MIKOŁAJCZAK, Karolina, ĆWIRKO, Hanna, and GARLAK, Urszula. Palliative Pain Treatment in Patients with Bone Metastasis – A Review. Quality in Sport. 2025;39:59070. eISSN 2450-3118.
https://doi.org/10.12775/QS.2025.39.59070
https://apcz.umk.pl/QS/article/view/59070

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 27.02.2025. Revised: 05.03.2025. Accepted: 25.03.2025 Published: 25.03.2025.

Palliative Pain Treatment in Patients with Bone Metastasis – A Review

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ABSTRACT

Finding cancer metastases to the bone in cancer patients significantly worsens their prognosis and transforms them into palliative patients. Unfortunately, as they are diagnosed more frequently, the health problems that result from the appearance of such lesions are becoming more and more common. Fortunately, there are a number of treatments for bone metastases that improve quality of life and prolong patient survival. These include classic methods, such as chemotherapy, radiation therapy, and surgical approaches, but doctors can also offer an increasing number of modern treatments, such as minimally invasive surgical methods and drugs that target bone directly. This article reviews the literature reports of current treatments for bone metastases.

Keywords: bone metastasis, cancer, pain, palliative treatment, chemotherapy, radiotherapy, minimally invasive surgery

Introduction

Bones are third most common location of metastases in the human body (1). According to the SEER database from 2010-2015*, de novo* bone metastases were detected annually in 18.8 people per 100,000 (2). The most common sources of them is prostate cancer and breast cancer - together about 70%. They also appear in advanced stages of the thyroid, lung, bladder, kidney cancers and malignant melanoma (1). Their appearance significantly affects the quality of life of cancer patients because of the severe pain they cause (3). Unfortunately, the prognosis of cancer patients also deteriorates significantly once bone metastases are detected. Due to the frequency and high impact of these changes on the lives of cancer patients, we should pay special attention to relieving pain and maintaining maximum comfort for these end-of-life patients (4).

Methods

A literature analysis was performed using the PubMed database. Publications from the last 30 years were included. The keywords used were bone metastasis searched alone or in combination with palliative treatment, chemotherapy, radiotherapy or minimally invasive surgery. Articles of various types were analysed. Only publications in English were used. Articles cited in the publication were selected by 3 independent researchers.

Types of bone metastasis

We can divide cancer metastases into three types, depending on the effect on the structure of bone tissue:

1. **Osteolytic metastases** - typical of breast, lung and urinary tract cancers and multiple myeloma. Rarefaction of the trabecular structure of bone and demineralization of bone is observed.
2. **Osteosclerotic metastases** - characteristic for prostate cancer, breast cancer and micro-cellular lung cancer. They cause thickening of bone structures by increasing the number and thickening of bone trabeculae.
3. **Mixed metastases** - occur in breast and prostate cancer. They have features of both of the above-mentioned types of metastases (5).The first clinical signs are usually pain in various parts of the spine, depending on the location of the metastasis, pathological fractures, episodes of hypercalcemia and neurological symptoms associated with pressing on various parts of the nervous system, although in many cases they can also be asymptomatic (6,7).

Characteristics of the pain caused by bone metastasis

Since the bones are highly afferently sensory innervated, bone lesions can cause very severe pain, impairing quality of life and disabling daily activities. They can occur during specific movements, but we also observe patients with chronic pain (8).

Pain receptors are found in equal numbers in the bone marrow and in the periosteum. However, periosteal pain is thought to be much more severe than pain caused by bone marrow lesions, most likely due to the lack of Aβ mechanoreceptors and Golgi-Mazzoni bodies in the bone marrow (9).

Receptors in the bone marrow may additionally be activated by increased intracranial pressure (10). Importantly, these nociceptors can also be activated by various chemokines responsible for the sensation of pain, heat, cold, reactive oxygen species, or acidity (11). In

addition, pain can be induced by inflammatory mediators, or tumor-produced extracellular ATP, TGF-β1, and IGF-1 (12).

Methods of pain treatment

As bone pain can sometimes be very awkward, there are many methods of treating it, and the choice of the right one depends mainly on the patient's condition and his subjective assessment of pain sensation. It should be remembered that pain management is the basis of palliative medicine, so particular attention should be paid to caring for the quality of life of patients and trying to relieve their pain as much as possible. Doctors should therefore be familiar with the latest treatments for bone pain. The most common methods described in the scientific literature for treating pain caused by cancer metastasis to the bone are mentioned below.

Non-opioid pain-killers

This group includes paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase 2 (COX-2) inhibitors. WHO guidelines suggest using them as first-line treatment due to their mildest effects. Adjuvant drugs can also be used along with them (13). The effectiveness of monotherapy for bone pain with NSAIDs is low, as they mainly relieve pain originating in the muscles and soft tissues and are dedicated to the treatment of mild pain (14).

However, there are literature reports that there are NSAIDs effective in the treatment of bone pain. One of these is ketorolac, an NSAID with strong analgesic effects, used mainly in patients with acute pain, especially after major surgery. In combination with opioids, it allows a significant reduction in their dose. It is used in subcutaneously at a dose of 60-120 mg per day in 250 ml of 0.9% NaCl in continuous infusion (15,16).

In addition, diclofenac also should be mentioned. An oral dose of 75 mg per day can control bone pain of low intensity (17). It has also been proven that its use as an adjuvant drug in opioid therapy can significantly reduce their applied doses. An even better effect is obtained when celecoxib is added to this combination (18).

The literature reports that oral paracetamol should not be routinely used for severe pain, as patients do not seem to benefit much from its addition to strong opioids. However, its use may be useful in the treatment of acute pain caused by bone metastases (19).

Opioid pain-killers

Opioids are the most commonly prescribed analgesics for cancer-related pain. For example, according to the literature, about 30-60% of patients suffering from breast cancer with

bone metastasis that are prescribed opioids in various doses (20). A major reason for this is their moderate-to-high action and the development of tolerance to their respiratory side effects, especially during gradual dose escalation. However, it should be kept in mind that along with tolerance, physical dependence also is developed (21,22). It should be remembered, though, that in palliative patients, in whom we do not consider discontinuing analgesics in the future, but are only trying to relieve the pain they experience at the end of life, the problem of addiction may be overlooked in considerations.

The most commonly used opioids for bone pain relief are pure μ-agonists, such as morphine, hydromorphone, fentanyl and oxycodone. Although the gold standard is still the administration of morphine, the studies suggest that each patient may respond individually to each of the substances mentioned, so it should be selected individually for the patient so that they experience as few side effects as possible with the best possible pain control at the lowest possible drug doses. Switching, however, should be done with caution, especially in patients taking high doses of drugs due to possible side effects. Be sure to calculate the appropriate dose equivalent (23–25).

When starting opioid therapy, it is preferred to use the lowest doses of medications per oral. It is possible with morphine and oxycodone. However, patients with bone metastases often require high doses of opioids, so often a more convenient route of administration are transdermal systems, available, for example, with fentanyl or buprenorphine, which provide continuous release of a constant dose of the drug without the need to take care of regularity of intake, as in the case of the oral route. In addition, intramuscular drug delivery, such as morphine, is also possible, but this is not the best solution due to the long absorption time of the drug by this route, which implies more difficult control of analgesic treatment, so it is not currently used. A better option for this drug is the subcutaneous or intravenous route (also used for fentanyl, buprenorphine) (25–28). In the case of fentanyl, there are also intranasal products, and their usage provides well-controlled analgesia (29).

Moreover, the results of studies published in 2020 and 2023 suggest that if existing opioid treatment is not effective in reducing patients' pain, the drug should be changed to methadone, which appears to be effective in pain refractory to standard treatment, as it is very effective in treating both nociceptive and neuropathic pain (30–32).

Adjuvant drugs

Bone metastasis pain originates mainly from infiltration of nervous system structures by tumor tissue. It is rarely a purely receptor pain. Thus, to potentiate the effect of standard

analgesics, numerous coanalgesic substances are used. Their effects can further offset the side effects of high doses of analgesics (33).

Among adjuvant drugs, we distinguish:

1) Antidepresants:
   a) selective serotonin reuptake inhibitors (e.g. fluoxetine, fluvoxamine, paroxetine, sertraline, escitalopram)
   b) serotonin and noradrenalin reuptake inhibitors (e.g. duloxetine)
   c) tricyclic antidepressants (e.g. amitriptyline, doxepin)
   d) quadricyclic antidepressants (e.g., mianserin)
   e) bupropion
   f) monoamine oxidase inhibitors (e.g., moclobemide)
   g) trazodone
   h) mitrazapine
2) anticonvulsants (e.g., pregabalin, gabapentin, lamotrigine, topiramate, carbamazepine)
3) NMDA receptor antagonists (e.g., memantine)
4) glucocorticosteroids (34,35).

The postulated way in which antidepressants facilitate pain control assumes that by increasing the concentrations of activating neurotransmitters such as serotonin, or norepinephrine, it results in modulating pain transmission and reducing the reception of stimuli from these sources. However, it is important to note that this action should be used in polytherapy with analgesics, as studies show that there is no significant improvement in patients taking antidepressants as monotherapy (36,37).

The most effective treatment is a combination of opioids and antidepressants, especially amitriptyline (32).

In addition, up to 25% of cancer patients with bone metastases suffer from depression. In its course, a significant increase in pain and a greater sense of suffering can be observed. Antidepressants also treat depression, resulting in a significant reduction in pain (38).

The use of anticonvulsants, especially gabapentin in combination with opioids, makes it possible to significantly reduce the dosage of used opioid analgesics (39,40). A main reason for this is their synergistic and additive effects in reducing pain impulsivity. Unfortunately, their additive effects also exacerbate side effects, especially sedation, which should be paid special attention to when using such drug combinations (40).

Since NMDA receptors are accumulated in large numbers at nociceptive synapses, their stimulation results in an increase in the patient's perception of pain. Administration of NMDA

receptor antagonists, such as memantine or ketamine, can abolish the aforementioned effect, thereby suppressing the nociceptive effect. The described mechanisms are particularly important for patients who have developed opioid hyperalgesia, as it can be abolished with the mentioned drugs (41,42).

Glucocorticosteroids (GCS) are the most commonly used adjuvant drugs in the treatment of patients with bone metastases. Their anti-inflammatory effect reduces the secretion of pro-inflammatory cytokines and prostanoids. In addition, they have an anti-edematous effect that reduces swelling around metastatic tissues. Both of these actions ultimately result in relief of the pain experienced by the patient (35). The most common drugs of choice are dexamethasone, prednisone and methylprednisolone in various doses, depending on the case (43). However, there are studies that suggest little improvement in pain control in relation to the numerous side effects induced in patients, so special care should be taken when using GCSs and they should be introduced for the shortest possible time (35,44).

Bone-targeting drugs

There are several drugs acting directly in bones that are used in metastasis pain treatment. One of the most commonly used are bisphosphonates. By causing osteoclast's apoptosis they prevent bone remodelling and weakening its structure. Thanks to that patients suffers from bone damages less frequently. There are also many evidences showing, that it's usage allows lowering pain-killers doses, but the mechanism is unknown (35,45). So that WHO strongly recommends using them in bone pain, but only in patients with good prognosis (46).

Another frequently used drug is denosumab. Its effects, like those of bisphosphonates, is a reduction in the incidence of bone damage due to the delay of emerging bone architecture changes in the course of cancer, but it appears to have a stronger analgesic effect compared to bisphosphonates. Studies have shown that its usage allows the later introduction of strong opioids, and in patients with bone lesions without complaints, delayed the onset of pain. Thus, it seems appropriate to use denosumab along with appropriate vitamin D and calcium supplementation even before the onset of complaints to improve the quality of life of patients (47). In addition, there are studies confirming the ability of denosumab to reduce the mass of tumor, which also implies less pain in patients (48).

On the other hand, there are sources that deny the direct analgesic effect of bisphosphonates and denosumab, and attribute the observed therapeutic effect to delaying the onset of pain (49).

Chemotherapy

End-of-life patients are rarely good candidates to continue classic chemotherapy. It is commonly treated as persistent therapy and discontinued. For such patients, a good alternative is the use of paclitaxel carried in lipid core nanoparticles. This form of the drug significantly reduces its toxic effects on the body with noticeable pain relief (50). However, this therapy is not yet available in clinical practice. However, numerous clinical trials are underway, the results of which may change the approach to palliative treatment of patients with bone metastases.

Radiation therapy

The impact of radiation therapy on the quality of life of patients with bone metastases is well understood. Its usage results in better pain control, and patients remain functional longer. Up to two-thirds of patients indicate a marked improvement in pain control after radiation therapy (51). A major therapeutic modality is therefore highly used. Its effect, however, does not occur immediately, but after a few days or weeks, so by then patients should have well-controlled pain with medication.

Radiation therapy affects tumor-affected bone by inducing ossification, restoring the balance between osteoblasts and osteoclasts, and destroying tumor cells which induces tumor shrinkage and reduces pain associated with infiltration of surrounding tissues (52).

The choice of radiotherapy fractionation mainly depends on the life expectancy of patients. It is possible to use a single-fraction scheme – 8 Gy administered in a single dose, or a multi-fraction scheme - e.g. 20 Gy in 5 fractions, 30 Gy in 10 fractions. The decision to use a specific fractionation scheme is left to radiation specialists, who, based on life expectancy and expected outcome, select it according to the clinical situation (53).

According to studies, for the treatment of so-called uncomplicated bone metastases (that is, those that do not cause the spinal cord compression and have not caused pathological fractures), there are no differences in the effectiveness of the two methods used. However, differences do arise when complications occur (54). Studies show that the most effective method of radiation therapy, for patients after spinal decompression surgery, is the delivery of 30 Gy in 10 fractions (55). It has even been hypothesized that this treatment can improve the stabilization of the pathological fracture and increase function and prolong survival (56).

45-60% of spinal cord compression (ESCC) cases result from bone metastases of prostate, breast and lung cancers. Although there is no clear definition of this condition, due to the many differences in patients' clinical status, the level of spinal cord lesions and epidural

involvement, there are treatment guidelines for ESCC, with radiological techniques playing a major role (57).

In patients disqualified from surgery, radiation treatment should be started with a single dose of 8-10 Gy. This radiation dose prevents complications of spinal cord compression (Level A, Class Ia recommendation) and relieves neuropathic pain (Level A, Class Ib recommendation). Re-irradiation is used after about 6 months, only if the cumulative radiation dose does not exceed 100-135.5 Gy (recommendation level B, class 2) (58).

For patients with multiply bone metastases, palliative half-body irradiation can be used. This method is an alternative to standard local field radiotherapy, but takes much less time, with similarly good pain control (59). Its use, however, is declining over time due to the purported toxicity of this method. However, studies show that this toxicity is negligible, with pain control improving in up to 76.3% of patients. After using this method, the 3-year progression-free survival rate is 77% (60).

Another widely used method of radiotherapy is stereotactic radiotherapy. This is a method that allows a high dose of radiation to be delivered precisely to the affected area, sparing the surrounding tissues (61), especially the spinal cord, nerves that run close to the lesions, and the plexus brachialis and lumbosacralis. MRI is often used in planning such treatment (62). It is currently considered that there are no poor prognosis factors for this method with good response in terms of lesion retreatment and pain control (63). Its use also reduces the risk of fractures of affected long bones (64).

When planning radiotherapy treatment, special attention should be paid to the treatment planning process itself. 2D and 3D methods are available. Studies show that 3D planning is better and more accurate, if only because of the even greater reduction in radiation inflicted on surrounding tissues (65–67).

Neither should we forget the use of intensity-modulated radiotherapy (IMRT), which is an alternative to standard multi-dose radiotherapy and appears to cause even fewer side effects, especially concerning organs at risk with similar efficacy in treating pain and increasing bone density (68–70).

Bone-targeting radiopharmaceutics

Radiopharmaceuticals are widely used in patients with bone metastases. They are most often used for diagnostics, such as bone scintigraphy. However, drugs in this group are becoming used more frequently to treat bone metastases. The essence of their action is to transmit as much radiation as possible directly to the cancer cells with the smallest possible

margines. Both β- and α-emitting chemical compounds are used. The most commonly used β -emitters are 89Sr-dichloride and 153Sm-ethylene diamine tetramethylene bisphosphonate. As a result of their long range and low energy, they are used to reduce pain, but they do not affect survival. Of the α-emitters, a new compound, 223Ra-dichloride, is now being used, which has a much higher energy and much lower range, so that its action targets tumor cells directly without damaging surrounding structures, which not only relieves cancer pain, but also prolongs patient survival (71,72).

Surgical treatment

Since the treatment of patients with bone metastases is palliative, surgical methods are rarely used as first-line treatment. Unfortunately, surgical removal of tumor masses can, instead of helping the patient, reduce bone strength and expose the patient to more frequent complications (73). As mentioned earlier, surgery is most often performed to treat complications of bone metastases, such as pathological fractures or spinal cord compression. Bones can be stabilized externally or internally, or osteosynthesis can be performed. If the patient, due to his general condition, is ineligible for surgery, minimally invasive techniques can be used, the greatest advantage of which is the low burden on the body and the possibility of combining these methods with other methods of treating bone pain in complicated bone metastases (73–75).

Minimally invasive techniques

1. **Percutaneus cementoplasty –** most commonly used method nowadays. It involves the insertion of polymethylmethacrylate into the bone through the working channel, which is a puncture needle, under fluoroscopy or CT scan guidance (76,77). Currently, the antitumor effect of the presented method is demented, but it is certain that it improves the quality of life of patients due to bone stabilization (78).
2. **Minimally invasive internal fixation procedures** – methods mainly used to stabilize bones due to bone abrasion or fractures. In this way, devices such as nails, hollows or screws can be placed intraperiosteally without the obligatory performance of surgery by the classic method. A definite advantage of such procedures is the protection of a large section of bone by an internal stabilizer, but the possibility of spreading tumor cells along the implanted foreign body must be kept in mind (79,80).
3. **Local ablation techniques –** the essence of ablation of cancerous tumors is their percutaneous destruction, in the case of bone metastases mainly for analgesic purposes. There are 3

most commonly used types of ablation: cryoablation, radiofrequency ablation and high intensity focused ultrasound (HIFU) (81). Cryoablation involves abruptly lowering the temperature of cancer cells to -40 degrees Celsius and then returning them to ambient temperature. This action causes the sudden death of these cells, mainly by dehydration and disintegration (82,83). Radiofrequency ablation involves the insertion of electrodes into the tumor under the control of an imaging study, which, through the application of current, causes an increase in the temperature of the tumor and the death of its cells. It has been proven that tumor cells are much more susceptible to high temperatures, so this method spares healthy tissue with great accuracy (83,84). HIFU takes advantage of the fact that the conduction of ultrasound through cortical bone is much lower than that of surrounding structures, and the absorption is much higher, resulting in the generation of high temperature and the destruction of surrounding cancer cells. The undoubted advantage of this method is that there is no need to break the continuity of the skin, so the procedure is completely non-invasive (85,86).

Summary

Although bone metastases are painful and troublesome lesions that significantly impair the quality of life of cancer patients, there are now many therapeutic options to improve the comfort and even survival time of patients. Therapeutic possibilities start with methods that have been used in medicine for a long time, such as classic chemotherapy or radiation therapy. Thanks to the development of technology in medicine and the emergence of newer and newer drugs, in therapeutic practice doctors have an increasing choice of treatment methods to use, making it much easier to help patients. Specialists in all fields of medicine, especially oncologists, radiation therapists, surgeons, orthopedic surgeons, but also family physicians, should observe the changes taking place in the guidelines of treatment of cancer metastasis to the bone, in order to be able to offer their patients better and more modern treatment methods to improve their quality of life and prognosis.

Author's Contribution

Conceptualization, Karolina Mikołajczak; methodology, Urszula Garlak; software, Hanna Ćwirko; check, Karolina Mikołajczak, Hanna Ćwirko and Urszula Garlak; formal analysis, Karolina Mikołajczak; investigation, Hanna Ćwirko, Urszula Garlak; resources, Hanna Ćwirko; data curation, Urszula Garlak; writing - rough preparation, Karolina Mikołajczak; writing - review and editing, Hanna Ćwirko, Urszula Garlak; visualization, Hanna Ćwirko; supervision, Karolina Mikołajczak; project administration, Karolina Mikołajczak;

All authors have read and agreed with the published version of the manuscript.

Funding Statement: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Institutional Review Board Statemen: Not applicable.

Informed Consent Statement: Not applicable.

Data availability: Not applicable.

Conflicts of interests: Authors declare that there is no conflict of interest.

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