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Therapeutic strategies for treating osteolytic bone metastases

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The recent progress in oncologic management of patients with localized cancer or metastatic disease has permitted a significant improvement in life expectancy. Nevertheless, bone metastases and their consequent skeletal-related events (SREs) are still associated with unfavorable prognosis and greatly affect quality of life. Global management of these bone metastases includes traditional local approaches (surgery, radiotherapy, *etc.*) and systemic administration of chemotherapeutic agents. This review focuses on treatments specific for bone metastases and, in particular, on inhibitors of bone resorption that are effective for preventing and delaying the development of SREs.

Introduction

Bone tissue is one of the most favored sites for metastasis of solid tumors (especially for prostate, breast, lung and kidney cancers), and bone lesions are preferentially localized in spine and pelvic bone. For example, up to 70% of all patients diagnosed with breast cancer will develop bone metastases. Normal bone development and maintenance are sustained through a balanced communication between osteoclasts and osteoblasts. Invasion of the bone compartment by cancer cells causes an imbalance in their activities and results predominantly in bone lysing or bone forming phenotypes depending on the origin of the cancer. In breast and renal carcinomas, bone metastases are predominantly osteolytic [1]. These lesions ultimately cause dramatic bone loss and compromised structural integrity resulting in severe bone pain, bone instability, fractures, spinal cord compression, hypercalcemia and bone marrow aplasia [2]. As described in a retrospective study from 617 women with breast cancer, 52% experienced at least one of these skeletal-related events (SREs) [3]. Particularly concerning metastatic spinal tumor, ~20% of cases exhibited neurological deficit as a result of: (i) mechanical spinal cord compression as a direct compression by tumor, displacement of the bone fragment and kyphotic deformity; and (ii) vascular insufficiency as a consequence of segmental artery occlusion by tumor emboli, venous thrombus and spinal cord injury as a result of edema caused by internal hemorrhage of the spinal cord.

The development of SREs considerably affects patient quality of life (Fig. 1) and, in some cases, increases the risk of death [4]. It is crucial to prevent or delay the onset of SREs. Radiotherapy, surgery and treatment based on antiresorptive agents are all useful in the clinical management of bone metastases. After briefly describing the pathophysiology of bone metastases, this review will focus on their global management, especially on pharmacological treatments specific to bone metastases.

Pathophysiology of osteolytic bone metastases

Metastasis pathway

Tumor metastasis is a multistep process including detachment of tumor cells followed by cellular invasion of adjacent tissue. Tumor cells produce some angiogenic factors, such as vascular endothelial growth factor (VEGF)-A and fibroblast growth factor (FGF)1 and FGF2, that considerably stimulate neovascularization of tumors [1,5,6]. This unfavorable phenomenon supplies nutrients and oxygen to tumor cells, and also favors tumor cell dissemination and the metastatic process. In addition, the epithelial to mesenchymal transition (EMT) property influences tumor cell metastatic ability. The process of EMT exploits plasticity of the extracellular

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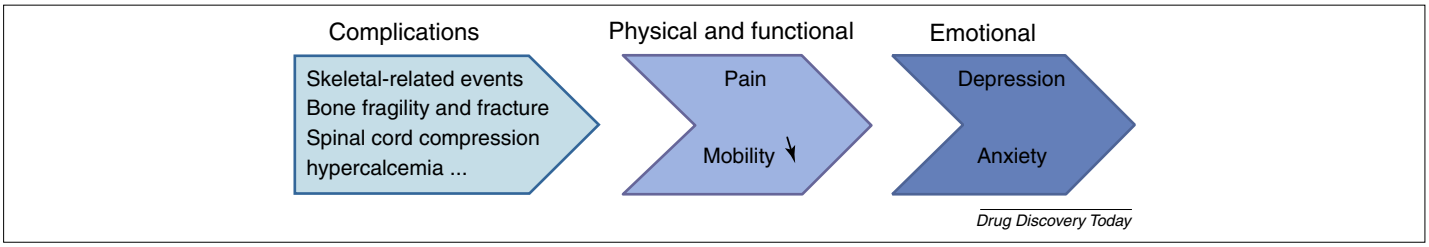

FIGURE 1

Repercussions of bone metastases on patient life in terms of physical, functional and emotional components. Quality of life is dramatically impacted by the development of skeletal-related events (SREs).

matrix characterized by cellular and molecular modifications. These include loss of cellular adhesion and cellular polarity, down-regulation of epithelial proteins such as cytokeratin, upregulation of mesenchymal proteins such as vimentin, reorganization of cytoskeleton to acquire more-spindle-like morphology, increased motility involving dynamic actin microfilament networks and increased resistance to apoptosis [7].

The 'seed and soil' theory

By secreting BMPs such as osteopontin, bonesialoprotein and osteonectin, cancer cells acquire bone-cell-like properties (a process known as osteomimicry) improving their homing, adhesion, proliferation and survival within bony sites [5]. Concomitantly, the bone environment provides a favorable niche for tumor cells given its rich store of growth regulatory factors released during bone resorption [8]. Among growth regulatory factors locally available, transforming growth factor (TGF)β is the most heavily implicated within osteolytic metastases by upregulating the expression of parathyroid hormone-related protein (PTHrP) *via* Smad and p38 mitogen-activated protein (MAP) kinase pathways. In addition, TGFβ inhibits the proliferation of epithelial cells, stimulates mesenchymal cell growth and synthesis of extracellular matrix proteins. This process has been defined as the theory of 'seed and soil' [9] (Fig. 2).

After bony site invasion, the balance between osteoblastic and osteoclastic cells is disrupted and, in the most common situation, tumor cells mediate bone destruction by stimulating osteoclastic activity, thus leading to osteolytic metastases. In fact, tumor cells secreted local factors, such as PTHrP, that enhance resorption activity of osteoclasts [10]. This is accomplished by: (i) increasing osteoblastic expression of the cell-membrane-associated protein termed receptor activator of nuclear factor (NF)κB ligand (RANKL); and (ii) reducing osteoblastic expression of osteoprotegerin (OPG), the soluble decoy receptor of RANKL. Binding of RANKL to RANK expressed on osteoclast membrane regulates osteoclastic differentiation and this crucial binding is disturbed in the presence of OPG, thus affecting maturation of osteoclasts. In addition to PTHrP, other soluble factors were released by tumor cells that also act directly on osteoclastic activity, thus resulting in increased bone resorption [8,11]. Finally, by removing the collagenous surface of osteoids before attachment of osteoclasts, matrix metalloproteinases (MMPs) released by tumor cells participate in osteolysis.

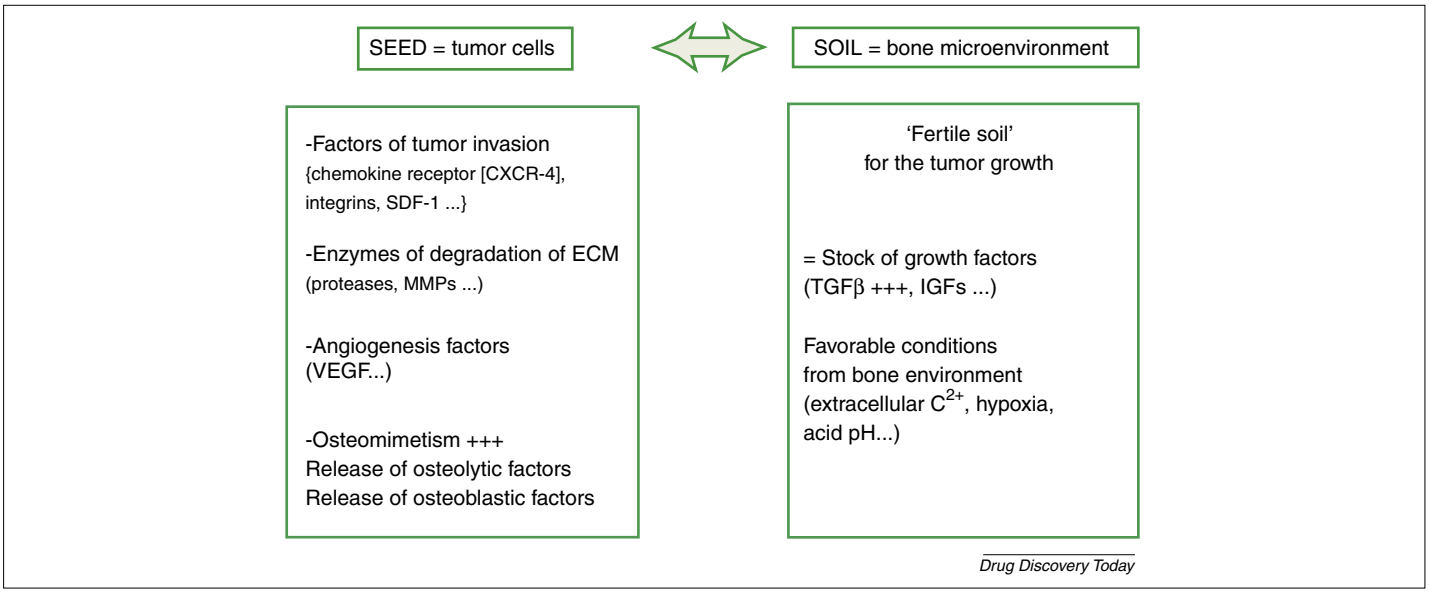

FIGURE 2

The theory of 'seed and soil' [9] initially described the relation between bone environment (the 'soil') and tumor cell (the 'seed'). Among growth factors contained in bone, transforming growth factor (TGF)β is the most implicated in activating tumor cells resulting in an excessive osteolytic process. *Abbreviations*: ECM, extracellular matrix; IGF, insulin-like growth factor; MMP, matrix metalloproteinase; SDF, stromal-cell-derived factor; VEGF, vascular endothelial growth factor.