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Management of cancer pain: ESMO Clinical Practice Guidelines†

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incidence of pain

According to a systematic review of the literature, pain prevalence ranges from 33% in patients after curative treatment to 59% in patients on anticancer treatment and to 64% in patients with metastatic, advanced or terminal phase [1]. No difference in pain prevalence was found between patients undergoing anticancer treatment and those in an advanced or terminal phase of the disease [1]. Factors influencing the development of chronic pain in cancer survivors who have completed treatment include peripheral neuropathy due to chemotherapy, radiation-induced brachial plexopathy, chronic pelvic pain secondary to radiation and postsurgical pain [2]. Pain has a high prevalence in specific cancer types such as pancreatic (44%) and head and neck cancer (40%) [3].

Moreover, another systematic review of the literature showed that nearly half of cancer patients were under-treated, with a high variability across study designs and clinical settings [4]. Recent studies conducted both in Italy and pan European [5, 6] confirmed these data, showing that different types of pain or pain syndromes [7, 8] were present in all phases of cancer (early and metastatic) (Table 1) and were not adequately treated in a significant percentage of patients, ranging from 56% to 82.3%. In a prospective study [9], the adequacy of analgesic care of cancer patients was assessed by means of the Pain Management Index in 1802 valid cases of in- and outpatients with advanced/metastatic solid tumors enrolled at centers specifically devoted to cancer and/or pain management (oncology/pain/palliative centers or hospices). The study showed that, even in these centers, patients were still classified as potentially under-treated in 9.8%–55.3% of the cases.

Contrary to the percentage of incidence of pain reported in hematologic patients in past literature, a significant proportion of patients with lymphoma and leukemia may suffer from pain not only in the last months of life (83%) [5, 10], but also at the time of diagnosis and during active treatment [10].

Despite published guidelines and educational programs on the assessment and treatment of cancer-related pain, in any stage of oncological disease, unrelieved pain continues to be a substantial worldwide public health concern in patients with either solid or hematological malignancies. Cancer-related pain may be presented as a major issue of healthcare systems worldwide if we consider that the incidence of cancer was 12.667.470 new cases in 2008 and, based on projections, it will be >15 million in 2020 [11].

assessment of patients with pain

Initial and ongoing assessment of pain and of patients with pain at any disease stage should clarify both the need for additional comprehensive evaluation and a rational plan of care. Table 2 presents the guidelines for the adequate assessment of patients with pain. The proper and regular self-reporting assessment of pain intensity (PI) with the help of validated assessment tools is the first step towards effective and individualized treatment. The most frequently used standardized scales [12] are reported in Figure 1 and are visual analogue scales (VAS), the verbal rating scale (VRS) and the numerical rating scale (NRS).

The assessment of the quality of pain improves the choice of the therapy: pain is termed nociceptive when it is caused by ongoing tissue damage, either somatic or visceral or neuropathic, if sustained by damage or dysfunction in the nervous system (Table 1) [2]. According to the literature, most patients with advanced cancer have at least two types of cancer-related pain which derives from a variety of etiologies [7, 10]. Sixty-nine percent of patients rate their worst pain at a level that impaired their ability to function [13].

recommendation

The intensity of pain and the treatment outcomes should be regularly assessed using (i) VAS, or (ii) VRS or (iii) the NRS [V, D].

In older age, the presence of limited communicative skills or of cognitive impairment such as during the last days of life

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Table 1. Causes of pain, other than cancer related pain, during natural history of cancer patient

Clinical Setting causes of pain	Acute Procedural Pain	Iatrogenic Pain due to:	Comorbidity-related pain	Pain in cancer survivors
Adjuvant setting	Diagnostic intervention Lumbar puncture ± headache Transthoracic needle biopsy Endoscopy ± visceral dilatation Bone marrow aspiration/ biopsy, Blood sampling, Central line position, Arterial line, Injections, Medication of skin ulcers Myelography and lumbar puncture Thoracocentesis	Surgery, Chemotherapy, Hormonal therapy, Target therapy Osteonecrosis of the jaw Radiation therapy Steroids can cause pain due to: skin lesions, peripheral neuropathy, mucositis aseptic head femoral necrosis, infections	Cardiovascular, Pulmonary Diabetic neuropathy, Vasomotor headache, Fibromyalgia, The comorbidity-related pain may be worsened by anticancer treatments and /or worse cancer-related pain Postherpetic neuralgia Acute thrombosis pain	Follow up procedures Persisting postsurgical pain Persisting anticancer drug-related pain Persisting radiation therapy-related pain Postherpetic neuralgia
Neoadjuvant setting	As adjuvant setting plus: Diagnostic and prognostic tissue biopsy	As adjuvant setting without surgery-related pain	As adjuvant setting	As adjuvant setting
Locally advanced setting	As adjuvant setting plus: Pleurodesis, tumor embolization, Suprapubic catheterization, Nephrostomy insertion	As adjuvant setting, plus: Cryosurgery, Radiothermoablation-high intensity focused ultrasound; Transarterial chemoembolization Spinal/epidural injection; Opioid hyperalgesia	As adjuvant setting	As adjuvant setting
Metastatic setting	As locally advanced setting plus: Liver, lung, soft tissue diagnostic biopsies, Wound care, Movement procedural pain	As neoadjuvant setting	As adjuvant setting	As adjuvant setting plus: Synergistic pain effects between iatrogenic and disease-related causes in long survivors

makes self-reporting of pain more difficult, although there is no evidence of clinical reduction in pain-related suffering. When cognitive deficits are severe, observation of pain-related behaviors and discomfort (i.e. facial expression, body movements, verbalization or vocalizations, changes in interpersonal interactions, changes in routine activity) is an alternative strategy for assessing the presence of pain (but not intensity) [14–17]. Different observational scales are available in the literature [16] but none of them is validated in different languages.

Assessment and management of pain in children are not considered in this manuscript because WHO guidelines on 'the pharmacological treatment of persisting pain in children with medical illness' are available.

recommendation

Observation of pain-related behaviors and discomfort is indicated in patients with cognitive impairment to assess the presence of pain (expert and panel consensus).

Psychosocial distress has to be assessed because it is strongly associated with cancer pain [18]. In fact, psychological distress may amplify the perception of pain-related distress and similarly, inadequately controlled pain may cause substantial psychological distress.

recommendation

The assessment of all components of suffering such as psychosocial distress should be considered and evaluated [II, B].

principles of pain management

- Inform the patients about the possible onset of pain in any stage of the disease, both during and after diagnostic interventions and as a consequence of cancer or anticancer treatments, and involve them in pain management. Patients must be encouraged to communicate with the physician and/ or the nurse about their suffering, the efficacy of therapy and side effects and to not consider analgesic opioids as a

Table 2. Guidelines for the adequate assessment of the patient with pain at any stage of the disease

1. Assess and re-assess the pain
   - causes, onset, type, site, absence/presence of radiating pain, duration, intensity, relief and temporal patterns of the pain, number of breakthrough pains, pain syndrome, inferred pathophysiology, pain at rest and/or moving
   - presence of the trigger factors and the signs and symptoms associated with the pain
   - presence of the relieving factors
   - use of analgesics and their efficacy and tolerability
   - require the description of the pain quality
     *aching, throbbing, pressure: often associated with somatic pain in skin, muscle and bone
     *aching, cramping, gnawing, sharp: often associated with visceral pain in organs or viscera
     *shooting, sharp, stabbing, tingling, ringing: often associated with neuropathic pain caused by nerve damage
2. Assess and re-assess the patient
   - clinical situation by means of a complete/specific physical examination and the specific radiological and/or biochemical investigations
   - presence of interference of pain with the patient's daily activities, work, social life, sleep patterns, appetite, sexual functioning, mood, well-being, coping
   - impact of the pain, the disease and the therapy on the physical, psychological and social conditions
   - presence of a caregiver, the psychological status, the degree of awareness of the disease, anxiety and depression and suicidal ideation, his/her social environment, quality of life, spiritual concerns/needs, problems in communication, personality disorders
   - presence and intensity of signs, physical and/or emotional symptoms associated with cancer pain syndromes
   - presence of comorbidities (i.e. diabetic, renal and/or hepatic failure etc.)
   - functional status
   - presence of opioidophobia or misconception related to pain treatment
   - alcohol and/or substance abuse
3. Assess and re-assess your ability to inform and to communicate with the patient and the family
   - Take time to spend with the patient and the family to understand their needs

therapeutic approach for dying patients [19], thus contributing to reduce opioidophobia. Patient involvement in pain management improves communication and has a beneficial effect on patients' pain experience [20].

recommendation

Patients should be informed about pain and pain management and be encouraged to take an active role in their pain management [II, B].

- Prevent the onset of pain by means of 'by the clock' administration, taking into account the half-life, bioavailability and duration of action of different drugs;

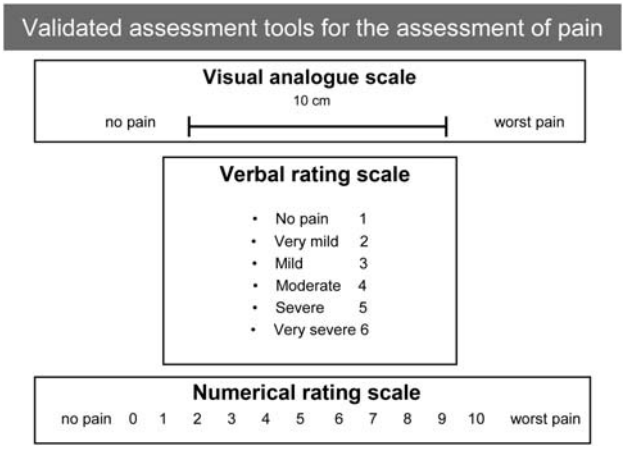


Figure 1 Validated and most frequently used pain assessment tools.

recommendation

Analgesic for chronic pain should be prescribed on a regular basis and not on an 'as required' schedule [V, D].

- Prescribe a therapy which can be administered simply and easily managed by the patients themselves and their families, especially when the patient is cared for at home. The oral route appears to be the most suitable to meet this requirement, and, if well tolerated, it must be considered as the preferred route of administration [21–26];

recommendation

The oral route of administration of analgesic drugs should be advocated as the first choice [IV, C].

- Assess and treat breakthrough pain (BTP) defined as 'a transitory flare of pain that occurs on a background of relatively well controlled baseline pain' [27]. Typical BTP episodes are of moderate to severe intensity, rapid in onset (minutes) and relatively short in duration (median 30 min) [27].

recommendation

Rescue dose of medications (as required or prn) other than the regular basal therapy must be prescribed for BTP episodes [V, D].

- Tailor the dosage, the type and the route of drugs administered according to each patient's needs. The type and dose of analgesic drugs are influenced by the intensity of pain and have to be promptly adjusted to reach a balance between pain relief and side effects. The rescue doses (prn) taken by the patients are an appropriate measure of the daily titration of the regular doses. An alternative route for opioid administration should be considered when oral intake is not possible because of severe vomiting, bowel obstruction, severe dysphagia or severe confusion, as well as in the presence of poor pain control which requires rapid dose escalation and/or in the presence of oral opioid-related adverse effects.

pain management

In 1986, the World Health Organization (WHO) proposed a strategy for cancer pain treatment based on a sequential three-step analgesic ladder from non opioids to weak opioids to strong opioids according to PI [28]. Twenty years after the publication of the first edition [21], the WHO cancer pain relief program remains the reference point for pain management. According to WHO guidelines, opioid analgesics are the mainstay of analgesic therapy and are classified according to their ability to control pain from mild to mild–moderate to moderate–severe intensity [25, 29–31].

Opioid analgesics may be combined with nonopioid drugs such as paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) (Algorithm 1) and with adjuvant drugs [32, 33].

recommendation

The analgesic treatment should start with drugs indicated by the WHO analgesic ladder appropriate for the severity of pain [II, B].

Pain should already be managed during the diagnostic evaluation. Most cancer patients can attain satisfactory relief of pain through an approach that incorporates primary antitumor treatments, systemic analgesic therapy and other noninvasive techniques such as psychological or rehabilitative interventions.

treatment of mild pain

Nonopioid analgesics such as acetaminophen/paracetamol or an NSAID are indicated for the treatment of mild pain. NSAIDs are superior to placebo in controlling cancer pain in single dose studies. Paracetamol and NSAIDS are universally accepted as part of the treatment of cancer pain at any stage of the WHO analgesic scale. There is no evidence to support superior safety or efficacy of one NSAID over any other [34]. In a randomized clinical trial (RCT) carried out in a small sample of cancer patients on a strong opioid regimen, paracetamol improved pain and well-being [35]. A recent systematic review of the literature shows that the addition of an NSAID to WHO Step III opioids can improve analgesia or reduce opioid dose requirement [36].

It is mandatory to periodically monitor and revise the long-term use of NSAIDs or cyclo-oxygenase-2 (COX-2) selective inhibitors [37] because they can induce severe toxicity such as: gastrointestinal bleeding, platelet dysfunction and renal failure. COX-2 selective inhibitors may increase the risk of thrombotic cardiovascular adverse reactions [38] and do not offer protection from renal failure.

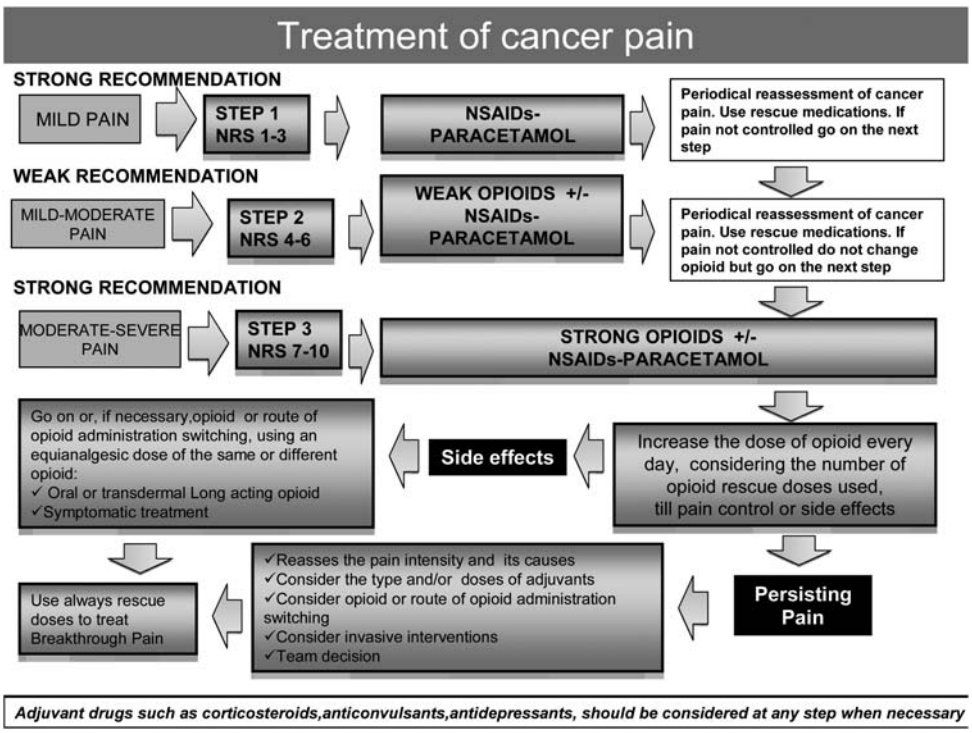
recommendations

Paracetamol and/or a NSAID are effective for treating mild pain [I, A].

Paracetamol and/or a NSAID are effective for treating all intensities of pain, at least in the short term and unless contraindicated [I, A].

treatment of mild–moderate pain

In the meta-analysis of Grond et al. [39] on the analgesic efficacy and tolerability of weak opioids versus placebo 10/16 RCTs show the superiority of opioids. However, 14/16 RCTs were single dose studies and no data are available on long-term use.



Algorithm 1

Recently, tramadol at doses of 1 and 1.5 mg/kg every 6 h was compared with placebo in 36 patients with neuropathic pain (NP) [40]. In the 18 patients on tramadol, significant improvements in pain relief, Karnofsky Performance Status and sleep, as well as much more frequent adverse effects such as nausea, vomiting and constipation were found.

In an RCT [41], the analgesia and tolerability of two doses of hydrocodone/paracetamol (25 or 50/2500 mg/day) were compared with two doses of tramadol (200 or 400 mg/day) in 118 patients. The PI reduction was evident after the double dose intake, but a significant difference in analgesia was not found. Moreover, the patients treated with tramadol had a significant major incidence of nausea, vomiting, vertigo, anorexia and asthenia.

In an RCT, the efficacy and tolerability of oral tramadol versus hydrocodone and versus codeine was compared in 177 patients [42]. No significant difference in analgesic efficacy was found; however the use of tramadol produced a significantly higher percentage of side effects.

Traditionally [21], patients with mild–moderate pain have been treated with a combination product containing acetaminophen, aspirin or NSAID plus a weak immediate-release opioid such as codeine, dihydrocodeine, tramadol or propoxyphene.

The use of drugs of the second step of the WHO ladder has several controversial aspects. The first criticism concerns the absence of a definitive proof of efficacy of weak opioids: in a meta-analysis of data reported from clinical randomized controlled trials [43], no significant difference was found in the effectiveness between nonopioid analgesics alone, and the combination of these with weak opioids. The available studies do not demonstrate a clear difference in the effectiveness of the drugs between the first and the second step [44].

Uncontrolled studies also show that the effectiveness of the second step of the WHO ladder has a time limit of 30–40 days for most patients and that the shift to the third step is mainly due to insufficient analgesia achieved, rather than to adverse effects [45]. A further limitation in the use of weak opioids is represented by the 'ceiling effect', for which more than a certain threshold of dose cannot increase the effectiveness of the drug, but only influence the appearance of side effects. Many authors have proposed the abolition of the second step of the WHO analgesic ladder, in favor of the early use of morphine at low doses. The few studies on this specific topic [46–48], though suggestive, have reported inconclusive results due both to the low number and representativeness of the patient sample studied and to the relatively low statistical power.

An RCT is strongly needed to address the relevant issue of the role of WHO step II because data supporting the role of the modified two-step analgesic ladder or oral tramadol as an alternative to codeine/paracetamol are insufficient to recommend their routine use in cancer patients with mild to moderate cancer pain [49].

recommendations

For mild to moderate pain, weak opioids such as codeine, tramadol and dihydrocodeine should be given in combination with non opioid analgesics [III, C].

As an alternative to weak opiods, low doses of strong opiods in combination with nonopiod analgesics should be considered [III, C].

treatment of moderate–severe pain

Strong opioids are the mainstay of analgesic therapy in treating moderate–severe cancer-related pain. In some countries, pain relief is hampered by lack of availability of, or barriers to accessibility to, opioid analgesics [50]. Morphine, methadone, oxycodone, hydromorphone, fentanyl, alfentanyl, buprenorphine, heroin, levorphanol, oxymorphone are the most used strong opioids in Europe [50, 51]. In recent years, in some countries, the consumption of oxycontin and patches of fentanyl and buprenorphine has been increasing [52]. However, there is no evidence from high-quality comparative studies that other opioids are superior to morphine in terms of efficacy and tolerability. New opioid analgesics are now available, e.g. oxycodone/naloxone combination, which have been shown to be effective and potentially have fewer side effects in some clinical settings although further research into their clinical effects in cancer patients is needed.

In many countries, since 1977, oral morphine has been used in hospices and palliative care units as the drug of choice for the management of chronic cancer pain of moderate to severe intensity because it provides effective pain relief, is widely tolerated, simple to administer and inexpensive. Moreover, morphine is the only opioid analgesic considered in the WHO essential drug list for adults and children with pain [53].

recommendation

The opioid of first choice for moderate to severe cancer pain is oral morphine [IV, D].

Although the oral route of administration is advocated, patients presenting with severe pain that needs urgent relief should be treated and titrated with parenteral opioids, usually administered by the subcutaneous (s.c.) or intravenous (i.v.) route.

If given parenterally, the equivalent dose is one-third of the oral medication. The relative potency ratio of oral to parenteral (subcutaneous or intravenous) morphine (not subject to 'first pass' metabolism) [54, 55] might vary according to the circumstances in which morphine is used and among individual patients. When converting from oral to parenteral morphine, the dose should be divided by two or three to get a roughly equianalgesic effect, but upward or downward adjustment of the dose may then be required [56].

recommendations

The average relative potency ratio of oral to intravenous morphine is between 1:2 and 1:3 [II, A].

The average relative potency ratio of oral to subcutaneous morphine is between 1:2 and 1:3 [IV, C].

Hydromorphone or oxycodone, in both immediate-release and modified-release formulations for oral administration and oral methadone [51] are effective alternatives to oral morphine.

Transdermal fentanyl and transdermal buprenorphine are best reserved for patients whose opioid requirements are stable.

They are usually the treatment of choice for patients who are unable to swallow, those with poor tolerance of morphine and patients with poor compliance. Although not recommended in the NCCN Clinical Practice Guidelines in Oncology for Adult Cancer Pain [22] because it is a partial agonist, buprenorphine has a role in the analgesic therapy of patients with renal impairment and undergoing hemodialysis treatment [57, 58] where no drug reduction is necessary, with buprenorphine being mainly extracted through the liver to norbuprenorphine (a metabolite 40 time less potent than the parent compound). Methadone is a valid alternative but, because of marked interindividual differences in its plasma half-life and duration of action, it is still considered as a drug which should be initiated by physicians with experience and expertise in its use [51]. Strong opioids may be combined with ongoing use of a non opioid analgesic (step 1).

recommendations

In the presence of renal impairment, all opioids should be used with caution and at reduced doses and frequency [IV, C].

Fentanyl and buprenorphine via the transdermal route or intravenously are the safest opioids of choice in patients with chronic kidney disease stages 4 or 5 (estimated glomerular filtration rate <30 ml/min) [IV, C].

Opiod switching is a practice used to improve pain relief and/or drug tolerability. The most frequent switch is from morphine, oxycodone, hydromorphone, fentanyl to oral methadone [51, 59, 60]. There is no high-quality evidence to support this practice; however, a switch to an alternative opioid is frequently used in clinical practice [61]. This approach requires familiarity with equianalgesic doses of the different opioids [62].

scheduling and titration

Opioid doses should be titrated to take effect as rapidly as possible. Titration is a process in which the dose of the opioid is speedily modified to obtain the tailored dose which provides adequate relief of pain with an acceptable degree of side effects. Normal-release morphine has a short half-life and is indicated: during the titration phase; for treating BTP episodes; and for treating predictable episodes of acute pain in patients on regular analgesics (administration should take place 20-30 minutes before the predictable episode of acute pain). Intravenous titration is indicated in patients with severe pain (table 3) [63].

All patients should receive round-the-clock dosing with provision of a 'rescue dose' to manage transient exacerbations of pain. The 'breakthrough dose' is usually equivalent to +10% to 15% of the total daily dose. If more than four 'rescue doses' per day are necessary, the baseline opioid treatment with a slow-release formulation has to be adapted. Opioids with a rapid onset and short duration are preferred as rescue medications. Following the titration period, slow-release opioids are indicated. However, immediate release opioids have always to be prescribed as a **rescue** medication.

recommendations

Individual titration of dosages by means of normal release morphine administered every 4 h plus rescue doses (up to hourly) for BTP are recommended in clinical practice [IV, C].

The regular dose of slow-release opioids can then be adjusted to take into account the total amount of rescue morphine [IV, C].

management of opioid side effects

Many patients develop adverse effects such as constipation, nausea/vomiting, urinary retention, pruritus and central nervous system (CNS) toxicity (drowsiness, cognitive impairment, confusion, hallucinations, myoclonic jerks and—rarely—opioid-induced hyperalgesia/allodynia). Sometimes, the reduction of the opioid dose may reduce the incidence and/or severity of adverse events. This may be achieved by using a

Table 3. Intravenous titration (dose finding) with morphine for severe cancer pain (Ref. [63])

RCT. 62 strong opioid naïve in patients, pain intensity NRS ≥5, patients were randomized to receive i.v. morphine ($n = 31$) or oral IR morphine ($n = 31$)	i.v. group: 1.5 mg bolus every 10 min until pain relief (or adverse effects). Oral group: IR morphine 5 mg every 4 h in opioids naive patients. 10 mg in patients on weak opioids. Rescue dose: the same dose every 1 h max.	i.v. group: Oral IR morphine q 4 h, on the basis of the previous IV requirements. IV: PO conversion 1:1. Rescue dose: the same dose every 1 h max. Oral group: follow the same scheme	% of patients achieving satisfactory pain relief: -after 1 h: i.v. group, 84%; oral group, 25% ($P < 0.001$) -after 12 h: i.v. group 97%; oral group 76% ($P < 0.001$) -after 24 h: i.v. group and oral group similar. i.v. group: Median morphine dosage (i.v.) to achieve pain relief: 4.5 mg (range 1.5–34.5). In the same group, mean morphine dosage (PO) after stabilization: 8.3 (range 2.5–30) mg. Oral group: Median morphine dosage to achieve pain relief: 7.2 (2.5–15) mg. No significant adverse events

IR, immediate release; i.v., intravenous; NRS, numerical rating scale; PO, per os; RCT, randomized controlled trial.

coanalgesic or an alternative approach such as a nerve block or radiotherapy (RT). Other strategies include the continued use of antiemetics for nausea, laxatives for constipation, major tranquilizers for confusion and psychostimulants for drowsiness. However, since some of the side effects may be caused by accumulation of toxic metabolites, switching to another opioid agonist and/or another route may allow titration to adequate analgesia without the same disabling effects. This is especially true for symptoms of CNS toxicity such as opioid-induced hyperalgesia/allodynia and myoclonic jerks [64]. Treatment of opioid-related CNS symptoms: there is little evidence for the use of methylphenidate in the management of opioid-induced sedation and cognitive disturbance [65]. It is not possible to recommend other individual drugs for the treatment of any other central side effect. Dose reduction or opioid switching is a potential effective way to manage delirium, hallucination, myoclonus and hyperalgesia [65]. Treatment of opioid-related constipation: there is a strong recommendation to routinely prescribe laxatives for prophylaxis and management of opioid-induced constipation [66]. Methylnaltrexone administered by subcutaneous injection should be used in the treatment of opioid-related constipation resistant to traditional laxatives [66].

Naloxone is a short-acting opioid antagonist for i.v. use able to reverse symptoms of accidental severe opioid overdose. The potential clinical effects on constipation of new pharmacological developments (e.g. oxycodone and naloxone) have been demonstrated by a recent randomized, double-blind, study aimed to investigate the safety and efficacy of oxycodone/naloxone association in subjects with moderate to severe chronic cancer pain [67].

Metoclopramide and antidopaminergic drugs are the drugs most frequently used for treatment of opioid-related nausea/vomiting with a weak grade [68, 69].

recommendations

Laxatives must be routinely prescribed for both the prophylaxis and the management of opioid-induced constipation [I, A].

Metoclopramide and antidopaminergic drugs should be recommended for treatment of opioid-related nausea/vomiting [III, B].

breakthrough pain

A systematic literature review shows that there is no widely accepted definition, classification system or any well validated assessment tools for cancer-related BTP [70] and the setting of care [71]. These findings could explain why the prevalence is reported with a wide range from 19% to 95% [71–73]. Of interest in the study of Greco et al. [71] 110 centers recruited 1801 cancer patients of which 40.3% had BTP at baseline. A strong association has been found with the type of recruiting centers, with oncological wards reporting a lower proportion of patients with BTP (−30%) when compared with palliative centers.

Available pharmacological treatment options include oral transmucosal, buccal, oral immediate-release morphine sulfate (IRMS) or nasal, subcutaneous or intravenous opioids; however few RCTs are available [74–76]. Seven RCTs were found: 5 studies were placebo controlled studies that evaluated oral transmucosal fentanyl citrate (OTFC), intranasal fentanyl spray (INFS), fentanyl buccal tablet; one trial compared OTFC versus oral morphine [77]; and one trial compared INFS versus OTFC [78].

Recently, a fentanyl pectin nasal spray (FPNS) was developed to optimize the absorption profile of fentanyl across the nasal mucosa. An RCT trial showed that a dose of FPNS provides superior pain relief compared with placebo with a pain reduction after five minutes with further and significant reductions after 10 min [76].

Davies et al. [79] studied the consistency of efficacy, tolerability and patient acceptability of FPNS versus IRMS in 110 patients experiencing one to four BTP episodes/day during background pain treatment with oral morphine or equivalent opioids ≥60 mg/day. At baseline and during an open dose titration phase (maximum 2 weeks) followed by a double blind, double dummy treatment phase (from 3 to 21 days) and an end-of-treatment phase (1 to 14 days after the last dose) the PI was evaluated by means of the NRS, and pain relief was measured on a 5-point numeric scale (0 = none, 4 = complete) and recorded in an e-diary at 5, 10, 15, 30, 45 and 60 min after dosing. Moreover, the patients rated the overall satisfaction and satisfaction with speed of relief (30 and 60 min), and reliability 60 min after the nasal spray using a 4-point scale (1 = not satisfied; 4 = very satisfied). After the last treated BTP episode patients rated the ease of use and convenience of the nasal spray.

The per-episode analysis showed statistically significant differences in PI scores and in pain relief in favor of FPNS versus IRMS by 10 min after administration ($P<0.05$). Overall acceptability scores were significantly greater for FPNS than for IRMS at 30 ($P < 0.01$) and 60 ($P < 0.05$). Most of the patients were 'satisfied/very satisfied' with the convenience (79.8%) and ease of use (77.2%) of FPNS. Nobody reported significant nasal effects.

In a prospective, multicenter phase IV study [80] sublingual fentanyl orally disintegrating tablet (sublingual fentanyl ODT) was studied in 181 patients. During the study, 3163 episodes of BTP were treated with a mean dose of 401.4 mcg per episode. With respect to baseline, a significant improvement of maximum BTP intensity was seen with sublingual fentanyl ODT ($P < 0.0001$) within 5 min of administration in 67.7% of episodes and a maximum effect within 30 min in 63% of episodes. Quality of life assessed by means of the modified pain disability index and emotional distress assessed by Hospital Anxiety and Depression Scale (HADS) significantly improved during an observational period of 28 days. The drug was well tolerated.

recommendations

Immediate release formulation of opioids must be used to treat exacerbations of controlled background pain [I, A].

Immediate release oral morphine is appropriate to treat predictable episodes of BTP (i.e. pain on moving, on swallowing, etc.) when administered at least 20 min before such potential pain triggers [II, A].

Intravenous opioids; buccal, sublingual and intranasal fentanyl drug delivery have a shorter onset of analgesic activity in treating BTP episodes in respect to oral morphine [I, A].

bone pain

Treatment of bone pain should always take into consideration the use of analgesic drugs according to Algorithm 1. Moreover, RT, radioisotopes and targeted therapy given in association with analgesics have an important role in bone pain management (Algorithm 2).

radiotherapy

RT has specific and critical efficacy in providing pain relief caused by bone metastases, present in about 75% of patients with cancer-related disease, and metastatic spinal cord compression (MSCC) [81]. Numerous randomized prospective trials show improvements in pain relief in 60%–80% of patients after RT [82]. The American Society for Radiation Oncology (ASTRO), reviewing randomized published trials on RT for painful bone metastases, showed pain relief equivalence for different regimens, including 10 × 3Gy, 6 × 4Gy, 5 × 4Gy and 8-Gy single dose [82]. Although fractionated RT regimens have been associated with an 8% repeat treatment rate to the same anatomic site because of recurrent pain versus 20% after 8-Gy single dose, this last approach should be considered the regimen of choice for patients with painful bone metastases because it optimizes patient and caregiver convenience. So, considering the equivalence in outcome of various RT regimens, and the feasibility of reirradiation when necessary, 8-Gy single dose is recommended in the majority of patients with painful bone metastases. More protracted fractionated regimens should be reserved for well-selected patients on the basis of better-expected outcomes [82].

Stereotactic body radiosurgery has emerged as a new treatment option which permits the administration of very high/radioablative doses—typically in single fraction (10–16 Gy) or in hypofractionation (3 × 9 or 5 × 6–8 Gy)—to the tumor avoiding excessive doses to surrounding critical normal tissues such as the vertebrae or the spinal cord [83].

recommendations

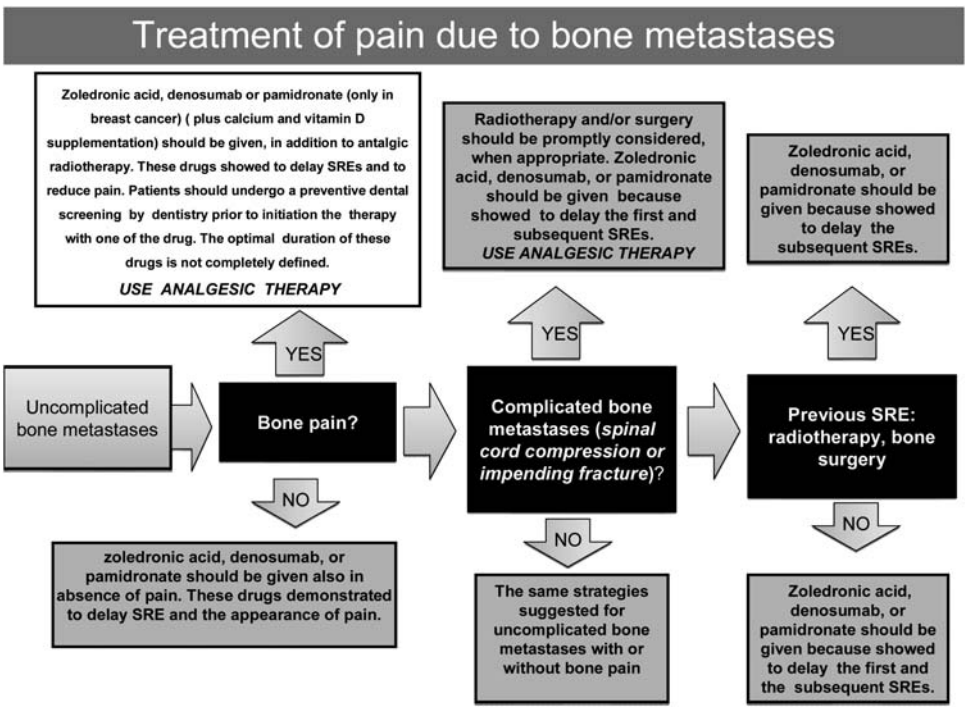
All patients with painful bone metastases should be evaluated for external beam RT and the dose prescription should be 8-Gy single dose [I, A].

Higher doses and protracted fractionations can be reserved only for selected cases [II, B].

Stereotactic body radiosurgery should be used for fit patients enrolled in clinical trials [V, D].

Spinal cord compression requires urgent oncologic care [84]. Pain accompanies MSCC in ∼95% of patients, and usually precedes the diagnosis by days to months. Pain can be local (back or neck pain), radicular or both. Patients with neurologic deficits have a poor prognosis, thus early clinical and MRI diagnosis and prompt therapy are powerful predictors of outcome in MSCC [85–87].

Steroids should be given immediately when the clinical-radiological diagnosis of MSCC is obtained. Dexamethasone is the most frequently used drug, with doses ranging from moderate (16 mg/day) to high (36–96 mg/day) eventually preceded by a bolus of 10–100 mg intravenously. The steroids are usually tapered over 2 weeks. Although no study has been



Algorithm 2

published comparing high-dose to moderate dexamethasone dose, 16 mg/day remains the more often used prescription [84].

MSCC can be treated with surgery followed by RT or RT alone. RT is the first line treatment for the majority of patients with MSCC; it provides back pain relief in 50%–58% of cases with an interesting rate of pain disappearing (30%–35% of cases) [85]. The optimal RT schedule remains unknown. As suggested by many prospective [85] and two phase III clinical trials [86, 87], hypofractionated RT regimen can be considered the approach of choice, while more protracted RT regimens (e.g. 5×4, 10×3 Gy) can be used in selected MSCC patients with a long life expectancy.

On the basis of the published evidence, it can be concluded that surgery should be considered for a carefully selected group of patients, i.e. with single-level MSCC and neurological deficits. Other possible indications for surgery include the necessity of stabilization, vertebral body collapse causing bone impingement on the cord or nerve root, compression recurring after RT and an unknown primary requiring histological confirmation for diagnosis [85, 88].

Radioisotope treatment has also been investigated in a systematic review [89]: the results showed only a small beneficial effect on pain control in the short and medium term (1–6 months), with no modification of the analgesics used. Few RCTs, involving small numbers, have shown that isotopes can relieve bone pain in patients with breast cancer and lung cancer, while they produced inconsistent results in patients with hormone refractory prostate cancer [90, 91].

recommendations

Early diagnosis and prompt therapy are powerful predictors of outcome in MSCC [I, A]. The majority of patients with MSCC should receive RT alone and surgery should be reserved only for selected cases [II, B].

Hypofractionated RT regimen can be considered the approach of choice [I, A], while more protracted RT regimens can be used in selected MSCC patients with a long life expectancy [III, B].

Dexamethasone should be prescribed in patients with MSCC [II, A] at a medium dose [III, B].

Radioisotope treatment can be evaluated in selected patients with multiple osteoblastic bone metastases [II, C].

targeted therapy and bone pain

bisphosphonates

Bisphosphonates (BPs) form part of the standard therapy for hypercalcemia and the prevention of skeletal-related events (SREs) in some cancers. There is sufficient evidence supporting the analgesic efficacy of BPs in patients with bone pain due to bone metastases from solid tumors and multiple myeloma [92]. However, the prescription of BPs should not be considered as an alternative to analgesic treatment and their administration should be started after preventive dental measures [93, 94]. After the first i.v. infusions of BP, pain can appear or its intensity increase, and the use of analgesics such as paracetamol or a basal analgesic dose increase is necessary.

recommendations

Bisphosphonates should be considered as part of the therapeutic regimen for the treatment of patients with/without pain due to metastatic bone disease [II, B].

Preventive dental measures are necessary before starting bisphosphonate administration [III, A].

denosumab

Denosumab, a targeted RANK ligand inhibitor, is a new therapy for the prevention of SREs. Three prominent clinical trials were conducted to establish the efficacy of denosumab [95–97]. In two of three trials, denosumab was found to delay the time to first skeletal-related event significantly more than zoledronic acid in patients with breast or castration-resistant prostate cancer with bone metastasis. The third trial found denosumab to be non-inferior to zoledronic acid in patients with metastases from solid tumors, excluding breast and prostate solid tumors.

The integrated analysis of pain outcomes, presented only in the form of an abstract [98], found a superiority of denosumab when compared with zoledronic acid in delay time to moderate/severe pain occurrence and in reducing analgesic use. The prescription of denosumab should be started after preventive dental measures [99].

recommendations

Denosumab should be considered as a valid alternative to BPs for the treatment of patients with/without pain due to metastatic bone disease from solid tumors [I, A].

The role of denosumab in delaying bone pain occurrence is promising but deserves further investigation [III, B].

Preventive dental measures are necessary before starting denosumab administration [III, A].

neuropathic pain

Although NP is considered frequent in cancer patients and difficult to manage, only a few studies on the prevalence of NP are available. A 1-month follow-up prospective epidemiological multicenter study was carried out to assess the prevalence of NP and to evaluate its management in 46 oncological units in Spain during a mean period of four weeks [100]. Of 8615 screened patients, 2567 (30%) suffered from pain. From these, 33% had NP according to investigators and only 19% were confirmed by DN4 $\geq$4. Sixty-nine percent of NP cases were tumor related and up to 43% treatment related. In those cases related to treatment, 79% were due to chemotherapy or biologic therapy. At baseline, physicians prescribed opioids to 88% of patients and oxycodone was most frequently used (74%) followed by fentanyl (46%), morphine (22%), tramadol (38%); nonopioid analgesic treatment was prescribed to 67% of patients with NSAIDs as the most frequently used (71%); and co-adjuvants with gabapentin as the most frequently used (52%). After 1 month, PI decrease was significant in patients with metastases ($P < 0.01$). This is the first prospective study including a large sample of cancer patients evaluating the prevalence and the pharmacological treatment of NP.

NP, either caused by tumor infiltration or due to paraneoplastic or treatment-induced polyneuropathy, may be adequately controlled by opioids alone ± adjuvant drugs. Evidence from studies in patients without cancer has been reviewed as the pathological mechanism of NP involved is believed to be the same. There is evidence from systematic reviews [101, 102] that both tricyclic antidepressants [101] and anticonvulsant drugs are effective in the management of NP [101, 103, 104] even if the number NNT (number needed to treat) for these drugs is 3–5. Two specific systematic reviews have been identified on the role of anticonvulsant drugs in NP: one dealing with gabapentin in the management of pain and the other dealing with various anticonvulsants [104].

In cancer patients with NP, non-opioid and opioid analgesics may be combined with tricyclic antidepressant drugs or anticonvulsants (Algorithm 3). The efficacy and tolerability of the therapy have to be monitored over time. Steroids should be considered in the case of nerve compression. There is evidence in adults that intravenous lidocaine and its oral analogue mexiletine are more effective than placebo in decreasing NP and can relieve pain in selected patients [105].

In a phase III randomized trial in 270 patients with bone metastasis treated with 8 Gy in one versus 20 Gy in five fractions of RT for NP due to bone metastases, the higher dose was more effective than the single dose of 8 Gy used for uncomplicated bone metastasis [106].

recommendations

Patients with NP should be treated with non opioid and opioid drugs [III, B].

Patients with NP should be given either a tricyclic antidepressant or a anticonvulsant and subjected to side effects monitoring [I, A].

In patients with neropathic pain due to bone metastases RT at the dose of 20 Gy in five fractions should be considered [II, B].

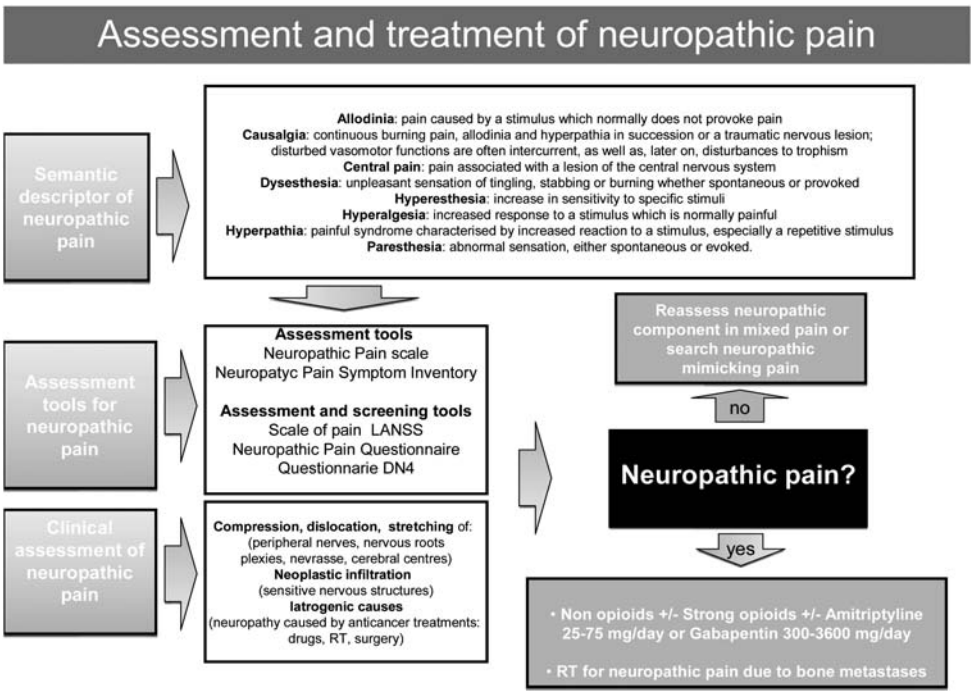
invasive management of refractory pain

About 10% of cancer patients have pain which is difficult to manage with oral or parenteral analgesic drugs. Interventional techniques such as nerve blocks and intrathecal drug delivery (ITDD) (spinal or epidural) [107] may allow those patients refractory to all conventional strategies and/or dose limiting analgesic-related side effects to reach pain control when used as unique therapy or, more frequently, in combination with systemic therapy.

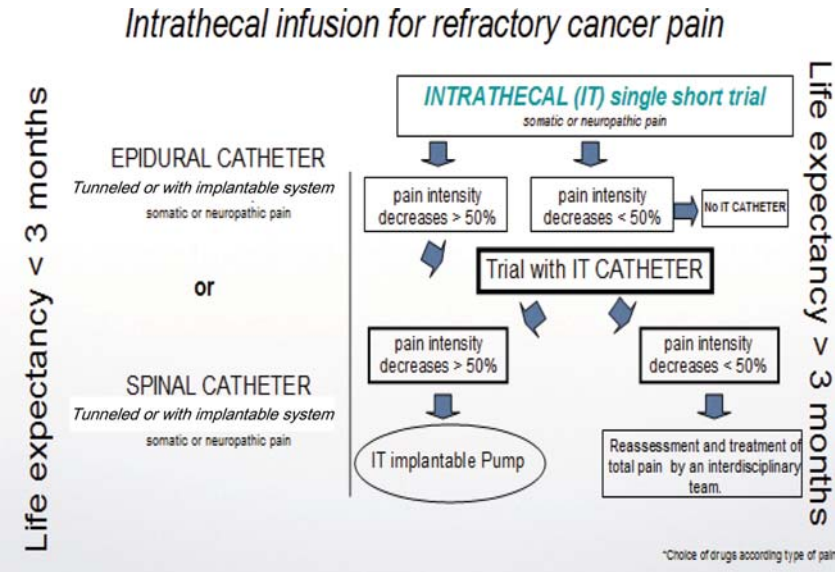
Two prospective comparative trials between oral and spinal morphine, have compared the analgesia and tolerability of morphine administered orally or by epidural [108, 109]. An improvement in pain control as well as in adverse effects was shown by switching from oral to epidural or continuous subcutaneous infusion of morphine [108]. Of interest, Kalso showed no significant benefits, either in efficacy or in adverse effects, by administering morphine epidural compared with the subcutaneous route. The authors concluded that the co-administration of local anesthetic agents, alpha-2-adrenergic agonists or *N*-methyl-D-aspartate (NMDA) antagonists may significantly improve the quality of epidural analgesia as compared with the SC route [109].

intrathecal drug delivery

Spinal opioids work by binding to the mu receptor in the substantia gelatinosa and can be administered epidurally or



Algorithm 3



Algorithm 4

intrathecally via percutaneous catheters, tunneled catheters, or implantable programmable pumps (Algorithm 4). The spinal route leads to decreased opioid consumption: if the opioid is delivered via the epidural route, only 20%–40% of the systemic dose is required to reach equianalgesia and if the intrathecal route is adopted, only 10% of the systemic dose for equianalgesia is required. The intrathecal route of opioid administration should be considered in patients experiencing pain in various anatomic locations: head and neck, upper and lower extremities, trunk. The fully implanted systems offer less risk of infection and need lower maintenance than the percutaneous, but the positioning is more complex [109]. These interventional strategies are not appropriate in patients with infections, coagulopathy, or very short life expectancy. Many authors [108–113] indicate the use of a trial of intraspinal analgesia using a temporary epidural or spinal catheter to determine efficacy and appropriate dose range before pump implantation.

When compared with epidural drug delivery, ITDD presents fewer catheter problems, smaller drugs dose requirement and less adverse effects. In addition, it gives better pain control and decreased risk of infection. Intrathecal administration has the advantage of being less affected by the presence of extensive epidural metastasis and morphine, ziconotide and baclofen are the drugs most used, sometimes with local anesthetics (bupivacaine 0.125%–0.25%) [112, 114]. Limited evidence supports the use of subanesthetic doses of ketamine, an NMDA antagonist, in intractable pain.

ITTD or epidural administration of opioids may be useful in patients with: (i) inadequate pain relief despite systemic opioid escalating doses; (ii) non-effective response to switching the opioid or the route of administration as well as when side effects increase because of dose escalation; (iii) life-expectancy >6 months justifies the implantable IT pump but only after a trial using a temporary epidural or spinal catheter [115].

recommendation

Intraspinal techniques monitored by a skilled team should be included as part of cancer pain management strategy, but widespread use should be avoided [II, B].

pheripheral nerve block

Peripheral nerve blocks or plexus blocks can be used when pain occurs in the field of one or more peripheral nerves, or if pain is caused by complications such as pathological fracture or vascular occlusion [116]. However, peripheral nerve blocks as the principal pain treatment is very rare, and they are always used together with systemic analgesia according to a multi-pharmacologic approach as in postoperative pain treatment. The use of neurolytic agents on peripheral nerves produces a significant incidence of neuritis; so in patients with good prognosis, this can result in symptoms more difficult to control than the original pain.

neurolytic blockade

Neurolytic blocks should be limited to those patients with short life expectancy because they usually produce a block lasting 3–6 months. For the sympathetic system, neurolytic blocks should be considered as adjuvants to decrease the use of oral and/or parenteral analgesics because the visceral pain mechanisms are complex and change with progression of the disease.

This technique is used for the superior hypogastric plexus block, *ganglion impar* block, when pelvic pain or perineal pain of visceral origin is present respectively, but above all for the celiac plexus block, when visceral pain is due to pancreatic cancer.

Table 4. Summary of Recommendations

- The intensity of pain and the treatment outcomes should be regularly assessed using (i) visual analogue scales (VAS), or (ii) the verbal rating scale (VRS) or (iii) the numerical rating scale (NRS) [V, D].
- Observation of pain-related behaviors and discomfort is indicated in patients with cognitive impairment to assess the presence of pain (expert and panel consensus).
- The assessment of all components of suffering such as psychosocial distress should be considered and evaluated [II, B].
- Patients should be informed about pain and pain management and be encouraged to take an active role in their pain management [II, B].
- Analgesic for chronic pain should be prescribed on a regular basis and not on an 'as required' schedule [V, D].
- The oral route of administration of analgesic drugs should be advocated as the first choice [IV, C].
- Rescue dose of medications (as required or prn) other than the regular basal therapy must be prescribed for breakthrough pain (BTP) episodes [V, D].
- The analgesic treatment should start with drugs indicated by the WHO analgesic ladder appropriate for the severity of pain [II, B].
- Paracetamol and/or a non-steroidal anti-inflammatory drug (NSAID) are effective for treating mild pain [I, A].
- Paracetamol and/or NSAID are effective for treating all intensities of pain, at least in the short term and unless contraindicated [I, A].
- For mild to moderate pain, weak opioids such as codeine, tramadol and dihydrocodeine should be given in combination with non opioid analgesics [III, C].
- As an alternative to weak opiods consider low doses of strong opiods in combination with non-opioid analgesics [III, C].
- The opioid of first choice for moderate to severe cancer pain is oral morphine [IV, D].
- The average relative potency ratio of oral to intravenous morphine is between 1:2 and 1:3 [II, A].
- The average relative potency ratio of oral to subcutaneous morphine is between 1:2 and 1:3 [IV, C].
- In the presence of renal impairment all opioids should be used with caution and at reduced doses and frequency [IV, C].
- Fentanyl and buprenorphine via transdermal route or intravenously are the safest opioids of choice in patients with chronic kidney disease stages 4 or 5 (estimated glomerular filtration rate <30 ml/min) [IV, C].
- Individual titration of dosages by means of normal release or immediate-release (IR) morphine administered every 4 h plus rescue doses (up to hourly) for BTP are recommended in clinical practice [V, C].
- The regular dose of slow-release opioids can then be adjusted to take into account the total amount of rescue morphine [IV, C].
- Laxatives must be routinely prescribed for both the prophylaxis and the management of opioid-induced constipation [I, A].
- Metoclopramide and antidopaminergic drugs should be recommended for treatment of opioid-related nausea/vomiting [III, B].
- Immediate release formulation of opioids must be used to treat exacerbations of controlled background pain [I, A].
- Immediate release oral morphine is appropriate to treat predictable episodes of BTP (i.e. pain on moving, on swallowing etc) when administered at least 20 min before such potential pain triggers [II, A].
- Intravenous opioids; buccal, sublingual, intranasal fentanyl drug delivery have a shorter onset of analgesic activity in treating BTP episodes with respect to oral morphine [I, A].
- All patients with painful bone metastases should be evaluated for external beam RT and the dose prescription should be 8-Gy single dose [I, A].
- Higher doses and protracted fractionations can be reserved only to selected cases [II, B].
- Stereotactic body radiosurgery should be used for fit patients enrolled in clinical trials [V, D].
- Early diagnosis and prompt therapy are powerful predictors of outcome in MSCC [I, A]. The majority of patients with MSCC should receive RT alone and surgery should be reserved only to selected cases [II, B].
- Hypofractionated RT regimen can be considered the approach of choice [I, A], while more protracted RT regimens can be used in selected MSCC patients with a long life expectancy [III, B].
- Dexamethasone should be prescribed in patients with MSCC [II, A] at medium dose [III, B].
- Radioisotope treatment can be evaluated in selected patients with multiple osteoblastic bone metastases [II, C].
- Bisphosphonates should be considered as part of the therapeutic regimen for the treatment of patients with/without pain due to metastatic bone disease [II, B].
- Preventive dental measures are necessary before starting bisphosphonate administration [III, A].
- Denosumab should be considered as a valid alternative of BPs for the treatment of patients with/without pain due to metastatic bone disease from solid tumors [I, A].
- The role of denosumab in delaying bone pain occurrence is promising but deserves further invtestigation [III, B].
- Preventive dental measures are necessary before starting denosumab administration [III, A].
- Patients with neuropathic pain should be treated with non opioid and opioid drugs [III, B].
- Patients with neuropathic pain should be given either a tricyclic antidepressant or a anticonvulsant and subjected to side effects monitoring [I, A].
- In patients with neropathic pain due to bone metastases RT at the dose of 20 Gy in five fractions should be considered [II, B].
- Intraspinal techniques monitored by a specialized team, should be included as part of cancer pain management strategy, but widespread use should be avoided [II, B].
- CPB appears to be safe and effective for the reduction of pain in patients with pancreatic cancer, with a significant advantage over standard analgesic therapy until 6 months [II, B].

neurolysis of celiac plexus

Celiac plexus block (CPB) is useful when pain is of visceral etiology only and due to cancer in the upper abdomen or pancreas; it leads to pain control and frequently to a decrease in the total amount of systemic drugs and their side effects [117].

The technique used to perform CPB (anterior or posterior approach; amount and concentration of nerolytic agent and time) may affect the results and the duration of the analgesic effect. One new way to perform this kind of CPB is represented by echo-endoscope guidance, placed in the stomach just below the cardia [118]. CPB should be performed in the presence of visceral pain and only if the clinical condition of the patient is not poor. Previous studies have suggested that when there is evidence of disease outside the pancreas, such as celiac or portal adenopathy, or both, the success rate of this block decreases significantly [119].

recommendation

CPB appears to be safe and effective for the reduction of pain in patients with pancreatic cancer, with a significant advantage over standard analgesic therapy until 6 months [II, B].

end of life pain

Recent data suggest that 53%–70% of patients with cancer-related pain require an alternative route for opioid administration, months and hours before death [120]. On some occasions, as patients are nearing death, pain is perceived to be 'refractory'. Pain is often accompanied by other symptoms such as dyspnea, agitation, delirium and anxiety. A careful assessment of the total suffering is mandatory to plan the appropriate therapeutic intervention. In deciding that pain is refractory, the clinician must, after a meticulous assessment of physical pain and total suffering, perceive that the further application of standard interventions as described above is either: (i) incapable of providing adequate relief, (ii) associated with excessive and intolerable acute or chronic morbidity or (iii) unlikely to provide relief, so that other interventional approaches may be necessary to control pain caused by obstruction of hollow organs. In this situation, sedation may be the only therapeutic option capable of providing adequate relief. The justification of sedation in this setting is that it is an appropriate and proportionate goal. However, before administering sedative drugs, all the possible causes of 'suffering' must be carefully assessed and evaluated by means of a multidisciplinary specialist approach which includes also psychiatric, psychological and pastoral care personnel. Commonly used agents include opioids, neuroleptics, benzodiazepines, barbiturates and propofol. Irrespective of the agent or agents selected, administration initially requires dose titration to achieve adequate relief, followed subsequently by provision of ongoing therapy to ensure maintenance of effect. A continuous assessment of the suffering of the patient should be performed during the sedation process.

conclusions

The review of published data shows that only a few RCTs have been performed in the setting of cancer patients with pain. This is the major reason for which the level of evidence and the grade of recommendation are not strong in many cases. Further well executed studies on large samples of patients are needed in order to answer the many scientific questions and to be able to treat patients in the best way..

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conflict of interest

All authors have reported no potential conflicts of interest.

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