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

SUMMARY

SUPPORTIVE TREATMENT FOR CANCER – PART 3: TREATMENT OF CANCER PAIN: MOST COMMON PRACTICES

Belgian Health Care Knowledge Centre

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GOOD CLINICAL PRACTICE

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MARIJKE EYSSEN, NADIA BENAHMED, ANJA DESOMER

2013 www.kce.fgov.be

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FOREWORD

No one is a stranger to pain and as pain is part of our very existence and an unavoidable part of the disease, it makes us all the more vulnerable. Cancer pain moves us even more deeply, if only on account of the connotation associated with the word cancer itself. The seriousness of the disease makes the pain experience a more complex phenomenon as it does not only encompass physical aspects but also psychological, social and spiritual aspects. And even though it is the patient who suffers the pain, it also affects his nearest and dearest who can only stand by and watch. Impossible as it may be to grasp the meaning of pain objectively, it still calls for a scientific approach if we want to find the most effective means to tackle and treat it.

Over the years, the KCE has gained considerable expertise in developing guidelines on cancer treatment. These also included guidelines on the necessary supportive care to help patients deal with the discomforts and side effects of cancer and cancer treatments, irrespective of the type of cancer they are suffering from. This guideline, which deals with cancer pain across the board, is not any different.

It was drawn up in collaboration with a panel of experts composed of both clinicians and representatives of patient organisations. It was also presented for discussion to a group of stakeholders that did not only consist of representatives of the professional and patient organisations but also of patients who had first-hand experience of the disease and suffering.

This original approach allowed us to formulate recommendations which, not entirely unexpectedly, recognise patients' ability to assess their own pain, and give them a central role in tackling pain, with the help of the necessary information.

It is now up to the College of Oncology to ensure that this guideline is put into practice by disseminating it among all care providers in an attractive format.

We would like to thank all of you who were involved in this process; your involvement attested to the tremendous interest there is in tackling pain suffered by cancer patients. This process also brought to light that it is indeed possible to approach the phenomenon of pain, which at times seems to defy all rationality, in a rigorous manner.

Christian LÉONARD
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ABSTRACT

1. INTRODUCTION

The development of guidelines 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 developed on a series of specific cancer types (breast cancer, colorectal cancer, upper gastrointestinal cancer etc. (www.kce.fgov.be)).

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 three reports on the supportive care of adult cancer patients. The first report (KCE report n° 185; 2012) deals with exercise treatment; the second report (KCE report n° 191; 2012) deals with prevention and treatment of adverse events related to chemotherapy and/or radiotherapy.

This report is the third and last one in this series on supportive care in adult cancer patients. It aims to formulate, on the basis of current scientific evidence, recommendations relative to the treatment of cancer-related pain. 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, surgeons, radiation oncologists, nuclear medicine specialists, anesthesiologists and pain specialists, palliative care specialists, general practitioners, medical specialists involved in the care of cancer patients, nurses, pharmacists etc. It could also be of particular interest for patients, for hospital managers and policy makers.

1. METHODS

The scope of the study included adults suffering from any type of cancer and at any stage of the disease. Only the phase of terminal care was excluded, defined as care during the process of dying, i.e. from days to a few weeks before death. Nine medical interventions for the treatment of cancer pain were selected by health care professionals involved in the care for cancer patients. The same group of professionals also defined the critical and important outcomes to be considered.

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 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: OVID Medline, EMBASE and CENTRAL. Searches were run between July 2012 and November 2012. Additionally, guideline databases and websites of international oncology guideline developers were searched for evidence-based guidelines relevant to the topic. 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. Recommendations not based on scientific evidence, but related to overall standards of practice and/or to ethical considerations, were formulated as "Good Clinical Practice".

A draft of good clinical practice standards and recommendations was discussed on several occasions with a multidisciplinary panel of experts (the Guideline Development Group). This panel included professionals and representatives of patient associations (see colophon). Based on these discussions, conclusions and recommendations were adapted. Next, all recommendations prepared by the KCE team and the consulted experts were discussed with a panel of stakeholders consisting of patients, representatives of professional associations and representatives of patient associations (see colophon). Based on these discussions, conclusions and recommendations were adapted to their final formulation.

2. HOW TO USE THIS GUIDELINE?

The reader is invited to follow the chart to be guided to the ad hoc recommendations according to the cancer patient's needs.

At each step of the flow chart physicians should, depending on their own expertise, consider collaboration with a physician with expertise in pain treatment or palliative care.

Figure 1 – How to use this guideline?

Continuation of Figure 1 (Table), see next page

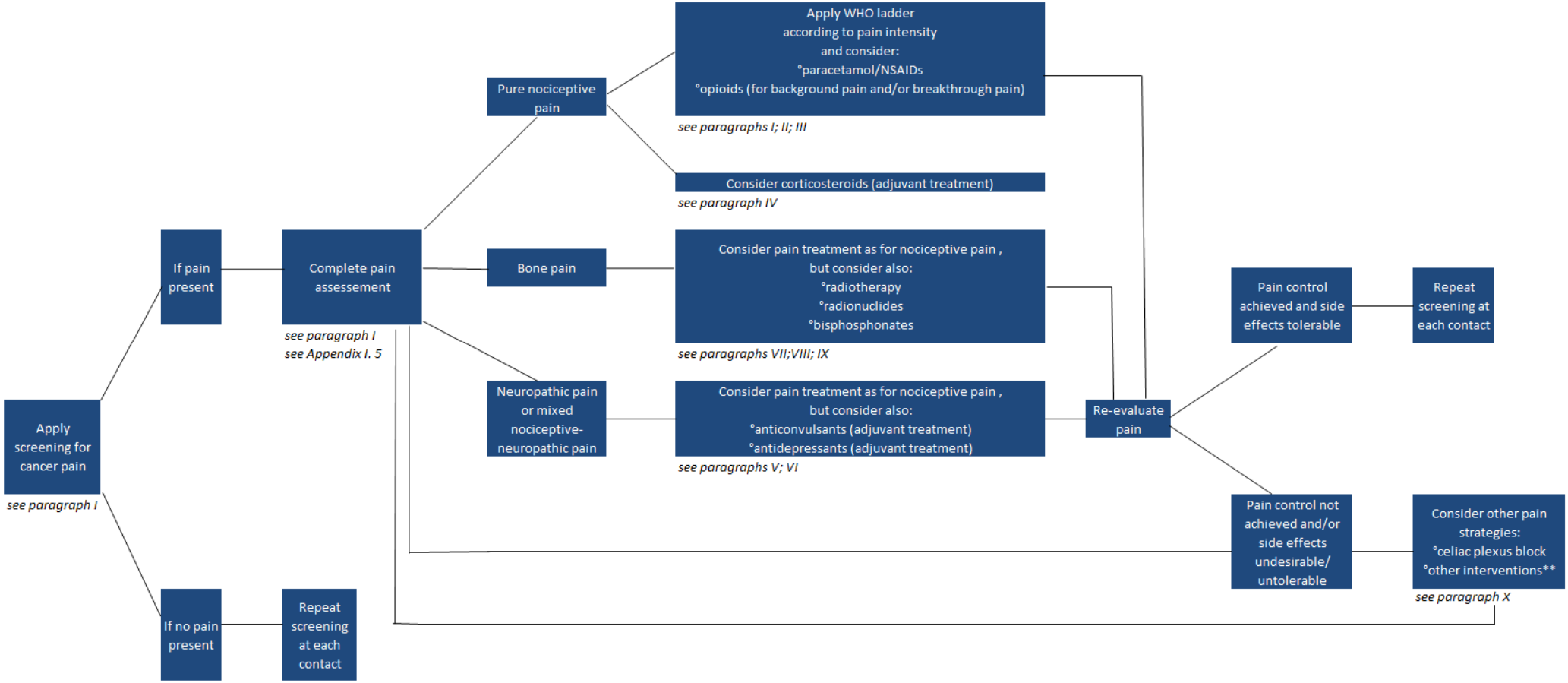


Figure 1 (continuation) – How to use this guideline?

Treatment options not included in this report are:

1. **Interventional pain treatment:

- epidural/intrathecal drug administration: see KCE report n° 189 (2012)[1]
- neuro-ablative treatment including peripheral nerves, visceral block of plexus hypogastricus, other (e.g. chordotomy)
- neurostimulation of the spinal cord: see KCE report n° 189 (2012)[1]
- neurostimulation of peripheral nerves, deep brain stimulation

2. Pharmacotherapy:

- topical agents (e.g. lidocaine)
- other drugs for neuropathic pain relief (e.g. intravenous lidocain, baclofen, clonazepam, ketamine)
- other drugs for painful bone metastases (e.g. calcitonine)
- other drugs for bowel obstruction (e.g. anticholinergic drugs, somatostatine analogue)

3. Disease-modifying treatment**:**

surgery, chemotherapy, radiotherapy for soft-tissue masses etc

4. Complementary or alternative treatment modalities:

e.g. acupuncture: see KCE report 148, 153, 154[2-4]

Information regarding to exercise treatment, and to prevention and treatment of adverse events related to chemotherapy and radiotherapy can be found in other KCE reports (see KCE report 185 and report 191)[5, 6]

3. RESULTS

Below, some general principles of pain treatment and overall GCP standards are outlined (paragraph I). For each of the studied interventions, the recommendations are presented (paragraph II to X).

With a few exceptions, the evidence supporting the recommendations was of low or very low quality.

For an extensive review of the evidence, see the scientific report.

3.1. Basic principles

3.1.1. Assessment of pain

Good Clinical Practice

- Prior to treatment, an accurate assessment should be performed to determine the cause, type and severity of pain, and its functional and psychosocial impact on the patient. Validated assessment questionnaires should be used as well as clinical evaluation and, if necessary, medical investigations. The assessment should be repeated if treatment does not alleviate the pain even after careful adjustment.
- The patient is the most reliable assessor of pain and should, whenever possible, be the prime assessor of his/her pain.
- Patients with cancer pain should have their pain monitored regularly using unidimensional pain instruments such as visual analogue scales (VAS), numerical rating scales (NRS) or verbal rating scales (VRS). Multidimensional pain instruments should be used for complex pain syndromes. Examples are the McGill Pain questionnaire and the Brief Pain Inventory, which incorporate NRS and VRS. Observational pain rating scales should be preferred in patients who cannot complete a self assessment scale.
- The minimal objective of pain treatment should be a clinically relevant decrease of the pain (on a 0-10 scale, a decrease by 2 points, and/or a decrease of 30%, and preferentially a pain intensity <5).
- Patients should be given information about pain and instruction about pain management; they should be encouraged to take an active role in their pain management.

3.1.2. Pain intensity and the WHO analgesic ladder

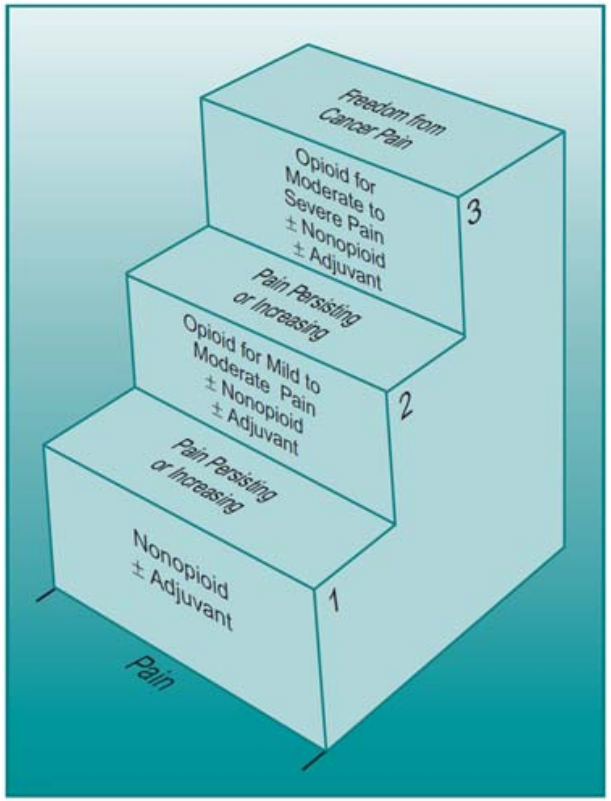
In 1986, the World Health Organization (WHO) launched a three-step analgesic ladder as a systematic approach to cancer pain control (see Figure 2). This ladder is based on intensity of pain. In this report, mild pain is defined as (1- 4) on a numerical rating scale (0 - 10); moderate pain as (>4 - 7); and severe pain as (>7 - 10).

The WHO ladder prescribes the use of non-opioid analgesics (paracetamol/NSAIDs) for mild or moderate cancer pain (Step I); if the pain persists, the use of weak opioid analgesics can be considered, combined or not with non-opioid analgesics (Step II). If the patient is in severe pain, the use of strong opioid analgesics can be considered, combined or not with non-opioid analgesics (Step III). In the WHO approach, strong opioids combined or not with non-opioid analgesics can also be considered if mild or moderate pain persists despite the use of weak opioids.

Examples of WHO Step II opioids include codeine and tramadol. Examples of WHO Step III opioids are morphine, hydromorphone, oxycodone, methadone, fentanyl, buprenorphine. At each step, adjuvant drugs should also be considered. Adjuvant drugs are drugs that have a primary indication that is not analgesia, but they can be used as analgesics under certain circumstances (e.g. antidepressants, anticonvulsants).

There is evidence that by application of the WHO analgesic ladder pain relief can be achieved in 75-90% of cancer patients (very low level of evidence). The WHO analgesic ladder does not include interventional pain strategies, e.g. celiac plexus block.

Figure 2 – The 3-step analgesic ladder developed by the World Health Organization (WHO)



Source: Miguel R. Interventional treatment of cancer pain: the fourth step in the World Health Organization analgesic ladder? Cancer Control. 2000;7(2):149-56

Recommendation

The principles of treatment outlined in the WHO analgesic ladder should be followed when treating pain in patients with cancer (very low level of evidence; strong recommendation).

3.1.3. *Information to patients*

Good Clinical Practice

- Patients should be informed on the benefits and potential side-effects associated with the use of pain treatment (NSAIDs, opioids, corticosteroids, antidepressants, anticonvulsants, radiotherapy schemes, bone-seeking radio-isotopes, bisphosphonates, celiac plexus block). Their preferences should be taken into account when deciding on the treatment.

3.2. NSAIDs and paracetamol

Recommendation

- Paracetamol at a correct dose (1 gr/dose; up to 4 gr/day for adults; up to 3gr/day for older patients) and/or an NSAID are recommended as the first-line treatment option for mild to moderate cancer pain (WHO step I) (paracetamol: very low level of evidence, NSAID: moderate level of evidence). An NSAID can be preferred for specific indications, such as bone pain or inflammatory conditions (very low level of evidence). Relative contra-indications such as pre-existing gastro-intestinal, cardiovascular, hematological, renal or hepatic conditions should be taken into consideration, and side-effects should be carefully monitored and instructed to the patient, especially with NSAIDs (strong recommendation).
- It is not possible to recommend for or against one NSAID over another in patients with cancer pain, but the individual sensitivity of each patient should be taken into account (very low level of evidence; weak recommendation).
- The available evidence does not allow to draw firm conclusions on the comparison of analgesic effect or short term side-effects between NSAIDs, and WHO step II or step III opioids in the treatment of moderate to severe cancer pain. Therefore it is not possible to recommend on whether an NSAID or a Step II or Step III opioid should be recommended as first-line treatment option for moderate to severe cancer pain (very low level of evidence).
- There are indications that NSAIDs as add-on to WHO step III opioids, in comparison to step III opioids alone, offer no advantage or offer a low clinical advantage only (<25% difference), for the treatment of mild or moderate to severe cancer pain. It is not possible to draw firm conclusions from the literature on the comparison of short term adverse events in both groups. Therefore the use of NSAIDs as add-on to a stabilized regimen of WHO step III opioids should not be considered as a routine treatment option (very low level of evidence; weak recommendation).
- There are indications that paracetamol as add-on to a stabilized regimen of WHO step III opioids for mild cancer pain shows no difference in pain relief as compared to the step III opioids alone. Therefore the use of paracetamol as add-on to a stabilized regimen of WHO step III opioids should not be considered as routine treatment (very low level of evidence; strong recommendation).

3.3. Opioids

For background information on opioid dosing, titration, and frequent adverse effects such as constipation, see scientific report chapter 4.3.1.

Recommendation

General principles

- Strong interindividual differences in response to opioids are a well-known clinical phenomenon, underpinned by recent scientific insights in genetic variation in opioid metabolism. Therefore, all opioids should be titrated according to individual analgesic response and occurrence of side-effects (very low level of evidence; strong recommendation).
- Based on clinical experience, oral delivery of opioids is effective and simple. Therefore, the oral route should be used for the administration of opioids, if practical and feasible. However, depending on the evolution of the patient's condition and taking into account his/her preferences, the route of administration should be adjusted dynamically and transdermal, subcutaneous, or intravenous opioid administration should be considered. Rarely, intrarectal, intramuscular or intraspinal administration can be considered. Slow release oral opioids cannot be administered by gastric tube since it is not allowed to crush these formulations. However, one slow release oral formulation is an exception since the capsules have been specifically developed to be opened although they should not be crushed (slow release hydromorphone: Palladone Slow Release®) (very low level of evidence; strong recommendation).

Weak opioids

- If paracetamol/NSAIDs no longer adequately relieve(s) the pain, an opioid drug should be considered. In line with the principles of the WHO analgesic ladder, weak opioids (Step II) should be considered in the management of mild to moderate cancer pain after conventional treatment with paracetamol/NSAIDs failed, and patient outcomes should be monitored (very low level of evidence; strong recommendation). This is based on the following evidence. There is conflicting evidence as to the question whether combining an NSAID or paracetamol with a WHO step II opioid is superior to an NSAID or paracetamol alone in patients with cancer pain (very low level of evidence). There are indications that oral codeine and tramadol are effective and well-tolerated drugs as compared to placebo in the management of mild to moderate cancer pain never treated with opioids (low level of evidence). There are indications that initiating strong opioids (Step III) instead of weak opioids (Step II) for mild to moderate cancer pain after conventional treatment with NSAIDs and/or paracetamol failed, leads to better pain control but at the cost of more side effects (very low level of evidence).
- When weak opioids are considered in the management of mild to moderate cancer pain after conventional treatment with paracetamol/NSAIDs failed, codeine and tramadol can be considered as equivalent treatment options, and the choice for one of them should depend on the tolerance of each individual patient (very low level of evidence; weak recommendation). This is based on the following evidence. There are indications that there is no difference in efficacy between tramadol and codeine combined with paracetamol (low level of evidence). RCTs directly evaluating other combinations of weak opioids against each other are not available for this indication.

Strong opioids

- Oral morphine should be considered as the drug of first choice and the gold standard for moderate to severe cancer pain (very low level of evidence; strong recommendation). This is based on the following evidence. There are indications that the effectiveness of oral morphine in the treatment of cancer pain compares well to other available strong opioids (oxycodone, hydromorphone, methadone) when titration to effect is performed (very low level of evidence). There are indications that for oral morphine treatment side effects are common, but that intolerable adverse effects occur in a small number of patients only (4%) and that non-respons is infrequent (very low level of evidence).
- Depending on the tolerability of each individual patient, other oral strong opioids in their equi-analgesic dose can be considered as an alternative to oral morphine in the first-line treatment of moderate to severe cancer pain. Likewise, transdermal fentanyl, in an equi-analgesic dose, can be used as an alternative to oral opioids for moderate to severe cancer pain, after a stable opioid regimen has been established (very low level of evidence; strong recommendation). This is based on the following evidence. There are indications that oral morphine, oral oxycodone, oral hydromorphone and transdermal fentanyl, when titration to effect is performed, have a similar efficacy and toxicity in cancer-related pain (very low level of evidence).
- It is not possible to draw conclusions from the literature on the relative efficacy and side-effects of transdermal buprenorphine as compared to oral morphine, to other oral opioids or to transdermal fentanyl for moderate to severe cancer pain. Based on its pharmacological properties and mixed working mechanism, oral or transdermal buprenorphine might be considered as a treatment option (very low level of evidence; weak recommendation).
- It should be considered to restrict the initiation of a treatment with methadone for analgesic purposes (such as in cancer patients with moderate to severe pain) to medical experts in pain treatment or palliative care. Once optimal dosage has been identified, maintenance treatment can be carried out by another physician (very low level of evidence; strong recommendation). This is based on the following evidence. The pharmacological properties of methadone suggest that it might be useful in the treatment of neuropathic pain. However, based on the available evidence it is not possible to conclude on the superiority of methadone to morphine in patients with neuropathic cancer pain (very low level of evidence). There are indications that oral methadone and morphine have a similar efficacy in the treatment of nociceptive or mixed types of moderate to severe cancer pain (very low level of evidence). Because of its pharmacokinetics and pharmacodynamics, the adverse effects of methadone may become more prominent with repeated dosing. One of its specific although rare adverse effects is prolongation of the QT interval leading to cardiac dysrhythmias, especially at high doses.
- Individual patient assessment should determine the appropriate treatment option in cancer patients with neuropathic pain or with a mixed type of pain including neuropathic components, and opioids can be considered alone, or combined with adjuvant analgesics (antidepressants, anticonvulsants) (very low level of evidence; strong recommendation).

Breakthrough cancer pain

Breakthrough pain is a transient increase in pain intensity over background pain. It is a common and distinct component of cancer pain that is typically of rapid onset, severe in intensity, and generally self-limiting with an average duration of 30 minutes. Two subtypes of breakthrough pain have been described: incident pain, which is precipitated by factors such as movement and is predictable; and spontaneous pain, which occurs in the absence of a relationship to specific activities, and which is not predictable. It is important to differentiate between breakthrough pain and end of dose failure, the latter resulting from an inadequate analgesic dose or too long an interval between administrations.

- For cancer patients on a stable around-the-clock (ATC) regimen of opioids presenting with breakthrough pain, the first aim should be to optimize the ATC regimen to differentiate between breakthrough pain and end of dose pain (very low level of evidence; strong recommendation).

- Breakthrough pain in cancer patients on a stable and optimized ATC regimen of opioids can be treated by oral or intranasal fentanyl regardless of which opioid is used for the maintenance therapy. In Belgium, sublingual fentanyl tablets and intranasal fentanyl spray are available but not reimbursed by the compulsory health insurance system (July 2013). Although there are indications that oral and intranasal fentanyl might be superior, oral morphine (e.g. as a syrup) can be considered as an effective and cheaper alternative in Belgium (weak recommendation). This is based on the following evidence. For cancer patients on a stable and optimized ATC regimen of opioids, different formulations of oral and intranasal fentanyl are effective and safe as compared to placebo in the treatment of breakthrough cancer pain (low level of evidence). Publications are lacking on the effectiveness and safety in this indication of immediate release oral morphine as well as other forms of oral opioids commonly used for breakthrough pain (oxycodone, hydromorphone). No conclusions can be drawn on whether one form of oral or intranasal fentanyl is superior to another (very low level of evidence). There are indications that oral transmucosal fentanyl citrate and fentanyl pectin nasal spray might be superior to immediate release morphine sulfate (low level of evidence). No conclusions can be drawn on whether one of the other oral opioids is superior to another (very low level of evidence).
- Based on expert opinion, it should be considered to start the medication for breakthrough pain immediately at a dose proportional to the total ATC opioid dose; and then titrate it further in the same way as the around-the-clock opioid medication is titrated (very low level of evidence; strong recommendation).
- Both intravenous and subcutaneous morphine titration is adequate for the treatment of patients with persisting exacerbations of cancer pain, after adequate oral opioid treatment has failed (very low level of evidence; weak recommendation).

Opioid rotation

Opioid rotation or switching is the term given to the clinical practice of substituting one strong opioid with another, in an attempt to achieve a better balance between pain relief and side effects.

- The available evidence does not allow to conclude on the effectiveness of opioid rotation in patients with inadequate pain relief and intolerable opioid-related toxicity or adverse effects. However, opioid rotation can be a treatment option in some of these patients, after a thorough reassessment of pain management has been performed (very low level of evidence; strong recommendation).

Combination of Opioids

The available evidence does not allow to conclude on the effectiveness of the concurrent use of two strong opioids for background analgesia in cancer patients with inadequate pain relief and/or intolerable opioid-related adverse effects while using a single strong opioid. However, the concurrent use of two carefully selected strong opioids can be a treatment option in some of these patients, after a thorough reassessment of pain management has been performed. It should be considered to restrict the initiation of such treatment to medical experts in pain treatment or palliative care. Once optimal dosage has been identified, maintenance treatment can be carried out by another physician (very low level of evidence; weak recommendation).

3.4. Corticosteroids

Recommendation

Corticosteroids alone or combined with other therapeutic options can be considered in cancer patients for pain related to a mass effect of the tumour, e.g. headache caused by raised intracranial pressure, pain due to spinal cord compression, multifocal bone pain, abdominal pain from liver capsule distention, intestinal obstruction. They may also be used to help manage other symptoms in cancer patients at an advanced or terminal stage of the disease, e.g. anorexia, nausea, fatigue, general weakness or feelings of malaise and depression. Side-effects should be monitored carefully (very low level of evidence; strong recommendation).

3.5. Antidepressants

Recommendation

It is not possible to recommend for or against the use of antidepressants for the treatment of neuropathic pain in cancer patients. Individual patient assessment should determine the appropriate treatment option in cancer patients with neuropathic pain or with a mixed type of pain including neuropathic components, and antidepressants can be considered alone, sequentially, or with other analgesic agents, including opioids. Their effectiveness and side-effects should be monitored carefully. This recommendation is based on consensus that the proven benefit of antidepressants (e.g. amytriptiline) as a first-line drug to treat neuropathic pain in non-cancer patients can be extended to patients suffering from neuropathic cancer pain (very low level of evidence, strong recommendation).

3.6. Anticonvulsants

Recommendation

- The available evidence on the use of gabapentin or pregabalin for the treatment of neuropathic pain in cancer patients does not allow to recommend for or against it (very low level of evidence). Individual patient assessment including sensory symptoms, should determine the appropriate treatment option in cancer patients with neuropathic pain or with a mixed type of pain including neuropathic components, and anticonvulsants, including gabapentin and pregabalin, can be considered alone, sequentially, or with other analgesic agents, including opioids. Their effectiveness and side-effects should be monitored carefully. This recommendation is based on a consensus that the proven benefit of anticonvulsants as first-line drug to treat neuropathic pain in non-cancer patients can be extended to patients suffering from neuropathic cancer pain (very low level of evidence; strong recommendation (gabapentin), weak recommendation (pregabalin)).
- Carbamazepine is the preferred anticonvulsant to treat neuropathic pain resulting from cancerous involvement of the trigeminal nerve. This recommendation is based on a consensus that the demonstrated effectiveness of carbamazepine for the treatment of trigeminal neuralgia in non-cancer patients can be extended to cancer patients (very low level of evidence; strong recommendation).
- It is not possible to recommend whether or not anticonvulsants should be preferred over antidepressants, in the first-line or add-on treatment of neuropathic cancer pain (very low level of evidence).

3.7. Radiotherapy for painful bone metastases

Recommendation

- Aspects such as life expectancy, clinical condition of the patient and curability of the bone metastases should be considered when deciding on the preferred radiotherapy scheme for pain relief in bone metastases (very low level of evidence; strong recommendation).
- The use of single fraction radiotherapy for short term complete or partial pain relief in patients with uncomplicated bone metastases is recommended as treatment of first choice. However, the definitive decision on the treatment modality should also take into consideration the preferences of the patient after he/she has been well-informed; and aspects such as life expectancy, clinical condition of the patient and curability of the bone metastases should be considered (strong recommendation). This is based on the following evidence. It is plausible that single and multiple fraction radiotherapy are equally effective for short term (4 to 8 weeks) complete or partial pain relief in patients with uncomplicated bone metastases, regardless the primary tumour site (moderate level of evidence). It is also plausible that radiotherapy by a single fraction is associated with more retreatments (moderate level of evidence) and more pathological fractures (low level of evidence), but the overall rate of retreatment and pathological fractures is relatively low.
- The use of a 8-Gy single fraction radiotherapy rather than a 4-Gy single fraction radiotherapy for short term (4 to 8 weeks) complete or partial pain relief in patients with uncomplicated bone metastases is the option of first choice, after aspects such as life expectancy and clinical condition of the patient, curability of the bone metastases and patient preferences have been taken into account (very low level of evidence; weak recommendation).
- A multimodal pain treatment approach should be considered for uncomplicated or complicated bone metastases. Besides local treatment with single or multiple fraction radiotherapy, systemic therapies should also be considered throughout the treatment course, e.g. NSAIDs, opioids, cytotoxic chemotherapy, anticancer hormone therapy etc. This is supported by the significant number of patients with uncomplicated bone metastases who do not obtain total pain relief from single or multiple fraction radiotherapy (very low level of evidence; strong recommendation).
- Decompressive surgical tumor resection with or without stabilization of the spine and followed by radiotherapy is the option of first choice in patients with metastatic spinal cord compression, after aspects such as duration of the spinal cord compression, status and type of the disease, prior and available anticancer therapies, use of corticosteroids, life expectancy, and patient preferences have been taken into account (very low level of evidence; weak recommendation).
- There is insufficient evidence to advice on the preferred radiation dose for the treatment of pain due to metastatic spinal cord compression (very low level of evidence).
- Hemibody irradiation can be a treatment option in patients with widespread bone metastases who suffer from pain after all systemic pain treatment options failed, and after life expectancy and patient preferences have been taken into account (very low level of evidence; weak recommendation).
- There is insufficient evidence to advice on the preferred schedule for hemibody irradiation as treatment of pain in patients with widespread bone metastases (very low level of evidence).

3.8. Radionuclides for painful bone metastases

Recommendation

- When conventional treatment failed, bone-seeking radio-isotopes can be considered as a secondary option to obtain complete or partial (more than 50%) pain relief in the short and medium term (up to 6 months) for widespread painful osteoblastic bone metastases in cancer patients regardless of the primary tumour site (low level of evidence; weak recommendation).
- It is recommended to inform patients that this treatment can be associated with an increased incidence of severe adverse events, such as hematological toxicity and in particular leucocytopenia (low level of evidence; strong recommendation).

3.9. Bisphosphonates for painful bone metastases

Recommendation

Bisphosphonates cannot be considered as first-line, purely analgesic treatment option of metastatic bone pain in the short, medium or long term, given the available evidence on efficacy (very low level of evidence), and on possible adverse events (moderate level of evidence; strong recommendation). This report does not deal with the usefulness of bisphosphonates for other indications in patients with metastatic bone involvement, e.g. hypercalcemia, pathological fractures, impending fractures, spinal cord compression.

3.10. Celiac Plexus Block

Recommendation

- Celiac plexus block (CPB) can be considered as a pain treatment option for patient suffering from pancreatic cancer, although CPB should not be the treatment of first choice. Patients should be timely informed on this treatment option. This recommendation is based on the limited short term (around 4 weeks) effectiveness of CPB on pain as compared to standard analgesic treatment, on its short term possible positive effect on opioid consumption, on the need to repeat the procedure and on the rare but important complications that can be associated with the procedure; it takes into account that the life expectancy of patients with pancreatic cancer is mostly limited (very low level of evidence; weak recommendation).
- It is recommended to inform patients with pancreatic cancer clearly on the limited short term (around 4 weeks) effectiveness of CPB on pain as compared to standard analgesic treatment, but also on the short term (around 4 weeks) possible positive effect on opioid dosing. They should also be informed on the need to repeat the procedure over time, and on the possible side-effects and complications of CPB (very low level of evidence; strong recommendation).
- A multimodal pain treatment approach should be considered for cancer pain. In patients who underwent CPB, other analgesic therapies should still be considered throughout the treatment course, e.g. NSAIDs, opioids (very low level of evidence; weak recommendation).

4. LIMITATIONS

Due to time constraints, the scope of this report needed to be focused. Choices were made in collaboration with health professionals involved in the care for cancer patients. Consequently, the report is not comprehensive and does not discuss all treatment options for cancer patients suffering from pain. For an overview of the excluded treatment options, see Figure 1.

With a few exceptions, publications on combined interventions corresponding to the inclusion criteria of the report could not be found in the literature. This could be a shortcoming for the clinician who wants to combine different treatments in order to obtain an optimal pain relief.

In this report the focus is on the effectiveness of specific medical interventions, without taking into account the organization of health services. In clinical practice, a multidisciplinary approach should be encouraged. This approach should not only cover the medical needs of the patient but should also consider the psychosocial needs related to cancer pain.

For most of the included interventions, the evidence supporting the recommendations was of low or very low quality. The selected trials were often poorly designed, and/or the outcomes were poorly reported. All this is reflected in the level of evidence as evaluated with the GRADE system. This highlights the need for well-conducted high-quality research.

It can be considered as a limitation that this report focused on (systematic reviews of) RCTs. For some outcome domains of the selected interventions, no or very few RCTs with several methodological flaws were identified, leading to gaps in the evidence base. An additional search for observational studies would have covered these gaps, but was not feasible within this project.

POLICY RECOMMENDATIONS[a]

To the College of Oncology

- **The implementation of this guideline should be facilitated by the College of Oncology (www.collegeoncologie.be).**
- **This guideline should be updated every 5 years. If, in the meantime, important new evidence would become available, this should be mentioned on the website of the College of Oncology (www.collegeoncologie.be).**

To the scientific and professional associations

- **The dissemination of this guideline should be supported by transforming this material into attractive and user-friendly tools tailored to specific groups of caregivers. The associations should also play a key role in the dissemination through diverse channels such as websites or continuing medical education.**

To the research community

- **High-quality studies are needed to investigate treatments that currently are often used for cancer pain, but have been little investigated, e.g. weak opioids.**

[a] The KCE has sole responsibility for the recommendations.

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