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Treatment of Metastatic Bone Disease and the Emerging Role of Radium-223

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Bone metastases are common in advanced malignancy and, despite the developments in both anticancer and bone-targeted therapies in recent years, new therapeutic strategies are still needed. Traditionally, radioisotopes have been rarely used in part owing to concerns about bone marrow toxicity that limits retreatment and may prevent safe administration of subsequent chemotherapy. Radium-223 dichloride (Ra-223) is a calcium mimetic that binds preferentially to newly formed bone in areas of bone metastases, is the first alpha-emitting radionuclide to be developed for clinical use, and is approved for treatment of castration-resistant prostate cancer and symptomatic bone metastases. In this setting, it improves overall survival and delays symptomatic skeletal complications. The high linear energy transfer of the emitted alpha particles causes predominantly nonrepairable double-stranded deoxyribonucleic acid breaks in tumor cells, and the large size of the alpha particle, compared with other forms of radiation, results in a short path length and highly localized tissue destruction. As a result, Ra-223 has a highly favorable safety profile with a low level of myelosuppression. The role of Ra-223 in malignancy is discussed and the prospects for future development outlined.
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Introduction

Metastatic bone disease is most commonly seen with specific cancer types, notably from tumors arising from the breast, prostate, lung, and kidney, as well as multiple myeloma. The most common sites for bone metastases are within the axial skeleton and, whether lytic or blastic in appearance, they often lead to skeletal complications typically referred to as skeletal-related events (SREs). The need for radiotherapy to relieve pain or improve bone structure and pathologic fractures through diseased bone is the most common skeletal event, reflecting the burden of bone pain and structural damage caused by metastatic involvement. Surgery to bone for impending or actual fracture, spinal cord compression, and hypercalcemia are other less frequent SREs. Many of these complications are associated with life-altering morbidity and can reduce overall survival. Therapeutic strategies that maintain the structural integrity of bone are thus an important adjunct to standard anticancer treatments.[1]

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Mechanisms of Bone Metastasis

Bone remodeling, the coordinated sequence of bone resorption by osteoclasts, followed by de novo synthesis of a bone matrix by osteoblasts provides constant skeletal turnover and is the key to mechanical adaptation. Bone homeostasis is under systemic and local control, integrating mechanical, paracrine, neural, and endocrine stimuli. Among the latter, estrogens, 1,25 dihydroxy-vitamin D, and parathyroid hormone are among the classical key endocrine regulators of bone metabolism. More recently, the importance of the activin and inhibin system, potent regulators of reproduction, has also been highlighted, as activin A is an inhibitor of bone regeneration and mineralization.[2]

In the process of bone metastasis, tumor cells do not directly destroy bone but use the cellular and molecular machinery of bone metabolism. For more than 2 decades, the concept of a vicious cycle between tumor cells and osteoclasts has been proposed based on solid experimental and clinical evidence.[3] Factors, including tumor necrosis factor alpha, interleukin (IL)-6, IL-8, IL-11, IL-15, and IL-17, receptor activator of nuclear factor kappa B ligand (RANKL), prostaglandins, and leukemia-inhibitory factor derived from tumor cells per se, interact with mesenchymal stem cells and adjacent immune cells to stimulate osteoclastic bone resorption that leads to bone

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destruction. Most of these tumor-derived cytokines upregulate osteoclast functions directly or via enhancing the RANKL to osteoprotegerin ratio. Estrogen deficiency may also upregulate the expression of several osteoclastogenic cytokines (tumor necrosis factor alpha, IL-6, IL-11, IL-17, and RANKL) and suppress antiosteoclastogenic factors, such as transforming growth factor beta (TGF-β) and osteoprotegerin.[4] Excessive bone resorption also releases large amounts of calcium and growth factors, such as TGF-β and insulin-like growth factors, from the matrix, which in turn stimulates tumor growth.[2,3] Interrupting this vicious cycle is an obvious therapeutic option and has been successfully achieved with bisphosphonates and, more recently, the RANKL inhibitor denosumab.

Osteotropic tumors may also suppress osteoblast function.[2] By producing inhibitors of the Wnt signaling pathway such as DKK-1, myeloma cells suppress osteoblast function and bone formation.[5] Myeloma cells also produce other inhibitors of osteoblast function, such as sclerostin and activin. Activin A serum levels are elevated in myeloma bone disease, and activin A has been implicated to enhance the osteolytic activity and to concurrently inhibit osteoblast differentiation. Breast cancer cells also secrete inhibitors of bone formation that interfere with the TGF-β and Wnt signaling pathway.[6]

Therapeutic Options

The effect of cancer on the skeleton can be devastating and typically results in a major decline in quality of life (QOL) as well as reduced survival. Over the past decade or more, as we have learnt a great deal about the cellular interactions that lead to the colonization of bone by tumor cells and subsequent formation of metastases, we have used this improved knowledge to develop a range of bone-targeted treatments that have profoundly affected the clinical course of metastatic bone disease across the range of primary tumors that can affect the skeleton.[1] These agents have complemented the improvements in specific drug treatments for cancer, radiation treatments, and orthopedic surgery and become part of the standard of care for patients with spread of cancer to bone. We now have a range of agents with proven efficacy, including several bisphosphonates and denosumab, a highly specific monoclonal antibody that targets RANKL. Multiple, randomized, controlled trials have clearly demonstrated that they are effective in reducing skeletal morbidity from metastatic cancer.[1]

Targeted radiotherapy with therapeutic radioisotopes has theoretical advantages over external-beam radiotherapy in that the radiation dose may be delivered more specifically to the tumor and normal tissues partially spared unnecessary irradiation. Follicular carcinoma of the thyroid commonly metastasizes to bone and the treatment of bone metastases with 131-iodine (^{131}I) is well established.[7] In prostate and breast cancers with blastic metastases, useful palliation of bone pain has been demonstrated with ^{89}strontium (Sr-89)[8] and ethylene diamine tetramethylene phosphonate-^{153}samarium (Sm-153).[9] Most recently, the bone-seeking, α-particle-emitting radiopharmaceutical ^{223}radium dichloride (Ra-223) has been developed.[10] Ra-223 is an alpha-emitting pharmaceutical with a half-life of 11.4 days that mimics calcium, thereby allowing it to form complexes with the bone mineral hydroxyapatite in areas where there is increased bone turnover, such as bone metastases.[11] Ra-223 induces a highly localized antitumor effect on adjacent bone metastases while limiting damage to the surrounding normal tissue. Additionally, owing to the binding of Ra-223 to bone, the daughter isotopes are retained in the bone matrix.[12]

The beta-emitting radioistopes ^{89}Sr and ^{153}Sm produce relatively low energy radiation with a track length in tissues of up to several millimeters (mm). By contrast, alpha emitters produce high linear energy transfer radiation with ultrashort penetration (< 100 μm; 2-10 cell diameters). These differences in physical attributes would predict increased antitumor activity with relative sparing of the bone marrow and consequent effects on hematopoiesis.[11]

Potent antitumor effects of Ra-223 seen in animal models led to the evaluation of its efficacy and safety in clinical trials.[13] A phase I trial of a single intravenous injection of Ra-223 in 25 patients with metastatic bone disease (15 prostates and 10 breasts) showed that doses of 50-250 kBq/kg were well tolerated.[10] Grade III leukopenia was seen in only 3 of 25 patients and no patient developed grade III or IV thrombocytopenia. No dose-limiting toxicities were observed. Gastrointestinal (GI) tract adverse events were most frequent with diarrhea (Grade I or II) reported in 10 of 25 patients. Imaging studies, using the small amount of gamma irradiation emitted, showed preferential uptake in skeletal metastases compared with healthy bone and excretion mainly through the GI tract, explaining the GI tract adverse events.[10] Significant decreases in alkaline phosphatase (ALP) were seen at all doses tested, and on the basis of these effects led to the 50 kBq/kg dose being selected for future studies with the main focus on advanced prostate cancer.

Phase II studies in metastatic prostate cancer demonstrated promising responses in palliation of bone pain, positive effects on changes in bone ALP (bALP) and prostate-specific antigen (PSA) levels, and improved survival with limited toxicity.[14] On the basis of these results, a phase III registration study, Alpharadin in Symptomatic Prostate Cancer patients (ALSYMPCA), was conducted to evaluate the efficacy and safety of Ra-223 in advanced castration-resistant prostate cancer (CRPC).[15]

ALSYMPCA included 921 patients with histologically confirmed CRPC and two or more bone metastases and receiving best standard of care; patients were randomized 2:1 to receive Ra-223 (at a dose of 50 kBq/kg IV) or matching placebo every 4 weeks for 6 doses (Fig. 1). The primary end point of the study was overall survival. Efficacy assessments included survival status, clinically evaluated SREs, total ALP, and PSA concentrations and safety. Patients were stratified before randomization by baseline ALP value (< 220 vs ≥ 220 U/L), bisphosphonate use at baseline (yes vs no), and prior treatment with docetaxel (yes vs no).

Results from the primary efficacy intention to treat (ITT) analysis indicated that Ra-223 significantly improved overall survival from 11.3 months in the placebo group to 14.9