Update on the Pharmacological Prevention of Skeletal-related Events in Cancer Patients

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Abstract: Metastases to the bone are a frequent complication of advanced cancer. Bone metastases have been linked to skeletal-related events, which is the composite endpoint used in clinical trials evaluating therapy to minimize these complications. This article discusses bisphosphonates, which are the historical standard for the prevention of skeletal-related events in patients with metastases from solid tumors and multiple myeloma, and denosumab, which is the first Food and Drug Administration-approved receptor activator of nuclear factor kappa-β ligand (RANKL) inhibitor.

Metastases to the bone are a frequent complication of advanced cancer. Patients affected by the most common cancers—lung, breast, and prostate—are more commonly plagued by bone metastases. Despite the widespread occurrence of bone metastasis, reliable figures for the prevalence or incidence of patients with bone metastases remain elusive. It has been estimated that up to 70% of patients with advanced breast or prostate cancer and 15% to 30% of patients with lung cancer will develop bone metastases. In the United States alone, approximately 350,000 people who die annually from cancer will have bone metastases. Multiple myeloma, occurring less frequently than the previously mentioned cancers, is a cancer of plasma cells and is frequently implicated in the development of widespread bony involvement.

Homeostasis of healthy bone is maintained by the opposing actions of osteoblasts and osteoclasts. The microenvironment created by constant bone resorption (osteoclasts) and formation (osteoblasts) creates a highly favorable environment as a site of metastases. Adhesive molecules manufactured by the tumor cells allow binding to marrow stromal cells and the bone matrix. High blood flow through the red marrow of bone also creates ample opportunity for metastatic cells to come in contact with this new environment.

Consequences from bone metastases range from bone pain and fractures to hypercalcemia and spinal cord compression. Historically, bone metastases have been classified as either strictly osteolytic (bone destructing) or osteoblastic (bone forming). The complication encountered is often a product of the type of bone lesion, which is most commonly subject to the type of cancer involved. For example, bone metastases secondary to multiple myeloma are purely osteolytic lesions that result in an unbalanced erosion of the bone. With the exception of multiple myeloma, most bone metastases contain features of both lytic and blastic involvement.

It is important to note that clinical trials investigating treatment options for metastatic bone disease use a composite endpoint termed skeletal-related events. Bone metastases are highly correlated with skeletal-related events, hence the use of the composite endpoint in clinical trials. Skeletal-related events most commonly encompass pathologic fractures, spinal cord compression, surgery for the prevention and treatment of pathologic fractures or spinal cord compression, or radiation for bone pain. Hypercalcemia is also sometimes included in this definition.

Historically, bisphosphonates have been the treatment of choice for the prevention of skeletal-related events. This article provides a brief histori-
Nephrotoxicity is a common adverse event that is reported to occur in approximately 7% of patients receiving either pamidronate or zoledronic acid. Dose adjustments are recommended for both agents in patients experiencing renal dysfunction at baseline, as well as interruptions of therapy in patients experiencing drastic increases in serum creatinine. Osteonecrosis of the jaw is a rare but serious complication associated with the use of bisphosphonates. A recent meta-analysis, which pooled the 3 major identical clinical trials comparing zoledronic acid to denosumab in the prevention of skeletal-related events, determined that osteonecrosis of the jaw occurred in 1.3% of patients receiving zoledronic acid compared with 1.8% of those treated with denosumab ($P=.13$). A separate retrospective analysis of multiple myeloma patients reported that 11% of patients receiving a bisphosphonate developed osteonecrosis of the jaw. The authors concluded that when individual bisphosphonates were compared, zoledronic acid was associated with a 9.5-fold greater risk of osteonecrosis of the jaw compared with pamidronate ($P=.042$). Other toxicities may include flu-like symptoms, myalgia, and arthralgia (Table).

**DENOSUMAB**

Denosumab is a human monoclonal antibody that targets the receptor activator of nuclear factor kappa-β ligand (RANKL). In patients with metastatic bone disease from solid tumors, there is excess osteoclastic activity that is mediated by RANKL. This, in turn, results in changes of bone architecture potentially leading to skeletal-related events.

Denosumab binds to RANKL, thereby inhibiting osteoclast-mediated bone destruction. Denosumab is marketed as both Xgeva (Amgen, Thousand Oaks, California) and Prolia (Amgen) in the United States. It is important to note that the 2 marketed products have received different FDA-approved indications and are not interchangeable. For the purpose of this discussion, all indications in this article refer to Xgeva, which is currently approved by the FDA for the prevention of skeletal-related events in patients with bone metastases from solid tumors but not from multiple myeloma.

Three phase III trials have led to the approval of deno-
Denosumab delayed time to first on-study skeletal-related event by 18% (20.6 months for denosumab vs 16.3 months for zoledronic acid; P < .001 for noninferiority, P = .01 for superiority) and was also found to be superior in regard to time to first and subsequent on-study skeletal-related event (P = .001).11

Fizazi et al12 compared the same regimens for the treatment of bone metastases in men with castration-resistant prostate cancer. Denosumab delayed time to first on-study skeletal-related event by 18% (median, 20.7 months for denosumab vs 17.1 months for zoledronic acid; P = .002 for noninferiority, P = .008 for superiority) and was found to be superior for time to first and subsequent on-study skeletal-related event (P = .008).12

Henry et al13 compared denosumab to zoledronic acid for the treatment of bone metastases in patients with advanced cancer or multiple myeloma, excluding breast and prostate cancer. Denosumab delayed time to first on-study skeletal-related event by 16% but was not found to be superior for time to first and subsequent on-study skeletal-related event (P = .0007 for noninferiority, P = .06 for superiority). Overall survival and disease progression were similar in both study groups. However, an ad hoc analysis of overall survival found that patients with multiple myeloma had a two-fold higher risk of death in the denosumab arm.13 Adverse effects were similar in both study groups, including the risk for osteonecrosis of the jaw. However, more patients in the denosumab group experienced hypocalcemia.

The most common adverse effects associated with denosumab use include fatigue, anemia, hypophosphatemia, and nausea. Patients taking this medication need to have serum magnesium, phosphorus, and calcium levels checked monthly (Table). The risk of hypocalcemia is increased in patients with a creatinine clearance <30 mL/minute or those on dialysis. All patients should receive calcium and vitamin D supplementation. When initiating denosumab therapy, hypocalcemia should be corrected first.14

None of the bone-modifying agents currently available have demonstrated a survival advantage over the others; therefore, no consensus exists for a treatment pathway. Zoledronic acid has largely supplanted pamidronate in the clinical setting because infusion time is greatly reduced with zoledronic acid. Both pamidronate and zoledronic acid carry a risk of nephrotoxicity and need to be adjusted in renal dysfunction.

Potential advantages of denosumab are that it does not require adjustment in renal impairment and it is easier to administer relative to the other bone-modifying agents (Table). In a patient with renal impairment, denosumab may provide a unique advantage over the others, although the risk of hypocalcemia may be increased in the setting of renal dysfunction. All of these agents require a baseline and regular dental examination to prevent patients with poor dentition from receiving an agent that may cause osteonecrosis of the jaw. The risks of osteonecrosis of the jaw appear to be similar between zoledronic acid and denosumab, but differences among the available bisphosphonates are less clear.

**References**


