Review

Managing metastatic bone pain: New perspectives, different solutions

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A B S T R A C T

Bone metastases are the most frequent cause of cancer-induced bone pain (CIBP). Although palliative radiotherapy and pharmacotherapy conducted according to World Health Organization (WHO) analgesic ladder are the treatment of choice for CIBP reduction, these methods are not always successful, especially with regard to alleviation of incidental pain. Antiresorptive drugs (bisphosphonates) are able to inhibit bone destruction (loss), proliferation of cancer cells and angiogenesis, but their prolonged use may lead to a spectrum of adverse effects. In this paper, types of bone metastases, their complications, as well as diagnostic and therapeutic implications are presented. Moreover, the paper discusses presently used CIBP treatment methods and research directions for future methods, with special focus on bone metastases.

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1. Introduction

1.1. Types of bone metastases

Bone metastases can be categorized on the basis of radiological and histopathological image data and divided into osteolytic, osteosclerotic and mixed types.

Osteolytic metastases are responsible for bone destruction. These types of lesions are related with breast, lung, thyroid, kidney and multiple myeloma cancer.
The second type of bone metastasis, referred to as the osteosclerotic type, is able to stimulate new bone tissue formation and is associated with prostate and breast cancer.

The third type, called mixed metastasis, occurs mainly with lymphoma, breast and lung cancer. This type of metastasis is related to local interactions of metastatic cells with osteoclasts and osteoblasts [1,2].

Regardless of their type, metastases alter normal bone architecture and increase the risk of complications referred to as skeletal-related events (SRE) [1–3]. The processes of bone resorption and formation are closely interrelated and, although they may be impaired due to ongoing cancerogenesis, they occur at the site of the metastasis (independently of its type) in nearly all types of cancer [4]. There are two exceptions from this rule. The first is osteosarcoma (the 3rd most frequent type of cancer in children and youth) which is related to pure osteosclerotic metastasis [5] and the second is multiple myeloma giving exclusively metastases of “purely” osteolytic character [6]. In all other types of cancers, the process of bone formation is secondary to osteolysis [7].

Prostate and bladder cancers are responsible mainly for osteosclerotic (aka. osteoblastic) metastases [8], however intense osteolysis is also observed in these types of cancers. Therefore, the application of antiresorptive drugs decreases pain and risk of pathological fractures in patients with prostate cancer [9–11].

Breast and lung cancers and lymphomas lead to simultaneous osteosclerotic and osteolytic metastases. These types of lesions are therefore referred to as mixed- type metastases.

In patients with breast and lung cancer, osteolytic lesions prevail. In 25% of patients suffering from breast cancer, blastic metastasis is also present, while osteosclerotic metastases prevail in 15–20% of such patients [1,3,12]. In the case of thyroid, kidney and multiple myeloma cancers, osteolytic metastasis is the most frequent type of lesion [13].

Biochemical markers of bone turnover (i.e. cell-secreted peptides and proteins as well as cellular products of degradation) are assessed for quick evaluation of cellular activity in the bone [14]. The levels of the above-mentioned markers may be increased in female breast cancer patients even in the absence of clinical manifestations of metastases [15].

### 1.1.1. Osteolytic metastases

Osteoclasts are polynuclear cells adhered to the bone using αvβ3 integrin. Due to the secretion of collagenases, proteases and hydrogen ions, they are able to demineralize the bone matrix. Osteoclasts’ main growth factors are called RANKL (Receptor Activators of Nuclear Factor κB Ligand) and M-CSF (macrophage colony stimulating factor) [16,17]. RANKL activates osteoclastogenesis, prolongs the time of osteoclasts’ survival by binding on these cells and their precursors’ surface [18–21]. In turn, M-CSF increases RANKL expression on the surface of bone stromal cells, has a chemotactic effect on osteoclasts and prolongs their life span by inhibiting apoptosis [22].

IL-11 is another cellular factor that induces and escalates osteoclastogenesis [23]. There are many other growth factors that can directly or indirectly induce osteoclasts’ formation, stimulate their activity or prolong their life span. One of them is Parathyroid Hormone-Related Peptide (PTHrP), produced by a majority of solid tumor cells (e.g. breast cancers). PTHrP binds to PTHrP1 receptor (i.e. receptor of PTH) and induces RANKL expression on cells of stromal bone marrow (see Fig. 1) [24,25].

TGFβ, in turn, stimulates the production of PTHrP by breast cancer cells [26,27]. It has been found that PTHrP production was increased in 92% of patients with metastases from breast to bone, while the presence of this peptide was confirmed in only 50% of patients suffering from breast cancer without metastasis to bone tissue [28].

Phenotypic similarity of breast cancer cells to osteoblasts is the reason why breast cancer tends to metastasize to the bone. Barns et al. have shown ectopic expression of the transcription factor referred to as the RUNX2 protein (Runt-Related Transcription Factor 2) that stimulates bone sialoprotein (BSP) synthesis in breast cancers [29]. BSP level correlates positively with the frequency of metastasis to the bone [30]. BSP plays a role in angiogenesis, micro-calciﬁcation and protection from complement-induced cell lysis [31]. RUNX2 protein also stimulates osteoblasts’ differentiation. Breast cancer and multiple myeloma cells produce cytokines that inhibit osteoblasts’ activity, namely activin A and DKK-1 (dikkopf-related protein 1) [32,33]. DKK-1 is a
soluble inhibitor of the Wnt signal path which is important for the process of growth and differentiation of osteoblasts.

1.1.2. Osteosclerotic (osteoblastic) metastases

The cells of some cancer types, such as adenocarcinoma, secrete or induce the secretion of various factors stimulating osteoblasts' proliferation [34,35], such as transforming growth factor β (TGFβ) and urokinase [36]. Other factors responsible for the formation and activation of osteoblasts are Wnt (wingless int) proteins that stimulate these cells' differentiation and activation, prolong their life span and suppress osteoclastic activity [37]. Also Platelet-Derived Growth Factor (PDGF) increases osteoblasts' activity and stimulates angiogenesis [38].

Osteoblasts produce Insulin-Growth Factors (IGFs, and so do bone endothelial cells) and insulin-like growth factor-binding proteins (IGF-BPs). The IGF axis imbalance promotes tumor invasion and tumor-induced angiogenesis. IGF balance depends on urokinase plasminogen activator (uPA), synthesized by tumor and endothelial cells. IGF and uPA mutually boost their activity. High uPA levels are responsible for the degradation of IGF-BPs and by the same token for the increase in IGFs. This in turn stimulates the growth of metastatic cells and osteoblasts. IGF-1 also activates metalloproteinases in cancer cells [39].

It was shown that Insulin-Growth Factors (IGF-1 and IGF-2) stimulated the proliferation of osteoblasts and prolong their life span [40]. Adrenomedulin (ADM) promotes angiogenesis. Prostate cancer cells were observed to produce osteogenic factors, including Wnt proteins which are osteoinductive and oncogenic. DKK-1 is a Wnt antagonist and inhibits bone growth within osteoblastic metastases [41]. Endothelin-1 (ET-1) stimulates ETAR and using N-terminal portion of PTHrP down-regulates DKK-1 produced by tumor cells. It leads to osteoblasts' proliferation, drop of osteoclasts' activity, to an increase in bone mineralization and to the activation of other pro-osteosclerotic growth factors [42,43]. This is rooted in the fact that the endothelin system is crucial for numerous physiological and pathological processes, including cancerogenesis and osteosclerotic metastases. Endothelins influence the following signaling pathways: Ras, β-catenin/T-cell factor/lymphoid enhancer factor, mitogen activated protein kinases, nuclear factor-kB (NFkB), mammalian target of rapamycin (mTOR) and the zinc-finger transcriptional factors (Snail) [44].

Also another particle, described as Vascular Endothelial Growth Factor (VEGF) is able to stimulate osteoblasts' differentiation and is involved in osteolysis [45]. Its expression is dependent on the mentioned IGF-1 levels in serum [39]. Another growth factor – Fibroblast Growth Factor [2,6,25,46–48] stimulates not only osteoblasts' differentiation but also their proliferation.

During bone cancerogenesis, the activated osteoblasts secrete various growth factors that are later used by cancer cells to proliferate and to increase their odds for survival. These proliferating cancer cells secrete increased numbers of pro-osteoblastic factors that stimulate cancerogenesis. This path turns into a vicious circle [6]. Over a half a century ago, a theory was proposed according to which all types of metastasis to the bone are preceded by osteolysis [49]. Although this theory has not been confirmed to this day, it has been proven that by stopping osteolysis, cancer cells proliferation may be decreased (even in cases of osteosclerotic metastases) thanks to the drop in the secretion of cancer-inducing growth factors released from the bone matrix [47].

Apart from its impact on osteoclasts and osteoblasts, cancer cells in bone mobilize and modulate the function of bone marrow cells (in particular platelets and white cells) as well as neurons and cells responsible for angiogenesis [50–52].

Osteolytic metastases may be a reason of such para-neoplastic symptoms, such as hypercalcemia (nausea, vomiting, constipation, abdominal pain, debilitation, anorexia, body mass loss, polyuria, nephrolithiasis, ascitance, impaired consciousness, coma and death). These symptoms occur predominately in the course of myeloma myelitis (in 33% of patients), breast cancer (19% of patients) and lung cancer [53,54].

Neurological impairments (due to pressure on the nerve) and pathological bone fractures causing pain and spinal cord compression are the most frequent results/complications of osteolytic and osteosclerotic metastases. These complications concern mainly such long bones as femur or humerus, which are exposed to weight bearing. Less frequent complications include: limited mobility (resulting in bedsores, clots, embolism, infections, muscle dystrophy) and spinal cord instability. Not only do the above-mentioned complications significantly decrease the patients' quality of life, but they are also life-threatening [55,56].

2. Diagnostics of cancer induced bone pain (CIBP)

The majority (70–75%) of patients with metastases to the bone suffer from pain [57]. Thus, from the therapeutic point of view, pain diagnostics is of paramount importance.

Bone pain may be of localized nature and be present in one (in 10% of patients) or a few areas of the bone system. It may also be generalized. The latter type of pain is frequent after bone marrow replacement and it is referred to as the bone marrow replacement syndrome [58–60]. The occurrence and intensity of CIBP depends among others on the location of the cancer and/or metastases and on the degree of bone tissue destruction [61]. However, some patients complain from CIBP weeks or months before bone structure damage can be confirmed by radiology or scintigraphy [62]. On the other hand, only 25% patients with metastases to the bone do not feel CIBP [63].

A very important issue that must be addressed when treating cancer patients is the question of permanent cancer-induced bone pain (localized, frequently described as “deep” and “dull”). In the early stage of the disease it may be of occasional nature, but the patient's motion and weight-bearing activities may intensify it. Also night pain and pain at rest are characteristic for patients with bone cancer.

CIBP can be also felt during palpation and percussion examination. Other typical syndromes are backbone deformation, oedema, increased muscle tonus in the lesion area, radiating pain and synaglia (e.g. presence of lesion in Th12-L1 vertebrae may be felt as lateral/bilateral pain of wing of ilium/sacro-iliac joint; see Table 1).

If metastases to the bone are suspected, their diagnostics should be performed as soon as possible by means of:

- anamnesis and physical examination, imaging examination: x-ray, bone scintigraphy (displaying high sensitivity but low specificity), computed tomography (CT), nuclear magnetic resonance imaging (MRI, highly sensitive and specific, it is the diagnostic method of choice), positron emission tomography (PET),
- laboratory tests: evaluation of peripheral blood morphology (bone marrow cells suppression), assessment of plasma levels of: ionized calcium, albumins (hipoalbuminemia – increase of ionized calcium), urea, creatinine, alkaline phosphatase,
- biopsy – histological and pathological confirmation of an ongoing disease process.

One should be aware of non-symptomatic vertebral fractures that are discovered only in bone imaging [67]. In case of metastases
to the bones, medical treatment is aimed to increase life quality and to alleviate or to significantly reduce pain. Moreover, it should prevent bedsores formation, immobilization and provide anti-clotting prophylaxis.

The treatment consists of:

- assessment of expected time of survival and physical fitness,
- assessment of fracture risk,
- surgical consultation: assessment of usefulness of such interventions as vertebroplasty, use of orthopedic appliances,
- radiotherapeutic consultation to assess the possibility of tele-radiotherapy and radioisotopic therapy.

Bone pain decreases the patient’s mobility, causes anxiety, depression, increased risk of respiratory system infection, thromboembolism and bedsores formation, thus decreasing the quality of life [68].

3. Therapeutic implications of CIBP

The following procedures are applied in the prophylaxis and treatment of metastases to the bone:

1. Systemic treatment that consists of hormone therapy, chemotherapy, radio-isotopic therapy (Sr89, Sm 153, Ren 186 decrease pain and have a cytoselective effect), application of drugs preventing bone loss, such as bisphosphonates and denosumab. Radium-223 dichloride (Ra-223) is also considered a bone-targeting agent whose intake results in pain decrease and, in some patients, metastases stabilization or remission [70].

2. Local treatment e.g. by means of palliative radiotherapy that leads to regression of metastases and to calcification of osteolytic lesions; another procedure is surgical treatment that is used to join bone shards, to introduce implants and endoprostheses, to perform vertebroplasty and external fixation of bones.

3. Symptomatic treatment: treatment of chronic and acute pain (according to the WHO three-step ladder for cancer pain relief it is the so-called “fourth-step” i.e. invasive, anesthetic methods Table 2), hypercalcemia and anemia treatment.

The significance of bone resorption suppression in the prevention of occurrence of new and of progression of diagnosed metastases to the bone is still not fully elucidated. There are reports indicating a beneficial impact of such suppression [71–74]. The unique pathophysiology of metastases to the bone may be confirmed by the fact that the application of antiresorptive drugs does not correlate with tumor growth in soft tissues [75].

Antiresorptive drugs used for the treatment of metastases are presented in Table 3.

The currently used antiresorptive drugs (osteoclastogenesis inhibiting), i.e. bisphosphonates and denosumab (antibody binding to the ligand of receptor activator of nuclear factor kappa-beta) significantly decrease the number of bone-related complications in cases of metastases to the bones and display an additional antitumor effect. However, in ca. 30–50% of patients with metastases to the bone who use antiresorptive drugs, new metastases and complications are observed, as well as progression of previously existing lesions [6,84,85]. The above clearly indicates a need for new therapeutic options. New drugs able to affect the pathophysiology of metastasis to bone that are used currently or are at the stage of clinical trials are as follows:

- Recombined, RANKL-blocking OPG drugs (OPG analogs) [86],
- Soluble RANK-Fc suppressing RANKL [21,87]
- Oligonucleotides that block P2 × 7 receptor of NK-kB and suppress its activation [88],
- Humanized anti-PTHRp antibodies that stop RANKL-induced osteolysis [25],
- Atrasentan – inhibitor of endothelin ETA receptor able to stop osteosclerotic metastases in patients with prostate cancer [40],
- Activin A (ACE-011) inhibitors [89,90] and inhibitors of metalloproteinases of the bone matrix able to stop metastatic cells and the angiogenesis process [91]. In the case of metastases to the bone, the fibers of afferent CGRP and NF200 neurons undergo pathological reorganization referred to as sprouting. Among sprouting CGRP and NF200 fibers surrounded by bone marrow cancer cells colony, increased numbers of TrkA receptors (high affinity to nerve growth factor receptor/tropomiosin receptor kinase A) [92] and of GAP43 protein (growth associated protein 43) are observed. The TrkA receptor binds NGF (nerve growth

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of bone cancer pain [56,64–86]</th>
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<tbody>
<tr>
<td><strong>Bone Cancer Pain</strong></td>
<td><strong>Characteristics</strong></td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Permanent Pain (may be periodic at the beginning) Incidental 1) Spontaneous at rest (pain without cause) 2) Breakthrough pain (BTP), dependent/independent of the patient (e.g. motion-induced/cough-induced) So-called wandering pain (appears and disappears, sometimes completely, and shifts to another location; frequent in hematologic cancers)</td>
</tr>
<tr>
<td><strong>Nature</strong></td>
<td>Frequent descriptions: 1) Permanent – “dull”, “deep” 2) Incidental – “acute”, “throbbing”</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td>Severe (60% of patients); moderate (30%); weak (10%). Intensity of pain increases along with progression of disease</td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td>Backbone (in 13%, Th most frequently); generalized pain (metastases, multiple metastases in 10.2% of patients), pelvis bones (in 71%), thorax (ribs in 6.8%, long bones (in 3.9%)</td>
</tr>
<tr>
<td><strong>Radiation</strong></td>
<td>*</td>
</tr>
<tr>
<td><strong>Sympalgia</strong></td>
<td>*</td>
</tr>
<tr>
<td><strong>Other symptoms</strong></td>
<td>(e.g. lesion in the pelvis is felt as a pain in the knee)</td>
</tr>
<tr>
<td><strong>Pain triggers/aggravating factors</strong></td>
<td>Dependent and independent on the patient: motion, weight-bearing activities</td>
</tr>
<tr>
<td><strong>Alleviating factors</strong></td>
<td>See text below and Tables 2 and 3 (treatment)</td>
</tr>
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</table>
Table 2
Drugs used in Poland for the treatment of chronic and acute bone pain according to the WHO three-step pain relief ladder [69].

<table>
<thead>
<tr>
<th>Group of drugs</th>
<th>Drugs</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st choice drugs</td>
<td>KETOPIROFEN, diclofenac, ibuprofen, naproxen, oxycodone, buprenorphine, methadone</td>
<td>Efficacy in 75% of patients</td>
</tr>
<tr>
<td>2nd choice drugs</td>
<td>Dexamethasone, prednisone</td>
<td>Morphine and oxycodone are not recommended for patients with renal insufficiency</td>
</tr>
<tr>
<td>Recommended in case of efficacy or impaired efficacy of NSAIDs; always recommended in case of possible or performed compression of spinal cord – very high initial dosage should be decreased with time to the lowest efficient dose</td>
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</tr>
</tbody>
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Table 3
Antiresorptive drugs used in the treatment of bone metastases.

<table>
<thead>
<tr>
<th>Group of drugs/ Drug</th>
<th>Mechanism of action</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates (BPs) pamidronate zoledronate</td>
<td>They have a direct and indirect effect: by preventing bone loss and cancer cell proliferation they stop the vicious circle of cancer cell and osteoclasts interaction in the microenvironment of the bone tissue. Bisphosphonates stimulate the differentiation of T-cell subpopulation (ly6 cells) responsible for the destruction of cancer cells – this effect is especially strong in zoledronate; they strongly suppress osteoclastic activity, decrease cancer cells’ survival (complex mechanism); they stop angiogenesis and display immuno-modulative effect[76–79].</td>
<td>Recommendations for pamidronate: osteolytic metastases: shorter T1/2, lower risk of nephrotoxicity and bone necrosis than for zoledronate. Zoledronate – recommendations: osteoblastic and osteolytic metastases, significant nephrotoxicity and risk of bone necrosis [72]. Long-term effect; during application, temporary suppression of bone formation may be observed leading to jaw necrosis (the effect is stronger in the case of zoledronate) Regular use of BPs as means of oncoligic and palliative treatment leads to high cumulative doses</td>
</tr>
</tbody>
</table>

Monoclonal Human Antibody (IgG2) denosumab | It binds the ligand of receptor activator of nuclear factor kappa beta (RANKL). It leads to the suppression of formation, activity and survival of osteoclasts and to the drop in the resorption of trabecular and cortical bone. It prevents the formation and treats metastases to the bone; it prevents Skeletal-Related Events (more effectively than BPs) and displays anticancer effect (confirmed in patients with bone marrow cancer) [80–82] | Recommendations (apart from osteoporosis): Skeletal-Related Events Prevention in adult patients with solid tumor metastases to the bones [pathological fractures, need of bone radiation, pressure on spinal cord, need of surgical treatment of bones. The drug is administered in the dose of 120 mg s.c. 1×/4 weeks. In case of treatment of adults or young people with a mature bone system and suffering from inoperable giant-cell tumor of the bone, the dosage is 120 mg s.c. 1×/4 weeks and on day 8 and 15 of the treatment, additional doses of 120 mg are given [81]. In comparison to zoledronate, the use of denosumab leads to a longer delay in the occurrence of the first skeletal-related event in patients with metastases of breast or prostate cancer to the bone [73]. |
are but unfortunately often insufficient to effectively heal incidental pain.

Antiresorptive drugs used as co-analgesics (e.g. bisphosphonates and denosumab) stop bone loss, cancer cell proliferation and angiogenesis. However, their prolonged use may lead to adverse effects. Therefore, there is an urgent need not only for further research on these complicated and still not fully elucidated mechanisms of metastases formation but also for the search for new therapeutic measures in the treatment of Cancer-Induced Bone Pain.

References


