CLINICAL VIGNETTE

Clinical Update – New Advances in the Treatment of Bone Metastasis

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Bone metastases are a frequent and costly occurrence in cancer patients. In fact, on postmortem examination 70 to 85 percent of patients with advanced breast or prostate cancer have bone metastases[1,2]. Now that patients are living longer with advanced cancer, if their bone metastases are left untreated, they will inevitably cause significant morbidity, such as pathologic fractures, spinal cord compression fractures, nerve compression, pain, or hypercalcemia. Each of these serious skeletal related events (SRE) will require immediate treatment, which may delay cancer therapy, and come at a high price, not only to the patient, but also to our healthcare industry as a whole.

Although bone directed treatments, such as intravenous bisphosphonates (IVBP), have been FDA approved since 2002, for one reason or another they have been underutilized in this population of patients. A recent retrospective study identified more than fifty percent of patients with bone metastases went untreated with IVBP[3]. Zoledronic acid, an IVBP, has shown efficacy in reducing SRE's[4]. Bisphosphonates are synthetic analogues of pyrophosphate, which have been shown to inhibit osteoclast activity, resulting in decreased bone resorption[5]. However, this class of agents comes with side effects including nephrotoxicity, osteonecrosis of the jaw (ONJ), and flu-like syndrome, amongst others. More recently, in November of 2010, a monoclonal antibody to receptor activator of nuclear factor-Kappa (RANK) ligand, denosumab was approved by the FDA for the prevention of SRE's in patients from bone metastases from solid tumors, excluding multiple myeloma[6-8].

To understand the mechanism of RANK ligand inhibitors such as denosumab, we will review the normal physiology of bone remodeling and then the pathophysiology of bone metastases. The normal adult skeleton is in a constant state of turn over and remodeling coordinated through the steady activity of osteoclasts and osteoblasts. This is a well-balanced sequence in which osteoclasts first resorb bone, and then undergo apoptosis, allowing osteoblasts to regenerate new, healthy bone at the same site[9].

In addition to systemic factors, such as parathyroid hormone and 1,25-dihydroxyvitamin D3, the bone microenvironment produces growth factors such as macrophage colony stimulating factor and RANK ligand locally through the activity of stromal cells and osteoblasts. RANK ligand, expressed on the surface of osteoblasts, is released and binds to receptors on osteoclasts precursors from the monocyte-marcrophage lineage, which in turn assists in the formation activated osteoclasts. Activated osteoclasts are able to adhere to the bone surface and secrete proteases that dissolve the matrix, releasing minerals and other cytokines, such as transforming growth factor Beta, insulin-like growth factors I and II, fibroblast growth factor, platelet-derived growth factors, amongst others, into the microenvironment[9]. In this manner RANK ligand plays an integral role in stimulating osteoclast formation, activation, adherence, and survival, all leading to increased bone resorption[10]. In normal bone, this effect of RANK ligand is counteracted by osteoprotegerin (OPG), a soluble, tumor necrosis factor (TNF) receptor family member that competitively binds RANK

ligand. In effect this acts as an "antagonist" receptor to RANK receptors, balancing the amount of RANK activation on osteoclast precursors[10].

The pathophysiology behind bone metastasis is a dysregulation of this normal, well-balanced process, which occurs once tumor cells enter the bone microenvironment. The steady supply of growth factors, high blood flow, and presence of angiogenic factors within the bone microenvironment makes it an optimal site for metastasis of tumor cells[9]. Whether the metastasis is radiologically classified as an osteolytic or osteoblastic lesion, the end result is an imbalance in bone formation that leads to structurally substandard bone, allowing a higher likelihood of SRE's in our patients.

For instance, breast cancer cells have been known to produce parathyroid hormone-related peptide (PTHrP), which assists in stimulating the formation of osteoclasts, making breast cancer induced lesions more "osteolytic" in nature[9]. As seen above, once osteoclasts resorb bone, tumor growth factors are released, which induce further bone destruction and tumor growth, creating a "vicious circle"[9]. On the other hand, prostate cancer has been associated with predominately osteoblastic metastases on radiologic studies. However, in animal models it has been shown the neoplastic prostate cancer cells initially activate osteoclast activity and osteolysis, by increasing RANK-ligand expression on osteoblasts. This in turn leads to the imbalanced bone remodeling at the sites of bone resorption, leading to the primarily osteoblastic appearance of prostate cancer[10]. Whether the lesions are classified as "osteoblastic" or "osteolytic", they still trigger the same process of bone resorption leading to increased release of tumor and bone-remodeling growth factors in the microenvironment of bone metastasis.

An antagonist to RANK ligand, whether it is the physiologic OPG or an engineered molecule such as denosumab, can attempt to partially halt this "vicious circle". Denosumab is a fully human monoclonal antibody with an affinity and specificity for RANK ligand, shown to significantly decrease osteoclastic activity in patients with metastases to bones[11]. Therefore, this new molecule was tested against the previous standard of care for treatment of bone metastasis, IVBP's. Three randomized, double-blind phase III trials have been published comparing this agent to zoledronic acid in patients with bone metastases, looking at SRE's as the primary endpoint. One trial looked at only breast cancer, another at only prostate cancer, and a third including all other solid tumors including multiple myeloma[6-8].

In breast cancer models, levels of stromal RANK-ligand are increased, likely through the effects of PTHrP, as discussed previously. A phase III study comparing it to zoledronic acid, in patients with bone metastases from breast cancer looking at time to first on-study SRE's was recently published. Patients were randomized to one of two arms: denosumab 120mg subcutaneous injection every four weeks or zoledronic acid intravenously every four weeks. In the published results, we saw a statistically significant hazard ratio (HR) of 0.82 in favor of denosumab for first on-study SRE, showing clinical superiority[6].

In prostate cancer, a predominately "osteoblastic" disease, a similar study was also performed. Patients with bone metastasis from prostate cancer were again randomized to one of the two arms comparing denosumab to zoledronic acid for primary endpoint of time to first on-study SRE. Again a statistically significant HR of 0.82 in favor of denosumab was obtained. In addition, a greater suppression of bone turnover markers was also observed in the denosumab patients compared with zoledronic acid[7]. Furthermore, a third phase III study looking at all other tumor types showed that denosumab was noninferior to zoledronic acid in risk reduction of SRE's[8].

Overall survival was essentially the same in both arms for all three trials.

Denosumab is also a well-tolerated therapy. The most common adverse reactions in both arms of these three trials were nausea, fatigue, and hypophosphatemia[6-8]. However, a higher incidence of hypocalcaemia was specifically associated with denosumab. It is recommended that all patients receiving denosumab also take calcium and vitamin D supplements. And finally, in terms of ONJ, in patients treated with denosumab, 1.8 percent developed ONJ, in comparison to 1.3 percent in the zoledronic acid arms (p=0.13) (6-8). Preventative dental actions are recommended prior to and during treatment with denosumab, as it is with zoledronic acid. This would include a routine dental clinical examination prior to initiating therapy, and instructed to avoid elective, invasive dental procedures.

Bone metastasis continues to be a serious and troubling complication in the course of treating cancer patients. SRE's leave many patients in a significantly worse condition than at the time of their initial diagnosis. New therapeutic tools targeting specific pathways in this "vicious cycle," such as inhibiting RANK ligand with a monoclonal antibody, denosumab have proven to be tolerable and efficacious. Ongoing trials are examining the possibility of preventing bone metastasis in advance cancers as well as preventing chemotherapy induced bone loss. As we learn more about this integral pathway, further improvement in our patient's quality of life will follow.

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