamycin OR 4' epi adriamycin OR 4'-epi-DXR OR 4' epi DXR OR epirubicin hydrochloride OR hydrochloride, epirubicin OR farmorubicin OR IMI-28 OR IMI 28 OR IMI28 OR NSC 256942 OR NSC-256942 OR NSC256942 OR epirubicin OR epirubic* OR adriablastine OR adriblastin OR adriablastin OR adriamycin OR DOX-SL OR DOX SL OR doxorubicin hydrochloride OR hydrochloride doxorubicin OR doxorubic* OR adriamyc* OR dauno-rubidomycine OR dauno rubidomycin OR rubidomycin OR rubomycin OR daunomycin OR cerubidine OR daunoblastin OR daunoblastine OR daunorubicin hydrochloride OR hydrochloride, daunorubicin OR daunorubic* OR rubidomyc* OR NSC-82151 OR NSC 82151 OR NSC82151 OR daunoxome OR daunosom* OR doxil OR caelyx OR liposomal doxorubicin OR doxorubicin, liposomal OR myocet OR doxorubicin OR daunorubicin #2 heart OR heart diseases OR heart disease OR disease, heart OR diseases, heart OR cardiac diseases OR cardiac disease OR diseases, cardiac OR disease, cardiac OR cardiotoxicity OR cardiomyopathy OR heart failure, congestive OR heart failure OR cardiomyopathy, congestive OR ventricular dysfunction OR ventricular dysfunction, left OR ventricular dysfunction, right #3 dexrazoxane OR cardioxane OR ADR-529 OR ICRF-187 OR zinecard OR razoxane OR piperazines OR dexrazoxan* OR cardioxan* OR ADR-5* OR ICRF* OR zinecar* OR razoxan* OR piperazin* OR carnitine OR carnit* OR probucol OR probuc* OR coenzymes OR coenzyme Q10 OR coenzym* OR ubiquinone Q10 OR CoQ10 OR CoQ 10 #4 acetylcysteine OR acetylcyst* OR NAC OR N-acetylcysteine OR N-acetylcyst* #5 acetylcysteine OR acetylcyst* OR NAC OR N-acetylcysteine OR N-acetylcyst* OR vitamin E OR alpha-tocopherol OR tocopherols OR alpha-tocopher* OR tocopherol* OR tocotrienols OR tocotrien* OR digoxin OR digitalis glycosides OR digitalis OR digox* OR digitalis glycosid* OR angiotensin-converting enzyme inhibitors OR angiotensin-converting enzyme inhibitor* OR ACE inhibitors OR enalapril OR enalapri* OR angiotensin converting enzyme antagonist* OR renitec #6 phenetylamines OR phenetylam* OR verapamil OR verapam* OR prenylamine OR prenylam* OR deferoxamine OR deferoxam* OR desferal OR desfer* OR desferrioxamine OR desferrioxam* OR edetic acid OR EDTA OR edetic* OR ethylenediaminetetraacetic acid OR superoxide dismutase OR superoxide dismut* OR hydroxyethylrutoside OR hydroxyethylrutos* OR frederine OR frederin* OR vitamin C OR ascorbic acid OR ascorbic ac* #7 guanidines OR guanidi* OR metaiodobenzylguanidine OR metaiodobenzylguanidi* OR cytochromes OR cytochrom* OR vitamin A OR retinol OR tretinoin OR retinoic acid OR vitamin A acid OR carotenoids OR retinoids OR retinoi* OR tretinoi* OR

	carotenoi* OR sildenafil OR sildenafil citrate OR viagra OR sildenaf* OR selenium OR selen* OR glutathione OR glutathione disulfide OR S-nitrosoglutathione OR glutathion* OR valsartan OR valsart* OR angiotension II receptor antagonist OR carvedilol OR carvedil* OR trimetazidine OR vastarel OR idaptan OR vasartel OR trimetazid* OR piperazines OR piperazin* OR amifostine OR amifostin* OR aminopropylaminoethylthiophosphoric acid OR APAETP #8 #3 OR #4 OR #5 OR #6 OR #7 #9 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) AND "humans"[MeSH Terms] #10 #1 AND #2 AND #8 AND #9 AND ("2010/01/01"[PDAT] : "3000/12/31"[PDAT])
Note	Search performed by Edith Leclerq, Trials Search Co-ordinator, Cochrane Childhood Cancer Group

Table 48 – Cardiac toxicity: search CENTRAL

Date	**17-04-2012**
Database	CENTRAL
Search Strategy	#1 (anthracyclines OR anthracycline antibiotics OR doxorubicin OR adriamycin OR epirubicin OR idarubicin OR daunorubicin OR rubidomycin OR daunoxome OR myocet OR caelyx OR doxil) and (heart OR heart disease OR heart diseases OR cardiac disease OR cardiac diseases OR cardiotoxicity OR cardiomyopathy OR cardiomyopathies OR heart failure OR Congestive heart failure OR ventricular dysfunction), from 2010 to 2012 in Trials #2 (anthracyclines OR anthracycline antibiotics OR doxorubicin OR adriamycin OR epirubicin OR idarubicin OR daunorubicin OR rubidomycin OR daunoxome OR myocet OR caelyx OR doxil) and (heart OR heart disease OR heart diseases OR cardiac disease OR cardiac diseases OR cardiotoxicity OR cardiomyopathy OR cardiomyopathies OR heart failure OR Congestive heart failure OR ventricular dysfunction) in Trials #3 (dexrazoxane OR cardioxane OR zinecard OR ADR-529 OR ICRF-187 OR razoxane OR piperazines OR dexrazoxan* OR cardioxan* OR zinecar* OR ADR-5* OR ICRF* OR razoxan* OR piperazin*)OR (carvedilol OR carvedil*)OR (ascorbic acid OR vitamin C OR ascorbic ac*) OR (vitamin a OR tretinoin OR retinoic acid OR carotenoids OR retinoids OR retino* OR tretinoi* OR carotenoi*) OR (trimetazidine OR vastarel OR idaptan OR vasartel OR trimetazid* OR piperazines OR piperazin*) OR (glutathione OR glutathione disulfide OR S-nitrosoglutathione OR glutathion*) OR (coenzymes OR coenzym* OR coenzyme Q10 OR ubiquinone OR ubiquinone Q10 OR CoQ10 OR CoQ 10), from 2010 to

	2012 in Trials #4 (ethylenediaminetetraacetic acid OR edetic acid OR EDTA OR edetic*) OR (acetylcysteine OR N-acetylcysteine OR acetylcyst* OR N-acetylcyst*) OR (hydroxyethylrutoside OR frederine OR frederin* OR hydroxyethylrutos*) OR (deferoxamine OR desferal OR desferrioxamine OR deferoxam* OR desfer* OR desferrioxam*) OR (digoxin OR digitalis OR digitalis glycosides OR digitalis glycosid* OR digox*) OR (amifostine OR aminopropylaminoethylthiophosphoric acid OR APAETP OR amifostin*) OR (vitamin E OR alpha-tocopherol OR tocopherols OR tocotrienols OR tocotrien* OR tocopherol* OR alpha-tocopher*) OR (phenethylamines OR phenethylam* OR verapamil OR verapam* OR prenylamine OR prenylam*) OR (valsartan OR valsart* OR angiotensin II receptor antagonist) , from 2010 to 2012 in Trials #5 (angiotensin-converting enzyme inhibitors OR enalapril OR angiotensin-converting enzyme antagonists OR renitec OR ACE inhibitor* OR angiotensin-converting enzyme inhibitor* OR enalapri* OR angiotensin-converting enzyme antagonist*) OR (carnitine OR l-carnitine OR carnit*) OR (superoxide dismutase OR superoxide dismut*) OR (guanidines OR guanidi* OR metaiodobenzylguanidi*) OR (probucol OR probuc*) OR (cytochromes OR cytochrom*) OR (sildenafil OR sildenafil citrate OR viagra OR sildenaf*) OR (selenium OR seleni*), from 2010 to 2012 in Trials #6 (#1 AND (#3 OR (#4 AND OE AND #5))) #7 (#3 OR #4 OR #5) #8 (#3 OR #4 OR #5), from 2010 to 2012
Note	Search performed by Edith Leclerq, Trials Search Co-ordinator, Cochrane Childhood Cancer Group

Table 49 – Cardiac toxicity: search EMBASE

Date	**17-04-2012**
Database	EMBASE via OVID
Search Strategy	1 Randomized Controlled Trial/ (319715) 2 Controlled Clinical Trial/ (387873) 3 randomized.ti,ab. (329292) 4 placebo.ti,ab. (171287) 5 randomly.ti,ab. (213996) 6 trial.ti,ab. (373679) 7 groups.ti,ab. (1401984) 8 drug therapy.sh. (247550) 9 or/1-8 (2316273) 10 Human/ (13305835) 11 9 and 10 (1599313) 12 left ventricular dysfunction.mp. or exp Heart Left Ventricle Failure/ (19609) 13 exp Heart/ or exp Heart Right Ventricle Failure/ or exp Echocardiography/ or right ventricular dysfunction.mp. or exp Heart Failure/ (783243) 14 echocardiography.mp. (174671) 15 ventricular dysfunction.mp. (15200) 16 heart failure.mp. or exp Heart Failure/ (261172) 17 congestive heart failure.mp. or exp Congestive Heart Failure/ (81744) 18 cardiomyopathy.mp. or exp CARDIOMYOPATHY/ or exp CONGESTIVE CARDIOMYOPATHY/ (89857) 19 cardiotoxicity.mp. or exp CARDIOTOXICITY/ (30056) 20 heart disease.mp. or exp Heart Disease/ (1146224) 21 cardiac disease.mp. (12021)

22 or/12-21 (1432755)
23 dexrazoxane.mp. or exp Razoxane/ (1988)
24 cardioxane.mp. (132)
25 ICRF-187.mp. (504)
26 ADR-529.mp. (63)
27 zinecard.mp. (109)
28 piperazines.mp. or exp Piperazine Derivative/ (257140)
29 (piperazin$ or dexrazoxan$ or cardioxan$ or razoxan$ or zinecar$ or ICRF$ or ADR-5$).mp. (39902)
30 vitamin A.mp. (19890)
31 exp RETINOL/ (29889)
32 retinoic acid.mp. or exp Retinoic Acid/ (40936)
33 retinol.mp. (39257)
34 tretinoin.mp. (1600)
35 vitamin a acid.mp. (295)
36 carotenoids.mp. or exp Carotenoid/ (97975)
37 retinoids.mp. or exp Retinoid/ (75671)
38 (retino$ or Tretinoi$ or carotenoi$).mp. (179120)
39 trimetazidine.mp. or exp TRIMETAZIDINE/ (1555)
40 trimethazidine.mp. (4)
41 vastarel.mp. (132)
42 trimetazid$.mp. (1559)
43 L-carnitine.mp. or exp Carnitine/ (10552)
44 carnit$.mp. (15702)
45 superoxide dismutase.mp. or exp Superoxide Dismutase/ (62447)
46 superoxide dismut$.mp. (62611)
47 ACE inhibitor.mp. (9209)
48 angiotensin-converting enzyme inhibitor.mp. (7648)
49 angiotensin-converting enzyme antagonist.mp. or Enalapril/ (20619)
50 renitec.mp. (423)
51 (angiotensin converting enzyme antagonist$ or enalapri$ or angiotensin-converting enzyme inhibitor$).mp. (37339)
52 amifostine.mp. or exp AMIFOSTINE/ (3251)
53 APAETP.mp. (10)
54 aminopropylaminoethylthiophosphoric acid.mp. (4)
55 amifostin$.mp. (3253)
56 carvedilol.mp. or exp CARVEDILOL/ (9093)
57 carvedil$.mp. (9095)
58 exp DEFEROXAMINE MESYLATE/ or exp DEFEROXAMINE/ or deferoxamine.mp. (11661)
59 desferal.mp. (1473)
60 desferrioxamine.mp. (3489)
61 (desferrioxam$ or desfer$ or desferoxam$).mp. (5137)
62 digoxin.mp. or exp DIGOXIN/ (35479)
63 exp DIGITALIS INTOXICATION/ or exp DIGITALIS/ or DIGITALIS GLYCOSIDE/ or digitalis.mp. (18770)
64 (digitalis glycosides or dogox$ or digitalis glycosid$).mp. (4886)
65 edetic acid.mp. or exp Edetic Acid/ (28735)
66 (EDTA or ethylenediaminetetraacetic acid or edetic$).mp. (47160)
67 exp GLUTATHIONE DERIVATIVE/ or exp GLUTATHIONE DISULFIDE/ or exp GLUTATHIONE/ or glutathione.mp. (115492)
68 glutathion$.mp. (116064)
69 s-nitrosoglutathione.mp. or exp S Nitrosoglutathione/ (1506)
70 guanidines.mp. or exp Guanidine Derivative/ (81746)
71 metaiodobenzylguanidine.mp. or exp "(3 Iodobenzyl)Guanidine"/ (3449)
72 guanidi$.mp. (29174)
73 hydroxyethylrutoside.mp. or exp Monoxerutin/ (522)

74 (frederine or frederin$ or monoxerut$ or hydroxyethylrutos$).mp. (532)
75 n-acetylcysteine.mp. or exp Acetylcysteine/ (21743)
76 ACETYLCYSTEINE DERIVATIVE/ (358)
77 (acetylcyst$ or N-acetylcyst$).mp. (22485)
78 phenetylamines.mp. or exp Phenethylamine/ (1804)
79 prenylamine.mp. or exp PRENYLAMINE/ (1443)
80 exp VERAPAMIL/ or verapamil.mp. or exp VERAPAMIL DERIVATIVE/ (48944)
81 (phenetylam$ or verapam$ or prenylam$).mp. (49851)
82 exp PROBUCOL/ or probucol.mp. (3657)
83 probuc$.mp. (3660)
84 exp SELENIUM DERIVATIVE/ or exp SELENIUM/ or selenium.mp. (33220)
85 seleni$.mp. (36035)
86 exp VALSARTAN/ or valsartan.mp. (7579)
87 exp Angiotensin 2 Receptor Antagonist/ (5925)
88 angiotensin II receptor antagonist.mp. (1441)
89 exp Angiotensin II Antagonist/ (1488)
90 (angiotensin II inhibitor or valsart$).mp. (7612)
91 ascorbic acid.mp. or exp Ascorbic Acid/ (65835)
92 vitamin c.mp. (17721)
93 ascorbic ac$.mp. (65535)
94 vitamin E.mp. (24732)
95 alpha tocopherol.mp. (54471)
96 exp Alpha Tocopherol/ (50567)
97 tocopherols.mp. or exp Tocopherol/ (54639)
98 tocotrienols.mp. or exp Alpha Tocotrienol/ (1067)
99 (tocotrien$ or alpha tocopher$ or tocopherol$).mp. (57779)
100 coenzymes.mp. or exp Coenzyme/ (5654)
101 coenzyme Q10.mp. or exp Ubidecarenone/ (5577)
102 ubiquinone.mp. or exp UBIQUINONE DERIVATIVE/ or exp UBIQUINONE/ (12892)
103 (ubiquinone Q10 or CoQ10).mp. (1396)
104 cytochromes.mp. or exp Cytochrome/ (129547)
105 cytochrom$.mp. (150510)
106 sildenafil.mp. or exp SILDENAFIL/ (13072)
107 viagra.mp. (3721)
108 or/23-107 (1156974)
109 exp ANTHRACYCLINE ANTIBIOTIC AGENT/ or exp ANTHRACYCLINE/ or exp ANTHRACYCLINE DERIVATIVE/ (150198)
110 (anthracycline or anthracyclines).mp. (22318)
111 anthracyclin$.mp. (22613)
112 doxorubicin.mp. or exp DOXORUBICIN DERIVATIVE/ or exp DOXORUBICIN/ (118072)
113 adriamycin.mp. (20630)
114 exp DAUNORUBICIN DERIVATIVE/ or daunorubicin.mp. or exp DAUNORUBICIN/ (20897)
115 rubidomycin.mp. (113)
116 epirubicin.mp. or exp EPIRUBICIN/ (19092)
117 exp IDARUBICIN DERIVATIVE/ or exp IDARUBICIN/ or idarubicin.mp. (6754)
118 (doxorubic$ or adriamyc$ or daunorubic$ or rubidomyc$ or epirubic$ or idarubic$).mp. (145022)
119 (daunoxome or doxil or caelyx or myocet).mp. (2200)
120 or/109-119 (156136)
121 11 and 22 and 108 and 120 (650)
122 limit 121 to yr="2010 -Current" (78)
123 limit 108 to yr="2010 -Current" (153060)
124 limit 11 to yr="2010 -Current" (244326)
125 limit 22 to yr="2010 -Current" (199941)
126 limit 120 to yr="2010 -Current" (22124)

	127 123 and 124 and 125 and 126 (78)
Note	Search performed by Edith Leclerq, Trials Search Co-ordinator, Cochrane Childhood Cancer Group

APPENDIX 2. IN- AND EXCLUDED STUDIES

Appendix 2.1. Oral complications

Appendix 2.1.1. Systematic reviews

Nineteen SRs (Alterio 2007, Bjordal 2011, Clarkson 2000, Clarkson 2010, Donnelly 2003, Elad 2011, Hodson 2003, Kwong 2004, Lalla 2006, Lotfi-Jam 2008, McGuire 2006, Migliorati 2006, O'Sullivan 2010, Potting 2006, Sasse 2006, Sonis 2010, Stokman 2006, Sutherland 2001, Worthington 2011) were retrieved in full-text of which five (Clarkson 2000, Clarkson 2010, Potting 2006, Sasse 2006, Worthington 2011) fulfilled all inclusion criteria. One SR (O'Sullivan 2010) was excluded because the objective of the review was to investigate the effect of interventions on xerostomia. The presented results did not focus explicitly on patients with cancer receiving chemo- or radiotherapy. Three SRs (Hodson 2003, Stokman 2006, and Sutherland 2001) did not assess all relevant domains of risk of bias of the included RCTs. Other criteria not met for inclusion are summarized in Table 50.

After the inclusion phase, another review was identified (Worthington 2010) that turned out to be part of a series of four Cochrane reviews regarding this topic (Clarkson 2009, Clarkson 2010, Worthington 2010, Worthington 2011). Therefore, six reviews were included.

Table 50 – Oral complications: in and excluded systematic reviews

Systematic review	Treatment / prevention of chemotherapy- or radiotherapy related adverse events	Outcomes indicated by KCE	Searched MEDLINE and at least one other electronic database	Indicated date of search	Included assessment of risk of bias (concealment of allocation, blinded outcome assessment and completeness of follow-up)	Included
Alterio 2007	+	+	-	+	-	No
Bjordal 2011	+	+	+	-	+	No
Clarkson 2000	+	+	+	+	+	Yes
Clarkson 2010	+	+	+	+	+	Yes
Donnelly 2003	+	+	-	+	+	No
Elad 2011	-	+	-	+	-	No
Hodson 2003	+	+	+	+	-	No
Kwong 2004	+	+	-	+	-	No
Lalla 2006	+	+	-	+	-	No
Lotfi-Jam 2008	-	+	+	+	-	No
McGuire 2006	+	+	-	+	+	No
Migliorati 2006	+	+	-	+	-	No
O'Sullivan 2010	-	-	+	+	+	No
Potting 2006	+	+	+	+	+	Yes
Sasse 2006	+	+	+	+	+	Yes
Sonis 2010	+	+	-	-	-	No
Stokman 2006	+	+	+	+	-	No
Sutherland 2001	+	+	+	+	-	No
Worthington 2011	+	+	+	+	+	Yes

+ Inclusion criterion met; - Inclusion criterion not met

Table 51 presents the characteristic of the included SRs.

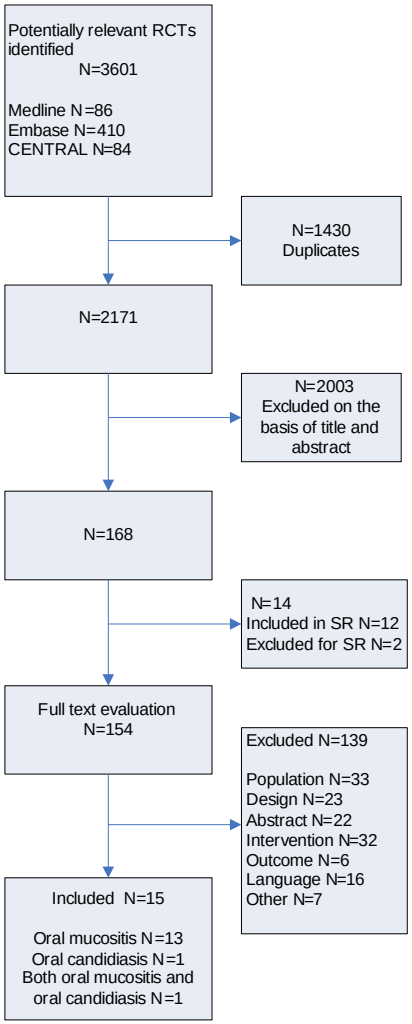
Table 51 –Oral complications: characteristics of included systematic reviews

Systematic review	Search	Objective	Experimental intervention	Control intervention
Clarkson 2009	Aug 2009	'To assess the effectiveness of interventions (which may include placebo or no treatment) for the prevention of oral candidiasis for patients with cancer receiving chemotherapy or radiotherapy or both'	'Any antifungal intervention for the prevention of oral candidiasis'	'May be placebo or no treatment, or another active intervention'
Clarkson 2010	May 2010	'To assess the effectiveness of interventions for treating oralmucositis or its associated pain in patientswith cancer receiving chemotherapy or radiotherapy or both'	'Any intervention for the treatment of oral mucositis or its associated pain'	'May be placebo, no treatment, or another active intervention'
Potting 2006	Sept 2004	'Therefore, we undertook to search the international literature afresh to ascertain whether these mouthwashes actually contribute to the prevention of oral mucositis among patients who undergo treatment with cytostatic chemotherapy'	Mouthwashes	Not specified
Sasse 2006	Apr 2005	'Whether or not amifostine protects tumor cells as well as normal cells, and also to quantify the degree of the reduction of side effects'	Radiotherapy plus amifostine	Radiotherapy
Worthington 2010	June 2010	'To assess the effectiveness of interventions for the treatment of oral candidiasis for patients with cancer receiving chemotherapy or radiotherapy or both.'	'Active agents: any antifungal intervention for the treatment of oral candidiasis.'	'Control: may be placebo or no treatment, or another active intervention.
Worthington 2011	Feb 2011	'To evaluate the effectiveness of interventions for the prevention of oral mucositis in patients with cancer receiving radiotherapy, chemotherapy or targetedtherapies'	'Any agent prescribed as prophylaxis for oral mucositis'	'May be placebo or no treatment, or another active intervention'

Appendix 2.1.2. Randomized controlled trials

On April 16, 2012 an update of the search of the systematic reviews of Clarkson 2000 [28], Clarkson 2010 [24], Worthington 2010 [30] and Worthington 2011 [11] was performed by the Cochrane Oral Health Group. The study flow is presented in Figure 1.

Figure 1 – Oral complications: study flow RCTs update systematic reviews of Clarkson 2009 and Worthington 2010 (oral candidiasis) and of Clarkson 2010 and Worthington 2011 (oral mucositis)



There were 3601 potential relevant references identified. After removal of duplications, 2171 references remained. Based on title and abstract 168 were withheld. Twelve studies were already included in the systematic reviews of Clarkson and Worthington (Clarkson 2009, Clarkson 2010, Worthington 2011) and two were excluded by the review authors. Of the 154 references for full text screening, 139 were not included with reason (Table 54 and Table 55). Finally, 15 RCTs were included that were not yet included in one of the included reviews (Clarkson 2009, Clarkson 2010, Worthington 2010, Worthington 2011) (Table 52 and Table 53).

Table 52 – Oral complications: included RCTs regarding oral mucositis

Reference	Interventions
Bardy 2012	Manuka honey versus golden syrup (placebo)
Carvalho 2011*	Gallium aluminum–arsenate (InGaAlP) diode laser (Twin laser – MMOptics_, MMOptics Ltda., São Carlos, São Paulo, Brazil) with continuous wavelength 660 nm and spot size 4 mm2 Group 1: power 15 mW, energy density delivered 3.8 J/cm2 Group 2: power 5 mW, energy density delivered 1.3 J/cm2
Djuric 2006	Prechemotherapy intensive dental care (dental treatment and plaque and calculus removal prior to chemotherapy and supervised oral hygiene measures during chemotherapy) versus maintained usual oral hygiene, without interference in oral hygiene measures
Gouvea de Lima 2012	Low level laser therapy (660-nm wavelength galliumaluminum-arsenide, 10-mW laser, with a spot size of 4 mm2) with average energy density delivered to the oral mucosa was 2.5 J/cm2, and the energy dose delivered to the treated surface 0.1 J versus placebo laser
Henke 2011	Arm 1: palifermin (180 µg/kg/ wk) throughout radiochemotherapy (ie, for at least seven doses) Arm 2: palifermin (180 µg/kg/wk) for four doses and then placebo throughout the remainder of radiochemotherapy Arm 3: placebo throughout radiochemotherapy. (Dose of palifermin in arms 1 and 2 were adjusted to 120 µg/kg/ wk)
Katranci 2011	Oral cryotherapy versus routine care
Khanal 2010	Honey (extracted from beehives of the Western Ghats forests) versus Lignocaine (gel)
Lanzos 2010	Perio-Aid Tratamiento ® (Dentaid, Cerdanyola del Valles, Spain) composed of 0.12% CHX (chlorhexidine) and 0.05% CPC (cetyl-pyridinium chloride) versus placebo mouth rinse
Le 2011	Palifermin 180 g/kg versus matching IV placebo (1.2 mL of sterile water, 4% mannitol, 2% sucrose, 10 mmol/L histidine, 0.010% polysorbate-20, pH 6.5, and no preservatives)
Meca 2009	Chlorhexidine (0.12%), sodium fluoride (0.5%) or sodium iodine (2%); no treatment
Mehdipour 2011	The test group received 10ml 0.2% zinc sulfate mouthwash, and the control group received 10ml 0.2% chlorhexidine gluconate mouthwash, twice a day for a period of two weeks.
Oton-Leite 2012	Outpatients were randomly assigned into 2 groups. The laser group received applications and the placebo group received sham laser.
Satheeshkumar 2010	The study group was advised to use triclosan mouthwash containing triclosan 0.03% W/V and sodium bicarbonate 2 mg mouth wash for the control Group.
Yen 2012	Standard oral care plus 5 mL of either phenylbutyrate 5% mouthwash or placebo (mouthwash vehicle) taken four times daily (swish and spit).

Table 53 – Oral complications: included RCTs regarding oral candidiasis

Reference	Interventions
Lanzos 2011	antiseptic, non-alcohol based, mouth rinse containing chlorhexidine (CHX) and cetyl-pyridinium chloride (CPC) versus placebo mouth rinse
Meca 2009	Chlorhexidine (0.12%), sodium fluoride (0.5%) or sodium iodine (2%); no treatment

Table 54 – Oral complications: excluded RCTs regarding oral mucositis

Reference	Reason for exclusion
Abdulrhman 2012	Children
Adkins 2010	Abstract
Antunes 2007	Bone marrow transplantation patients
Antunes 2011	Abstract
Ashktorab 2010	Article in Farsi (?)
Ayago Flores 2010	Article in Spanish, no RCT
Baharvand 2010	Intervention not of interest to KCE (topical phenytoin (ant seizure medication that promotes wound healing))
Barker 2008	Abstract
Bensadoun 2012	No RCT
Bouteloup 2011	Intervention not of interest to KCE
Buntzel 2010	Intervention not of interest to KCE (substitution of selenium)
Caluwaerts 2010	Animal study
Castelino 2010	Document not available
Castro 2009	Abstract
Cauwels 2011	No RCT
Chambers 2006	Outcome is not oral mucositis, but xerostomia
Chambers 2006	Abstract
Chen 2007	Article in Chinese
Chierchietti 2006	Intervention not of interest to KCE (intravenous L-alanyl-L-glutamine)
Coda 1997	Intervention not of interest to KCE (morphine/hydromorphone/sufentanil)
Cruz 2007	Children
Cubukcu 2007	Children
Dai 2009	Intervention not of interest to KCE (Yangyin Humo Decoction)
Das 2011	Intervention not of interest to KCE (Yashtimadhu)
De Koning 2007	Childhood cancer patients
Demiroz 2009	Abstract
Dimsdale 2010	Intervention not of interest to KCE (sedative hypnotic eszopiclone)
Dörr 2007	Intervention not of interest to KCE (Proteolytic enzymes (Wobe-Mugos® E)
Eisenberg 2011	No RCT
El Housseiny 2007	Children
Elad 2006	Bone Marrow transplantation patients
Ergenoglu 2010	Intervention not of interest to KCE (intravenous morphine infusion)
Ernrooth 1999	Abstract
Ferretti 1985	No RCT
Ferretti 1987	Abstract
Gobetti 1999	Abstract
Gori 2007	Bone marrow transplantation patients
Gouvea de Lima 2010	Abstract of an already included study (Gouvea de Lima 2012)
Gouvea de Lima 2010	No RCT
Grzegorczyk-Jaywinska 2004	Article in Polish, stem cell transplantation patients
Grzegorczyk-Jazwinska 2006	Stem cell transplantation patients
Han 2010	Intervention not of interest to KCE (jimlong capsules)
Haritha 2009	Abstract
Hartmann 1995	Abstract
He 2011	No RCT
He, 2008	article in Chinese, intervention not of interest to KCE (alanyl-glutamine (Ala-Gln) dipeptide)

Reference	Reason for exclusion
Hodgson 2011	Intervention not of interest to KCE (near infrared LED light treatment)
Huang 2003	Article in Chinese
Huang 2007	Stem cell transplantation patients
Huscher 2010	No RCT
Imaeda 2011	Intervention not aimed at oral complications
Jagasia 2012	Stem cell transplant patients
Jham 2009	Intervention not of interest to KCE (bethanechol)
Ju 2009	Article in Chinese
Kabeya 2011	Abstract, article probably in Japanese, possibly no RCT
Kamian 2007 (Kazemian 2009 is the article identified with this reference)	Intervention not of interest to KCE (Benzidamine (non-steroidal agent with analgesic, anaesthetic, anti-inflammatory and antimicrobial properties)
Khademi 2009	Article in Farsi
Khouri 2009	Stem cell transplant patients
Khuntia 2008	Abstract
Kim 2010	Stem cell transplant patients
Kiprian 2009	No RCT
Kuk 2011	Abstract
Lacouture 2011	No RCT
Ladenstein 2010	Children
Lalla 2011	Stem cell transplant patients
Le 2008	Abstract
Lee 2008	Abstract
Li 2006	Intervention not of interest to KCE (oral glutamine)
Lilleby 2006	Stem cell transplantation patients
Lin 2010	Intervention not of interest to KCE (zinc supplementation)
Loo 2010	Intervention not of interest to KCE (Rhodiola algida, widely used in traditional Chinese medicine)
Mandhaniya 2011	RCT in children
Mansouri 2012	Intervention not of interest to KCE (zinc sulfate capsule 220 mg (50mg zinc elemental, Alhavi factory), and the other group took placebo, both twice a day with 12-h interval. Therefore, the zinc sulfate group had 440 mg zinc sulfate (100 mg zinc elemental) per day.)
Mitrokhin 2011	RCT published in Russian The patients of one group were treated with fluconazole (Diflucan) and those of the other group were treated with voriconazole (Vifend).
Morales 2012	No outcomes of interest to KCE + participants 4-19 y
Nagy 2007	No outcomes of interest to KCE
NCIC Clinical Trials Group 2010	Intervention not of interest to KCE (giving radiation therapy at different times of the day)
Oudot 2011	RCT in children
Pädiatrische Praxis 2010	No RCT
Penpattanagul 2007	Intervention not of interest to KCE (WF10 for intravenous infusion after dilution, a chlorite-based drug which contains the active ingredient OXO-K993 (referred to as TCDO or tetrachlorodeca-oxygen in the literature))
Peterson 2007	Intervention not of interest to KCE (Saforis (MGI Pharma, Inc., Bloomington, MN) is composed of glutamine in a novel, proprietary drugdelivery system (UpTec) that is administered orally)
Peterson 2009	Intervention not of interest to KCE (Recombinant Human Intestinal Trefoil Factor Oral Spray)
Puataweepong 2009	Intervention not of interest to KCE (oral Aloe Vera juice)
Qin 2007	Article in Chinese
Radiation Therapy Oncology Group and National	Trial not finished yet

Reference	Reason for exclusion
Cancer Institute 2010	
Ryu 2007	Intervention not of interest to KCE (granulocyte-macrophage colony stimulating factor (GM-CSF))
Rzepecki 2009	No RCT
Santos 2009	Intervention not of interest to KCE (vitamin E and selenium in mucositis prevention in patients with head and neck cancer submitted to radiotherapy [abstract])
Santos 2011	Patients who undergo hematopoietic stem cell transplantation (HSCT)
Schmid 2006	Children
Schubert 2007	Bone marrow transplantation patients
Shabanloei 2009	Outcome not of interest to KCE
Sharma 2009	Abstract, intervention not of interest to KCE
Sharma 2012	Intervention not of interest to KCE (Lactobacillus brevis = probiotic)
Shea 2008	Abstract
Shidfar 2008	Abstract
Shukla 2010	Outcome not of interest to KCE (intestinal mucositis)
Silva 2011	Stem cell transplantation patients
Simoes 2010	No RCT
Song Chi 2011	RCT published in Korean
Sorensen 2006	Abstract of study published by Sorensen in 2008 (already included in SR of Worthington 2011)
Southwest Oncology Group and National Cancer Institute 2010	Intervention not of interest to KCE (glutamine)
Sportes 2003	Stem cell transplantation patients
Stiff 2006	Stem cell transplantation patients
Su 2003	Abstract of study published by Su in 2004
Su 2004	Intervention not of interest to KCE (Aloe Vera)
Sugisaki 2011	Article in Japanese; not sure whether this is an RCT (crossover study?)
Sung 2007	Children
Svanberg 2010	Bone marrow transplantation patients
Tacyildiz 2010	Children, no RCT
Talaipour 1995/2000	Article in Persian
Tan 2011	Intervention not of interest to KCE (RCT regarding galactomannan screening)
Tosaka 2011	RCT published in Japanese (rinsed using rebamipide solution (R solution), or Poraprezinc-alginate sodium solution (P-A solution) (both considered to be effective for oral mucositis). A mouth rinsed with sodium azulene sulfonate (S solution) was used as a control.)
Uderzo 2011	Children undergoing allogeneic hematopoietic stem-cell transplantation (HSCT) for malignant haematological diseases were randomly assigned to standard total parenteral nutrition (S-TPN) or glutamine-enriched (GE)-TPN solution consisting of 0.4 g/kg/day of L-alanine-glutamine dipeptide.
University of Miami Sylvester Comprehensive Cancer Center 2010	Trial not finished yet
Vadhan-Raj 2008	Abstract
Verhagen 2009	No RCT
Wu 2008	Abstract of study published by Wu in 2010
Wu 2009	Intervention not of interest to KCE (Recombinant Human Epidermal Growth Factor (RhEGF))
Wu 2010	Intervention not of interest to KCE (intravenous Actovegin (deproteinized extract))
Zanin 2010	Unclear whether this is a RCT

Reference	Reason for exclusion
Zhang 2011	RCT published in Chinese (gargling with Calcium folinic)

Table 55 – Oral complications: excluded RCTs regarding oral candidiasis

Reference	Reason for exclusion
Arrieta 2011	Pediatric patients, no RCT
Bryant 2011	No RCT
Buntzel 2010	Intervention not of interest to KCE
Cornely 2011_1	No RCT
Cornely 2011_2	No RCT
Dranitsaris 2011	No RCT
Girmenia 2010	No RCT
Goto 2010	No RCT
Groll 2010	Patients not of interest to KCE (stem cell recipients)
Henkin 1984	Abstract
Jang 2010	No RCT
Jham 2009	Intervention not of interest to KCE
Kang 2010	Article in Korean
Lazzaro 2010	No RCT
Maertens 2010	Pediatric patients
Mattiuzzi 2011	Outcome not of interest to KCE (invasive fungal infection)
McCoy 2009	Stem cell transplantation patients
Mehta 2010	Children who undergo stem cell transplantation

Appendix 2.2. Skin toxicity

Appendix 2.2.1. Systematic reviews

Six SRs (Anderson 2009, Baker 2009, Bolderston 2005, Bolderstin 2006, Jull 2008, Koukourakis 2010, Richardson 2005, Tan 2009) were retrieved in full-text of which one (Richardson 2005) fulfilled all inclusion criteria. The other reviews did not assess all relevant domains of risk of bias of the included RCTs and one other review did not address the treatment or prevention of chemotherapy- or radiotherapy related adverse events (Table 56).

Table 56 – Skin toxicity: in and excluded systematic reviews

Systematic review	Treatment / prevention of chemotherapy- or radiotherapy related adverse events	Outcomes indicated by KCE	Searched MEDLINE and at least one other electronic database	Indicated date of search	Included assessment of risk of bias (concealment of allocation, blinded outcome assessment and completeness of follow-up)	Included
Anderson 2009	+	+	+	+	-	No
Baker 2009	+	+	+	+	-	No
Bolderston 2005	+	+	+	+	-	No
Bolderston 2006	+	+	+	+	-	No
Jull 2008	-	+	+	+	-	No
Koukourakis 2010	+	+	+	+	-	No
Richardson 2005	+	+	+	+	+	Yes
Tan 2009	+	+	+	+	-	No

+ Inclusion criterion met; - Inclusion criterion not met

Table 57 presents the characteristic of the included SR.

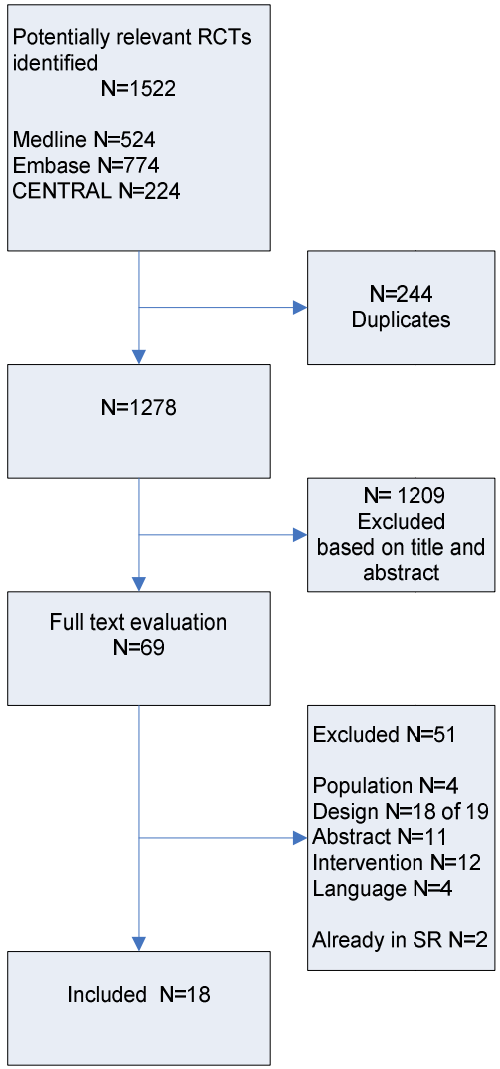
Table 57 – Skin toxicity: characteristics of the included systematic review

Systematic review	Search	Objective	Experimental intervention	Control intervention
Richardson 2005	August 2004	'To review systematically the currently available evidence on the effectiveness of Aloe vera for the prevention and minimisation of radiation-induced skin reactions in cancer patients To systematically review and critically appraise the evidence for effectiveness of Aloe vera gel for radiation-induced skin reactions'	'Aloe vera gel'	'Any other intervention'

Appendix 2.2.2. Randomized controlled trials

On May 4, 2012 MEDLINE, Embase and CENTRAL were searched for RCTs regarding interventions for skin toxicity in patients with cancer receiving radiotherapy or chemotherapy or both. The study flow is presented in Figure 2.

Figure 2 – Skin toxicity: study flow RCTs regarding interventions



Fifteen hundred and twenty-two potential relevant references were identified. After deduplication 1278 references remained. Based on title and abstract 69 studies were selected for full text screening. Of those, two studies (Heggie 2002, Williams 1996) were already included in the systematic review of Richardson (Richardson 2005). Forty-nine other studies were not included with reason (Table 59). Finally, 18 RCTs were included (Table 58).

Table 58 – Skin toxicity: included RCTs

1	Interventions
Boström 2001	Corticosteroid cream (mometasone furoate) vs. emollient crème (placebo)
Campbell 1992	No washing vs. washing with water vs. washing with water and soap.
Fenig 2001	Biafine ointment vs. Lipiderm ointment vs. no treatment
Glees 1979	Hydrocortisone cream vs. clobetasone butyrate
Gosselin 2010	Placebo, Aquaphor (ointment), Biafine RE (cream) or RadiaCareTM (gel)
Kirova 2011	Hyaluronic acid cream vs. simple emollient
Lacouture 2010	Pre-emptive treatment (consisting of skin moisturizers, sunscreen, topical steroid, and doxycycline 100 mg twice per day) vs. reactive treatment (consisting of any treatments the investigator deemed necessary)
Liguori 1997	Hyaluronic acid creams vs. placebo
Lokkevik 1996	Bepanthen cream vs. no topical ointment
Maiche 1991	Chamomile cream vs. almond ointment
Moolenaar 2006	Honey vs. paraffin
Omidvari 2007	Corticosteroid (behametasone) vs. petrolatum vs. control
Pommier 2001	Calendula vs. trolamine
Ribet 2008	Avène thermal spring water anti-burning gel vs. trolamine based cream.
Roy 2001	Washing with water and soap vs. no washing
Schmuth 2002	Corticosteroid cream vs. dexpanthenolcream (+ preliminary cohort as control group)
Shukla 2006	Beclomethason vs. no intervention.
Westbury 2000	No washing irradiated area vs. usal scalp care.

Table 59 – Skin toxicity: excluded RCTs

Reference	Reason for exclusion
Anonymous 1976	Language (Swedish), no cancerpatients
Anonymous 2009	Conference abstract, intervention not relevant
Bardychev 1979	Language (Russian)
Becker-Schiebe 2011	No RCT
Birgin 2005	No patients, but volunteers
Chu 2008	No RCT (review, hand foot syndrome)
Cotliar 2011	No RCT (editorial)
Delaney 1997	Intervention (sucralfate cream)
Eng 2009	No RCT
Gentry 1973	No cancer patients
Gollins 2008	Intervention (gentian violet vs. hydrogel dressing)
Gordon 2012	Conference abstract
Graham 2004	Intervention (No-Sting barrier film)
Gratacos 1981	Language (Spanish)
Halperin 1993	Intervention (vitamin C)
Heggie 2002	Already included in systematic review of Richardson 2005
Jegge 1977	No cancer patients
Kirova 2010a	Conference abstract
Kirova 2010b	Conference abstract

Reference	Reason for exclusion
Kirova 2010c	Conference abstract
Kouvaris 2001	Intervention (GM-CSF)
Lacouture 2009	No RCT
Li 2009	No RCT (review)
Lipworth 2009	No RCT (review)
Lockley 2009	Intervention not relevant, probably no RCT
Lorusso 2007	No RCT (review)
Lorusso 2009	No RCT (review)
Maiche 1994	Intervention (sucralfate cream)
Mak 2005	Intervention (gentian violet vs. non adherent absorbent dressing)
Markouizou 2007	No RCT (review)
Miko Enomoto 2005	Intervention (RayGel)
Momm 2003	No RCT
Murillo 2009	Conference abstract
Naidoo 2011	Conference abstract
Netikova 2009	Conference abstract
Ocvirk 2008	No RCT
Omidvari 2011	Language (Arabic/Persian)
Pardo Masferrer 2010	No RCT
Perez 2009	Conference abstract
Petersen 1993	No cancerpatients
Potera 1982	No RCT
Robert 2009	No RCT (review)
Roper 2004	No RCT
Schreck 2002	Intervention (cream vs. powder)
Shinohara 2011	Conference abstract
Shoma 2010	Intervention (Pentoxifyllin, addition of honey)
Wasif Saif 2007	No RCT
Williams 1996	Already included in systematic review of Richardson 2005
Wolf 2010	Conference abstract
Yang 2010	No RCT (review)
Yoshimoto 2010	Intervention (Pyridoxine)

Appendix 2.3. Neuropathy

Appendix 2.3.1. Systematic reviews

Four SRs (Albers 2011, Amara 2008, Baker 2009, CCO Amifostine 2003) were retrieved in full-text of which one (Albers 2011) fulfilled all inclusion criteria. Three SRs (Amara 2008, Baker 2009, CCO Amifostine 2003) did not assess all relevant domains of risk of bias of the included RCTs. Other criteria not met for inclusion are summarized in Table 60.

Table 60 – Neuropathy: in- and excluded systematic reviews

Systematic review	Treatment / prevention of chemotherapy- or radiotherapy related adverse events	Outcomes indicated by KCE	Searched MEDLINE and at least one other electronic database	Indicated date of search	Included assessment of risk of bias (concealment of allocation, blinded outcome assessment and completeness of follow-up)	Included
Albers 2011	+	+	+	+	+	Yes
Amara 2008	+	+	-	+	-	No
Baker 2009	+	+	+	+	-	No
CCO Amifostine 2003	+	+	+	+	-	No

+ Inclusion criterion met; - Inclusion criterion not met.

Table 61 presents the characteristics of the included SR.

Table 61 – Neuropathy: characteristics of the included systematic review

Systematic review	Search	Objective	Experimental intervention	Control intervention
Albers 2011	Aug 2010	'To systematically review the evidence from randomized controlled trials concerning the ability of chemoprotective agents to prevent or limit the neurotoxicity of cisplatin among human patients'	'Any form of chemoprotective treatment, such as acetyl-L-carnitine, acetylcysteine, ACTH, amifostine, BNP7787, calcium and magnesium, Org 2766, glutathione, oxcarbazepine, vitamin E, and growth factors, used to prevent or limit cisplatin-induced neurotoxicity'	'Compared with placebo, no treatment, or other treatments'

Appendix 2.3.2. Randomized controlled trials

On March 26, 2012 an update of the search of the systematic review of Albers 2011 was performed by the Cochrane Neuromuscular Disease Group. The study flow is presented in Figure 3.

We identified 152 potential relevant references. After deduplication 125 references remained. Based on title and abstract 75 were withheld. Nineteen studies were already included in the SR of Albers (Albers 2011) and 13 were excluded by the review authors. Eighteen references remained for full text screening. Of those 16 were not included with reason (Table 63). Finally, two RCTs were included that were not yet included in the existing review (Chay 2010; Grothey 2011).

For Glutamine, KCE performed an additional search in Medline, Embase and CENTRAL on August 6th, 2012. 1164 potentially relevant abstracts were identified of which 1148 were excluded based on title and abstract. Based on full text evaluation, another 13 were excluded leaving 3 aricles for inclusion.

Figure 3 – Neuropathy: study flow RCTs update Albers et al. (2011)

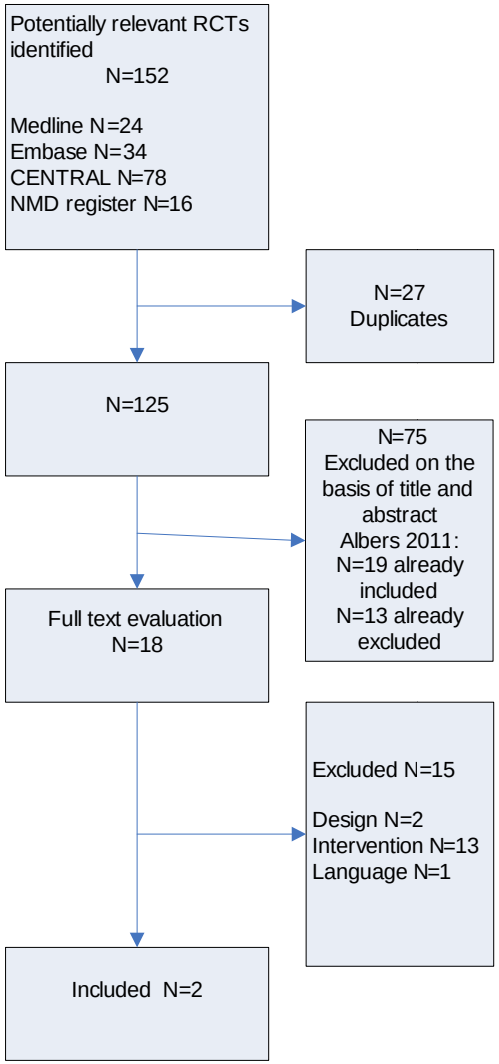


Table 62 – Neuropathy: included RCTs

Reference	Interventions	Remarks
Loven 2009	Oral glutamine	
Wang 2007	glutamine	
Strasser 2008	Oral glutamine	
Chay 2010	Calcium and magnesium infusions	
Grothey 2011	Calcium and magnesium infusions	

Table 63 – Neuropathy: excluded RCTs

Reference	Reason for exclusion
Colombo 1995	Intravenous glutathione, not oral
Dong 2010	Article in Chinese
Gallardo 1999	Intervention not of interest to KCE
Gallegos 2007	Intervention not of interest to KCE
Kemp 2006	Intervention not of interest to KCE
Knijn 2011	Post hoc analysis on RCT results. No randomized comparison of intervention of interest.
Kottschade 2011a	Intervention not of interest to KCE
Kottschade 2011b	Letter
Lissoni 1997	Intervention not of interest to KCE
Lu 2008	Intervention not of interest to KCE
Movsas 2005	Intervention not of interest to KCE
Pang 2011	Intravenous glutathione, not oral
Romano 2011	Intervention not of interest to KCE
Rose 1996	Intervention not of interest to KCE
Rudolph 2001	Intervention not of interest to KCE
Wen 2005	Intervention not of interest to KCE

Appendix 2.4. Neutropenia and neutropenic fever

Appendix 2.4.1. Systematic reviews

Thirty-six SRs (Aapro 2006, Berghmans 2002, Bhana 2007, Bohlius 2008, Bow 2002, Campbell 2003, Carstensen 2008, Clark 2009, Cooper 2011, Cruciani 2003, Drogna 2007, Furno 2002, Gafter-Gvili 2005, Gafter-Gvili 2007, Grossi 2006, Gunzer 2010, Hackshaw 2004, Herbst 2009, Heuser 2011, Johansen 2009, Jorgensen 2006, Kouroukis 2009, Kuderer 2007, Lyman 2002 AMJ, Lyman 2011, Madarnas 2009, Mank 2003, Massey 2009, Paul 2003, Paul 2010, Perez-Velasco 2010, Pinto 2007, Sung 2007, Van de Wetering 2005, Vidal 2004, Wang 2009 II) were retrieved in full-text of which five (Clark 2009, Gafter-Gvili 2005, Herbst 2009, Madarnas 2009, Massey 2009) fulfilled all inclusion criteria. Eleven SRs (Bohlius 2008, Bow 2002, Drogna 2007, Furno 2002, Johansen 2009, Jorgensen 2006, Mank 2003, Paul 2003, Paul 2010, Van de Wetering 2005, Vidal 2004) were excluded because the presented results did not focus explicitly on patients with cancer receiving chemo- or radiotherapy. Fifteen SRs (Aapro 2006, Berghmans 2002, Bhana 2007, Campbell 2003, Cooper 2011, Cruciani 2003, Gafter-Gvili 2007, Heuser 2011, Kouroukis 2009, Kuderer 2007, Lyman 2011, Perez Valasco 2010, Pinto 2007, Sung 2007, Wang 2009 II) did not assess all relevant domains of risk of bias of the included RCTs. Other criteria not met for inclusion are summarized in Table 64.

On June 28, 2012 two searches were performed in The Cochrane Library (with 68 reviews identified) and on July 26, 2012, two searches for SRs were performed in MEDLINE (with 96 reviews identified). Of those, eight were also included (Eckmanss 2006, Gafter-Gvili 2012, Gotzsche 2011, Johansen 2011, Jorgensen 2009, Teuffel 2011, Vidal 2009, Zitella 2006).

Table 64 – Neutropenia: in and excluded systematic reviews

Systematic review	Treatment / prevention of chemotherapy- or radiotherapy related adverse events	Outcomes indicated by KCE	Searched MEDLINE and at least one other electronic database	Indicated date of search	Included assessment of risk of bias (concealment of allocation, blinded outcome assessment and completeness of follow-up)	Included
Aapro 2006	+	+	+	+	-	No
Berghmans 2002	+	+	+	+	-	No
Bhana 2007	+	+	+	+	-	No
Bohlius 2008	-	+	+	+	+	No
Bow 2002	-	+	+	+	-	No
Campbell 2003	+	+	+	+	-	No
Carstensen 2008	+	+	-	-	-	No
Clark 2009	+	+	+	+	+	Yes
Cooper 2011	+	+	+	+	-	No
Cruciani 2003	+	+	+	+	-	No
Drogna 2007	-	-	+	+	-	No
Furno 2002	-	-	-	+	-	No
Gafter-Gvili 2005	+	+	+	+	+	Yes
Gafter-Gvili 2007	+	+	+	+	-	No
Grossi 2006	+	+	-	-	-	No
Gunzer 2010	+	+	-	-	-	No
Hackshaw 2004	+	+	+	-	-	No
Herbst 2009	+	+	+	+	+	Yes
Heuser 2011	+	+	+	+	-	No
Johansen 2009	-	+	+	+	-	No
Jorgensen 2006	-	+	+	+	-	No
Kouroukis 2009	+	+	+	+	-	No
Kuderer 2007	+	+	+	+	-	No
Lyman 2002 AMJ	+	+	+	-	-	No

Systematic review	Treatment / prevention of chemotherapy- or radiotherapy related adverse events	Outcomes indicated by KCE	Searched MEDLINE and at least one other electronic database	Indicated date of search	Included assessment of risk of bias (concealment of allocation, blinded outcome assessment and completeness of follow-up)	Included
Lyman 2011	+	+	+	+	-	No
Madarnas 2009	+	+	+	+	+	Yes
Mank 2003	-	+	+	-	-	No
Massey 2009	+	+	+	+	+	Yes
Paul 2003	-	+	+	+	-	No
Paul 2010	-	+	+	+	+	No
Perez Velasco 2010	+	+	+	+	-	No
Pinto 2007	+	+	+	+	-	No
Sung 2007	+	+	+	+	-	No
Van de Wetering 2005	-	+	+	+	+	No
Vidal 2004	-	+	+	+	-	No
Wang 2009 II	+	+	+	+	-	No

*+ Inclusion criterion met; - Inclusion criterion not met; * included despite lack of full risk of bias assessment*

Table 65 – Neutropenia and neutropenic fever: characteristics of included systematic reviews

Systematic review	Search	Objective	Experimental intervention	Control intervention
Bohlius				
Clark 2009	2002	'To evaluate the safety and effectiveness of adding colony stimulating factors to ATB when treating febrile neutropenia caused by cancer chemotherapy'	'G-CSF or GM-CSF plus antibiotics antibiotic alone'	'Antibiotic alone'
Eckmanss 2006	June 2005	To compare the effectiveness of high-efficiency particulate air (HEPA) filtration with that of non-HEPA filtration in decreasing the rates of mortality and fungal infection among patients with diagnosed hematological malignancies and neutropenia or among patients with bone marrow transplants	HEPA filtration	Non-HEPA filtration were
Gafter-Gvili 2005	Dec 2004	'To evaluate whether antibiotic prophylaxis in neutropenic patients reduces mortality and incidence of infection and to assess related adverse events'	'Antibiotic prophylaxis'	'Placebo, no intervention or other antibiotics'
Gafter-Gvili 2012	March 2011	'To evaluate whether antibiotic prophylaxis in neutropenic patients reduces mortality and incidence of infection and to assess related adverse events'	'Antibiotic prophylaxis'	'Placebo, no intervention or other antibiotics'
Gotzsche 2011	July 2011	To assess the effect of antifungal drugs in cancer patients with neutropenia.	Amphotericin B, fluconazole, ketoconazole, miconazole, itraconazole or voriconazole	Placebo or no treatment
Herbst 2009	Jan 2008	'To identify, critically evaluate, describe, statistically analyse, and summarise the evidence regarding the effectiveness of prophylactic antibiotic treatment compared to prophylactic use of colony stimulating factors in preventing febrile neutropenia (FN), severe infections, infection-related mortality, and overall mortality in cancer patients undergoing myelosuppressive chemotherapy. This includes bonemarrow transplantation and stemcell transplantation'	G(M)-CSF	Antibiotics

Systematic review	Search	Objective	Experimental intervention	Control intervention
Johansen 2011	July 2011	To compare the effect of fluconazole and amphotericin B on morbidity and mortality in patients with cancer complicated by neutropenia	Fluconazole	Amphotericin B
Jorgensen 2009	November 2007	To compare the benefits and harms of voriconazole with those of amphotericin B and fluconazole when used for prevention or treatment of invasive fungal infections in cancer patients with neutropenia	Voriconazole	Amphotericin B or fluconazole.
Madarnas 2009	Aug 2009	'1) Does the use of filgrastim as primary prophylaxis in patients with early stage (I, II, or III) breast cancer receiving myelosuppressive chemotherapy with curative intent improve clinical outcomes? 2) Does the use of filgrastim as secondary prophylaxis in patients with early stage (I, II, or III) breast cancer receiving myelosuppressive chemotherapy with curative intent improve clinical outcomes? 3) Does the use of filgrastim as secondary prophylaxis in patients with advanced stage (IV) breast cancer receiving palliative myelosuppressive chemotherapy after previous dose reduction for neutropenia improve clinical outcomes?'	'Primary or secondary prophylactic use of filgrastim'	'Placebo, no filgrastim or best supportive care (including prophylactic antibiotics)'
Teuffel 2011	February 2010	To evaluate the efficacy and safety of outpatient management of febrile neutropenia	Any inpatient antibiotic treatment	Any outpatient antibiotic treatment
Vidal 2009	September 2007	To compare the efficacy of oral antibiotics versus intravenous (IV) antibiotic therapy in febrile neutropenic cancer patients.	Oral antibiotics	Intravenous antibiotic's
Zitella 2006	2005	To examine the relevant literature to determine the level of evidence for nursing interventions that contribute to the prevention of infection in patients with cancer	Isolation (and many other nursing interventions)	No isolation

Appendix 2.4.2. Randomized controlled trials

Prophylactic and therapeutic G-CSF / GM-CSF

On August 1, 2012 a combined search was performed to identify RCTs regarding prophylactic G-CSF / GM-CSF and therapeutic G-CSF / GM-CSF. MEDLINE and Embase were searched from 2002 (search date of the systematic review of Clark 2009) and 1122 potential relevant references were identified (Figure 4). After deduplication 950 references remained. Based on title and abstract 908 studies were withheld. Of the remaining 42 studies one was already included in the special advice report (guideline) (Madarnas 2009) and another 38 studies were excluded with reason (Table 68 and Table 69). Three studies were included: two regarding prophylactic G-CSF / GM-CSF and one regarding therapeutic G-CSF / GM-CSF (Table 66 and Table 67).

Figure 4 – Neutropenia: study flow selection of RCTs regarding prophylactic and therapeutic G-CSF / GM-CSF

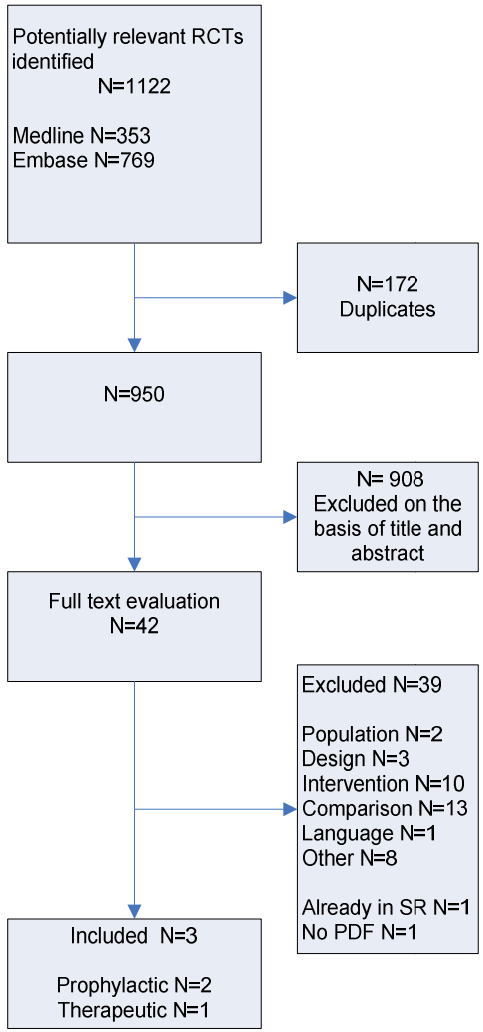


Table 66 – Neutropenia: included RCTs regarding prophylactic G-CSF / GM-CSF

Reference	Interventions
Brugger 2009	Pegfilgrastim versus no G-SCF support
Hecht 2010	Pegfilgrastim 6 mg versus placebo

Table 67 – Neutropenia: included RCTs regarding therapeutic G-CSF / GM-CSF

Reference	Interventions
Er 2004	Adding G-CSF (5 µg/kg per day subcutaneously) to antibiotic therapy versus not adding G-CSF to antibiotic therapy

Table 68 – Neutropenia: excluded RCTs regarding prophylactic G-CSF / GM-CSF

Reference	Reason for exclusion
Engert 2009	Intervention not of interest to KCE (biosimilar)
Flores 2010	No RCT
Gascon 2010	Intervention not of interest to KCE (biosimilar)
Giebel 2012	No RCT
Hashino 2008	Comparison not of interest to KCE (two active interventions)
Kahan 2008	Intervention not aimed at neutropenia
Liu 2008	Study already included in the special advice report (guideline) of Madarnas 2009
Loibl 2011	Comparison not of interest to KCE (two active interventions)
Sheikh 2011	Intervention not aimed at neutropenia
Sierra 2008	Comparison not of interest to KCE (two active interventions)
Yakushijin 2011	Comparison not of interest to KCE (two active interventions)

Table 69 – Neutropenia: excluded studies regarding therapeutic G-CSF / GM-CSF

Reference	Reason for exclusion
Amadori 2005	Intervention not aimed at neutropenia
Balducci 2007	Prophylaxis (date < 2008)
Burris 2010	No RCT
Castagna 2010	Patients (peripheral blood stem cell support)
Channa 2002	No PDF available
Del Giglio 2008	Intervention not of interest to KCE (biosimilar)
Engert 2006	Intervention not aimed at neutropenia
Gatzemeier 2009	Intervention not of interest to KCE (biosimilar)
Green 2003	Comparison not of interest to KCE (two active interventions)
Grigg 2003	Comparison not of interest to KCE (two active interventions)
Grigg 2005	Comparison not of interest to KCE (two active interventions)
Hidaka 2003	No relevant intervention
Hofmann 2002	Comparison not of interest to KCE (two active interventions)
Holmes 2002	Comparison not of interest to KCE (two active interventions)
Holmes 2002b	Prophylaxis (date < 2008)
Martin 2006	Prophylaxis (date < 2008)
Mey 2007	Intervention not aimed at neutropenia
Rinehart 2003	Prophylaxis (date < 2008)
Romieu 2007	Prophylaxis (date < 2008)
Seidel 2008	Patients (bone marrow transplantations)
Thomas 2004	Prophylaxis (date < 2008)
Tsavaris 2004	Comparison not of interest to KCE (two active interventions)
Usuki 2002	Prophylaxis (date < 2008)
Viens 2002	Comparison not of interest to KCE (two active interventions)
Von Lilienfeld 2007	Prophylaxis (date < 2008)
Vose 2003	Comparison not of interest to KCE (two active interventions)

Reference	Reason for exclusion
Waller 2010	Intervention not of interest to KCE (biosimilar)
Zhou 2011	Article in Chinese

Prophylactic antifungals

On July 6, 2012 an update of the search of the included systematic reviews (Gotzsche 2011a, Johansen 2011a, Jorgensen 2009) was performed (> 2007) in MEDLINE and Embase, by which 41 potential relevant references were identified (Figure 5). After deduplication 34 references remained. Based on title and abstract 28 studies were withheld. Of the remaining 6 studies one was already included in one of the systematic reviews (Gotzsche 2011a) and the other five studies were excluded with reason (Table 70). Therefore, no new RCTs were identified that have been published after the search dates of the reviews.

Figure 5 – Neutropenia: study flow selection of RCTs regarding prophylactic antifungals

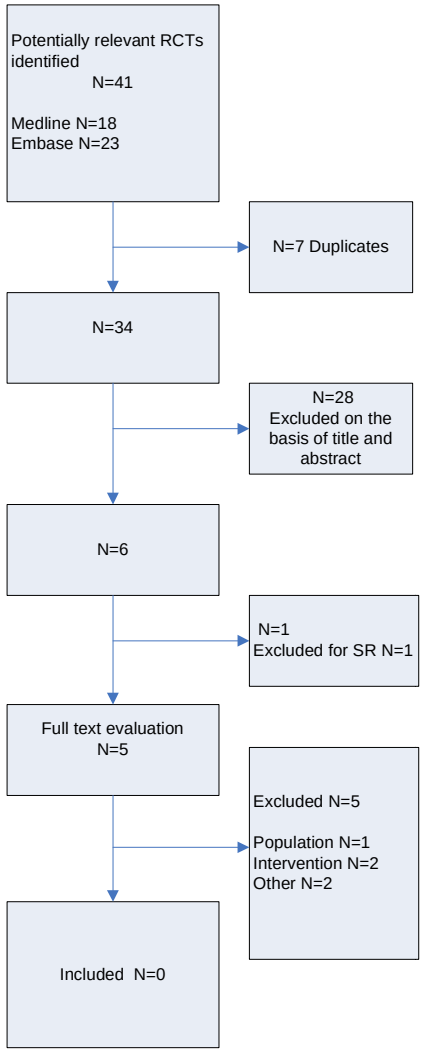


Table 70 – Neutropenia: excluded studies regarding prophylactic antifungals

Reference	Reason for exclusion
Girmenia 2010	Commentary
Grau 2012	Cost-effectiveness study
Kim 2011	Children
Ruping 2011	Dose finding study
Tan 2011	Diagnostic management study
Vehreschild 2007	Already excluded in included systematic review

Prophylactic antibiotics

It was decided not to update the search of the included review (Gafter-Gvili 2012), given the very recent search date.

Therapeutic antibiotics: oral versus IV

On July 6, 2012 an update of the search of the included systematic review (Vidal 2009) was performed in MEDLINE and Embase (> 2007), by which 49 potential relevant references were identified (Figure 6). After deduplication 35 references remained. Based on title and abstract 32 studies were withheld. Of the remaining 3 studies two were excluded with reason (Table 72) and one RCT was included (Sebban 2008) that was not yet included in the existing review (Table 71).

Figure 6 – Neutropenia: study flow selection of RCTs regarding therapeutic antibiotics – oral versus IV

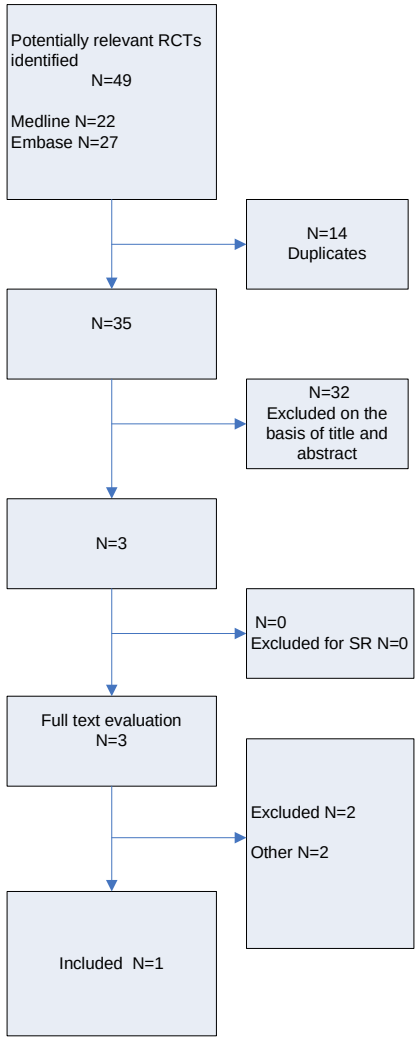


Table 71 – Neutropenia: included RCTs regarding oral versus intravenous therapeutic antibiotics

Reference	Interventions
Sebban 2008	Oral moxifloxacin compared to intravenous ceftriaxone

Table 72 – Neutropenia: excluded RCTs regarding oral versus intravenous therapeutic antibiotics

Reference	Reason for exclusion
Hendricks 2011	Cost-effectiveness study
Lopez Hernandez 2010	Spanish

Inpatient treatment versus outpatient treatment

On August 17, 2012 an update of the search of the included systematic review (Teuffel 2011) was performed in MEDLINE and Embase (> 2010), by which 95 potential relevant references were identified (Figure 7). After deduplication 85 references remained. Based on title and abstract 79 studies were withheld. Of the remaining six studies five were excluded with reason (Table 74) and one RCT was included (Table 73) that was not yet included in the existing review.

Figure 7 – Neutropenia: study flow selection of RCTs regarding inpatient versus outpatient management

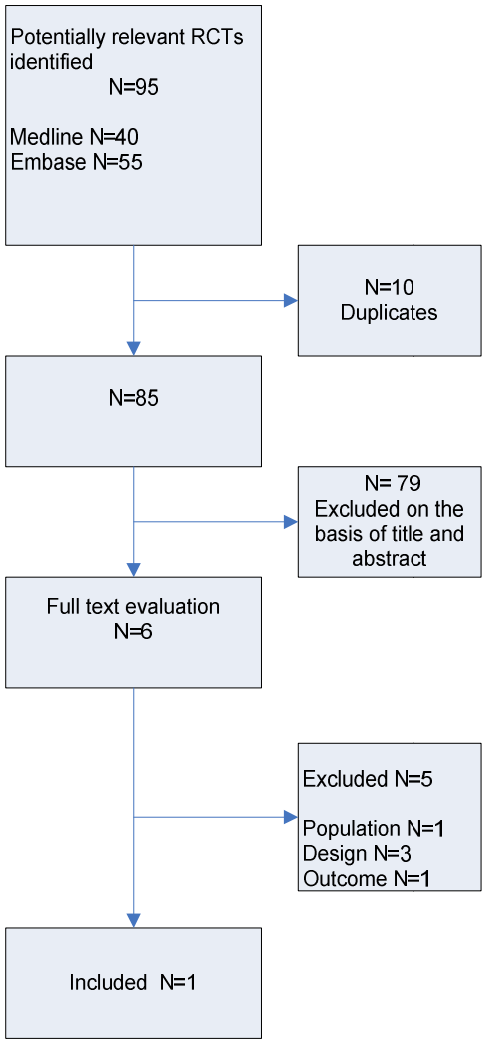


Table 73 – Neutropenia: included RCTs regarding inpatient versus outpatient management

Reference	Interventions
Talcott 2011	Continued inpatient antibiotic therapy versus early discharge to receive identical antibiotic treatment at home

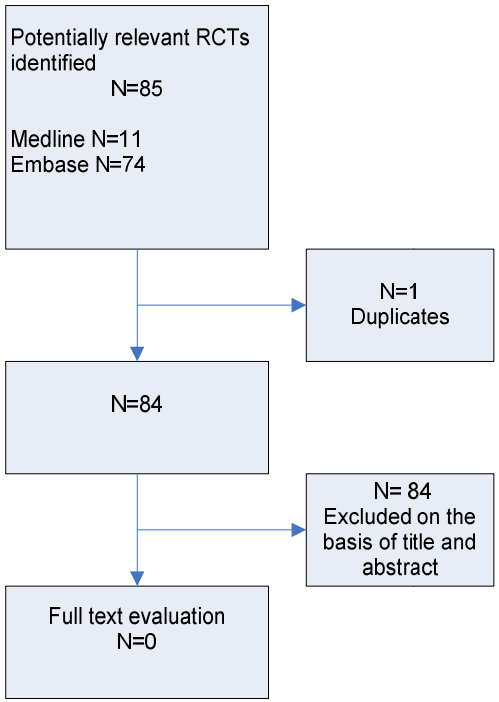
Table 74 – Neutropenia: excluded RCTs regarding inpatient versus outpatient management

Reference	Reason for exclusion
Belesso 2011	No RCT
Freifield 2011	No RCT
Orme 2010	Patients (children)
Rolston 2010	No RCT
Teuffel 2011	Outcome (cost-effectiveness)

Nursing practices: isolation

On August 17, 2012 a search was performed in MEDLINE and Embase (> 2005, from the search date of the included reviews of Eckmann 2006 and Zitella 2006), by which 85 potential relevant references were identified (Figure 8). After deduplication 84 references remained. Based on title and abstract all 84 studies were excluded.

Figure 8 – Neutropenia: study flow selection of RCTs regarding nursing practices - isolation



Appendix 2.5. Radioproctitis

Appendix 2.5.1. Systematic reviews

Three SRs (Denton 2009, Putta 2005, Sasse 2006) were retrieved in full-text of which one fulfilled all inclusion criteria (Sasse 2006) (Table 75). The other two reviews failed to assess all relevant domains of risk of bias. One of those (Denton 2009) included nine studies. For this review the search will be updated and a full risk of bias will be done for all included studies.

Table 75 – Radioproctitis: in and excluded systematic reviews

Systematic review	Treatment / prevention of chemotherapy- or radiotherapy related adverse events	Outcomes indicated by KCE	Searched MEDLINE and at least one other electronic database	Indicated date of search	Included assessment of risk of bias (concealment of allocation, blinded outcome assessment and completeness of follow-up)	Included
Denton 2009	+	+	+	+	-	yes*
Putta 2005	+	+	+	+	-	No
Sasse 2006	+	+	+	+	+	Yes

*+ Inclusion criterion met; - Inclusion criterion not met; * Review will be updated and full risk of bias will be assessed.*

Table 76 – Radioproctitis: characteristics of included systematic reviews

Systematic review	Search	Objective	Experimental intervention	Control intervention
Denton 2009	April 2007	'Non surgical interventions for late radiation proctitis in patients who have received radical radiotherapy to the pelvis'	'1) Anti-inflammatory agents i.e. amino-salicylic acid derivatives and steroids 2) Sucralfate 3) SCFA 4) Thermal coagulation therapy 5) Formalin 6) HBO and agents for treating the ischaemic and fibrotic component 7) Studies were included that involved a trial of these and any other agents identified'	'Placebo or no treatment, or any another active intervention'
Sasse 2006	Apr 2005	'Whether or not amifostine protects tumor cells as well as normal cells, and also to quantify the degree of the reduction of side effects'	Radiotherapy plus amifostine	Radiotherapy

Appendix 2.5.2. Randomized controlled trials

Two searches regarding interventions for the prevention or treatment of radioproctitis have been performed. The first concerned an update of the search for non surgical interventions of the included systematic review (Denton 2007), the second concerned an additional search for surgical and probiotic interventions.

The update of the search of the systematic review of Denton 2007 was performed on January 10, 2012. The study flow is presented in Figure 9. In April, 2012 the search for additional interventions (surgery and probiotics) was performed. The study flow is presented in Figure 10.

Figure 9 – Radioproctitis: study flow RCTs update Denton et al. (2007)

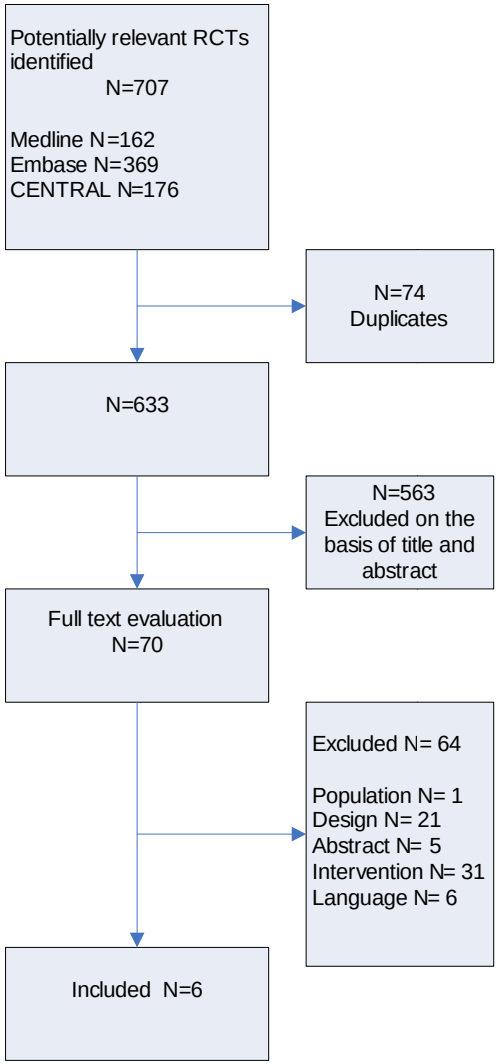
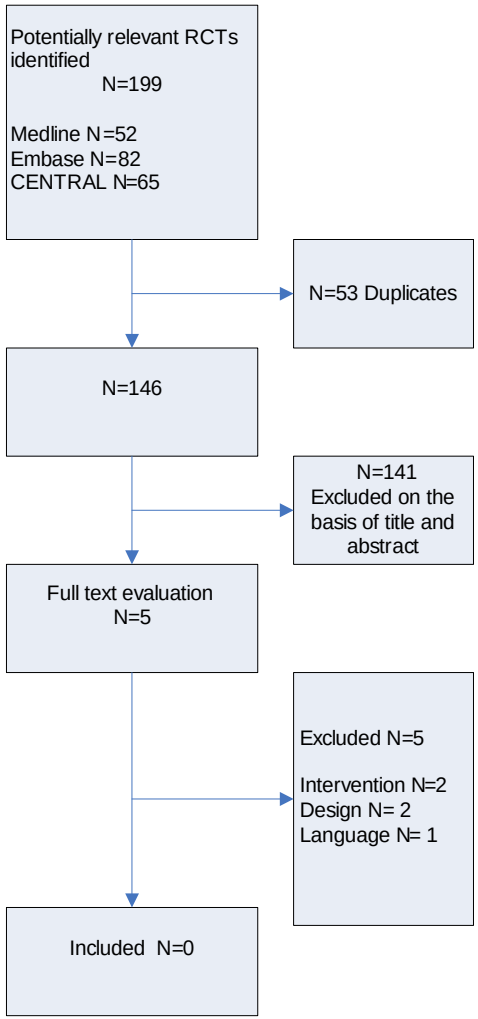


Figure 10 – Radioproctitis: study flow of RCTs regarding surgery or probiotics for radioproctitis



Three studies (Jensen 1997; Kochhar 1991; Rougier 1992) of the original review of Denton (2007) addressed non-surgical interventions that were of interest to the guideline committee. Through the update, 707 potential relevant references were identified. After deduplication 633 references remained. Based on title and abstract, 563 references were excluded. Of the remaining 70 references full text was screened. Of those, six RCTs were included (Table 77). Sixty-four references were excluded with reason (Table 78). In total, nine studies were included (three of the original review and six indentified by the literature update of the review) of which two studies discuss the preventive treatment of radioproctitis (Delia 2007; Fuccio 2011).

The additional search for surgical interventions or probiotics identified 199 potential relevant references. After deduplication, 146 references remained. Based on title and abstract 141 references were excluded. Of the remaining 5 references full text was screened. Of those, none RCT was included. However, one RCT concerning probiotics (Delia 2007) was identified in the literature update of the review of Denton 2007 and was included.

Table 77 – Prevention and treatment of radioproctitis: included RCTs

Reference	Interventions	Remarks
Prevention of radioproctitis		
Delia 2007	Probiotics	
Fuccio 2011	Corticosteroids	
Treatment of radioproctitis		
Clarke 2008	Hyperbaric oxygen	
Gheorghe 2003	Argon plasma coagulation	
Jensen 1997	Heater probe versus bipolar electrocoagulation probe	Already included in Denton 2007
Kochhar 1991	Sulfasalazine	Already included in Denton 2007
Lenz 2010	Argon plasma coagulation versus bipolar electrocoagulation	
Rougier 1992	Hydrocortisone versus betamethasone	Already included in Denton 2007
Sidik 2007	Hyberbaric oxygen	

Table 78 – Prevention and treatment of radioproctitis: excluded RCTs

Reference	Reason for exclusion
Prevention of radioproctitis	
Bujko 2001	No RCT (literature review)
Chen 2002	Chinese
Kietlinska 1984	Intervention not of interest to KCE (comparison of two interventions for cancer treatments)
Morley 1976	No RCT
Perez 1987	Intervention not of interest to KCE (comparison of two interventions for cancer treatments)
Treatment of radioproctitis	
Alvaro-Villegas 2010	No randomized comparison of intervention of interest.
Benk 1993	Intervention not of interest to KCE (dose reduction)
Benk 1992	Intervention not of interest to KCE (dose reduction)
Botten 2011	Conference abstract
Carlomagno 2009	Intervention not of interest to KCE (preoperative treatment for rectal cancer)
Cavci 2000	Intervention not of interest to KCE (metronidazole)
Chattopadhyay 2010	No RCT
Chen 2002	Chinese
Dai 2004	Intervention not of interest to KCE (Du Yi Wei Capsule)
De Parades 2008	No RCT
Dearnaley 1999	RCT addressing cancer treatment (conformal vs. conventional radiotherapy)
Doi 2010	Experimental rat model/acute radioproctitis
Edsmyr 1976	Intervention not of interest to KCE (orgotein)
Ehrenpreis 2005	Intervention not of interest to KCE (retinol palmitate (vitamin A))
Engen 2009	Intervention not of interest to KCE (vitamin E and C)
Feldmeier 2011	No RCT
Fuccio 2010	Conference abstract (full article included)

Reference	Reason for exclusion
Fuccio 2011	Conference abstract (full article included)
Garrido 2009	Spanish
Generali 2009	Intervention not of interest to KCE (misoprostol)
Gonzales 2009	Intervention not of interest to KCE (Epidermal growth factor)
Haas 2007	No RCT
Hayne 2008	No RCT
Hemati 2010	Conference abstract
Hille 2008	No RCT
Hille 2005	Intervention not of interest to KCE (misoprostol)
Hovdenak 2005	Intervention not of interest to KCE (sucralfate)
Jahraus 2005	Intervention not of interest to KCE (balsalazide)
Kanaev 2007	Bulgarian
Kanaev 2010	Russian
Karamanolis 2009	No RCT
Kim 2008	No RCT
Kneebone 2001	Intervention not of interest to KCE (sucralfate)
Kneebone 2004	Intervention not of interest to KCE (sucralfate)
Kronberger 2010	No RCT
Lee 2007	No RCT
Mateos Domingues 2010	No RCT
Menander-Huber 1978	Intervention not of interest to KCE (orgotein)
Montana 1992	Intervention not of interest to KCE (WR-2721, S-2 (3-aminopropylaminoethyl) phosphorothioic acid)
Ozaslan 2010	No RCT
Peterson 2009	No RCT
Pilepich 2006	Intervention not of interest to KCE (pentosanpolysulfate)
Pinto 1999	Intervention not of interest to KCE (short chain fatty acid enemas)

Reference	Reason for exclusion
Qadeer 2008	No RCT
Raman 2007	No RCT
Sahakitrungruang 2010	No RCT
Seo 2011	No RCT
Seo 2011	No RCT
Sharma 2010	No RCT
Stern 2007	No RCT
Talley 1997	Intervention not of interest to KCE (short-chain fatty acids)
Tam 2011	Conference abstract
Tian 2008	Chinese
Tonoiso 2011	No RCT
Tsibouris 1999	Commentary
Venkitaraman 2008	Intervention not of interest to KCE (pentoxifylline)
Ventikaraman 2008b	Erratum (intervention not of interest to KCE)
Vernia 2000	Intervention not of interest to KCE (topical sodium butyrate)
Vuong 2011	Intervention not of interest to KCE/acute radioproctitis (Botox-A)
Wang 2009	Intervention not of interest to KCE (Qingre Buyi Decoction)
Wang 2009b	Intervention not of interest to KCE (Qingre Buyi Decoction)
Wedlake 2009	Intervention not of interest to KCE (colesevelam hydrochloride)
Xie 1995	Intervention not of interest to KCE (Huoxue Huayu Shengji Jianji)

Appendix 2.6. Infertility

Appendix 2.6.1. Systematic reviews

Seven SRs (Beck-Fruchter 2008, Bedaiwy 2011, Ben-aharon 2010, Blumenfield 2008, Cruz 2010, Lee 2006, Peate 2009) were retrieved in full-text and evaluated. As five SRs (Beck-Fruchter 2008, Ben-aharon 2010, Blumenfield 2008, Cruz 2010, Lee 2006) failed to either include or report a risk of bias assessment, only one review fulfilled our inclusion criteria (Table 79).

Table 79 – Infertility: in and excluded systematic reviews

Systematic review	Treatment / prevention of chemotherapy- or radiotherapy related adverse events	Outcomes indicated by KCE	Searched MEDLINE and at least one other electronic database	Indicated date of search	Included assessment of risk of bias (concealment of allocation, blinded outcome assessment and completeness of follow-up)	Included
Beck-Fruchter 2008	+	+	-	+	-	No
Bedaiwy 2011	+	+	+	+	+	Yes
Ben-aharon 2010	+	+	+	+	-	No*
Blumenfield 2008	+	+	-	+	-	No
Cruz 2010	+	+	+	+	-	No
Lee 2006	+	+	+	+	-	No
Peate 2009	-	-	+	+	-	No

*+ Inclusion criterion met; - Inclusion criterion not met; * See remarks*

Table 80 presents the characteristics of the included SR.

Table 80 – Infertility: characteristics of the included systematic review

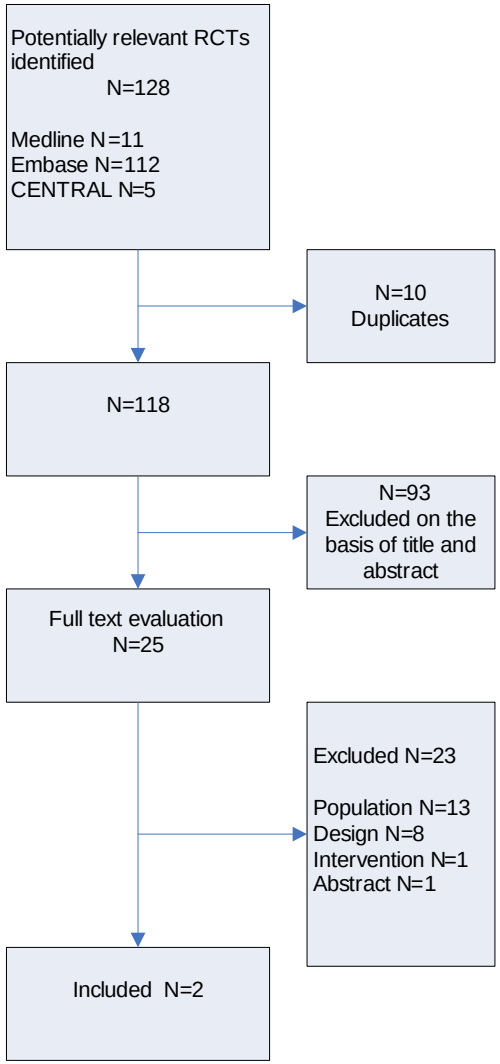
Systematic review	Search	Objective	Experimental intervention	Control intervention
Bedaiwy 2011	Jan 2010	'To determine whether gonadotropin-releasing hormone (GnRH) analog co treatment with chemotherapy provides better reproductive outcomes for woman at risk of premature ovarian failure (POF) as a side-effect of gonadotoxic chemotherapy'	'Gonadotropin-releasing hormone (GnRH) analog co treatment with chemotherapy'	Chemotherapy

Appendix 2.6.2. Randomized controlled trials

Two searches regarding additional interventions related to infertility as a result of gonadotoxic chemotherapy were performed. One concerned an update of the search of the systematic review of Bedaiwy 2011 (GnRH analogues) and the other concerned a search for additional interventions other than GnRH analogues.

The update of the search of the systematic review of Bedaiwy 2011 was performed on April 4, 2012. Study flow is presented in Figure 11.

Figure 11 – Infertility: study flow RCTs update Bedaiwy et al. (2011)



We identified 128 potential relevant references. After de-duplication 118 references remained. Based on title and abstract 93 references were excluded. Of the remaining 25 references full text was screened. Of those two RCTs were included (Del Mastro 2011; Gerber 2011) (Table 81) and 23 were excluded with reason (Table 82).

Table 81 – Infertility: included RCTs regarding GnRH-analogues (update Bedaiwy 2011)

Reference	Interventions
Del Mastro 2011	Chemotherapy + GnRHa (Triptorelin) vs. chemotherapy alone
Gerber 2011	Chemotherapy + GnRHa (Goserelin) vs. chemotherapy alone

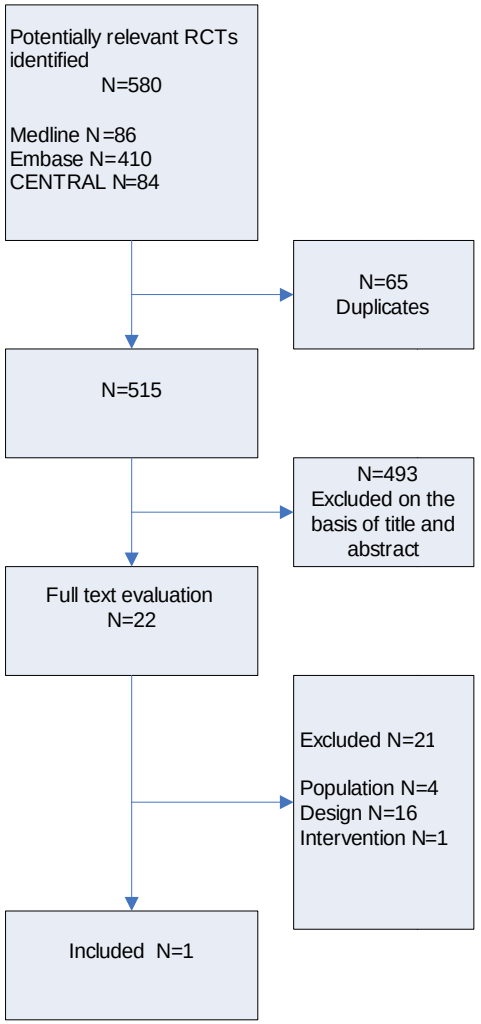
Table 82 – Infertility: excluded RCTs regarding additional GnRH-analogues (update Bedaiwy 2011)

Reference	Reason for exclusion
Bellver, 2010	No relevant patients
Brannian, 2010	No relevant patients
Celik, 2011	No relevant patients
Check, 2012	Conference abstract, no RCT, no relevant patients
Cheng, 2010	Conference abstract of same data as published in Cheng 2012 (no RCT)
Cheng, 2012	No RCT
Cota, 2011	No relevant patients
Davar, 2010	No relevant patients
Diluigi, 2011	No relevant patients
Duan, 2010	Article in Chinese. No relevant patients
Elgindy 2011	Abstract
Fabregues, 2011	No relevant patients
Firouzabadi, 2010	No relevant patients
Ghoshdastidar, 2010	No relevant patients

Reference	Reason for exclusion
Karimzadeh, 2010	No relevant patients
Kasapi, 2011	No RCT, no relevant patients, abstract only
Khalaf, 2010	No relevant patients, intervention not of interest to KCE
Park, 2010	No RCT
Stovall, 2010	No RCT
Tehraninejad, 2010	No relevant patients
Unlu, 2010	No RCT
Von Wolff, 2011	No RCT
Zhang, 2010	No intervention (model building)

On March 28, 2012 the search for additional interventions other than GnRH-analogues regarding infertility as side-effect of gonadotoxic chemotherapy was performed. Study flow is presented in Figure 12.

Figure 12 – Infertility: study flow RCTs interventions other than GnRH analogues



We identified 580 potential relevant references. After de-duplication 515 references remained. Based on title and abstract 493 references were excluded. Of the remaining 22 references full text was screened. Of those 1 RCT was included (Behringer 2010) (Table 83) and 21 were excluded with reason (Table 84).

Table 83 – Infertility: included RCTs interventions other than GnRH-analogues

Reference	Interventions	Remarks
Behringer 2010	Oral contraceptives versus GnRH- analogue co treatment	

Table 84 – Infertility: excluded RCTs interventions other than GnRH-analogues

Reference	Reason for exclusion
Ambrosetti 2009	No RCT
Anderson 2009	No RCT
Boughton 2001	No RCT
Buendgen 2010	No RCT, no relevant patients
Del Mastro 2006	No RCT
Diaz 2010	No RCT, no relevant patients
Frambach 2009	No RCT
Guastalla 2004	No RCT
Ignashina 1997	No RCT, article in Russian
Kasapi 2011	No relevant patients
Kovac 1996	No RCT
Levy 2008	No RCT
Maier 1988	No relevant patients
Masala 1997	No relevant patients
Oktay 2010	No RCT
Partridge 2007	No RCT
Rimington 1997	No relevant patients
Van der Kaaij 2007	Intervention not of interest to KCE
Von Wolff 2011	No RCT
Wildiers 2006	No RCT
Nature Reviews Nephrology 2009	No RCT

Appendix 2.7. Gastrointestinal complications

Appendix 2.7.1. Nausea & vomiting

Systematic reviews

Seventeen SRs (CCO 2003, Ballatori 2003, Ben Amar 2006, Billio 2010, Botrel 2011, Dando 2004, Ezzo 2006, Machado Rocha 2008, Maranzano 2005, Richardson 2007, Basch 2011a, Basch 2011b, Basch 2011c, Colagiuri 2010, Jordan 2007, Likun 2011, Lofti-Jam 2008, Lu 2007, Warr CCO 2005) were retrieved in full-text and evaluated. Four (Basch 2011a, Basch 2011b, Basch 2011c, Billio 2010, Likun 2011, Machado Rocha 2008) of these fulfilled the inclusion criteria (Table 85). When running a search for various interventions on August 24, 2012, by coincidence a recent Clinical Evidence report was identified (Keeley 2009), which was also included.

Table 85 – Nausea & vomiting: in and excluded systematic reviews

Systematic review	Treatment / prevention of chemotherapy- or radiotherapy related adverse events	Outcomes indicated by KCE	Searched MEDLINE and at least one other electronic database	Indicated date of search	Included assessment of risk of bias (concealment of allocation, blinded outcome assessment and completeness of follow-up)	Included
Ballatori 2003	-	+	-	+	-	No
Basch 2011a, Basch 2011b, Basch 2011c,	+	+	+	+	-+	Yes
Ben Amar 2006	+	+	+	+	-	No
Billio 2010	+	+	+	+	+	Yes
Botrel 2011	+	+	+	-	-	No
CCO 2003	+	+	+	+	-	No
Colagiuri 2010	-	-	+	+	-	No
Dando 2004	+	+	+	+	-	No
Ezzo 2006	-	+	+	+	+	No
Jordan 2007	+	+	+	-	-	No
Likun 2011	+	+	+	+	+	Yes
Lofti-Jam 2008	+	+	+	+	-	No
Lu 2007	?	?	+	+	-	No
Maranzano 2005	+	+	+*	+	-	No
Richardson 2007	-	+	+	+	+	No
Machado Rocha 2008	+	+	+	+	-	Yes**
Warr CCO 2005	+	+	+	+	-	No

*+ Inclusion criterion met; - Inclusion criterion not met; * search insufficiently specified (MEDLINE and 'other' databases); ** Review authors addressed concealment of allocation only.*

Table 86 presents the characteristics of the included SRs.

Table 86 – Nausea & vomiting: characteristics of included systematic reviews

Systematic review	Search	Objective	Experimental intervention	Control intervention
Basch 2011a, Basch 2011b, Basch 2011c	December 2009	Update ASCO guideline 2006	5-HT3 RAs, dexamethasone and NK1 RAs	Placebo or drugs of those classes
Billio 2010	March 2009	'To compare efficacy of different serotonin receptor antagonists (5-HT3 RAs) in the control of acute and delayed emesis induced by highly emetogenic chemotherapy'	5-HT3 RAs	'Any other drug of this class'
Keeley 2009	April 2008	What are the effects of treatments for nausea and vomiting occurring as a result of either the disease or its treatment in adults with cancer?	5-HT3 receptor antagonists, dexamethasone, NK1 receptor antagonists, cannabinoids, benzodiazepines and other interventions	Each other or placebo
Likun 2011	March 2010	'We performed a systematic review and meta-analysis to compare treatment effectiveness and adverse effects in cancer patients receiving chemotherapy with palonosetron to prevent chemotherapy-induced- nausea and vomiting'	'Chemotherapy with palonosetron'	'Any other 5-HT3 RAs'
Machado Rocha 2008	December 2006	To evaluate cannabis as a therapeutic agent for treating chemotherapy-induced nausea and vomiting in cancer patients.	Pharmacological interventions based on substances derived from C. sativa and/or smoked cannabis	Placebo, no intervention or any other intervention

Randomized controlled trials: cannabinoids

On August 24, 2012 a search was performed to identify RCTs evaluating the anti-emetic efficacy of cannabinoids in cancer patients receiving chemotherapy. MEDLINE and Embase were searched from 2006 (search date of the systematic review of Machado Rocha 2008), 115 potential relevant references were identified (Figure 13). After removing duplications, 106 references remained. Seventy-four studies were excluded based on title and abstract, another 30 studies were excluded with reason (Table 88). Eventually, two studies were included (Duran 2010; Meiri 2007) (Table 87).

Figure 13 – Nausea & vomiting: study flow RCTs regarding the anti-emetic efficacy of cannabinoids

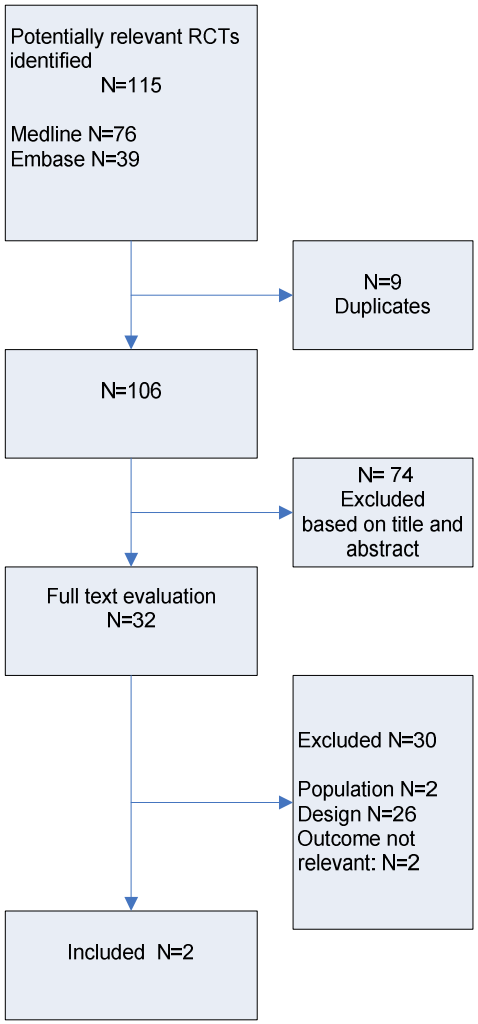


Table 87 – Nausea & vomiting: included RCTs regarding cannabinoids

Reference	Interventions
Duran 2010	Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting.
Meiri 2007	Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting.

Table 88 – Nausea & vomiting: excluded RCTs regarding cannabinoids

Reference	Reason for exclusion
Ben Amar 2006	Systematic review (previously excluded)
Biedrzycki 2007	No RCT
Darmani 2009	Review
Davis 2007	No RCT
Davis 2008	No RCT
Divall 2007	Narrative review
Ernst 2008	No RCT
Gerra 2010	No RCT
Hsu 2010	No RCT
Izzo 2010	No RCT
Johnson 2010	Outcome not relevant to KCE (pain)
Klumpers 2011	No cancer patients
Kreutz 2007	No RCT
Lenk 2008	No RCT
Maida 2008	No RCT
Merimann 2008	No RCT
Narang 2008	Outcome not relevant to KCE (pain)
Parker 2011	No RCT

Reference	Reason for exclusion
Peat 2010	No RCT
Perwitasari 2011	No RCT
Pisanti 2009	No RCT
Rivers 2010	No RCT
Schwartzberg 2007	No RCT
Slatkin 2007	No RCT
Strasser 2006	Anorexia-cachexia syndrome
Sutton 2006	No RCT
Todaro 2012	No RCT
Toth 2008	No RCT
Turcotte 2010	Narrative review
Zutt 2006	No RCT

Randomized controlled trials: benzodiazepines

On August 24, 2012 a search was performed (from 2008 onwards) in MEDLINE and Embase to identify RCTs evaluating the anti-emetic efficacy of benzodiazepines in cancer patients receiving chemotherapy or radiotherapy. The search resulted in 192 potential relevant references (Figure 14). After deduplication 187 references remained. All but one study were excluded based on title and abstract and one study was excluded with reason (Table 89). Eventually, no new RCTs were identified.

Figure 14 – Nausea & vomiting: study flow RCTs regarding the anti-emetic efficacy of benzodiazepines

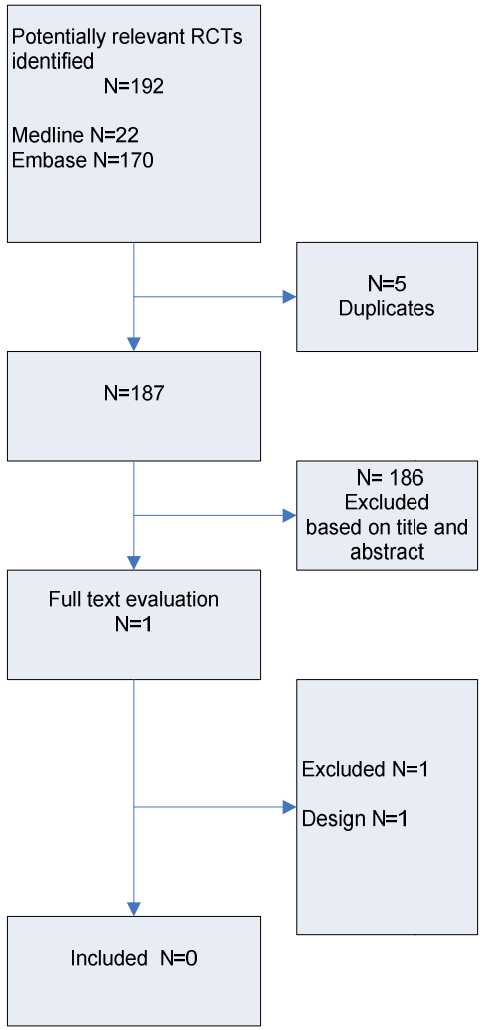


Table 89 – Nausea & vomiting: excluded RCTs benzodiazepines

Reference	Reason for exclusion
Hayashi 2010	No RCT

Appendix 2.7.2. Diarrhoea

Systematic reviews

Five (Fuccio 2009, Bhattacharya 2009, Major 2003, Major 2003 CCO, McGough 2004) SRs were retrieved in full-text and evaluated. As three (Bhattacharya 2009, Major 2003, Major 2003 CCO) SRs failed to either include or report a risk of bias assessment, only two reviews (Fuccio 2009, McGough 2004) fulfilled our inclusion criteria (Table 90).

Table 90 – Diarrhoea: in and excluded systematic reviews

Systematic review	Treatment / prevention of chemotherapy- or radiotherapy related adverse events	Outcomes indicated by KCE	Searched MEDLINE and at least one other electronic database	Indicated date of search	Included assessment of risk of bias (concealment of allocation, blinded outcome assessment and completeness of follow-up)	Included
Fuccio 2009	+	+	+	+	+	Yes
Bhattacharya 2009	+	+	+	+	-	No
Major 2003	+	+	+	+	-	No
Major 2003 CCO	+	+	+	+	-	No
McGough 2004	+	+	+	+	-	Yes

*+ Inclusion criterion met; - Inclusion criterion not met; * search insufficiently specified (MEDLINE and 'other' databases); ** Review authors addressed c oncealment of allocation only.*

Table 91 presents the characteristics of the included SR.

Table 91 – Diarrhoea: characteristics of the included systematic review

Systematic review	Search	Objective	Experimental intervention	Control intervention
Fuccio 2009	January 2009	'To estimate the efficacy of probiotic supplementation for prevention and treatment of radiation-induced diarrhea'	Probiotic supplementation	Placebo
McGough 2004	May 2003	'First, to assess the incidence and significance of malnutrition in patients undergoing pelvic radiotherapy and those with chronic bowel side effects resulting from pelvic radiotherapy and second, to examine the efficacy of therapeutic nutritional interventions used to manage gastrointestinal side effects of pelvic radiotherapy'	Therapeutic nutritional interventions	Placebo or any other intervention

Randomized controlled trials

On August 24, 2012 a search was performed to identify RCTs assessing the prophylactic and/or therapeutic effect on chemotherapy-induced or radiotherapy-induced diarrhoea of the following interventions: somatostatin analogues general; octreotide; probiotics; nutritional supplements and loperamide. MEDLINE and Embase were searched and 113 potential relevant references were identified (Figure 15). After deduplication 111 references remained. Based on title and abstract 90 studies were excluded. Of the remaining 21 studies 14 were excluded with reason (Table 93) and seven studies were included (Table 92).

Figure 15 – Diarrhoea: study flow of selection of RCTs regarding the prevention and/or treatment of radio- or chemotherapy induced diarrhoea

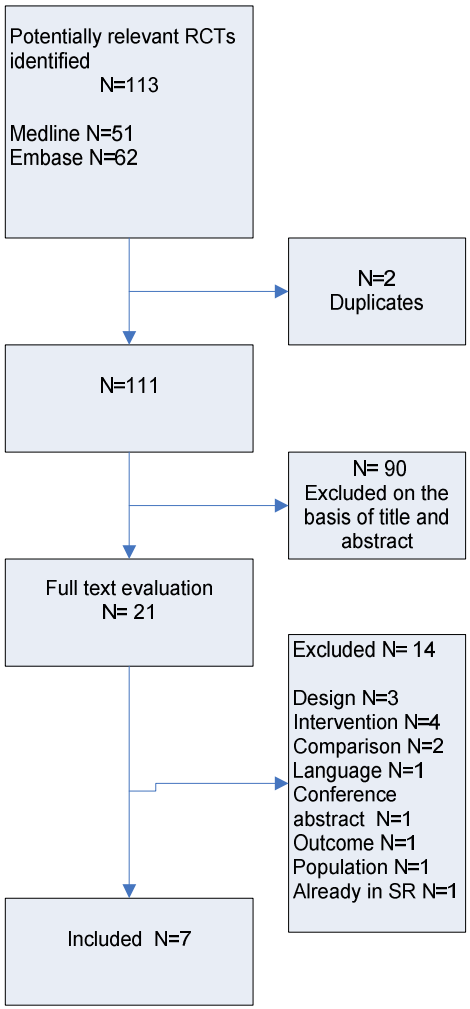


Table 92 – Diarrhoea: included RCTs

Reference	Interventions
Cascinu 1993	Octreotide versus loperamide
Cascinu 1994	Octreotide versus placebo
Gebbia 1993	Octreotide versus loperamide
Martenson 2008	Octreotide versus placebo
McGough 2008	Nutritional supplements
Yeoh 1993	Loperamide versus placebo
Zachariah 2010	Octreotide versus placebo

Table 93 – Diarrhoea: excluded RCTs

Reference	Reason for exclusion
Cascinu 2000	No RCT
Delia 2007	Already included in SR of Fuccio 2009
Dorval 1995	No RCT
Henriksson 1992	Intervention not of interest to KCE (sucralfate)
Lopez 2012	Conference abstract
McGough 2006	Outcomes not relevant to KCE
Rosenoff 2006	Comparison not of interest to KCE (two dose levels of octreotide)
Valss 1999	Spanish
Yavuz 2002	Comparison not of interest to KCE (diphenoxylate hydrochloride plus atropine sulphate)
Geller 1995	Population not of interest to KCE (bone marrow transplant)
Wadler 1995	No RCT
Rinke 2009	Intervention not aimed at diarrhoea
Kozelsky 2003	Intervention not of interest to KCE (Glutamine)
Rotovnik 2011	Intervention not of interest to KCE (Glutamine)

Appendix 2.8. Cardiotoxicity

Appendix 2.8.1. Systematic reviews

Six SRs (Cvetkovic 2005, Hensley 2009, Seymour 2004, Smith 2010, Van Dalen 2010, Van Dalen 2011) were retrieved in full-text and evaluated. As three SRs (Cvetkovic 2005, Hensley 2009, Seymour 2004) failed to either include or report a risk of bias assessment and two other SRs (Smith 2010, Van Dalen 2010) did not asses a treatment of interest, only one review (Van Dalen 2011) fulfilled our inclusion criteria (Table 94).

Table 94 – Cardiotoxicity: in and excluded systematic reviews regarding cardiac toxicity

Systematic review	Treatment / prevention of chemotherapy- or radiotherapy related adverse events	Outcomes indicated by KCE	Searched MEDLINE and at least one other electronic database	Indicated date of search	Included assessment of risk of bias (concealment of allocation, blinded outcome assessment and completeness of follow-up)	Included
Cvetkovic 2005	+	+	+	+	-	No
Hensley 2009	+	+	+	+	-	No
Seymour 2004	+	+	+	+	-	No
Smith 2010	-	+	+	+	+	No
Van Dalen 2010	-	+	+	+	+	No
Van Dalen 2011	+	+	+	+	+	Yes

+ Inclusion criterion met; - Inclusion criterion not met

Table 95 presents the characteristics of the included SR.

Table 95 – Cardiotoxicity: characteristics of the included systematic review

Systematic review	Search	Objective	Experimental intervention	Control intervention
Van Dalen 2011	2010	'The objective of this review was to assess the efficacy of different cardioprotective agents in preventing heart damage in cancer patients treated with anthracyclines'	'Anthracycline therapy together with a cardioprotective agent'	'Anthracycline therapy with or without a placebo'

Appendix 2.8.2. Randomized controlled trials

On April 17, 2012 an update of the search of the systematic reviews of van Dalen 2011 was performed by the Cochrane Childhood Cancer Group. The study flow is presented in Figure 16.

Hundred and twenty-seven potential relevant references were identified. After deduplication, 117 references remained. Based on title and abstract, six studies were selected for full text screening. Of those, none were included (Table 96).

Figure 16 – Cardiotoxicity: study flow RCTs update Van Dalen et al. 2011.

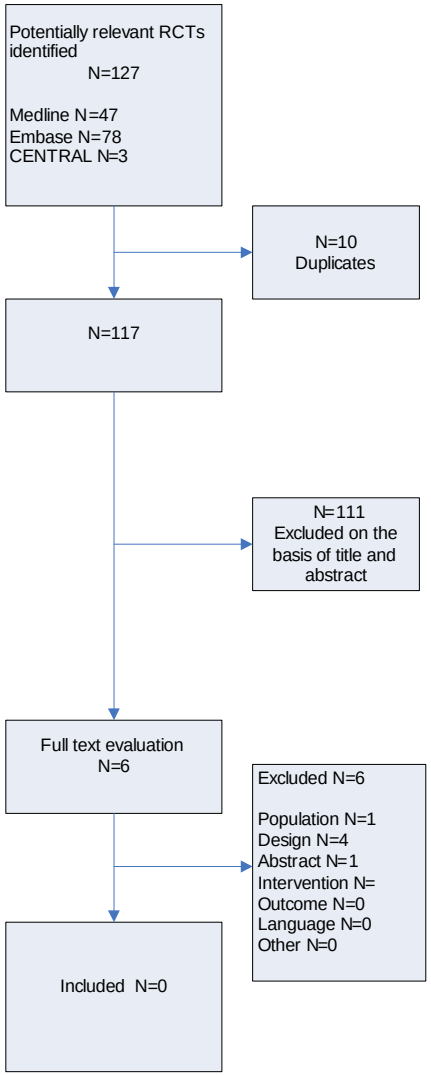


Table 96 – Cardiotoxicity: excluded studies regarding cardiac toxicity.

Reference	Reason for exclusion
Baravelli 2011	Conference abstract
Geisberg 2010	No RCT
Goey 2010	Review
Hawkes 2011	Letter
Monsuez 2010	Review
Vrooman 2011	Population: children

APPENDIX 3. QUALITY APPRAISAL

Appendix 3.1. Instruments

Appendix 3.1.1. Amstar

Table 97 – AMSTAR

Question	Answer
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	□ Yes □ No □ Can't answer □ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	□ Yes □ No □ Can't answer □ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	□ Yes □ No □ Can't answer □ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	□ Yes □ No □ Can't answer □ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	□ Yes □ No □ Can't answer □ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be	□ Yes □ No

reported.	□ Can't answer □ Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	□ Yes □ No □ Can't answer □ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	□ Yes □ No □ Can't answer □ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	□ Yes □ No □ Can't answer □ Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	□ Yes □ No □ Can't answer □ Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	□ Yes □ No □ Can't answer □ Not applicable

Appendix 3.2.1. Cochrane Collaboration's tool for assessing risk of bias

Table 98 – Cochrane Collaboration's tool for assessing risk of bias

Domain	Support for judgement	Review authors' judgement
Selection bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment
Performance bias		
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias		
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessors
Attrition bias		
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes)	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any reinclusions in analyses performed by the review authors	Attrition bias due to amount, nature or handling of incomplete outcome data
Reporting bias		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found	Reporting bias due to selective outcome reporting
Other bias		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool If particular questions/entries were prespecified in the review's protocol, responses should be provided for each question/entry	Bias due to problems not covered elsewhere in the table

Appendix 3.3. Oral complications

Appendix 3.3.1. Systematic reviews

After the inclusion phase, another review was identified (Worthington 2010) that turned out to be part of a series of four Cochrane reviews regarding this topic (Clarkson 2009, Clarkson 2010, Worthington 2010, Worthington 2011). Therefore, six reviews were included. The methodological quality of those SRs (Clarkson 2009, Clarkson 2010, Potting 2006, Sasse 2006, Worthington 2010, Worthington 2011) is summarized in Table 99.

Two reviews (Worthington 2010, Worthington 2011) scored 'Yes' for all items. In one SR (Potting 2006) the grey literature was not systematically searched and one SR (Sasse 2006) used a language restriction ('only western languages') for selecting RCTs. Only two SRs (Worthington 2010, Worthington 2011) considered the methodological quality of the included RCTs in formulating conclusions. Overall, all included SRs are considered as having a 'low risk' of bias.

Table 99 – Oral complications: methodological quality of included systematic reviews (AMSTAR)

Systematic review	A priori study design	Duplicate study selection and data extraction	Compre-hensive literature search	Publica-tion status not used as inclusion	List of in- and excluded studies	Charac-teristics of included studies provided	Study quality assess-ed and docu-mented	Quality assess-ment used in conclus-ions	Appro-priate methods to combine findings	Likelihood of publica-tion bias assessed	Conflict of interest stated
Clarkson 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	ReviewYes Studies No
Clarkson 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Review Yes Studies No
Potting 2006	Yes	?	Yes*	No*	No	Yes	Yes	No	Yes	No	Review No Studies No
Sasse 2006	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	Review No Studies Yes
Worthington 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Review Yes Studies No
Worthington 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Review Yes Studies No

*? Can't answer; N.A. Not applicable; * Electronic searches adequate, no systematic search for 'grey literature' (therefore scored 'No' for 'Publication status not used as inclusion criterion')*

Appendix 3.3.2. Randomized controlled trials

Figure 17 – Oral complications, prevention: risk of bias summary of RCTs

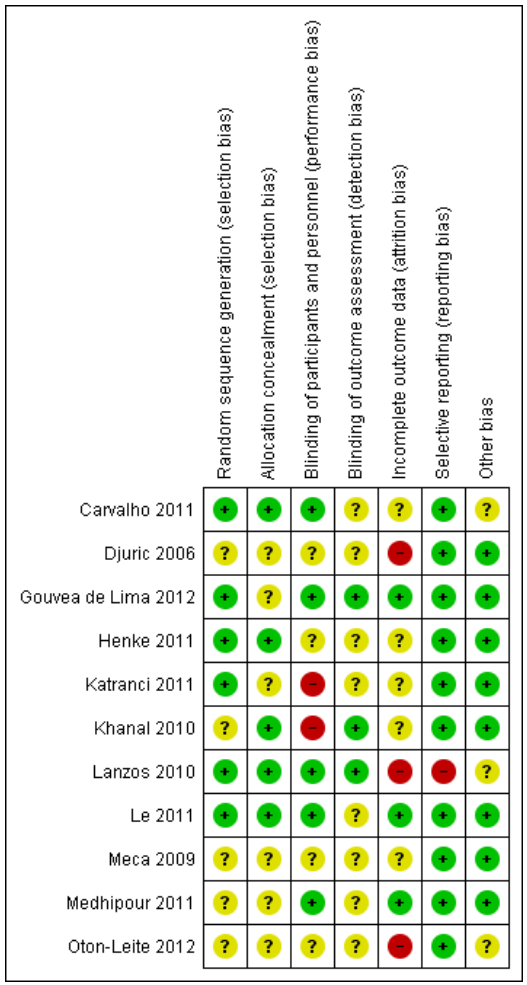


Figure 18 – Oral complications, prevention: risk of bias graph of RCTs

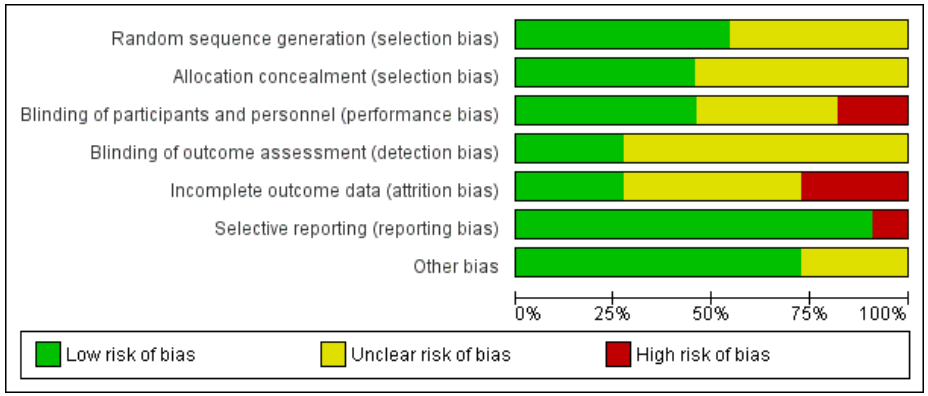


Figure 19 – Oral complications, treatment: risk of bias summary of RCTs

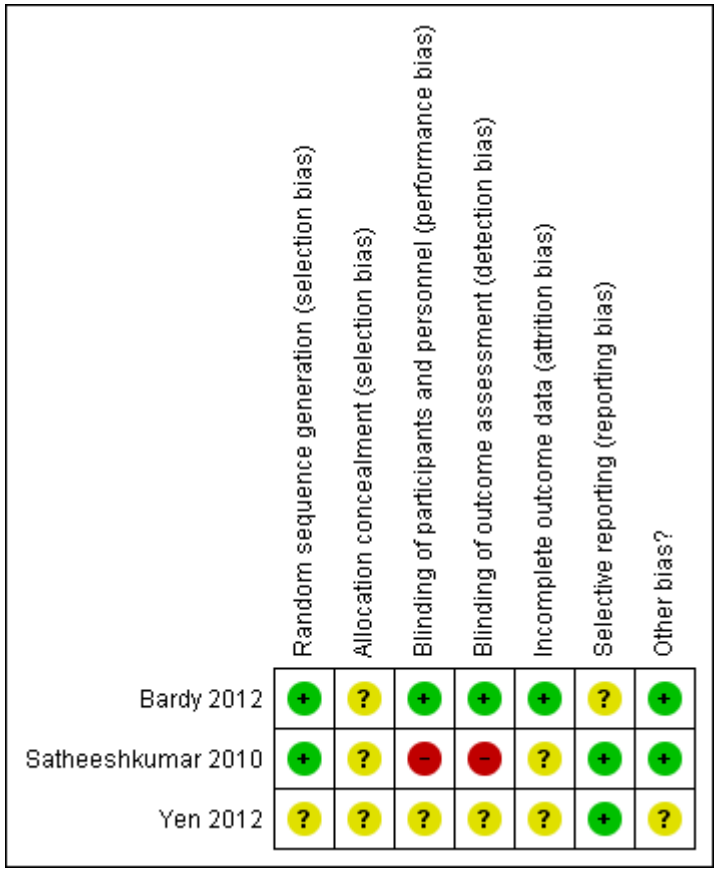
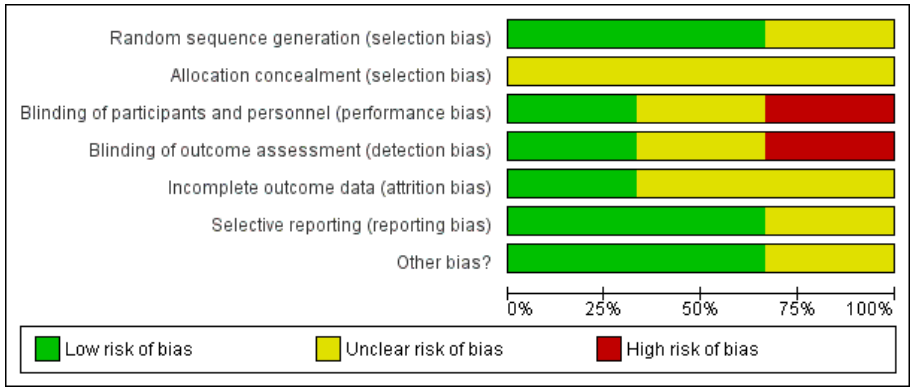


Figure 20 – Oral complications, treatment: risk of bias graph of RCTs



Appendix 3.4. Skin toxicity

Appendix 3.4.1. Systematic reviews

The methodological quality of the included SR (Richardson 2005) is summarized in Table 100. The review authors did not provide a list of in- and excluded studies and did not assess possible publication bias and conflicts of interest. Based on the three key domains of AMSTAR the overall risk of bias of this SR was considered 'low'.

Table 100 – Skin toxicity: methodological quality of the included systematic review (AMSTAR)

Systematic review	A priori study design	Duplicate study selection and data extraction	Compre-hensive literature search	Publica-tion status not used as inclusion criterion	List of in- and excluded studies	Charac-teristics of included studies provided	Study quality assess-ed and docu-mented	Quality assess-ment used in conclus-ions	Appro-priate methods to combine findings	Likelihood of publica-tion bias assessed	Conflict of interest stated
Richardson 2005	?	Yes	Yes	Yes	No	Yes	Yes	Yes	N.A.*	No	No

Appendix 3.4.2. Randomized controlled trials

Figure 21 – Skin toxicity: risk of bias summary of RCTs

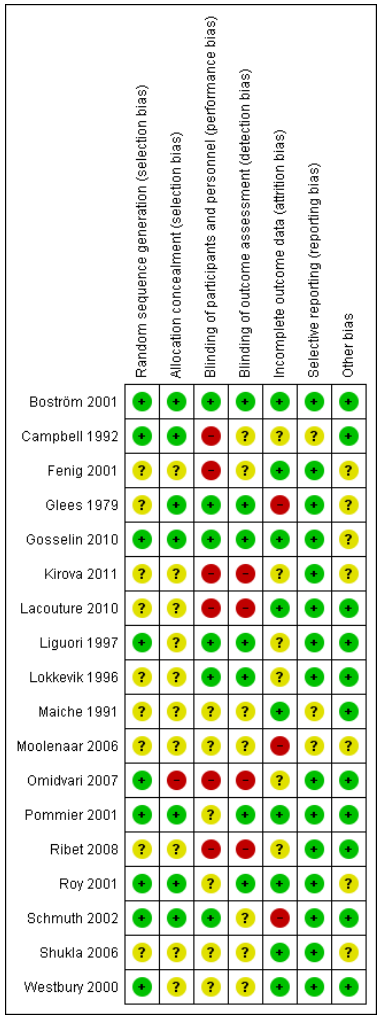
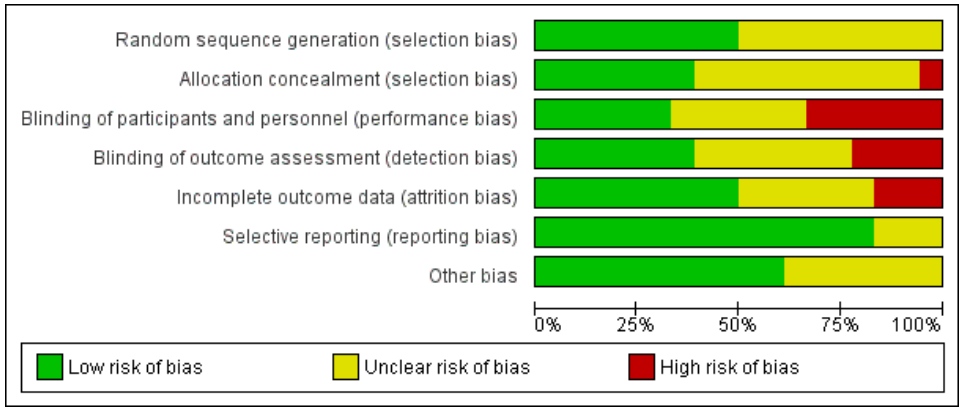


Figure 22 – Skin toxicity: risk of bias graph of RCTs



Appendix 3.5. Neuropathy

Appendix 3.5.1. Systematic reviews

The methodological quality of the included SR (Albers 2011) is summarized in Table 101. Most items were scored 'Yes'. The review authors did not search for grey literature and possible publication bias was not assessed. Although the authors mentioned that no meta-analyses were performed, they presented four meta-analyses which were done according to correct methods. Therefore, we considered the overall risk of bias of this SR as 'low'.

Table 101 – Neuropathy: methodological quality of the included systematic review (AMSTAR)

Systematic review	A priori study design	Duplicate study selection and data extraction	Compre-hensive literature search	Publica-tion status not used as inclusion criterion	List of in- and excluded studies	Charac-teristics of included studies provided	Study quality assess-ed and docu-mented	Quality assess-ment used in conclus-ions	Appro-priate methods to combine findings	Likelihood of publica-tion bias assessed	Conflict of interest stated
Albers 2011	Yes	Yes	Yes*	No*	Yes	Yes	Yes	Yes	Yes	No	Review Yes Studies No

*? Can't answer; N.A. Not applicable; * Electronic searches adequate, no systematic search for 'grey literature' (therefore scored 'No' for 'Publication status not used as inclusion criterion'); ** Text reports that no meta-analyses were performed, however four meta-analyses were presented as forest-plot*

Appendix 3.5.2. Randomized controlled trials

Figure 23 and Figure 24 show the results of the risk of bias assessment of the three identified RCTs. Two trials were stopped early (Chay 2010; Grothey 2011), which was due to preliminary reports from another trial (Hochster 2007) that suggested that Ca/Mg decreased treatment efficacy (which data later were found to be incorrect). We have, however, not been able to retrieve any report regarding this early stopped trial.

The method of randomization was unclear in the other two studies and concealment of allocation was insufficiently described in one study (Chay 2010). One study scored low risk of bias on all three key domains (allocation concealment; blinding of outcome assessment and completeness of follow-up) and was considered low risk of bias (Grothey 2011), the other study (Chay 2010) scored low risk of bias on two key items and unclear risk of bias for allocation concealment and was, therefore, considered unclear risk of bias.

Figure 23 – Neuropathy: risk of bias summary of RCTs

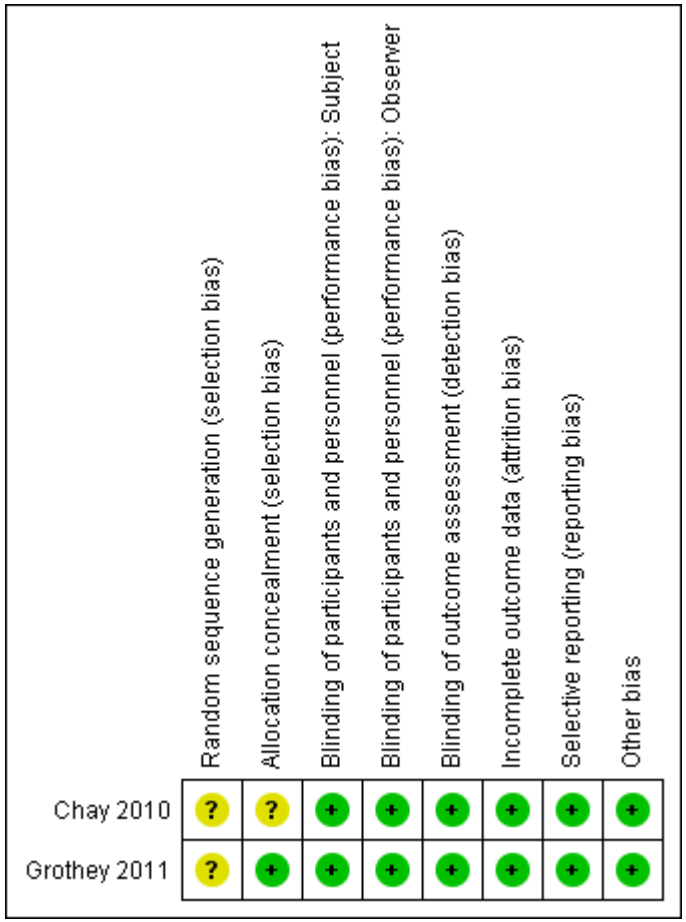
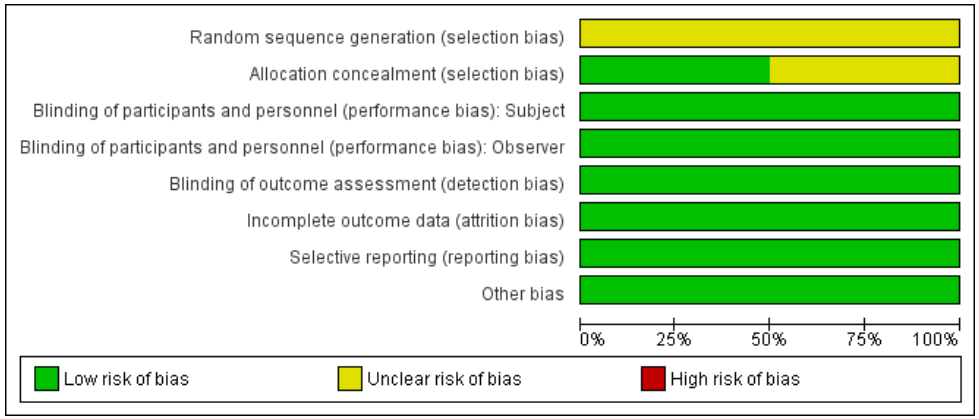


Figure 24 – Neuropathy: risk of bias graph of RCTs



Appendix 3.6. Neutropenia and neutropenic fever

Appendix 3.6.1. Systematic reviews

The methodological quality of the 13 included SRs (Bohlius 2008, Clark 2009, Eckmanss 2006, Gafter-Gvili 2005, Gafter-Gvili 2012, Gotzsche 2011, Herbst 2009, Johansen 2011, Jorgensen 2009, Madarnas 2009, Teuffel 2011, Vidal 2009, Zitella 2006) is summarized in Table 102. The review of Gafter-Gvili 2005 was superseded by an update that was published in the Cochrane Database of Systematic Reviews (Gafter-Gvili 2012). The reviews scored 'Yes' for most items. Two reviews were included despite a lack of full risk of bias assessment (Eckmanss 2006, Zitella 2006).

Table 102 – Neutropenia: methodological quality of included systematic reviews (AMSTAR)

Systematic review	A priori study design	Duplicate study selection and data extraction	Compre-hensive literature search	Publica-tion status not used as inclusion	List of in- and excluded studies	Charac-teristics of included studies provided	Study quality assess-ed and docu-mented	Quality assess-ment used in conclus-ions	Appropr-iate methods to combine findings	Likelihood of publica-tion bias assessed	Conflict of interest stated
Bohlius 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Review Yes Studies Yes
Clark 2009	Yes	Yes	Yes	?	Yes	Yes	Yes	Yes	Yes	No*	ReviewY es Studies No
Eckmanns 2006	?	?	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Review No Studies No
Gafter-Gvili 2005	Yes	Yes	Yes**	No**	Yes	Yes	Yes	Yes	Yes	Yes	Review Yes StudiesN o
Gafter-Gvili 2012	Yes	Yes	Yes	?	Yes	Yes	Yes	Yes	Yes	Yes	Review Yes Studies Yes
Gotzsche 2011	Yes	Yes	Yes	?	Yes	Yes	Yes	Yes	Yes.	Yes	ReviewY es Studies Yes
Herbst 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N.A.	Yes	ReviewY es Studies

Systematic review	A priori study design	Duplicate study selection and data extraction	Compre-hensive literature search	Publica-tion status not used as inclusion	List of in- and excluded studies	Charac-teristics of included studies provided	Study quality assess-ed and docu-mented	Quality assess-ment used in conclus-ions	Appro-priate methods to combine findings	Likelihood of publica-tion bias assessed	Conflict of interest stated
											No
Johansen 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes.	Yes	ReviewYes StudiesYes
Jorgensen 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes.	Yes	ReviewYes StudiesYes
Madarnas 2009	Yes	Yes	Yes	?	No	Yes	Yes	Yes	N.A.	No	ReviewYes StudiesNo
Teuffel 2011	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Review Yes Studies No
Vidal 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	ReviewYes StudiesYes
Zitella 2006	?	?	Yes	No	No	No	Yes	Yes	N/A	No	Review Yes Studies No

*? Can't answer; N.A. Not applicable; * Methods state that a funnel plot test was performed, but no results are presented in the text; ** Electronic searches adequate, no systematic search for 'grey literature' (therefore scored 'No' for 'Publication status not used as inclusion criterion')*

Appendix 3.6.2. Randomized controlled trials

Prophylactic use of G-CSF or GM-CSF

Two studies regarding the prophylactic use of G-CSF or GM-CSF for neutropenia in cancer patients are presented in Figure 25 and Figure 26 (Brugger 2009; Hecht 2010). One study scored a low risk of bias on all risk of bias assessment items, except for the risk on "other bias" (Brugger 2009). The other study scored an unclear risk of bias on the items random sequence generation, allocation concealment and attrition bias (Hecht 2010).

Figure 25 – Neutropenia: Risk of bias summary of studies regarding the prophylactic use of G-CSF or GM-CSF

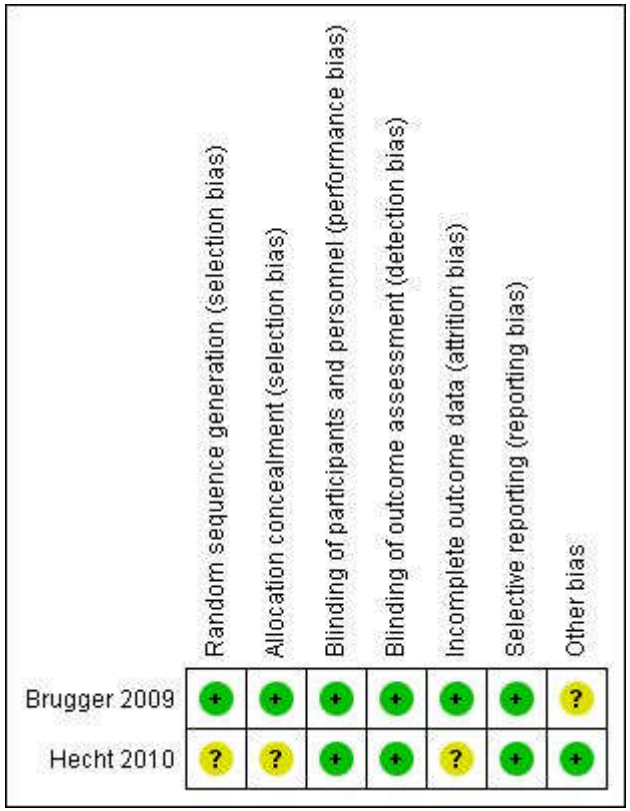


Figure 26 – Neutropenia: Risk of bias graph of studies regarding the prophylactic use of G-CSF or GM-CSF

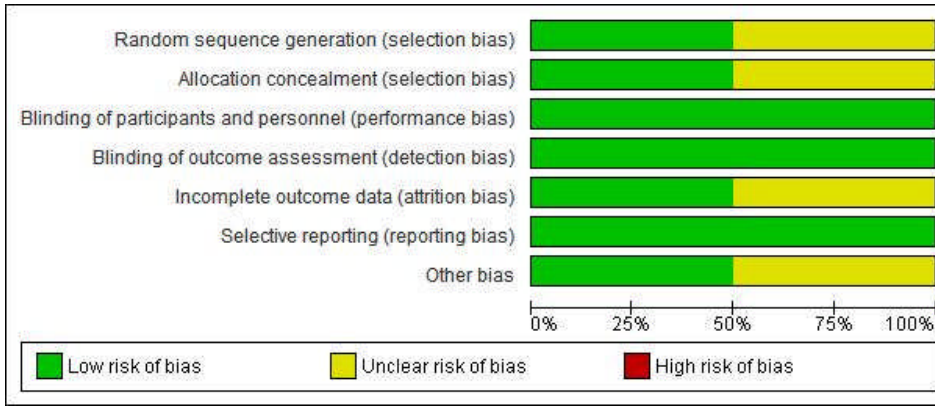
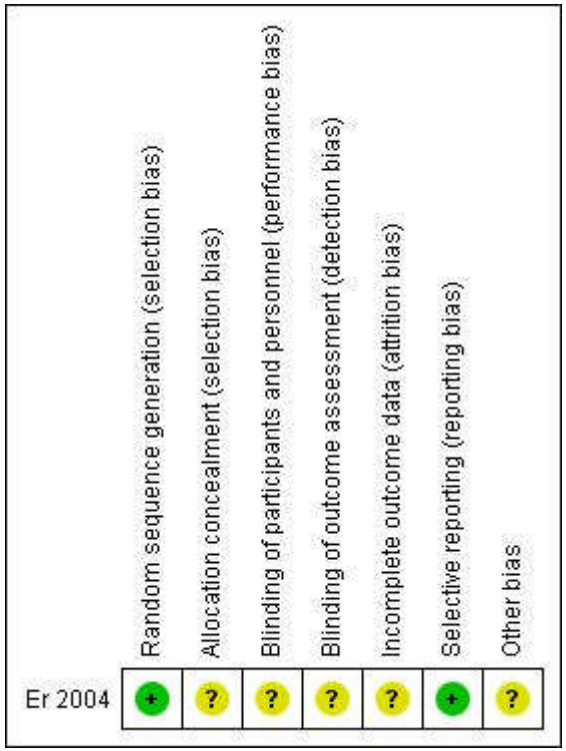


Figure 27 – Neutropenia: risk of bias summary of studies regarding the therapeutic use of G-CSF or GM-CSF



Therapeutic use of G-CSF or GM-CSF

One study regarding the therapeutic use of G-CSF or GM-CSF for the treatment of neutropenia in cancer patients is presented in Figure 27 and Figure 28 (Er 2004). The study scored a low risk on selection bias and reporting bias. An unclear risk of bias was scored for the remaining items.

Figure 28 – Neutropenia: risk of bias graph of studies regarding the therapeutic use of G-CSF or GM-CSF

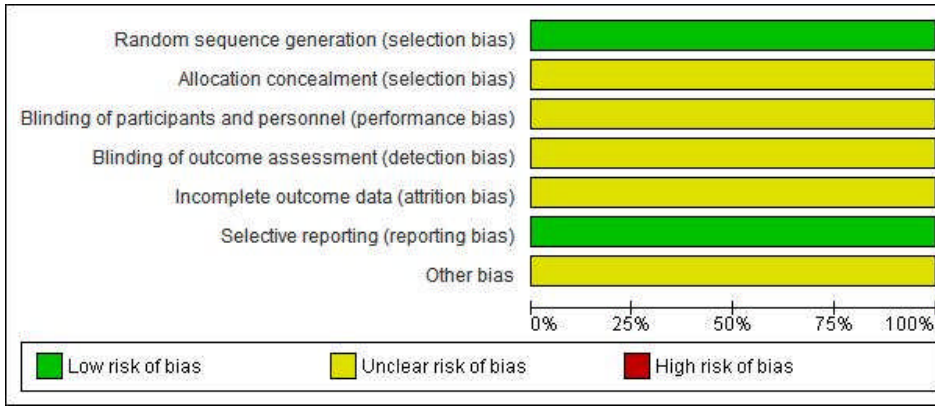
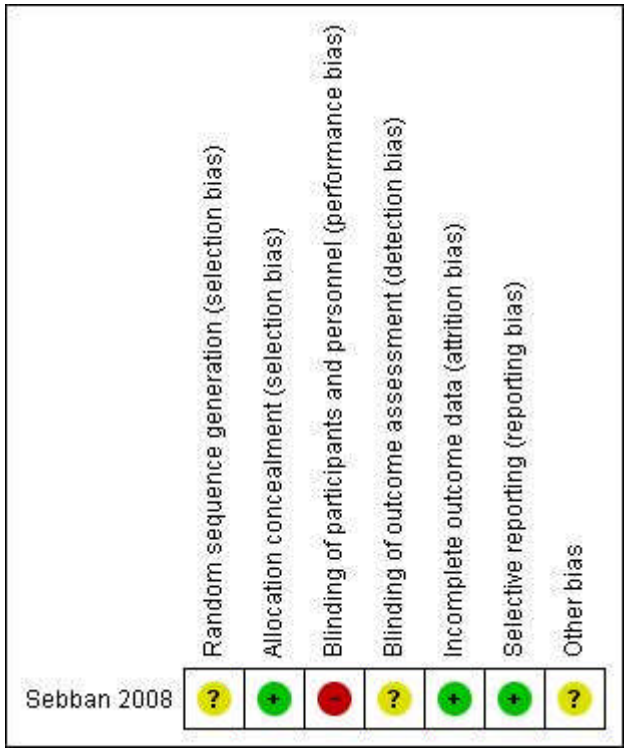


Figure 29 – Neutropenia: risk of bias summary of studies regarding the therapeutic use antibiotics



Therapeutic antibiotics: oral antibiotics versus intravenous antibiotics

One study regarding the therapeutic use of antibiotics is presented in Figure 29 and Figure 30 (Sebban 2008).

The study scored a low risk of selection bias and reporting bias. An unclear risk of bias was scored for the remaining items.

Figure 30 – Neutropenia: risk of bias graph of studies regarding the therapeutic use antibiotics

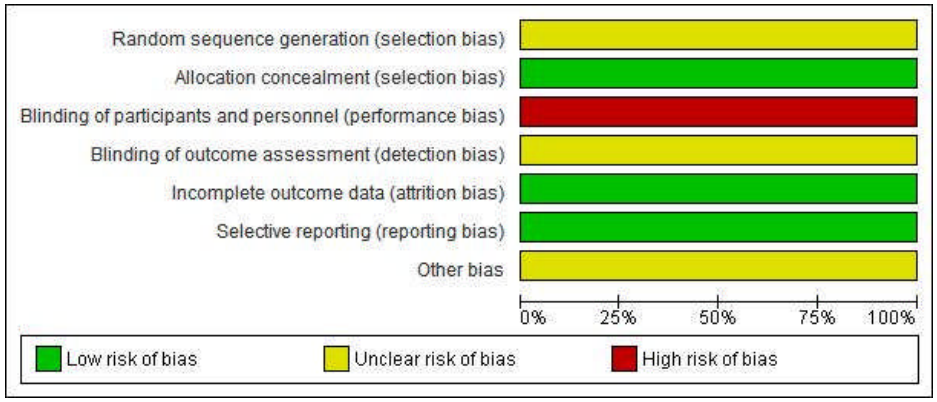
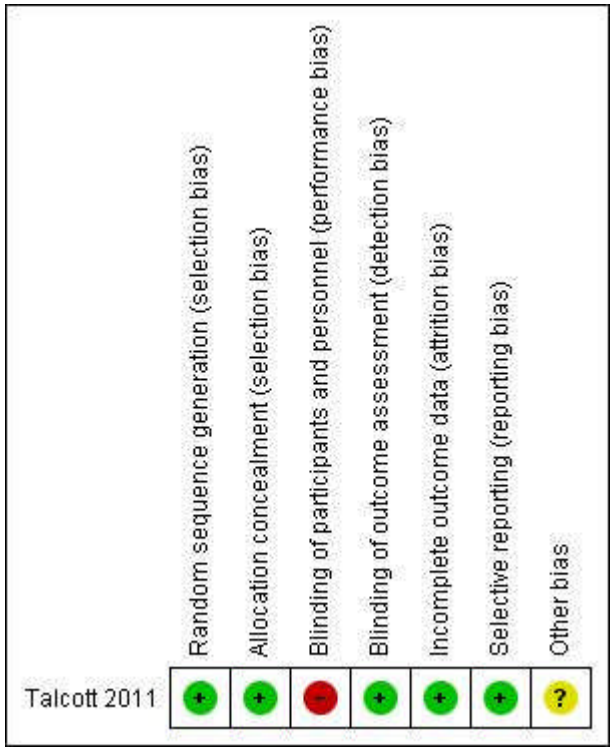


Figure 31 – Neutropenia: risk of bias summary of studies regarding inpatient versus outpatient management

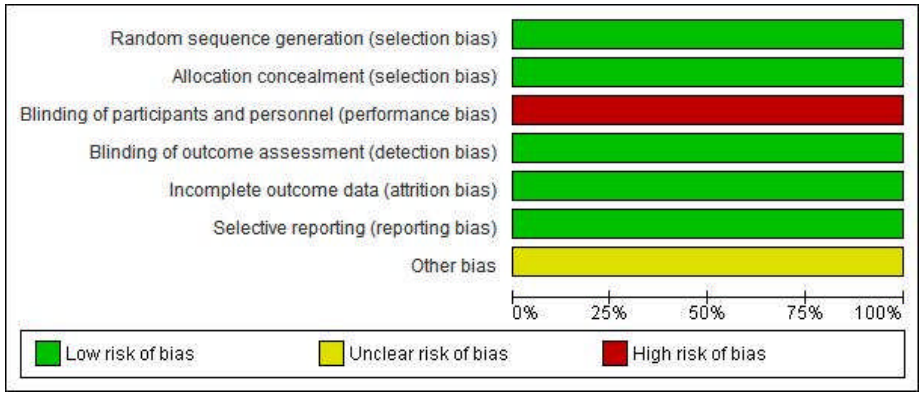


Inpatient versus outpatient management

One study regarding the inpatient versus outpatient management of neutropenic cancer patients is presented in Figure 31 and Figure 32 (Talcott 2011).

The study scored a low risk on selection bias and reporting bias. An unclear risk of bias was scored for the remaining items.

Figure 32 – Neutropenia: risk of bias graph of studies regarding inpatient versus outpatient management



Appendix 3.7. Radioproctitis

Appendix 3.7.1. Systematic reviews

The methodological quality of the included SRs is summarized in

Table 103. Both reviews were considered as high quality (low risk of bias), although for the review that will be updated (Denton 2009) risk of bias was only assessed for concealment of allocation.

Table 103 – Radioproctitis: methodological quality of the included systematic reviews (AMSTAR)

Systematic review	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion criterion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Denton 2009	Yes	Yes	Yes	Yes	Yes	Yes	No[§]	No[§]	Yes	Yes	Review Yes Studies No
Sasse 2006	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	Review No Studies Yes

[§] *Review will be updated and full risk of bias will be assessed*

Appendix 3.7.2. Randomized controlled trials

Figure 33 shows the results of the risk of bias assessment for the nine included studies. Figure 34 provides a summary of the risk of bias assessment across all studies. The method of randomization was unclear in all but two studies. Concealment of allocation was insufficiently described in six studies. Information on blinding was insufficiently reported in four studies and one study (Sidik 2007) was unblinded and therefore scored a high risk of bias on this item. Completeness of follow up was not adequately described in three studies and another three studies scored a high risk of bias as a substiantial number of participants dropped out in these studies for unclear reasons. One study (Rougier 1992) scored a high risk of bias on the items selective reporting and other bias (baseline imbalances). Focusing on the three key items (allocation concealment; blinding of outcome assessment and completeness of follow-up), not one of the studies scored low risk of bias on all three items.

Figure 33 – Radioproctitis: risk of bias summary of RCTs

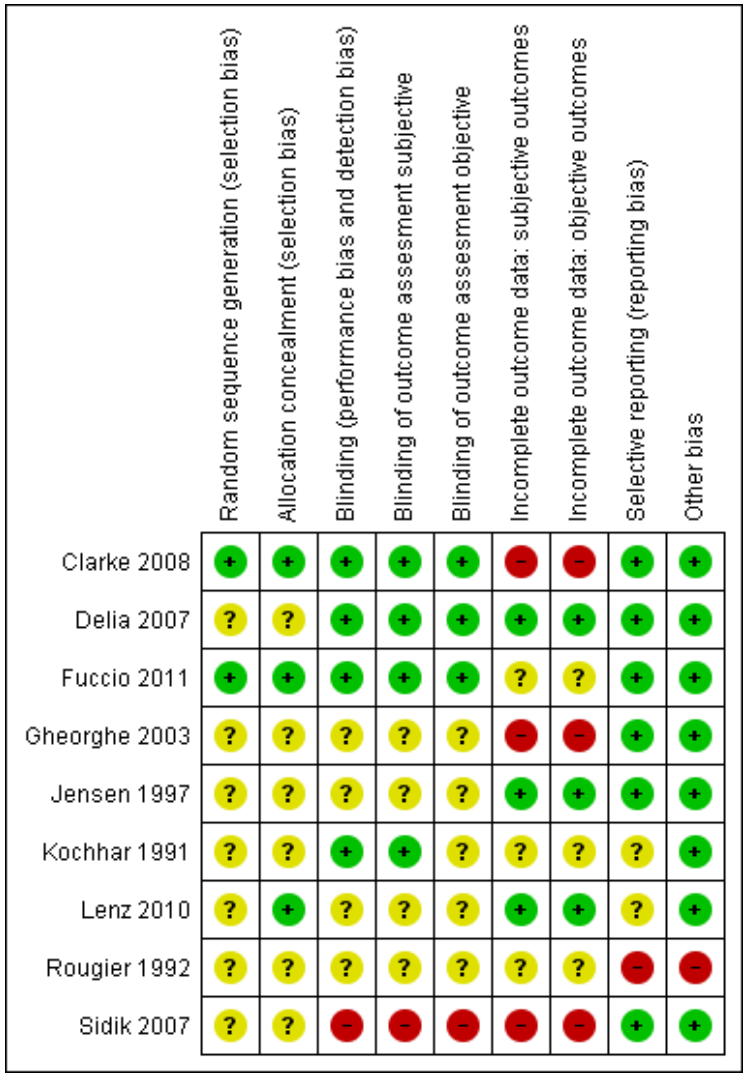
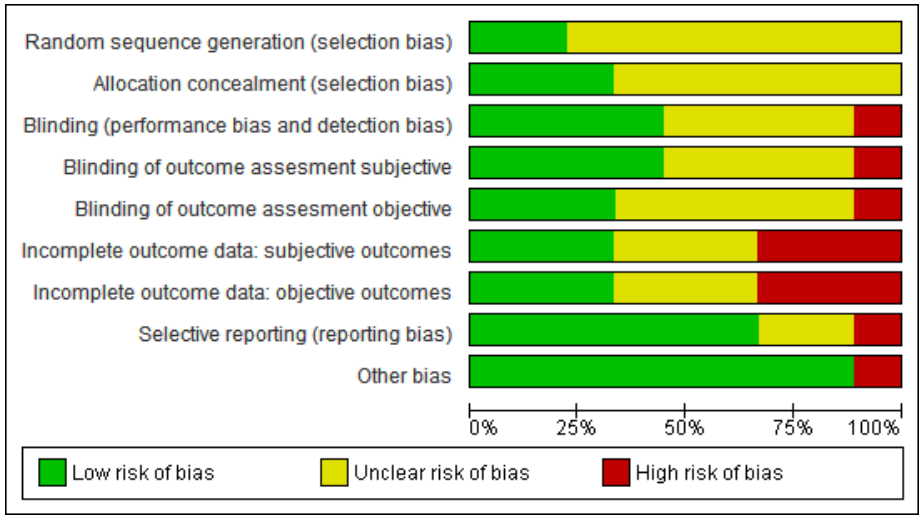


Figure 34 – Radioproctitis: risk of bias graph of RCTs



Appendix 3.8. Infertility

Appendix 3.8.1. Systematic reviews

Of the included review[96] quality appraisal through the AMSTAR criteria was performed. The SR failed to provide a list of both included and excluded studies. As for the last item (conflict of interest stated), the review scored a 'Yes' for the SR and a 'No' for the included studies, meaning that the sponsorship of the included studies had not been reported. Nevertheless, the review scored positively on the majority of the items and was therefore considered to be of low risk of bias (high methodological quality) (see Table 104).

Table 104 – Infertility: methodological quality of the included systematic review (AMSTAR)

Systematic review	A priori study design	Duplicate study selection and data extraction	Compre-hensive literature search	Publica-tion status not used as inclusion criterion	List of in- and excluded studies	Charac-teristics of included studies provided	Study quality assess-ed and docu-mented	Quality assess-ment used in conclus-ions	Appro-priate methods to combine findings	Likelihood of publica-tion bias assessed	Conflict of interest stated
Bedaiwy 2011	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Review: Yes Studies: No

? Can't answer; N.A. Not applicable

Appendix 3.8.2. Randomized controlled trials

Figure 35 and Figure 36 show the results of the risk of bias assessment of the three identified RCTs in which GnRH-a was studied as additional intervention in adult cancer patients at risk of infertility as a result of gonadotoxic chemotherapy (Del Mastro 2011; Elgindy 2011; Gerber 2011).

We considered one RCT, in which all items were scored low risk of bias, as low risk of bias (Del Mastro 2011). The second trial (Gerber 2011) was also considered unclear risk of bias. In this trial the items 'random sequence generation', 'concealment of allocation' and 'other bias' were scored unclear risk of bias.

Figure 35 – Infertility: risk of bias summary of RCTs GnRH analogues

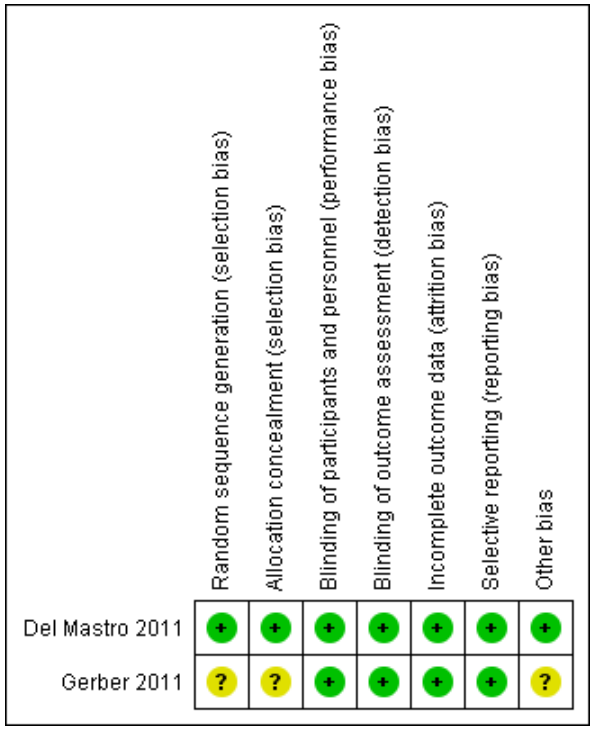
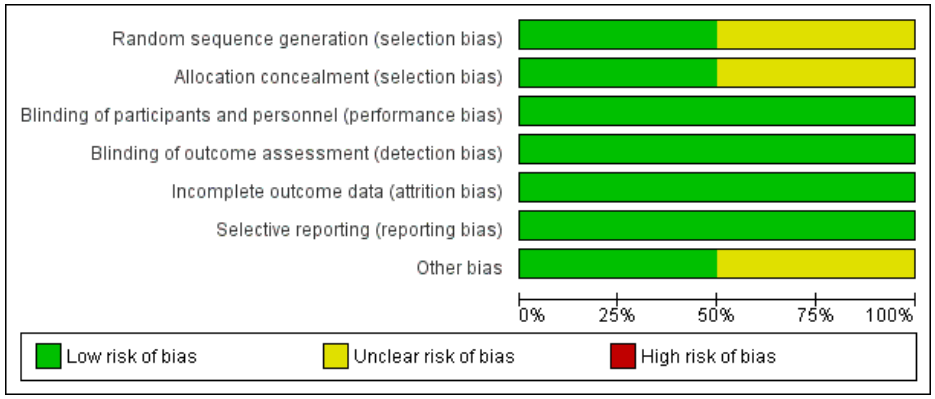
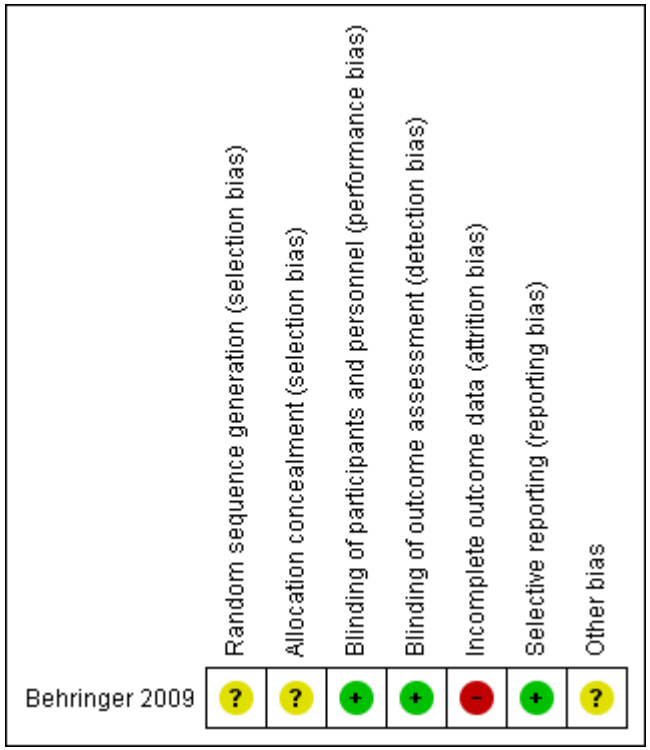


Figure 36 – Infertility: risk of bias graph of RCTs GnRH analogues



The summary of the risk of bias assessment of the RCT in which oral contraceptives were compared to GnRH-agonists as additional interventions (Behringer 2009) is presented in Figure 37. This trial was stopped early due to slow enrolment and upcoming concerns about a priori assumptions. Because of unclear risk of bias for 'random sequence generation', 'allocation concealment' and 'other bias' and high risk of attrition bias, this trial was considered as high risk of bias.

Figure 37 – Infertility: risk of bias summary of RCTs other interventions for fertility preservation



Appendix 3.9. Gastrointestinal toxicity

Appendix 3.9.1. Nausea & vomiting

Systematic reviews

When running a search for various interventions on August 24, 2012, by coincidence a recent Clinical Evidence report was identified (Keeley 2009), which was also included. Of the five included SRs (Basch 2011a, Basch 2011b, Basch 2011c, Billio 2010, Keeley 2009, Likun 2011, Machado Rocha 2008) quality appraisal through the AMSTAR criteria was performed (see Table 105). Four SRs (Basch 2011a, Basch 2011b, Basch 2011c, Billio 2010, Keeley 2009, Machado Rocha 2008) were judged to be of high qualityOverall, all five included SRs are considered having a low risk of bias.

Table 105 – Nausea & vomiting: methodological quality of included systematic reviews (AMSTAR)

Systematic review	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status as inclusion criterion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Basch 2011a; Basch 2011b; Basch 2011c;	?	?	Yes	Yes	Yes*	Yes	Yes	Yes	?	?	Review Yes Studies No
Billio 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Review Yes Studies No
Keeley 2009	?	Yes**	Yes	No	Yes*	Yes	Yes	Yes	N/A	?	Review Yes Studies No
Likun 2011	Yes	?	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Review Yes Studies No
Machado Rocha 2008	?	?	Yes	No	Yes	Yes	Yes***	Yes	Yes	Yes	Review Yes Studies No

*? Can't answer; N.A. Not applicable; * Only included studies; ** Preliminary selection by one researcher; *** Only concealment of allocation*

Randomized controlled trials: cannabinoids

Figure 38 and Figure 39 show the results of the risk of bias assessment of the two identified RCTs regarding the anti-emetic efficacy of cannabinoids (Ducan 2010; Meiri 2007). The method of randomization was adequate in one of the two trials (Duran 2010) and unclear in the other (Meiri 2007). Concealment of allocation was unclear in both trials. The risk of performance bias and detection bias was low in both trials. The risk of attrition bias was judged to be low in one trial (Duran 2010) and unclear in the other (Meiri 2007). The risk of reporting bias was unclear in the trial of Duran (2010) and low in the trial of Meuri (2007). The risk of other bias was high in both trials. None of the two studies scored low risk of bias on all three key domains (allocation concealment; blinding of outcome assessment and completeness of follow-up).

Figure 38 – Nausea & vomiting: risk of bias summary of RCTs regarding cannabinoids

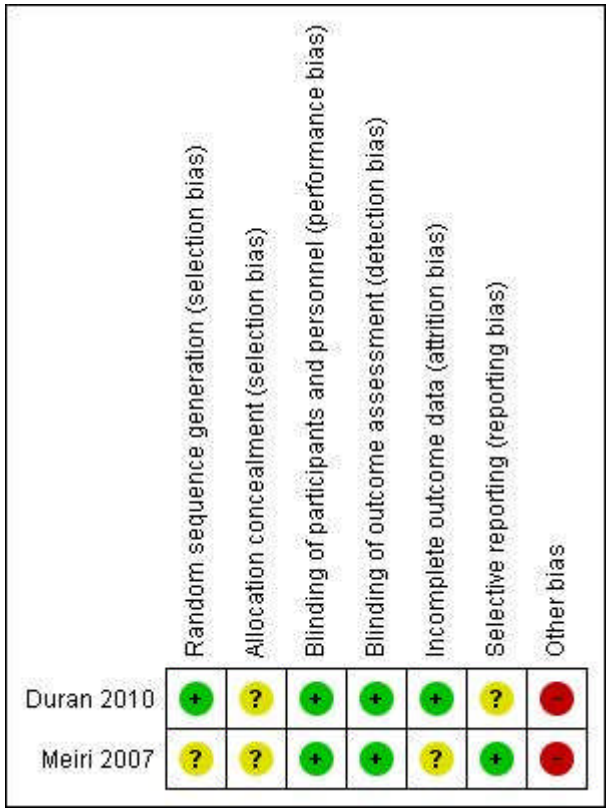
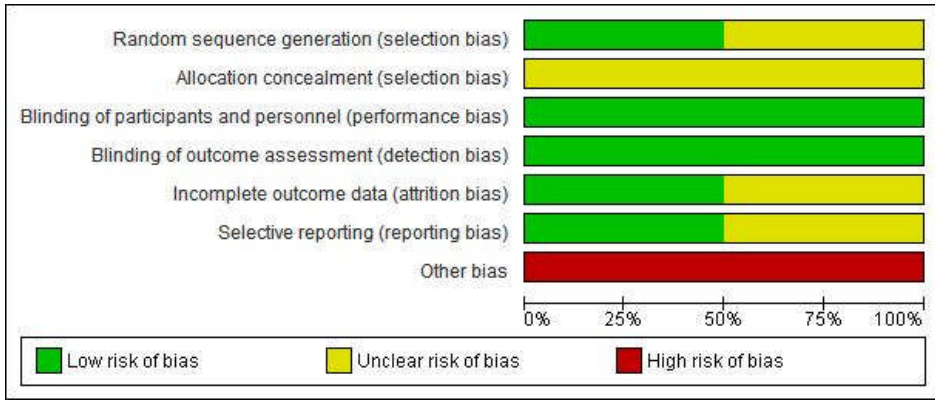


Figure 39 – Nausea & vomiting: risk of bias graph of RCTs regarding cannabinoids



Appendix 3.9.2. Diarrhoea

Systematic reviews

Of both included reviews (Fuccio 2009, McGough 2004), quality appraisal through the AMSTAR criteria was performed, the results are summarized in Table 106.The review scored positively on the majority of the items. However, the SR failed to provide a list of both included and excluded studies and scored a 'Yes' for the SR and a 'No' for the included studies on the last item, meaning that the sponsorship of the included RCTs had not been reported. Overall, the review is considered as having a 'low risk' of bias.

Table 106 – Diarrhoea: methodological quality of included systematic reviews (AMSTAR)

Systematic review	A priori study design	Duplicate study selection and data extraction	Compre-hensive literature search	Publica-tion status as inclusion criterion	List of in- and excluded studies	Charac-teristics of included studies provided	Study quality assess-ed and docu-mented	Quality assess-ment used in conclus-ions	Appropr-iate methods to combine findings	Likelihood of publica-tion bias assessed	Conflict of interest stated
Fuccio 2009	Yes	Yes	Yes	Yes	Yes*	Yes	Yes	Yes	Yes	Yes	Review Yes Studies No
McGough 2004	Yes	?	Yes	Yes	Yes*	Yes	Yes	Yes	N/A	?	Review Yes Studies No

Randomized controlled trials

Figure 40 and Figure 41 show the results of the risk of bias assessment of the seven identified RCTs regarding the prevention and/or treatment of radiotherapy-induced or chemotherapy-induced diarrhoea (Cascinu 1993; Cascinu 1994; Gebbia 1993; Martenson 2008; McGough 2008; Yeoh 1993; Zachariah 2010). The method of randomization was adequate in four (Cascinu 1993; Cascinu 1994; Martenson 2008; Zachariah 2010) and unclear in the remaining studies (Gebbia 1993; McGough 2008; Yeoh 1993). Concealment of allocation was adequate in five trials (Cascinu 1993; Cascinu 1994; Martenson 2008; McGough 2008; Zachariah 2010) and unclear in the two remaining trials (Gebbia 1993; Yeoh 1993). The risk of performance bias and detection bias was high in three trials (Cascinu 1993; Gebbia 1993; McGough 2008) and low in the remaining trials. The risk of attrition bias was judged to be low in all but one trial (Zachariah 2010) and the risk of reporting bias was low in all seven trials. Lastly, the risk of other bias was high in one trial (Martenson 2008) and unclear in another (McGough 2008).

Figure 40 – Diarrhoea: risk of bias summary of RCTs

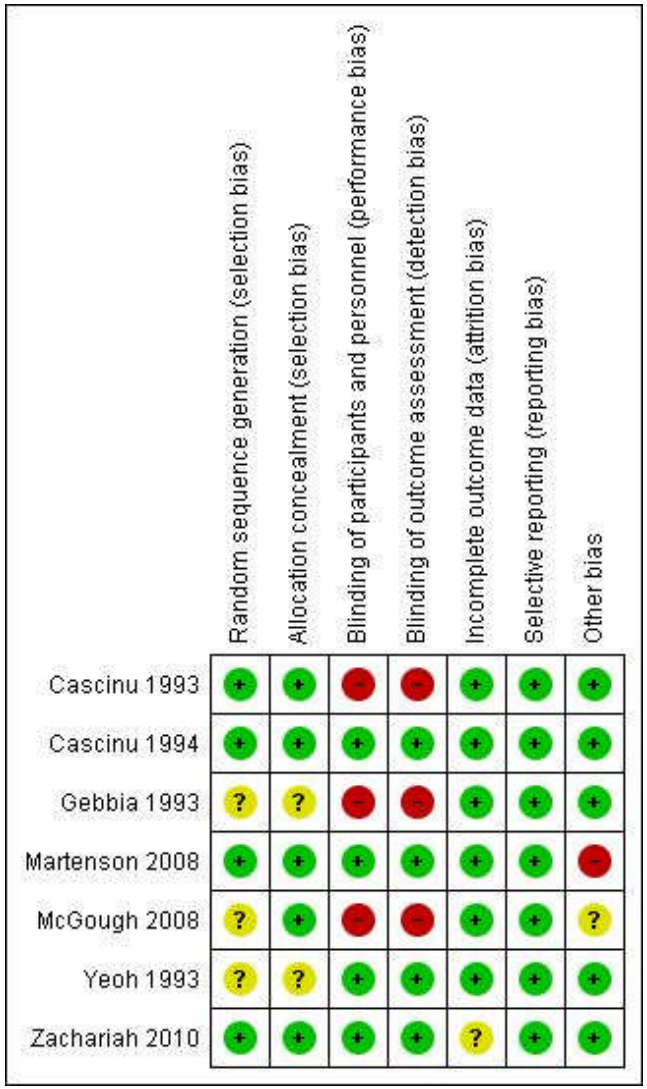
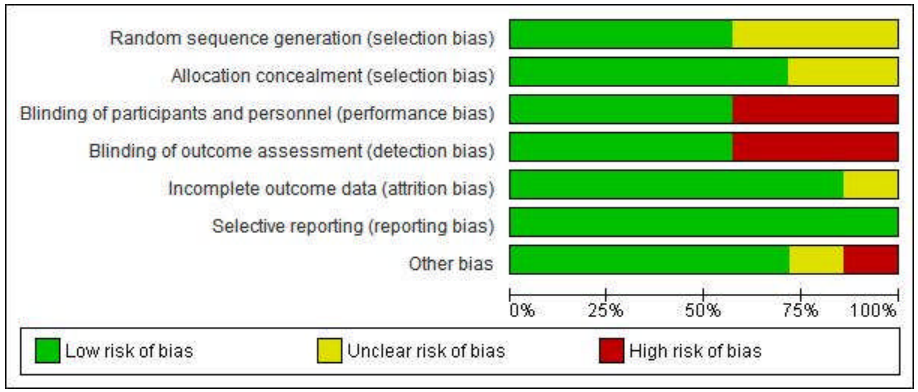


Figure 41 – Diarrhoea: Risk of bias summary of RCTs



Appendix 3.10. Cardiotoxicity

Appendix 3.10.1. Systematic reviews

Of the one included review (Van Dalen 2011), quality appraisal through the AMSTAR criteria was performed. The review scored positively on the majority of the items. However, the SR failed to address whether there was a conflict of interest for both the review and the included studies. Overall, the SR is considered as having a 'low risk' of bias (Table 36).

Table 107 – Cardiotoxicity: methodological quality of the included systematic review (AMSTAR)

Systematic review	A priori study design	Duplicate study selection and data extraction	Compre-hensive literature search	Publica-tion status as inclusion criterion	List of in- and excluded studies	Charac-teristics of included studies provided	Study quality assess-ed and docu-mented	Quality assess-ment used in conclus-ions	Approp-riate methods to combine findings	Likelihood of publica-tion bias assessed	Conflict of interest stated
Van Dalen 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Review No Studies No

? Can't answer; N.A. Not applicable

APPENDIX 4. GRADE PROFILES BY INTERVENTION AND OUTCOME

Appendix 4.1. Oral complications

Table 108 – Oral complications: overview of results and GRADE-profiles of the effect of chemoprotective agents to prevent oral mucositis as a result of radiotherapy and/or chemotherapy

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Oral cooling versus placebo (SR: 5 studies, 502 participants + 1 RCT 60 participants)								
Incidence of oral mucositis (any grade): RR = 0.74 (95%CI 0.57 to 0.92) (Worthington 2011, Katranci 2011)	5	-2	0	0	-1	0	1: 4 of 5 studies high risk of bias 4: confidence interval includes CDT (RRR 10%)	Very low
Incidence of oral mucositis (moderate plus severe): RR = 0.51 (95%CI 0.31 to 0.84) (Worthington 2011, Katranci 2011)	5	-2	0	0	0	0	1: 4 of 5 studies high risk of bias 4: Wide confidence interval, but upper limit = 0.84 and effect is large	Low
Incidence of oral mucositis (severe): RR = 0.34 (95%CI 0.17 to 0.70) (Worthington 2011, Katranci 2011)	5	-2	0	0	0	0	1: 4 of 5 studies high risk of bias	Low
Mouthwashes:								
Allopurinol mouth rinse versus placebo/no treatment (SR: 4 trials, 146 participants)								
Mucositis (any grade): RR = 0.77 (95%CI 0.50 to 1.19) (Worthington 2011)	4	-2	-1	0	-1	0	1: 3 of 4 studies high risk of bias 2: Inconsistent results 4: CI includes both appreciable benefit and harm (RRR/RRI 10%)	Very low
Mucositis (moderate plus severe): RR = 0.66 (95%CI 0.50 to 0.86) (Worthington 2011)	2	-1	0	0	-1	0	1: 1 study high risk of bias 4: CDT (RRR 10%) not included, but OIS not reached, only 54 patients (underpowered)	Low
Mucositis (severe): RR = 0.81 (95%CI 0.63 to 1.04) (Worthington 2011)	2	-1	0	0	-2	0	1: 1 study high risk of bias 4: Confidence interval includes benefit and no effect, only 54 patients	Very low
Benzydamine mouthwash versus placebo (SR: 4 studies, 332 participants)								

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Mucositis (any grade): RR = 0.67 (95%CI 0.47 to 0.97) (Worthington 2011)	1	-1	-2	0	-1	0	1: Unclear risk of bias study 2: Single small study 4: Confidence interval includes CDT (RRR 10%)	Very low
Mucositis (severe): RR = 0.55 (95%CI 0.38 to 0.82) (Worthington 2011)	1	-1	-2	0	0	0	1: Unclear risk of bias study 2: Single small study	Very low
Chlorhexidine mouthwash versus placebo/no treatment (SR: 7 studies, 536 participants)								
Mucositis (any grade): RR = 0.76 (95%CI 0.47 to 1.24) (Worthington 2011)	4	-1	-1	0	-1	0	1: 1 study high risk of bias, 3 unclear risk of bias 2: Heterogeneity of results 4: Confidence interval includes appreciable benefit and harm	Very low
Mucositis (moderate plus severe): RR = 0.93 (95%CI 0.72 to 1.21) (Worthington 2011)	3	-1	-1	0	-1	0	1: 1 study high risk of bias, 2 unclear risk of bias 2: Heterogeneity of results 4: Confidence interval includes appreciable benefit and harm	Very low
Mucositis (severe): RR = 0.82 (95%CI 0.54 to 1.23) (Worthington 2011)	4	-1	-1	0	-1	0	1: 2 studies high risk of bias, 2 unclear risk of bias 2: Heterogeneity of results 4: Confidence interval includes appreciable benefit and harm	Very low
Initial dental treatment + chlorhexidine gluconate (0.12%) vs. no treatment (1 study, 60 participants)								
Incidence of oral mucositis immediately after radiotherapy: RR = 1.11 (95%CI 0.82 to 1.49) (Meca 2009)	1	-1	-1	0	-1	0	1: Unclear risk of bias study 2: Small single-centre study 4: Wide confidence interval that includes appreciable benefit and harm, small sample size	Very low
Incidence of oral mucositis six months after radiotherapy: RR = 0.51 (95%CI 0.22 to 1.19) (Meca 2009)	1	-1	-1	0	-1	0	1: Unclear risk of bias study 2: Small single-centre study 4: Wide confidence interval that includes appreciable benefit and harm, small sample size	Very low
Initial dental treatment + sodium fluoride (0.5%) vs. no treatment (1 study, 60 participants)								
Incidence of oral mucositis immediately after radiotherapy:	1	-1	-1	0	-1	0	1: Unclear risk of bias study 2: Small single-centre study	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
RR = 1.09 (95%CI 0.80 to 1.49) (Meca 2009)							4: Wide confidence interval that includes appreciable benefit and harm, small sample size	
Incidence of oral mucositis six months after radiotherapy: RR = 0.43 (95%CI 0.16 to 1.15) (Meca 2009)	1	-1	-1	0	-1	0	1: Unclear risk of bias study 2: Small single-centre study 4: Wide confidence interval that includes appreciable benefit and harm, small sample size	Very low
Sucralfate mouthwash versus placebo (SR: 9 studies, 516 participants)								
Mucositis (any grade): RR = 0.98 (95%CI 0.88 to 1.10) (Worthington 2011)	3	-1	0	0	0	0	1: 1 of 3 studies high risk of bias	Moderate
Mucositis (moderate plus severe): RR = 0.75 (95%CI 0.54 to 1.04) (Worthington 2011)	4	-1	-1	0	-1	0	1: 1 of 4 studies high risk of bias 2: Heterogeneity of results 4: Confidence interval includes benefit and no effect	Very low
Mucositis (severe): RR = 0.67 (95%CI 0.48 to 0.92) (Worthington 2011)	7	-1	0	0	-1	-1	1: 2 of 7 studies high risk of bias 4: CI includes CDT (RRR 10%) 5: Publication bias suggested as effect shown only in small studies	Very low
Mouth rinse containing 10 ml of 0.2% zinc sulphate vs. mouth wash 10 ml of 0.2% chlorhexidine (1 study, 30 participants)								
Mean severity scored (oral mucositis index): Mean severity scores were generally lower in the test group compared to the controls at all four time intervals evaluated; but only the differences in weeks of 2 and 3 were statistically significant (P=0.025) (Medhipour 2011)	1	-1	-1	0	-2	0	1: Unclear risk of bias 2: Small single centre study 4: No quantification of CI	Very low
Amifostine versus no treatment/control (SR: total of 9 studies, 834 participants)								
Mucositis (any grade) RR = 0.95 (95%CI 0.91 to 0.99) (Worthington 2011)	3	-2	0	0	0	0	1: All 3 studies high risk of bias	Low
Mucositis (moderate plus severe)	6	-2	-1	0	-1	0	1: 5 of 6 studies high risk of bias	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
RR = 0.75 (95%CI 0.58 to 0.96) (Worthington 2011)							2: Statistical and visual heterogeneity (CI not overlapping for several studies) 4: Confidence interval includes CDT (25%)	
Mucositis (severe) RR = 0.68 (95%CI 0.45 to 1.03) (Worthington 2011)	9	-2	-1	0	-1	0	1: 8 of 9 studies high risk of bias 2: Statistical and visual heterogeneity (CI not overlapping for several studies) 4: Wide confidence interval that includes both appreciable benefit and no effect	Very low
Nausea OR = 2.47; 95%CI 1.38 to 4.40 (Sasse 2006)	7	-2	0	0	0	0	1: Same studies as in Worthington 2011	Low
Vomiting: grade 3-4 OR = 2.23; 95%CI 1.09 to 4.56	5	-2	0	0	-1	0	1: Same studies as in Worthington 2011 4: CI includes CDT (25%)	Very low
Hypotension: grade 3-4 RD = 0.03; 95%CI 0.01 to 0.05	?	-2	0	0	-1	0	1: Same studies as in Worthington 2011 4: CI includes CDT (25%)	Very low
Oral care protocol versus none (SR: 1 study, 30 participants; RCTs: 1, 34 participants)								
Mucositis (any grade) RR = 0.62 (95%CI 0.43 to 0.91) (Worthington 2011) RR = 0.63, 95%CI 0.24 to 1.71 (day 28, Djuric 2006)	2	-2	0	0	-2	0	1: Both studies high risk of bias 2: Single small study 4: No quantification of overall effect	Very low
Oral care: Initial dental treatment + chlorhexidine gluconate (0.12%) vs. no treatment (1 study, 60 participants)								
Incidence of oral mucositis immediately after radiotherapy: RR = 1.11 (95%CI 0.82 to 1.49) (Meca 2009)	1	-1	-1	0	-1	0	1: Unclear risk of bias study 2: Small single-centre study 4: Wide confidence interval that includes appreciable benefit and harm, small sample size	Very low
Incidence of oral mucositis six months after radiotherapy: RR = 0.51 (95%CI 0.22 to 1.19) (Meca 2009)	1	-1	-1	0	-1	0	1: Unclear risk of bias study 2: Small single-centre study 4: Wide confidence interval that includes appreciable benefit and harm, small sample size	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Oral care: Initial dental treatment + sodium fluoride (0.5%) vs. no treatment (1 study, 60 participants)								
Incidence of oral mucositis immediately after radiotherapy: RR = 1.09 (95%CI 0.80 to 1.49) (Meca 2009)	1	-1	-1	0	-1	0	1: Unclear risk of bias study 2: Small single-centre study 4: Wide confidence interval that includes appreciable benefit and harm, small sample size	Very low
Incidence of oral mucositis six months after radiotherapy: RR = 0.43 (95%CI 0.16 to 1.15) (Meca 2009)	1	-1	-1	0	-1	0	1: Unclear risk of bias study 2: Small single-centre study 4: Wide confidence interval that includes appreciable benefit and harm, small sample size	Very low
Keratinocyte growth factor (Palifermin or Velafermin) versus placebo (SR: 7 studies, 646 participants; RCTs: 2 studies, 374 participants)								
Mucositis (any grade) RR = 0.82 (95%CI 0.71 to 0.94) (Worthington 2011)	2	-1	-1	0	0	0	1: Moderate risk of bias in both studies (unclear allocation concealment) 2: Heterogeneity in population that is confirmed by statistical tests (p = 0.001; I^2 = 90%) 4: No downgrading for imprecision: RRR = 18%, number of events = 136, control event rate = 91%; upper limit of 95%CI of RR = 0.94, but low-risk intervention and NNT = 9.6	Low
Mucositis (moderate plus severe) RR = 0.74 (95%CI 0.62 to 0.89) (Worthington 2011)	7	-1	-1	0	0	0	1: 2 of 7 high risk of bias studies, no study with low risk of bias, 6/7 had unclear allocation concealment 2: Important non-overlap of CI (confirmed by statistical tests: p < 0.00001, I^2 = 88%) 4: No downgrading for imprecision: RRR = 26%, number of events = 507, control event rate = 90%; upper limit of 95%CI of RR = 0.89, but low-risk intervention and NNT = 5.4	Low
Mucositis (severe) RR = 0.74 (95%CI 0.65 to 0.85) (Worthington 2011, Henke 2011, Le 2011)	8	-1	0	0	0	0	1: 2 of 8 high risk of bias studies 4: No downgrading for imprecision: RRR = 26%, number of events = 555, control event rate = 70%; upper limit of 95%CI of RR = 0.85, but low-risk intervention and NNT = 5.3	Moderate
Median duration of severe mucositis 4.5 vs 22.0 days (P= 0.037) (Henke 2011)	2	-1	0	0	-2	0	1: Unclear blinding 4: No quantification of overall CI	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Median duration of severe mucositis for intent-to-treat patients was shorter in the palifermin arm than in the placebo arm (5 vs 26 days) (Le 2011)								
Incidence of supplemental nutrition RR = 1.48 (95%CI 0.85 to 2.56) (Henke 2011, Le 2011)	2	0	0	0	-1	0	1: One study unclear risk of bias (Henke 2011), but Le 2011 is of low risk of bias, and would lead to the same conclusions on its own: no down-grading 4: inadequately powered (OIS = 480 to detect RRR of 10%), lower limit of 95%CI includes clinical decision threshold of 0.90	Moderate
Incidence of at least one adverse event: RR = 1.05 (95%CI 0.98 to 1.12) (Le 2011)	1	0	-2	0	-1	0	2: Single study 4: CI includes CDT (10%)	Very low
Progression free survival: HR = 1.13 (95%CI, 0.75 to 1.71) (Le 2011)	1	0	-2	0	-1	0	2: Single study 4: Wide confidence interval that includes clinical decision threshold of 0.90 and crosses line of no effect	Very low
Honey vs no treatment/control (SR: total of 3 studies, 120 participants; 1 RCT 40 participants)								
Prevention of any mucositis: RR = 0.70 (95%CI 0.56 to 0.88) (Worthington 2011)	3	-2	-1	0	-1	0	1: 3 high risk of bias studies 2: Non-overlap between CI, I^2 81% 4: Small sample size (658 pts needed for RRR of 10%, assuming a CER of 88%)	Very low
Moderate plus severe mucositis: RR = 0.48 (95%CI 0.31 to 0.74) (Worthington 2011)	2	-2	0	0	-1	0	1: 2 high risk of bias studies 4: Small sample size (942 pts needed for RRR of 10%, assuming a CER of 78%)	Very low
Severe mucositis: RR = 0.19 (95%CI 0.10 to 0.37) (Worthington 2011, Khanal 2010)	3	-2	0	0	-1	-1	1: 3 high risk of bias studies 4: Small sample size (1426 pts needed for RRR of 10%, assuming a CER of 78%) 5: Doubt about publication bias: 3 small and positive studies	Very low
Laser vs sham laser or no treatment (SR: total of 5 studies, 234 participants; 3 RCTs, 205 participants)								
Mucositis (any grade) RR = 0.91 (95%CI 0.71 to 1.17) (Worthington 2011)	3	-1	0	0	-1	0	1: All studies high or unclear risk of bias 2: Overlapping CI, I^2 = 29%	Low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
							4: Wide confidence interval that includes clinical decision threshold of 0.80 and crosses line of no effect; small sample size (490 pts needed assuming CER = 63% and RRR = 20%)	
Mucositis (moderate plus severe) RR = 0.64 (95%CI 0.38 to 1.08) (Worthington 2011)	2	-2	-1	0	-1	0	1: Both studies high risk of bias 2: Inconsistent results, I^2 = 78% 4: Wide confidence interval that includes clinical decision threshold of 0.80 and crosses line of no effect; small sample size (1044 pts needed assuming CER = 42% and RRR = 20%)	Very low
Mucositis (severe) RR = 0.26 (95%CI 0.12 to 0.56) (Worthington 2011, Gouvea de Lima 2012)	3	-1	0	0	-1	0	1: All studies high or unclear risk of bias 4: Small sample size (1590 pts needed assuming CER = 32% and RRR = 20%)	Low
QOL (poor and very poor compared to rest) after 30 RT sessions Health related quality of life: RR = 0.09 (95%CI 0.01 to 1.46) (Oton-Leite 2012)	1	-2	-2	0	-1	0	1: High risk of bias study 2: Small single-centre study 4: CI includes benefit and harm	Very low
QOL (poor and very poor compared to rest) after 30 RT sessions Overall quality of life: RR = 0.47 (95%CI 0.05 to 4.78) (Oton-Leite 2012)	1	-2	-2	0	-1	0	1: High risk of bias study 2: Small single-centre study 4: CI includes benefit and harm	Very low
Need for feeding tube: RR = 0.11 (95%CI 0.01 to 1.97) (Oton-Leite 2012)	1	-2	-2	0	-1	0	1: High risk of bias study 2: Small single-centre study 4: Wide confidence interval	Very low

** GRADE scores: 1. Limitations; 2. Inconsistency; 3. Indirectness; 4. Imprecision; 5. Reporting bias.*

Table 109 – Oral complications: overview of results and GRADE-profiles of the effect of chemoprotective agents to treat oral mucositis associated with radiotherapy and/or chemotherapy

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
MOUTHWASHES GENERAL								
Benzydamine mouthwash versus placebo (SR: 2 studies, 102 participants)								
Improvement in mucositis RR = 1.22 (95%CI 0.94 to 1.60) *(Clarkson 2010)*	2	-2	-1	0	-1	0	1: Both studies at high risk of bias 2: 1 clearly negative study, 1 study no difference; I^2 = 90% 4: Confidence interval excludes clinical decision threshold of 0.90, but low sample size (OIS = 2890 for CER = 52% and RRR = 10%)	Very low
Sucralfate (mouthwash and gel) versus placebo/salt and water/salt and soda (SR: 2 studies, 84 participants)								
Eradication of mucositis RR 1.13 (95%CI 0.66 to 1.94) *(Clarkson 2010)*	2	-1	0	0	-1	0	1: Both studies at unclear risk of bias 4: Confidence interval includes clinical decision threshold of 0.90, low sample size (OIS = 7108 for CER = 30% and RRR = 10%)	Low
Sucralfate (mouthwash) versus salt and soda (SR: 1 study, 34 participants)								
Time to heal mucositis (days) MD 13.10 (95%CI -6.30 to 32.50) *(Clarkson 2010)*	1	-1	-2	0	-1	0	1: Unclear risk of bias (unclear allocation concealment) 2: Single small study 4: Small sample size	Very low
Allopurinol mouthwash vs placebo (SR: 1 study, 44 participants)								
Improvement in mucositis RR 6.33 (95%CI 2.18 to 18.37) *(Clarkson 2010)*	1	-1	-2	0	-1	0	1: Unclear risk of bias (unclear allocation concealment) 2: Single small study 4: Confidence interval well above clinical decision threshold of 1.10, but small sample size	Very low
Mucositis eradicated RR 19.00 (95% 1.17 to 307.63) *(Clarkson 2010)*	1	-1	-2	0	-1	0	1: Unclear risk of bias (unclear allocation concealment) 2: Single small study 4: Confidence interval above clinical decision threshold of 1.10, but small sample size	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Time to heal mucositis (days) MD -4.50 (95%CI -5.77 to - 3.23) *(Clarkson 2010)*	1	-1	-2	0	-1	0	1: Unclear risk of bias (unclear allocation concealment) 2: Single small study 4: Small sample size	Very low
Chlorhexidine versus salt and soda (SR: 1 study, 142 participants)								
Mucositis eradicated RR 1.10 (95%CI 0.90 to 1.35) *(Clarkson 2010)*	1	-2	-2	0	-1	0	1: Study at high risk of bias 2: Single study 4: Confidence interval just includes clinical decision threshold of 0.90, but small sample size (OIS = 1446 for CER = 69% and RRR = 10%)	Very low
Time to heal mucositis (days) MD -0.40 (95%CI -1.49 to 0.69) *(Clarkson 2010)*	1	-2	-2	0	-1	0	1: Study at high risk of bias 2: Single study 4: Small sample size (< 400)	Very low
'Magic' mouthwash versus salt and soda (SR: 1 study, 142 participants)								
Mucositis eradicated RR 0.98 (95%CI 0.78 to 1.24) *(Clarkson 2010)*	1	-2	-1	0	-1	0	1: Study at high risk of bias 2: Single study 4: Confidence interval includes clinical decision threshold of 0.90, and low sample size (OIS = 1446 for CER = 69% and RRR = 10%)	Very low
Time to heal mucositis (days) MD 0.17 (95%CI -0.97 to 1.31) *(Clarkson 2010)*	1	-2	-1	0	-1	0	1: Study at high risk of bias 2: Single study 4: Small sample size (< 400)	Very low
Standard oral care plus 5 mL of phenylbutyrate 5% mouthwash vs. standard oral care plus 5 mL of placebo (1 study, 36 participants)								
Severity of oral mucositis Oral mucositis at cumulative RT doses of 5500–7500 cGy WHO score MD -0.35 (95%CI -1.11 to 0.41) OMAS ulceration score: MD -0.41 (-1.05 to 0.23) *(Yen 2012)*	1	-1	-2	0	-1	0	1: Study at unclear risk of bias (only unclear blinding of outcome assessors) 2: Single small study 4: Small sample size (< 400) Overall low (counts for all outcomes for this comparison)	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Severity of oral mucositis Percentage of patients with severe mucositis WHO score ≥3: RR 0.91 (95%CI 0.24 to 3.41) OMAS score ≥2: RR 0.30 (95%CI 0.04 to 2.42) *(Yen 2012)*	1	-1	-2	0	-1	0	1: Study at unclear risk of bias (only unclear blinding of outcome assessors) 2: Single small study 4: Wide confidence intervals that include both benefit and risk, small sample size	Very low
Adverse events Incidence of at least one AE: RR 0.88 (95%CI 0.74 to 1.05) *(Yen 2012)*	1	-1	-2	0	-1	0	1: Study at unclear risk of bias (only unclear blinding of outcome assessors) 2: Single small study 4: Wide confidence intervals that include both benefit and risk, small sample size	Very low
Adverse events Incidence of mild to moderate irritation using mouthwash: RR 3.35 (95%CI 0.38 to 29.27) *(Yen 2012)*	1	-1	-2	0	-1	0	1: Study at unclear risk of bias (only unclear blinding of outcome assessors) 2: Single small study 4: Wide confidence intervals that include both benefit and risk, small sample size	Very low
Adverse events Incidence of nausea/vomiting: RR 0.50 (95%CI 0.19 to 1.32) *(Yen 2012)*	1	-1	-2	0	-1	0	1: Study at unclear risk of bias (only unclear blinding of outcome assessors) 2: Single small study 4: Wide confidence intervals that include both benefit and risk, small sample size	Very low
Adverse events Incidence of constipation: RR 0.89 (95%CI 0.29 to 2.80) *(Yen 2012)*	1	-1	-2	0	-1	0	1: Study at unclear risk of bias (only unclear blinding of outcome assessors) 2: Single small study 4: Wide confidence intervals that include both benefit and risk, small sample size	Very low
Adverse events Incidence of cough: RR 1.12 (95%CI 0.33 to 3.79) *(Yen 2012)*	1	-1	-2	0	-1	0	1: Study at unclear risk of bias (only unclear blinding of outcome assessors) 2: Single small study 4: Wide confidence intervals that include both benefit and risk, small sample size	Very low
Adverse events Incidence of pharyngeal pain: RR 1.86 (95%CI 0.52 to 6.65) *(Yen 2012)*	1	-1	-2	0	-1	0	1: Study at unclear risk of bias (only unclear blinding of outcome assessors) 2: Single small study	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
							4: Wide confidence intervals that include both benefit and risk, small sample size	
Incidence of insomnia: RR 1.30 (95%CI 0.55 to 3.12) *(Yen 2012)*	1	-1	-2	0	-1	0	1: Study at unclear risk of bias (only unclear blinding of outcome assessors) 2: Single small study 4: Wide confidence intervals that include both benefit and risk, small sample size	Very low
Adverse events Incidence of hyper pigmentation skin: RR 0.56 (95%CI 0.12 to 2.68) *(Yen 2012)*	1	-1	-2	0	-1	0	1: Study at unclear risk of bias (only unclear blinding of outcome assessors) 2: Single small study 4: Wide confidence intervals that include both benefit and risk, small sample size	Very low
Adverse events Incidence of metabolic and nutrition disorders: RR 1.12 (95%CI 0.33 to 3.79) *(Yen 2012)*	1	-1	-2	0	-1	0	1: Study at unclear risk of bias (only unclear blinding of outcome assessors) 2: Single small study 4: Wide confidence intervals that include both benefit and risk, small sample size	Very low
Adverse events "No patient experienced severe study drug-related side effects." *(Yen 2012)*	1	-1	-2	0	-2	0	1: Study at unclear risk of bias (only unclear blinding of outcome assessors) 2: Single small study 4: No quantification of CI	Very low
Need for parenteral feeding Number of visits with tube feeding or 'nothing per oral': RR 0.61 (95%CI 0.06 to 6.02) *(Yen 2012)*	1	-1	-2	0	-1	0	1: Study at unclear risk of bias (only unclear blinding of outcome assessors) 2: Single small study 4: Wide confidence intervals that include both benefit and risk, small sample size	Very low
Triclosan mouth wash vs. sodium bicarbonate mouth rinse (1 study, 24 participants) *(Satheeskumar 2010)*								
Duration of mucositis Reversal mucositis to grade 0: <28 days vs. > 45 days *(Satheeskumar 2010)*	1	-2	-2	0	-2	0	1: Study at high risk of bias 2: Single small study 4: No quantification of CI, small sample size	Very low
Severity of mucositis	1	-2	-2	0	-1	0	1: Study at high risk of bias	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Incidence of grade 4 mucositis RR 0.10 (95%CI 0.02 to 0.66) *(Satheeskumar 2010)*							2: Single small study 4: Strong effect with confidence interval well below clinical decision threshold of 0.90, but small sample size	
Food intake Number of days it took for a change in way of feeding from solid to liquid: MD 0.00 (95%CI -3.85 to 3.85) *(Satheeskumar 2010)*	1	-2	-1	0	-1	0	1: Study at high risk of bias 2: Single small study 4: Small sample size (< 400)	Very low
Food intake Number of days it took for a change in way of feeding from liquid to solid: MD -19.57 (95%CI -30.80 to -8.34) *(Satheeskumar 2010)*	1	-2	-1	0	-1	0	1: Study at high risk of bias 2: Single small study 4: small sample size (< 400)	Very low
MUCOSAL AGENTS, E.G. GELCLAIR								
Sucralfate (gel) versus placebo (SR: 1 study, 40 participants)								
Improvement in mucositis RR 0.93 (95%CI 0.71 to 1.24) *(Clarkson 2010)*	1	0	-2	0	-1	0	2: Single small study 4: Confidence interval includes benefit and harm	Very low
HONEY								
Manuka honey vs. golden syrup (placebo) (1 study, 131 participants)								
Incidence of grade 3 mucositis (Radiation Therapy Oncology Group scale) RR 1.07 (95%CI 0.88 to 1.29) *(Bardy 2012)*	1	-1	-2	0	-1	0	1: Unclear risk of bias (unclear allocation concealment) 2: Single study 4: Wide confidence interval that includes clinical decision threshold of 0.90, small sample size	Very low
Severity and duration of mucositis "There was no significant difference (p = 0.79) in the severity or duration of mucositis in the AMH group and the golden syrup group" *(Bardy 2012)*	1	-1	-2	0	-2	0	1: Unclear risk of bias (unclear allocation concealment) 2: Single study 4: Not quantified: not able to estimate precision	Very low
Need for tube feeding RR 1.03 (95%CI 0.64 to 1.65) *(Bardy 2012)*	1	-1	-2	0	-1	0	1: Unclear risk of bias (unclear allocation concealment) 2: Single study 4: Wide confidence interval that includes clinical decision threshold of 0.90, low sample size	Very Low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
ATHERMIC LASER / LOW-LEVEL LASER								
Low level laser versus sham procedure (SR: 2 studies, 57 participants)								
Mild to moderate mucositis RR 5.28 (95%CI 2.30 to 12.13) *(Clarkson 2010)*	2	-1	0	-1	-1	0	1: One trial unclear risk of bias 3: One trial only included children 4: Confidence interval well above clinical decision threshold of 1.20, but small sample size (OIS = 4240 for CER = 16.7% and RRR 20%	Very Low
INTRA-ORAL FLUORIDE RELEASING SYSTEM	0							
Sucralfate mouthwash plus gel on skin versus placebo mouthwash plus gel on skin (SR: 1 study, 60 participants)								
Improvement of mucositis: RR = 0.93 (95%CI 0.71 to 1.24) (Clarkson 2011)	1	-1	-2	0	-1	0	1: Unclear risk of bias study 2: Small single-centre study 4: Wide confidence interval that includes appreciable benefit and harm, small sample size	Very low

** GRADE scores: 1. Limitations; 2. Inconsistency; 3. Indirectness; 4. Imprecision; 5. Reporting bias*

Table 110 – Oral complications: GRADE-profiles (based on one study, unless specified otherwise) of the effect of additional interventions to prevent oral candidiasis associated with radiotherapy and/or chemotherapy

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Drugs absorbed from the GI tract (fluconazole/ketoconazole/itraconazole) vs. placebo or 'no treatment' (SR: total of 7 studies, 1636 participants)								
Incidence of oral candidiasis: RR 0.47 (95%CI 0.29 to 0.78) (Clarkson 2009)	7	0	0	0	-1	-1	4: OIS 1377 for RRR 25%, CDT (RRR 25%) within CI 5: Evidence for publication bias with Egger test	Low
Systemic fungal infection: RR 0.65 (95%CI 0.37 to 1.14) (Clarkson 2009)	6	0	0	0	-1	-1	4: CI includes substantial benefit and harm 5: Evidence for publication bias with Egger test	Low
Death: RR 1.44 (95%CI 0.14 to 15.43) (Clarkson 2009)	3	-1	0	0	-2	0	1: 2 of 3 studies moderate risk of bias 4: CI includes substantial benefit and harm	Very low
Toxicity: RR 1.18 (95%CI 0.84 to 1.67) (Clarkson 2009)	3	-1	0	0	-1	0	1: 2 of 3 studies moderate risk of bias 4: CI includes substantial harm	Low
Itraconazole vs. fluconazole (SR: 1 study, 213 participants)								
Incidence of oral candidiasis: RR 0.14 (95%CI 0.01 to 2.73) (Clarkson 2009)	1	-2	-2	0	-1	0	1: High risk of bias for study 2: One small study 4: Wide confidence interval includes substantial benefit and harm	Very low
Systemic fungal infection: RR 1.00 (95%CI 0.26 to 3.89) (Clarkson 2009)	1	-2	-2	0	-1	0	1: High risk of bias for study 2: One small study 4: Wide confidence interval includes substantial benefit and harm	Very Llow
Death: RR 0.14 (95%CI 0.01 to 2.73) (Clarkson 2009)	1	-2	-2	0	-1	0	1: High risk of bias for study 2: One small study 4: Wide confidence interval includes substantial benefit and harm	Very low
Toxicity: RR not estimable (Clarkson 2009)	2	-2	0	0	-2	0	1: Both studies high risk of bias 4: Sample size < 400 cases, CI not calculable	Very low
Ketoconazole vs. itraconazole (SR: 1 study, 40 participants)								

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Incidence of oral candidiasis: RR 0.17 (95%CI 0.02 to 1.14) (Clarkson 2009)	1	-2	-2	0	-1	0	1: High risk of bias for study 2: One small study 4: CI includes substantial benefit and harm	Very low
Drugs absorbed vs. drugs not absorbed (SR: total of 8 studies, 2169 participants)								
Incidence of oral candidiasis: RR 0.40 (95%CI 0.21 to 0.76) (Clarkson 2009)	8	-2	-1	0	-1	-1	1: All studies high risk of bias 2: Inconsistent results (see forest plot) within meta-analysis 4: OIS for RRR = 2736 5: Evidence for publication bias with Egger test	Very low
Systemic fungal infection: RR 0.59 (95%CI 0.33 to 1.06) (Clarkson 2009)	8	-2	0	0	-1	-1	1: All studies high risk of bias 4: OIS for RRR = 4386 5: Evidence for publication bias with Egger test	Very low
Death: RR 1.25 (95%CI 0.38 to 4.13) (Clarkson 2009)	3	-1	0	0	-1	0	1: 3 studies high risk of bias 4: Wide confidence interval includes benefit and harm	Low
Toxicity: RR 0.88 (95%CI 0.33 to 2.30) (Clarkson 2009)	6	-2	-1	0	-1	0	1: All 6 studies high risk of bias 2: Inconsistent results (see forest plot) within meta-analysis 4: Wide confidence interval includes substantial benefit and harm	Very low
Drugs partially absorbed (clotrimazole, miconazole) vs. placebo (SR: total of 4 studies, 452 participants)								
Incidence of oral candidiasis: RR 0.16 (95%CI 0.06 to 0.46) (Clarkson 2009)	4	0	0	0	-1	0	1: 2 studies low risk of bias, 2 studies moderate risk of bias; all 4 studies had concealed allocation and blinding of outcome assessment, in 2 studies withdrawals were unclear 4: OIS for RRR 25% = 408	Moderate
Drugs not absorbed (amphotericin B nystatin, chlorhexidine, thymostimulin, natamycin, norfloxacin) vs. placebo or no treatment (SR: total of 8 studies; 521 participants)								
Incidence of oral candidiasis: RR 0.68, 95%CI 0.46 to 1.02) (Clarkson 2009)	8	-2	-1	0	-1	-1	1: 7 studies high risk of bias 1 low risk of bias 2: Inconsistent results (forest plot) 4: CI includes CDT (RRR 25%)	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
							5: Evidence for publication bias with Egger test	
Systemic fungal infection: RR 0.10 (95%CI 0.01 to 1.75 (Clarkson 2009)	2	-2	0	0	-1	0	1: Both studies high risk of bias 4: Wide confidence interval includes substantial benefit and harm	Very low
Death: RR 0.16 (95%CI 0.01 to 2.95) (Clarkson 2009)	1	-2	-2	0	-1	0	1: High risk of bias 2: Single study 4: Wide confidence interval includes substantial benefit and harm	Very low
Mouth rinse containing chlorhexidine (CHX) and cetyl-pyridinium chloride (CPC) vs. placebo (1 study, 36 participants)								
No statistically significant differences between groups were found for detection of Candida spp. in mucosa and tongue samples (Lanzos 2011).	1	-2	-2	0	-2	0	1: High risk of bias 2: Single small study 4: No quantification of effect	Very low
No relevant adverse effects were reported in any group (Lanzos 2011).	1	-2	-2	0	-2	0	1: High risk of bias 2: Single small study 4: No quantification of effect	Very low
Initial dental treatment + chlorhexidine gluconate (0.12%) vs. no treatment (1 study, 60 participants)								
Incidence of oral candidiasis immediately after radiotherapy RR 0.35 (95%CI 0.12 to 1.01) (Meca 2009)	1	-1	-2	0	-1	0	1: Unclear risk of bias 2: Single small study 4: Wide confidence interval includes benefit and no effect	Very low
Incidence of oral candidiasis six months after radiotherapy RR 0.13 (95%CI 0.01 to 2.22) (Meca 2009)	1	-1	-2	0	-1	0	1: Unclear risk of bias 2: Single small study 4: Wide confidence interval includes benefit and no effect	Very low
Initial dental treatment + sodium fluoride (0.5%)vs. no treatment (1 study, 60 participants)								
Incidence of oral candidiasis immediately after radiotherapy RR 0.41 (95%CI 0.14 to 1.16) (Meca 2009)	1	-1	-2	0	-1	0	1: Unclear risk of bias 2: Single small study 4: Wide confidence interval includes benefit and no effect	Very low
Incidence of oral candidiasis six months after radiotherapy	1	-1	-2	0	-1	0	1: Unclear risk of bias	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
RR 0.33 (95%CI 0.04 to 2.63) (Meca 2009)							2: Single small study 4: Wide confidence interval includes benefit and no effect	
Initial dental treatment + sodium iodine (2% in hydrogen peroxide 10 v/v) vs. no treatment (1 study, 60 participants)								
Incidence of oral candidiasis immediately after radiotherapy RR 0.43 (95%CI 0.17 to 1.08) (Meca 2009)	1	-1	-2	0	-1	0	1: Unclear risk of bias 2: Single small study 4: Wide confidence interval includes benefit and no effect	Very low
Incidence of oral candidiasis six months after radiotherapy RR 0.12 (95%CI 0.01 to 2.04) (Meca 2009)	1	-1	-2	0	-1	0	1: Unclear risk of bias 2: Single small study 4: Wide confidence interval includes benefit and no effect	Very low

** GRADE scores: 1. Limitations; 2. Inconsistency; 3. Indirectness; 4. Imprecision; 5. Reporting bias.*

Table 111 – Oral complications: GRADE-profiles (based on one study, unless specified otherwise) of the effect of additional interventions to treat oral candidiasis associated with radiotherapy and/or chemotherapy

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Ketaconazole vs. placebo (SR: 1 study, 56 participants)								
Clinical eradication of oral candidiasis RR 3.61 (95%CI 1.47 to 8.88)	1	-1	-2	0	-1	0	1: Unclear risk of bias for two of the three key items 2: Single small study 4: OIS for RRR 25% not reached	Very low
Mycological eradication of oral candidiasis RR 5.09 (95%CI 0.73 to 35.49)	1	-1	-2	0	-1	0	1: Unclear risk of bias for two of the three key items 2: Single small study 4: OIS for RRR 25% not reached	Very low
Clotrimazole vs. placebo (SR: 1 study, 16 participants)								
Clinical eradication of oral candidiasis RR 3.43 (95%CI 0.51 to 22.94)	1	-1	-2	0	-1	0	1: Unclear risk of bias 2: Single small study 4: OIS for RRR 25% not reached	Very low
Mycological eradication of oral candidiasis	1	-1	-2	0	-1	0	1: Unclear risk of bias	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
RR 6.13 (95%CI 0.38 to 99.14)							2: Single small study 4: OIS for RRR 25% not reached	
Fluconazole vs. itraconazole (SR: 2 studies, 332 participants)								
Clinical eradication of oral candidiasis RR 1.14 (95%CI 1.00 to 1.30)	2	-1	0	0	-1	0	1: One study at high risk of bias, other unclear risk 4: CI includes CDT (RRI 25%) and no difference	Low
Mycological eradication of oral candidiasis RR 1.17 (95%CI 1.04 to 1.33)	2	-1	0	0	-1	0	1: One study at high risk of bias, other unclear risk 4: CI includes CDT (RRI 25%) and no difference	Low
Flucoconazole vs. ketoconazole (SR: 1 study, 40 participants)								
Clinical eradication of oral candidiasis RR 1.02 (95%CI 0.72 to 1.42)	1	0	-2	0	-1	0	2: Single small study 4: Wide confidence interval includes appreciable benefit and harm	Very low
Mycological eradication of oral candidiasis RR 0.95 (95%CI 0.52 to 1.72)	1	0	-2	0	-1	0	2: Single small study 4: Wide confidence interval includes appreciable benefit and harm	Very low
Drugs absorbed from GI tract vs. drugs not absorbed from GI tract (SR: 3 studies, 305 participants)								
Clinical eradication of oral candidiasis RR 1.29 (95%CI 1.09 to 1.52)	3	-2	-1	0	-1	0	1: All three studies high risk of bias 2: Non overlap of CIs 4: CI includes CDT (25%)	Very Low
Mycological eradication of oral candidiasis RR 1.82 (95%CI 1.28 to 2.57)	3	-2	-1	0	-1	0	1: All three studies high risk of bias 2: Non overlap of CIs 4: OIS for RRR 25% = 892	Very Low

Appendix 4.2. Skin toxicity

Table 112 – Skin toxicity: GRADE profiles by intervention and outcome

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Gentle skin washin versus no washing								
Severity of itching, erythema, desquamation Campbell: ”trend for less symptoms with washing” Roy: “significant difference favouring the washing group” Westbury: “no significant differences”	3	-1	0	0	-2	0	1: Two studies with unclear risk of bias 4: No estimate of pooled effect due to insufficient and heterogeneous reporting.	Very low
Neutral hydrophilic cream versus placebo Severity of acute radiodermatitis								
Itching grade 3 RR = 1.0 (95%CI 0.06-15.71)	1	-1	-1	0	-1	0	1 : Unclear risk of bias 2 : Single small trial 4: CI includes harm and benefit	Very low
Erythema grade 3 RR = 1.03 (95%CI 0.75-1.40)	1	-1	-1	0	-1	0	1 : Unclear risk of bias 2 : Single small trial 4: CI includes harm and benefit	Very low
Desquamation grade 3-4 RR = 0.83 (95%CI 0.53-1.29)	1	-1	-1	0	-1	0	1 : Unclear risk of bias 2 : Single small trial 4: CI includes harm and benefit	Very low
Pain grade 3 RR = 1.0 (95%CI 0.06-15.71) (results calculated using RevMan5)	1	-1	-1	0	-1	0	1 : Unclear risk of bias 2 : Single small trial 4: CI includes harm and benefit	Very low
Corticosteroid cream verus placebo								
Severity of acute skin reaction Bostrom: erythema score 3-7 RR = 0.72 (95%CI 0.53 to 0.98) Omidvari: no significant difference (not quantified) Shukla: Erythema RR = 1.31; 95%CI 0.87 to 1.97 Dry desquamation RR = 1.67; 95%CI 0.44 to 6.36 wet desquamation RR = 0.36; 95%CI 0.13 to 1.01	3	-1	0	0	-2	0	1 : One study unclear risk of bias, one study high risk of bias 4: No estimate of pooled effect due to insufficient and heterogeneous reporting.	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Aloe vera versus placebo								
Severity of acute skin reaction "No difference between groups was seen in these trials" (Richardson 2004)	3	-1	0	0	-2	0	1: All studies unclear or high risk of bias 4: No estimate of pooled effect due to insufficient and heterogeneous reporting	Very low
Hyaluronic acid (prevention)								
Incidence of moderate-severe acute skin reaction Liguori: week 5 RR = 0.30 (95%CI 0.18-0.52)	1	-2	-1	0	-1	0	1: High risk of bias 2: Single small trial 4: Optimal information size not reached	Very low
Adverse events Liguori: RR = 0.23; 95%CI 0.03 to 1.99	1	-2	-1	0	-1	0	1: High risk of bias 2: Single small trial 4: CI includes harm and benefit	Very low
Hyaluronic acid (treatment)								
Failure of treatment Kirova: RR = 0.72; 95%CI 0.46 to 1.13	1	-2	-1	0	-1	0	1: High risk of bias 2: Single small trial 4: CI includes harm and benefit	Very low
Quality of life Kirova: no significant difference	1	-2	-1	0	-2	0	1: High risk of bias 2: Single small trial 4: No estimate of pooled effect due to insufficient and heterogeneous reporting, outcome can not be judged with sufficient precision	Very low
Trolamine based cream (Biafine) versus placebo								
Severity of skin reaction No significant difference (Fenig 2001, Gosselin 2010)	2	-1	0	0	-2	0	1: One study high risk of bias 4: CI study Fenig includes benefit and harm, no quantification of overall effect by meta-analysis	Very low
Lipiderm ointment versus placebo								
Severity of skin reaction No significant difference	1	-2	-2	0	-1	0	1: High risk of bias 2: Single small study 4: OIS for RRR 20% is 762 participants;	Very low
Radiacare gel versus placebo								
Severity of skin reaction No significant difference	1	0	-2	0	-2	0	2: Single small study 4: No quantification of effect	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Aquaphor ointment versus placebo								
Severity of skin reaction No significant difference	1	0	-2	0	-2	0	2: Single small study 4: No quantification of effect	Very low
Calendula versus Trolamine based cream								
Incidence/Severity of skin reaction (gr2-3) RR = 0.65; 95%CI 0.51-0.83	1	0	-2	0	-1	0	2: Single study 4: OIS for RRR 20% is 484 participants	Very low
Allergic reaction RD = -0.03; 95%CI -0.06 to 0	1	0	-2	0	0	0	2: Single study	Low
Avene thermal spring water anti-burning gel versus Trolamine based cream								
Severity of dermatitis MD = -0.21; 95%CI -0.53 to 0.11	1	-2	-2	0	-1	0	1; High risk of bias 2; Single small trial 4: Sample size less than 400 for continuous variable	Very low
Kamilosan cream versus almond ointment								
Severity of skin reaction (gr 2-3) RR 0.83; 95%CI 0.48 to 1.45	1	-1	-1	0	-1	0	1: Unclear risk of bias 2: Single small trial 4: CI includes harm and benefit	Very low
Allergic reaction RD 0.02; 95%CI -0.05 to 0.09	1	-1	-1	0	0	0	1: Unclear risk of bias 2: Single small trial	Low
Pre-emptive versus reactive treatment								
Skin toxicities ≥ gr 2 = 0.47; 95%CI 0.29 to 0.78	1	-2	-1	0	-1	0	1: High risk of bias 2: Single study (multi-centre but no info on heterogeneity between sites) 4: OIS for RRR 20% is 502 participants	Very low
Adverse events RR = 0.75; 95%CI 0.57 to 0.98	1	-2	-1	0	-1	0	1: High risk of bias 2: Single study (multi-centre but no info on heterogeneity between sites) 4: OIS for RRI 10% is 608 participants	Very low
Quality of Life quality of life was less impaired in the pre-emptive group (change in score from baseline at week 3 1.3 versus 4.2)	1	-2	-1	0	-1	0	1: High risk of bias 2: Single study (multi-centre but no info on heterogeneity between sites)	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
							4: Sample size less than 400 for continuous variable	
PFS HR = 1.0; 95%CI 0.6 to 1.6	1	-2	-1	0	-1	0	1: High risk of bias 2: Single study (multi-centre but no info on heterogeneity between sites) 4: CI includes important harm	Very low
Honey gauze versus paraffin gauze								
Time to healing of radiodermatitis gr 3 MD = -1.40; 95%CI -7.36 to 4.56	1	-2	-1	0	-1	0	1: High risk of bias 2: Single small study 4: CI includes harm and benefit	Very low
Symptoms (VAS score) Trend towards less symptoms in honey treated group	1	-2	-1	0	-2	0	1: High risk of bias 2: Single small study 4: No quantification of results	Very low
Adverse events No relevant side effects noted	1	-2	-1	0	-2	0	1: High risk of bias 2: Single small study 4: No quantification of results	Very low

Appendix 4.3. Neuropathy

Table 113 – Neuropathy: GRADE profiles by intervention and outcome

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Glutamine versus placebo								
Incidence of (severe) neuropathy "not significantly different" (Loven 2009) "lower in glutamine arm after 4 and 6 cycles p=0.05; p=0.04" (Wang 2007) "lower in the glutamine group p=0.048" (Sasser 2008)	3	-1	-1	0	-2	0	1: Two studies high risk of bias 2: Benefit versus no effect 4: No quantification of overall effect and CI	Very low
Adverse events "2/23 patients had severe skin rash" (Loven 2009) "no significant difference in non-neurological adverse events grade3-4" (Wang 2007)	2	-2	0	0	-2	0	1: High risk of bias 4: No quantification of overall results, OIS for 10% difference 230	Very low
ADL "interference with ADL lower in the intervention arm" (Wang 2007)	1	-2	-2	0	-1	0	1: High risk of bias 2: Single small study 4: OIS for 25% RRR is 722	Very low
OS Median survival time 17.3 versus 18.6 months (p=0.79) (Wang 2007)	1	-2	-2	0	-1	0	1: High risk of bias 2: Single small study 4: < 400 patients for continuous variable	Very low
Calcium and magnesium vs. placebo								
Incidence of ≥ grade 2 neurotoxicity RR = 0.69; 95%CI 0.40 to 1.19	3	-1	0	0	-1	0	1: Early closure of all trials 4: CI includes benefit and harm	Low
Adverse effects "no differences in any of the elicited toxicities"	1	0	-1	0	-2	0	2: Single trial 4: No quantification, < 400 patients	Very low

** GRADE scores: 1. Limitations; 2. Inconsistency; 3. Indirectness; 4. Imprecision; 5. Reporting bias.*

Appendix 4.4. Neutropenia & neutropenic fever

Table 114 – Neutropenia & neutropenic fever: GRADE profiles by intervention and outcome

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Prophylactic G-CSF/GM-CSF in malignant lymphoma								
Incidence of severe neutropenia RR = 0.67; 95%CI 0.60 to 0.73	7	-1	0	0	0	0	1: Majority of studies high risk of bias	Moderate
Incidence of febrile neutropenia RR = 0.59; 95%CI 0.42 to 0.72	3	-1	0	0	0	0	1: No blinding	Moderate
Overall survival RR = 0.97; 95%CI 0.87 to 1.09	11	0	0	0	0	0		High
Freedom of treatment failure HR = 1.11; 95%CI 0.91 to 1.35	6	-1	0	0	-1	0	1: 4 studies no blinding 4: CI includes CDT (RRI 25%)	Low
Quality of life No differences	1	-2	-2	0	-2	0	1: High risk of bias 2: Single study 4: No quantification of CI	Very low
Bone pain attributable to G-CSF and GM-CSF RR : 3.57; 95%CI 2.09 to 6.12	10	-1	0	0	0	0	1: Majority of studies not blinded	Moderate
Prophylactic G-CSF/GM-CSF in breast cancer patients								
Incidence of febrile neutropenia: RR = 0.10; 95%CI 0.05 to 0.19	2	-1	0	0	-1	0	1: Unclear risk of bias 4: OIS for RRR 25% = 2940	Low
5-year OS 80.6% versus 79.6%	1	-1	-2	0	?	0	1: Unclear risk of bias 2: Single study 4: No CI	Very low
5-year DFS 67.2% versus 72.9% (p=0.21)	1	-1	-2	0	?	0	1: Unclear risk of bias 2: Single study 4: No CI	Very low
Adverse events: bone pain RR = 1.16: 95%CI 0.95 to 1.42	1	-1	0	0	-1	-1	1: Unclear risk of bias 2: Single study but multinational, multicentre 4: CI includes CDT (RRI 25%) 5: Only one sponsored (positive) study	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Withdrawal due to adverse events RR = 1.11; 95%CI 0.60 to 2.04	1	-1	0	0	-1	-1	1: Unclear risk of bias 2: Single study but multinational, multicentre 4: CI includes CDT (RRI 25%) 5: Only one sponsored (positive) study	Very low
G-CSF or GM-CSF plus antibiotics versus antibiotics alone								
Overall mortality OR = 0.68; 95%CI 0.43 to 1.08	12	-1	0	0	-1	0	1: 8 studies high risk of bias 4: CI includes appreciable benefit and no benefit	Low
Infection-related mortality OR = 0.51; 95%CI 0.26 to 1.00	9	-1	0	0	-1	0	1: 6 studies high risk of bias 4: CI includes appreciable benefit and no benefit	Low
Length of hospitalisation HR = 0.63; 95%CI 0.49 to 0.82	8	-2	-1	0	-1	0	1: Studies high risk of bias 2: Non-overlap of CIs, I^2 = 73% 4: CI includes CDT (RRR 25%)	Very low
Bone, joint pain and flu like symptoms OR = 2.05; 95%CI 1.22 to 3.46	6	-1	0	0	0	0	1: 4 studies high risk of bias	Moderate
Prophylactic antifungal treatment versus placebo								
Death RR = 0.94; 95%CI 0.81 to 1.09	26	0	0	0	0	0	1: Effect estimates unchanged if only high quality studies included	High
Incidence of invasive fungal infection RR = 0.41; 95%CI 0.24 to 0.73	30	0	0	0	0	0	1: Effect estimates unchanged if only high quality studies included 2: I^2=61% but no important non-overlap of CIs	High
Amphotericin (prophylactic)								
Death RR = 0.67; 95%CI 0.45 to 0.98	6	0	0	0	-1	0	4: CI upper boudery includes minimal important difference	Moderate
Incidence of invasive fungal infection RR = 0.48; 95%CI 0.26 to 0.89	6	0	0	0	-1	0	4: CI upper boudery includes minimal important difference	Moderate
Amphotericin (empirical)								
Death RR = 0.75; 95%CI 0.40 to 1.40	3	-1	0	0	-1	0	1: 2 studies unclear risk of bias 4: CI includes benefit and harm	Low
Incidence of invasive fungal infection	2	-2	0	0	-1	0	1: 2 studies high risk of bias	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
RR = 0.21; 95%CI 0.05 to 0.90							4: CI upper boudery includes minimal important difference	
Fluconazole (prophylactic)								
Death RR = 1.04; 95%CI 0.84 to 1.30	7	0	0	0	-1	0	4: OIS for RRR 25% is 2164	Moderate
Incidence of invasive fungal infection RR = 0.39; 95%CI 0.27 to 0.5	8	0	0	0	-1	0	1: 3 trials high risk of bias, 1 trial unclear risk of bias but no downgrading as effect confirmed by studies with low risk of bias and large effect 4: OIS for RRR 25% is 3560	Moderate
Ketoconazole (prophylactic)								
Death RR = 0.97; 95%CI 0.63 to1.49	4	0	0	0	-1	0	4: OIS for RRR 25% is 2398	Moderate
Incidence of invasive fungal infection RR = 1.32; 95%CI 0.68 to 2.54	7	-1	0	0	-1	0	1: 5 trials unclear risk of bias 4: OIS for RRR 25% is 9170; CI boundaries include minimal important difference	Low
Itraconazole (prophylactic)								
Death RR = 0.94; 95%CI 0.63 to 1.40,	4	0	0	0	-1	0	4: CI boundaries include minimal important difference	Moderate
Incidence of invasive fungal infection RR = 0.53; 95%CI 0.29 to 0.97	4	0	0	0	-1	0	4: Upper boundary include minimal important difference	Moderate
Miconazole (prophylactic)								
Death RR = 1.16;95%CI 0.71 to1.87	2	0	0	0	-1	0	4: CI boundaries include minimal important difference	Moderate
Incidence of invasive fungal infection RR = 0.52; 95%CI 0.20 to 1.31	2	0	0	0	-1	0	4: CI boundaries include minimal important difference	Moderate
Fluconazole versus Amphotericin B (prophylactic)								
Overall mortality RR = 0.96; 95%CI 0.74 to 1.23	7	0	0	0	-1	0	4: CI lower boudery includes minimally important difference, OIS for 25% RRR is 3136	Moderate
Incidence of invasive fungal infection RR = 0.83; 95%CI 0.54 to 1.26	7	-1	0	0	-1	0	1: No blinding in all studies 4: CI includes harm and benefit	Low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Dropouts RR = 0.87; 95%CI 0.70 to 1.08	4	-1	0	0	-1	0	1: No blinding in all studies 2: Overlapping CIs, all including line of no effect 4: Lower boundary CI includes CDT (RRR 25%)	Low
Dropouts due to adverse events RR = 0.13; 95%CI 0.06 to 0.29	7	-1	0	0	-1	0	1: No blinding in all studies 4: OIS for 25% RRR is 7352	Low
Fluconazole versus Amphotericin B (empirical)								
Overall mortality RR = 0.76; 95%CI 0.56 to 1.04	6	0	0	0	-1	-1	4: CI includes benefit and no effect 5: 5 studies sponsored, funnel plot suggestive of publication bias	Low
Incidence of invasive fungal infection RR = 1.06; 95%CI 0.74 to 1.51	5	-1	0	0	-1	0	1: All studies no/unclear blinding 4: CI includes benefit and harm	Low
Dropouts RR = 0.56; 95%CI 0.25 to 1.22	2	-1	0	0	-1	0	1: all studies no/unclear blinding 4: CI includes benefit and harm	Low
Dropouts due to adverse events RR = 0.15; 95%CI 0.06 to 0.41	4	-1	0	0	-1	0	1: All studies no/unclear blinding 4: OIS for 25% RRR is 5100	Low
Voriconazole verus Amphotericin B								
Overall mortality RR = 1.37; 95%CI 0.96 to 1.96	1	-2	-1	0	-1	0	1: No allocation concealement, no ITT, no blinding 2: Single study 4: CI includes no effect and significant harm	Very low
Incidence invasive fungal infections RD 1.8%; 95%CI -1.0% to 4.7%	1	-2	-1	0	0	0	1: No allocation concealement, no ITT, no blinding 2: Single study	Very low
Discontinuation of therapy due to toxicity 19 versus 23 (absolute numbers)	1	-2	-1	0	0	0	1: No allocation concealement, no ITT, no blinding 2: Single study	Very low
Prophylactic antibiotics versus placebo/no intervention								
Overall mortality RR = 0.66; 95%CI 0.55 to 0.79	46	-1	0	0	0	0	1: Majority unclear allocation concealement and unclear or no ITT	Moderate
Side effects RR 1.58; 95%CI 1.19 to 2.12	35	-1	0	0	0	0	1: Majority unclear allocation concealement and unclear or no ITT	Moderate
IV versus oral antibiotics								
Mortality	9	0	0	0	-1	0	4: CI includes benefit and harm	Moderate

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
RR = 0.95; 95%CI 0.54 to 1.68								
Adverse effects that required discontinuation (overall) RR 1.80 [95%CI 0.58 to 5.60	12	-1	0	0	-1	0	1: Only few studies with blinding 4: CI includes benefit and harm	Low
Adverse effects that required discontinuation (initial oral) RR = 3.66; 95%CI 1.45 to 9.23 RD = 3%; 95%CI 1 to 5%	8	-1	0	0	0	0	1: Only few studies with blinding 4: CI absolute effect not clinically significant	Moderate
Inpatient versus outpatient treatment								
treatment failure at 30 days RR = 0.79; 95%CI 0.52 to 1.20	4	-1	0	0	-1	0	1: All studies high/unclear risk of bias 4: CI includes harm and benefit	Low
mortality RR = 0.96; 95%CI 0.27 to 3.43	4	-1	?	0	-2	0	1: All studies high/unclear risk of bias 4: CI includes appreciable harm and benefit, no info on heterogeneity	Very low
Quality of life “No differences were observed for the Consumer Satisfaction or General Well-Being instruments” Overall effect measured by EORTC QLQ C-30 not reported	1	-2	-2	0	-2	0	1: High risk of bias 2: Single study 4: No quantification of overall effect as measured by different instruments	Very low
Protective isolation								
Mortality RR = 0.86; 95%CI 0.65 to 1.14	6	?	0	-1	-1	0	3: Only protected environments with HEPA included, 4 out of 6 studies in BMT patients 4: CI includes benefit and harm	Low
Incidence of fungal infections RR = 0.57; 95%CI 0.13 to 2.53	4	?	0	-1	-2	0	3: Only protected environments with HEPA included, 1 out of 4 studies in BMT patients 4: CI includes appreciable benefit and harm	Very low

Appendix 4.5. Radioproctitis

Appendix 4.5.1. Prevention of radioproctitis

Table 115 – Prevention of radioproctitis: GRADE profiles by intervention and outcome

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
3 mg beclomethasone dipropionate enema versus identical-looking placebo (Fuccio 2011; 120 participants)								
Modified Simple Clinical Colitis Activity Index At 3 and 12 months after the end of radiotherapy: no significant differences of SCCAI total scores between the groups, except for item bleeding rate (blood in the stool, at least once a week): 12/55 (22%) vs. 25/ 59 patients (42%); OR = 0.38 (95%CI 0.17 to 0.86)	1	-2	-2	0	-1	0	1: High risk of bias 2: Single study 4: Small sample size	Very low
Radiation Therapy Oncology Group acute and late toxicity scales Three and 12 months after the end of radiotherapy, no differences were found between the two treatment groups based on the RTOG⁄EORTC toxicity scales.	1	-2	-2	0	-2	0	1: High risk of bias 2: Single study 4: No quantification	Very low
Inflammatory Bowel disease Quality of Life Index: After 12 months of follow-up the reduction of the total IBDQ scores between the two groups was significantly more pronounced for patients on placebo (p=0.034)	1	-2	-2	0	-2	0	1: High risk of bias 2: Single study 4: No quantification	Very low
Vienna rectoscopy score: Three months after the end of radiotherapy, no difference was noted between the two treatment groups. However, after 12 months of follow-up, the Vienna Rectoscopy Score was significantly lower in the beclomethasone dipropionate group.	1	-2	-2	0	-2	0	1: High risk of bias 2: Single study 4: No quantification	Very low
Severe hemorrhagic proctopathy: During the whole period of the study, severe haemorrhagic proctopathy, was diagnosed in 10 patients, four in the BDP arm and six in the placebo arm. ITT: OR 0,69 (95%CI 0.18 to 2.60) PP: OR 0,67 (95%CI 0.18 to 2.51)	1	-2	-2	0	-1	0	1: High risk of bias 2: Single study 4: Small sample size	Very low
No patients reported adverse events related to the study treatments	1	-2	-2	0	-2	0	1: High risk of bias	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
							2: Single study 4: No quantification	
High-potency probiotic preparation VSL#3 versus placebo (Delia 2007; 490 participants)								
Incidence of radiation-induced diarrhea 77/243 (31.6%) vs. 124/239 (51.8%) p<0.001; RR: 0.61 (95%CI 0.49 to 0.76)	1	-2	-2	0	0	0	1: Unclear risk of bias 2: Single study	Very low
Severity of radiation-induced diarrhea (WHO grading) Grade 3 or 4 diarrhea: 8/77 (1.4%) vs. 69/124 (55.4%) (p<0.001); RR: 0.19 (95%CI 0.10 to 0.37)	1	-2	-2	0	0	0	1: Unclear risk of bias 2: Single study	Very low
Daily number of bowel movements 5.1 ± 3 vs. 14.7 ± 6 (p<0.05) MD: -9.60 (95%CI -10.45 to -8.75)	1	-2	-2	0	0	0	1: Unclear risk of bias 2: Single study	Very low

** GRADE scores: 1. Limitations; 2. Inconsistency; 3. Indirectness; 4. Imprecision; 5. Reporting bias.*

Appendix 4.5.2. Non-surgical interventions for radioproctitis

Table 116 – Non-surgical interventions for radioproctitis: GRADE profiles by intervention and outcome

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Hyperbaric oxygen vs. placebo (Clarke 2008; 120 participants; Sidik 2007; 65 participants)								
Improvement of SOMA-LENT score: 5.0 points (95%CI 3.96 to 6.03) vs. 2.61 points (95%CI 1.51 to 3.70) (p=0.0019). Estimated difference (repeated measures model) = 1.93 points (95%CI 0.38 to 3.48, p=0.0150) "ratio of acute side effects before and soon after of intervention" 44.12% ± 28.22 vs. 0.71% ± 30.16 vs. (p<0.001) "ratio of late side effects before and soon after of intervention" 33.64 ± 57.64 vs. -19.69 ± 69.44 (p=0.008)	1 1 1	-2	-2	0	-1	0	1: Clarke 2008: 30 patients excluded after randomization; no ITT analysis / Sidik 2007 high risk of bias 2: Small single study 4: CI includes clinically non-significant result	Very low
Clinical evaluation: proportion healed or improved: 56/63 (88.9%) vs. 35/65 (62.5%); RR = 1.65; 95%CI 1.30 to 2.10. Estimated OR (repeated measures model) for improvement = 5.93; 95%CI 2.04 to 17.24	1	-2	-2	0	-1	0	1: 30 patients excluded after randomization; no ITT analysis 2: Small single study 4: Small sample size	Very low
Quality of life: marked improvement on Expanded Prostate Cancer Index Composite quality of life after treatment for bowel bother (14% vs. 5%) and bowel function (9% vs. 6%)	1	-2	-2	0	-2	0	1: 30 patients excluded after randomization; no ITT analysis/ high risk of bias 2: Small single study 4: No quantification (no comparison between groups)	Very low
Performance status (Karnofsky score, direct after intervention) "ratio of quality of life before and soon after intervention" 19.67 ± 9.64 vs. 4.53 ± 10.74 (p <0.001)	1	-2	-2	0	-1	0	1: High risk of bias 2: Small single study 4: Small sample size	Very low
Performance status (Karnofsky score, after 6 months) "ratio of quality of life before and after 6 months of intervention" 15.27 ± 14.74 vs. 2.47 ± 16.11 p =0.007)	1	-2	-2	0	-1	0	1: High risk of bias 2: Small single study 4: Small sample size	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Coagulation therapy: bipolar heater probe vs. bipolar electrocoagulation probe (Jensen 1997; 21 participants)								
Severe rectal bleeds after 1 year: 1/9 (11%) vs. 3/12 (33%): RR = 0.44; 95%CI 0.05 to 3.60 Mean number of bleeding episodes: 0.4 vs. 0.3	1	-1	-2	0	-1	0	1: unclear risk of bias 2: Single study 4: very small study	Very low
Argon plasma coagulation versus bipolar electrocoagulation (Lenz 2010; 30 participants)								
Success rates: 12/15 vs. 14/15: RR = 0.86 (95%CI 0.64 to 1.14)	1	-1	-2	-1	-1	0	1: unclear risk of bias 2: single study 3: success defined as eradication of telangiestasias, not based on symptoms 4: wide CI includes benefit and harm	Very low
Minor complications: 5/15 vs. 13/15: RR = 0.38 (95%CI 0.18 to 0.81)	1	-1	-2	0	-1	0	1: unclear risk of bias 2: single study 4: Small sample size	Very low
Major complications: 1/15 vs. 5/15: RR = 0.20 (95%CI 0.03 to 1.51)	1	-1	-2	0	-1	0	1: unclear risk of bias 2: single study 4: very wide CI, includes benefit and harm	Very low
Relapse of rectal bleeding: 1/12 vs. 2/14; RR = 0.58 (95%CI 0.06 to 5.66)	1	-1	-2	0	-1	0	1: unclear risk of bias 2: single study 4: very wide CI, includes benefit and harm	Very low
Argon plasma coagulation, electrical power setting of 60 vs. argon plasma coagulation, electrical power setting of 50 W (Gheorghe 2003; 42 participants)								
Improvement of rectal bleeding No bleeding: 56.5% vs. 26.3% (p=0.16) RR 2.15 (95%CI 0.93 to 4.94) Minor intermittent bleeding: 43.5% vs. 73.7% RR 0,59 (95%CI 0.34 to 1.01)	1	-2	-2	0	-1	0	1: high risk of bias for incomplete outcome data 2: single study 4: wide CI includes benefit and harm, low number of events	Very low
Oral sulfasalazine + rectal prednisolone vs. oral placebo + rectal sucralfate (Kochar 1997; 37 participants)								
Clinical improvement: 8/15 vs. 16/17: RR = 0.57 (95%CI 0.35	1	-1	-2	0	-1	0	1: unclear risk of bias	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
to 0.92)							2: single study 4: wide CI, low number of events	
Endoscopic improvement: 7/15 vs. 12/17: RR = 0.66 (95%CI 0.35 to 1.23)	1	-1	-2	0	-1	0	1: unclear risk of bias 2: single study 4: very wide CI, includes harm and benefit	Very low
Side effects: two patients in the sulfasalazine group did not tolerate the drugs due to myalgia, nausea and headaches	1	-1	-2	0	-1	0	1: unclear risk of bias 2: single study 4: low number of events; small study	Very low
Corticosteroids: hydrocortisone acetate mousse vs. betamethasone lavage (Rougier 1992; 32 participants)								
At 4 weeks of treatment: improvement of endoscopic appearance: 12/16 vs. 5/14: RR = 2.10 (95%CI 0.98 to 4.48)	1	-1	-2	0	-1	0	1: severe baseline imbalances 2: single study 4: small study; wide CI (covering the neutral value)	Very low
Poor tolerance of enema: 2/16 vs. 10/14: RR = 0.18 (95%CI 0.05 to 0.67)	1	-1	-2	0	-1	0	1: severe baseline imbalances 2: single study 4: small study	Very low

** GRADE scores: 1. Limitations; 2. Inconsistency; 3. Indirectness; 4. Imprecision; 5. Reporting bias.*

Appendix 4.6. Infertility

Table 117 – Infertility: GRADE profiles by intervention and outcome

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
GnRH-agonist vs. no additional intervention (SR: total of 7 studies, 340 participants; 3 RCTs, 281+100+61=442)								
Pregnancy rate, life birth rate								
Incidence of spontaneous pregnancy (4 studies): OR = 0.83 (95%CI 0.24 to 2.81) (Giuseppe 2007, Waxman 1987, Gerber 2011, Del Mastro 2011)	4	-1	0	0/ -1	-1	0	1: 2 studies high risk of bias, 1 study unclear risk of bias 3: as the rate of miscarriage can be increased, indirect evidence for life birth rate 4: CI includes benefit and harm	Low/very low
Overall survival								
Death: "At last follow up: 8 deaths chemotherapy plus triptorelin group and 3 in the chemotherapy-alone group" (Del Mastro 2011) RR = 2.32; 95%CI 0.63 to 8.55	1	0	-2	0	-1	0	2: single study 4: CI includes benefit and harm	Very low
Recurrences: "At last follow up: 14 recurrences in the chemotherapy plus triptorelin group, 13 in the chemotherapy-alone group" (Del Mastro 2011) RR = 0.94; 95%CI 0.46 to 1.92	1	0	-2	0	-1	0	2: single study 4: CI includes benefit and harm	Very low
Adverse events of intervention								
Hot flushes OR 1.61 (95%CI 0.87 to 2.97) (Del Mastro) OR 2.29 (95%CI 0.80 to 6.50) (Gerber 2011)	2	0	0	0	-1	0	4: Wide confidence intervals that include benefit and harm	Moderate
Mood modification OR 0.91 (95%CI 0.43 to 1.93) (Del Mastro) OR 1.00 (95%CI 0.13 to 7.60) (Gerber 2011)	2	0	0	0	-1	0	4: Wide confidence intervals that include benefit and harm	Moderate
Sweating OR 1.76 (95%CI 0.81 to 3.80) (Del Mastro)	1	0	-2	0	-1	0	2: single study 4: Wide confidence interval that includes benefit and harm	Very low
Headache OR 1.42 (95%CI 0.75 to 2.72) (Del Mastro)	1	0	-2	0	-1	0	2: single study 4: Wide confidence interval that includes benefit and harm	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Insomnia OR 5.80 (95%CI 0.63 to 53.01) (Gerber 2011)	1	0	-2	0	-2	0	2: single study 4: Very wide confidence interval, small sample size	Very low
Vaginal dryness OR 1.01 (95%CI 0.45 to 2.27) (Del Mastro)	1	0	-2	0	-1	0	2: single study 4: Wide confidence interval	Very low
Urogenital symptoms OR 7.25 (95%CI 0.82 to 64.46) (Gerber 2011)	1	0	-2	0	-2	0	2: single study 4: Very wide confidence interval, small sample size	Very low
Ovarian function								
Incidence of women with spontaneous ovulation OR = 5.70 (95%CI 2.29 to 14.20) (Bedaiwy 2011: Badawy 2009, Waxman 1987)	2	-2	0	0	-1	0	1: Overall risk of bias of both studies was high 4: Small sample size	Very low
Incidence of women with spontaneous menstruation RR 1.49 (95%CI 1.14 to 1.94) (Bedaiwy 2011: Badawy 2009, Gilani, 2007, Giuseppe 2007, Sverisdottir 2009a, Sverisdottir 2009b, Waxman 1987; Gerber 2011, Del Mastro 2011)	8	-1	-1	0	-1	0	1: Most studies included in the meta-analysis (Bedaiwy 2011) had high risk of bias. 2: Non-overlap between CI 4: Wide confidence interval, lower value may not be clinically relevant	Very low
Long-term ovarian function reserve and fertility, AMH > 0.2 µg/L, 4/8 vs. 3/9, OR 2.00 (95%CI 0.28 to 14.20) (Median time from random assignment to measurement of AMH was 4 y.) (Gerber 2011)	1	0	-2	-1	-1	0	2: single study 3: AMH level representing long-term ovarian function reserve and fertility 4: Wide confidence interval	Very low
Oral Contraceptives (OC) vs. GnRH analogue (one RCT, 23 participants)								
Pregnancy rate, life birth rate								
Birth rate 18 months after end of therapy: No woman gave birth to a child after HL treatment in both arms.	1	-2	-2	0	-2	0	1: High risk of attrition bias, unclear risk of selection bias and other bias 2: single study 4: very small sample size	Very low
Ovarian function								
Incidence of amenorrhea 18 months after end of therapy RR 3.33 (95%CI 0.42 to 26.58)	1	-2	-2	0	-2	0	1: High risk of attrition bias, unclear risk of selection bias and other bias 2: single study 4: very small sample size	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Incidence of irregular menses 18 months after end of therapy RR 2.22 (95%CI 0.24 to 20.57)	1	-2	-2	0	-2	0	1: High risk of attrition bias, unclear risk of selection bias and other bias 2: single study 4: very small sample size	Very low
Incidence of regular menses 18 months after end of RR 0.48 (95%CI 0.17 to 1.31)	1	-2	-2	0	-2	0	1: High risk of attrition bias, unclear risk of selection bias and other bias 2: single study 4: very small sample size	Very low
Protection of the ovarian reserve 12 months after end of therapy: Anti-Mullerian Hormone (AMH), median µg/l (range): OC: <0.017 (<0.017-0.032) GnRH-a: <0.017 (<0.017-0.681) Follicle stimulating hormone (FSH), median U/l (range): OC: 78.4 (7.2-116) GnRH-a: 58.6 (7.9-185) “neither OC nor GnRH-a cotreatment is able to ensure a meaningful protection of the ovarian reserve”	1	-2	-2	-1	-2	0	1: High risk of attrition bias, unclear risk of selection bias and other bias 2: single study 4: very small sample size	Very low

Appendix 4.7. Gastrointestinal toxicity: nausea & vomiting, diarrhoea

Appendix 4.7.1. Nausea & vomiting

Table 118 – Nausea & vomiting: overview of GRADE-profiles of the effect of cannabinoids, based on one systematic review (Machado Rocha 2008) and two RCTs (Duran 2010; Meiri 2007)

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Cannabinoids vs. placebo								
Anti-emetic efficacy (complete response): RR = 3.11, 95%CI 1.57 to 6.18	4	-2	0	0	0	0	1:. all studies had high risk of bias	Low
Adverse events (based on Keeley): "High" sensation: RR = 10.6; 95%CI 6.86 to 16.50 Drowsiness, sedation, somnolence: RR = 1.66; 95%CI 1.46 to 1.89 Withdrawal because of adverse effects: RR = 4.67; 95%CI 3.07 to 7.09	4	-2	0	0	0	0	1: all studies high risk of bias	Low

GRADE scores: 1. Limitations; 2. Inconsistency; 3. Indirectness; 4. Imprecision; 5. Reporting bias

Appendix 4.7.2. Diarrhoea

Table 119 – Diarrhoea: overview GRADE-profiles of the effect of octreotide, probiotics, nutritional supplements and loperamide

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Prophylactic octreotide vs. placebo (3 RCTs)								
Incidence of grade ≥ 2 diarrhoea RR = 1.01; 95%CI 0.76 to 1.35	2	-1	0	0	-1	0	1: one study high risk of bias 4: CI includes appreciable benefit and harm	Low
Quality of life 7.7 versus 7.8 on a 1-10 scale (Martenson) No statistiscally significant difference (Zachariah)	2	-1	0	0	-2	0	1: one study high risk of bias 4: no quantification CI	Very low
Severe adverse events “nearly equally distributed” (Zachariah) “no major side effects” (Cascinu)	2	0	0	0	-2	0	4: no quantification CI	Low
Octreotide vs. loperamide (2 RCTs)								
Diarrhea treated day 3 RR = 6.03; 95%CI 2.11 to 17.28 (Cascinu) RR = 2.67; 95%CI 1.32 to 5.39 (Gebbia)	2	-2	0	0	-1	0	1: 2 studies high risk of bias 4: OIS for 25% RRR = 697	Very low
Probiotics								
Development of radio-induced diarrhea OR = 0.47; 95%CI 0.13 to 1.67	3	-1	-1	0	-1	0	1: high risk of bias in one study; unclear in two 2: no overlap of CIs 4: CI includes benefit and harm	Very low
Cure of diarrhea “no significant differences”	1	-1	-2	0	-2	0	1: unclear risk of bias 2: single study 4: no quantification CI	Very low
Adverse events “no major events reported”	3	-1	0	0	0	0	1: All studies unclear or high risk of bias 4: no quantification of CI but large sample size and no major adverse events in both groups, thus decision not to down grade	Moderate
Elemental diet supplementation to normal diet								
Incidence and severity of diarrhea “significant decrease” “no differences”	2	-1	-1	0	-2	0	1: high and unclear risk of bias 2: inconsistent conclusions 4: no quantification of CI	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Quality of life No differences	1	-2	-2	0	-2	0	1: high risk of bias 2: single study 4: no quantification of results	Very low
Elemental diet supplementation to low rouphage diet								
Incidence and severity of diarrhea “no difference”	1	-2	-2	0	-2	0	1: high risk of bias 2: single study 4: no quantification CI	Very low
Enzyme supplementation								
Incidence of moderate to severe bowel symptoms 57% versus 36% (p=0.11)	1	-1	-2	0	0	0	1: unvalidated scale for assessing bowel symptoms 2: single study	Very low
Loperamide versus placebo								
Severity of bowel symptoms (stool frequency per 3 days) 5, range 1-10 vs. 7, range 2-14; p<0.05	1	0	-2	0	-1	0	2: single small study 4: OIS not reached	Very low
Adverse events “no significant adverse events were reported”	1	0	-2	0	-1	0	2: single small study 4: OIS not reached	Very low

Appendix 4.8. Cardiac toxicity

Table 120 – Cardiac toxicity: GRADE profiles by intervention and outcome

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Dexrazoxane vs placebo (SR: total of 10 studies, 1619 participants)								
Clinical heart failure (RR 0.18, 95%CI 0.10 to 0.32) (Van Dalen 2011)	8	0	0	0	-1	0	1: Not downgraded since 2 studies with low risk of bias reached similar results as the meta-analysed point estimate 4: Optimal information size not reached (4658 for RR 25% and CER 8.7%)	Moderate
Clinical and subclinical heart failure combined: (RR 0.29, 95%CI 0.20 to 0.41) (Van Dalen 2011)	5	0	0	0	-1	0	1: Not downgraded since 2 studies with low risk of bias reached similar results as the meta-analysed point estimate 4: Optimal information size not reached	Moderate
Overall survival: (HR 1.04; 95%CI 0.88 to 1.23) (Van Dalen 2011)	4	0	0	0	-1	0	1: Not downgraded since 2 studies with low risk of bias reached similar results as the meta-analysed point estimate 4: Confidence interval includes no effect and appreciable harm (HR 1.10)	Moderate
Progression free survival: (HR 1.01; 95%CI 0.86 to 1.18) (Van Dalen 2011)	4	0	-1	0	-1	0	1: Not downgraded since 2 studies with low risk of bias reached similar results as the meta-analysed point estimate 2: Inconsistent results, non-overlap between CI 4: Confidence interval includes no effect and appreciable harm (HR 1.10)	Low
Response rate: (RR 0.89, 95%CI 0.78 to 1.02) (Van Dalen 2011)	6	-1	0	0	-1	0	1: 4 of 6 studies high risk of bias 4: Confidence interval includes clinical decision threshold (RRR 90%)	Low
Adverse events								
Thrombocytopenia gr 3-4 RR 1.04; 95%CI 0.49 to 2.21 Platelet count at nadir gr 3-4 RR 0.92; 95%CI 0.53 to 1.59	2 2	-1	0	0	-1	0	1: Unclear/high risk of bias 4: CI includes appreciable harm and benefit	Low
Neutropenia gr 3-4 RR 1.04; 95%CI 0.90 to 1.21 Granulocyte count at nadir gr 3-4 RR 1.04; 95%CI 0.97 to 1.11	2 2	-1	0	0	-1	0	1: Unclear/high risk of bias 4: CI includes appreciable harm and benefit	Low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Anaemia gr 3-4 RR 1.40 95%CI 1.08 to 1.81	3	-1	0	0	-1	0	1: Unclear/high risk of bias 4: CI includes no and appreciable harm	Low
Stomatitis gr 3-4 RR 0.85; 95%CI 0.60 to 1.21	3	-1	0	0	-1	0	1: Unclear/high risk of bias 4: CI includes benefit and harm	Low
Nausea gr 3-4 RR 0.69; 95%CI 0.49 to 0.94	3	-1	0	0	-1	0	1: 1 of 3 studies high risk of bias 4: CI includes benefit and no benefit.	Low
Vomiting gr 3-4 RR 0.79; 95%CI 0.55 to 1.14	3	-1	0	0	-1	0	1: 1 of 3 studies high risk of bias 4: CI includes benefit and harm	Low
Anorexia gr 3-4 RR 0.97; 95%CI 0.57 to 1.64	2	_1	0	0	-1	0	1: Unclear/high risk of bias 4: CI includes benefit and harm	Low
Neurotoxicity gr 3-4 RR 0.62; 95%CI 0.03 to 13.45	2	-1	0	0	-2	0	1: Unclear/high risk of bias 4: CI includes benefit and harm	Very low
Fever gr 3-4 RR 1.44; 95%CI 0.81 to 2.53	2	-1	0	0	-1	0	1: Unclear/high risk of bias 4: CI includes benefit and harm	Low

APPENDIX 5. FOREST PLOTS

Figure 42 – Mucositis: forest plot cryotherapy – prevention of any mucositis

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Year
Mahood 1991	-0.462	0.26	12.2%	0.63 [0.38, 1.05]	1991
Cascinu 1994	-0.4526	0.271	11.7%	0.64 [0.37, 1.08]	1994
Lilleby 2006	-0.4479	0.174	17.7%	0.64 [0.45, 0.90]	2006
Gori 2007	-0.02	0.04	27.0%	0.98 [0.91, 1.06]	2007
Sorensen 2008	-0.36	0.14	20.3%	0.70 [0.53, 0.92]	2008
Katranci 2011	-0.4925	0.2825	11.1%	0.61 [0.35, 1.06]	2011
Total (95% CI)			**100.0%**	**0.72 [0.57, 0.92]**	

Heterogeneity: Tau² = 0.05; Chi² = 16.87, df = 5 (P = 0.005); I² = 70%
Test for overall effect: Z = 2.65 (P = 0.008)

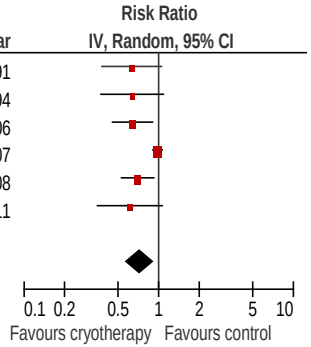


Figure 43 – Mucositis: forest plot cryotherapy – prevention of moderate to severe mucositis

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Year
Mahood 1991	-1.2	0.57	11.1%	0.30 [0.10, 0.92]	1991
Cascinu 1994	-0.673	0.38	16.0%	0.51 [0.24, 1.07]	1994
Lilleby 2006	-1.197	0.408	15.2%	0.30 [0.14, 0.67]	2006
Gori 2007	0.01	0.09	24.1%	1.01 [0.85, 1.20]	2007
Sorensen 2008	-0.65	0.25	20.1%	0.52 [0.32, 0.85]	2008
Katranci 2011	-0.8755	0.4655	13.6%	0.42 [0.17, 1.04]	2011
Total (95% CI)			**100.0%**	**0.51 [0.31, 0.84]**	

Heterogeneity: Tau² = 0.26; Chi² = 21.32, df = 5 (P = 0.0007); I² = 77%
Test for overall effect: Z = 2.63 (P = 0.009)

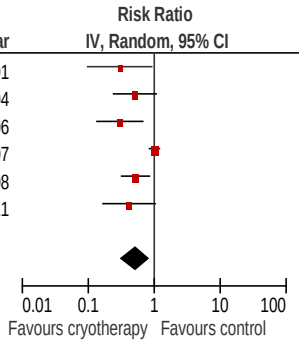


Figure 44 – Mucositis: forest plot cryotherapy – prevention of severe mucositis

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Year
Mahood 1991	-2.04	0.9	10.3%	0.13 [0.02, 0.76]	1991
Cascinu 1994	-1.022	0.55	17.1%	0.36 [0.12, 1.06]	1994
Lilleby 2006	-1.6399	0.552	17.1%	0.19 [0.07, 0.57]	2006
Gori 2007	-0.13	0.18	26.4%	0.88 [0.62, 1.25]	2007
Sorensen 2008	-1.08	0.41	20.7%	0.34 [0.15, 0.76]	2008
Katranci 2011	-1.7918	1.0488	8.4%	0.17 [0.02, 1.30]	2011
Total (95% CI)			**100.0%**	**0.34 [0.17, 0.70]**	

Heterogeneity: Tau² = 0.46; Chi² = 15.83, df = 5 (P = 0.007); I² = 68%
Test for overall effect: Z = 2.96 (P = 0.003)

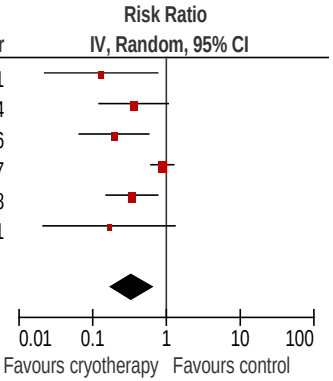


Figure 45 – Mucositis: forest plot keratinocyte GF versus placebo – prevention of severe mucositis

Study or Subgroup	KGF Events	KGF Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Henke 2011	47	92	63	94	17.4%	0.76 [0.60, 0.97]
Le 2011	51	94	65	94	18.7%	0.78 [0.62, 0.99]
Freytes 2004	4	28	1	14	0.4%	2.00 [0.25, 16.26]
Spielberger 2004	67	106	104	106	27.2%	0.64 [0.56, 0.75]
Blazar 2006	43	65	24	31	16.4%	0.85 [0.66, 1.11]
Rosen 2006	1	28	4	36	0.4%	0.32 [0.04, 2.72]
Brizel 2008	43	65	26	32	17.8%	0.81 [0.64, 1.04]
Vadhan-Raj 2010	4	32	8	16	1.6%	0.25 [0.09, 0.71]
Total (95% CI)		**510**		**423**	**100.0%**	**0.74 [0.65, 0.85]**
Total events	260		295			

Heterogeneity: Tau² = 0.01; Chi² = 11.02, df = 7 (P = 0.14); I² = 36%
Test for overall effect: Z = 4.31 (P < 0.0001)

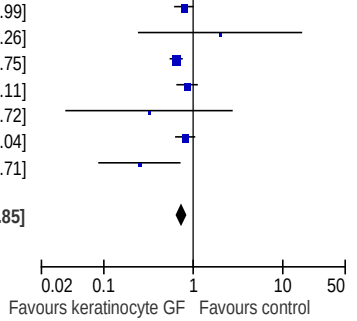


Figure 46 – Mucositis: forest plot keratinocyte GF versus placebo – incidence of supplemental nutrition

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Henke 2011	48	52	49	52	18.0%	0.73 [0.16, 3.46]
Le 2011	63	94	52	94	82.0%	1.64 [0.91, 2.97]
Total (95% CI)		**146**		**146**	**100.0%**	**1.48 [0.85, 2.56]**
Total events	111		101			

Heterogeneity: Chi² = 0.90, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 1.39 (P = 0.16)

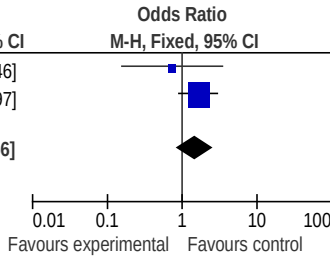


Figure 47 – Mucositis: forest plot honey versus placebo – prevention of severe mucositis

Study or Subgroup	Honey Events	Honey Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Biswal 2003	4	20	15	20	35.7%	0.27 [0.11, 0.66]	2003
Rashad 2008	3	20	12	20	28.6%	0.25 [0.08, 0.75]	2008
Khanal 2010	1	20	15	20	35.7%	0.07 [0.01, 0.46]	2010
Total (95% CI)		**60**		**60**	**100.0%**	**0.19 [0.10, 0.37]**	
Total events	8		42				

Heterogeneity: Chi² = 1.90, df = 2 (P = 0.39); I² = 0%
Test for overall effect: Z = 4.87 (P < 0.00001)

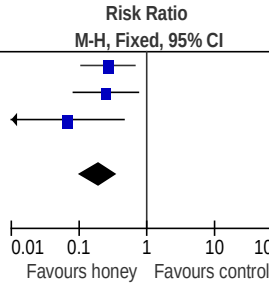


Figure 48 – Mucositis: forest plot laser versus placebo – prevention of severe mucositis

Study or Subgroup	Laser Events	Laser Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Cruz 2007	2	28	3	31	10.3%	0.74 [0.13, 4.10]	2007
Antunes 2007	1	19	13	19	47.0%	0.08 [0.01, 0.53]	2007
Gouvea de Lima 2012	4	37	12	38	42.8%	0.34 [0.12, 0.97]	2012
Total (95% CI)		**84**		**88**	**100.0%**	**0.26 [0.12, 0.56]**	
Total events	7		28				

Heterogeneity: Chi² = 3.23, df = 2 (P = 0.20); I² = 38%
Test for overall effect: Z = 3.44 (P = 0.0006)

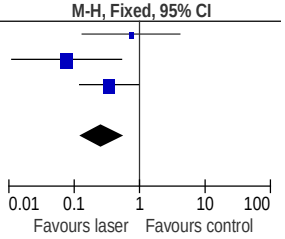


Figure 49 – Neuropathy: forest plot Ca/Mg – prevention of Grade 2 or more neurotoxicity

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chay 2010	3	9	2	10	8.1%	1.67 [0.36, 7.82]
Grothey 2011	11	50	21	52	87.6%	0.54 [0.29, 1.01]
Ishibashi 2010	2	17	1	16	4.4%	1.88 [0.19, 18.80]
Total (95% CI)		**76**		**78**	**100.0%**	**0.69 [0.40, 1.19]**
Total events	16		24			

Heterogeneity: Chi² = 2.55, df = 2 (P = 0.28); I² = 21%
Test for overall effect: Z = 1.32 (P = 0.19)

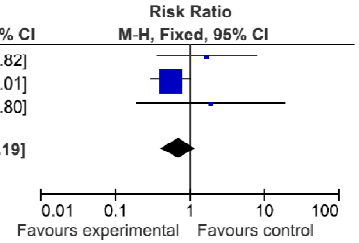


Figure 50 – Neutropenia: forest plot empirical amphotericin B versus placebo – mortality

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
EORTC 1989	11	80	14	77	73.3%	0.76 [0.37, 1.56]
Goldstone 1994	1	64	1	69	4.9%	1.08 [0.07, 16.88]
Kelsey 1999	11	74	12	87	0.0%	1.08 [0.51, 2.30]
Penack 2006	4	75	8	57	0.0%	0.38 [0.12, 1.20]
Perfect 1992	3	91	11	91	0.0%	0.27 [0.08, 0.95]
Pizzo 1982	3	18	4	16	21.8%	0.67 [0.18, 2.54]
Riley 1994	0	17	4	18	0.0%	0.12 [0.01, 2.03]
Suda 1980	13	39	13	31	0.0%	0.79 [0.43, 1.46]
Tollemar 1993	5	42	3	42	0.0%	1.67 [0.43, 6.53]
Total (95% CI)		**162**		**162**	**100.0%**	**0.75 [0.40, 1.40]**
Total events	15		19			

Heterogeneity: Chi² = 0.10, df = 2 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.90 (P = 0.37)

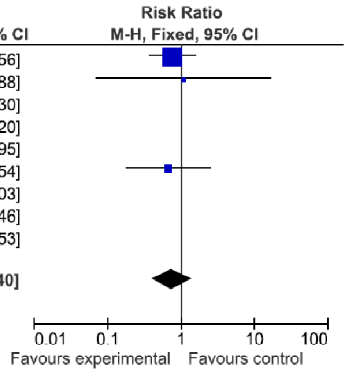


Figure 51 – Neutropenia: forest plot prophylactic amphotericin B versus placebo – mortality

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
EORTC 1989	11	80	14	77	0.0%	0.76 [0.37, 1.56]
Goldstone 1994	1	64	1	69	0.0%	1.08 [0.07, 16.88]
Kelsey 1999	11	74	12	87	20.8%	1.08 [0.51, 2.30]
Penack 2006	4	75	8	57	17.2%	0.38 [0.12, 1.20]
Perfect 1992	3	91	11	91	20.8%	0.27 [0.08, 0.95]
Pizzo 1982	3	18	4	16	0.0%	0.67 [0.18, 2.54]
Riley 1994	0	17	4	18	8.3%	0.12 [0.01, 2.03]
Suda 1980	13	39	13	31	27.3%	0.79 [0.43, 1.46]
Tollemar 1993	5	42	3	42	5.7%	1.67 [0.43, 6.53]
Total (95% CI)		**338**		**326**	**100.0%**	**0.67 [0.45, 0.98]**
Total events	36		51			

Heterogeneity: Chi² = 7.92, df = 5 (P = 0.16); I² = 37%
Test for overall effect: Z = 2.07 (P = 0.04)

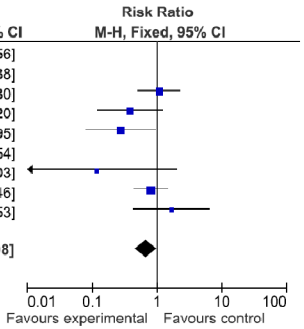


Figure 52 – Neutropenia: forest plot prophylactic amphotericin B versus fluconazole – death

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akiyama 1993	2	40	2	36	2.0%	0.90 [0.13, 6.06]
Anaissie 1996	9	84	9	80	0.0%	0.95 [0.40, 2.28]
Bodey 1994	7	46	5	44	4.8%	1.34 [0.46, 3.91]
Koh 2002	22	100	25	86	25.3%	0.76 [0.46, 1.24]
Malik 1998	14	52	16	48	0.0%	0.81 [0.44, 1.47]
Marie 1993	0	65	2	66	0.0%	0.20 [0.01, 4.15]
Menichetti 1994	44	420	40	400	38.6%	1.05 [0.70, 1.57]
Meunier 1991	5	30	8	29	7.7%	0.60 [0.22, 1.63]
Silling 1999	7	51	11	47	0.0%	0.59 [0.25, 1.39]
Teshima 1994	3	53	2	55	1.8%	1.56 [0.27, 8.95]
Viscoli 1996	2	57	3	57	0.0%	0.67 [0.12, 3.84]
Winston 2000	27	158	34	159	0.0%	0.80 [0.51, 1.26]
Wolff 2000	24	196	19	159	19.8%	1.02 [0.58, 1.80]
Total (95% CI)		**885**		**809**	**100.0%**	**0.96 [0.74, 1.23]**
Total events	107		101			

Heterogeneity: Chi² = 2.61, df = 6 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.35 (P = 0.73)

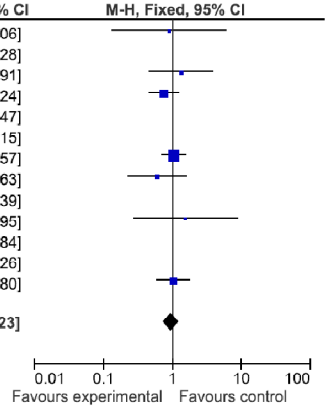


Figure 53 – Neutropenia: forest plot prophylactic amphotericin B versus fluconazole – invasive infections

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akiyama 1993	1	40	2	36	4.8%	0.45 [0.04, 4.76]
Anaissie 1996	29	84	24	80	0.0%	1.15 [0.74, 1.80]
Bodey 1994	2	46	3	44	7.0%	0.64 [0.11, 3.64]
Koh 2002	12	100	11	86	26.9%	0.94 [0.44, 2.02]
Marie 1993	2	65	3	66	0.0%	0.68 [0.12, 3.92]
Menichetti 1994	10	420	8	400	18.6%	1.19 [0.47, 2.99]
Meunier 1991	4	30	5	29	11.6%	0.77 [0.23, 2.60]
Silling 1999	4	49	5	49	0.0%	0.80 [0.23, 2.80]
Teshima 1994	1	53	0	55	1.1%	3.11 [0.13, 74.72]
Viscoli 1996	0	57	0	57		Not estimable
Winston 2000	15	158	14	159	0.0%	1.08 [0.54, 2.16]
Wolff 2000	8	196	12	159	30.1%	0.54 [0.23, 1.29]
Total (95% CI)		**885**		**809**	**100.0%**	**0.83 [0.54, 1.26]**
Total events	38		41			

Heterogeneity: Chi² = 2.64, df = 6 (P = 0.85); I² = 0%
Test for overall effect: Z = 0.89 (P = 0.37)

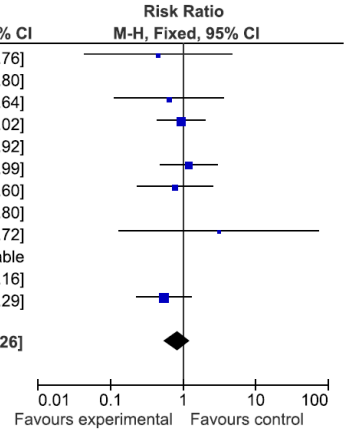


Figure 54 – Neutropenia: forest plot empirical amphotericin B versus fluconazole – death

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akiyama 1993	2	40	2	36	0.0%	0.90 [0.13, 6.06]
Anaissie 1996	9	84	9	80	12.0%	0.95 [0.40, 2.28]
Bodey 1994	7	46	5	44	0.0%	1.34 [0.46, 3.91]
Koh 2002	22	100	25	86	0.0%	0.76 [0.46, 1.24]
Malik 1998	14	52	16	48	21.7%	0.81 [0.44, 1.47]
Marie 1993	0	65	2	66	3.2%	0.20 [0.01, 4.15]
Menichetti 1994	44	420	40	400	0.0%	1.05 [0.70, 1.57]
Meunier 1991	5	30	8	29	0.0%	0.60 [0.22, 1.63]
Silling 1999	7	51	11	47	14.9%	0.59 [0.25, 1.39]
Teshima 1994	3	53	2	55	0.0%	1.56 [0.27, 8.95]
Viscoli 1996	2	57	3	57	3.9%	0.67 [0.12, 3.84]
Winston 2000	27	158	34	159	44.2%	0.80 [0.51, 1.26]
Wolff 2000	24	196	19	159	0.0%	1.02 [0.58, 1.80]
Total (95% CI)		**467**		**457**	**100.0%**	**0.76 [0.56, 1.04]**
Total events	59		75			

Heterogeneity: Chi² = 1.44, df = 5 (P = 0.92); I² = 0%
Test for overall effect: Z = 1.73 (P = 0.08)

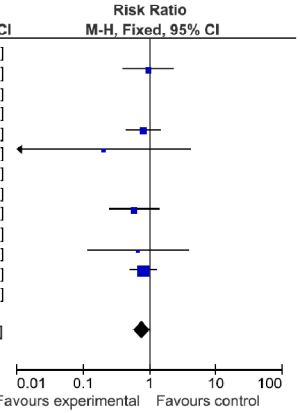


Figure 55 – Neutropenia: forest plot empirical amphotericin B versus fluconazole – invasive infections

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akiyama 1993	1	40	2	36	0.0%	0.45 [0.04, 4.76]
Anaissie 1996	29	84	24	80	52.9%	1.15 [0.74, 1.80]
Bodey 1994	2	46	3	44	0.0%	0.64 [0.11, 3.64]
Koh 2002	12	100	11	86	0.0%	0.94 [0.44, 2.02]
Marie 1993	2	65	3	66	6.4%	0.68 [0.12, 3.92]
Menichetti 1994	10	420	8	400	0.0%	1.19 [0.47, 2.99]
Meunier 1991	4	30	5	29	0.0%	0.77 [0.23, 2.60]
Silling 1999	4	49	5	49	10.7%	0.80 [0.23, 2.80]
Teshima 1994	1	53	0	55	0.0%	3.11 [0.13, 74.72]
Viscoli 1996	0	57	0	57		Not estimable
Winston 2000	15	158	14	159	30.0%	1.08 [0.54, 2.16]
Wolff 2000	8	196	12	159	0.0%	0.54 [0.23, 1.29]
Total (95% CI)		**413**		**411**	**100.0%**	**1.06 [0.74, 1.51]**
Total events	50		46			

Heterogeneity: Chi² = 0.58, df = 3 (P = 0.90); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)

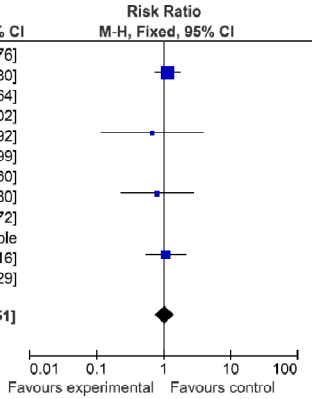


Figure 56 – Diarrhoea: forest plot octreotide versus placebo – moderate to severe diarrhoea

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Martenson 2008	32	62	27	63	41.4%	1.20 [0.83, 1.75]
Zachariah 2010	48	109	52	106	58.6%	0.90 [0.67, 1.20]
Total (95% CI)		**171**		**169**	**100.0%**	**1.01 [0.76, 1.35]**
Total events	80		79			

Heterogeneity: Tau² = 0.01; Chi² = 1.50, df = 1 (P = 0.22); I² = 33%
Test for overall effect: Z = 0.09 (P = 0.92)

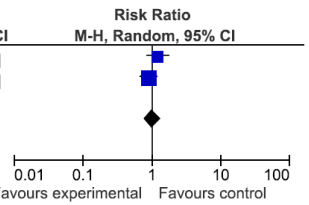
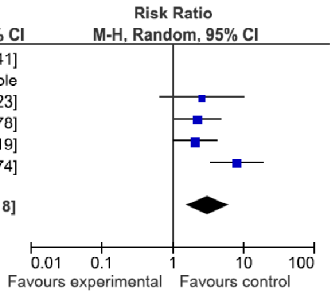


Figure 57 – Nausea & vomiting: forest plot cannabinoids versus placebo – complete response

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Chang 1979	8	15	0	15	0.0%	17.00 [1.07, 270.41]
Chang 1981	0	8	0	8		Not estimable
Duran 2010	4	7	2	9	15.7%	2.57 [0.65, 10.23]
Frytak 1979	16	38	7	37	28.3%	2.23 [1.04, 4.78]
Meiri 2007	40	50	5	13	29.9%	2.08 [1.03, 4.19]
Orr 1980	40	55	5	55	26.1%	8.00 [3.42, 18.74]
Total (95% CI)		**150**		**114**	**100.0%**	**3.11 [1.57, 6.18]**
Total events	100		19			

Heterogeneity: Tau² = 0.28; Chi² = 7.33, df = 3 (P = 0.06); I² = 59%
Test for overall effect: Z = 3.25 (P = 0.001)



APPENDIX 6. EVIDENCE TABLES

Appendix 6.1. Oral complications

Table 121 – Oral complications: evidence table of systematic reviews regarding the prevention of oral mucositis in patients with cancer who are treated with chemotherapy or radiotherapy

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Worthington 2011	• SR • Funding: none • Search date: February 2011 • Databases: Cochrane Oral Health Group Trials Register, Cochrane Pain, Palliative and SupportiveCare (PaPaS),Group Trials Register, CENTRAL, MEDLINE, EMBASE, CANCERLIT, LILACS, CINAHL	Anyone with cancer who receives radiotherapy, chemotherapy or targeted therapies.	Any agent prescribed as prophylaxis for oral mucositis vs. placebo, no treatment or another active intervention.	**Oral cooling** vs. no treatment or placebo Mucositis (any) (5 trials) RR = 0.74 (95%CI 0.57 to 0.95) Mucositis (moderate plus severe) (5 trials) RR = 0.53 (95%CI 0.31 to 0.91) Mucositis (severe) (5 trials) RR = 90.36 (95%CI 0.17 to 0.77) "One further trial demonstrated that oral cryotherapy alleviated the development of mucositis and oral pain, which resulted in a reduction in the number of days of iv opioids for patients treated with autologous bone marrow transplantation (BMT)." **Mouth washes** Allopurinol mouth rinse versus placebo/no treatment Mucositis (any grade) (4 trials) RR = 0.77 (95%CI 0.50 to 1.19) Mucositis (moderate plus severe) (2 trials) RR = 0.66 (95%CI 0.50 to 0.86) Mucositis (severe) (2 trials) RR = 0.81 (95%CI 0.63 to 1.04) Benzydamine mouthwash versus placebo Mucositis (any) (1 trial) RR = 0.67 (95%CI 0.47 to 0.97)	Quality SR: low risk of bias Quality included trials: The patient groups studied were diverse, the associated treatment modalities were varied and the strength of the evidence of effectiveness was variable. Overall conclusion of the review authors: "This review has highlighted several interventions with evidence of effectiveness from more than one trial included in a meta-analysis. Further research into the benefits and harms of these interventions and whether these results can be generalized to other forms of cancer and its treatment should be conducted."

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
				Mucositis (severe) (1 trial) RR = 0.55 (95%CI 0.38 to 0.82) "Two further studies both compared benzydamine with placebo and used other mucositis indices to evaluate the outcome. Both trials reported statistically significant differences in favour of benzydamine" Chlorhexidine mouthwash versus placebo/no treatment Mucositis (any grade) (4 trials) RR = 0.76 (95%CI 0.47 to 1.24) Mucositis (moderate plus severe) (3 trials) RR = 0.93 (95%CI 0.72 to 1.21) Mucositis (severe) (4 trials) RR = 0.82 (95%CI 0.54 to 1.23) Two further trials reported statistically significant differences in mean mucositis scores in each group which favoured chlorhexidine over placebo. Sucralfate mouthwash vs. placebo Mucositis (any) (3 trials) RR = 0.98 (95%CI 0.88 to 1.10) Mucositis (moderate plus severe) (4 trials) RR = 0.75 (95%CI 0.54 to 1.04) Mucositis (severe) (7 trials) RR = 0.67 (95%CI 0.48 to 0.92) A further two trials reported outcome data in a different format, but neither found a statistically significant difference between sucralfate and placebo in the prevention of mucositis.	

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
				Sucralfate mouthwash plus gel on skin versus placebo mouthwash plus gel on skin) Mucositis (any) (1 trial) RR = 1.07 (95%CI 0.96 to 1.20) Mucositis (moderate plus severe) (1 trial) RR = 1.21 (95%CI 1.00 to 1.46) Mucositis (severe) (1 trial) RR = 1.13 (95%CI 0.89 to 1.44) Amifostine versus no treatment or placebo Mucositis (any) (3 trials) RR = 0.95 (95%CI 0.91 to 0.99) Mucositis (moderate plus severe) (6 trials) RR = 0.75 (95%CI 0.58 to 0.96) Mucositis (severe) (9 trials) RR = 0.68 (95%CI 0.45 to 1.03) A further trial provided a graph of weekly mean mucositis scores and the text indicated that there was a statistically significant difference in favour of amifostine compared to no treatment at 2 weeks, however no overall result was given in this paper Oral care protocol versus none Mucositis (any) (1 study) RR = 0.62 (95%CI 0.43 to 0.91) Keratinocyte growth factor (Palifermin or Velafermin) versus placebo Mucositis (any) (2 trials) RR = 0.82 (95%CI 0.71 to 0.94) Mucositis (moderate plus severe) (7 trials)	

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
				RR = 0.74 (95%CI 0.62 to 0.89) Mucositis (severe) (6 trials) RR = 0.72 (95%CI 0.58 to 0.90) "From these seven trials there is some evidence that keratinocyte growth factor is effective in the prevention of mucositis." Honey versus no treatment Mucositis (any) (3 trials) RR = 0.70 (95%CI 0.56 to 0.88) Mucositis (moderate plus severe) (2 trials) RR = 0.48 (95%CI 0.31 to 0.74) Mucositis (severe) (2 trials) RR = 0.26 (95%CI 0.13 to 0.52) "However, in view of the considerable statistical heterogeneity and high risk of bias these results should be interpreted with caution." Laser versus placebo or sham control Mucositis (any) (3 trials) RR = 0.91 (95%CI 0.71 to 1.17) Mucositis (moderate plus severe) (2 trials) RR = 0.64 (95%CI 0.38 to 1.08) Mucositis (severe) (2 trials) RR = 0.20 (95%CI 0.06 to 0.62). Parallel group study mucositis measured on 0-4 scale. Mean calculated for each patient over 7 weeks. Quote "the mean grade of mucositis during radiotherapy was 2.1 +/ 0.26 for the group without laser and 1.7 +/- 0.26 for the group with laser (p=0.01)."	

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
				OMI appropriate index (Schubert 1992). Quote: "Figure 1 shows the mean OMI over time by treatment group. The placebo patient scores are higher on average than the laser patient scores at nearly every time point, signifying more severe mucositis over the course of the study." The authors then present day 11 data and statistical test for that day (P = 0.06). "The peak severity of mucositis that generally occurs during the second week of transplant was reduced in the 650 nm laser group." The results of the overall burden over time in Table 2 showed the differences in the unadjusted model to be non-significant. Only one difference comparing low-level laser with placebo was significant in the adjusted model (P = 0.03).	
Sasse 2006	• SR • Funding: 'logistic support' by Schering-Plough Brasil • Search date: April 2005 • Databases: MEDLINE, LILACS, CENTRAL	Patients with head or neck cancer undergoing radiotherapy	Radiotherapy plus amifostine vs. radiotherapy alone	Occurrence of grade 3-4 mucositis (5 studies): OR = 0.44 (95%CI 0.30 to 0.65)	Quality SR: low risk of bias Quality included studies: High risk of bias. In one study concealment of allocation was adequate and in the other 4 studies unclear; all studies were not blinded and not placebo controlled.

Table 122 – Oral complications: evidence table of RCTs regarding interventions for prevention of oral mucositis in patients with cancer receiving chemotherapy or radiotherapy

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Carvalho 2011	• Design: RCT • Source of funding: Fundação de Amparo à Pesquisa do Estado de São Paulo • Setting: Stomatology and Radiology Department, Hospital A.C. Camargo, São Paulo, Brazil • Sample size: n=70 • Duration: 7 weeks	Eligibility criteria: patients with malignant neoplasms in the oral cavity and/or oropharynx who were submitted to conventional three-dimensional conformal radiotherapy (RTC3D) or intensity modulated radiation therapy (IMRT) with doses in facial fields equal to or higher than 4000 cGy, either exclusively or associated with chemotherapy (cisplatin 100 mg/m2 every 21 days or 50 mg/m2 per week). Patient characteristics: mean age 56.2 ± 14.5 y vs 58.1 ± 10.9 y; M/F 25/10 vs 21/14; clinical stage 1/2/3/4: 4/6/11/14 vs 0/6/10/19 Comparable groups; however slightly more severe conditions in group 2	Gallium aluminum–arsenate (InGaAlP) diode laser (Twin laser – MMOptics_, MMOptics Ltda., São Carlos, São Paulo, Brazil) with continuous wavelength 660 nm and spot size 4 mm2 Group 1: power 15 mW, energy density delivered 3.8 J/cm2 Group 2: power 5 mW, energy density delivered 1.3 J/cm2	Mean time to development of oral mucositis Mean time to mucositis grade II (WHO) 13.5 days (range 6–26 days) vs 9.8 days (range 4–14 days) (P= 0.005) mean time to mucositis grade II (NCI) 13.5 days (range 6–26 days) vs 9.8 days (range 4–14 days) Mean time to mucositis grade III (WHO) 23.6 days (range 11–31 days) vs 17.1 days (range 10–31 days) (P= 0.014) mean time to mucositis grade III (NCI) 19.1 days (range 11–32 days) vs 17.2 days (range 8–33 days) (P=0.498) Mean grade of mucositis (WHO and NCI) No significant differences in weeks 6 (27 patients evaluated) and 7 (17 patients evaluated)	Risk of bias: unclear Dropouts: N= 16 (I: n=8, C: n=8) reasons equally distributed; at weeks 6 and 7 only 27 and 17 patients were evaluated, respectively. Results critical appraisal: adequate randomisation, concealment, blinding patients and of care givers. Blinding of outcome assessors unclear. Unclear risk of bias of incomplete outcome data. Low risk of reporting bias. Unclear risk of other bias.
Djuric 2006	• Design: RCT • Source of funding: not reported • Setting: Clinic of Hematology, Medical	Eligibility criteria: Acute leukemia patients, about to receive aggressive chemotherapy	Prechemotherapy intensive dental care (dental treatment and plaque and calculus removal	Incidence of oral mucositis (any grade) Day 7: 4/15 (27%) vs 8/19 (42%) RR 0.63 (95%CI 0.24 to 1.71)	Risk of bias: high Dropouts: four patients were excluded from the study due to their poor

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
	Faculty in Novi Sad, Serbia and Montenegro, • Sample size: n=40 (but only 34 were presented) • Duration: 28 days	(induction remission therapy), and should have their own teeth (at least ten) Patient characteristics: I: mean age 51y; M/F 9/6 C: mean age 47 y; M/F 11/8 Comparable groups	prior to chemotherapy) and supervised oral hygiene measures during chemotherapy vs Maintained usual oral hygiene, without interference in oral hygiene measures In both group of patients, 0.12% chlorhexidine gluconate mouth rinse mixed with 3% hydrogen peroxide and nystatin 100,000 IU three times a day, was administered as a standard oral care protocol in this hematology unit.	Day 14: 6/15 (40%) vs 10/19 (52%) RR 0.76 (95%CI 0.36 to 1.61) Day 21: 6/15 (40%) vs 9/19 (47%) RR 0.84 (95%CI 0.39 to 1.84) Day 28: 4/15 (27%) 8/19 (42%) RR 0.63 (95%CI 0.24 to 1.71) NB: some participants seem to have had mucositis at baseline.	general health condition at the admission. Two additional patients were excluded because of death during chemotherapy. Results critical appraisal: Method of randomization and concealment not described, no information on blinding. High risk for incomplete outcome data, low risk of reporting bias and other bias.
Gouvea de Lima 2012	• Design: RCT • Source of funding: not described • Setting: not described • Sample size: n=75 • Duration: follow up 6 weeks; (long term follow up (median of 2 years) will be reported separately)	Eligibility criteria: 18–75 years old, with previously untreated, histologically confirmed, head-and-neck squamous cell carcinoma of the oropharynx, hypopharynx, nasopharynx, larynx, or oral cavity;	Low level laser therapy (660-nm wavelength galliumaluminum-arsenide, 10-mW laser, with a spot size of 4 mm2) with average energy density delivered to the oral mucosa was 2.5 J/cm2, and the	Incidence oral mucositis Grade 3 mucositis in second week of CRT: 4/37 vs 5/38; RR 0.82 (95%CI 0.24 to 2.82) in fourth week: 4/37 vs 12/38; RR 0.34 (95%CI 0.12 to 0.97) in sixth week: 8/37 vs 9/38; RR 0.91 (95%CI 0.39 to 2.11) No Grade 4 mucositis was detected	Risk of bias: low Dropouts: none Results critical appraisal: adequate randomisation method, concealment of allocation unclear,

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
		undifferentiated nasopharyngeal carcinoma, or cervical metastasis with an unknown primary site. All patients were candidates for adjuvant or definitive chemo-radiotherapy (CRT) Patient characteristics: mean age 55y (53.1 ± 9.4 y vs. 53.2 ± 10.3 y); M/F 57/15 (27/10 vs. 30/8); T stage T1-T2/T3-4: 10/26 vs. 6/30; N stage N0/N1-2/N3/unknown: 6/25/5/1 vs. 5/26/5/2 Comparable groups	energy dose delivered to the treated surface . vs placebo laser The patients underwent laser applications daily for 5 consecutive days (Monday to Friday), every week, immediately before each fraction and during all RT sessions. Lasertherapy was delivered intraorally outside the malignant tumor-located area	throughout the study period.	patients and outcome assessors blinded, no dropouts. Low risk of reporting and other bias.
Henke 2011	• Design: RCT • Source of funding: This study was supported by Amgen • Setting: multicentre (38 centers in Australia, Austria, Canada, France, Germany, Italy, Spain, and the United Kingdom) • Sample size: n=186 • Duration: follow up 24 months	Eligibility criteria: Patients who had been resected for pathohistologically documented high-risk stages II to IVB squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx; were older than 18 years; and had an Eastern Cooperative Oncology Group performance status of 0	Initially, patients were allocated to three arms: Arm 1: palifermin (180 µg/kg/ wk) throughout radiochemotherapy (ie, for at least seven doses) Arm 2: palifermin (180 µg/kg/wk) for four doses and then	Incidence of severe oral mucositis (WHO grade 3 or 4) 47/92 vs 63/94; RR 0.76 (95%CI 0.60 to 0.97) Median duration of severe oral mucositis 4.5 vs 22.0 days (P= 0.037) Median time to onset of severe oral mucositis 45.0 vs. 32.0 days (P=0.022) Incidence of supplemental nutrition 48/52 vs 49/52 RR 0.98 (95%CI 0.88 to 1.09)	Risk of bias: low Dropouts: 25 dropouts (I: n=13, C: n=12) Adverse events were the main reason for discontinuation of palifermin. Results critical appraisal: adequate

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
		to 2. Patient characteristics: mean age: 56.5 ± 8.5 y (56.3 ± 8.4 vs. 56.7 ± 8.7), M/F 153/33 (78/14 vs. 75/19); Tumor stage (I/II/III/IV): 1/10/15/66 vs. 2/5/25/62; regional lymph nodes (N0/N1/N2/N3): 15/19/53/5 vs. 17/21/53/3. Comparable groups except for tumor stage: in Palifermin group relatively more grade II and less grade III as compared to placebo group.	placebo throughout the remainder of radiochemotherapy Arm 3: placebo throughout radiochemotherapy. However, after one serious adverse event of respiratory insufficiency was reported in one of the first 10 patients, the data monitoring committee concluded that the study should be restarted with a lower palifermin dose (120 µg/kg/wk). (This report describes only the efficacy and safety of the results after the protocol was amended). Also, because of slow enrollment, the study arm of palifermin 120 µg/kg for four doses (arm 2) was halted after enrollment of 38 patients. Efficacy results for the four-dose palifermin arm were analyzed separately	Adverse events (only a difference of at least five percentages reported) Dysphagia 32/92 vs 20/94 RR 1.63 (95%CI 1.01 to 2.64) Dehydration 6/92 vs 13/94 RR 0.47 (95%CI 0.19 to 1.19) Leukopenia 12/92 vs 20/94 RR 0.61 (95%CI 0.32 to 1.18) Insomnia 5/92 vs 12/94 RR 0.43 (95%CI 0.16 to 1.16) Fatigue 7/92 vs 14/94 RR 0.51 (95%CI 0.22 to 1.21) Diarrhea 11/92 vs 5/94 RR 2.25 (95%CI 0.81 to 6.22) Mucosal inflammation 4/92 vs 10/94 RR 0.41 (95%CI 0.13 to 1.26) Asthenia 13/92 vs 8/94 RR 1.66 (95%CI 0.72 to 3.82) Headache 9/92 vs 4/94 RR 2.30 (95%CI 0.73 to 7.20) Abdominal pain 7/92 vs 2/94 RR 1.88 (95%CI 0.73 to 7.20) Back pain 6/92 vs 1/94 RR 6.13 (95%CI 0.75 to 49.93) Febrile neutropenia 1/92 vs 0/94 RR 3.06 (95%CI 0.13 to 74.27) Progression-free survival Hazard ratio: 1.01 (95%CI 0.60 to 1.69)	randomisation and concealment of allocation. Unclear whether patients and outcome assessors were blinded. Unclear risk of bias for attrition bias, low risk of reporting and other bias.
Khanal 2010	• Design: RCT	Eligibility criteria:	Honey (extracted	“At the commencement of the study all	Risk of bias: high

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
	• Source of funding: none • Setting: Department of Oral and Maxillofacial Surgery, Manipal College of Dental Sciences, Manipal University, Mangalore India (single centre) • Sample size: n=40 with mucositis were evaluated. Unclear whether there were patients without mucositis who were not evaluated. • Duration: 6 weeks	patients with oral carcinoma at the authors' hospital, planned for radiation therapy (6000 cGy of radiation to the head and neck over 6 weeks; once a day, 5 days a week) not having xerostomia, poorly controlled diabetes mellitus, chemotherapy, oral surgery within the previous 6 weeks, anti-inflammatory medications by oral, topical or parenteral route and poor oral hygiene. Patient characteristics: not specified Comparable groups: unclear	from beehives of the Western Ghats forests) vs. Lignocaine (gel) Each patient would receive an intervention 15 min prior to radiation, 15 min after radiation and once before going to bed: a trained co-worker administering 20 ml of either honey or lignocaine gel which would have to be swished about the oral cavity for 2 min and expectorated.	participants were verified to have no mucositis of the oral cavity." 40 patients with mucositis were evaluated, unclear whether these were all the patients enrolled or whether there were also patients without mucositis. Severity of oral mucositis Incidence of intolerable mucositis (scores 3 and 4) (Radiation Therapy Oncology Group (RTOG) scale) 1/20 vs. 15/20, RR 0.07 (95%CI 0.01 to 0.46)	Dropouts: Three patients were lost to the study, two due to diabetes mellitus and one did not consent. Unclear to which studygroup the dropouts belonged. Results critical appraisal: no blinding of patients and carers resulting in a possible high risk of bias. Also high risk of attrition bias as exact numbers of enrolled patients are not clear.
Katranci 2011	• Design: RCT • Source of funding: None reported • Setting: Oncology Hospital Chemotherapy Unit affiliated with Gaziantep University Şahinbey Research and Application Hospital, Turkey • Sample size: n=60 • Duration: 21 days	Eligibility criteria: Cancer patients who received outpatient chemotherapy: only bolus intravenous 5-fluorouracil and leucovorin being administered as the initial course, presence of healthy oral mucosa, and no dental problems.	Oral cryotherapy vs Routine care The ice chips were given to the patients in the experimental group 5 min before	Incidence of oral mucositis (WHO scale): Grade 1+ mucositis: Day = 7: 5/30 vs 18/30 RR 0.28 (95%CI 0.12 to 0.65) Day 21: 11/30 vs 18/30 RR = 0.61 (95%CI 0.35 to 1.06) Grade 2+ mucositis: Day = 7: 1/30 vs. 6/30 RR 0.17 (95%CI 0.02 to 1.30)	Risk of bias: unclear Dropouts: none/not reported Results critical appraisal: adequate randomisation, concealment of allocation unclear, no

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
		Patient characteristics: mean age: not described M/F 30/30 (15/15 vs. 15/15); stage (2/3/4): 5/10/12 vs. 5/11/14 Comparable groups	treatment, during treatment, and within 15 min after treatment, for a total of 30 min of continued administration.	Day 21: 5/30 vs 12/30 RR = 0.42 (95%CI 0.17 to 1.04) Grade 3+ mucositis: Day 7: 0/30 vs. 1/30 RR = 0.50 (95%CI 0.05 to 5.22) Day 21: 1/30 vs 6/30 RR = 0.17 (95%CI 0.02 to 1.30)	information on blinding, no dropouts reported. Low risk of reporting and other bias.
Lanzos 2010	• Design: RCT • Source of funding: none reported • Setting: Oncological Radiotherapy Service “Hospital 12 de Octubre” (Madrid, Spain) • Sample size: n=36 • Duration: follow up 28 days	Eligibility criteria: patients irradiated as part of therapy of head-and-neck cancer, aged 18-75, with at least 10 teeth, and willing to sign an informed consent Patient characteristics: mean age 49.4y ± 15.4 vs. 54.3y ± 16.1; 32M/4F; oncology therapy included radiation in doses ranging from 50-80 Gy, delivered in 5 periods. Three test patients and six control patients were smokers at baseline. Comparable groups, except for presence of oral mucositis at baseline (n=5 vs. n=2)	Perio-Aid Tratamiento ® (Dentaid, Cerdanyola del Valles, Spain) composed of 0.12% CHX (chlorhexidine) and 0.05% CPC (cetyl-pyridinium chloride). vs. Placebo mouth rinse Patients should carry out their usual tooth-brushing and oral hygiene procedures, and then they should rinse with 15 mL of the assigned product, for 30 second, twice a day (morning and evening).	Evaluation of Mucositis (Scale of the Radiation Therapy Oncology Group/European Organization Research and Treatment of Cancer (RTOG/EORTC)) Degree of Mucositis – change from baseline to 4 weeks No change: 5/14 vs. 2/12 Increase: 9/14 vs. 9/12 Decrease: 0/14 vs. 1/12 NB: some participants seem to have had mucositis at baseline. Adverse effects No adverse effects were reported in either group.	Risk of bias: high Dropouts: Intervention group: n=4 (n=1 surgery, n=1 admitted to hospital, n=2 difficulties to comply due to health related problems) Control group: n=6 (n=1 died; n=5 difficulties to comply due to health related problems) From the tables it can be concluded that for some outcomes even less people were evaluated. These dropouts are not elucidated. Results critical appraisal: adequate randomisation and allocation concealment, adequate blinding,

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
					substantial number of dropouts (without elucidation) high risk of reporting and unclear risk of other bias.
Le 2011	• Design: RCT • Source of funding: GlaxoSmithKline, Amgen • Setting: 46 centers in North America and Europe • Sample size: n=188 • Duration: Enrollment began on August 3, 2005. The last patient completed the 4-month follow-up on September 11, 2007, and long-term survival and tumor progression data through April 30, 2010, were included in the analysis.	Eligibility criteria: Patients with newly diagnosed, unresected stage III to IVB squamous cell carcinoma of the oral cavity, oropharynx, nasopharynx, hypopharynx, or larynx; no evidence of a secondary malignancy; and planned radiotherapy dose of more than 50 Gy to two different subsites of the inspected oral cavity and oropharynx. Patient characteristics: Mean age: 55.5 ± 8.5 (55.5 ± 8.6 vs. 55.4 ± 8.3); M/F 159/29 (29M/15F vs. 80M/14F); Tumor stage III/IVA/IVB: 26/60/8 vs. 29/54/11; Lymph nodes N0/N1/N2/N3: 11/17/61/5 vs. 9/23/53/9 Comparable groups	Palifermin 180 g/kg Vs Matching IV placebo (1.2 mL of sterile water, 4% mannitol, 2% sucrose, 10 mmol/L histidine, 0.010% polysorbate-20, pH 6.5, and no preservatives) Both treatments were administered as a bolus injection over 30 to 60 seconds in eight weekly doses, starting 3 days (typically a Friday) before CRT initiation and then once weekly after the week's last RT treatment.	The incidence of severe oral mucositis (WHO grade 3 or 4) 51/94 vs 65/94 RR 0.78 (95%CI 0.62 to 0.99) Median duration of severe oral mucositis Median duration of severe OM for intent-to-treat patients was shorter in the palifermin arm than in the placebo arm (5 vs 26 days) Median time to onset of severe oral mucositis Median time to develop severe OM was longer in the palifermin arm compared with the placebo arm (47 vs 35 days) Incidence of supplemental nutrition 63/94 vs 52/94 RR 1.21 (95%CI 0.96 to 1.53) Adverse events Incidence of at least one adverse event: 92/94 vs 85/91 RR 1.05 (95%CI 0.98 to 1.12) Incidence of study drug–related adverse events 33/94 (35%) vs. 10/91 (11%) RR 3.19 (95%CI 1.67 to 6.10) Incidence of serious adverse events related	Risk of bias: low Dropouts: n=26 (I: n=15, C: n=11) Results critical appraisal: adequate randomisation and concealment of allocation, double blind study but unclear whether outcome assessors have been blinded, substantial number of dropouts reported. Low risk of reporting and other bias.

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
				to study treatment 5/94 vs. 2/91, RR 2.42 (95%CI 0.48 to 12.16) Progression free survival HR = 1.13 (95%CI 0.75 to 1.71)	
Meca 2009	• Design: RCT • Source of funding: This study was partially supported by grants of Fundacao do Amparo a Pesquisa do Estado de Sao Paulo (FAPESP), proc. 2002/07371-0 e 07/54851-0. • Setting: Department of Dentistry of the Barretos Cancer Hospital, SP, Brazil and the Megavoltage Radiotherapy Center, SP, Brazil • Sample size: n=60 • Duration: follow up 6 months after radiotherapy	Eligibility criteria: histopathological diagnosis of malignant disease; at least ten teeth after initial dental treatment (IDT) and able to comply with the preventive clinical protocols. Patients with previous diagnosis of HIV-infection, use of antibiotics 3 months before first visit, uncontrolled significant cardiovascular, pulmonary, renal, hepatic disease were excluded. Patient characteristics: age 18-63 years (mean age 49.75 years); M/F 52/8; n=50 squamous cell carcinoma, n=3 adenocarcinoma, n=6 with Hodgkin lymphoma, n=1 liposarcoma. Comparable groups?	Group I: Initial dental treatment (IDT), 3-4 weeks before radiotherapy + chlorhexidine gluconate (0.12%) once daily during radiotherapy and for 6 months after end of treatment. Oral hygiene instructions were reinforced at each visit Group II: IDT + sodium fluoride (0.5%, aqueous solution) daily and oral hygiene instructions were reinforced at each visit. Group III: IDT + sodium iodine (2% in hydrogen peroxide 10 v/v) once daily and oral hygiene instructions were	Incidence of oral mucositis (grade not reported) Comparisons with no treatment for all interventions IDT + chlorhexidine gluconate (0.12%) After radiotherapy 12/13 vs. 10/12 RR 1.11 (95%CI 0.82 to 1.49) 30 days after radiotherapy 8/13 vs. 8/11 RR 0.85 (95%CI 0.48 to 1.48) 6 months after radiotherapy: 4/10 vs. 7/9 RR 0.51 (95%CI 0.22 to 1.19) IDT + sodium fluoride (0.5%) After radiotherapy 10/11 vs. 10/12 RR 1.09 (95%CI 0.80 to 1.49) 30 days after radiotherapy 7/11 vs. 8/11 RR 0.88 (95%CI 0.49 to 1.55) 6 months after radiotherapy 3/9 vs. 7/9 RR 0.43 (95%CI 0.16 to 1.15) IDT + sodium iodine (2% in hydrogen peroxide 10 v/v) After radiotherapy 11/14 vs. 10/12 RR 0.94 (95%CI 0.65 to 1.37) 30 days after radiotherapy 8/12 vs. 8/11 RR 0.92 (95%CI 0.53 to 1.57) 6 months after radiotherapy 4/11 vs. 7/9 RR 0.47 (95%CI 0.20 to 1.10)	Risk of bias: unclear Dropouts: "…out of the 60 patients initially examined, 10 did not conclude radiotherapy and 11 other patients were not in physical conditions to be submitted to final intra-oral examinations." Results critical appraisal: method of randomization and allocation concealment unclear, no information on blinding, Substantial number of dropouts, almost equally distributed between groups. Low risk of reporting bias and other bias.

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
			reinforced at each visit. Group IV: No preventive dental treatment. Patients were instructed to look for professional care in public dental clinics, but no one did; they received medical treatment with no odontological assistance and received oral hygiene instructions only during and after RT. The mean radiation dose received by the patients varied from 5.040 to 7.020 cGy, and the fractioning dose was 180 cGy.	Other comparisons IDT + chlorhexidine gluconate (0.12%) vs. IDT + sodium fluoride (0.5%) After radiotherapy 12/13 vs. 10/11 RR 1.02 (95%CI 0.80 to 1.30) 30 days after radiotherapy 8/13 vs. 7/11 RR 0.97 (95%CI 0.52 to 1.80) 6 months after radiotherapy: 4/10 vs. 3/9 RR 1.20 (95%CI 0.36 to 3.97) IDT + chlorhexidine gluconate (0.12%) vs. IDT + sodium iodine (2% in hydrogen peroxide 10 v/v) After radiotherapy 12/13 vs. 11/14 RR 1.17 (95%CI 0.86 to 1.61) 30 days after radiotherapy 8/13 vs. 8/12 RR 0.92 (95%CI 0.51 to 1.66) 6 months after radiotherapy: 4/10 vs. 4/11 RR 1.10 (95%CI 0.37 to 3.27) IDT + sodium fluoride (0.5%) vs. IDT + sodium iodine (2% in hydrogen peroxide 10 v/v) After radiotherapy 10/11 vs. 11/14 RR 1.16 (95%CI 0.83 to 1.61) 30 days after radiotherapy 7/11 vs. 8/12 RR 0.95 (95%CI 0.52 to 1.74) 6 months after radiotherapy: 3/9 vs. 4/11 RR 0.92 (95%CI 0.27 to 3.07)	
Medhipour 2011	• Design: RCT • Source of funding: not reported • Setting: Shahid Gazi Hospital in Tabriz, Iran • Sample size: n=30 • Duration: follow up 8	Eligibility criteria: patients>15 years with acute leukemia under chemotherapy, without any systemic disase with other diagnosis of malignancies or	10 ml of 0.2% zinc sulphate mouthwash two times per day for 14 days vs.	Mean severity scored (oral mucositis index) Mean severity scores were generally lower in the test group compared to the controls at all four time intervals evaluated; but only the differences in weeks of 2 and 3 were statistically significant (P=0.025).	Risk of bias: unclear Dropouts: none Results critical appraisal:

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
	weeks	chemotherapy-induced oral mucosits, no oral ulcers and mucositis before start of chemotherapy Patient characteristics: not described Comparable groups	10 ml of 0.2% chlorhexidine mouthwash two times per day for 14 days		Unclear randomisation, concealment, patients and investigators blinded. No dropouts, Low risk of reporting bias and other bias.
Oton-Leite 2012	• Design: RCT • Source of funding: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq); contract grant number: 402322/2008 8 • Setting: Radiotherapy Department of the Araújo Jorge Hospital, Association of Cancer Combat of Goiás, Goiania, Brazil • Sample size: n=60 • Duration: 6-7 weeks (30 RT sessions)	Eligibility criteria: patients > 18 years with head and neck cancer who were scheduled to receive radiotherapy that involved the region of the major salivary glands Patient characteristics: age median 55.6 y (range 30-80 y); M/F 22/8 and 27/3; primary tumor oral cavity 9 vs 10, pharynx 9 vs 12, larynx 10 vs 6, unknown 2 vs 2. Comparable groups: slight difference in disease severity	InGaAlP diode laser (Thera Lase; DMC Equipments Ltda, Sao Carlos, Brazil), operating at 685 nm, 35-mW output power, in a continuous wave and at a fluence of 2 J/cm2, performed daily vs Sham laser	Incidence of oral mucositis The authors presented oral mucositis only for patients that discontinued RT. QOL (poor and very poor compared to rest) after 30 RT sessions Health related: 0/19 vs 5/18 RR = 0.09 (95%CI 0.01 to 1.46) Overall: 1/19 vs 2/18 RR = 0.47 (95%CI 0.05 to 4.78) QOL Brazilian version of the University of Washington–Quality of Life (Version 4) questionnaire (UWQOL) after 30 sessions (end of RT) compared to baseline Reduction in all QOL domain scores in both groups; pain (p = .03), chewing (p = .004), and saliva (p < .001) domains were more affected in the placebo group. Need for feeding tube 3/30 vs 7/30 RR = 0.43 (95%CI 0.12 to 1.50)	Risk of bias: high Dropouts: 4 patients died (2 in each group), 2 in placebo group did not attend follow-up session. At the end, however, 11/30 and 12/30 patients did not complete the QOL assessments. Results critical appraisal: randomisation method and concealment unclear. Blinding of care givers unclear. Patients blinded. Substantial number of dropouts, Low risk of reporting bias, unclear risk of other bias.

Table 123 – Oral complications: evidence table of systematic reviews regarding the treatment of oral mucositis in patients with cancer who are treated with chemotherapy or radiotherapy

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Clarkson 2010	• SR • Funding: none • Search date: June 2010 • Databases: Cochrane Oral Health Group Trials Register, Cochrane Pain, Palliative and Supportive Care (PaPaS) Group Trials Register, CENTRAL, MEDLINE, EMBASE, CINAHL, CANCERLIT, OpenSIGLE, LILACS	Anyone with cancer who is receiving chemotherapy or radiotherapy or both and has oral mucositis.	Any intervention for the treatment of oral mucositis or its associated pain vs. Placebo, no treatment or another active intervention	Mouth washes Benzydamine mouthwash versus placebo Improvement in mucositis (2 trials) RR = 1.22 (95%CI 0.94 to 1.60) Sucralfate (mouthwash and gel) versus placebo/salt and water/salt and soda Eradication of mucositis (2 trials) RR = 1.13 (95%CI 0.66 to 1.94) Low level laser versus sham procedure Mild to moderate mucositis (2 trials) RR = 5.28 (95%CI 2.30 to 12.13) Single trials Allopurinol mouthwash vs placebo Improvement in mucositis: 19/22 vs 3/22 RR = 6.33 (95%CI 2.18 to 18.37) Mucositis eradicated: 9/22 vs 0/22 RR = 19.00 (95% 1.17 to 307.63) Time to heal mucositis (days): 4 (±1.16) 8.5 (±2.82) MD = -4.50 (95%CI -5.77 to -3.23) Chlorhexidine versus salt and soda Mucositis eradicated: 51/67 vs 49/71 RR = 1.10 (95%CI 0.90 to 1.35) Time to heal mucositis (days): 6.6 (2.57) vs 7.0 (2.99) 49 MD = -0.40 (-1.49 to 0.69)	Quality SR: low risk of bias Quality included trials: The setting of the included trials varied with the majority being conducted by medical teams who did not report any involvement with a dentist or hygienist (68%). Several different scoring systems were used to assess mucositis severity and in some trials the scoring systems were not defined. This variability may have led to discrepancies between trials. Futhermore, it was not possible to detect any existing publication bias, as there were insufficient trials in each meta-analysis investigating the same interventions. Overall conclusion of the review authors: “There is a need for further, well designed trials, preferably including a placebo or no treatment control, assessing the effectiveness of interventions considered in this review and new interventions for managing oral mucositis.’

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
				Hickey (0-3 scale) index for mucositis used over 4-week period. During the third and fourth weeks the average mucositis scores were significantly higher in the control group. Phenytoin mouthrinse versus placebo Quality of life (unknown validated scale, score ranged from 35 to 130) MD -15.10 (95%CI -26.04 to -4.16) 'Magic' versus salt and soda Mucositis eradicated 42/62 vs 49/71 RR 0.98 (95%CI 0.78 to 1.24) Time to heal mucositis (days) 7.17 (±2.57) vs 7.00 (±2.99) MD 0.17 (95%CI -0.97 to 1.31) Sucralfate (gel) versus placebo Improvement in mucositis 14/17 vs 15/17 RR 0.93 (95%CI 0.71 to 1.24)	

Table 124 – Oral complications: evidence table of RCTs regarding interventions for treatment of oral mucositis in patients with cancer receiving chemotherapy or radiotherapy

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Bardy 2012	• Design: 2-arm, double-blind, randomised, controlled trial • Sources of funding: Booth Fund, Christie Charitable Trust, Comvita (donated manuka honey) • Setting: outpatient clinic at a cancer centre in the northwest of England • Sample size: n=131 (intervention n=67, placebo n=64) • Duration: 6 weeks	Eligibility criteria: patients with squamous cell carcinoma of oropharynx or oral cavity who had been listed to have 4 weeks (20 fractions) of accelerated radiotherapy at a dose between 50 and 55 Gy. Synchronous or induction chemotherapy, or both, was permitted; no allergy to honey, no insulin dependent diabetes, no history of nervous or psychiatric illness, no prior megavoltage radiotherapy Patient characteristics: median age (range): 59y (39-85y) vs. 58y (38-83y); 53M/11F vs. 46M/17F Comparable groups, although some differences in M/F and site of tumour	Manuka honey vs. Golden syrup (placebo) The mixture comprised of 98% interventional product (honey or golden syrup) and 2% sodium alginate. As both products are potentially cariogenic patients were provided with strong fluoride toothpaste (Duraphat 5500) and a soft toothbrush, and given verbal and written instructions about use and oral hygiene. Participants were advised to have saline mouthwashes 4 times a day, and every 2 h when the mouth became sore.	Incidence of grade 3 mucositis (Radiation Therapy Oncology Group scale) 51/64 vs. 47/63, RR 1.07 (95%CI 0.88 to 1.29) Severity and duration of mucositis “There was no significant difference (p = 0.79) in the severity or duration of mucositis in the AMH group and the golden syrup group” Need for tube feeding 23/64 vs. 22/63, RR 1.03 (95%CI 0.64 to 1.65)	Risk of bias: unclear Dropouts: I: N=3: 2 cases ≤ 5 fractions and 1 case had an increase in dose making them ineligible. C: N=1: patient did not attend for radiotherapy. Results critical appraisal: low risk of bias for all items, except an unclear risk of bias for allocation concealment
Satheeskumar 2010	• Design: RCT • Source of funding: none • Setting: Radiation oncology department of regional cancer centre Trivandrum	Eligibility criteria: histopathologically confirmed cases of oral squamous cell carcinoma, selected for external beam radiotherapy (no post surgical radiation or	Triclosan mouth wash (readymade commercial mouth rinse containing triclosan 0.03% W/V) vs.	Severity and duration of oral mucositis Mean number of days it took for a change in the grade of mucositis (WHO grading) to occur. Grade 0 to 1: 10.7±1.78 vs. 10.33±1.92, MD 0.37 (95%CI -1.11 to 1.85)	Risk of bias: high Dropouts: nothing reported about dropouts

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
	(Kerala, India) in association with the department of Oral medicine and Radiology, Dental College, Trivandrum. • Sample size: n=24 • Duration: January 2000 – June 2000; weekly follow-up during radiation treatment period and post radiation treatment period till 45 days.	palliative doses of radiotherapy) who gave informed consent; no (concomitant) chemotherapy or history of previous radiotherapy or chemotherapy. Patient characteristics: mean age (SD): 65.9 (11.5) vs. 63.67 (12.9); 5M/7F vs. 7M/5F; stage of tumor (T1/T2/T3) 1/10/1 vs. 6/6/0, nodal status (N0/N1/NX): 10/2/0 vs. 6/6/5/1; Comparable groups, except some differences for stage of tumour and nodal status (of which the authors say groups are comparable).	Sodium bicarbonate mouth rinse (2g of sodium bicarbonate powder, available with the chemist, dissolved in lukewarm water) Patients in both groups used the mouth wash three times a day during radiation treatment and continued the same regimen for 1,5 month after completion of radiotherapy.	Grade 1 to 2: 4.0±1.04 vs. 4.0±1.86, MD 0.00 (95%CI -1.21 to 1.21) Grade 2 to 3: 4.58±1.08 vs. 3.92±1.88, MD 0.66 (95%CI -0.57 to 1.89) Grade 3 to 4: 23.6±4.58 vs. >36.5±12.02 Reversal mucositis to grade 0: <28 days vs. > 45 days Incidence of grade 4 mucositis 1/12 vs. 10/12 RR 0.10 (95%CI 0.02 to 0.66) Food intake Number of days it took for a change in way of feeding Solid to liquid: 16.83±5.9 vs. 16.83±3.4, MD 0.00 (95%CI -3.85 to 3.85) Liquid to solid: 25.1±12.0 vs. 44.67±15.8, MD -19.57 (95%CI -30.80 to -8.34)	Results critical appraisal: No blinding in this study giving high risk of bias for these items, unclear risk of bias for the items 'allocation concealment', 'incomplete outcome data addressed' and 'free of selective reporting'. Low risk of bias for 'random sequence generation and 'other bias'.
Yen 2012	• Design: RCT • Source of funding: ASAN Laboratories, Taipei, Taiwan • Setting: two medical centers in Taiwan • Sample size: n=36 • Duration: unclear	Eligibility criteria: patients age 20 years or older with documented histologic diagnosis of squamous HNC and World Health Organization (WHO) performance status 0 to 2; not having T1-2 glottic cancer, serious concomitant illness or induction chemotherapy before radiotherapy; not	Standard oral care plus 5 mL of phenylbutyrate 5% mouthwash (swish and spit) applied four times daily vs. Standard oral care plus 5 mL of placebo (contained the same base of	Severity of oral mucositis Oral mucositis at cumulative RT doses of 5500–7500 cGy WHO score 1.84±1.00 vs. 2.19±1.17, MD -0.35 (95%CI -1.11 to 0.41) OMAS ulceration score: 0.82±0.82 vs. 1.23±1.00, MD -0.41 (-1.05 to 0.23) Intensity of ulceration at RT of 6000-7000 cGy: OMAS score 0.7 (mean) vs. 1.2 (mean), p=0.0485	Risk of bias: unclear Dropouts: Intervention group n=3 (n=1 died, n=2 withdrew with moderate mucositis after cumulative RT dose of 4400cGy and 36000cGy) Control group n=2

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
		requiring surgery during the course of the trial; not having used investigational drug within 30 days before enrolment. Patient characteristics: mean (SD) age in years 51.1(10.6) vs. 54.8 (12.1); 11M/6F vs. 17M/2F; tumor stage III 11 vs. 11, stage IVA 6 vs. 8 Comparable groups except for concurrent chemotherapy	mouthwash but no phenylbutyrate.) All patients were instructed to gargle 5 mL of study medication around the mouth and hold at least 1 min and then spit out; they were instructed not to rinse the mouth, drink, or eat for at least 30 min after dosing. The standard oral care included treatment of dental lesions before RT, and frequent rinsing of the mouth with boiled water during the RT course. Lidocaine spray was used to manage pain for hospitalized patients and analgesics were prescribed to patients as needed.	The percentage of patients with severe mucositis WHO score ≥3: 18.4 vs. 24.3, RR 0.91 (95%CI 0.24 to 3.41) OMAS score ≥2: 9.4 vs. 23.8, RR 0.30 (95%CI 0.04 to 2.42) Duration of oral mucositis (median (range) days) Severe: 2 (0-56) vs. 12 (0-82) (p=0.3455) Symptomatic: 16 (0-70) vs. 50 (0-82) (p=0.3784) Adverse events during radiotherapy (with/without concurrent chemotherapy) Nausea/vomiting 4/17 vs. 9/19, RR 0.50 (95%CI 0.19 to 1.32) Constipation 4/17 vs. 5/19, RR 0.89 (95%CI 0.29 to 2.80) Cough 4/17 vs. 4/19, RR 1.12 (95%CI 0.33 to 3.79) Pharyngeal pain 5/17 vs. 3/19, RR 1.86 (95%CI 0.52 to 6.65) Insomnia 7/17 vs. 6/19, RR 1.30 (95%CI 0.55 to 3.12) Hyper pigmentation skin 2/17 vs. 4/19, RR 0.56 (95%CI 0.12 to 2.68) Metabolic and nutrition disorders 4/17 vs. 4/19, RR 1.12 (95%CI 0.33 to 3.79) At least one AE: 15/17 vs. 19/19, RR 0.88 (95%CI 0.74 to 1.05) No patient experienced severe study drug-	(car/traumatic accident) Results critical appraisal: Low risk of bias for selective reporting, all other items were judged as unclear risk of bias

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
				related side effects. Mild to moderate irritation using mouthwash 3/17 vs. 1/19, RR 3.35 (95%CI 0.38 to 29.27) Visit with tube feeding or 'nothing per oral' 3.8% vs. 9.0%, RR 0.61 (95%CI 0.06 to 6.02)	

Table 125 – Oral complications: evidence table of systematic reviews regarding interventions for prevention of oral candidiasis in patien ts with cancer receiving chemotherapy or radiotherapy or both

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Clarkson 2009	• SR • Funding: None • Search date: July/August 2009 • Databases: • Cochrane Oral Health Group Trials Register, Cochrane Pain, Palliative and Supportive Care (PaPaS) Group Trials Register, CENTRAL, MEDLINE, EMBASE, CINAHL, CANCERLIT, OpenSIGLE, LILACS.	Anyone with cancer who received chemotherapy or radiotherapy or both.	Active agents: any antifungal intervention for the prevention of oral candidiasis. Control: may be placebo or no treatment, or another active intervention. Drugs were categorised as absorbed (fluconazole, ketoconazole, itraconazole), partially absorbed (clotrimazole, miconazole) or not	Twenty-eight trials involving 4226 patients were included in this review. **Comparisons with placebo/no treatment** Oral candidiasis present Drugs absorbed (7 studies) RR 0.47 (95%CI 0.29 to 0.78) Drugs partially absorbed (4 studies) RR 0.16 (95%CI 0.06 to 0.46) Drugs not absorbed (8 studies) RR 0.69 (95%CI 0.47 to 1.01) Systemic fungal infection Drugs absorbed (6 studies) RR 0.65 (95%CI 0.37 to 1.14) Drugs partially absorbed (1 study) RR 2.27 (95%CI 0.23 to 22.56) Drugs not absorbed (2 studies) RR 0.10 95%CI 0.01 to 1.75)	Quality SR: low risk of bias Quality of included studies: Five studies were assessed as at low risk of bias, 10 at moderate risk and 12 at high risk of bias. Allocation concealment was adequate for 21 studies and unclear for seven. Blinding of outcome assessment was performed in 16 studies, not performed in four and unclear for the remaining eight trials. Missing data were adequately reported in 18 trials and were unclear or not reported in ten. Overall conclusion of the review authors: "There is strong evidence, from randomised controlled trials, that drugs absorbed or partially absorbed from the GI tract prevent

Study ID	Method	Patient characteristics	Intervention(s)		Results	Critical appraisal of review quality
			absorbed (amphotericin nystatin, chlorhexidine, thymostimulin, natamycin, norfloxacin).	B	Death Drugs absorbed (3 studies) RR 1.44 (95%CI 0.14 to 15.43) Drugs partially absorbed (0 studies) Drugs not absorbed (1 study) RR 0.16 (95%CI 0.01 to 2.95) Toxicity Drugs absorbed (3 studies) RR 1.18 (95%CI 0.84 to 1.67) Drugs partially absorbed (2 studies) Not estimable (no adverse events in either groups) Drugs not absorbed (0 studies) **Comparisons between drugs absorbed from GI tract and those not absorbed** Oral candidiasis present (8 studies) RR 0.40 (95%CI 0.21 to 0.76) Systemic fungal infection (8 studies) RR 0.59 (95%CI 0.33 to 1.06) Death (3 studies) RR 1.25 (95%CI 0.38 to 4.13) Toxicity (6 studies) RR 0.88 (95%CI 0.33 to 2.30) **Comparison of drugs absorbed from the GI tract**	oral candidiasis in patients receiving treatment for cancer. There is also evidence that these drugs are significantly better at preventing oral candidiasis than drugs not absorbed from the GI tract.”

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
				Oral candidiasis present Itraconazole versus fluconazole (1 study) RR 0.14 (95%CI 0.01 to 2.73) Ketoconazole versus itraconazole (1 study) RR 0.17 (95%CI 0.02 to 1.14) Ketoconazole (400 mg) versus ketoconazole (200 mg) (1 study) RR not estimable Systemic fungal infection Intraconazole versus fluconazole (1 study) RR 1.00 (95%CI 0.26 to 3.89) Death Itraconazole versus fluconazole (1 study) RR 0.14 (95%CI 0.01 to 2.73) Toxicity Itraconazole versus fluconazole (2 studies) RR not estimable **Comparison of drugs not absorbed from GI tract** Oral candidiasis present Chlorhexidine versus nystatin (1 study) RR 0.89 (95%CI 0.36 to 2.21) Chlorhexidine versus chlorhexidine plus nystatin (1 study) RR 1.62 (95%CI 0.64 to 4.10) Nystatin versus chlorhexidine plus nystatin (1 study) RR 1.82 (95%CI 0.73 to 4.54)	

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
				Nystatin versus natamycin (1 study) RR 1.07 (95%CI 0.83 to 1.37) Norfloxacin + amphotericin B versus amphotericin B (1 study) RR 0.38 (95%CI 0.15 to 1.00) Systemic fungal infection norfloxacin + amphotericin B vs. amphotericin B (1 study) RR 0.67, 95%CI 0.20 to 2.23)	

Table 126 – Oral complications: evidence table of RCTs regarding interventions for prevention of oral candidiasis in patients with cancer receiving chemotherapy or radiotherapy or both

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Lanzos 2011	• Design: RCT • Source of funding: The study was supported by a research grant (contract between University Complutense and Dentaid - Cerdanyola del Vallés, Spain) • Setting: Oncological Radiotherapy Service "Hospital 12 de Octubre" (Madrid, Spain) • Sample size: n=36 • Duration: 3 visits: baseline, 14 days and 28 days after start radiotherapy	Eligibility criteria: patients irradiated as part of therapy of head-and-neck cancer, aged 18-75, with at least 10 teeth, and willing to sign an informed consent Patient characteristics: mean age 49.4y ± 15.4 vs. 54.3y ± 16.1; 32M/4F; oncology therapy included radiation in doses ranging from 50-80 Gy, delivered in 5 periods. Three test patients and six control patients were smokers at baseline. Unclear whether comparable groups	antiseptic, non-alcohol based, mouth rinse containing chlorhexidine (CHX) and cetyl-pyridinium chloride (CPC) vs. placebo mouth rinse participants should rinse with 15 mL of the assigned product, for 30 seconds, twice a day (morning and evening).	Detection of Candida spp. in mucosa No statistically significant differences between groups were found. (information from tables is unclear, therefore it is not possible to calculate RR) Detection of Candida spp. in tongue samples No statistically significant differences between groups were found. (information from tables is unclear, therefore it is not possible to calculate RR) Adverse effects No relevant adverse effects were reported in any group.	Risk of bias: high Dropouts: 36 patients were included, from the tables it can be concluded that 30 (table 1), 27 (table 2) or 25 (table 3) people were evaluated at baseline. At 4 weeks there were 9 people evaluated in the test group and 11 or 9 in the control group. Nothing is described about dropouts; no reasons for loss to follow up are given. Results critical appraisal: high risk of

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
					bias for completeness of outcome data and unclear risk of other bias. All the other items scored low risk of bias.
Meca 2009	• Design: RCT • Source of funding: This study was partially supported by grants of Fundacao do Amparo a Pesquisa do Estado de Sao Paulo (FAPESP), proc. 2002/07371-0 e 07/54851-0. • Setting: Department of Dentistry of the Barretos Cancer Hospital, SP, Brazil and the Megavoltage Radiotherapy Center, SP, Brazil • Sample size: n=60 • Duration: follow up 6 months after radiotherapy	Eligibility criteria: histopathological diagnosis of malignant disease; at least ten teeth after initial dental treatment (IDT) and able to comply with the preventive clinical protocols. Patients with previous diagnosis of HIV-infection, use of antibiotics 3 months before first visit, uncontrolled significant cardiovascular, pulmonary, renal, hepatic disease were excluded. Patient characteristics: age 18-63 years (mean age 49.75 years); 52M/8F; n=50 squamous cell carcinoma, n=3 adenocarcinoma, n=6 with Hodgkin lymphoma, n=1 liposarcoma. Unclear whether comparable groups?	Group I: Initial dental treatment (IDT), 3-4 weeks before radiotherapy + chlorhexidine gluconate (0.12%) once daily during radiotherapy and for 6 months after end of treatment. Oral hygiene instructions were reinforced at each visit Group II: IDT + sodium fluoride (0.5%, aqueous solution) daily and oral hygiene instructions were reinforced at each visit. Group III: IDT + sodium iodine (2% in hydrogen peroxide 10 v/v) once daily and oral hygiene instructions were reinforced at	Incidence of oral candidiasis Comparisons with no treatment for all interventions IDT + chlorhexidine gluconate (0.12%) After radiotherapy 3/13 vs. 8/12 RR 0.35 (95%CI 0.12 to 1.01) 30 days after radiotherapy 1/13 vs. 5/11 RR 0.17 (95%CI 0.02 to 1.24) 6 months after radiotherapy: 0/10 vs. 3/9 RR 0.13 (95%CI 0.01 to 2.22) IDT + sodium fluoride (0.5%) After radiotherapy 3/11 vs. 8/12 RR 0.41 (95%CI 0.14 to 1.16) 30 days after radiotherapy 2/11 vs. 5/11 RR 0.40 (95%CI 0.10 to 1.64) 6 months after radiotherapy 1/9 vs. 3/9 RR 0.33 (95%CI 0.04 to 2.63) IDT + sodium iodine (2% in hydrogen peroxide 10 v/v) After radiotherapy 4/14 vs. 8/12 RR 0.43 (95%CI 0.17 to 1.08) 30 days after radiotherapy 1/12 vs. 5/11 RR 0.18 (95%CI 0.03 to 1.33) 6 months after radiotherapy 0/11 vs. 3/9 RR 0.12 (95%CI 0.01 to 2.04) Other comparisons	Risk of bias: unclear Dropouts: "…out of the 60 patients initially examined, 10 did not conclude radiotherapy and 11 other patients were not in physical conditions to be submitted to final intra-oral examinations." Results critical appraisal: unclear risk of selection bias, performance bias and selection bias. Substantial number of dropouts, almost equally distributed between groups. Low risk of reporting bias and other bias.

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
			each visit. Group IV: No preventive dental treatment Patients were instructed to look for professional care in public dental clinics, but no one did; they received medical treatment with no odontological assistance and received oral hygiene instructions only during and after RT. The mean radiation dose received by the patients varied from 5.040 to 7.020 cGy, and the fractioning dose was 180 cGy.	IDT + chlorhexidine gluconate (0.12%) vs. IDT + sodium fluoride (0.5%) After radiotherapy 3/13 vs. 3/11 RR 0.85 (95%CI 0.21 to 3.38) 30 days after radiotherapy 1/13 vs. 2/11 RR 0.42 (95%CI 0.04 to 4.06) 6 months after radiotherapy: 0/10 vs. 1/9 RR 0.30 (95%CI 0.01 to 6.62) IDT + chlorhexidine gluconate (0.12%) vs. IDT + sodium iodine (2% in hydrogen peroxide 10 v/v) After radiotherapy 3/13 vs. 4/14 RR 0.81 (95%CI 0.22 to 2.94) 30 days after radiotherapy 1/13 vs. 1/12 RR 0.92 (95%CI 0.06 to 13.18) 6 months after radiotherapy: 0/10 vs. 0/11 RR not estimable IDT + sodium fluoride (0.5%) vs. IDT + sodium iodine (2% in hydrogen peroxide 10 v/v) After radiotherapy 3/11 vs. 4/14 RR 0.95 (95%CI 0.27 to 3.40) 30 days after radiotherapy 2/11 vs. 1/12 RR 2.18 (95%CI 0.23 to 20.84) 6 months after radiotherapy: 1/9 vs. 0/11 RR 3.60 (95%CI 0.16 to 79.01)	

Table 127 – Oral complications: evidence table of systematic review regarding interventions for treatment of oral candidiasis in patients with cancer receiving chemotherapy or radiotherapy or both

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Worthington 2010	• SR • Funding: None • Search date: June 2010 • Databases: • Cochrane Oral Health Group Trials Register, Cochrane Pain, Palliative and Supportive Care (PaPaS) Group Trials Register, CENTRAL, MEDLINE, EMBASE, CINAHL, CANCERLIT, OpenSIGLE, LILACS.	Anyone with cancer who received chemotherapy or radiotherapy or both and had overt oral candidiasis.	Active agents: any antifungal intervention for the treatment of oral candidiasis. Control: may be placebo or no treatment, or another active intervention. Drugs were categorised as absorbed, partially absorbed and not absorbed from the GI tract.	Ten trials involving 940 patients were included. Clinical or mycological eradication of oral candidiasis Drug absorbed (ketoconazole) vs. placebo (1 study) Clinical: RR 3.61 (95%CI 1.47 to 8.88) Mycological: RR 5.09 (95%CI 0.73 to 35.49) Drug partially absorbed (clotrimazole) vs. placebo (1 study) Clinical: RR 3.43 (95%CI 0.51 to 22.94) Mycological: RR 6.13 (95%CI 0.38 to 99.14) Drug absorbed vs. drug absorbed fluconazole vs. itroconazole (2 studies) Cinical: RR 1.14 (95%CI 1.00 to 1.30) Mycological: RR 1.17 (95%CI 1.04 to 1.33) fluconazole vs. ketoconazole (1 study) Clinical: RR 1.02 (95%CI 0.72 to 1.42) Mycological: RR 0.95 (95%CI 0.52 to 1.72) Drug absorbed (fluconazole / ketoconazole) vs. drug not absorbed (amphotericin / nystatin) (3 studies) Clinical: RR 1.29 (95%CI 1.09 to 1.52) Mycological: RR 1.82 (95%CI 1.28 to 2.57) Drug partially absorbed vs. drug partially absorbed clotrimazole 50 mg vs. 10 mg (1 study) Clinical: RR 1.00 (95%CI 0.90 to 1.11) Mycological: RR 2.00 (95%CI 1.11 to 3.60) miconazole 50 mg tablet vs. 500mg gel (1 study) Clinical: RR 1.16 (95%CI 0.91 to 1.47)	Quality SR: low risk of bias Quality of included studies: only one of the ten trials was assessed as at low risk of bias. Adequate sequence generation and allocation concealment were observed in four trials. In four trials participants and carers were blinded to the allocated intervention., Blinding of outcome assessors was adequate for five trials. In six trials, incomplete outcome data was assessed as adequate. All trials were considered to be free of selective reporting. Overall conclusion of the review authors: “There is insufficient evidence to claim or refute a benefit for any antifungal agent in treating candidiasis.”

Appendix 6.2. Skin toxicity

Table 128 – Skin toxicity: evidence table systematic review

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Richardson 2005	• SR • Funding: Support and advice by advisory groups for the NHS Priorities Project, which is funded by the Department of Health. • Search date: August 2004 • Databases: MEDLINE, EMBASE, CINAHL, PsycINFO, CENTRAL, The Cochrane Database of Systematic Reviews and DARE (Database of Abstracts of Reviews of Effects). Specialist complementary and alternative medicine databases including AMED and CISCOM, National Research Register (UK) and Clinicaltrials.gov (US) together with contacting experts in the field. Reference lists of relevant	Cancer patients	Aloe vera gel applied as a specific intervention for the prevention and/or treatment of radiation-induced skin reactions vs. Any other intervention	Review authors identified1 SR and 5 additional RCTs. Results presented narratively Author's conclusion: "The trials reviewed here confirm established risk factors for radiation skin reaction, namely radiation dose, skin complexion, weight and bra cup size, age, concomitant chemotherapy and smoking. They also highlight differences between patient and clinician rating of severity of skin reactions, a point useful for future research into treatment effects. There is no evidence based on current research to suggest that Aloe vera gel is effective for the prevention and/or treatment of radiation-induced skin reactions in either adults or children with a diagnosis of cancer. Furthermore, in two studies, Aloe vera gel was shown to be less effective than other creams. Although no serious adverse effects were reported in the literature included in this review, five patients had an allergic reaction to Aloe vera gel. Lack of detail regarding the aloe vera products used in these clinical trials, together with their methodological limitations, suggest that an appropriately powered RCT using standardised aloe vera product compared with current best practice is required. Radiation-induced skin reactions continue to be burdensome for cancer patients, and are seen as an inevitable side effect. In addition, some of these creams can add to the expense of	Quality SR: low risk of bias Quality included studies: "Methodological limitations in the literature reported in this review include a lack of reporting of the methods of randomisation, blinding, sampling and recruitment, handling of missing values or losses to follow-up. However, differences in appearance, smell or texture between Aloe vera gel and the other products used may cause difficulties in ensuring adequate blinding."

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
	articles were reviewed			treatment for the patient. Despite radiation dermatitis being common and a major patient concern, randomised trials are relatively scant, and future research into this area should be encouraged."	

Table 129 – Skin toxicity: evidence table RCTs

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Boström 2001	• Design: RCT • Source of funding: grants from the • Swedish Cancer Society, Lions Cancer Research foundation, • Torsten and Ragnar Söderberg's Foundation. Schering-Plough AB, Sweden contributed to the study with the blinded tubes and a minor research grant. • Setting: Sweden • Sample size: n=50 • Duration: during radiotherapy and until 3 weeks after completion of radiation	Eligibility criteria: women undergoing breast-conserving surgery for histopathologically proven primary breast adenocarcinoma without lymph node metastasis; scheduled for fractionated radiotherapy of the breast parenchyma with the same accelerator. Patient characteristics: age: 58 (range 48-72) vs. 60 (range 47-76); TNM: T1N0M0: 23/24 vs. 25/25, T2N0M0: 1/24 vs. 0/25 Comparable groups, except for 'axillary node dissection' which was more present in the emollient group	Mometasone furoate (MMF) cream 0.1% (Elocon, Schering-Plough) vs. Emollient cream (Diprobase, Schering-Plough) used as placebo Patients of both groups were instructed to apply the cream on irradiated area twice a week up to 24 Gy, thereafter once daily until 3 weeks after completion of radiotherapy Both groups additionally received non-blinded	Total patient erythema index (TPE) (mean scores) (range) 7.2 (4.0 – 11.2) vs. 5.4 (2.3 – 7.9) Total patient melanin index (TPM) (mean scores) (range) 4.1 (0.2 – 8.0) vs. 3.4 (0.8 – 7.7) Maximum erythema scores (E-score) 4 (2-6) vs. 3 (2-6) The maximal assessed erythema score: Score 3 or higher: 16/24 vs. 23/25: RR 0.72 (95%CI 0.53 to 0.98) Subjective experience of pain, burning and itching (measured using a VAS scale) Patients in the group receiving MMF cream experienced less itching and burning than in the group treated with emollient cream only, but the difference did not reach the significance (P = 0:069 and P = 0:087, respectively) level. No difference in pain was seen (P = 0:42) Numbers of failures in the emollient and the	Risk of bias: low Dropouts: n=1 (refused further participation before the start of the MMF treatment and any evaluation). Results critical appraisal: Low risk for all items.

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
			emollient cream once daily.	mometasone furoate groups Six patients in the emollient group required further topical treatment because of subjective severe symptoms from the regions with moist desquamation. None of the patients had any clinical sign of infection in the skin. Three patients in the MMF group needed further treatment because of severe moist desquamation in the axilla. However, two of these patients forgot to apply the study cream in the axilla during the treatment period. These two patients started to use MMF (the blinded tube) again in the axilla and then improved.	
Campbell 1992	• Design: RCT • Source of funding: not stated • Setting: Mersey Regional Centre for Radiotherapy and Oncology, Clatterbridge Hospital, UK • Sample size: n=99 • Duration: 8 weeks	Eligibility criteria: patients receiving adjuvant postoperative radiotherapy following treatment of a breast carcinoma by either local excision or mastectomy. Patient characteristics: mean age: no bolus: 48 vs. 47 vs.50, bolus: 49 vs. 51 vs. 52; overall age range 33-75 years. Comparable groups	No washing vs. Washing with water vs. Washing with water and soap Analysis was done separately for patients who did and did not receive a bolus	Itching Patients who were randomized to washing had itching scores either similar to or less than those not washing in both the no bolus and the bolus groups. Several of the comparisons showed a statistically significant reduction in itching at P<0.05. There were minor differences between washing with water alone and washing with soap and water, with a trend favouring the latter. Erythema (EORTC/RTOCG acute skin reaction scoring system) The average scores for erythema rose progressively during observation with a maximum at 4 to 6 weeks after starting treatment. There was little difference between the washing groups, and a small trend for the non-washing groups to have the highest reactions. Several of the comparisons again showed a statistically significant reduction in	Risk of bias: high Dropouts: n=4, n=2 had previously undergone chemotherapy treatment including doxorubicin and were judged ineligible since exaggerated skin reactions might be expected; n=1 withdrawn by radiotherapist; n=1 withdrew Results critical appraisal: Unclear risk of

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
				erythema associated with washing. Desquamation (EORTC/RTOCG acute skin reaction scoring system) The average scores for desquamation had a later peak than itching or erythema, with maximum reactions at 6 to 8 weeks after starting treatment. Patients who were washing had markedly smaller scores than patients who were not washing, again with some comparisons reaching statistical significance.	detection bias, attrition bias and reporting bias. High risk of performance bias.
Fenig 2001	• Design: RCT • Source of funding: not reported • Setting: Israel • Sample size: n=74 • Duration: treatment from 10 days before until 10 days after completion of radiation therapy, follow up unclear	Eligibility criteria: patients after conservative surgery for early breast cancer surgery (T1-T2N0M0, diagnosis and staging confirmed) referred for adjuvant external beam radiation, no complicated surgical wound, no history of skin or collagen disease, not prior to concomitant chemotherapy Patient characteristics: mean age±SD: 64±10 vs. 69±9 vs.71±8; M/F not reported; T1/T2 21/4 vs. 21/3 vs. 19/6 Comparable groups: lower mean age Biafine group, relatively more T2 in control group, less Tamoxifen use in Biafine group, relatively less	Biafine vs. Lipiderm vs. No prophylactic treatment Biafine or Lipiderm was applied twice daily from 10 days prior to onset of radiotherapy until 10 days after completion of radiation therapy. If clinically necessary treatment was started or upgraded	Subjective outcomes Patient's impression: incidence of grade 3-4 reaction (subjective comparison scaled 1-4) Biafine vs. control: 15/23 vs. 12/23, RR 1.25 (95%CI 0.76 to 2.04) Lipiderm vs. control: 17/22 vs. 12/23, RR 1.48 (95%CI 0.94 to 2.33) Biafine vs. lipiderm: 15/23 vs. 17/22, RR 0.84 (95%CI 0.58 to 1.23 Nurse's impression: incidence of grade 3-4 reaction (Skin reaction of the Radiation Therapy Oncology Group) Biafine vs. control: 6/24 vs. 6/24, RR 1.00 (95%CI 0.38 to 2.66) Lipiderm vs. control: 5/22 vs. 6/24, RR 0.91 (95%CI 0.32 to 2.56) Biafine vs. lipiderm: 6/24 vs. 5/23, RR 1.15 (95%CI 0.41 to 3.25) Radiotherapist's impression: incidence of grade 3-4 reaction (Skin reaction of the Radiation Therapy Oncology Group) Biafine vs. control 6/20 vs. 5/16, RR 0.84 (95%CI 0.32 to 2.22)	Risk of bias: high Dropouts: n=5 (n=2 missed follow up meetings, n=2 long hospitalizations unrelated to study, n=1 quit study) Results critical appraisal: Unclear risk of selection bias, detection bias and other bias. High risk of performance bias.

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
		diabetic patients in Lipiderm group	(steroid treatment, antibiotic treatment, pause in radiotherapy)	Lipiderm vs. control: 10/17 vs. 5/16, RR 1.88 (95%CI 0.82 to 4.31) Biafine vs. lipiderm: 6/20 vs. 10/17, RR 0.51 (95%CI 0.23 to 1.11)	
Glees 1979	• Design: RCT • Source of funding: Not stated • Setting: Department of Radiotherapy, The Royal Marsden Hospital, London (UK) • Sample size: n=57 • Duration: "Lasting the duration of radiotherapy" (in most cases five to six weeks of radiotherapy)	Eligibility criteria: all patients with a diagnosis of carcinoma of the breast requiring radical radiotherapy to the breast or chest wall if they had had a mastectomy. Patient characteristics: M/F: 2/52, age: not reported Comparable groups: unclear, no baseline characteristics reported.	1% hydrocortisone cream vs. 0.05% clobetasone butyrate (Eumovate)	Incidence of skin reactions as assessed by the authors at the end of a course of treatment Maximum 7/28 vs. 17/26 RR 0.38 (95%CI 0.19 to 0.77) Moderate or maximum 27/28 vs. 2326 RR 1.09 (95%CI 0.93 to 1.27) Benefit of cream according to authors 23/28 vs. 20/26, RR 1.07 (95%CI 0.81 to 1.40) Skin reactions during treatment (assessed by radiotherapists, only available for 29 participants) Maximum: 7/14 vs. 10/15 RR 0.75 [95%CI 0.40 to 1.41] Moderate or maximum: 12/14 vs. 13/15 RR 0.99 [95%CI 0.74 to 1.32] Dry: 3/14 vs. 3/15 RR 1.07 [95%CI 0.26 to 4.45] Moist: 6/14 vs. 6/15 RR 1.07 [95%CI 0.45 to 2.55]	Risk of bias: high Dropouts: n=10 (Group 1: n=2, Group 2: n=5). 3 pt's unclear from which group they were derived. Results critical appraisal: Unclear risk of selection bias and other bias, high risk of attrition bias.
Gosselin 2010	• Design: RCT • Source of funding: Not stated • Setting: Radiation oncology department at a National Cancer Institute (designated	Eligibility criteria: Female gender, a diagnosis of breast cancer, older than 18 years of age, Karnofsky performance status of 80 or higher, and the	Placebo (sterile water mist) vs. Aquaphor (ointment)	Severity of the skin reaction (measured by the Radiation Therapy Oncology Group (RTOG) acute radiation morbidity scoring criteria) "None of the skin care products demonstrated a statistically significant difference in	Risk of bias: low Dropouts: none Results critical appraisal: unclear risk

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
	comprehensive cancer center) in the southeastern United States. • Sample size: n= 208 • Duration: follow-up 6 weeks	ability to read and write in English. Patient characteristics: mean age (SD): 55.8 (11.9) vs. 54.8 (10.6) vs. 56 (10.8) vs. 55.6 (8.15) Comparable groups	vs. Biafine␣RE (cream) vs. RadiaCareTM (Carrington Labo-ratories, Inc.) (gel)	minimizing the incidence of a grade 2–4 skin reaction compared to placebo. Subsequent increases in the proportion with a skin reaction appeared similar for placebo and for participants using Aquaphor and RadiaCare. Increases were greatest among participants using Biafine␣RE."	of other bias.
Kirova 2011	• Design: RCT • Source of funding: Laboratoire Genevrier France • Setting: France (single institution, Department of Radiation Oncology, Institut Curie Paris, France) • Sample size: n=200 • Duration: 30 days	Eligibility criteria: women, ≥18 years, who were undergoing normo-fractionated locoregional radiotherapy for breast cancer with a grade I (according to the RTOG scale) radio-induced dermatitis during or after irradiation; no concurrent chemotherapy, no tumoral wound in irradiated area, no cognitive disorder. Patient characteristics: age, median (range): 53y (28–76) vs. 53y (27–83) Comparable groups, except for colorimetric levels and the level of pain	Hyaluronic acid cream (100 mg tube of Ialuset® containing 200 mg of hyaluronate sodium, Genevrier, France) once a day Vs. Simple emollient (200 ml tube of Topicrem® containing urea 2% and glycerol 9.5%, Charlieu, France) once a day Patients were advised to take one-two showers a day with a neutral liquid soap, then to dry themselves with	Clinical evaluation of the erythema (RTOG scale) Failure: ITT analyses: 27/99 vs. 38/101, RR 0.72 (95%CI 0.48 to 1.09) Per-protocol: 23/95 vs. 32/95, RR 0.72 (95%CI 0.46 to 1.13) Quality of life (measured by the European Organization for Research and Treatment of Cancer (EORTC) QLQC30 questionnaire) The hyaluronic group tends to score better on the quality of life assessment items, however, no significant differences on any of the domains were found.	Risk of bias: high Dropouts: n=73 (hyaluronic group: n=35, emollient group: n=38) Main reasons for treatment interruption were worsening of epithelitis, patient's refusal, change of treatment or combination with another local product, allergy, or patients lost to follow-up (reasons not significantly different between the two treatment arms (p = 0.59). Results critical appraisal: unclear risk of selection bias,

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
			a clean towel, one shower in the morning before their radiotherapy appointment, one in the evening before applying the topical treatment.		attrition bias and other bias. High risk of performance and detection bias.
Lacouture 2010	• Design: RCT • Source of funding: OSI Pharmaceuticals, Bayer Pharmaceuticals, Onyx, Amgen, Hana • Setting: multicenter study, United States • Sample size: n=95 • Duration: six week treatment period, evaluation in week 7 and median follow up of 31.0 vs. 40.7 weeks thereafter.	Eligibility criteria: Patients aged ≥ 18y with metastatic adenocarcinoma of the colon or rectum (with at least one unidimensional measurable lesion that could not be cured by surgical resection) and disease progression or unacceptable toxicity with first-line treatment containing fluoropyrimidine and oxaliplatin-based chemotherapy with or without bevacizumab;; adequate hematologic, renal, metabolic, and hepatic function; no prior irinotecan treatment,anti-EGFR therapy or vaccine treatment and no incidence of pulmonary embolism, deep vein thrombosis, or any other significant throm-boembolic event within 8	Pre-emptive treatment (consisting of skin moisturizers, sunscreen, topical steroid, and doxycycline 100 mg twice per day) vs. Reactive treatment (consisting of any treatments the investigator deemed necessary for the management of emergent skin toxicity and could be administered at any time during weeks 1 to 6. Patients were not prohibited from using skin moisturizer or sunscreen at any time during the study if they chose to do so).	Incidence of specific grade ≥ 2 skin toxicities 14/48 vs. 29/47 RR 0.47 [95%CI 0.29 to 0.78] Median time to first occurrence of specific ≥ grade 2 skin toxicities of interest Was not reached in the pre-emptive group and was 2.1 (95%CI, 2.1 to 6.3) weeks in the reactive group. Median progression-free survival time (months) 4.7 vs. 4.1 HR 1.0 (95%CI 0.6 to 1.6) Adverse events Incidence of grade 3 or higher adverse event 29/48 vs. 38/47, RR 0.75 (95%CI 0.57 to 0.98) No grade 5 adverse events were observed. Incidence of serious adverse events (SAE) 13/48 vs. 23/47, RR 0.55 (95%CI 0.32 to 0.96) Incidence of adverse events (any grade) commonly observed after panitumumab	Risk of bias: high Dropouts: none As of the data cutoff date (September 3, 2008) for this analysis, all patients had discontinued second-line treatment; the most common reason was disease progression (30 patients in the pre-emptive group, 28 patients in the reactive group). Results critical appraisal: Unclear risk of selection bias, High risk of performance bias and detection bias.

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
		weeks before random assignment were allowed. Patient characteristics: median age (range): 60 (24-84) vs. 61 (40-86), M/F: 32/16 vs. 26/21; ECOG performance status 0/1/2: 24/12/2 vs. 30/17/0 Comparable groups, however, small differences between the distribution of sex and race between treatment groups.		administration: Dermatitis acneiform 37/48 vs. 19/47, RR 1.91 (95%CI 1.30 to 2.79) Pustular rash 13/48 vs. 19/48, RR 0.67 (95%CI 0.38 to 1.20) Paronychia (17% v 36%) 8/48 vs. 17/47, RR 0.41 (95%CI 0.20 to 0.85) Incidence of other adverse events Pruritus 30/48 vs. 32/47, RR 0.92 (95%CI 0.68 to 1.23) Nausea: 32/48 vs. 26/47, RR 1.21 [95%CI 0.87 to 1.67] Vomiting: 22/48 vs. 17/47, RR 1.27 [95%CI 0.78 to 2.07] Fatigue: 29/48 vs. 27/47, RR 1.05 [95%CI 0.75 to 1.47] Diarhhea: 27/48 vs. 40/47, RR 0.66 [95%CI 0.50 to 0.87] Neutropenia: 9/48 vs. 20/47, RR 0.44 [95%CI 0.22 to 0.87] Hypomagnesemia: 7/48 vs. 13/47, RR 0.53, [95%CI 0.23 to 1.20] Dehydration: 6/48 vs. 16/47, RR 0.37 [95%CI 0.16 to 0.86] Patient-reported QOL (assessed using the Dermatology Life Quality Index (DLQI)) Mean DLQI change in score from baseline at week 3: 1.3 points vs. 4.2 points	

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
				"Results from the DLQI indicated that QOL was less impaired in the pre-emptive group compared with the reactive group".	
Liguori 1997	• Design: RCT • Source of funding: Institut Biochimique (IBSA), Lugano, Switzerland. • Setting: Multicentre • Sample size: n=134 • Duration: 10 weeks (The topical treatment of the irradiated area was continued over a 6- week period whereas the post-radiotherapeutic follow-up lasted 4 weeks).	Eligibility criteria: Patients of both sexes, aged 20 to 85 years, presenting with either a head and neck, pelvic or breast carcinoma of any stage, and given a fractionated radiation therapy. Patient characteristics: age (mean ± SD): 59.9 ± 12.7 vs. 55.7 ± 11.8, stage of disease: early 20 vs. 19; advanced 29 vs. 28 M/F: 34/36 vs. 40/24 Comparable groups, but sex ratio differed	Hyaluronic acid 0.2% cream (Ialugen) vs. Identical placebo cream	Status of the irradiated skin surface (score >1 vs 0-1) Statistically significant difference in favor of Ialugen from week 3 - week 7 (end of radiotherapy) and at the first two follow-up measurements. While no significant difference was observed at week 9, the difference level was significant again at week 10. Global efficacy and tolerability evaluation (expressed by the physician and by the patient) "In both cases, a statistically significant difference in favour of the Ialugen group was reported according to both the physician and the patient (Pearson chi-square): P< 0.01 and P< 0.05, respectively. "the majority of the patients and the investigators judged the tolerability of the test drugs to be 'good' or 'excellent" Side effects 1/70 vs. 4/64; RR 0.23 (95%CI 0.03 to 1.99)	Risk of bias: high Dropouts: N=18 (Group 1: n=6 Group 2: n=12, reasons stated) These 18 cases were excluded from the analysis. Unclear whether this was related to the intervention. Results critical appraisal: Unclear risk of selection bias and high risk of attrition bias.
Lokkevik 1996	• Design: within patient RCT (randomising body parts) • Source of funding: not stated • Setting: Department of Oncology, Norwegian Radium Hospital • Sample size: n= 86 • Duration: treatment during	Eligibility criteria: Patients with laryngeal cancer (TI-2) or breast cancer (all stages) who were previously treated surgically either with mastectomy or with breast conserving surgery undergoing	Bepanthen cream, starting from day 1 of radiotherapy, twice a day. vs. No topical ointment	At end of radiotherapy (laryngeal cancer patients) or 2 weeks after radiotherapy (breast cancer patients): Erythema grade No statistical difference between treatment and control (p=1.00)	Risk of bias: unclear Dropouts: n=7 withdrawn (4 due to non-compliance (mental state, change of radiotherapy, lost during follow-up, missing data) and 3

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
	radiotherapy and two weeks after completed radiotherapy, follow up 6-8 weeks after finished radiation therapy.	radiotherapy.. Patient characteristics: 63 breast cancer patients: median age 55 (range, 31 to 78); 16 laryngeal cancer patients: median age 69 (range 51 to 85) Comparable groups: patients served as their own controls.		Desquamation grade Significant difference in favour of treatment (p=0.027) Itching grade No significant differences (p=0.43)	because of untoward/allergic reactions during the treatment with Bepanthen) Results critical appraisal: Unclear risk of selection bias and attrition bias.
Maiche 1991	• Design: RCT (presented as a short communication) • Source of funding: not reported, AP Medical AB, Stockholm, Sweden provided kamillosan. • Setting: Department of Radiotherapy • and Oncology, Helsinki University Central Hospital, • Helsinki Finland, and • The Deaconess Hospital, • Helsinki, • Finland,.. • Sample size: n=50 • Duration: 7 weeks (follow up until three months from the discontinuation of radiotherapy)	Eligibility criteria: Women operated on for local breast cancer who were to receive radiotherapy to the scar area. Patient characteristics: age: mean age: 56 y (range 30-79y) M/F: 0/50 Comparable groups (patients served as their own controls)	Kamillosan cream vs. Almond ointment The drugs were applied gently to the skin twice daily, the first application 30 min before irradiation and the second before bedtime, throughout the radiotherapy course.	Acute skin reaction “The comparison between the reaction in kamillosan cream and almond ointment areas showed no statistically significant difference.” “Grade 1 changes were present in all areas at different times and there were 7 patients with grade 2 reactions in the kamillosan group compared to 13 patients in the almond ointment group. Grade 3 reactions appeared in five cases: three areas treated with almond ointment and two areas with kamillosan cream.” Allergic reaction (resembling urticaria) “Allergic reaction resembling urticaria was observed in two kamillosan cream and one almond ointment areas.” Subjective evaluation “The subjective symptoms like itching and pain were quite equally uncommon in the two groups.”	Risk of bias: unclear Dropouts: n=2 (discontinued the radiotherapy for personal reasons) Results critical appraisal: Unclear risk of selection, performance bias and detection bias.

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Moolenaar 2006	• Design: RCT, presented in a letter to the editor • Source of funding: none reported • Setting: The Netherlands • Sample size: n=26 • Duration: patients were followed until complete healing of skin toxicity	Eligibility criteria: adult Caucasian females who received radiotherapy to the breast or thoracic wall in daily fractions of 2 Gy over five weeks (total dose of 50 Gy) with grade 3 skin toxicities (RTOG Criteria) larger than 15 mm in diameter; without cutaneous diseases or previous radiotherapy in the region of the skin toxicity Patient characteristics: not reported Unclear whether groups were comparable	Honey gauze once daily Vs. Parrafin gauze once daily	Mean time to complete healing (SD) (days) 18.4 ± 7.62 vs. 19.8 ± 7.27, MD -1.40 (95%CI -7.36 to 4.56) Mean time to closure (SD) (days) 11.9 ± 5.20 vs. 13.9 ± 6.58, MD -2.0 (95%CI -6.74 to 2.74) The VAS results showed a trend towards less pain, itching, irritation in the honey population. No relevant side effects of either skin treatments were noted.	Risk of bias: high Dropouts: n=5 (n=1 died, n=4 withdrew reason not reported) Results critical appraisal: high risk of attrition bias, unclear risk of bias for all other items
Omidvari 2007	• Design: RCT • Source of funding: supported by the Shiraz University of Medical Sciences • Setting: Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, Iran • Sample size: n=58 • Duration: 7 weeks (five weeks of radiation therapy (RT) and two weeks following its completion)	Eligibility criteria: Female patients (20-70yrs) who underwent modified radical mastectomy for stage II or III pathologically proved breast cancer and needed RT in addition to surgery and chemotherapy, without history of previous RT, confirmed diabetes mellitus or systemic connective tissue disease. Patient characteristics: mean age (range): 47.6y (35-66) vs. 52.5 (39-65)	Group 1: topical betamethasone 0.1% during radiotherapy and two weeks after its completion Group 2: petrolatum during radiotherapy and two weeks after its completion Group 3: no topical therapy during radiotherapy and two weeks after its completion	Frequency and severity of acute radiation dermatitis (ARD) (measured using Radiation Therapy Oncology Group acute radiation morbidity scoring criteria) “Mean ARD grade was significantly increasing over the observation time for all groups and was lower for betamethasone receiving patients throughout the study, but significant difference was observed only at the end of the third week (p =0.027)”. “ARD occurs later in the observation period for betamethasone-receiving patients and low-grade ARD (Grades 0 and 1) are more frequent in the early phases in this group, but later on both low- and high-grade ARD occur with comparable frequencies in the three	Risk of bias: high Dropouts: n=7 (seven patients failed to complete the study course or were excluded because of declining to participate, new onset of diabetes mellitus and prolonged radiation course due to other causes (such as zona), numbers not specified per group) Results critical appraisal: High risk of selection,

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
		vs. 48 (34-60), Comparable groups		arms." "At the end of the third week, only 26.3% of the betamethasone group developed Grade I dermatitis, compared with 64.7% and 66.7% in the emollient and control arms, respectively. Chi square and Kruskal-Wallis tests revealed that this difference was statistically significant (p = 0.027). At the end of the seventh week, which was also the end of the topical treatment and the last evaluation for dermatitis, 15.8% of the betamethasone group had only Grade I dermatitis but this rate was 6.7% for the control group. All petrolatum-receiving patients developed Grade II or higher ARD. At the same time, all patients had some degree of ARD; although betamethasone-receiving patients had lower mean dermatitis grade than the other two arms, this difference did not reach significance but approached it (p=0.055). Maximum observed ARD grade for each arm "Betamethasone-receiving patients had lower maximum ARD grades than the other two groups but this difference did not reach significance. In general, we found that the severity of ARD in the betamethasone group was less than the other two arms at any time during the study, but this was significant only at the end of the third week. We also found that the frequency of RD early in the course of RT (up to the third week) was lower for the betamethasone group than the other arms; but, later in the observation period, both the severity and frequency of RD were comparable for all three arms. There was no	performance, and detection bias. Unclear risk of attrition bias.

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
				statistically significant difference between the petrolatum and control arms throughout the study."	
Pommier 2001	• Design: RCT • Source of funding: Supported by a grant from the Department • of Research and Development, • Boiron Ltd, France. • Setting: Department of Radiotherapy at the regional cancer center, Centre Léon Bérard (Lyon, France) • Sample size: n=254 • Duration: Unclear (during radiotherapy, apparently 6 weeks)	Eligibility criteria: Women of 18 to 75 years of age with a nonmetastatic breast adenocarcinoma treated by either lumpectomy or mastectomy with or without adjuvant postoperative chemotherapy or hormonal treatment, and referred for radiotherapy. No concomitant chemotherapy was allowed. Patient characteristics: mean age (range): 56.5y (28.5-74.5) vs. 55.1 (26.5-74.3) Comparable groups, except for the use of a bolus (12/126 vs 6/128)	Calendula (Pommade au Calendula par Digestion; Boiron Ltd, Levallois-Perret, France) on the irradiated fields after each session. vs. Trolamine (Biafine; Genmedix Ltd, France) on the irradiated fields after each session. Patients were asked to start topical application of their ointment on irradiated skin at the onset of radiotherapy, twice a day or more, depending on the occurrence of dermatitis and pain, until completion of their radiotherapy.	Acute dermal toxicity (evaluated according to the Radiation Therapy Oncology Group (RTOG)) Overall skin toxicity: Grade 2-3: 52/126 vs 81/128 RR 0.65 [95%CI 0.51 to 0.83] "No grade 4 toxicity was observed" Allergic reactions 0/126 vs. 4/128 RR 0.11 [95%CI 0.01 to 2.07]	Risk of bias: low Dropouts: none Results critical appraisal: Unclear risk of performance bias.
Ribet 2008	• Design: RCT • Source of funding: none reported	Eligibility criteria: patients with breast cancer or head and	Avène thermal spring water anti-burning gel, applied	Incidence and severity of radiation dermatitis Incidence of radiation dermatitis on day 42 (National Cancer institute classification)	Risk of bias: high Dropouts: n=10:

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
	• Setting: multicenter, France • Sample size: n=69 • Duration: 10 weeks	neck cancer requiring radiotherapy Patient characteristics: mean age ± sd (y): 57.4 ± 9.5 vs. 58.4 ± 13.1; M/F: 5/30 vs. 3/31. Comparable groups except for gender: relatively more men in ATSW gel group.	5 times per day during 10 weeks vs. Trolamine based cream (Biafine®), applied 5 times per day during 10 weeks	23/30 vs. 22/29, RR 1.01 (95%CI 0.76 to 1.34) Median time to occurrence of first radiation dermatitis signs (days) 31 vs. 29 Severity of radiation dermatitis (mean grade ± sd) (National Cancer institute classification) mean grade ± sd 1.43±0.59 vs. 1.64±0.66, MD -0.21 (95%CI -0.53 to 0.11) Incidence of pruritus Median time to occurrence of pruritus (days) 46 vs. 27 Global efficacy on day 70 (investigator) “excellent”: 46.7% vs. 17.2% Global efficacy on day 70 (patient) “very satisfied”: 59.3% vs.38.5% Global tolerance on day 70 (investigator) “very good”: 65.5% vs. 40.7% “good”: 34.5% vs. 55.6% “bad”: 0 vs. 1 Global tolerance on day 70 (patient) “very satisfied”: 74.1% vs. 50% Soothing effect (reported for Avène group only):	Avène group n=5 (n=3 exsudative radiation dermatitis, n=2 lost to follow up) Trolamine group n=5 (n=2 withdrew consent on day one, n=1 lost to follow up, n=1 skin toxicity, n=1 allergy to product) Results critical appraisal: high risk of performance bias and detection bias; unclear risk of selection bias and attrition bias; low risk of reporting bias and other bias.

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
				"very satisfied and satisfied": 77.8% (n=18 and n=5 respectively) Agrément: "Very satisfied": 59.3% vs. 38.5%	
Roy 2001	• Design: RCT • Source of funding: not reported • Setting: Department of Radiation Oncology, Centre Hospitalier Universitaire de QueÂbec, Canada • Sample size: n=100 • Duration: follow up until one month after completion of radiation therapy	Eligibility criteria: Patients >18y scheduled to be treated with adjuvant external beam radiotherapy to the breast or chest wall were included, total prescribed dose > 40 Gy, use of megavoltage X-rays. Patient characteristics: median age (range) 56.0y (33.2-78.0) vs. 58.4 y (27.6-84.2); Stage: T0/T1/T2/T3/T4/Tx: 9/30/9/0/1/0 vs. 5/26/14/1/2/2, N0/N1: 36/13 vs. 38/12. Comparable groups but some differences in cancer treatment other than radiotherapy (fewer patients in group 2 received chemotherapy, more of them received anthracycline-based regimens. More patients in group 1 had concomitant chemotherapy than in group 2).	Group I: no washing of the treatment field during the course of radiation therapy vs. Group II: gentle washing with warm water and mild soap These general recommendations were given to patients in both groups: do not erase ink marks; do not apply deodorant, lotion, cream, make up, perfume or any other product on the irradiated skin unless prescribed by your physician; do not apply water soaks to relieve itching or pain; avoid the use of dressing on the treatment field; and avoid exposure to the sun.	Acute skin toxicity (measured by the Radiation Therapy Oncology Group (RTOG) acute toxicity scale) Maximum toxicity scores at any time during treatment (no washing vs. washing, in %; p = 0:04) grade 0, 2% vs. 0% grade 1, 41% vs. 64% grade 2, 57% vs. 34%; grade 3 0% vs. 2% grade 4, 0% vs. 0% Mean time to maximal toxicity score achieved (no washing vs. washing, in weeks) 3.3 (95%CI 2.9 to 3.8) vs. 3.1 (95%CI 2.8 to 3.5), MD 0.2 (95%CI -2.29 to 0.69) Maximum erythema score: no significant differences Moist desquamation 16/49 vs. 7/50, RR 2.33 (95%CI 1.05 to 5.17)	Risk of bias: low Dropouts: n=1 (Group 1: one patient withdrew after being randomized but prior to beginning of her radiotherapy) Results critical appraisal: Unclear risk of performance bias and other bias.
Schmuth 2002	• Design: RCT	Eligibility criteria:	0.5% dexpanthenol	Clinical course	Risk of bias: high

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
	• Source of funding: none • Setting: Department of Radiation Therapy, Innsbruck, Austria • Sample size: n=23 • Duration: 8 weeks (approximately 6 weeks of fractionated radiation therapy and a 2-week follow-up period)	Women aged 18–80 years, receiving radiation therapy for breast cancer; no Karnofsky index < 70, no prior radiation dermatitis, no history of prior radiation therapy to same area, no atopic dermatitis, psoriasis and ichthyiosis, no systemic corticosteroids during two-week period prior to or during radiation. Patient characteristics: Median age (range) 44y (35-74) vs. 62y (39-75); Tumour stage pT1a-2N0-1M0 vs. pT1a-2N0-1M0 Comparable groups	cream (Bepanthen®, Hoffmann LaRoche, Berne, Switzerland) vs. 0.1% methylprednisolone aceponate cream (Advantan®, Schering, Vienna, Austria)	Scale 0 (none), 1 (mild), 2 (moderate), 3 (severe) for Erythema, Desquamation, Erosion, Induration and Hyperpigmentation 19 of 21 patients treated developed clinical signs of radiation dermatitis, an incidence comparable with that in the untreated control group. There were fewer patients with scores ≥4 in the methylprednisolone than in the dexpanthenol group (p<0.05). Comparison of mean severity scores between the treatment groups suggested a less severe clinical course in patients who received methylprednisolone than in those who received the dexpanthenol formulation, but the differences did not reach statistical significance. Adverse effects (dexpanthenol vs. methylprednisolone aceponate) Itching 1/30 vs. 2/30, RR 0.50 (95%CI 0.05 to 5.22) Burning 1/30 vs. 0/30, RR 3.00 (95%%CI 0.13 to 70.83) Quality of life General health (SF-36) Our data show that QOL dimensions, reflecting general health, improved after the termination of radiation therapy, as indicated by increased SF-36 scores in post-treatment vs. pretreatment (baseline) scores (not	Dropouts: n=2 in methylprednisolone group (n=1 patients'request, n=1 inadequate adherence to treatment) Results critical appraisal: Unclear risk of detection bias, high risk of attrition bias.

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
				significant). Skin-related (Skindex) Overall, the Skindex scores largely deteriorated from pretreatment (baseline) to post-treatment, reflecting the appearance of radiation dermatitis in virtually all subjects. In the dexpanthenol group, this deterioration reached statistical significance for the dimensions of depression, embarrassment, discomfort and limitations (P < 0.05). In the corticosteroid group only four of seven dimensions worsened. The difference between the two treatment groups was significant for the dimension of embarrassment (P < 0.05) and approached significance for the dimensions of fear (P=0.06) and physical discomfort (P=0.057)	
Shukla 2006	• Design: RCT • Source of funding: none • Setting: not reported (India) • Sample size: n=60 • Duration: 5 weeks radiotherapy, follow up 1 month after end of radiotherapy	Eligibility criteria: Clinico-pathological indication of axillary lymphatic drainage area irradiation after modified radical mastectomy or breast conservation surgery with axillary lymph nodes dissection; no skin disease or abscess in area to be irradiated. Patient characteristics: median age 44.6y (28-60) vs. 45.9y (29-60); M/F not reported, probably women as it concerns breast cancer Comparable groups	Beclomethasone dipropionate spray on irradiated axilla, two puffs each time over morning and evening, seven days a week from day one of radiotherapy. vs. Refrainment from applying anything in the irradiated area. Both groups of patients were advised not to shave	Radiation induced skin reaction Skin erythema 21/30 vs. 16/30, RR 1.31 (95%CI 0.87 to 1.97) Dry desquamation 5/30 vs. 3/30, RR 1.67 (95%CI 0.44 to 6.36) Wet desquamation 4/30 vs. 11/30, RR 0.36 (95%CI 0.13 to 1.01)	Risk of bias: unclear Dropouts: No dropouts Results critical appraisal: unclear risk of selection bias, performance bias and detection bias. Low risk of attrition bias, reporting bias and other bias.

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
			hairs of irradiated axilla and use of soap, oil and cream in the irradiated area was restricted.		
Westbury 2000	• Design: RCT • Source of funding: Supported in part by the Cancer Research Campaign, Neuro-oncology Research Fund and the Royal Marsden NHS Trust • Setting: UK • Sample size: n= 109 • Duration: 10 weeks	Eligibility criteria: Patients undergoing cranial irradiation aged over 16 years, able to give informed consent and have a level of comprehension and communication to be able to participate. Patient characteristics: median age (range): 52y (16-81) vs. 48y (21-79), M/F: 34/21 vs. 25/27, Diagnosis: Astrocytoma/ oligodendroglioma: 41 vs. 36; Ependymoma/ medulloblastoma: 1 vs. 4; Pituitary/ craniopharyngioma/ meningioma: 8 vs. 5; Brain metastases: 5 vs. 7 Comparable groups	Group 1: normal scalp care (patients were advised to continue normal scalp care) vs. Group 2: no washing (patients were adviced to avoid washing the irradiated area) NB: The information sheet for patients in group 2, did not prohibit hair washing but advised to avoid it.	Skin reaction (median scores) (assessed clinically using erythema/desquamation score (RTOG/EORTC) Erythema week 1: 1 vs. 1 week 6: 2.5 vs. 3 Desquamation week 1: 0 vs. 0 week 6: 1 vs. 1 Itching week 1: 1 vs. 1 week 6: 2 vs. 2 “There were no significant differences between scores of skin reaction in the two groups for each of the variables measured.”	Risk of bias: unclear Dropouts: n=2 (group 2) one declined to participate and one did not undergo radiotherapy. Results critical appraisal: Unclear risk of selection bias, performance bias and detection bias.

Appendix 6.3. Neuropathy

Table 130 – Neuropathy: evidence table systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results*	Critical appraisal of review quality
Albers 2011	• SR • Funding: none • Search date: August 2010 • Databases: Cochrane Neuromuscular Disease Group Specialized Register, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, LILACS, CINAHL	Adult participants of either sex undergoing chemotherapy with cisplatin (or related oncologic platinum compounds including oxaliplatin or carboplatin) as an antineoplastic medication.	Any form of chemoprotective treatment, such as acetyl-L-carnitine, acetylcysteine, ACTH, amifostine, BNP7787, calcium and magnesium, Org 2766, glutathione, oxcarbazepine, vitamin E and growth factors, used to prevent or limit cisplatin-induced neurotoxicity.	**Glutathione (GSH) vs. placebo (total of 6 studies, 354 participants)** Development of neuropathy symptoms: RR = 0.75 (95%CI 0.56 to 0.99) Developing neurotoxicity WHO criteria: RR = 0.19 (95%CI 0.08 to 0.47) Developing neurotoxicity NCI-CTC criteria: RR = 0.13 (95%CI 0.02 to 0.89) No change in WHO neurotoxicity in either group in one study Developing NCI grade 2 to 4 neurotoxicity: combined RR (2 studies) = 0.45 (95%CI 0.28 to 0.70) Change in neurological disability score by > 12 points: RR = 0.53 (95%CI 0.21 to 1.29) Adverse effects: RR for oliguria = 0.48 (95%CI 0.28 to 0.81) Need for hemotransfusions, the incidence of thrombocytopenia and anemia lower in the intervention group (results not quantified) QoL: results not quantified	• Quality SR: low risk of bias • Quality included studies: The quality and characteristics of the trials reviewed were quite variable, and included different measures of neuropathy (qualitative and subjective), different durations of follow-up, and different analyses. Overall conclusion of the review authors: “At present, the data are insufficient to conclude that any of the purported chemoprotective agents (acetylcysteine, amifostine, calcium and magnesium, diethyldithiocarbamate, glutathione, Org 2766, oxycarbazepine, or Vitamin E) prevent or limit the neurotoxicity of platin drugs among human patients.”

Study ID	Method	Patient characteristics	Intervention(s)	Results*	Critical appraisal of review quality
				N-acetylcysteine (NAC) vs. placebo (1 study, 14 participants) NCI-CTC toxicity rating scale: incidence of ≥ Grade 1, 2, and 3 neurotoxicity 80, 20, and 0% amongst the 5 participants in the NAC group and 100, 89, and 33% in the control group (P=0.01) after 12 cycles of treatment **Acetyl-L-carnetine** No studies found **Calcium and magnesium vs. placebo (1 study, 33 participants)** Incidence of ≥ grade 1, 2, and 3 neurotoxicity after six cycles of treatment: NCI-CTC: 100, 6, and 6% vs. 94, 6, and 0% (not significant) DEB-NTS: 100, 71, and 6% vs. 94, 56, and 0% (not significant)	

** Results based on one single study, unless specified otherwise.*

Table 131 – Neuropathy: evidence table RCTs glutamine

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Loven, 2008	• Design: RCT, double blind • Sources of funding: Solgar Health Products • Setting: multicentre, Israel • Sample size: 67 • Duration: not stated	• Eligibility criteria: women with ovarian cancer planned for treatment with carboplatin-paclitaxel without neuropathy or diabetes mellitus, < 80y. • Patients characteristics: median age 59 years (range 35-80 years)	• Intervention(s): Oral glutamate • Comparator(s): placebo	• Frequency of neuropathy on electro-diagnostic studies: 30.4% versus 30% • Symptoms Tingling: 12/23 vs. 9/18 (p=0.147) Numbness: 8/23 vs.9/18/ (p=0.109 Pain: 3/23 vs.9/18 (p=0.011) Loss of strength: 0/23 vs. 4/18 (p=0.187) • Signs Reduced touch perception: p=0.47 Reduced pain perception: p=0.474 Reduced deep sensation: p=0.395 Impaired tendon reflexes: p=1.0	• Toxicity that could be attributed to glutamate: severe rash in 2/34 patients	• Dropouts: 24/67 enrolled patients were excluded for various reasons (irregular or discontinued intake, incomplete data, progressive disease, skin rash, change of treating centre • Results critical appraisal: high risk of bias as no ITT and high number of dropouts, early stop of recruitment
Wang, 2007	• Design: RCT • Sources of funding: • Setting: single centre, China • Sample size: 86 patients • Duration: Sept 2004-Dec 2005	• Eligibility criteria: colorectal adenocarcinoma stage IV treated with oxaliplatin, no previous treatment for metastatic disease, PS 0-2, normal organ function. No pre-existing neuropathy, DM, alcoholic disease or central nervous system metastasis. • Patients characteristics: M/V 56/30, age ≥ 50y 52,	• Intervention(s): Oral glutamine • Comparator(s): no intervention	• Grade 3-4 neuropathy after 4 cycles: 26.2% versus 36.4% (p=0.05) • Grade 3-4 neuropathy after 6 cycles: 11.9% versys 31.8% (p=0.04) • Interference with ADL: 16.7% versus 40.9% (p=0.02)	• Patients needing oxaliplatin dose reduction: 7.1% versus 27.3% (p=0.02) • Response to chemotherapy: 52.4% versus 47.8% (p=0.90) • Median survival time: 17.3 months versus 18.6 months (p=0.79)	• Dropouts: 0 • Results critical appraisal: high risk of bias as unclear allocation concealment and no blinding

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		age < 50y 34				
Strasser, 2008	• Design: RCT • Sources of funding: Baxter, Bristol-Myers Squibb • Setting: single centre, Switzerland • Sample size: 52 patients • Duration: March 2004 – March 2006	• Eligibility criteria: cancer patients receiving taxanes for the first time, PS 0-2, no oral candidiasis, no Zinc insufficiency • Patients characteristics: M/V 28/13	• Intervention(s): Oral glutamine • Comparator(s): maltodextrin as placebo	• Sensory neuropathy more frequent in glutamine group: 5/21 versus 0/20 (p=0.48)		• Dropouts: 11 dropouts • Results critical appraisal: overall low risk of bias but no ITT

Table 132 – Neuropathy: evidence table other RCTs

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Chay 2010	• Design: RCT • Source of funding: funding of $40 400 came from Sanofi-Snythelabo Pte Ltd Eloxatin Clinical Study Grant • Setting: single center (Singapore) • Sample size: n=27, but 8 patients (4 in each group) did not complete study due to early trial termination	• Eligibility criteria: histologically verified colorectal cancer requiring oxaliplatin-based chemotherapy; Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; life expectancy of more than 3 months; aged 18 to 75 years • Patient characteristics: mean age 55 vs. 53 y; M/F 8/5 vs. 6/8; ECOG status (0/1) 12/1 vs. 13/1	• Calcium gluconate 1g (10 mL of commercially available 10% calcium gluconate) plus 15% magnesium sulfate 1g (2 mL of commercially available 49.3% magnesium sulfate) diluted into 100 mL of normal saline, infused over 15 min before and after oxaliplatin infusion • 100 mL of normal saline infused over 15 min before and after	Incidence of neuropathy (not clear on what scale this was based) Grade 0: 2 vs. 0 Grade 1: 0 vs. 3 Grade 2: 4 vs. 7 Grade 3: 3 vs. 0 Oxaliplatin-specific scale (OSS): Grade 1: 2 vs. 0 Grade 2: 1 vs. 2	Risk of bias: unclear Dropouts: 8 patients (4 in each group) did not complete study due to early trial termination unrelated to the study Results critical appraisal: unclear method of randomisation and allocation; all other items considered low risk of bias.

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
	unrelated to the study • Duration: follow up planned for 3 y, but study was terminated after median follow-up of 8.7 mo	• Comparable groups	oxaliplatin infusion. Both groups either • XELOX (consisting of oral capecitabine 1000 mg/m^2 twice a day for day 1 to 14 and Oxaliplatin 130 mg/m^2 on day 1 every 21 days (22 patients) or • FOLFOX-4 (consisting of oxaliplatin 85 mg/ m^2 on day 1 with bolus 400 mg/m^2 5FU and leucovorin 200 mg/m^2	Grade 3: 2 vs. 0 Not done: 1 vs. 1 Missing: 3 vs. 7 (?) No significant differences between the groups with respect to the OSS and CTC grade for cumulative neuropathy during or at the end of treatment Median time to onset of grade 1 numbness (oxaliplatin-specific toxicity scale) 18 vs. 13 weeks (log-rank test: p=0.5) Median time to onset of grade 2 or 3 numbness (NCI-CTC) 18.1 vs. 19.6 weeks (log-rank test: p=0.7) No significant difference for recurrence	
Grothey 2011	• Design: RCT • Source of funding: supported in part by Public Health Service grants; three authors have received research funding	• Eligibility criteria: adults with stage II or stage III adenocarcinoma of the colon; adequate hematologic parameters to allow chemotherapy; serum total bilirubin, creatinine, and calcium concentrations <=	1g calcium gluconate plus 1g magnesium sulfate pre- and post-oxaliplatin Vs.	**Incidence of grade >=2 sensory neurotoxicity:** NCI CTCAE: 11/50 vs. 21/51; RR = 0.53 (95%-CI 0.29 to 0.99) OSS: 14/50 vs. 26/51; RR = 0.55 (95%-CI 0.33 to 0.92)	Risk of bias: low Dropouts: 2/52 in Ca/Mg group and 1/52 in placebo group were not included in the analyses. Results critical appraisal: randomisation

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
	from related parties • Setting: multicenter trial USA • Sample size: n=104 • Duration: follow up stopped after 127 days because of premature study closure	1.5 * upper normal limit; negative pregnancy test. • Patient characteristics: age <65y 66% vs. 63%; males 54% vs. 52%; 96% caucasian in both groups • Comparable groups	Placebo Both groups: infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX)	Onset of grade >=2 sensory neurotoxicity significantly delayed in favor of Ca/Mg **PRO numbness and tingling:** less symptoms in favor of Ca/Mg **Adverse effects:** hypercalcemia in 0/50 vs. 1/51 (2%) hypermagnesemia in 7/50 (14%) vs. 8/51 (16%)	procedure unclear; all other items low risk of bias.

Appendix 6.4. Neutropenia and neutropenic fever

Table 133 – Neutropenia: evidence table of systematic reviews regarding the prevention of (febrile) neutropenia in patients with cancer treated with chemotherapy – prophylactic G-CSF / GM-CSF

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Bohlius 2008	• SR • Funding: University of Cologne, Germany; BMBF, Germany • Search date: April 2008 • Databases: (CENTRAL), MEDLINE, EMBASE, CancerLit, Medikat, • Russmed Articles, SOMED, Toxline,	Patients older than 16 years with non-Hodgkin's lymphoma (NHL) or Hodgkin's disease (HD), confirmed by biopsy. Acute and chronic leukaemias, including chronic lymphatic leukaemia, multiple myeloma and human immunodeficiency virus (HIV) associated lymphoma were excluded because they	G-CSF or GM-CSF (given at doses of at least 1 µg/kg/day, intravenously or subcutaneously, as primary prophylaxis) Vs. Placebo/no prophylaxis	Overall survival (11 studies) GM-CSF: RR 1.19 (95%CI 0.63 to 2.27) G-CSF: RR 0.96 (95%CI 0.85 to 1.09) Overall: RR 0.97 (95%CI 0.87 to 1.09) Mortality during chemotherapy (9 studies) RR 0.93 (95%CI 0.60 to 1.43) Freedom from treatment failure (6 studies): HR 1.11 (95%CI 0.91 to 1.35) Incidence of neutropenia (8 studies): RR 0.67 (95%CI 0.60 to 0.73)	Quality SR: Low risk of bias Quality included studies: adequate allocation concealment in ten of thirteen trials, adequate blinding in five trials. Nine studies included intention-to-treat calculations in the analysis. Withdrawals and losses to follow up were stated in ten trials. Overall conclusion of the authors (pertaining to all studies): "G-CSF and GM-CSF reduce the risk of neutropenia, febrile neutropenia and infection. However, based on the randomised trials currently available, there is no evidence that either G-CSF or GM-CSF provide a significant

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
	BIOSIS Previews and • LILACS. Also ASCO conference proceedings and databases for grey literature (SIGLE) and ongoing trials were searched.	include disease specific immunodeficiencies that may confound the results. Total number of included studies: 13		Incidence of febrile neutropenia (defined as ANC 1.0 x 109/litre; 5 studies) RR 0.74 (95%CI 0.62 to 0.89) Quality of Life (1 study): No significant differnces between the groups for QoL measured by EuroQol, EORTC Quality of Life Questionnaire and the Multidimensional Fatigue Inventory Adverse events Bone pain: RR 3.57 (95%CI 2.09 to 6.12) (8 studies) GM-CSF: RR 1.37 (95%CI 0.54 to 3.47) (2 studies) G-CSF: RR 5.33 (95%CI 2.66 to 10.68) (6 studies) Thromboembolic complications: RR 1.29 (95%CI 0.56 to 3.01) (5 studies) Skin rash injection site reaction: RR 7.69 (95%CI 2.84 to 20.82) (2 studies) Injection site reaction: RR 6.55 (95%CI 3.01 to 14.25) (2 studies) Myalgia: RR 0.95 (95%CI 0.60 to 1.45) (2 studies) Mucositis: RR 0.95 (95%CI 0.64 to 1.41) (3 studies) Headache: 2 studies, no pooled estimate presented.	advantage in terms of complete tumour response, freedom from treatment failure and overall survival".
Madarnas 2009	• Guideline • Funding: the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. • Search date:	Adult patients receiving myelosuppressive chemotherapy for breast cancer. Included studies: 3 guidelines, 1 SR, 4 RCTs, abstracts of 3	Primary or secondary prophylaxis with filgrastim Vs.	Recommendations of the authors: Primary prophylaxis with CSFs is justified for patients with early stage breast cancer treated with curative intent who receive any adjuvant dose dense chemotherapy regimen or any adjuvant chemotherapy regimen with expected rates of febrile neutropenia (FN) ≥20% (e.g., FEC-D, TC, CEF/FEC100) or any adjuvant	Quality guideline: low risk of bias Quality included studies: 3 high quality guidelines; 1 SR with 4 of 11 AMSTAR items scored positive; 7 RCTs: allocation concealment not reported in all studies; blinding not reported in four studies, no blinding in two studies, adequate blinding (not

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
	• August 2009 • Databases: MEDLINE , EMBASE, Cochrane Library, conference proceedings of the American Society of Clinical Oncology (ASCO) 2005 to 2009, the American Society of Hematology (ASH) (2004 to 2008), and the San Antonio Breast Cancer Symposium (2004 to 2008), treference lists were searched for additional trials. Personal files were also searched.	RCTs	Placebo/no filgrastim or best supportive care (including prophylactic antibiotics)	chemotherapy regimen with expected rates of FN <20% in the presence of patient related risk factors (age>65yrs, comorbidity that in the opinion of the treating physician may increase the risk of FN, or that may be complicated by the development of FN,poor performance status or poor nutritional status). Secondary prophylaxis with CSFs is justified for patients with early-stage breast cancer treated with curative intent who did not receive primary CSF prophylaxis and have experienced a neutropenic event, or a dose delay, with a prior cycle of chemotherapy and who require continued treatment where a reduced dose may compromise treatment outcome For patients with advanced breast cancer receiving palliative myelosuppressive therapy who have suffered FN despite an initial schedule or dose adjustment, and for whom continued treatment is required and the treating physician feels that a further reduction in dose or schedule delay may compromise treatment outcome, secondary prophylaxis with CSF is appropriate. For patients with advanced breast cancer receiving palliative myelosuppressive chemotherapy, a schedule or dose adjustment, with or without prophylactic antibiotics, is the preferred initial strategy to minimize the risk of FN. However, in exceptional circumstances where even with such an intervention, the treating physician feels that there is a persistent and substantial risk of FN, primary prophylaxis with CSF can be considered on a case by case basis via the Expanded Access Program.	reported who was blinded) in one study; one study described the randomization method; two studies reported on including intention-to-treat analysis; losses to follow up were stated in one study. Overall conclusion of the authors: “The incidence and severity of neutropenia, as well as the rate of complications due to neutropenia can be significantly reduced with the use of CSFs”.

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Herbst 2009	• SR • Funding: University of Cologne, Germany; BMBF, Germany • Search date: January 2008 • Databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, conference proceedings of the American Society of Clinical Oncology and the American Society of Hematology. In addition databases of ongoing trials, references, relevant reviews and guidelines were screened.	Cancer patients (any type; both solid and heamatological) of all ages, male and female, receiving myelosuppressive chemotherapy or bone marrow or stem cell transplantation. Total number of included studies: 2	Prophylaxis with G(M)-CSF Vs. Prophylaxis with antibiotics Both study arms had to receive identical chemotherapy regimes and other supportive care.	Overall survival (1 study) Identical Kaplan Meier curves for the duration of observation (1000 days) Two-year survival was identical (6% in each arm) Infection-related mortality (2 studies) Study 1: no mortality in 18 weeks Study 2: GM-CSF vs. cotrimoxazole: 3/78 vs. 3/77, OR 0.99 (95%CI 0.21 to 4.74) Treatment-related or early mortality (1 study) 100 day mortality: GM-CSF vs. antibiotic group: 7/78 vs. 5/77, OR 1.38 (95%CI 0.46 to 4.17) Incidence of microbiologically or clinically documented infections (1 study) GM-CSF vs. cotrimoxazole: 17/78 vs. 11/77, RR 1.53 (95%CI 0.77 to 3.04) Hospitalization for febrile neutropenia (1 study) G-CSF vs. ciproploxacin and amphotericin B: 7/18 vs. 7/22, RR 1.22 (95%CI 0.53 to 2.84)	Quality SR: low risk of bias Quality included studies: one trial describes randomisation procedure. No blinding of patients and caregivers in either of the studies, blinding of outcome assessment was not reported. Baseline characteristics balanced in both arms of the two studies. One study describes losses to follow-up and withdrawals. One study reports intention-to-treat analysis, the other a per protocol analysis. Overall conclusion of the authors: “There is no evidence for or against antibiotics compared to G(M)-CSFs for the prevention of infections in cancer patients.”

Table 134 – Neutropenia: evidence table of RCTs regarding the prevention of (febrile) neutropenia in patients with cancer treated with chemotherapy – prophylactic G-CSF / GM-CSF

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Brugger 2009	• Design: RCT • Source of funding: Amgen • Setting: multicenter study, Europe • Sample size: n=60 • Duration: not clear	Eligibility criteria: chemotherapy naïve women (aged ≥ 65 yrs) with histologically confirmed node-positive stage II-III breast cancer, eligible for up to six cycles of FEC 100, with ECOG performance status ≤2, ANC ≥1.5x109/L, platelets ≥100x109/L. Patient characteristics: median age (range) 67.5 (65-77) vs. 69.0 (65-75); all female; disease stage II/III: 15/15 vs. 18/11; ECOG performance status 0/1: 28/2 vs. 24/5. Comparable groups, except for disease stage (relatively more stage II in secondary prophylaxis group) and ECOG performance status (relatively more '0' in primary prophylaxis group)	Pegfilgrastim Vs. No G-CSF support	Incidence of grade 4 neutropenia (ANC <0.5×109/L) 23/30 (77%) vs. 21/29 (72%), RR 1.06 (95%CI 0.79 to 1.43) Duration of grade 3-4 neutropenia (National Cancer Institute Common Toxicity Criteria) "Mean duration was shorter with pegfilgrastim than with no G-CSF support." Day of nadir (mean per group): 8 vs. 14 Day of ANC recovery above 1.0×109/L (mean per group): 9 vs. 16-18: "Duration of neutropenia averaged 1 day in pegfilgrastim-treated patients compared with 3 days in patients not receiving G-CSF in cycle 1"	Risk of bias: low Dropouts: 1 participant in the primary prophylaxis group did not receive treatment, reason not reported Results critical appraisal: low risk of bias for all items, except for risk of other bias, which was scored unclear.
Hecht 2010	• Design: RCT • Source of funding: Amgen • Setting: multicenter (54 sites), USA • Sample size: n=252 • Duration: treatment during	Eligibility criteria: patients ≥18 years of age with locally advanced or metastatic colorectal adenocarcinoma not	Pegfilgrastim 6 mg Vs. Placebo	Overall survival Estimated percentages (Kaplan-Meier method) of patients who died 46% vs 58% "At the last follow-up 49/118 patients in the placebo group had died compared with 47/123 in the pegfilgrastim group".	Risk of bias: unclear Dropouts: pegfilgrastim: dropouts n=52 (main reasons: death n=19, consent withdrawn n=8,

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
	4 cycles of chemotherapy, 30 months follow up	curable by surgery and not amenable to curative radiation therapy; life expectancy ≥12 weeks; ECOG performance status 0-2; adequate hematopoietic, liver and kidney functions. Patients could have received adjuvant chemotherapy and up to 1 previous chemotherapy regimen, provided that 30 days had elapsed since the last dose Patient characteristics: mean age (range): 62.4y (28-85) vs. 62.9y (18-87); M/F: 78/45 vs. 84/34; disease stage (II/III/IV/unclear): 1/1/112/4 vs. 0/2/119/2; ECOG status (0/1/2/missing): 58/52/11/2 vs. 40/67/11/0 Comparable groups except for difference in ethnicity (relatively more Hispanic in placebo group)		Progression free survival Estimated percentages (Kaplan-Meier method) of patients with PFS 85% vs 91% Incidence of grade 3/4 neutropenia (ANC < 1.0 x 109/l) 13% vs. 43%; OR 0.19 (95%CI 0.10 to 0.37) Incidence of grade 3/4 febrile neutropenia (temperature ≥38.2ºC and ANC < 1.0 x 109/l) 2% vs. 8%, OR 0.27 (95%CI 0.07 to 1.00) Incidence of neutropenia related hospitalization 6% vs. 8%, P=0.55 Incidence of adverse events Treatment related adverse events: 19% vs. 12%. Incidence of serious and all adverse events was similar between the groups. No serious adverse events were considered related to study medication. "The incidence of bone pain was low across both treatment groups, although higher in the pegfigrastim group (10%) compared with placebo group (1%)" "Seven patients in each group died during treatment period. No event leading to death was considered related to study drug."	lost to follow up n=6; not reported: n=19); placebo: dropouts n=65 (main reasons: death n=25, consent withdrawn n=9, lost to follow up n=6; not reported: n=25) Results critical appraisal: unclear risk of selection bias and attrition bias; low risk of bias for all other items.

Table 135 – Neutropenia: evidence table of systematic reviews regarding the prevention of (febrile) neutropenia in patients with cancer treated with chemotherapy – therapeutic G-CSF / GM-CSF

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Clark 2009	• Design: SR • Funding: H Lee Moffitt Cancer Center, USA • Search date: 2001/2002/2003 (depending on database searched) • Databases: CANCERLIT, EMBASE, LILACS, MEDLINE, SCI, The Cochrane Central Register of Trials, CENTRAL; experts were consulted; references of relevant articles were screened.	People undergoing chemotherapy for cancer who experience neutropenia (absolute neutrophil count less than 1 x 109/l) and fever (body temperature higher than 38.5°C on one occasion or higher than 38°C on two or more occasions). Total number of included studies: n=13 (1518 patients)	G-CSF or GM-CSF plus antibiotics Vs. antibiotic alone	Overall mortality (12 studies, 1303 participants) OR 0.68, (95%CI 0.43 to 1.08) Infection related mortality (9 studies, 872 participants) OR 0.51, (95%CI 0.26 to 1.00) Length of hospitalization (8 studies, 1221 participants) HR 0.63 (95%CI 0.49 to 0.82) (heterogeneity was detected due to one influential study; significance of the effect was still maintained after exclusion of that study: HR 0.72 (95%CI 0.55 to 0.95)) Incidence of side effects Deep vein thrombosis (4 studies, 389 participants): OR 2.49 (95%CI 0.72 to 8.66) Bone, joint pain and flu like symptoms (6 studies, 622 participants): OR 2.05 (95%CI 1.22 to 3.46)	Quality SR: low risk of bias Quality included studies: seven studies described an adequate method of randomization and five reported an adequate concealment of allocation; six trials were double-blinded and seven were placebo controlled; intention to treat analysis was performed in nine studies. Overall conclusions of the authors: “The use of CSF in patients with febrile neutropenia due to cancer chemotherapy does not affect overall mortality, but reduces the amount of time spent in hospital and the neutrophil recovery period. It was not clear whether CSF has an effect on infection-related mortality.”

Table 136 – Neutropenia: evidence table of RCTs regarding the prevention of (febrile) neutropenia in patients with cancer treated with chemotherapy – therapeutic G-CSF / GM-CSF

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Er 2004	• Design: RCT • Source of funding: none • Setting: Erciyes University Oncology Hospital, Turkey • Sample size: n=53 • Duration: until therapy was discontinued	Eligibility criteria: Adult patients ≥18 years, histologically proven malignant solid tumor, on chemotherapy, presented with chemotherapy-induced FN. ANC<500/mm3 or a count of <1000/mm3 but expected to fall <500/mm3 within 48 hours, single measurement of axillary temperature >38.5ºC or 38.0ºC on two or more occasions within 12 hours. Patient characteristics: M/F:18/12 vs. 21/9; age (median, range) 52.2(17-72) vs. 48.5(19-73); ANCx109/L 0.1(0.0-0.5) vs. 0.1(0.0-0.7) Comparable groups	G-CSF (5 µg/kg per day subcutaneously) plus antibiotics Vs. antibiotics alone	Mortality 1 versus 3 (p=0.49) Median (range) days of hospitalization 8(5-17) versus 9(6-14) p=0.24 Side effects Transient increase in transaminases: 1 in each group. “Side effects were mild and there was no treatment-related death.”	Risk of bias: unclear Dropout: n=4 (group 1: n=1; group 2: n=3) Results critical appraisal: low risk of bias for sequence generation and selective reporting; all other items unclear risk of bias.

Table 137 – Neutropenia and neutropenic fever: evidence table prophylactic antifungals

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Gotzsche 2011	• SR • Funding: Rigshospitalet, Copenhagen, Denmark • Search date: July 2011 • Databases: CENTRAL, MEDLINE, reference lists of relevant articles, proceedings of the ICAAC, General Meeting of the ASM, and the European Congress of Clinical Microbiology and Infectious Diseases, contact with researchers in • the field.	Cancer patients with neutropenia caused by chemotherapy or bone marrow transplantation Total number of included studies: 32 NB: studies addressing children and patients who underwent bone marrow transplantation were also included.	Amphotericin B, fluconazole, ketoconazole, miconazole, itraconazole or voriconazole Vs. Placebo or no intervention	All-cause mortality (26 studies, 3902 participants; I2 = 0%) Any antifungal RR 0.94 (95%CI 0.81 to 1.09) Amphotericin B RR 0.69 (95%CI 0.50 to 0.96) Fluconazole RR 1.04 (95%CI 0.84 to 1.30) Ketoconazole RR 0.97 (95%CI 0.63 to1.49) Miconazole RR 1.16 (95%CI 0.71 to1.87) Itraconazole RR 0.94 (95%CI 0.63 to 1.40) Mortality related to fungal infection (23 studies, 3490 participants; I2 = 0%) Any antifungal RR 0.52 (95%CI 0.38 to 0.71) Amphotericin B RR 0.45 (95%CI 0.26 to 0.76) Fluconazole RR 0.42 (95%CI 0.24 to 0.73) Ketoconazole RR 1.49 (95%CI 0.55 to 4.04) Miconazole RR 0.13 (95%CI 0.01 to 2.33) Itraconazole RR 0.70 (95%CI 0.31 to 1.56) Invasive fungal infections (30 studies, 4044 participants; I2 = 0%) Any antifungal	Quality SR: low risk of bias Quality included studies: adequate allocation concealment and blinding in 13 studies. Other items not addressed / not reported in detail. Overall conclusion of the authors (pertaining to all studies): “Intravenous amphotericin B was the only antifungal agent that reduced total mortality. It should therefore be preferred when prophylactic or empirical antifungal therapy in cancer patients with neutropenia is instituted.”

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
				RR 0.50 (95%CI 0.39 to 0.64) Amphotericin B RR 0.41 (95%CI 0.24 to 0.73) Fluconazole RR 0.39 (95%CI 0.27 to 0.57) Ketoconazole RR 1.32 (95%CI 0.68 to 2.54) Miconazole RR 0.52 (95%CI 0.20 to 1.31) Itraconazole RR 0.53 (95%CI 0.29 to 0.97) Itraconazole/ketoconazole/amphotericin RR not estimable Harm "The reporting of harms was far too variable from trial to trial to allow a meaningful overview." In general, many more treatment discontinuations when on trial drug. Effect estimates were similar for the 13 trials that had adequate allocation concealment and were blinded.	
Johansen 2011	• SR • Funding: Rigshospitalet, Copenhagen; JASCHA-fonden, Sygekassernes Helsefond, Nordic Council of Ministers, Denmark; Swedish Society of Medicine,	Cancer patients with neutropenia caused by chemotherapy or bone marrow transplantation Total number of included studies: 17 NB: studies addressing children and patients who underwent bone marrow transplantation	Fluconazole Vs. Amphotericin B	All-cause mortality (15 studies, 3151 participants; I2 = 0%) RR 0.88 (95%CI 0.73 to 1.05) Mortality related to fungal infection (10 studies, 2279 participants; I2 = 0%) OR 0.95 (95%CI 0.57 to 1.58) Invasive fungal infections (15 studies, 3587 participants; I2 = 0%) RR 0.93 (95%CI 0.72 to 1.21)	Quality SR: low risk of bias Quality included studies: adequate allocation concealment in 7 studies, no study was blinded. Other items not addressed / not reported in detail. Overall conclusion of the authors (pertaining to all studies): "Fluconazole and amphotericin B appeared to have similar efficacy. Amphotericin B has been disfavoured in several of the trials through their design or analysis, or both. Since

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
	Sweden. • Search date: July 2011 • Databases: CENTRAL, MEDLINE, reference lists of relevant articles, proceedings of the ICAAC, General Meeting of the ASM, and the European Congress of Clinical Microbiology and Infectious Diseases, contact with researchers in • the field.	were also included.		Dropouts (8 studies, 1122 participants; I2 = 56%; REM) RR 0.76 (95%CI 0.44 to 1.29) Dropouts because of adverse effects (14 studies, 3489 participants; I2 = 56%; REM) RR 0.33 (95%CI 0.14 to 0.78) Harm: "The major harms were hepatic impairment and gastrointestinal adverse effects with fluconazole and infusion-related toxicity, renal impairment and gastrointestinal adverse effects with amphotericin B. Five patients treated with amphotericin B underwent haemodialysis. Due to heterogeneity it was not possible to provide a meaningful overview of the harms with the two drugs."	intravenous amphotericin B is the only antifungal agent for which an effect on mortality has been shown, and since it is considerably cheaper than fluconazole, it should be the preferred agent."
Jorgensen 2009	• SR • Funding: Copenhagen Hospital Corporation, Denmark • Search date: November 2007 • Databases: CENTRAL, MEDLINE, reference lists of relevant articles, contact with researchers in • the field and drug manufacturers.	Patients with cancer complicated by neutropenia Total number of included studies: 2 of which 1 pertained to the treatment of invasive fungal infection; only the prophylactic study is presented here.	Voriconazole intravenously followed by orally Vs. Liposomal amphotericin B intravenously	One prophylactic study (871 participants) All-cause mortality: RR 1.37 (95%CI 0.96 to 1.96) (review authors' calculation after having obtained additional information from the drug company) Invasive fungal infections: RD 1.8% (95%CI -1.0% to 4.7%) (review authors' calculation) Adverse effects: Nephrotoxicity "29 patients receiving voriconazole versus 32 patients receiving liposomal amphotericin B experienced a two-fold increase in S-creatinine	Quality SR: low risk of bias Quality included study: no adequate allocation concealment; no blinding. 22 more patients than those accounted for in the trial report had been randomised; one of these patients, from the voriconazole group, died. The trial report described 849 patients who received at least one dose of trial drug, but only 837 patients were included in the analysis. Other items not addressed / not reported in detail. Overall conclusion of the authors: "Liposomal amphotericin B is significantly more effective than voriconazole for empirical therapy of neutropenic cancer patients and

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
				levels as compared to baseline." Discontinuing therapy due to toxic effects 19 versus 23 (not significant) Discontinuing due to lack of efficacy 22 versus 5 (significant) Visual disturbances 21.9% versus 0.7% (significant) Visual hallucinations 4.3% versus 0.5% (significant) Dyspnoea 0.7% versus 8.8% (significant)) Serum potassium below 2.5 mmol/L 2.4% versus 5.0% (significant).	should be preferred."

Table 138 – Neutropenia and neutropenic fever: evidence table prophylactic antibiotics

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Gafter-Gvili 2012	• SR • Funding: Rabin Medical Center, Israel; European Commission (TREAT Project, Contract 1999-11459), not specified. • Search date: March 2011 • Databases: CENTRAL, Cochrane Cancer Network Register of Trials, MEDLINE, EMBASE,	Patients with cancer and neutropenia induced by chemotherapy or following bone marrow transplantation Total number of included studies: 109 NB: studies addressing children, patients who underwent bone marrow transplantation and 'immunocompromised patients' (e.g. patients with AIDS) were also included.	Antibiotics (oral or intravenous) Vs. Other antibiotic, placebo or no intervention	Antibiotic vs. placebo/no intervention All-cause mortality (46 studies, 5635 participants; I2 = 20%) Any antibiotic RR 0.66 (95%CI 0.55 to 0.79) (NNT to prevent one death 34 (95%CI 26 to 56)) Quinolones RR 0.54 (95%CI 0.40 to 0.74) TMP-SMZ RR 0.71 (95%CI 0.49 to 1.02) Other systemic RR 0.96 (95%CI 0.65 to 1.43) Nonadsorbable RR 0.64 (95%CI 0.44 to 0.94)	Quality SR: low risk of bias Quality included studies: adequate allocation concealment in 27 studies, 30 studies double-blinded (all other studies were open), full intention-to-treat analyses for mortality and infection reported in 24 studies, for mortality alone in six, no loss to follow-up in 14 studies Overall conclusion of the authors (pertaining to all studies): "Antibiotic prophylaxis in afebrile neutropenic patients significantly reduced all-cause mortality. In our review, the most significant reduction in mortality was observed in studies assessing prophylaxis with quinolones. The benefits of antibiotic prophylaxis

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
	reference lists of relevant articles, conference proceedings, contact with researchers.			Occurrence of febrile episodes (54 studies, 6658 participants; I2 = 89%) Any antibiotic RR 0.80 (95%CI 0.74 to 0.87) Quinolones RR 0.74 (95%CI 0.65 to 0.84) TMP-SMZ RR 0.80 (95%CI 0.69 to 0.92) Other systemic RR 0.94 (95%CI 0.85 to 1.04) Nonadsorbable RR 0.88 (95%CI 0.67 to 1.16) Side effects (mostly gastrointestinal, including diarrhea and nausea) (37 studies, 5103 participants) Any antibiotic RR 1.58 (95%CI 1.19 to 2.12) Quinolones RR 1.51 (95%CI 1.12 to 2.04) TMP-SMZ RR 1.70 (95%CI 1.12 to 2.59) Other systemic RR 1.82 (95%CI 0.72 to 4.55) Nonadsorbable RR 0.94 (95%CI 0.79 to 1.11) Side effects requiring discontinuation of the assigned antibiotic therapy (18 studies, 2281 participants) RR 2.06 (95%CI 1.32 to 3.19) Quinolone (8 studies, 1513 participants) RR 2.04 (95%CI 1.10 to 3.81) TMP-SMZ (5 studies, 305 participants)	outweighed the harm such as adverse effects and the development of resistance since all-cause mortality was reduced. As most studies in our review were of patients with haematologic cancer, we strongly recommend antibiotic prophylaxis for these patients, preferably with a quinolone. Prophylaxis may also be considered for patients with solid tumours or lymphoma.”

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
				RR 3.63 (95%CI 1.32 to 9.98) Other systemic RR 1.21 (95%CI 0.51 to 2.88) Nonadsorbable RR 3.18 (95%CI 0.14 to 72.75) Various sensitivity analyses didn't change the results qualitatively Antibiotic vs. other antibiotic (only significant results presented) All-cause mortality No significant differences Occurrence of febrile episodes No significant differences Side effects (mostly gastrointestinal, including diarrhea and nausea) Quinolone vs. TMP-SMZ RR 0.62 (95%CI 0.43 to 0.90) Systemic plus nonadsorbable vs. systemic RR 1.75 (95%CI 1.02 to 3.00) Side effects requiring discontinuation of the assigned antibiotic therapy Quinolone vs. TMP-SMZ RR 0.37 (95%CI 0.16 to 0.87) Quinolone plus other vs. quinolone RR 4.92 (95%CI 1.61 to 15.01) Nonadsorbable vs. systemic RR 0.04 (95%CI 0.00 to 0.69)	

Table 139 – Neutropenia and neutropenic fever: evidence table oral verus IV antibiotics

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Vidal 2009	• SR • Funding: internal support from Steering Committee for Research Promotion at Rabin Medical Center, Israel • Search date: September 2007 • Databases: CENTRAL, MEDLINE, EMBASE, LILACS; reference lists of relevant articles, conference proceedings, databases for ongoing studies.	Neutropenic cancer patients with fever of all ages (including patients who underwent bone marrow transplantation)	Oral antibiotics Vs. Intravenous antibiotics (IV) Oral antibiotics could be given as initial treatment ('initial oral') or after IV treatment (i.e. sequential IV – oral therapy)	Mortality (9 studies, 1392 participants) RR 0.95 (95%CI 0.54 to 1.68) Treatment failure at 30 days all studies (18 studies, 2763 participants) RR 0.95 (95%CI 0.85 to 1.07) Treatment failure at 30 days adults only (11 studies, 1558 participants) RR 0.99 (95%CI 0.86 to 1.14) Adverse effects requiring discontinuation of the assigned antibiotic therapy (12 studies, 1577 participants) RR 1.80 (95%CI 0.58 to 5.60) Gastrointestinal adverse events RR 5.14 (95%CI 3.15 to 8.38) for initially oral treatment (9 studies, 1216 participants) RR 2.81 (95%CI 1.03 to 7.66) for sequential IV to oral antibiotic treatment (4 studies, 784 participants) Post-hoc subgroup analyses addressing the setting (oral-outpatient vs. intravenous-inpatients, inpatients only or outpatients only) and type of antibiotic (quinolones only, quinolones in combination with other antibiotics, cefixime or new quinolones) did not reveal any significant results (but it's unclear to what outcome these analyses apply). Various sensitivity analyses didn't change the results qualitatively.	Quality SR: low risk of bias Quality included studies: adequate allocation concealment in eight studies, one trial double blinded, one trial outcome assessors blinded; 5% (median; range 0% to 18%) of the patients excluded from the final analysis; patients was unit of randomisation in four studies and episode of febrile neutropenia in the other studies. Overall conclusion of the authors (pertaining to all studies): "Oral antibiotic therapy can be safely offered to febrile children and adults with neutropenia who are haemodynamically stable, have no organ failure, can take oral medications, and do not have pneumonia, infection of a central line or a severe soft-tissue infection and do not suffer from acute leukaemia."

Table 140 – Neutropenia: evidence table systematic reviews inpatient vs outpatient management

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Teuffel 2011	• SR • Funding: Swiss Cancer League; Canadian Cancer Society, Canadian Institutes of Health Research and Canadian Institute of Health Research • Search date: February 2010 • Databases: CENTRAL, MEDLINE, EMBASE;: reference lists of relevant articles, conference proceedings	Cancer patients (children and adults) requiring management of febrile neutropenia	Any inpatient antibiotic treatment vs. any outpatient antibiotic treatment (intravenous (IV) antibiotics vs. IV (1 study); IV vs. oral (2 studies); oral vs. oral (1 study)	Treatment failure at 30 days in adults (4 studies, 470 participants): RR 0.79 (95%CI 0.52 to 1.20) Mortality (4 studies, 474 participants): RR 0.96 (95%CI 0.27 to 3.43) Toxicity (1 study, number of participants unknown): No results reported Various sensitivity analyses didn't change the results qualitatively	Quality SR: low risk of bias Quality included studies (adults only): probably low risk of bias (blinding not possible, but may not have had a major impact on the outcomes studied) (allocation generation and concealment information were reported for one and three studies, respectively. None of the studies were blinded. Withdrawal information could be retrieved from three studies; no study reported ITT analysis.) Overall conclusion of the authors (pertaining to all studies): "Our meta-analysis suggests that outpatient treatment of FN is a safe and efficacious alternative to inpatient management."

Table 141 – Neutropenia: evidence table RCTs inpatient vs outpatient management

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Talcott 2011	• Design: RCT • Source of funding: National Cancer Institute • Setting: multicenter study in various hospitals USA • Sample size: n=121 • Duration: unclear; study observation	• Eligibility criteria: adult outpatients with postchemotherapy fever at presentation or by patient measurement at home and neutropenia that persisted after at least 24-hour inpatient	Continued inpatient antibiotic therapy Vs. Early discharge to receive identical antibiotic treatment at home	**Mortality:** • No patient died **Major medical complications:** • 5 (8%) vs. 4 (9%) episodes; RD -1% (exact 95%CI -10% to 13%) **Quality of Life:** • Reported pain slightly increased for hospitalized patients and decreased for home care patients (change, 2.72 vs. - 13.1; P =	Risk of bias: high Dropouts: Eight of 121 episodes excluded (five episodes considered as ineligible and three because of inadequate documentation of the study outcome, reasons equally distributed between groups). Results critical appraisal: High risk of bias for lack of blinding; low risk of bias for randomization,

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
	continued until resolution of neutropenia discontinuation of antibiotics, and resolution of any new medical problems. In most cases, antibiotics were discontinued when resolution of neutropenia was documented, but the treating physician could order additional treatment or observation.	observation • Patient characteristics: median (range) age in years 47 (20-81) vs. 47 (25-74); 33M/33F vs. 19M/28F; use of GSF 25/66 vs. 17/47 • Baseline differences with respect to GSF use, ethnicity, and status of job / medical insurance, but not with respect to clinical characteristics		.01). • Role Function subscale of the EORTC QLQ C-30 increased more for hospitalized patients than for home care patients (change, 0.78 v 0.58; P = .05) • Emotional Function scores declined for hospitalized patients but increased for homecare patients (change, -6.94 vs. 3.27; P = .04). • No other QLQ-C30 subscale differences were evident. • No differences for the Consumer Satisfaction or General Well-Being instruments **Need for hospitalization** N/A (“4 outpatient episodes resulted in hospital readmission”)	concealment of allocation, blinding of outcome assessment, attrition bias and selective reporting; unclear risk of other bias The study was terminated early due to poor accrual.

Table 142 – Neutropenia: evidence table systematic reviews nursing practices - isolation

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Eckmanns 2006	• SR • Funding: supported by the European Community • Search date: June 2005 • Databases: Medline. additional search for guidelines, books, the ; bibliographies of review articles, monographs, and articles identified	Patients with hematological malignancies who have neutropenia due to their illness or its treatment (i.e., chemotherapy or BMTs [no stem cell transplantation]) or patients without cancer who have BMTs (no stem cell transplantation) for other reasons. Total number of included studies: 16	High-efficiency particulate air (HEPA) filtration, with or without laminar airflow (LAF) Vs. Standard ventilation of patient hospital rooms with no air filtration (non-HEPA filtration)	**Mortality** RR 0.86 (95%CI 0.65 to 1.14) **Fungal infection** RR 0.57 (95%CI 0.13 to 2.53)	• Quality SR: high risk of bias • Quality included studies: no information on method of randomization, allocation concealment of attrition bias was reported; none of the studies was blinded; no studies involved the appropriate control subjects, who should have been situated in rooms with air conditioning but without HEPA filters. Duration of follow up was mentioned in 10 studies. • Overall conclusion of the authors (pertaining to all studies): “The results of these meta-analyses

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
	in the initial search				suggest that patients with hematological malignancies with severe neutropenia or patients with bone marrow transplants receive some benefit if they are placed in a protected environment. Nevertheless, the evidence is still somewhat ambiguous. Even if it does seem to be beneficial to place in protected areas patients with hematological malignancies and severe neutropenia or patients with bone marrow transplants, at present, no final conclusion can be drawn from the data available."
Zitella 2006	• SR • Funding: "No significant financial relationship to disclose" • Search date: June 2005 • Databases: MEDLINE, The National Guideline Clearinghouse, several organizations' Websites	Adult neutropenic patients with cancer Total number of included studies: 5 (of which 1 RCT)	Nursing practice interventions that impact infection, among which protective isolation	The review describes several nursing interventions, only protective isolation is discussed here. **Incidence of infection** "A randomized study of adult neutropenic patients with cancer demonstrated no difference in infection for patients in protective isolation compared to those not in isolation; another study supported the findings, indicating no significant differences in median days with a fever, number of days before the first use of systemic antibiotics, or the use of antifungals." **Incidence of febrile episodes** "Although the published studies had small sample sizes, no statistically significant differences existed in the incidence of febrile episodes, the number of infections, or the use of antibiotics for patients in protective isolation and those not isolated. Because no evidence suggests that protective isolation reduces the risk of infection, the practice is no longer recommended.	• Quality SR: low risk of bias • Quality included studies: evidence quality was assessed, but not reported per study (only one RCT was included). Overall conclusion of the authors (pertaining to all included studies): "Additional studies are needed to further define practice interventions that impact infection. Most of the interventions for managing hospitalized patients with neutropenia continue to be based on tradition and theoretical considerations; very few well-controlled research studies have been conducted."

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
				However, healthcare providers should continue to recommend that neutropenic patients avoid or minimize exposure to potentially infectious people. Visitors should be screened for symptoms indicating potential respiratory infection and instructed not to visit patients if an infection is found."	

Appendix 6.5. Radioproctitis

Appendix 6.5.1. Prevention of radioproctitis

Table 143 – Prevention of radioproctitis: evidence table RCTs corticosteroids

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Fuccio 2011	• Design: RCT • Source of funding: Sofar s.p.a., (Trezzano Rosa, Milan, Italy) • Setting: single centre (S.Orsola-Malpighi University Hospital, Italy) • Sample size: n=120 • Duration of follow-up: 12 months	• Eligibility criteria: Patients with prostate cancer without distant metastases, undergoing a course of external beam radiation therapy • Patient characteristics: mean age 70.2 y, M/F 120/0 • Comparable groups	3 mg beclomethasone dipropionate enema vs identical-looking placebo	**Modified Simple Clinical Colitis Activity Index** At 3 and 12 months after the end of radiotherapy no significant differences of SCCAI total scores between the groups, except for item bleeding rate (blood in the stool, at least once a week): 12/55 (22%) vs. 25/59 patients (42%); OR = 0.38 (95%CI 0.17 to 0.86) **Radiation Therapy Oncology Group acute and late toxicity scales** Three and 12 months after the end of radiotherapy, no differences were found between the two treatment groups based on the RTOG⁄EORTC toxicity scales. **Inflammatory Bowel disease Quality of Life**	Risk of bias: low Dropouts: Six patients did not take any of the study drugs and were excluded from the analyses (BDP arm: 5; placebo arm: 1); four more patients were lost to follow-up (BDP arm: 1; placebo arm: 3) Results critical appraisal: method of randomization, allocation concealment and information on blinding clearly described, no correct ITT

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
				Index After 12 months of follow-up the reduction of the total IBDQ scores was significantly more pronounced for patients on placebo (P=0.034) **Vienna rectoscopy score** Three months after the end of radiotherapy, no difference was noted between the two treatment groups. However, after 12 months of follow-up, the Vienna Rectoscopy Score was significantly lower in the beclomethasone dipropionate group. **Severe hemorrhagic proctopathy** During the whole period of the study, severe haemorrhagic proctopathy, was diagnosed in 10 patients, four in the BDP arm and six in the placebo arm. ITT: OR 0,69 (95%CI 0,18 to 2,60) PP: OR 0,67 (95%CI 0,18 to 2,51) **Adverse events** None	

Table 144 – Prevention of radioproctitis: evidence table RCTs probiotocs

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Delia 2007	• Design: RCT • Source of funding: none reported • Setting: University of Messina, Italy • Sample size: N=490 • Duration of follow-up: 1 month	• Eligibility criteria: patients who received adjuvant postoperative radiation therapy after surgery for sigmoid, rectal, or cervical cancers and had no contraindication for probiotic or antibiotic therapy or radiation therapy • Patient characteristics: not specified • Comparable groups	VSL#3 ((*L. casei, L. plantarum, L. acidophilus, and L. delbruekii subsp. bulgaricus*), (*B. longum, B. breve, and B. infantis*), *Streptococcus salivarius subsp. Thermophilus*) one sachet t.i.d. vs identical appearing placebo	**Incidence of radiation-induced diarrhoea** 77/243 (31.6%) vs. 124/239 (51.8%) P<0.001; RR: 0.61 (95%CI 0.49 to 0.76) **Severity of radiation-induced diarrhea (WHO grading)** Grade 3 or 4 diarrhea: 8/77 (1.4%) vs. 69/124 (55.4%) (P<0.001); RR: 0.19 (95%CI 0.10 to 0.37) Grade 1 or 2 diarrhea: 34/77 vs. 50/124; RR: 1.10 (95%CI 0.79 to 1.52) **Daily number of bowel movements** 5.1 ± 3 vs. 14.7 ± 6 (P<0.05) **Adverse events** No tumor- or treatment-related deaths or deaths from other causes were recorded in either group during the period of radiation therapy, and no case of bacteremia, sepsis, or septic shock due to the probiotic lactobacilli was reported.	Risk of bias: low Dropouts: N=8 I: (N=2) one patient withdrew consent after the first session of radiation therapy, one patient died of myocardial infarction after three sessions of radiation therapy; both patients were excluded from analysis of the results. C: (N=6) six patients were withdrawn after a few sessions of radiation therapy due to the occurrence of severe diarrhea resistant to loperamide and the usual standard of care; these patients were excluded from the analysis of results. Results critical appraisal: method of randomization and allocation concealment not described, and blinding of outcome assessors unclear. No ITT

Appendix 6.5.2. Treatment of radioproctitis

Table 145 – Treatment of radioproctitis: evidence table RCTs hyperbaric oxygen

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Sidik 2007	• Design: RCT • Source of funding: not reported • Setting: university hospital, Indonesia • Sample size: n=65 • Duration of follow up: 6 months	• Eligibility criteria: patients age ≤55 y with stage I – IIIB uterine cervical cancer, that had received pelvic radiation • Patient characteristics: M/F ?, mean age 47.0 and 44.7Y • Comparable groups	100% oxygen with pressure between 2-3 ATA vs Control treatment (unclear what this contained; apparently no intervention)	**SOMA LENT score:** "ratio of acute side effects before and soon after of intervention" 44.12 ± 28.22 vs. 0.71 ± 30.16 vs. (p<0.001) "ratio of late side effects before and soon after of intervention" 33.64 ± 57.64 vs. -19.69 ± 69.44 (p=0.008) **Karnofsky score** "ratio of quality of life before and soon after intervention" 19.67 ± 9.64 vs. 4.53 ± 10.74 (p <0.001) "ratio of quality of life before and after 6 months of intervention"15.27 ± 14.74 vs. 2.47 ± 16.11 p =0.007)	Risk of bias: high Dropouts: HBOT group: 3 failed to complete treatment, 6 died Control group: 4 failed to evaluate (lived to far away), 3 dropped out (not explained why), 9 died, 2 moved to another city Results critical appraisal: inadequate and unconcealed allocation, no blinding, large number of drop outs. No ITT analysis.
Clarke 2008	• Design: RCT • Source of funding: supported in part by grants from the Lotte and John Hecht Memorial Foundation and National Baromedical Services, and equipment from Sechrist Industries • Setting: multicenter	• Eligibility criteria: late rectal radiation tissue injury present for >= 3 months that hasn't responded sufficiently to other therapies • Patient characteristics: M/F 14/106 • Comparable groups	100% oxygen at 2.0 ATA for 90 min, once daily, five times weekly vs 21% oxygen (normal air) at 1.1 ATA for 90 min (sham treatment), once daily, five times weekly	**SOMA-LENT score (improvement)** 5.00 vs. 2.61 MD (based on repeated measurements model) = 1.93 (95%CI 0.38 to 3.48) **Clinical evaluation** Proportion healed or improved: 56/63 (88.9%) vs. 35/65 (62.5%); RR = 1.65; 95%CI 1.30 to 2.10	Risk of bias: high Dropouts: none after the intervention period. However, 150 patients were randomized but 11 and 19 patients were excluded from the analyses because of 'protocol violations'. At 1 year, 5 pt's (4%) had died and 9 (8%) had been lost to FU Results critical appraisal: adequate and concealed allocation, adequate blinding.

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
	trial • Sample size: n=120 • Duration of follow up: 5 y			OR for improvement (based on repeated measurements model) = 5.93; 95%CI 2.04 to 17.24 **Quality of life** Improvement on Expanded Prostate Cancer Index Composite quality of life: • bowel bother: 14% vs. 5% • bowel function: 9% vs. 6%	Reasons for drop outs not clear. No ITT analysis.

Table 146 – Treatment of radioproctitis: evidence table RCTs coagulation therapy

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Jensen 1997	• Design: RCT • Source of funding: NIH ROI Grant and Human Studies Core of NIH NIDDK Grant • Setting: not reported • Sample size: n=21 • Duration of follow up: 1 y	• Eligibility criteria: patients being considered for surgery, having failed 1 y of medical therapy, pelvic RT at least 2 y earlier, rectal bleeds at least three times p/w, anaemia and a life expectancy of 2 y • Patient characteristics: mean age 75 y, M/F 18/3 • Comparable groups	Heater probe vs. Bipolar electrocoagulation	**Severe bleeding episodes after 1 y** 1/9 (11%) vs. 3/12 (33%): RR = 0.44; 95%CI 0.05 to 3.60 Mean no. of episodes: 0.4 vs. 0.3 **Complications** No major complications occurred	Risk of bias: unclear Dropouts: none Results critical appraisal: no details on method of randomisation, allocation concealment and blinding
Gheorghe 2003	• Design: RCT • Source of funding: not reported • Setting: single center (Fundeni Clinical Institute, Romania)	• Eligibility criteria: Patients with hematochezia (rectal bleeding) caused by radiation proctitis • Patient characteristics: mean age 68.6 y, M/F 14/28 • Comparable groups	Argon plasma coagulation, electrical power setting of 60 W vs. Argon plasma	**Improvement of rectal bleeding** No bleeding: 56.5% vs. 26.3% (p=0.16) RR 2.15 (95%CI 0.93 to 4.94) Minor intermittent bleeding:	Risk of bias: high Dropouts: Group B: 4 (unclear reasons) Results critical appraisal: no details on method of randomisation,

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
	• Sample size: n=42 • Duration of follow up: 3 months?		coagulation, electrical power setting of 50 W	43.5% vs. 73.7% RR 0,59 (95%CI 0.34 to 1.01)	allocation concealment and blinding; relatively high number of drop outs in Group B
Lenz 2010	• Design: RCT • Source of funding: not reported • Setting: UNIFESP hospital, Sao Paulo, Brazil • Sample size: n=30 • Duration: mean follow-up 12.5 months (range 3–30)	• Eligibility criteria: recurrent rectal bleeding, started 6 months after radiotherapy with at least 1 bleeding episode in the week before and endoscopically confirmed radiation telangiectasias • Patient characteristics: mean age 67.4 (SD 11.8); M/F 16/14; 10% grade 1 (bleeding once or less weekly); 43.3% grade 2; 26.7% grade 3; 20% grade 4 (bleeding requiring transfusion) • Comparable groups	Argon plasma coagulation vs Bipolar electrocoagulation	**Eradication of all telangiectasias** 12/15 vs. 14/15; RR = 0.86 (95%CI 0.64 to 1.14) **Complications** Minor: 5/15 vs. 10/15; RR = 0.50 (95%CI 0.22 to 1.11) Major: 1/15 vs. 5/15; RR = 0.20 (95%CI 0.03 to 1.51) **Relapse** 1/12 vs. 2/14; RR = 0.58 (95%CI 0.06 to 5.66)	Risk of bias: unclear Dropouts: APC: 2 (1 died, 1 refused further therapy after successful reduction of rectal bleeding) Results critical appraisal: adequate concealment of allocation, no details on method of randomisation and blinding

Table 147 – Treatment of radioproctitis: evidence table RCTs sulfasalazine

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Kochhar 1991	• Design: RCT • Source of funding: not reported • Setting: one hospital • Sample size: n=37 • Duration of follow-up: 4 weeks	• Eligibility criteria: symptomatic radiation-induced proctosigmoiditis • Patient characteristics: mean age 49.5 y, M/F 1/36 • Comparable groups	Oral sulfasalazine (1g) + rectal prednisolone (20 mg bd) for 4 wks vs Oral placebo + rectal sucralfate (2g bd) for 4 wks	**Clinical improvement** 8/15 vs. 16/17: RR = 0.57 (95%CI 0.35 to 0.92) **Endoscopic improvement** 7/15 vs. 12/17: RR = 0.66 (95%CI 0.35 to 1.23) **Side effects** Two patients in the sulfasalazine group did not tolerate the drugs due to myalgia, nausea and headaches	Risk of bias: unclear Dropouts: Sulfasalazine/steroid: 3 (1 not explained why, 2 did not tolerate the drug) Sucralfate: 2 (not explained why) Results critical appraisal: method of randomisation, allocation concealment and blinding of outcome assessors unclear. Completeness of follow up unclear

Table 148 – Treatment of radioproctitis: evidence table RCTs corticosteroids

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Rougier 1992	• Design: RCT • Source of funding: unknown • Setting: single centre • Sample size: n=32 • Duration of follow-up: 4 weeks	• Eligibility criteria: radioproctitis confirmed and graded on sigmoidoscopy • Patient characteristics: M/F 3/29 • Comparable groups regarding demographic characteristics, but not regarding grade of disease (more aggressive grade of proctitis in betamethasone group)	Hydrocortisone acetate mousse 90 mg od for 4 weeks vs Betamethasone lavage 5 mg od. for 4 weeks	**Improvement of endoscopic appearance** 12/16 vs. 5/14: RR = 2.10 (95%CI 0.98 to 4.48) **Poor tolerance of enema** 2/16 vs. 10/14: RR = 0.18 (95%CI 0.05 to 0.67)	Risk of bias: high Dropouts: Betamethasone lavage: 2 (reasons not explained) Results critical appraisal: method of randomization and allocation concealment unclear and no information on blinding. There is possibly a high risk of selective reporting and other bias (baseline imbalances)

Appendix 6.6. Infertility

Appendix 6.6.1. Addition of GnRH analogue to gonadotoxic chemotherapy

Table 149 – Infertility: evidence table addition of GnRH analogue to gonadotoxic chemotherapy: systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results*	Critical appraisal of review quality
Bedaiwy 2011	• SR • Funding: none • Search date: January 2010 • Databases: MEDLINE, EMBASE, CENTRAL, Ovid Healthstar, ClinicalTrials.gov	Premenopausal women at risk of premature ovarian failure (POF) as a side-effect of gonadotoxic chemotherapy Not included were trials which reported only on women who underwent bilateral oophorectomy (surgical castration), used different chemotherapy regimens in the GnRH and control groups, or did not provide data of relevance to this review	GnRH cotreatment with chemotherapy vs. chemotherapy alone	Incidence of spontaneous pregnancy (3 studies): OR = 0.44 (95%CI 0.07 to 2.59)** Incidence of women with spontaneous ovulation (2 studies): OR = 5.70 (95%CI 2.29 to 14.20) Incidence of not having POF / women with spontaneous menstruation (7 studies): OR = 3.46 (95%CI 1.13 to 10.57)	• Quality SR: low risk of bias • Quality included studies: o The majority of the included studies were either small in size, still ongoing, and/or did not provide analyzable data. Furthermore, all studies had a short follow-up period that limit any conclusions on their long-term efficacy o Data relating to possible bias for the majority of the outcomes in this review were not available, denoting a possible selective reporting of trial results

** Results based on one single study, unless specified otherwise.*
*** OR from forest plot; another result is presented in the text of the review: OR 0.26 (95%CI 0.03 to 2.52).*

Table 150 – Infertility: evidence table addition of GnRH analogue to gonadotoxic chemotherapy: RCTs

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Del Mastro 2011	• Design: RCT • Source of funding: Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy; Associazione Italiana per la Ricerca sul Cancro, Italy; Ipsen, Milan, Italy (triptorelin). • Setting: multicenter trial, Italy • Sample size:	• Eligibility criteria: histologically proven stage I, II, or III breast cancer and candidates for adjuvant or neoadjuvant chemotherapy • Patient characteristics: median age (range) chemotherapy alone: 39 (25-45)y chemotherapy+triptorelin 39 (24-45)y • Comparable groups, except	Patients allocated to receive triptorelin were given an intramuscular dose of 3.75 mg at least 1 week before starting chemotherapy and then every 4 weeks for the duration of the treatment (the last dose was given before the last	**Pregnancy rate, life birth rate** At the time of the last annual follow-up (number of evaluated patients not reported): 1 fullterm pregnancy in the chemotherapy alone group and 3 pregnancies (1 fullterm, 1 premature delivery, and 1 voluntary	Risk of bias: low Dropouts: n=21 unevaluable: 12 in chemotherapy-alone group (n=6 no chemotherapy, n=6 lost to follow-up), 9 in chemotherapy plus triptorelin group (n=2 no chemotherapy, n=7 lost to follow-up). Results critical appraisal: all items low risk of bias

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
	n=281, n=21 unevaluable: 12 in chemotherapy-alone group (n=6 no chemotherapy, n=6 lost to follow-up), 9 in chemotherapy plus triptorelin group (n=2 no chemotherapy, n=7 lost to follow-up). • Duration: October 24 2003 - January 14 2008; last follow-up date 12 months after chemotherapy. Annual follow-up to record pregnancies, recurrences, and deaths (last annual follow-up, October 28, 2010).	for tumor grade: relatively more stage II than I in chemotherapy alone group as opposed to chemotherapy+triptorelin group	cycle of chemotherapy). Control Group: no additional intervention Both groups: adjuvant or neoadjuvant treatment with anthracyclinebased, anthracycline plus taxane–based, or CMF-based (100 mg/m^2 of oral cyclophosphamide on days 1-14 or 600 mg/m^2 of intravenous cyclophosphamide on days 1 and 8; 40mg/m^2 of methotrexate on days 1 and 8; and 600 mg/m2 of fluorouracil on days 1 and 8) chemotherapy.	abortion) in the chemotherapy plus triptorelin group were reported. • If all randomized patients are evaluated, dropouts included: 3/148 vs. 1/133 OR 2.73 (95%CI 0.28 to 26.58) • If dropouts were not taken into account and presuming pregnancy for all dropouts reported at 12 months:12/148 vs. 13/133 OR 0.81 (95%CI 0.36 tot 1.85) **OS** At last follow up (number of evaluated patients not reported): • 8 deaths chemotherapy plus triptorelin group and 3 in the chemotherapy-alone group. ▪ If all randomized patients are evaluated, dropouts included: 8/148 vs. 3/133 OR 2.48 (95%CI 0.64 to 9.53) ▪ If dropouts were not taken into account and presuming all	

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
				dropouts (reported at 12 months) are dead: 17/148 vs. 15/133 OR 1.02 (95%CI 0.49 tot 2.13) • 14 recurrences in the chemotherapy plus triptorelin group, 13 in the chemotherapy-alone group ▪ If all randomized patients are evaluated, dropouts included: 14/148 vs. 13/133 OR 0.96 (95%CI 0.44 to 2.13) ▪ If dropouts were not taken into account and presuming recurrence for all dropouts reported at 12 months: 23/148 vs. 25/133 OR 0.79 (95%CI 0.43 to 1.48) **Adverse events** Toxicity during chemotherapy: Hot flushes: 34/147 vs. 20/127, OR 1.61 (95%CI 0.87 to 2.97) Headache: 28/147 vs. 18/127, OR 1.42 (95%CI	

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
				0.75 to 2.72) Sweating:21/147 vs. 11/127, OR 1.76 (95%CI 0.81 to 3.80) Mood modification: 16/147 vs. 15/127, OR 0.91 (95%CI 0.43 to 1.93) Vaginal dryness: 14/147 vs. 12/127, OR 1.01 (95%CI 0.45 to 2.27) **Premature ovarian failure** Rate of early menopause: intention to treat analysis using imputed values for missing data: OR 0.28 (95%CI 0.14 to 0.56) available cases: 11/139 vs. 31/121, OR 0.25 (95%CI 0.12 to 0.52)	
Gerber 2011	• Design: RCT • Source of funding: Bernd Gerber, Novartis; Gunter von Minckwitz, AstraZeneca; Tanja Fehm, Novartis. • Setting: Multicenter phase II study, seems to have taken place in both university clinics as in general hospitals, Germany • Sample size: n=61 randomized, n=56 evaluated	• Eligibility criteria: Premenopausal (18-45y) patients with primary hormone-insensitive breast cancer undergoing anthracycline/cyclophosphamide (with or without taxane) – based neoadjuvant chemotherapy, who had requested preservation of ovarian function; regular and spontaneous menstrual periods before study entry, with follicular stimulating hormone (FSH) below 15 mIU/mL in the follicular phase of the menstrual cycle.	Goserelin group: first injection of 3.6 mg at least 2 weeks before start of chemotherapy independently from the day of menstrual cycle, then every 4 weeks (28 ± 3 days) until end of last chemotherapy cycle. Before the first administration of chemotherapy, ovarian suppression had to be proven. Control group: no additional intervention	**Pregnancy rate, life birth rate** Pregnancy: 1/30 vs. 1/30, OR 1.00 (95%CI 0.06 to 16.76) **Adverse events of interventions** Most common hematologic adverse events: leucopenia, neutropenia, and anemia; non hematologic: nausea, alopecia, and fatigue. None were considered to be related to goserelin. No treatment-related death occurred.	Risk of bias: unclear Dropouts: n=2 goserelin+chemotherapy group (n=1 adverse event, n=1 progression), n=3 chemotherapy group (n=1 no treatment, n=1 adverse event, n=1 patient wish) Results critical appraisal: unclear method of randomisation and allocation; unclear risk of other bias; all other items considered low risk of bias.

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
	• Duration: March 2005 - December 2007; follow-up 24 months after end of chemotherapy	• Patient characteristics: median age 36.5 (26-47)y • Comparable groups, Patients in the group with goserelin tended to be younger than those in the group without goserelin (35 *v* 38.5 years; *P* =.092).	Both groups: chemotherapy regimen including at least an anthracycline and cyclophosphamide with more than 500mg/m per cycle and more than 2,400mg/m in total per regimen, administered every 3 weeks for six or eight cycles.	Hot flashes: 16/30 vs. 10/30, OR 2.29 (95%CI 0.80 to 6.50) Mood swings: 2/30 vs, 2/30, OR 1.00 (95%CI 0.13 to 7.60) Insomnia: 5/30 vs. 1/30 OR 5.80 (95%CI 0.63 to 53.01) Urogenital symptoms: 6/30 vs. 1/30 OR 7.25 (95%CI 0.82 to 64.46) **Premature ovarian failure** Regular menses 6 months after end of therapy: 21/30 vs. 17/30, OR 1.78 (95%CI 0.62 to 5.17) Regular menses 12 months after end of therapy: 25/30 vs. 24/30 OR 1.25 (95%CI 0.34 to 4.64) long-term ovarian function reserve and fertility, AMH > 0.2 µg/L, 4/8 vs. 3/9, OR 2.00 (95%CI 0.28 to 14.20) (Median time from random assignment to measurement of AMH was 4 y.)	

Appendix 6.7.1. Addition of oral contraceptives vs. GnRH analogue to gonadotoxic chemotherapy

Table 151 – Infertility: evidence table oral contraceptives vs. GnRH analogues: RCTs

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Behringer 2009	• Design: RCT • Source of funding: Deutsche Krebshilfe; Kompetenznetz; Maligne Lymphome. • Setting: not reported • Sample size: n=23 • Duration: 2004 to 2007. Trial was stopped early due to slow enrolment and upcoming concerns about a priori assumptions. Median observation time was 25.4 months after randomization and 18.2 months after end of therapy (range 12.5–33.3 months).	• Eligibility criteria: aged 18-40 years; with biopsy-proven Hodgkin lymphoma (HL) at first diagnosis in advanced stages [clinical stage (CS) IIB with risk factor extranodal involvement or large mediastinal mass, all CS III + IV]; adequate organ function; history of spontaneous menstrual cycle, no primary ovarian failure, and follicle-stimulating hormone (FSH) levels ≤30 U/l at baseline • Patient characteristics: median age OC 25.95y, GnRH-a 25.26y • Comparable groups	Daily Oral Contraceptives (levonorgestrel 0.15 mg + ethinyl estradio 0.03 mg) vs. GnRH-a goserelin acetate 3.8 mg administered monthly subcutaneously Both groups: eight cycles of escalated combination therapy with bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPPesc))	**Pregnancy rate, life birth rate (at last follow up)** No woman gave birth to a child after HL treatment in both arms. **Protection of the ovarian reserve 12 months after end of therapy** Anti-Mullerian Hormone (AMH), median µg/l (range): OC: <0.017 (<0.017-0.032) GnRH-a: <0.017 (<0.017-0.681) Follicle stimulating hormone (FSH), median U/l (range): OC: 78.4 (7.2-116) GnRH-a: 58.6 (7.9-185) “neither OC nor GnRH-a co treatment is able to ensure a meaningful protection of the ovarian reserve” **Menstrual status OC vs. GnRH-a (at last follow up)** Amenorrhea: 3/9 vs. 1/10; RR 3.33 (95%CI 0.42 to 26.58) Irregular: 2/9 vs. 1/10; RR 2.22 (95%CI 0.24 to 20.57) Regular: 3/9 vs. 7/10 RR 0.48 (95%CI 0.17 to 1.31) Unknown: 1/9 vs. 1/10	Risk of bias: high Dropouts: 3/12 OC group (n=2 reason unclear), 1/11 GnRH-a group Results critical appraisal: no details on method of randomisation, allocation concealment and blinding, incomplete outcome data in small population, unclear risk of other bias because of early stopping of trial

Appendix 6.8. Gastrointestinal toxicity: nausea & vomiting, diarrhoea

Appendix 6.8.1. Nausea & vomiting

Table 152 – Evidence table: Nausea & vomiting: evidence table systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Basch 2011a; Basch 2011b; Basch 2011c	• SR in the realm of a guideline • Funding: American Society of Clinical Oncology (ASCO); Agency for Healthcare Research and Quality • Search date: • December 2009 • Databases: MEDLINE, Cochrane Library, meeting materials from ASCO and the Multinational Association for Supportive Care in Cancer, bibliographies from relevant articles	Patients undergoing chemotherapy or radiation therapy Included studies: previous ASCO guideline, 2 SRs, 37 RCTs	5-HT3 receptor antagonists (ondansetron, granisetron, dolasetron, palonosetron, ramosetron, and tropisetron), dexamethasone and NK1 receptor antagonists (aprepitant, fosaprepitant) Vs. Each other or placebo	Recommendations Chemotherapy-induced nausea and vomiting "The three-drug combination of an NK1 receptor antagonist (days 1-3 for aprepitant; day 1 only for fosaprepitant), a 5- HT3 receptor antagonist (day 1 only), and dexamethasone (days 1-3 or 1-4) is recommended for patients receiving highly emetogenic chemotherapy." "The two-drug combination of palonosetron (day 1 only) and dexamethasone (days 1-3) is recommended for patients receiving moderately emetogenic chemotherapy. If palonosetron is not available, clinicians may substitute a first-generation 5-HT3 receptor antagonist, preferably granisetron or ondansetron. Limited evidence also supports adding aprepitant to the combination. Should clinicians opt to add aprepitant in patients receiving moderate-risk chemotherapy, any one of the 5-HT3 antagonists is appropriate." "A single 8-mg dose of dexamethasone before chemotherapy with low emetogenic agents is suggested." "No antiemetic should be administered routinely before or after chemotherapy with minimally emetogenic agents." "In combination chemotherapy patients should be administered antiemetics appropriate for the component chemotherapeutic (antineoplastic) agent of greatest emetic risk." "Lorazepam or diphenhydramine are useful adjuncts to antiemetic drugs but are not	Quality SR: low risk of bias Quality included studies: 1 existing high quality guideline; 1 high quality Cochrane review (the other SR pertained to children); the quality of the 37 included RCTs is presented in Tables (but not summarised). Overall conclusion of the authors: "Combined anthracycline and cyclophosphamide regimens were reclassified as highly emetic. Patients who receive this combination or any highly emetic agents should receive a 5-HT3 receptor antagonist, dexamethasone, and a neurokinin 1 (NK1) receptor antagonist. A large trial validated the equivalency of fosaprepitant, a single-day intravenous formulation, with aprepitant; either therapy is appropriate. Preferential use of palonosetron is recommended for moderate emetic risk regimens, combined with dexamethasone. For low-risk agents, patients can be offered dexamethasone before the first dose of chemotherapy. Patients undergoing high emetic risk radiation therapy should receive a 5-HT3 receptor antagonist before each fraction and for 24 hours after treatment and may receive a 5-day course of dexamethasone during fractions 1 to 5. The Update

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
				recommended as single-agent antiemetics." "No published randomized controlled trial data that met inclusion criteria are currently available to support a recommendation about complementary therapies." "It is suggested that antiemetics appropriate for the emetogenic risk class of the chemotherapy be administered for each day of the chemotherapy and for 2 days after, if appropriate. The Update Committee suggests, based on limited data, that patients receiving 5-day cisplatin regimens be treated with a 5-HT3 antagonist in combination with dexamethasone and aprepitant." "Clinicians should re-evaluate emetic risk, disease status, concurrent illnesses, and medications; ascertain that the best regimen is being administered for the emetic risk; consider adding lorazepam or alprazolam to the regimen; and consider adding olanzapine to the regimen or substituting high-dose intravenous metoclopramide for the 5-HT3 antagonist or adding a dopamine antagonist to the regimen." "Use of the most active antiemetic regimens appropriate for the chemotherapy being administered to prevent acute or delayed emesis is suggested. Such regimens should be used with initial chemotherapy, rather than assessing the patient's emetic response with less effective treatment. If anticipatory emesis occurs, behavioural therapy with systematic desensitization is effective and suggested." Radiation-induced nausea and vomiting It is recommended that all high risk patients should receive a 5-HT3 antagonist before each fraction and for at least 24 hours after completion of radiotherapy. Patients should also receive a 5-day course of dexamethasone during fractions 1-	Committee noted the importance of continued symptom monitoring throughout therapy. Clinicians underestimate the incidence of nausea, which is not as well controlled as emesis."

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
				5.” Moderate risk patients should receive a 5-HT3 antagonist before each fraction for the entire course of radiotherapy. Patients may be offered a short course of dexamethasone during fractions 1-5. For low risk patients a 5-HT3 antagonist alone as either prophylaxis or rescue is recommended. For patients who experience radiation-induced nausea and vomiting while receiving rescue therapy only, prophylactic treatment should continue until radiotherapy is complete. Patients at minimal risk should receive rescue therapy with either a dopamine receptor antagonist or a 5-HT3 antagonist. Prophylactic antiemetics should continue throughout radiation treatment if a patient experiences radiation-induced nausea and vomiting while receiving rescue therapy. Combined chemotherapy and radiation therapy “Patients should receive antiemetic prophylaxis according to the emetogenicity of chemotherapy, unless the emetic risk with the planned radiotherapy is higher.”	
Keeley 2009	• SR (clinical evidence) • Funding: none reported. • Search date: • April 2008 • Databases: MEDLINE, Embase, CENTRAL, DaRE and HTA database (CRD)	Patients with cancer undergoing chemotherapy or radiation therapy Included studies: 9 SRs, RCTs, or observational studies Criteria for inclusion in the review were: published SRs and	5-HT3 receptor antagonists, dexamethasone, NK1 receptor antagonists, cannabinoids, benzodiazepines and other interventions vs. each other or	Chemotherapy induced nausea and vomiting Dexamethasone + antiemetics vs. antiemetics (mainly 5HT3 antagonists) (1 SR with 25 RCTs) No vomiting within 24 hours of chemotherapy: OR = 2.22 (95%CI 1.89 to 2.60) No vomiting within 1–7 days of chemotherapy: OR = 2.04 (95%CI 1.63 to 2.56) Adverse effects:	Quality SR: low risk of bias Quality included studies: not presented per study, but the authors applied GRADE for the various outcomes.

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
		RCTs in any language, at least single-blinded, containing more than 20 individuals of whom more than 80% were followed up. All studies described as "open", "open label", or not blinded unless blinding was impossible were excluded.	placebo	"Most RCTs found adverse effects "mild and tolerable"; several RCTs in the included review reported increased hiccups/gastrointestinal symptoms with dexamethasone (no further data reported). One person on dexamethasone had haematemesis" Dexamethasone plus 5HT3 antagonists versus 5HT3 antagonists alone (1 SR with 11 RCTs + 10 RCTs included in another review) Vomiting: OR 0.42 (95%CI 0.34 to 0.51) Aprepitant versus placebo in people receiving 5HT3 receptor antagonist plus dexamethasone (2 RCTs) Complete response at 5 days (no vomiting and no use of rescue drug treatment): 63% vs. 43% ($p < 0.001$) Complete response (no vomiting and no use of rescue drug treatment at day 1 (acute phase), days 2–5, and overall): 85%, 66%, and 63% vs. 75%, 51%, and 49% (all $p < 0.01$) Adverse effects: "Similar rates" (no p-values reported) No significant differences for asthenia/fatigue, constipation, hiccups Cannabinoids (oral nabilone, oral dronabinol (tetrahydrocannabinol), and intramuscular levonantradol) vs placebo (1 SR)	

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
				Complete control of nausea: RR 1.21 (95%CI 1.03 to 1.42) Complete control of vomiting: RR 1.84 (95%CI 1.42 to 2.38) Adverse effects: "High" sensation: RR 10.6 (95%CI 6.86 to 16.50) Drowsiness, sedation, somnolence: RR 1.66 (95%CI 1.46 to 1.89) Withdrawal because of adverse effects: RR 4.67 (95%CI 3.07 to 7.09) Other adverse effects: euphoria, dizziness, dysphoria or depression, hallucination, paranoia, arterial hypertension: all significantly more frequent after cannabinoids Cannabinoids compared with other antiemetics (1 SR) Complete control of nausea: RR 1.38 (95%CI 1.18 to 1.62) Complete control of vomiting: RR 1.28 (95%CI 1.08 to 1.51) Adverse effects: not formally assessed for this comparison (see placebo-controlled studies) Lorazepam plus methylprednisolone versus methylprednisolone (1 RCT) Mild nausea: 60% vs. 68% (NS) Compete control of vomiting: 33% vs 35% (NS) Sedation: 86-92% vs 8-10% (significant)	

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
				Amnesia: 48-50% vs. 0% (significance not reported) Radiotherapy induced nausea and vomiting Corticosteroids versus placebo in people receiving 5HT3 antagonists (1 RCT) Complete control of emesis after 15 fractions of radiotherapy: 23% vs. 12% (p = 0.02) Average nausea scores after 15 fractions of radiotherapy (max score 4): 0.28 vs. 0.39 (p <0.03) Complete control of nausea: 15% vs. 9% (p = 0.14) Adverse effects (over the course of 15 fractions of radiotherapy): Sleep quality: favours placebo (p <0.002) Constipation: favours placebo (p <0.003)	
Machado Rocha 2008	• Design: SR • Funding: none • Search date: December 2006 • Databases: • MEDLINE (PUBMED), EMBASE, PSYCINFO, LILACS, CENTRAL; bibliographies and references of selected studies.	People with any type of cancer receiving chemotherapeutic treatment, irrespective of gender, age and place of treatment. The chemotherapeutic schemes included those of low, moderate and high emetic potential. Total number of included studies: 30	Pharmacological interventions based on substances derived from C. sativa and/or smoked cannabis, irrespective of the time of intervention and of the association with other types of therapy for nausea and vomiting in cancer patients receiving chemotherapy.	Anti-emetic efficacy: dronabinol versus placebo (2 studies) RR = 0.47 (95%CI 0.19 to 1.16)	Quality SR: low risk of bias Quality studies included in the meta-analysis: one study low risk of bias, other moderate risk of bias. Overall conclusions of the authors: “Although there was not a statistically significant difference between the cannabinoid dronabinol and placebo for cancer patients receiving chemotherapy, a clinically significant difference in favour of dronabinol was observed.”

Table 153 – Nausea & vomiting: evidence table RCTs

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Duran 2010	• Design: RCT • Source of funding: local Department of Health • Setting: Oncology Services of three University hospitals in Barcelona, Spain • Sample size: N=16 • Duration: 5 days	Eligibility criteria: patients > 18 years with a Karnofsky score ≥70 with CINV lasting > 24 h according to the Morrow Assessment of Nausea and Emesis (MANE) questionnaire despite prophylaxis with standard anti-emetic treatment after the administration of 1-day MEC were enrolled during the following chemotherapy cycle Patient characteristics: age median (range) 50 (41-70) vs. 50 (34-76); M/F 0/7 vs. 1/8; MANE (mean, SD) for nausea severity 63.6 (26.5) vs. 56.22 (20.3); nausea duration (h) 15.0 (7.9) vs. 15.3 (10.9); vomiting severity 52.3 (32.9) vs. 64.3 (22.8); vomiting duration (h) 11.6 (11.0) vs. 11.1 (10.0); Functional Living Index-Emesis (FLIE) (median – range) 67.0 (18.0–96.0) vs. 54.0 (26.0–110.0); all with solid tumours. Comparable groups, except for primary cancer diagnoses, cancer extension, MANE and FLIE; differences not clinically relevant according	Standard anti-emetic treatment plus a cannabis-based drug (Sativex®) consisting of a mixture of delta-9-tetrahydrocannabinol (THC) and cannibidiol (CBD) in a ratio of approximately 1:1, together with small amounts of other cannabinoid derivatives, delivered via an oromucosal spray Vs. Standard anti-emetic treatment alone. Standard anti-emetic treatment included corticosteroids as well as 5-HT3R antagonists or metoclopramide. The study drug was added to the standard treatment during the study cycle.	Complete response (no vomiting + mean nausea VAS score ≤10mm) Day 1 5/7 vs. 6/9; RD 4.8% (95%CI -36.7% to 42.1%) Over-all (whole period): 5/7 vs. 2/9; RD 49% (95%CI 1% to 75%) Nausea No delayed nausea (VAS <10mm) 4/7 vs. 2/9; RD 34.9% (95%CI -10.8% to 66.3%) No significant delayed nausea (VAS < 25mm) 5/7 vs. 4/9; RD 27.0% (95%CI -18.0% to 59.7%) Vomiting No delayed emesis 5/7 vs. 2/9; RD 49.2% (95%CI 1.0% to 75.0%) Quality of life “No differences in the quality of life measurements in the two groups (no patients in either group scored □108 in the FLIE questionnaire)” Adverse events (AE) At least one AE: 6/7 vs. 6/9; RD 19% (95%CI -23.7% to 52.4%) Severe AE: 1/7 vs. 1/9; RD 0.03 (95%CI -0.30 to 0..36) Drug tolerance 6/7 vs. 9/9; RD -14.3% (95%CI -40.2% to	Risk of bias: high Dropout: 1 in treatment group (but ITT analysis) Results critical appraisal: high risk of bias for other bias (very small study); low risk of bias for sequence generation, blinding, incomplete outcome data; unclear risk of bias for allocation concealment and selective reporting

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
		to authors		11.6%)	
Meiri 2007	• Design: RCT • Source of funding: Solvay Pharmaceuticals • Setting: USA • Sample size: N=64 • Duration: 5 (8?) days	Eligibility criteria: Patients aged ≥ 18 years, required to have malignancy that did not involve the bone marrow, undergoing chemotherapy including a moderately to highly emetogenic regimen, oxaliplatin at doses employed for the treatment of colon cancer, or the combination of doxorubicin with cyclophosphamide with or without taxanes for the treatment of breast cancer. Patient characteristics: age (y), mean (SD): 61.6 (14.2) vs. 55.6 (16.1) vs. 56.8(10.9) vs. 57.2 (8.6); M/F: 9/8 vs. 4/10 vs. 6/11 vs. 5/8 Comparable groups, except for primary cancer diagnosis	1: Dronabinol 2: Ondansetron 3: Dronabinol and ondansetron 4: Placebo Patients received a standard prechemotherapy regimen of dexamethasone (20 mg) and ondansetron (16 mg). Patients in the three active treatment groups also received 2.5 mg dronabinol prechemotherapy and postchemotherapy. Placebo patients received matching placebo prechemotherapy and postchemotherapy on day 1.	Dronabinol (group 1) vs placebo (group 4) Total response (nausea intensity < 5 mm on 100 mm VAS, no vomiting/retching, no rescue antiemetic) during active treatment 54% vs. 20% (NS) Absence of nausea 71% vs. 15% (p < 0.05) Vomiting/retching episodes “No statistically significant difference was observed among groups for mean number of episodes of vomiting and/or retching. Vomiting/retching were lowest in patients treated with dronabinol.” Patients’ wellness (Eastern Cooperative Oncology Group (ECOG) Overall mean change from baseline to end point 0.058 vs. 0.077 (p=0.036 in favour of placebo) (”.. the statistically significant result was confounded by site differences.”) QoL (McCorkle Symptom Distress Scale, MSDS) Mean change from baseline for dronabinol: –2.0±4.2 “The only significant difference between groups was for the dronabinol group versus the combination therapy group (mean change from baseline with combination therapy: +3.6 ± 6.5; p =	Risk of bias: high Dropout: dronabinol n=4 (1 adverse event, 2 protocol violations, 1 other reason) ; placebo n=3 (2 withdrew consent, 1 other reason) Results critical appraisal: unclear risk of selection bias, attrition bias and other bias. low risk of performance bias, detection bias and reporting bias. Note: reporting very confusing.

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
				0.033, in favour of dronabinol).” Safety At least one treatment emergent AE: 14/17 vs. 7/14, RR 1.65 (95%CI 0.93 to 2.91) At least one serious AE 2/17 vs. 2/14, RR 0.82 (95%CI 0.13 to 5.12)	

Appendix 6.9.1. Diarrhoea

Table 154 – Diarrhoea: evidence table RCTs octreotide vs placebo

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Cascinu 1994	• Design: RCT • Source of funding: Not reported • Setting: Servizio di Oncologica, Ospedali Riuniti, Italy • Sample size: n=43 • Duration: 24 hours	Eligibility criteria: Only patients who had previously experienced diarrhoea (defined as three or more loose bowel movements) in the 24-hour period after a course of Cisplatin-related diarrhoea (CDDP) were eligible. Patients also had to have a white blood cell count of over 3,000/mm³. Patient characteristics: M/F: 13/10 vs. 10/10; median age (range) 61 (38-70) vs. 60 (43-68); performance status (0/1/2) 13/7/3 vs. 11/8/1 Comparable groups	Octreotide 0.1 mg (two doses by subcutaneous injection, 15 min and 6 h after CDDP therapy) Vs. Placebo (1 cm³ saline solution)	Incidence of diarrhoea (more than two loose bowel movements) 1/22 vs. 15/20 (RR = 0.06 (95%CI 0.01 to 0.42) Side effects "Octreotide was well tolerated and we observed no definite side effects related specifically to its use."	Risk of bias: Low Dropouts: None Results critical appraisal: low risk of bias on all items.
Martenson 2008	• Design: RCT • Source of funding: supported in part by Public Health Service • (grants nos provided); supplementary funding by Novartis (Basel, Switzerland). • Setting: Department of Radiation • Oncology, Mayo Clinic, • Rochester • Sample size: n= 130 • Duration: 29 days	Eligibility criteria: patients with histologic proof of cancer in the pelvis (without distant metastases) who were scheduled to receive a continuous course of radiation therapy, either as definitive treatment or in an adjuvant setting. Patients had to enter the study before the third radiation therapy fraction was administered and were required to have a planned daily radiation therapy dosage	Octreotide acetate (100 µg, administered subcutaneously on day 1, followed by depot octreotide, 20 mg, administered intramuscularly on days 2 and 29) Vs.	Grade 2 or 3 diarrhoea: 32/62 vs. 27/63 (RR 1.20; 95%CI 0.83 to 1.75) Grade 2 or 3 abdominal cramps: 14/62 vs. 16/63 (RR 0.89; 95%CI 0.48 to 1.66) Rectal bleeding: mild or moderate: 26/62 vs. 22/63 (RR 1.20; 95%CI 0.77 to 1.88) moderate: 2/62 vs. 0/63 (RR 5.08; 95%CI 0.25 to 103.71) Patient reported measures of bowel function (Bowel function questionnaire)	Risk of bias: high Dropouts: n=5 patients (4 vs. 1) decided to not receive any protocol treatment with placebo or octreotide. These five were not included in the analysis. N=2 patients did not provide info on symptoms. Results critical appraisal: high risk for

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
		of 1.7 to 2.1 Gy and a planned total dosage of 45.0 to 53.5 Gy. Patient characteristics: age and sex not reported; number of patients with a history of rectal surgery 2% vs. 17% Comparable groups, except for history of rectal surgery.	Placebo injection	"Octreotide-treated patients reported significantly more problems with nocturnal bowel movements, clustering, and blood with bowel movements (P<.05 for all). Patients treated with octreotide reported an average of 5.2 problems with bowel function compared with an average of 4.2 problems for those treated with the placebo (P = .03). The median patient-reported quality of life (scale, 0 to 10) during the study was 7.8 for patients treated with octreotide and 7.7 for patients receiving the placebo (P=.29)."	other bias (baseline imbalance in favour of octreotide); low risk of bias on the remaining items.
Zachariah 2010	• Design: RCT • Source of funding: supported in part by grants to the Radiation Therapy Oncology Group (RTOG) from the National Cancer Institute and Novartis. • Setting: department of Radiation Oncology, James A. Haley Veterans Administration Hospital, Tampa, US • Sample size: n=233 • Duration: the week before and on day 22 of pelvic radiation, median follow up 9.6 months	Eligibility criteria: patients receiving concurrent chemotherapy and pelvic radiation therapy for rectal or anal cancer, or patients with a history of chemotherapy. Patient characteristics: median age (range): 61 (27–83) vs. 61 (37–85) M/F: 69/42 vs. 69/39; diarrhoea at study entry (None/Grade 1/Grade 2): 91/17/3 vs. 89/15/3 Comparable groups	Long-acting octreotide acetate (LAO) Vs. Placebo All patients first received a 100-µg test dose of LAO to assess for sensitivity or allergy to the drug before the first dose of study drug administration.	Incidence of moderate or severe acute diarrhoea (CTCAE v3.0, grades 2–4): 48/109 vs. 52/106 (RR = 0.90 (95%CI 0.67 to 1.20) Adverse events Placebo group, one patient treatment-related severe (grade 4) dehydration; four treatment-related severe hematologic adverse events; one patient died because of multiorgan failure not attributed to protocol treatment. LAO group: one patient treatment-related severe infection; three patients treatment-related severe hematologic adverse events; two patients severe neurological events not attributed to protocol treatment. Quality of Life (QOL-RTI; EPIC-Bowel; FACE-Bowel; DAS) "No statistically significant difference between treatment groups in the proportion of patients who reported improved QoL or bowel function at 3 months (among evaluable patients) in any of the four assessments."	Risk of bias: low Dropouts: fourteen patients did not meet the eligibility criteria or withdrew their consent for participation in the trial after randomization. In addition two patients in each group did not have follow-up adverse event information. Results critical appraisal: unclear risk of attrition bias; low risk of bias on the remaining items.

Table 155 – Diarrhoea: evidence table RCTs octreotide vs loperamide

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Cascinu 1993	• Design: RCT • Source of funding: none reported • Setting: oncology department, Pesaro, Italy • Sample size: n=41 • Duration: 9 days	Eligibility criteria: patients with 5FU induced grade 2 or 3 diarrhoea (grade 4 excluded) Patient characteristics: median age (range) 57 (46-65) vs. 59 (42-68); M/F 11/10 vs. 11/9; ECOG performance status (0/1/2) 9/8/4 vs. 10/7/3; diarrhoea grade (2/3): 10/11 vs. 11/9 Comparable groups	Octreotide 0.1 mg s.c. twice daily for 3 days Vs. Loperamide initial dose 4 mg p.o. followed by 4 dd 2 mg for 3 days	Diarrhoea completely resolved: 19/21 vs. 3/20; RR 6.03 (95%CI 2.11 to 17.28) Stools frequency (day 1,2,3): 4/3/0 vs. 5/5/5 (sign. not reported) No response (requiring further hospital treatment): 1/21 vs. 10/20; RR 0.10 (95%CI 0.01 to 0.68) Side effects: none observed in any treatment arm	Risk of bias: high Dropouts: none Results critical appraisal: low risk of bias for randomization, concealment of allocation, attrition, selective reporting and other bias; high risk for blinding.
Gebbia 1993	• Design: RCT • Source of funding: none reported • Setting: chemotherapy department of university hospital, Palermo, Italy • Sample size: n=40 • Duration: 10 days	Eligibility criteria: patients with WHO-grade 3-4 diarrhoea after chemotherapy, age <70y, Karnofsky index >70 Patient characteristics: mean age 58 vs. 56; M/F 13/7 vs. 11/9, Karnofsky index 83 vs. 85 Comparable groups	Octreotide 3 dd 0.5 mg s.c. for 3 days Vs. Loperamide 3 dd 4 mg p.o. for 3 days	Complete resolution of loose bowel movements after 3 days: 16/20 vs. 6/20; RR 2.67 (95%CI 1.32 to 5.39) No response after 10 days: 1/20 vs. 5/20; RR 0.20 (95%CI 0.03 to 1.56) Side effects: 3/20 pain in injection site. 15% of all patients had mild abdominal pain	Risk of bias: high Dropouts: none Results critical appraisal: low risk of bias for attrition, selective reporting and other bias; high risk for blinding; unclear risk for randomization, concealment of allocation.

Table 156 – Diarrhoea: evidence table SRs probiotics

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Fuccio 2009	• SR • Funding: none • Search date: • January 2009 • Databases: MEDLINE, EMBASE, Cochrane library, Google Scholar, CENTRAL, metaRegister of Controlled Trials and National Institutes of Health	Patients undergoing radiotherapy for pelvic or abdominal tumors	Probiotic supplementation in the prevention or treatment of radiation-induced diarrhoea versus placebo or dietary restriction	Prevention (3 studies) Development of radiation-induced diarrhoea (3 studies): OR 0.47 (95%CI 0.13 to 1.67) Treatment (1 study) need antidiarrhoeal drugs: no significant difference between the groups number of bowel movements, diarrhoea grading, and stool consistency: no significant differences between the groups patients' rating of diarrhoea and feces consistency: "statistically significant difference in favour of probiotics; however, this difference was not confirmed when the parameter was rated by the investigators." Side-effects "No major adverse events owing to probiotic supplementation were reported in any study."	Quality SR: low risk of bias Quality included studies: Prevention studies: except for 1 trial, all studies were double-blind and placebo-controlled; generation of allocation sequence and the concealment of treatment allocation were not reported in any of the 3 studies; 1 trial was a pilot study, 1 other trial was prematurely terminated owing to difficulties with recruitment and did not reach the calculated sample size to achieve 80% power. All 3 trials presented results on a per-protocol basis. Treatment (1 study): study might be have been under-powered Overall conclusion of the review authors: "Collectively, these interventional studies did not provide definitive conclusions that probiotic supplementation may be effective for the prevention of radiation induced diarrhoea." "Although the authors concluded that probiotic supplementation showed a clearly superior treatment efficacy, only a nonstatistically significant trend was observed and conclusions were not firmly supported by results."

Table 157 – Diarrhoea: evidence table SRs nutritional supplements

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
McGough 2004	• Design: SR • Funding: unrestricted educational grant from SHS international • Search date: May 2003 • Databases: MEDLINE, EMBASE, The Cochrane Library; grey literature including abstracts of radiotherapy and nutrition conferences and UK doctoral theses; search engines such as 'Google', 'Microsoft Network' and 'Ask Jeeves' were carried out on the Internet	Patients with gynaecological, rectal or urological malignancy and measured acute or chronic gastrointestinal toxicity to pelvic radiotherapy. Total number of included studies: 36 of which 14 RCTs	Nutritional interventions to alleviate side effects of patients during or after a course of pelvic radiotherapy.	Nutritional interventions during radiotherapy Elemental diet Elemental supplementation to normal diet (providing approximately 900 kcal): statistically significant decrease in the incidence and severity of acute diarrhoeal symptoms (1 study published only as a conference abstract and a non-peer-reviewed summary booklet) Elemental supplementation to low roughage diet (providing 900 kcal) no significant differences in bowel symptoms (1 study). Elemental supplementation to low fibre diet: effect on gastrointestinal outcomes not assessed (1 study). Enzyme supplement (WOBE-MUGOS – 100 mg papain, 40 mg chymotrypsin and 40mg trypsin) (1 study): Intervention vs. control (diarrhoea scale of 0–3 (0 to >6 bowel movements per day)) Moderate or severe symptoms: 57% vs. 36% Nutritional interventions after radiotherapy No results from randomized studies	Quality SR: low risk of bias Quality included studies: methodology was often weak, with reporting of method of randomisation, concealment of allocation and blinding lacking from many papers (n=10) The choice of randomisation in papers that reported their methodology was adequate in two studies. Intention-to-treat analyses were described in two papers. Overall conclusions of the authors (based on all included studies): "Low-fat diets, probiotic supplementation and elemental diet may be beneficial in preventing acute gastrointestinal symptoms. The evidence for the use of nutritional intervention to manage chronic gastrointestinal symptoms is limited. The use of low-fat diets, therapeutic doses of antioxidant vitamins and probiotic supplementation may be helpful. A reduced intake of raw vegetables and fibrous foods may also be effective."

Table 158 – Diarrhoea: evidence table RCTs nutrional supplements

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
McGough 2008	• Design: RCT • Source of funding: unrestricted grant from SHS International (Liverpool, UK), all the elemental diet cartons or sachets were provided for free by the manufacturer. One of the authors acted as a consultant for Numico. • Setting: The Royal Marsden Hospital, London, UK • Sample size: n=50 • Duration: 5 weeks, follow up until 10th week.	Eligibility criteria: Patients with a histologically proven gynaecological, urological or lower gastrointestinal malignancy due for radical or adjuvant radiotherapy to the pelvis Patient characteristics: median age (range): 62.5 (29–79) vs. 58 (38–82); M/F: 8/17 vs. 13/12; BMI (kg/m2) 29 (22–39) 29 (22–41); radiotherapy dose (Gy) 50.4 (45–70) 54 (45–70); concomitant chemotherapy 11 (44%) vs. 7 (28%) Groups not comparable for age and gender; the intervention group included a greater proportion of patients with gynaecological malignancy (44% of the group) and the control arm included a greater proportion of patients with urological malignancy (36% of the group).	Elemental diet for the first 3 weeks of pelvic radiotherapy, replacing one normal meal per day with elemental formula (a selection of E028 Extra (SHS International, Liverpool, UK) ready to drink 250 mL cartons and E028 Extra flavoured powder sachets were provided. Vs. Habitual diet during radiotherapy treatment (i.e. intake from normal solid foods)	Severity and duration of diarrhoea Radiation Therapy Oncology Group (RTOG) toxicity scale (median and range): Week 3: 1 (0-2) vs. 2 (0-2) Week 5: 2 (0-2) vs. 2 (0-2) Week 10: 0.5 (0-2) vs. 0.5 (0-2) Quality of life Inflammatory Bowel Disease Questionnaire – Bowel specific sub-set (IBDQ-B) Week 3: 57 (23-66) vs. 60 (29-70) Week 5: 58 (35-67) vs. 60 (35-69) Week 10: 68 (54-70) vs. 69 (34-70) Vaizey Incontinence Questionnaire (VIQ) Week 3: 6 (0-22) vs. 4 (0-13) Week 5: 6 (0-18) vs. 4 (0-13) Week 10: 1 (0-13) vs. 1.5 (0-13)	Risk of bias: high Dropouts: n=3, reasons not described. Results critical appraisal: high risk of performance and detection bias, adequate allocation concealment, low risk of attrition and reporting bias, unclear method of randomization and unclear risk of other bias.

Table 159 – Diarrhoea: evidence table RCTs loperamide

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Yeoh 1993	• Design: RCT, crossover design • Source of funding: National Health and Medical Research Council of Australia, Janssen Pharmaceutica (Beerse, Belgium). • Setting: Departments of Radiation Oncology, Medicine, and Nuclear Medicine, Royal Adelaide Hospital, Adelaide, South Australia • Sample size: n=20 • Duration: 14 days	Eligibility criteria: patients with persistent diarrhoea 3-22 years after therapeutic pelvic irradiation for carcinoma of the genitourinary tract, not having had gastrointestinal surgery (except for appendicectomy) Patient characteristics: median age (range) 73 years (42-90); M/F: 4/16; median body weight 65 kg (54-114 kg) and median body mass index (BMI) 25,1 (18-8-31-4) Comparable groups	Loperamide oxide tablets (Janssen Pharmaceutica Beerse, Belgium) 2 dd 3 mg po Vs. Placebo (identical tablets without loperamide oxide) Cross over design, 14 days for each intervention, separated by a wash-out period of 14 days.	Gastrointestinal symptoms Median number of bowel actions per week (range): 13.5 (6-39) vs. 19 (9-53); p<0.001 Stool frequency per 3 days (median and range): 5 (1-10) vs. 7 (2-14); p<0.05 Adverse effects “No significant adverse effects were reported”	Risk of bias: low Dropouts: n=2 (could not cope with the programme of required evaluations) Results critical appraisal: unclear risk of selection bias, low risk of bias for all other items.

Appendix 6.10. Cardiac toxicity

Table 160 – Cardiac toxicity: evidence table systematic review

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
Van Dalen 2011	• SR • Funding: none • Search date: November 2010 • Databases: CENTRAL, MEDLINE, EMBASE, in addition: reference lists of	Cancer patients (children and adults) receiving anthracyclines	Anthracycline therapy together with a cardioprotective agent versus anthracycline therapy with or without a placebo	Dexrazoxane (10 studies, 1619 participants) Overall survival (4 studies): HR 1.04 [95%CI 0.88 to 1.23] Progression free survival (4 studies): HR 1.01 [95%CI 0.86 to 1.18] Occurrence of clinical heart failure (8 studies): RR 0.18 [95%CI 0.10 to 0.32] Occurrence of heart failure (clinical and	Quality SR: low risk of bias Quality included studies: Dexrazoxane (10 studies) The risk of bias in the included studies varied. In many studies bias could not be ruled out due to poor reporting.

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
	relevant articles, conference proceedings of the International Society for Paediatric Oncology (SIOP) and the American Society of Clinical • Oncology (ASCO), ongoing trials registers			subclinical heart failure combined) (5 studies): RR 0.29 [95%CI 0.20 to 0.41] Response rate (6 studies): RR 0.89 [95%CI 0.78 to 1.02] Adverse effects (7 studies): thrombocytopenia, abnormal platelet count at nadir, abnormal platelet count at recovery, neutropenia, abnormal granulocyte count at nadir, abnormal granulocyte count at recovery, abnormal white blood cell count at recovery, stomatitis, pain on injection, anorexia, alopecia, phlebitis, diarrhoea, fever, vomiting, neurotoxicity and secondary malignant disease: no significant differences between treatment groups. Abnormal white blood cell count at nadir grade 3 or 4: RR 1.16 [95%CI 1.05 to 1.29] Anaemia: RR 1.40 [95%CI 1.08 to 1.81] Nausea: RR 0.69 [95%CI 0.49 to 0.94] Platelets, infection not otherwise specified and unknown and pulmonary adverse events: significant difference in favour of the control group (RR's: 2.45 [95%CI 1.79 to 3.36]; 1.59 [95%CI 1.25 to 2.03]; 4.41 [95%CI 1.29 to 15.05], respectively).	

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