

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Breast Cancer In Focus

Denosumab Findings in Metastatic Breast Cancer

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H&O What is the current approach to preventing bone disease in metastatic breast cancer?

AS Up to 75% of patients with metastatic breast cancer develop bone metastases resulting in increased osteoclast activity and bone resorption. When left untreated, the majority of these patients develop bone-related complications including pathologic fracture, severe pain requiring radiation therapy, surgery to prevent impending fracture, spinal cord compression, or hypercalcemia of malignancy. The current standard of care for preventing skeletal-related complications is intravenous bisphosphonate therapy administered monthly. Despite optimal bisphosphonate therapy, up to 45% of patients will still develop skeletal-related complications. In addition, intravenous bisphosphonates are associated with serious side effects including renal toxicity, acute phase reactions, and osteonecrosis of the jaw. For these reasons, more effective and less toxic therapies for preventing or reducing the incidence of skeletal-related complications are needed.

H&O What is denosumab?

AS Denosumab (Prolia, Amgen) is very different from bisphosphonates and has an entirely different mechanism of action. It is a monoclonal antibody directed against the receptor activator of the nuclear factor kappa-B (RANK) ligand. RANK ligand is the major protein involved in osteoclast formation, function, and survival. Thus, by inhibiting RANK ligand, denosumab prevents osteoclast activation and bone resorption, and indirectly prevents complications resulting from bone metastases.

H&O Can you discuss the study you presented at the 2009 San Antonio Breast Cancer Symposium (SABCS)?

AS The study was an international, randomized, double-blind, placebo-controlled, phase III trial comparing monthly denosumab administered subcutaneously (120 mg) to intravenous infusion of zoledronic acid (4 mg every 4 weeks). The study population comprised patients with stage IV metastatic breast cancer involving bone. The primary endpoint was the time to first on-study skeletal-related event (SRE; pathologic fracture, radiation to bone for pain control, surgery to bone to prevent fracture, and spinal cord compression); other endpoints included time to first and subsequent SRE, time to first radiation of bone, time to first on-study SRE or hypercalcemia of malignancy, skeletal morbidity rate, and the proportion of patients with at least 1 on-study SRE.

The most important finding was that denosumab therapy resulted in a decrease in the number of SREs. Denosumab was superior to zoledronic acid at reducing the risk of first SRE or hypercalcemia of malignancy. Hence, compared to zoledronic acid, denosumab was a more potent osteoclast-inhibiting agent that extended the time to first SRE and decreased the incidence of SREs. With regard to toxicity, most adverse events were comparable between the arms. However, denosumab was better tolerated than the standard of care (zoledronic acid) in terms of acute phase reactions (eg, flu-like symptoms, bone pain, and aches) typically seen during the first 3 days of infusion and renal toxicity. Also of note was that the women who stayed on denosumab had a decreased

incidence of subsequent SREs compared to patients who stayed on zoledronic acid. Thus, over time, the benefit of denosumab increased. Denosumab was also superior to zoledronic acid at preventing patients from developing moderate or severe pain, which is a major quality of life issue for patients with bone metastases.

H&O Why are these findings important?

AS These findings were significant because we now have an agent that can be given subcutaneously. Denosumab is more convenient for patients because neither intravenous access nor a portacath are necessary for its administration. It also does not require renal monitoring or dose adjustments. The study findings showed that denosumab is better tolerated without the usual flu-like symptoms, is more efficacious in decreasing incidence of SREs, and is better at preventing pain—all the reasons why we administer these drugs.

H&O Why are bone metastases such a serious problem?

AS Bone is a very prevalent site of metastatic disease. Currently, 75% of women with breast cancer will develop bone metastases, which is a great burden in regard to pain. Bone pain is a very common type of cancer-related pain and is severe in many patients, requiring medications or therapy and compromising quality of life. SREs cause significant morbidity in patients. Complications of bone metastases include fractures, spinal cord compression, pain, and hypercalcemia. Treating bone pain is an integral part of managing metastatic breast cancer patients with bone metastases, which is why the study findings are so exciting.

H&O Has denosumab been studied in other cancers?

AS The study that I presented at SABCS was one of 3 identically designed studies comparing denosumab to zoledronic acid in preventing SREs in patients with advanced cancers. The second trial evaluated denosumab in the treatment of bone metastases in patients with advanced prostate cancer. The third study examined

denosumab in patients with multiple myeloma and solid tumors. All 3 studies have demonstrated denosumab's superiority over zoledronic acid in preventing SREs, improving pain control, and being less toxic with regard to renal toxicities and acute phase reactions. Other adverse events were similar between both arms in the studies. In the prostate trial, both overall survival and the time to cancer progression were balanced between treatment arms. Unfortunately, all 3 studies showed an incidence of osteonecrosis of the jaw, which suggests that when osteoclast activity is inhibited, bone formation is also thwarted. Thus, osteonecrosis of the jaw appears to be a class effect of osteoclast-inhibiting drugs.

H&O What are the future directions with denosumab?

AS Denosumab has been shown to be effective in treating osteoporosis in postmenopausal women and in preventing cancer therapy–induced bone loss. It is currently being evaluated in early-stage cancer patients to determine whether it can prevent the occurrence of bone metastases. There are ongoing studies of denosumab in early-stage patients with high-risk prostate cancer but no known bone metastasis, and studies are planned in early-stage breast cancer patients with the prevention of bone metastases as the primary endpoint.

Suggested Readings

- Stopeck A, de Boer R, Fujiwara Y, et al. A Comparison of Denosumab Versus Zoledronic Acid for the Prevention of Skeletal-Related Events in Breast Cancer Patients with Bone Metastases. Paper presented at: San Antonio Breast Cancer Symposium; December 9–13, 2009; San Antonio, TX.
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- Ellis GK, Bone HG, Chlebowski R, et al. Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. *J Clin Oncol.* 2008;26:4875-4882.
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