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Anti-Tumour Treatment

Targeted radio-nuclide therapy of skeletal metastases

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ABSTRACT

In this review, we will focus on one particular class of stromal targeted therapy, i.e. the bone seeking radiopharmaceuticals (BSRs), but will also highlight selected issues related to the bone stroma as these concepts are new, rapidly evolving, and clearly linked to the underlying BSR mechanisms of targeting and action. Herein we review clinical BSR-trials of significance with randomized trials at center stage. Furthermore, we cover a new class of BSR in late clinical development based on bone-stromal targeted alpha-particle irradiation. Lastly, we discuss potential advances in combining BSR with bisphosphonates and/or chemotherapy and emphasize the feasibility of repeated dosing.

Background

The skeleton is the most common site of symptomatic metastatic disease and cancers from prostate, breast, lung, kidney, and thyroid, as well as multiple myeloma, commonly spread into and through this organ. Though the number of patients with bone metastases is debatable, it has been estimated that approximately 400,000 such patients are diagnosed annually.[1] Prostate cancer and breast cancer are particularly important sources of bone metastases given the prevalence of these diseases, their bone tropism, and relatively prolonged natural history. Bone metastatic lesions are prone to a variety of morbid complications including pain, hypercalcemia, pathologic fracture, spinal cord and nerve root compression. Pancytopenia due to progressive growth of metastases within the axial skeleton displacing normal red bone-marrow is a common clinical problem; especially in advanced prostate cancer. These complications limit both quantity and quality of life.

A variety of treatment modalities including analgesic medications, radiation, surgery, chemotherapy, hormone treatment, bisphosphonates and/or bone-seeking radiopharmaceuticals (BSRs) may all be considered appropriate for individual patients and best treatment choices are often determined within the context of multi-disciplinary management. The appropriate choices depend on the extent of the skeletal involvement, symptoms, the underlying disease and the availability of systemic options, the life expectancy of the patient, the bone marrow function and the patient's co-morbidities.

Tumor biology of bone metastases

Though various mechanisms have been implicated in metastatic spread into the skeleton, the "seed and soil" hypothesis first promulgated by Paget in 1889[2] remains commonly accepted today. This hypothesis implicates a combination of factors including both tumor cells and a permissive stromal environment. Today there is a greater appreciation that neither the seed not the soil are static and that both tumor cells and a variety of stromal cells interact with a number of secreted paracrine factors in a "vicious cycle" that promotes the survival and proliferation of tumor cells.[3,4]

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Most studies implicate hematogenous spread as the source of tumor cells that lodge in bone. These circulating tumor cells are now increasingly well described.[5,6] It is clear that that only a small percentage of these "seeds" are capable of forming metastatic tumors and that the process of extravasation and metastatic tumor growth is complex. Molecular characterization of these events is ongoing in an effort to devise new anti-cancer strategies.

It is well recognized that the tumor cells can interact with stromal components[7–9] such as the extracellular matrix, various mesenchymal stromal cells, the immune system and vascular endothelial cells. In bone, cells such as the osteoblasts, osteoclasts, and hematopoietic cells (and their precursors) also represent components of the tumor micro-environment. Osteoclast activating factors are thought to be critical in enabling tumor growth to be established in bone, working in part through the nuclear factor-kappa B ligand (RANKL).[10] There is also evidence that malignant cell growth can be promoted by selected stromal secreted factors such as basic-FGF released.[8] Interestingly, experiments with fibroblasts derived from bone stroma combined with certain cancer cell lines display synergistic growth.[9]

There is a close balance between osteoclastic and osteoblastic activity within normal bone maintaining normal homeostasis; osteoclast and osteoblast activation by tumor disturb this balance.[11] Tumors can result in either relatively lytic metastases such as those of myeloma and renal cell cancer or relatively osteoblastic metastases; such as those present in prostate cancer. Mixed lytic/blastic lesion as are often encountered in breast cancer. It is the tumor associated upregulated osteoblastic activity that promotes new bone formation and incorporation of the 'bone seeking radioisotopes' used therapeutically.

The concept of a static bone stroma has passed but the new conceptual era of altering the bone stroma to enhance effectiveness of BSR action is only being discussed. The uptake of BSRs is proportional to the osteoblastic nature of the bone metastatic disease. Bisphosphonates are known to alter the lytic/blastic ratio in bone lesions supporting the concept of synergism when combining BSRs after chronic but not acute bisphosphonate administration. As shown in Fig. 1, a marginally bone scan positive patient with breast cancer pre-bisphosphonate is shown to have a markedly positive scan after chronic bisphosphonate therapy. This alteration in bone scan uptake should have a similar effect on BSR site-specific delivery. Similar effects might be expected after chronic but not acute administration of the RANKL antagonist denosumab. Bortezomib treatment in myeloma has also been shown to increase bone scan up take[12] (see Fig. 2).

Another approach to increase BSR uptake is through exploiting the 'flare' seen after LHRH agonists or abiraterone used in prostate cancer[13] or after hormonal therapies in breast cancer.[14] These therapies may be associated with a rises in alkaline phosphatase and increased bone scan uptake which are thought to signify healing of bone in the region of metastatic lesions. Timing BSR therapy administration to take advantage of this flare is an unexplored but attractive concept.

Chemical and radio-isotopic characterization of BSRs

The two FDA approved BSRs are beta-emitters with distinct half-lives, energies, and mechanisms of bone targeting.[15] ^{153}Sm-EDTMP (lexidronam/Quadramet) has relatively low average energy for beta emissions (0.22 MeV) and a short radioactive half-life (1.9 days). ^{89}Sr (Metastron) has a relatively prolonged half-life (50.5 days) and higher average beta emission energy (0.58 MeV). A variety of other beta-emitting isotopes have been utilized in clinical trials including ^{166}holmium, ^{177}lutetium, ^{186}rhenium, ^{188}rhenium, ^{131}iodine, and ^{90}yttrium. As seen in Table 1, the maximum and average beta energy varies considerably with each radionuclide. The highest average energy beta particle is seen with ^{90}yttrium and the lowest with ^{177}lutetium. ^{117m}tin (Sn) emits conversion electrons with two discrete energies. Conversion electrons have the same mass as beta particles and behave similarly in tissue. The energy of the conversion electrons is the lowest of any of the BSRs. Tissue penetration for the various beta particles and electrons are proportional to their energy so ^{117m}Sn emissions have the lowest penetrance of any radionuclide in this class. Tissue penetration may seem desirable on the surface but the depth of tissue penetration is also proportional to the marrow radiation, and hence hematological toxicity.

^{223}Radium is the first bone-targeted alpha emitter to be studied in clinical trials of skeletal metastases. Alpha particles are comprised of 2 protons and 2 neutrons (helium nucleus) and have a mass approximately 7300 times as large as a beta particle or

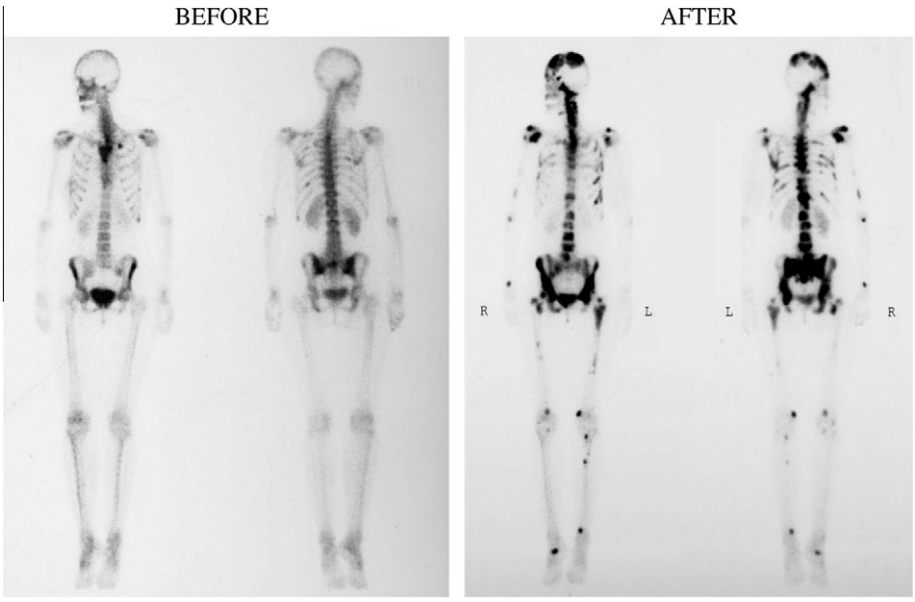

Fig. 1. Bone scans in a breast-cancer patient before/after chronic bisphosphonate therapy.