Bone Metastases - A Review

KARTHIKEYAN.S
Undergraduate Student,
Saveetha Dental College, Saveetha University,
Saveetha Institute of Medical and Technical Sciences,
Chennai, Tamilnadu, India.

Prof. Dr. GOWRI SETHU
Head of Department,
Department of Physiology,
Saveetha Dental College, Saveetha University,
Saveetha Institute of Medical and Technical Sciences,
Chennai, Tamilnadu, India.

Abstract: **Solid cancers metastasize to bone by a multistep process that involves interactions between tumor cells and normal host cells. Some tumors, most notably breast and prostate carcinomas, grow avidly in bone because the bone microenvironment provides a favorable soil. In the case of breast carcinoma, the final step in bone metastasis (namely bone destruction) is mediated by osteoclasts that are stimulated by local production of the tumor peptide parathyroid hormone-related peptide (PTH-rP), whereas prostate carcinomas stimulate osteoblasts to make new bone. The metastatic process can be interrupted either by neutralization of PTH-rP or by rendering the tumor cells unresponsive to TGF-β, both of which can be accomplished experimentally. The osteoclast is another available site for therapeutic intervention in the bone metastatic process. Osteoclasts can be inhibited by drugs such as the new-generation bisphosphonates; as a consequence of this inhibition, there is a marked reduction in the skeletal events associated with metastatic cancer to bone, such as pain, fracture, and hypercalcemia. However, studies with potent bisphosphonates such as ibandronate, pamidronate, and risedronate have clearly documented that reduction of bone turnover and osteoclast activity leads to beneficial effects not only on skeletal complications associated with metastatic cancer, but also on tumor burden in bone.**

Introduction:

Metastasize is a process that involves loss of intercellular cohesion, cell migration, angiogenesis, access to systemic circulation, survival in circulation, evasion of local immune responses, and growth at distant organs.[1,2] Bone is the third most frequent site of metastasis, behind lung and liver.[3] Prostate and breast cancer (BC) are responsible for the majority of the skeletal metastases (up to 70%).[4] This reflects both the high incidence and relatively long clinical course of these tumors. The overall incidence of bone metastasis is not known.[3] The relative incidence of bone metastasis by type of tumor, in patients with advanced metastatic disease, is: 65-75% in BC; 65-75% in prostate; 60% in thyroid; 30-40% in lung; 40% in bladder; 20-25% in renal cell carcinoma and 14-45% in melanoma. The median-survival from diagnosis of bone metastasis is: 6months in melanoma; 6-7 months in lung; 6-9 months in bladder; 12 months in renal cells carcinoma; 12-53 months in prostate; 19-25 months in BC and 48 months in thyroid.[5] Bone metastases are a major cause for morbidity, characterized by severe pain, impaired mobility, pathologic fractures, spinal cord compression, bone marrow aplasia and hypercalcemia.[4]

Bone is the most common and preferred site for metastatic involvement of cancer. Advanced cancers frequently develop metastases to the bone during the later phases of cancer progression. At least 100,000 patients develop bone metastases every year, although the exact number of bone metastases is not known.1 Multiple myeloma (MM), breast cancer, and prostate cancer are responsible for up to 70% of bone metastases cases.2 Gastrointestinal cancers contribute least to bone metastases: < 15% of all cases.2 The prognosis of bone metastases is generally poor, although it partly depends on the primary site of the original cancer and on the presence of any additional metastases to visceral organs. For example, it is known that survival times are longer for patients with primary prostate or breast cancer than for patients with lung cancer primary tumors.[3,4]

Prostate and breast cancers are the most common primary cancers of bone metastases. At postmortem studies, patients who died of prostate cancer or breast cancer revealed evidence of bone metastases in up to 75% of cases . Regardless of their survival expectancy, however, most patients with bone metastasis need immediate medical attention and active palliative therapy to prevent devastating complications related to bone metastasis, such as pathologic bone fractures and severe bone pain. Elucidation of mechanisms regulating bone metastasis has progressed significantly in recent years and this has translated to many new therapeutic options for patients with bone metastatic cancers. However, the rapid rate of progress in both the basic science literature and therapies undergoing clinical trials makes staying abreast with current developments challenging. This review seeks to provide an update on the current state of the science in bone metastasis research and give a snap shot of therapies in clinical trials for bone metastatic cancer.

Clinical features:

The most common clinical symptom of bone metastasis is bone pain, which is usually localized and progresses slowly. Patients may experience worsening of pain at night or while ambulating, depending on the site of bone metastasis. Pain may radiate to the lower extremities; however, radiating pain may not always correlate with nerve impingement.

Other symptoms related to bone metastases include hypercalcemia, spinal cord compression, immobility, vertebral fractures, and fractures of the long bones. The most common site of bone metastases is the axial skeleton, with the lumbar spine being the most frequent site of bone metastasis as a single site

Pathogenesis:

Bone is made up of an extracellular matrix (ECM) surrounding osteoclasts, osteoblasts, osteocytes and bone marrow stromal cells (BMSC). The ECM contains both an organic component, formed by type I collagen, proteoglycans and glycoproteins, and inorganic ions (calcium and phosphate) organized in hydroxyapatite crystals [12]. Normal bone tissue is made up of 2 different types of cells: osteoblasts and osteoclasts. New bone is constantly being produced while old bone is broken down. When tumor cells invade bone, the cancer cells produce 1 of 2 distinct substances; as a result, either osteoclasts or osteoblasts are stimulated, depending on tumor type metastasized to the bone. The activated osteoclasts then dissolve the bone, weakening the bone (osteolytic phenomenon), and the osteoblasts stimulate bone formation, hardening the bone (osteoblastic or sclerotic process). Osteoclasts derive from monocyte-macrophages and are deputed to bone resorption. Their activation is promoted by systemic and local factors; the former include 1,25-dihydroxyvitaminD3 and parathyroid hormone (PTH) while the latter comprise interleukin-1 (IL-1), IL-6, macrophage colony-stimulating factor (MCSF) and PTH related protein (PTH-rP). Anti-osteoclastogenic factors (e.g. calcitonin, IL-4, IL-18, interferon-β) prevent excessive bone resorption [13].

The receptor activator of nuclear factor-κB (NF-κB) ligand (RANK-L)/RANK/osteoprotegerin axis plays a major role in both osteoclastogenesis and osteoclast activation. RANK-L is a member of the tumor necrosis factor (TNF) family, produced by osteoblasts, stromal and active T-cells in response to pro-osteoclastogenic stimuli. Once RANK-L interacts with its receptor (RANK) expressed by osteoclast precursors, these are activated via NF-kB and Jun N-terminal kinase pathways. Osteoprotegerin, a soluble decoy receptor for RANK-L, prevents osteoclast hyper-activation[3].

Osteoblasts originate from mesenchymal stem cells and are deputed to osteogenesis. Their differentiation is promoted by endothelin-1 (ET-1), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), bone morphogenetic proteins (BMPs) and transforming growth factor β (TGF-β) which in turn activate the transcription factor Runx-2 [13]. Some osteoblasts are embedded in the bone matrix and become osteocytes, cells with dendritic protrusions acting as mechano-transducers [14].

Diagnosis:

However, it is quite difficult to diagnose metastatic bone disease at an early stage. Silbermann R group suggested that various advanced imaging techniques including (i) skeletal survey (SS), (ii) whole body computed tomography (WBCT), and (iii) positron emission tomography-CT (PET-CT) could be used for the detection of very small sized osteolytic lesions. They also emphasized the improved combination of WBCT and 18F fluoro-deoxyglucose (FDG) PET-CT for visualizing bone marrow infiltration along with whole body tumor burden [6-8].Similarly, both surgical and non-surgical multimodal treatment strategies are required to deal with metastatic bone disease. Choong PF research group emphasized that orthopedic surgeons have a critical role in the decision making to choose the most effective treatment strategy. This may depend on the site (e.g., femur, humerus, etc.) and bone metastasis type (e.g., breast, lung, etc.), since type of implants and surgical options available will influence the outcome [9,10].The most important first step in evaluating bone metastasis in a patient is to take a thorough, careful medical history and perform a physical examination. The examination not only helps locate suspected sites of bone metastases, but also helps determine necessary diagnostic studies [11,12].

The radiographic appearance of bone metastasis can be classified into 4 groups: osteolytic, osteoblastic, osteoporotic, and mixed. Imaging characteristics of osteolytic lesions include the destruction/thinning of bone, whereas osteoblastic (osteosclerotic) lesions appear with excess deposition of new bones. In contrast to malignant osteolytic lesions, osteoporotic lesions look like faded bone without cortical destruction or increased density.Although 1 type of lesion generally predominates, osteolytic lesions are most common in renal cell cancers and MM [15-18]. Bone metastases in prostate cancers are typically characterized by an osteoblastic picture due to excess bone deposition [19].

The main choice of imaging study for screening suspected bone metastases is usually the bone scan . Plain radiographs are not useful in the early detection of bone metastases, because bone lesions do not show up on plain films until 30% to 50% of the bone mineral is lost [20-22]. Although most metastatic bone lesions represent a mixture of osteoblastic and -lytic processes, metastatic lesions of lung cancer and breast cancer are predominantly osteolytic in contrast to mainly osteoblastic lesions of prostate cancer metastases.[10,23]

Treatment:

The importance of understanding the natural history of BM and preventing its onset is based on the fact that, nowadays, treatment options are limited and often inefficient to be completely curative; in fact, treatments aim still remains to prolong patient survival and ameliorate their QoL [24-27].Currently, applicable systemic therapies include chemotherapy and bone-targeted therapies (BTTs) as bisphosphonates and other antiresorptive molecules such as anti-RANK-RANKL inhibitors [28]. A recent multi-country cross-sectional study carried out by Body et al. (2019) on the management of patients with prostate cancer shows that the majority of BM patients (74%) are treated with BTTs, such as zoledronic acid (bisphosphonate) and denosumab (human monoclonal antibody against RANKL) especially if they are followed by an oncologist instead of a urologist. Other types of biological drugs direct on specific targets involved in BM formation such as anti-CXCR4 and Cathepsin-k Inhibitors have been investigated [6]. Apart from systemic therapeutic approaches, some local interventions are used: for example, radiotherapy with radioisotopes with affinity to bone (e.g., strontium-89, RAD001, Lu177-PMSA) represents another palliative option for BM intervention when metastases are a

few and easily confinable [29-31]. Recently, electrochemotherapy has also been used to treat BM, and the results of a phase II clinical study confirm that this treatment controls tumor growth and pain [32,33].

Pain is the most serious complication of bone metastases. Radiation therapy has been established as standard therapy and an effective pain palliation modality. Up to 80% of patients achieve partial pain relief, and > 33% of patients experience complete pain relief after radiation [34-37]. Although a 3,000 cGy given over a 2-week period has been commonly used, a standard dose-fraction radiation treatment regimen has not been established [38]. The surgical indications for managing bone metastases can vary, depending on disease location, surgeon's preference, and patient's overall disease status and related morbidities. Pain relief of fractured long bones (humerus, femur, or tibia) is crucial [39]. The main goals of surgical intervention in these cases include the restoration of stability and functional mobility, pain control, and improving QOL. Weight-bearing bones (humerus/tibia) are especially at risk of bone fracture, and compromise of these is an indication of surgery. Postoperative external-beam radiation is recommended in most cases to eradicate residual microscopic disease or tumor progression [40,41]. Treatment decisions depend on several parameters, for example, if bone disease is localized or widespread, if there is evidence of extraskeletal metastases, the kind of cancer and his features (like estrogen-receptors in BC), prior treatment history and disease response, the symptoms and the general state of health [43]. Treatments can often shrink or slow the growth of bone metastases and can help with the symptoms they are causing but, they are not curative.

Bisphosphonates are analogues of pyrophosphate, a natural inhibitor of bone demineralization.[28] Bisphosphonates bind avidly to exposed bone mineral around resorbing osteoclast and this leads to very high local concentrations of product in the resoption lacunae. Then, bisphosphonates are internalized by the osteoclast causing disruption of the chemical process involved in bone resorption.[5,42] Bisphosphonates also cause osteoclast apoptosis and some studies suggest that they may also have direct apoptotic effects on tumour cells.[5,43] In oncology, bisphosphonates are the standard treatment for tumour-induced hypercalcaemia and a new form of therapy for bone metastasis.[44]

With intravenous bisphosphonates and rehydration, 70-90% of patients will achieve normocalcaemia. The effect on pain in bone metastases is independent of the nature of the underlying tumour and the sclerotic lesions respond similarly to lytic metastases.[45] The studies are mainly done in BC and MM; lung, kidney and prostatic cancer have few studies.

They are well tolerated. The most common adverse events include flu-like symptoms (fever, arthralgia, myalgia and weakness), anemia, nausea, dyspnea and peripheral edema. These events are mostly limited and mild to moderate [5]. A rare but very serious side effect is osteonecrosis of the jaw. All bisphosphonates undergo renal clearance so, patients with renal impairment (serum creatinine level >3.0 mg/dL) should not receive the treatment.[46]

There are three generations of bisphosphonates: 1st generation, etidronate, clodronate, tiludronate; 2nd generation, pamidronate, alendronate, ibandronate; 3rd generation, risedronate, zoledronic acid. The approved ones are: oral clodronate at a daily dose of 1600 mg and oral ibandronate 50 mg; intravenous (IV) pamidronate 90 mg (infusion of 2 h), ibandronate 6 mg (infusion of 1 h), zoledronic acid 4 mg (infusion of 15 min). Zoledronic acid is the newer bisphosphonate approved for MM, lung, prostate and BC with bone metastasis. It is 100-times more effective than pamidronate.[47] Patients doing these treatments should take a supplement containing calcium and vitamin D.

Conclusion:

In brief, the articles published on the Research Topic "cancer and bone metastasis" emphasized the importance of various molecules, different cell types, and crucial signaling pathways working in various bone metastatic niches, and how they influence our understanding of metastatic bone disease. This is in addition to advancing imaging diagnostic techniques and various surgical options in dealing with such devastating disease. The Research Topic also suggested various non-surgical treatment options including proteasome inhibitors, small molecule inhibitors and microRNAs.

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