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Cancer Pain Management and Bone Metastases: An Update for the Clinician

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Breast cancer · Palliative care · Palliative medicine · Bone metastases · Cancer pain · Opioids · Guidelines

Summary
Breast cancer patients with bone metastases often suffer from cancer pain. In general, cancer pain treatment is far from being optimal for many patients. To date, morphine remains the gold standard as first-line therapy, but other pure μ agonists such as hydromorphone, fentanyl, or oxycodone can be considered. Transdermal opioids are an important option if the oral route is impossible. Due to its complex pharmacology, methadone should be restricted to patients with difficult pain syndromes. The availability of a fixed combination of oxycodone and naloxone is a promising development for the reduction of opioid induced constipation. Especially bone metastases often result in breakthrough pain episodes. Thus, the provision of an on-demand opioid (e.g., immediate-release morphine or rapid-onset fentanyl) in addition to the baseline (regular) opioid therapy (e.g., sustained-release morphine tablets) is mandatory. Recently, rapid onset fentanyls (buccal or nasal) have been strongly recommended for breakthrough cancer pain due to their fast onset and their shorter duration of action. If available, metamizole is an alternative non-steroid-anti-inflammatory-drug. The indication for bisphosphonates should always be checked early in the disease. In advanced cancer stages, glucocorticoids are an important treatment option. If bone metastases lead to neuropathic pain, coanalgetics (e.g., pregabalin) should be initiated. In localized bone pain, radiotherapy is the gold standard for pain reduction in addition to pharmacologic pain management. In diffuse bone pain radionuclids (such as samarium) can be beneficial. Invasive measures (e.g., neuroaxial blockage) are rarely necessary but are an important option if patients with cancer pain syndromes are refractory to pharmacologic management and radiotherapy as described above. Clinical guidelines agree that cancer pain management in incurable cancer is best provided as part of a multiprofessional palliative care approach and all other domains of suffering (psychosocial, spiritual, and existential) need to be carefully addressed ('total pain').

Schlüsselwörter
Brustkrebs · Palliative Care · Palliativmedizin · Knochenmetastasen · Tumorschmerz · Opioide · Leitlinien

Zusammenfassung
Brustkrebspatientinnen mit Knochenmetastasen (KM) leiden häufig unter Tumorschmerzen. Morphin ist bisher der Goldstandard bei der Opioidtherapie. Jedoch stellen andere reine μ-Agonisten wie Hydromorphon, Fentanyl oder Oxycodon wertvolle Therapieoption dar. Transdermale Opioide sind eine wichtige Therapieoption falls die orale Therapie nicht möglich ist. Der Einsatz von Methadon sollte auf Patientinnen mit schwer zu behandelnden Tumor-Schmerzsyndromen beschränkt sein. Die Verfügbarkeit eines Kombinationspräparats von Oxycodon und Naloxon ist eine viel versprechende Entwicklung zur Reduktion der Opioid-induzierten Obstipation. Insbesondere KM führen oft zu Durchbruchschmerzen. Somit ist die Verschreibung von einer Opioid-Bedarfsmedikation (z.B. unretardiertes Morphin oder schnell wirkende Fentanyle) zusätzlich zur Opioid Dauer- (oder Basis-)Medikation (z.B. retardiertes Morphin) besonders wichtig. Mittlerweile werden schnell wirkende (rapid onset) Fentanyle (nasal oder buccal) aufgrund ihres schnellen Wirkungseintritts und der kürzeren Wirkdauer von einigen europäischen Leitlinien als Goldstandard empfohlen. Falls verfügbar, ist Metamizol ein wertvolles alternatives nicht-steroidales Antiphlogistikum. Die Indikation für Bisphosphonate sollte schon im Frühstadium der Krankheit geprüft werden. In fortgeschrittenen Tumorstadien sind Glukokortikoide eine wichtige Behandlungsoption. Wenn KM zu neuropathischen Schmerzen führen, sollte eine Koanalgetika-Therapie (z.B. Pregabalin) eingeleitet werden. Bei lokalen Knochenschmerzen ist die Strahlentherapie der Goldstandard zusätzlich zu den pharmakologischen Interventionen. Wenn KM diffuse Schmerzen bereiten, können Radionuklide, wie z.B. Samarium, hilfreich sein. Regionalanästhetische Verfahren oder die intrathekale Opioidapplikation sind selten notwendig, stellen jedoch eine wichtige Behandlungsoption dar, wenn Patientinnen unter Tumorschmerzen leiden, die trotz medikamentöser und strahlentherapeutische Behandlung fortbestehen. International wird für Patienten in fortgeschrittenen Krankheitsstadien empfohlen, die Tumorschmerztherapie im Rahmen eines multiprofessionellen Palliative-Care-Konzeptes bereitzustellen, um die Beachtung aller anderen nicht körperlichen Domänen des Leidens (psychosozial, spirituell und existenziell) sicherzustellen («Total Pain»).

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Introduction

Patients with advanced breast cancer frequently suffer from cancer pain due to metastatic disease. The distress associated with this symptom adds significantly to the overall burden for patients and their families [1]. This review provides a framework and practical concept of pain assessment, and pharmacologic and non-pharmacologic interventions for safe and effective cancer pain management [2].

The treatment of cancer pain requires a *comprehensive* strategy. Pain is among the most prevalent symptoms and poses a challenge for the cancer health-care system [2]. Treatment guideline are readily available [2–9] and most authors agree that adherence to these guidelines together with close interdisciplinary cooperation results in sufficient pain relief for most patients [8, 10]. Unfortunately, to date one in two cancer patient still receives insufficient cancer pain management [2, 11]. Therefore, ongoing spread of the available information is imperative.

Pain Assessment

Cancer pain assessment should be a standard of care [7] including other concerns from different domains of suffering (table 1).

Cause of Pain

The *cause of pain* is a verifiable lesion or disorder that is likely to be sustaining pain through direct tissue injury or a related process, such as inflammation, [2, 12]. Especially in bone metastases, the identification of a cause of pain can indicate the need for disease-modifying treatment such as radiation, bisphosphonates, or radionuclide therapy for pain treatment [2, 13, 14].

Pain is called either *nociceptive* (either *somatic* or *visceral*) if it is caused by tissue lesions and *neuropathic* if it is cause by dysfunctions of the nervous system [2, 12–14]. Clinicians should be able to differentiate pain that is caused by the cancer itself and its metastases from other pain causes (e.g., pain in gastritis, urinary tract infections, osteoporosis or fractures). A cancer pain classification system has not been universally accepted yet, but the concepts supplied in table 2 are clinically meaningful and widely applied [2, 12].

Overall, 3 in 4 patients suffer from cancer related pain while most of the remaining pain syndromes are caused by disease modifying therapy [15]. Although psychological components significantly influence pain perception and pain expression, the term *psychogenic pain* is rarely ever applicable in cancer patients [2]. It describes pain syndromes that almost entirely rely on psychological factors.

Table 1. Key components of cancer pain assessment [2]

Take brief history of pain
– Severity (intensity)
– Daily fluctuation (night/day rhythm)
– Triggers (provocative factors)
– Breakthrough cancer pain (attacks, 'peaks' or episodes)
– Location
– Quality
– Pain syndrome (neuropathic, nociceptive, visceral or somatic)
– Resources (relieving factors)
– Cause and pathophysiology (cancer, non-cancer, treatment)?
– Psychosocial and spiritual factors that influence patients' pain perception ('total pain')
Identify effects of pain on quality-of-life
– Physical function
–Wellbeing
– Mood,
– Coping
– Role functioning and relationships
– Sleep
– Sexuality
Gather information:
– Extent of disease
– Realistic treatment goals
Identify medical and psychiatric comorbidities, e.g.:
– Renal failure
– Substance abuse
– Depression and anxiety
Identify further palliative care needs
– Other symptoms (e.g. dyspnoea or nausea)
– Psychosocial or spiritual concerns
– Caregiver burden
– Specific fears
– Communication, care coordination, and goal setting problems
– Existential suffering (e.g., 'life does not make sense', 'feeling of hopelessness')

Table 2. Cancer pain syndromes (examples)

1. Cancer related pain
1.1 Cancer related neuropathic pain
– Central (e.g., Leptomeningeal metastases)
– Different cranial nerve neuropathies ('mixed picture')
– Peripheral (e.g., bone and tissue metastases)
– Painful radiculopathy
– Peripheral mono- and polyneuropathies
1.2 Cancer related somatic nociceptive pain (examples)
– Local bone pain
– Multifocal bone pain (e.g., diffuse bone metastases, bone marrow expansion)
1.3 Cancer related visceral nociceptive pain (examples)
– Hepatic distension
– Intestinal obstruction
– Peritoneal carcinomatosis
– Retroperitoneal syndrome
– Ureteric obstruction
2. Treatment related pain syndromes
2.1. Chemotherapy
– Peripheral neuropathy
2.2 Radiatiotherapy
– Plexopathy
– Myelopathy
– Osteoradionecrosis
– Lymphoedema
– Enteritis and proctitis
2.3 Surgery
– Postmastectomy and other chronic postoperative pain syndromes
– Stump pain
– Phantom pain
2.4 Long-term steroids
– Osteoporosis
– Aseptic necrosis (especially femoral or humeral head)
– Vertebral compression fractures

Disease-Modifying Therapy

Along with the development of a plan of pharmacologic treatment, disease-modifying therapy such as radiation should always be considered, especially in pain caused by bone metastases or other somatic nociceptive pain syndromes [16]. If bone pain is *localized,* as for example due to tissue destruction by a metastasis, radiotherapy can be extremely effective [17]. Since in early stages of metastatic breast cancer, survival over many years is not uncommon, these patients often benefit from low- dose multi-fraction radiotherapy to prevent long-term complications and malignant fractures. Yet, if patients suffer from advanced cancer (survival prognosis < 1 year) and their performance status declines, metanalyses and guidelines strongly recommend a 1 or 3 fraction radiation whenever feasible [17]. If bone pain is *multifocal* or even diffuse, referral to a nuclear medicine specialist is often indicated to check for the possibility to apply radiopharmaceuticals (lanthanoids, such as strontium-89 or samarium-153) as a relatively safe and effective pain relieving intervention. These interventions are generally associated with a comparatively low burden for the patient [18]. Samarium for example can be applied by a single infusion and is only associated with a 30% depression of hematopoiesis for a period of a few weeks, while the pain relieving effect can last for 3 months. After 3 months, Samarium may be applied again.

Information about the analgesic effects of systemic chemotherapy are limited and precise information is unavailable due to methodological problems of many studies [2, 19]. If according to clinical judgment, tumor response is assumed, this will most probably also have analgesic benefits [2].

Opioid Management

Despite the potential benefits of disease modifying therapy, opioid-based pharmacotherapy still is the most important component of cancer pain management since the publication of the World Health Organisation's (WHO) analgesic ladder concept.

Addiction and Drug Abuse

Despite the provision of a multitude of evidence-based guidelines [3–6, 8], a great part of cancer pain management standards still solely rely on clinical experience (expert opinion) [2]. Despite all merits of opioid therapy, physicians have to acknowledge that drug misuse and addiction cannot completely be ruled out, especially in chronic cancer pain [20].

For addiction, the understanding of a few key issues is necessary [21]. Addiction is strongly related to genetic predisposition that is characterized by craving, loss of control, compulsive use, and continued use despite harm [2, 21]. It might or might not be associated with a risk for the *abstinence syndrome* (physical dependence) or *tolerance* (loss of drug effect over time) [2, 21]. Addiction should be differentiated from drug abuse which describes the use of any drug outside of medical or social norms. Therefore individual or public harm can be minimized if substance use disorder is explicitly addressed when taking patients' medical history [2]. In breast cancer, the obligation to minimize this problem is relevant in potentially curative stages of the disease or when metastatic disease (e.g., bone metastases) does not severely limit the patients' life expectancy. Especially in breast cancer patients with a curative approach or a survival prognosis of many years, expert opinion is recommended before initiating long-term therapy with on-demand or even rapid-onset opioids [2].

Drug Selection

Normally, the so-called pure μ-agonist opioids (e.g., morphine, hydromorphone, fentanyl, oxycodone) are the first choice for the treatment of cancer pain, but morphine still is the advocated gold standard despite its well-known potential for accumulation and neurotoxicity in patients with renal impairment [22]. Among the alternatives, only pethidine and dextropropoxyphene cannot be recommended due to their potential for serious adverse effects [2].

Most studies on opioid rotation reveal the importance of individual differences in the response to the different opioids [23, 24]. This suggests that there is no most suitable opioid for all patients [2]. The clinically relevant facts are that (i) opioid therapy should be initiated with any of the pure μ-agonist drugs the physicians and their teams are familiar with and (ii) clinicians should be prepared to rotate (switch) to another drug in case of dose escalation or adverse effects [2]. Especially in case of high daily opioid doses, switching should be performed carefully rather than by simply calculating the so-called equivalent dose. It is justifiable to switch to an alternate opioid with a comparatively low dose (far below the calculated equivalent dose) as long as it is assured that the patient can receive the necessary on-demand opioid rescue medications (immediate release opioids or rapid onset fentanyl) as often and as much as it is needed [22].

Current clinical practice still follows the recommendations of the WHO analgesic ladder. Yet, especially in cancer pain, any pure μ-agonist drug, such as morphine or hydromorphone, can be initiated at low doses (e.g. 20–30 mg sustained-release (SR) morphine daily) for safe and effective management of moderate pain ignoring the second step of the analgesic ladder [25].

While morphine remains first choice of most recommendations especially due to its world-wide availability and low cost, its metabolism (resulting in potentially neurotoxic metabolites) may be problematic in patients with renal impairment. If renal failure is diagnosed, many clinicians rely on hydromorphone, oxycodone or buprenorphine [26].

Despite the lack of a broad evidence base, methadone has been used increasingly for the management of cancer pain [2, 27]. Methadone is a racemic substance and in some countries

both, the isolated active isomer (levomethadone) and the racemate is available [28]. It is relatively cheap and lacks active metabolites, which may be favorable in renal impairment [23, 29–31]. Due to the inhibition of the central monamino re-uptake and its N-methyl-d-asparate (NMDA) antagonism, pain specialists assume a favorable role for patients with neuropathic pain or opioid tolerance. Yet, its peculiar pharmacology may result in a very long half-life (several days are not uncommon) and a risk of accumulation, the absence of conversion ratios remains a problem, and cardiotoxicity can be problematic [32–34]. It is advisable to rely on specialized palliative care expertise before performing opioid rotation to methadone.

In the last years, a combination of oral oxycodone and naloxone (naltrexone) has become available [35]. The rationale behind this combination is that oral naloxone is subject to extensive hepatic metabolism, with an almost 100% first-pass effect. Therefore the absorbed naloxone does not antagonise analgesia (as provided by oxycodone's central μ agonism behind the blood-brain barrier) but the remaining naloxone may reduce the opioid related constipation by local intestinal μ antagonism [2]. The concept is innovative but sound clinical experience with the drug combination is growing constantly and the evidence base (measured in available randomized controlled trials, RCTs) for the potential of this approach in indications other than cancer is broad. Meanwhile, first studies support these findings for patients with cancer pain [37].

After many decades, a new opioid has been synthesized recently. Tapentadol is a μ-agonist and inhibits the central monamino re-uptake [36]. RCTs have been performed for chronic non-cancer pain. They reveal a favorable profile for gastrointestinal side effects. Yet, the substance is only available as SR formulation. The data for tapentadol for the treatment of cancer patients is scarce [37]. In the future, as the evidence base for the drug's potential broadens, it will be possible to make more accurate recommendations [2].

Route of Administration

The oral (and thereafter the transdermal) route of SR opioids is preferred before alternative routes of opioid application should be considered [2]. Transdermal therapy, e.g. with fentanyl, is an option if the oral route is impossible [38]. In advanced cancer, cachexia, B symptoms or unstable pain syndromes its effectiveness is reduced [38]. Moreover, transdermal patches supply a constant dose while patients with advanced cancer have different opioid needs. For example, patients with bone metastases often require higher opioid doses during the day since movement related pain is a frequent problem. Meanwhile, soluble morphine granulate is available as a liquid but retarded formulation as an alternative for SR morphine tablets.

The intramuscular route is painful and does not exhibit any pharmacological advantage. Rectal opioid administration is rarely ever a good option [2]. Subcutaneous opioid administration is often useful and frequently applicable for patients in advanced illness. Subcutaneous infusion or injection of morphine and hydromorphone can be performed by placement of a narrow butterfly catheter inserted under the skin which can be left in place for a week or more [39]. Before choosing other drugs for subcutaneous injections or infusions, pharmaceutical counseling is deemed mandatory [40]. If applied as a baseline opioid, morphine or hydromorphone can either be administered every 4 h (according to their average duration of action) or continuously via a syringe driver [41]. Some palliative care teams favor the use of patient controlled analgesia via a pump [41]. If subcutaneous infusion is problematic or the patient is routinely treated with other intravenous drugs, the intravenous route is an option.

Invasive Strategies

Though peridural, incrathecal, or other local anesthetic interventions such as coliac blockade are only suitable and necessary for the minority of patients [2], selected patients can benefit from neuraxial or plexus infusion [2, 42]. In the case of bone metastases, especially patients with localized pain of the lumbar spine, the pelvis, or the legs may benefit if radiotherapy along with optimal pharmacologic management by a specialist team has been unsatisfactory [2]. Implanted programmable pumps can also apply additional doses as requested by the patient [43].

Combination of Sustained and On-Demand (Immediate-Release or Rapid-Onset) Opioids

The latest update of the European Association of Palliative Care (EAPC) guidelines resulted in 2 'strong recommendations' [22]. Of these, the most important is that cancer pain patients should always receive a combination of both a scheduled (baseline) opioid (such as SR or transdermal opioids) and a 'rescue' or 'on-demand' opioid (e.g. immediate-release opioids or rapid-onset fentanyl, buccal or nasal) for the treatment of breakthrough pain (pain episodes, pain attacks or pain peaks, see below). The regularly scheduled (baseline) opioid dose should be increased whenever worsening pain necessitates dose increments [2]. Normally, titration results in a 30–100% increase or in the addition of a dose equivalent equal to the consumption of additional doses for breakthrough pain during the last days [2].

Clinical example: If a patient is treated with 90 mg of oral SR morphine per day (e.g., 3×30 mg) and requires up to 6 additional doses of 15 mg each of immediate-release (IR) morphine per day for the treatment of breakthrough pain (pain episodes) without experiencing signs of opioid overdose, the daily morphine dose should be increased to a new daily dose of 180 mg morphine (e.g., 3×60 mg SR morphine). This concept of dose escalation ensures safety. If relatively high doses of morphine or equivalent, e.g. >200 mg per day occur, reassessment of toxic effects (sedation, delusions, agitation etc.), and drug-related behaviors is recommended [2]. If no adverse

effect becomes obvious, dose escalation can continue until there is a reasonable balance between analgesia and side effects, and a lack of patient burden due to the intake of a high number of tablets irrespective of the dosis. Normally, the interval between dose escalations should allow a steady state to be reached (e.g., 2 days for SR morphine or hydromorphone or 3–6 days for transdermal opioids, 5–6 days for methadone). However, if pain is severe, more vigorous dose increments are justifiable, especially if opioid therapy is adjusted and reassessed by an experienced team [2]. Very severe pain should be titrated by intravenous or subcutaneous bolus injections at very short intervals [44]. While such management achieves quick analgesia, it is associated with the risk of delayed toxic effects [2]. Obviously, if delayed somnolence or other adverse effects occur, the dose should be reduced.

Accordingly, the dose of the short-acting drug for breakthrough pain should also be adjusted over time to maintain effects [2]. Although most textbooks recommend to prescribe one 6th of the daily opioid equivalent as on-demand dose, clinical experience suggests that this dose is highly individual [2]. As a safe range 5–15% of the total daily dose can be recommended [2]. Yet, caution should be taken if the patient is treated with high daily opioid doses (>200 mg oral morphine or equivalent) or in opioid rotation.

The on-demand (rescue) medication is not necessarily the same substance as the baseline opioid. For example, it is comprehensible to combine SR morphine (as the baseline opioid) with rapid onset-fentanyl.

Breakthrough Pain and Rapid-Onset Fentanyl

Although there still is an academic debate about the precise definition of breakthrough cancer pain, the concept is highly relevant for clinical practice and patient comfort [45, 46]. In short, it describes pain episodes ('peaks') that occur despite the fact that a patient is without pain at rest ('pain-free').

Especially many patients with advanced cancer and bone metastases are 'pain-free' during many hours of the day, but due to physical activity (taking a shower, walking in the garden) they suffer from breakthrough pain that is very intense and often limits their physical activity.

In cancer pain and dyspnoea management, one of the main pharmacologic innovations during the past years is the development of readily available rapid-onset fentanyl formulations. Meanwhile, these drugs have become recommended as state-of-the-art treatment for breakthrough pain in the recent EAPC guidelines [22, 47]. These substances that are applicable either via the nasal or buccal route provide a faster onset of analgesia than IR opioids or fentanyl and has a shorter period of action [47]. Especially patients with bone metastases suffer from pain episodes indicating fast action opioids (e.g., movement related pain or pain attacks 'out of the blue'). While the older IR opioids (e.g., morphine solution) need 30–45 min until their onset of action, rapid-onset fentanyl provides a much quicker onset of analgesia (10–15 min) [47]. Moreover, the clinical duration of action of IR opioids (hydromorphone, morphine) is around 4 h, but the pain episode (e.g. taking a shower, going outside) only lasts for 30–60 min. Therefore, analgesia with IR opioids last longer than needed, making patients drowsy and sleepy once they return from their activity. In contrast, the rapid-onset fentanyl has a clinically meaningful shorter duration of action (approximately 2 h). A safe and easy approach for the initiation of treatment with rapid onset fentanyl is to ask the patient whether she would prefer nasal spray or a buccal tablet and then to initiate treatment with rapid-onset fentanyl at one of the lowest available dose. The patient should be prepared to rapidly increase the dosis according to the clinical effect (pain relieve vs. sedation/side effects) [2].

Non-Opioids

A recent metanalysis reported that it cannot yet be concluded that the combination of the non-opioid and opioid is more effective than only opioids [48]. In clinical practice, patients with bone metastases often suffer from somatic nociceptive pain and require a regularly administered non-opioid in addition to opioid therapy (e.g., metamizol 5 g/day or ibuprofen 1,800 mg/day) [2, 34]. Although non-steroid-anti-inflammatory-drugs (NSAIDs) are often used for mild or moderate bone pain, this is problematic. Most authors do have safety concerns with the use in cancer patients. Clinicians should be aware of the potential for renal, hematological, gastrointestinal, and cardiovascular toxic effects [2]. In some countries, paracetamol is used as an alternative drug but is also considered to be problematic due to its potential for liver damage and its limited effectiveness [2]. In other countries (e.g., Germany, Austria) dipyrone (metamizol, novaminsulfon) is readily available [34]. Since the substance was accused to be related to severe cases of agranulocytosis and nephritits, it has become unavailable in other parts of the world. In practice, many clinicians favor the use of dipyrone (e.g. 5×0.5–5×1 g/day) for patients with cancer pain [34]. When compared with the potential harm of long-term NSAID therapy this can be a reasonable alternative [34]. Yet, research unfortunately does not provide sufficient data for cancer patients [49, 50].

Similarly, glucocorticoids, especially dexamethasone, are often prescribed in advanced illness, although the evidence base largely relies on favorable clinical observations [2]. Especially in the case of multifocal bone pain glucocorticoids are combined with bisphosphonates, but always in combination with opioid therapy [7, 51].

If bone metastases result in compression of neural tissue (neuropathic cancer pain), coanalgesics, such as pregabalin, gabapentin, amitriptyline, or carbamazepine, should be prescribed, titrated and controlled according to their benefit or side effects [52]. Pregabalin is a safe and effective option that allows relatively fast dose adjustments and also provides anxiolytic action [34]. Amitriptylin is a cheap and effective option but associated with a number of anticholinergic side

effects (e.g. constipation, dry mouth, delirium). Carbamazepine is one of the drugs with the highest potential for drug interactions and may result in clinically relevant hyponatremia [34].

Non-Pharmacologic Interventions

Pain is much more than nociception and *total pain* is relevant for most of the patients with metastatic cancer [53]. Especially in the patient with life-threatening disease it is closely related and influenced by other forms of (existential) suffering [54]. Other interventions, especially if performed by a multiprofessional team with strong expertise in identifying and treating psychosocial and spiritual suffering are a mainstay of (pain-) therapy of patients with metastatic cancer [55]. Interventions may also introduce relaxation training, guided imagery, hypnosis, and biofeedback while self-efficacy can also be increased by careful physiotherapy and open and honest communication and decision-making [2, 56–58]. The fact that these strategies reduce pain and other domains of suffering emphasizes the value of recognizing emotions and limited autonomy as mediators of symptom distress [2]. Additionally, clinicians should actively address patients' worries concerning pharmacotherapy (e.g., opioid myths) as well as specific fears (e.g. ‚I will die in pain') [45], provide time to listen to the patients' worries and make use of readily comprehensible language (avoid medical terminology, talk slowly and calmly, allow for pauses) [45, 59]. Most authors agree that cancer pain management is best provided in close collaboration with a palliative care service (team) [2]. In a recent systematic review on cancer pain, Portenoy et al. [60] found that in (breast) cancer patients pain is rarely an isolated problem. Patients frequently suffer from many different symptoms and other worries. This burden can be substantially worsened by psychological or social factors, and heightened by spiritual or existential challenges [2]. According to Portenoy et al. [2], interventions to manage pain are often welcome, yet do not suffice to improve quality of life or reduce suffering if they are separated from the concerns associated with a serious and life-limiting disease that can only be adequately addressed by a conjoint palliative care approach. This can be provided as general palliative care by the primary treatment team and specialized care by an interdisciplinary palliative care team that is integrated along the trajectory of the disease [2, 61].

Conclusion

Most breast cancer patients suffering from pain resulting from bone metastases can be sufficiently treated if a number of measures are respected (table 3). Therefore, opioid therapy is the cornerstone of pharmacologic pain management. Morphine remains the gold standard but other pure μ-agonists can be considered alternatively. Transdermal opioids are an important option if the oral route is impossible, but should not be used as first-choice opioid. Due to its complex pharmacology, methadone should be restricted to patients with difficult

Table 3. Eleven basic rules for management of pain due to bone metastases

1. Rule out non-cancer related causes of pain! (E.g.: gastritis, urinary tract infection, pathologic fractures, myocardial infarction)
2. Consider radiotherapy in local bone (somatic nociceptive-) pain. Gold standard in combination with pharmacologic pain management
3. Consider radionuclids (e.g. samarium) in diffuse or multilocal bone pain.
4. Opioid therapy:
   - 4.1. If pain is moderate to severe: initiate opioid therapy according to WHO step III
   - 4.2. Start with potent pure μ agonist (e.g. morphine, hydromorphone, fentanyl, oxycodone)
   - 4.3. Provide both a baseline ('regular' or 'scheduled') opioid (e.g. SR morphine or SR hydromorphone) and on demand (rescue) opioid medication (e.g. immediate release morphine or rapid onset fentanyl)
     - Dosing of immediate release opioids: 1/6th or less than the daily dose of the baseline opioid
     - Beware of strict dose 'calculation' in case of high doses of baseline opioid and if baseline opioid is provided as transdermal opioid
     - Dosing of rapid onset fentanyl: start with lowest available dose, be prepared for rapid dose increase
   - 4.4. Adjust baseline opioids according to temporal pattern of pain; e.g.: If pain is higher during day, provide double morning dose of SR opioid
   - 4.5. Identify breakthrough pain (pain episodes, pain attacks)
   - Identify triggers (e.g. physical activity)
   - Educate patient to take on demand opioid in advance (e.g. 30 min before taking physical activity)
   - If pain episodes need fast onset of analgesia: rapid onset fentanyl (nasal / buccal)
   - 4.6. In case of dose escalation (>240 mg morphine/day) without suffient pain relief: consider opioid rotation
   - Calculate carefully, start with low doses but provide enough on-demand opioid medication
5. Identify concomitant neuropathic pain
   Initiate and titrate coanalgetic (e.g. pregabalin with anxiolytic effect)
6. Identify other factors that contribute to 'total pain'
   - Other symptoms (e.g. dyspnoea, anxiety, depression)
   - Psychosocial domain (feeling of left alone, no communication about disease, feeling urged to 'fight')
   - Spiritual burden (e.g. feeling of guilt)
   - Existential suffering (hopelessness, wish for hastening death, meaninglessness of life)
7. Advanced cancer: consider indication for glucocorticoids (e.g. dexamethasone 4 mg/d)
8. Provide non-opioid in a fixed, regular basis; e.g. dipyrone (metamizole, novaminsulfone) 2.5–5 g/d, ibuprofen 1,200–1,800 mg/d
9. Always check bisphosphonate therapy even if patient is 'pain free' or in early stage of the disease
10. Advanced disease: consider support of palliative care service
11. Invasive procedures (e.g. neuroaxial ananaesthesia): rarely necessary but important option

SR: Sustained-release.

pain syndromes. Especially bone metastases result in breakthrough pain episodes (especially related to physical activity) that require the provision of an on-demand opioid (e.g. IR morphine) in addition to the baseline (regular) opioid therapy (e.g., SR morphine or transdermal fentanyl). Recently, rapid-onset (buccal or nasal) fentanyls have been strongly recommended for breakthrough cancer pain episodes. In advanced cancer, glucocorticoids are an important treatment option in combination with opioid therapy. If bone metastases affect neural tissues, coanalgesics (e.g., pregabalin) should be initiated. In localized bone pain, radiotherapy is a very important option for pain reduction while in diffuse bone pain radionuclids should be considered. If available, metamizole or dipyrone is an alternative to non-steroid-anti-inflammatory-drugs. Especially in advanced cancer, pain is much more than nociception and a multi-professional palliative care approach is state of the art to addresses all domains of suffering ('total pain'). Invasive measures (e.g., neuroaxial block) are rarely necessary but provide an important treatment option for patients with cancer pain syndromes that are refractory to pharmacologic and non-pharmacologic management provided by specialized palliative care teams and not suitable for radiotherapy.

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Disclosure Statement

The authors declare no conflicts of interest.

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