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REVIEW

Bone metastases: a comprehensive review of the literature

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Abstract

The last report of the World Health Organization (WHO) stated that approximately four million people experience bone pain due to malignant diseases. Among them, metastatic bone pain is one of the most important sources of complaint. The estimated median survival in the presence of bone metastases ranks from 10 to 12 weeks. Bone represents a potential target of distant metastases for the majority of malignant tumours. However, the exact incidence of bone metastases is unknown. Bone metastases have an important socio-economic impact, and due to the enhancement of the overall survivorship, their incidence is increasing. Malignant neoplasms such as lung, thyroid, renal cancer, multiple myeloma, and melanoma often metastasize to the bone. Bone metastases commonly localize to the spinal column, pelvis, shoulder, and distal femur. The proper treatment for painful skeletal metastases is still unknown. Hence, the purpose of this review of the literature was to update current evidence concerning the aetiogenesis, biological behaviour, and treatment algorithms for painful skeletal metastases.

Keywords Bone · Metastases · Treatment

Introduction

The latest cancer report of the World Health Organization (WHO) stated that approximately four million people experience bone pain due to malignant disease [1]. Among them, metastatic bone pain is one of the most important sources of complaint [1]. Bone metastases are debilitating, lead to pain, impaired mobility, hypercalcemia, pathological fractures, and in the case of involvement of the spinal cord, neurological disorders and paralysis. Furthermore, the high quantity of calcium release into the circulatory system can lead to malign hypercalcemia, a serious medical illness [2] resulting in cardiac and kidney failure [3]. In the presence of bone metastases the median survival is described to range between 10 to 12 weeks [4]. Similar to organ parenchyma, bone represents a potential target of distant metastases for various malignant tumours [5]. The incidence of bone metastases is unknown [3]. Bone metastases have an important socio-economic impact, and due to the improvement of overall survivorship, the incidence is increasing [6]. Post-mortem, approximately 70% to 90% of patients who died of breast or prostate cancer show evidence of bone metastases [7, 8]. Lung, thyroid, renal cancer, multiple myeloma and melanoma often metastasize to the bones [9]. Irrespectively to the primary malignant, bone metastases are commonly located in the spine, pelvis, shoulder, and distal femur [10]. Elbow and knee metastases are suggestive of primary lung cancer [11]. The proper treatment for bone metastases requires multidisciplinary treatment of different specialists such as orthopaedic surgeons, radiologists, oncologists, and radiotherapists. As bone metastases may have high impact on patient's quality of life, occur as clinical characteristic in several types of tumour and involve different specialities our

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intention performing this review was to clarify the role of the pathogenesis and different options for treatment.

Bone metastases

Besides standard radiographs to assess skeletal involvement of metastases, a 99mTc phosphate bone scintigraphy can be required [12]. The uptake of radiotracers depends on the quantity of calcification of the metastases and the osteoblastic activity. According to the uptake of radiotracers, bone metastasis can be divided into osteoblastic or osteosclerotic and osteolytic. Mixed metastases are typical for squamous cell, lung, colorectal, pancreatic, and gastrointestinal tumours [5, 13, 14]. In patients with mixed metastases, there are both osteolytic and osteosclerotic lesions. Quattrocchi et al. [15] found that after the introduction of third generation bisphosphonates, breast cancer metastases phenotype can change from osteolytic to osteosclerotic. Osteosclerotic or osteoblastic lesions are characterized by the production of new bone tissue, characteristic of prostate cancer, small cell lung cancer, carcinoid, medulloblastoma, and Hodgkin lymphoma [5, 16]. In prostate cancer, Prostate-specific antigen (PSA), can inhibit PTH related peptide, resulting in an enhancement of osteoblast function [17]. Additional proteins like the Core binding factor alpha1 (Cbfa1) are involved in osteoblastic differentiation [18]. The most common osteolytic metastases are associated with non-Hodgkin lymphoma, non-small cell lung cancer, thyroid cancer, plasmacytoma, Langerhans-cell histiocytosis, and renal cell carcinoma [5, 16]. Osteolytic metastases lead to an increase in osteoclast function [4, 19] or ischemic processes [3]. PTH related peptide plays a key role in producing osteolytic lesions [20], but it is still unclear if cancer cells expressing PTHrP are inducted by the micro-environment or if they have a higher intrinsic PTHrP expression [21].

Role of the micro-environment

The first studies on tumour genesis demonstrated a "vicious cycle" between bone and tumour cells [22]. Tumour cells in bone that induce osteolytic metastases secrete osteolytic factors such as osteoclast activating factors (OAFs) and osteoblast inhibiting factors. Osteoclastic bone absorption releases growth factors such as TGF–β from the bone matrix, which in turn promotes tumour growth, and the cycle starts again. Tumor cells that result in osteoblastic bone metastases secrete factors that induce osteoblastic proliferation and differentiation (including VEGF, PDGF and ET1) [23]. Myeloma cells produce growth factors that stimulate the growth of bone marrow stromal cells, which in turn produce OAFs, such as IL-6, macrophage colony-stimulating factor, TNFa and RANKL from osteoblasts, promoting osteoclast bone absorption [8, 24]. Bone absorption releases growth factors, which in turn promotes tumour growth, and the cycle starts again. This is the rationale of the modern anti-tumoral therapies that often use osteoclast inhibition medications [25]. Osteoclast inhibitors, as well as other drugs, such as hormone deprivations (anti-androgen or anti-oestrogen) or corticosteroids, have a negative impact on bone quality, and can result in osteoporosis [26]. The *seed-and-soil* theory hypothesizes that, due to the presence of cytokines and growth factors, bone tissue (the *soil*) can provide an optimal field for the metastases (the *seed*) [27]. The process leading to metastatic growth is regulated by a signaling pattern between the micro-environment, tumour cells and bone homeostasis [22, 28]. Bone cells, namely osteoblasts and osteoclasts play crucial roles in tumour induced bone diseases. Osteoblasts enhance bone formation, contributing to absorption of bone and tumour growth. Furthermore, Osteoblasts release macrophage colony stimulating factor (MCSF) and RANKL, both essential for normal osteoclastogenesis and related functions thus controlling bone homeostasis [25, 29, 30]. Wang et al. [31] stated that the physical contact between osteoblasts and tumoral breast cells promote metastatic proliferation. Osteoblasts enhance the recruitment of hematopoietic stem cells [32–36]. Park et al. [37] stated in 2013 that osteoblasts can indirectly stimulate an increase in the myeloid-derived suppressor cells, thus promoting tumour growth and angiogenesis. Other studies found that osteoblasts indirectly stimulate angiogenesis within bone micro-environment by secreting vascular endothelial growth factor (VEGF) [38, 39]. The role of osteoclasts in tumour induced bone disease has been intensely investigated. These cells differentiate from myeloid progenitor cells under the influence of several cytokines and growth factors, especially MCSF and RANK [40]. Cell activation and resulting bone resorption are meticulously controlled by the RANK/RANKL/osteoprotegerin pathway [41, 42]. Downregulation of this pathway correlates with reduced bone quality and increased risk of fractures [43]. The role of the fibroblasts in the micro-environment is not fully understood. A recent study found fibroblasts to be either a promoter or repressor of cancer [44]. Fibroblasts are commonly found around malignant cells (Cancer-Associated-Fibroblasts, CAFs). CAFs have been found in both the primary tumour and in distant metastases, but their role is still unknown [45]. Before bone metastatic colonization, an expansion of bone marrow mesenchymal stem cells (BM-MSC) and fibroblasts have been observed [46]. In fact, once the malignant cells have localized to bone, they can induce BM-MSC to differentiate into fibroblasts, promoting tumorigenic cytokines and growth factors that

allow the bone metastatic process [47]. CAFs can promote tumour invasion, angiogenesis, and matrix stiffening [48], but can also be effective modulators of immune cell populations, negatively influencing tumour growth [49]. CAFs not only enhance tumour growth, but also "protect" the malignant cells from chemotherapy [50]. Other important cells involved in bone tumour progression and modulation are T and B lymphocytes, natural killer cells (NK), macrophages, and myeloid-derived suppressor cells (MDSCs). Lymphocytes are important modulators of tumorigenesis [51]. T cells have been reported to be associated with a reduction of tumour growth in mice [52], and induce the secretion of RANKL, activating osteoclastogenesis [78]. CD8 + T cells have a direct cytotoxic effect on malignant cells, being recognised as important anti-tumorigenic factors [53]. B cells can produce antibodies that target malignant phenotypes, stimulating tumour suppression [54, 55]. Conversely, T REG cells, positively modulate neoplastic cells, promoting tumour growth [56]. Furthermore, B cells can produce IL-10, that encourages tumour growth [55]. Very little is known regarding the role of NK cells. NK cells secrete interferon-gamma (INF-γ), modulating the immune system [57]. Macrophages are plastic cells that can be committed to several different lineages. Evidence suggest that they may encourage tumour progression [24]. In fact, macrophages promote the progression of different tumours such as lung, breast, and colon [24, 58, 59]. There are two different type of macrophages, the tumour-associated macrophages (TAMs) and metastasis-associated macrophages (MAMs) [60]. Under proper signalling, macrophages can differentiate into osteoclasts [40]. Bone resident macrophages are called osteomacs [61], and play several functions in bone homeostasis [62, 63]. However, their implication in tumour induced bone disease is still unknown. Myeloid-derived suppressor cells (MDSCs) are a heterogenous group of cells consisting of immature macrophages, granulocytes, dendritic cells, and myeloid progenitor cells [58]. These cells are involved both in tumour regression and progression [64]: by (a) modulating the immune system [65–70]; (b) predisposing the micro-environment for tumorigenesis; (c) stimulating the epithelial-to-mesenchymal transition (EMT) into malignant cells [71]. There are other factors identified that are involved in tumour induced bone disease. In the nervous system, the chronic stress, has been observed to positively influence tumour growth [72–75]. Bone is strongly innervated by adrenergic fibres that can directly stimulate osteoblasts to release cytokines that modulate the inflammatory system, leading to cell transferring and bone turnover [76]. These processes are involved in bone metastasis and progression of tumour induced bone disease [77]. Lastly, bone vascularization has been proposed to play a role in tumour induced bone disease. Increased micro-vessel density promote tumour growth in patients with breast cancer [78], as well as an increased density and impermeability of the vasculature [79].

Pharmacological management

In the sixties a Swiss physician, Herbert Fleisch, discovered bisphosphonates [80]. These drugs bind hydroxyapatite and interact with osteoclasts, promoting apoptosis, thus inhibiting bone absorption. It has been shown that bisphosphonates can slow the advancement of existing bone metastasis and reduce the risk of new lesions in patients with breast cancer and multiple myeloma [81, 82]. Bisphosphonates also reduce skeletal complications in hormone-refractory prostate cancer [83], non-small cell lung cancer, and other urologic malignancies [84, 85]. Their administration is recommended in patients affected by breast cancer with signs of bone metastasis [86]. Different bisphosphonate substances are administered on a clinical routinely basis. Zoledronic acid (ZA) is a nitrogenous bisphosphonate of the III generation and is considered to be the gold standard for bone metastasis [87, 88]. In addition to osteoclast inhibition, ZA is proposed to inhibit tumour growth by minimizing angiogenesis and modulating the immune response, thus improving overall survivorship [89–92]. Furthermore, ZA contributes to a reduction in hypercalcemia [2]. Denosumab is a monoclonal antibody targeted to RANKL. Inhibition of RANKL decreases the activity of osteoclasts, thus of great interest for the treatment of bone metastases, especially when zoledronate is no longer effective [93]. Furthermore, Denosumab does not accumulate in bone tissue, allowing a quickly reversible effect after suspension [94]. Complications with Denosumab related to jaw osteonecrosis were seen mostly in patients with poor oral hygiene, tooth extraction, or the use of dental appliance [95]. Whether bisphosphonates or an anti RANKL antibody is more effective has not yet been fully clarified [96]. The use of bisphosphonates or an anti RANKL antibody are essential in the non-surgical treatment since they reduce the risk of bone complications such as fractures [97]. External beam radiotherapy (EBRT) is considered to be the treatment of choice for uncomplicated bone metastases pain [98]. Chemotherapy strictly depends on the primary tumour. In lymphoma and germ cell tumours, chemotherapy can be considered as the treatment of choice, whereas very poor results are achieved in renal cell carcinoma or melanoma [3]. Chemotherapy will not be further evaluated in this work.

Nuclear medicine

Chow et al. [99] reported partial pain relief in 50% to 80% of patients affect by bone metastasis with EBRT. Furthermore, approximately 30% of the patients reported

complete relief from metastatic bone pain [99]. The cause of pain is still unknown [100]. Radiation destroys tumour cells, promoting the bone reparation. However, the rapid pain relief and the lack of dose response relationship pose a question on the true source of bone pain. Hoskin et al. [101] found a possible explanation of the reported pain relief after radiotherapy. They supposed that the source of pain is intrinsic to the bone (osteoclasts) rather than the tumour. This partially explains even the pain relief observed with bisphosphonates, since bisphosphonates act on osteoclasts. Furthermore, there is no consensus regarding the fractionation schemes [102]. However, several studies have shown that 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, or 8 Gy in a single fraction afford optimal pain control along with acceptable adverse effects [98]. Stereotactic radiosurgery is a modern technique to deliver higher biologically equivalent doses together with a highly accurate radiation beam. The accuracy ensures the minimum damage possible to the healthy tissues surrounding the lesion. The goal of this technique is to achieve better local control over the fractionated convectional radiotherapy and reduced stress for the patient even if increased financial burden [103–105]. Despite the excellent outcomes, there is a lack of evidence in the literature supporting the effect of Stereotactic radiosurgery [106–108]. Given that most patients have multifocal bone localizations of metastases that are no longer responsive to conventional analgesic treatments, it may be reasonable to perform systemic therapy [109]. Radiopharmaceutical therapy is a systemic therapy aimed at skeletal metastases, introduced by Pecher et al. [110] in 1941. Approximately 70–80% of patients suffering from bone metastatic breast and prostate cancer reported an improvement in quality of life [111]. Other primary tumours showed a reduced response, but currently several new radiopharmaceuticals for bone pain palliation are under investigation [16]. In Europe, for patients with bone metastasis secondary to prostate cancer, strontium ^{89}Sr-chloride is indicated [112]. Being that ^{89}Sr is a calcium analogue, it can be incorporated into hydroxyapatite crystals of the bone matrix [16]. Moreover, the samarium ^{153}Sm-ethylenediamine tetra methylene phosphonate (EDTMP) is a phosphonic acid generally indicated to treat pain of osteoblastic bone metastases [112]. The ^{153}Sm is radiolabelled to a bisphosphonate and the pharmacokinetics is similar to technetium ^{99}mTc-labelled bisphosphonates, the one used for diagnostic bone scintigraphy [16]. ^{32}P, as sodium phosphate, reported the same efficacy as ^{89}Sr in terms of pain palliation, but higher toxicity, especially to bone marrow [113]. The radionuclide therapy does not interfere with a concomitant third generation bisphosphonate therapy [114]. Recently Radium-223 has been introduced as being the first calcium mimetic and alpha emitter approved by the FDA [115]. It binds the hydroxyapatite crystal then induces cells apoptosis by breaking the double stranded DNA [116, 117]. Furthermore, the emission of alpha particles is short range, preserving the healthy bone tissue [118]. Hence, Radium-223 is active in high turnover areas, inducing apoptosis and irradiating the surrounding area [119]. Radium-223 is currently under investigation for the treatment of secondary metastases in other tumours, like breast, renal, and thyroid cancers [120, 121].

Surgical management

In evaluating surgical treatment, osteosynthesis of a pathological fracture due to bone metastasis is one of the indications for surgical intervention, as is spinal cord involvement or peripheral nerve compression [4]. Surgery can be performed in patients with high risk or imminent pathological fracture. Two retrospective cohort studies evaluated the outcomes of prophylactic surgical fixation of impending fractures [122, 123]. Fixation of impeding fractures reported a reduction of the total blood loss, shorter hospitalization, improved function, and longer survival compared to the surgical reparation of pathological fractures [122, 123]. Mirels criteria is a score capable of evaluating if patients are potential candidates for prophylactic surgery [124]. Recently, to evaluate potential candidates for prophylactic surgery, bone analysis assessed with CT has been introduced [125]. This technique compares the structural rigidity of the bone matrix of the contralateral side, and reports more sensitivity and specificity compared with Mirels criteria [125]. Patient surgical outcomes and survivorship strictly depend on the preoperative health [126]. The Goldman classification is a useful tool to evaluate patient pre-operatively health status [127]. This score assesses the surgical risk based on cardiac, respiratory, and other secondary factors. Nathan et al. [128], analysing death prognostic factors, found that primary diagnosis, use of systemic therapy, Eastern Cooperative Oncology Group (ECOG) performance status, number of bone metastases, presence of visceral metastases, and serum haemoglobin, albumin, and lymphocyte counts were significant for predicting survival. Lastly, in targeted treatment of metastatic lesions, ablation therapy has been proposed. In patients with single or double metastatic sites, the orthopaedic surgeon can take advantage of thermal ablation surgery. This technique has continued to expand in the last decades. A needle is located into the tumour core, and the disruption of the tumour occurs via radiofrequency, cryoablation, chemicals (ethanol or acetic acid), microwave ablation, laser ablation, ultrasound [129, 130]. Thermal ablation is safe, feasible, and effective for recurrences and pain control [129, 131–134].

Discussion

The correlation between progress of the molecular biology and medical therapy is inseparable. Computational and mathematical models have been introduced to understand the underlying mechanisms of how bone metastasis evolves [135]. New therapies aiming to reduce or eliminate the metastatic burden in the bone tissue may be proposed by this research. Even though different specialties are involved in research in metastasis, the last decades work in the development of protocols, procedures, and competences has been on continuous; but, the optimal treatment of painful skeletal metastases has not yet received solid consensus. Current data support these palliative multimodal strategies to enhance the of quality of life of affected patients. However, we have to remark that for different sites and types of metastasis, distinct therapeutic goals such as pain relief and alleviation of symptoms, prevention or improvement of neurological deficits, stabilization of the spine or other bones) require complex treatment considering patients individual factors (i.e. tumour progression, life expectancy).

Bone represents a potential target of distant metastases for various malignant tumours and is commonly found postmortem. Skeletal metastases represent a common cause of morbidity and mortality, with a high socio-economic impact. Insight concerning the micro and macro processes, along with the molecular patterns that regulate the genesis and development of metastases, will ameliorate direct treatment and may reduce disease associated morbidity and mortality. The correlation between progress of the molecular biology and medical therapy is inseparable. In the last decades work in the development of protocols, procedures, and competences has been on continuous; but, the optimal palliative treatment of painful skeletal metastases has not yet received solid consensus.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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