Denosumab an Option for Patients With Bone Metastasis From Breast Cancer

A recent study found that denosumab, a monoclonal antibody targeting receptor activator of nuclear factor kappa-B ligand (RANKL), was more effective at delaying skeletal-related events (SREs) than zoledronic acid in women with breast cancer metastatic to bone (J Clin Oncol. 2010;28:5132-5139). An SRE was defined as a pathological fracture, radiation therapy to bone, surgery to bone, or spinal cord compression, with hypercalcemia assessed separately.

“Oncologists now have another option for preventing skeletal-related events and palliating and preventing pain from bone metastases that is more effective, more convenient, and less toxic to the kidneys than the former standard of care,” says Alison Stopeck, MD, lead author of the study and associate professor of medicine at the University of Arizona at Tucson.

Denosumab was originally approved by the US Food and Drug Administration to treat postmenopausal osteoporosis, with a more recent indication for the prevention of SREs in patients with bone metastases from solid tumors. It is thought that tumor cells in bone secrete cytokines that induce osteoblasts to secrete RANKL, which then stimulates osteoclasts to resorb bone, releasing more growth factors that promote tumor cell survival and proliferation, creating a vicious cycle of bone destruction and increasing metastasis. Denosumab inhibits the function of RANKL, thus inhibiting bone destruction.

Patient Response
Dr. Stopeck and colleagues compared the efficacy and safety of denosumab with zoledronic acid in 2046 patients with breast cancer with at least 1 bone metastasis in a phase 3, double-blind, double-dummy study. Patients received either 120 mg of denosumab subcutaneously and intravenous placebo (n = 1026) or 4 mg of intravenous zoledronic acid and subcutaneous placebo (n = 1020) every 4 weeks. Any chemotherapy or hormonal therapy regimens were allowed in conjunction with the study. The primary endpoint was time to first SRE (noninferiority test). The superiority test of time to first SRE was a secondary endpoint, as was time to first and subsequent SREs.

Denosumab significantly delayed the time to first on-study SRE by 18% compared with zoledronic acid (P = .001 for noninferiority; P = .01 for superiority). The median time to first on-study SRE was 26.4 months in patients who received zoledronic acid and had not yet been reached at the time of last follow-up for those receiving denosumab. Denosumab also reduced the risk of developing multiple SREs (the secondary endpoint of time to first and subsequent SREs) by 23% compared with zoledronic acid (P = .001).

The patient characteristics were well balanced between the groups, with both groups having approximately 70% of patients with hormone receptor-positive and 18% of patients with human epidermal growth factor receptor 2 (HER2)-positive status. In addition, greater than 50% of patients had visceral metastasis in addition to bone disease. Similar numbers of patients were receiving cancer-specific therapies in both groups as well. The median time on study was 17 months, with 45% of patients still on study at the time of last follow-up.

Overall survival and disease progression rates were not significantly different between the 2 study arms. Although not an endpoint of the study, denosumab was found to significantly decrease the bone turnover markers urinary N-telopeptide-to-creatinine ratio and bone-specific alkaline phosphatase compared with zoledronic acid.

“Denosumab suppressed markers of bone resorption more completely than zoledronic acid, which is consistent with denosumab being a more effective inhibitor of osteoclast function,” Dr. Stopeck says.

Safety and Study Implications
Overall rates of severe or serious adverse events (AEs) were similar in both groups, with most of the AEs...
being caused by the underlying cancer or chemotherapy. Osteonecrosis of the jaw did not occur frequently, was similar between groups (2% for denosumab and 1.4% for zoledronic acid), and was observed as early as 6 months from the initiation of the study. Exploratory analysis of AEs showed that worsening renal function, hypercalcemia, and acute phase reactions such as fever, bone, and joint pain were more common with zoledronic acid; hypocalcemia was more common with denosumab.

In an accompanying editorial, Monica Fornier, MD, an assistant professor at Memorial Sloan-Kettering Cancer Center in New York City, writes that denosumab may be beneficial for patients not receiving intravenous therapy, for patients being treated with nephrotoxic compounds such as platinum agents, and for patients with decreased creatinine clearance.

According to Dr. Stopec, denosumab can be feasibly incorporated into guidelines and clinical use and can be used interchangeably with zoledronic acid in patients with bone metastases. Earlier use of denosumab or zoledronic acid in the adjuvant setting is unproven but currently under study in multiple phase 3 studies, she points out. “I think the role of zoledronic acid in the adjuvant setting is unclear at this time and more data are needed. There are encouraging preclinical data but inconsistent clinical trial results,” Dr. Stopec says.

Dr. Stopec considers both denosumab and zoledronic acid to be in the supportive care domain and not therapeutic options. Patients should not stop their anti-cancer therapy; activity against visceral metastasis is theoretically possible, but not supported by the current data, she adds.

“Perhaps the key point is that denosumab is yet another example of a drug successfully designed to target a specifically identified pathway and, therefore, represents a true from-bench-to-bedside paradigm of molecular targeting,” Dr. Fornier says.

Beyond Breast Cancer
In a similar trial performed in patients with solid tumors (not breast or prostate) and multiple myeloma, denosumab was found to be as effective as zoledronic acid in delaying SREs (J Clin Oncol. 2011;29:1125-1132).

In that trial, however, the secondary endpoint of superiority was not met. In a subset analysis including only patients with solid tumors, denosumab was superior to zoledronic acid in delaying both the time to first on-study SRE and the time to first and subsequent SREs (J Clin Oncol. 2010;28(15 suppl):9133).

A similar trial was performed in patients with hormone-resistant prostate cancer (J Clin Oncol. 2010;28(18 suppl): abstract LBA4507). In this trial, denosumab was found to be noninferior to zoledronic acid in delaying SREs and the secondary endpoint of superiority was met. No differences in overall disease progression or survival were observed in either trial.

During a discussion of this prostate cancer trial at an oral abstract session during the 2010 American Society of Clinical Oncology Annual Meeting in Chicago, Illinois, Robert Coleman, MD, professor of medical oncology at the University of Sheffield in the United Kingdom said there are several things we need to learn about denosumab, including whether certain patient groups, such as those with high bone turnover, benefit more from its use and whether it can delay the occurrence of bony metastasis in prostate cancer. The latter question is being addressed in an ongoing study (Clinical Trials.gov (J Clin Oncol. 2010;28(15 suppl): abstract 5010)).

“Denosumab represents an exciting new treatment option for patients with bone metastases from breast cancer, hormone-resistant prostate cancer, and solid tumors such as lung cancer,” Dr. Coleman stated in an interview with CA.

Although the current study may introduce a new clinical option, Dr. Fornier says there is still much work to do to address remaining questions, such as sequencing with bisphosphonates, duration of use, and other treatment combinations and settings.

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