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Bone Metastases: From Mechanisms to Treatment

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ABSTRACT

Objectives: Bone metastases are of high clinical relevance because they are a frequent complication of most types of common cancers, such as breast and prostate. The metastatic process is complex, requiring the completion of several different steps to allow successful dissemination and homing. In addition, preparation of the metastatic niche changes the constant cycle of bone matrix formation and degradation, leading to the clinical phenotypes of lytic and sclerotic lesions. We review our current knowledge on this topic and briefly explain the current treatment landscape of bone metastasis.
Data Sources: These include PubMed, international guidelines, and clinician experience.
Conclusion: Bone metastases remain a clinical challenge that negatively impacts patients prognosis and quality of life. A comprehensive understanding of the complex molecular mechanisms that results in bone metastasis is the basis for successful treatment of affected patients. The disruption of bone matrix metabolism is already recognized as the prerequisite for metastasis formation, but many open questions remain that need to be addressed in future research to establish individually tailored treatment approaches.
Implications for Nursing Practice: Patient-centered therapy of bone metastases requires suitable pharmacological options, and importantly a holistic approach in care delivery across the multidisciplinary team. Nurses provide the cornerstone of the multidisciplinary team and provide the closest and the most frequent contact to the patient and their families to provide timely intervention. Nurses require a basic understanding of the complex physiology of metastasis to inform practice.

Introduction

Over the last few decades, the treatment options for many tumors have considerably improved, and in most cases, early-stage cancer can now be well controlled. However, the occurrence of metastasis remains associated with a high burden of morbidity and mortality.[1,2] Different cancer entities display typical patterns of metastasis, with malignancies originating from the breast, the prostate, or lung being especially prone for colonization in the bone.[3] Although bone metastases are usually not a direct cause of death, they often lead to profound decrements in quality of life.[4] Complications arising from bone metastases are classified as skeletal-related events (SREs), which include pathological fractures, dependence on radiation or surgery due to pain or local instability, spinal cord compression, or hypercalcemia. SREs are commonly associated with severe cancer-induced bone pain and restrictions in mobility, which result in a compromised social life and risk of social isolation.[5,6]

The pathophysiology of bone metastases remains incompletely understood. Although the direct interactions of cancer cells with bone cells have been deciphered in some detail, it is now accepted that this is an oversimplification of a highly complex process that includes a multitude of different cell types, including immune cells and cells of the vasculature. To improve treatment options, it is therefore critical to further elucidate the underlying pathophysiological mechanisms. Therefore, this article aims to provide a comprehensive overview of the pathophysiological mechanisms of bone metastasis and the current treatment landscape in the context of cancer care.

Molecular Mechanisms of Bone Metastases

The initial "seed and soil theory" postulated that bone is a highly "fertile soil" that attracts cancer cells (the "seed") as it provides an abundance of "nutrients."[7,8] As existing knowledge on metastases has expanded, so has the complexity of this simple theory, which was first published in 1889.[8] The basic idea that cancer cells are attracted to the bone environment has been deciphered as a complex process that is dependent on numerous cellular and soluble factors and conditions. The metastatic process (Fig. 1) to bone is initiated when cancer cells evade the primary tumor and transit into the vasculature followed by extravasation of the circulating tumor cells

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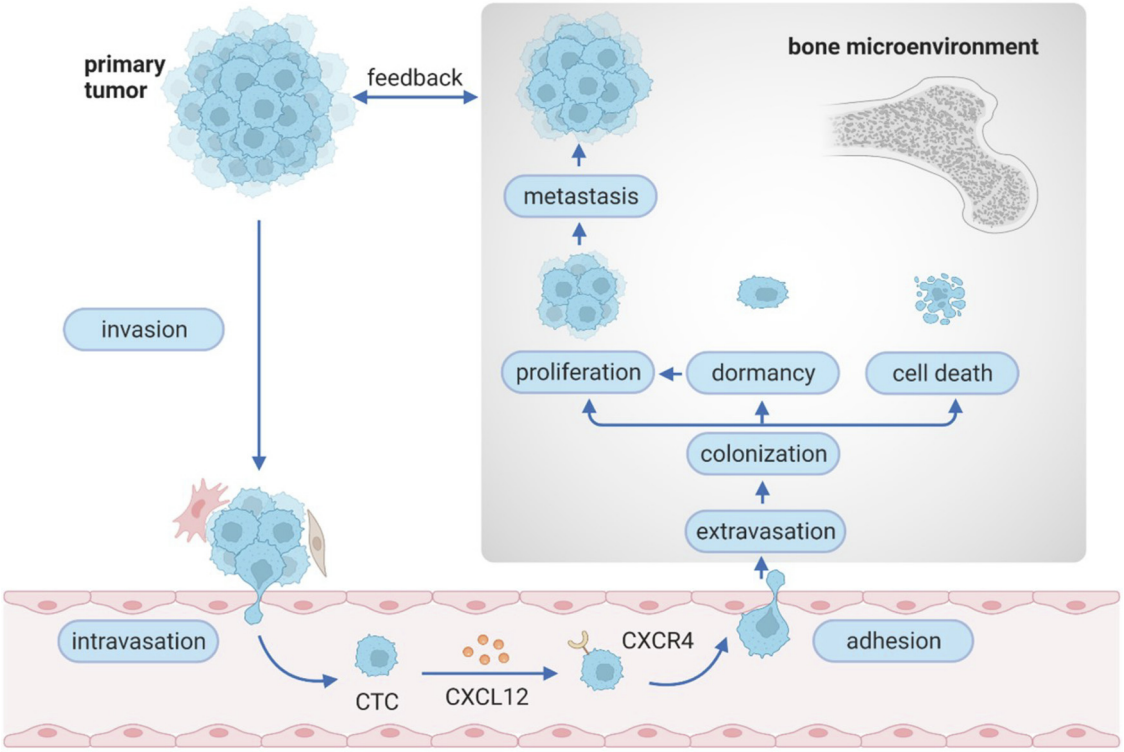

Figure 1. Bone metastasis. Hematogenous metastasis to the bone. Development from invasion, intravasation, circulation, and extravasation via adhesion to colonization of tumor cells. Even years later, dormant tumor cells can proliferate again and become detectable metastases. CTC, circulating tumor cell; C-X-C motif chemokine ligand 12; CXCR4, C-X-C motif chemokine receptor 4. Adapted from Coleman, Croucher, Padhani, et al.[39] Figure created using Biorender.com

(CTCs) into a metastatic niche at the site of future metastases. In the next step, CTCs colonize as disseminated tumor cells (DTCs) where they interact with cells from the bone, stroma, and immune system. Within the bone, cancer cells can either colonize and expand immediately or evolve to manifest metastases after a period of dormancy.[9]

Migration to Bone

In most cases, cells with accumulated mutations conferring oncogenic potential are rapidly eliminated by apoptosis in an autoprotective mechanism. Rendering resistance to this form of regulated cell death is a hallmark of cancer.[10] Having established a proliferative advantage, these cells are set to form a primary tumor.[11] Although already invasive and, thus malignant in nature, this process is still restricted to the original site. The progression into a metastatic state requires an additional set of mutations, which offer additional traits. Nonmalignant cells are bound to an environment of cell-cell and cell-matrix interaction; the loss of those causing apoptosis.[12] To enter into the circulation, malignant cells must shed these restrains and become "self-sufficient." Blood is a toxic environment for cells with high levels of redox stress and sheer forces of the fluid milieu. To overcome this step a rewiring of cellular metabolic processes is needed.[13] Finally, conquering of novel tissues to seed into a new organ requires readaption to a microenvironment with a specific extracellular context. Overall, the process of detachment and relocation known as anoikis constitutes the base for circulating and disseminating tumor cells.[14] The requisite of these processes largely explains why metastasis appears relatively late in most malignancies, although vascular invasion might be present earlier.

Metastasis into bone does not only depend on the successful colonization by circulating tumor cells but also on a plethora of additional tumor-derived factors, chemoattractants and the immune system to prime the bone for cellular attachment and to orchestrate the complex interplay between tumor cells and target tissue.[9,15] Such changes in the receiving tissue constitute the basis for an environment that has been termed "premetastatic niche."[16] Such an example is the secretion of heparinase by breast cancer cells, which promotes cell extravasation.[17] Furthermore, factors like the chemokine-like glycol-phosphoprotein osteopontin modulate the bone environment by promoting osteoclast mobility and activation as well as binding to $\alpha v\beta 3$ integrin, which helps to anchor circulating cells to their target tissue.[18,19] Matrix metalloproteinases also support the preparation of the extracellular matrix for integration of the circulating tumor cells.[17,18,20] Furthermore, bone homing factors such as extracellular matrix proteins and chemokines contribute to establish a metastatic niche.[15,16,21] In line with this, hematopoietic stem cells are known to migrate to established sites of metastasis and promote adhesion of additional circulating tumor cells.[22] The slow blood flow in the bone marrow might augment tumor cell adhesion to endothelia at these sites.[23]

Physiologically, the processes of bone remodeling are closely regulated by specialized bone cells like osteoblasts, osteocytes, and osteoclasts. All of them are controlled and balanced by a complex system of hormones, growth factors, cytokines, and immune cells. Overall changes in this system provides the perfect soil for tumor evolution.[24,25]

The importance of interleukin (IL)-1 signaling further underlines the strategic importance of osteoclast activation. In a murine breast cancer model, inhibiting both the IL-1 receptor or IL-1β, respectively, blocked spontaneous formation of metastases.[24,26] Interestingly, the processing of pro-IL-1β requires the activation of inflammatory caspases and is dependent on pyroptosis, which thus link tumor-site inflammation to systemic disease progression.[27,28]

In summary, the processes to establish a microenvironment as a soil for disseminating tumor cells are complex and is therefore still incompletely understood.

Dormancy and Progression of DTCs

Only a small number of CTCs survive the transition to bone to establish themselves as dormant DTCs.[15,29] However, these tumor cells are sufficient to cause relapse and expand to symptomatic bone metastases years after initial diagnosis. Dormant tumor cells can survive in the hematopoietic stem cell niche as well in the perivascular niche.[30] DTCs are predictive to the development of bone metastases and are associated with a poor prognosis.[31]

Dormant cancer cells first occupy and then interact with the niche mediated by a cellular reprogramming resulting in niche adaption. Afterward, a long-term dormancy sets in, which state might again shift to tumor cell reactivation for incompletely understood reasons. One theory is that the reactivation could be caused by an increase of nutrients.[32] Another theory proposes a critical role for changing circumstances of the immune system caused by reactive oxygen species, ageing, chemotherapeutics, or other immunomodulating drugs. Downregulation of innate and adaptive immune cells as well as bridging cytokines like IL-18 and transforming growth factor beta (TGFβ) promote an immune resistance by reduced antigen presentation and increased expression of molecules like the ligand of Programmed cell death protein 1.[33,34] Niche remodeling seems to be involved as well as bone remodeling osteoclasts have a monitoring function on dormant tumor cells.[35,36]

The cell cycle arrest of dormancy gives tumor cells the ability to survive up to decades, safely hidden away from the immune system, evading apoptosis and with a marked resistance to chemotherapy.[36,37]

Bone Metastases Classification

Bone metastases can be radiographically classified as osteolytic or osteoblastic (sclerotic) lesions. Although highly lytic lesions are more prone to fractures, both forms are associated with a reduced bone quality and strength.[38] Whereas radiologic imaging typically suggests a specific lesion type, a closer look reveals that in most cases both lytic and sclerotic areas occur within the same lesion.[39] Osteolytic metastases are observable in breast, lung, and renal cancer as well as in multiple myeloma, whereas prostate cancer is associated with osteoblastic lesions.[3]

Osteolytic Lesions

Osteolytic bone metastases are characterized by an increased bone resorption through over activation of osteoclasts.[40] Cancer cells secrete factors that induce bone resorption either directly or indirectly, promoting the release of factors from bone which, in turn, result in tumor proliferation and promote the vicious cycle associated with bone metastases (Fig. 2).[41] One of the best characterized factors is tumor-derived parathormone-related peptide (PTHrP), but also certain cytokines such as IL-6 and IL-8 represent important factors to promote osteoclastogenesis.[42,43] Osteoclast activity is regulated by receptor activator of nuclear factor-κB ligand (RANKL). RANKL levels are increased in the metastatic setting, and on binding to its cognate receptor, receptor activator of nuclear factor-κB (RANK) signaling results in differentiation and activation of osteoclasts.[44,45] Additional factors such as prostaglandin E2, tumor necrosis factor alpha, macrophage colony-stimulating factor, and IL-11 also contribute to osteoclast formation.[41] In many cases, these cytokines (PTHrP, interleukins, and prostaglandin E2) also cause a decrease of osteoprotegerin (OPG). OPG is a receptor that binds and blocks RANKL, preventing it from binding to its receptor RANK, which is situated on osteoclasts. Thus, decreased OPG levels lead to a higher bone resorption because more osteoclasts are activated by RANKL.[46] Furthermore, osteoclast activation and differentiation is initiated and regulated by numerous additional cytokines, matrix metalloproteinases, and other proteins such as TGFβ, insulin-like growth factor (IGF), bone morphogenetic protein, and fibroblast growth factor (FGF).[9,15,42,47,48] Subsequently, elevated calcium levels are another factor promoting tumor proliferation by an enhanced expression of calcium-sensitizing receptors.[49,50] In addition, inhibition of osteoblasts by Wnt-inhibitors such as dickkopf-1 (DKK-1) or sclerostin also shifts the balance toward bone resorption and prohibits physiological bone formation in the metastatic setting.[24,51] Patients with advanced breast cancer mostly develop bone metastases with an osteolytic appearance that are associated with a high occurrence of SREs.[43] Advanced breast cancers with metastasis to the bone show a median survival of about 2-3 years.[52,53] The attraction of breast cancer cells to this particular niche is subject of ongoing research. Most of the mechanisms described have also been demonstrated to be used by metastatic breast cancer.

Osteosclerotic Lesions

Sclerotic bone metastases seem to arise from an over activation of osteoblasts caused by tumor-derived factors, although the pathophysiology of sclerotic lesions remains less well understood than the mechanisms of osteolytic bone disease. Factors that contribute to this process include platelet-derived growth factor, IGF-1, FGF, and activated Wnt signaling.[41,54,55] Furthermore, the mitogenic factor endothelin-1 critically promotes osteoblast growth in addition to well-known factors such as FGFs and bone morphogenic factors.[56] Vice versa, osteoblasts respond to this stimulation by secreting IGF, FGFs, and TGFβ, which all stimulate tumor growth.[54] Especially in the case of prostate cancer, additional factors shaping the microenvironment such as chemokine (C-C motif) ligand 2, IL-6, and IL-8 are released.[57] The interplay of tumor cells and osteoblasts creates a vicious cycle promoting sclerotic lesions. It is this newly formed matrix, which is the optimal environment for infiltration of additional tumor cells; thus, finally leading to blooming of the metastases. To fuel this, both tumor cells and osteoblasts secrete factors like vascular endothelial growth factor to secure vascularization.[58] Furthermore, tumor cells are able to release extracellular vesicles such as tiny exosomes to interact with the microenvironment.[55]

Taken together, the deranged balance of bone homeostasis in favor of osteogenesis causes deformation of the usual bone structure, resulting in sclerotic lesions with a disordered spongiosa. In addition to osteoblast progenitors, osteomimicry seems to be a major contributing factor. This term denotes the ability of tumor cells to express bone specific proteins like osteopontin, osteocalcin, and RANKL, which promote formation of bone matrix assuming that cancer cells imitate bone cells.[59,60] Prostate cancer cells secrete a bouquet of factors, which promote bone metastasis either directly by activating osteoblasts or indirectly by modulating the bone microenvironment. On one hand, prostate cancer cells express physiological bone remodeling factors like BMPs and TGFβ as well as growth factors.[61] On the other hand, prostate cancer cells secrete factors that derange the bone microenvironment, including urokinase-type plasminogen activator, and prostate-specific antigen.[54,61] Prostate-specific antigen represents a serin protease, well known as prostate tumor marker, which can cleave PTHrP, resulting in less bone resorption and a shift toward osteoblastic activity.[62]

Therapy

As occurrence of bone metastases typically marks a transition toward a palliative concept, an approach by a multidisciplinary team should be emphasized to cover the range of different treatment options adequately. Major goals include prevention of SREs as well as broadly preserving quality of life, symptom management, and in particular, pain control. Treatment can consist of surgery, radio(-nuclide) therapy, pain management, psychological support, systemic cancer therapies as well as endocrine and bone-targeted therapies. Although there are an increasing number of individuals affected by metastases

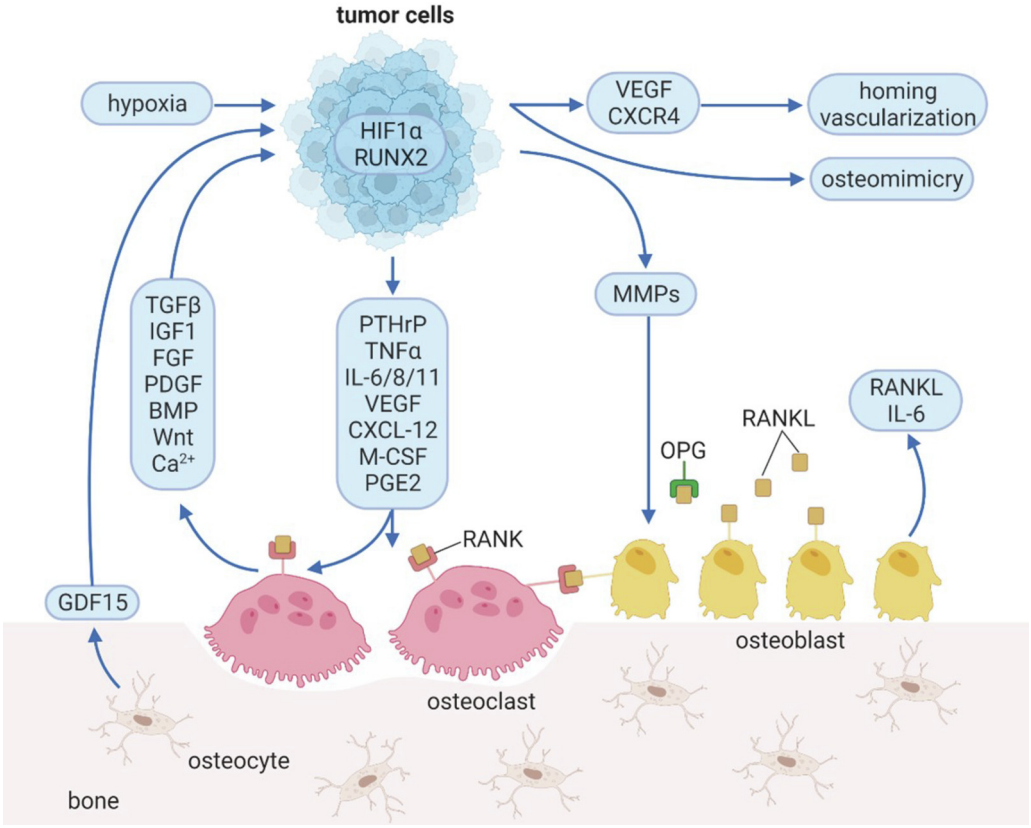

Figure 2. Vicious cycle of bone metastases. Tumor cells secrete factors that either directly or indirectly stimulate bone resorption that promote the release of factors from bone that in turn lead to tumor proliferation and promote the vicious cycle associated with bone metastases. BMP, bone morphogenic protein; Ca2+, ionized calcium; CXCR4, C-X-C motif chemokine receptor 4; CXCR12, C-X-C motif chemokine receptor 12; FGF, fibroblast growth factor; GDF15, growth differentiation factor 15; HIF1α, hypoxia-inducible factor 1α; IGF1, insulin-like growth factor 1; MMP, matrix metalloproteinase; OPG, osteoprotegerin; PDGF, platelet-derived growth factor; PGE2, prostaglandin E2; PTHrP, parathyroid hormone-related protein; RANK, receptor activator of nuclear factor-κB; RANKL, receptor activator of nuclear factor-κB ligand; RUNX2, Runt-related transcription factor 2; M-CSF, macrophage colony-stimulating factor; TGFβ, transforming growth factor β; TNFα, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor. Adapted from Coleman, Croucher, Padhani, et al.[39] Figure created using Biorender.com

where systemic therapies can achieve long-term tumor control, the majority of cases are not considered curative.[6,24] In this clinical scenario, bone-targeted agents have been a mainstay by lowering the incidence of SREs and maintaining quality of life.[63]

Bisphosphonates

Bisphosphonates are the oldest group of clinically established bone-targeted agents to reduce bone resorption through osteoclast inhibition.[64] First-generation bisphosphonates such as clodronate serve as pyrophosphate analogues and bear the additional ability to induce death of osteoclasts.[65,66] Modern nitrogen-containing bisphosphonates are termed "amino-bisphosphonates" and act as mevalonate pathway inhibitors, which plays a critical role in osteoclastic function.[67,68] While pamidronate and ibandronate have been tested and are approved for some metastatic conditions, zoledronic acid is considered the main agent with the best clinical data available in this class of drugs. These antiresorptive agents represent the standard therapy for bone metastases and osteoporosis, thereby reducing SREs including bone pain, fractures, and hypercalcemia.[69–73]

Denosumab

Denosumab is a monoclonal antibody against RANKL preventing its binding to RANK and acting like its physiological inhibitor OPG.[74] Three large randomized controlled trials compared denosumab to zoledronic acid in different metastatic conditions.[75-78] Superiority regarding prevention of SREs in metastatic breast cancer and castration-resistant prostate cancer was demonstrated, whereas overall survival and disease progression were equal.[76,77] Denosumab was noninferior in other advanced solid-tumor entities and in multiple myeloma compared with zoledronate.[78] Beside the approval for bone metastases, denosumab is also used for osteoporosis treatment in lower dosing and frequency.[79–81]

Side Effects of Antiresorptive Therapies

Compared to other cancer treatments, bisphosphonates and denosumab show a relatively small number of adverse effects. Both agents can induce hypocalcemia, osteonecrosis of the jaw, and atypical femoral fractures as expected from antiresorptive effects.[82] Bisphosphonates require dose adjustment for renal function, whereas denosumab can be administered independently of the estimated glomerular filtration rate. The supplementation of vitamin D and calcium remains important, especially in patients treated with denosumab and chronic kidney disease.[6,83] Osteonecrosis of the jaw is a rare but serious complication that mainly occurs in association with dental surgery, poor dental hygiene, smoking, diabetes mellitus, or glucocorticoid use.[39,84] In a few cases, antiresorptive long-term treatment with a high cumulative dose can lead to atypical femoral fractures.[85] Noteworthy, the effect of denosumab is reversible after termination and that it does not accumulate in bone.[86]

Implications for Practice and Conclusion

The prognosis of patients with cancer and their survival, even after occurrence of metastasis, has dramatically improved over the last 2 decades. However, SREs remain a clinical challenge in some of

the most common types of cancer. Both lytic and sclerotic lesions demonstrate typical features, but each tip the delicate balance of bone formation and degradation to one site or the other. These processes include the (inter)-action of different cell types such as osteoblasts and osteoclasts with the DTCs, as demonstrated in Fig. 1. Importantly, all these populations communicate reciprocally by various cytokines and direct interaction with the bone matrix (Fig. 2).

Of note, due to a lack of specific drugs for the treatment of sclerotic lesions, these are currently treated in a similar manner as predominantly osteolytic metastases with bisphosphonates or denosumab. Further research to understand the pathology of sclerotic lesions is needed to develop individual approaches for patients and to empower caregivers to provide support in a multidisciplinary team. The latter is the basis to provide significant improvements in quality of life.

Declaration of Competing Interest

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