ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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New Strategies to Prevent and Manage Bone Complications in Cancer

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H&O What factors are involved in the risk of bone complications associated with cancer?

AL There will be approximately 400,000 new patients with bone metastasis this year and between half and two-thirds of these patients will develop skeletal complications. People who have high markers of bone resorption, measured by n-telopeptide, are much more likely to have skeletal-related events (SREs). If there is presence of disease in weight-bearing bones, fractures are more likely to occur. Pain is another indicator; patients who have pain are more likely to have SREs. Metastasis from the main cancer is mainly the cause of bone complications.

H&O Can you discuss the bone remodeling process and its role in cancer?

AL Bone remodeling is the process of renewing bone. There are 2 main types of cells that are responsible for bone renewal: osteoclasts and osteoblasts. Osteoclasts are involved in the destruction/resorption of bone, and osteoblasts are involved in bone formation. In healthy people, there is a balance between resorption and formation. In cancer, as in osteoporosis, the imbalance of the cancer stimulates the osteoclasts to destroy bone faster than it can heal; this is called the vicious cycle. In this cycle, cancer cells—especially breast cancer cells—in the bone marrow microenvironment stimulate proteins like parathyroid hormone-related protein (PTHrP) to stimulate osteoclasts. Osteoclasts then destroy the surface of bone, which releases proteins (especially TGF-beta and the insulin growth factors), and they in turn stimulate the cancer cells to proliferate and to make more PTHrP. This vicious cycle results in the formation of dysfunctional new bone tissue, which is more fragile and is at a higher risk of developing complications. Our goal is to interrupt the vicious cycle of lytic bone destruction to prevent or slow bone loss.

H&O What are the different types of cancer-related bone complications?

AL Bone metastases can damage and weaken bones and may result in numerous complications. Bone pain is a very frequent and troublesome problem. Hypercalcemia of malignancy is another complication, although it is less frequently seen because of better management with bisphosphonates. Bone metastases can also result in SREs, which may include fractures, spinal cord compression, radiation therapy, and surgery.

H&O What are the treatment options for SREs?

AL Before 1991, when pamidronate was approved, there was no bone-specific therapy. We used chemotherapy and hormone therapy. In breast cancer and multiple myeloma, pamidronate was shown to decrease the rate of SREs. In 2001, zoledronic acid (Zometa, Novartis), a more potent bisphosphonate, was shown to be more effective than pamidronate. In November 2010, denosumab (Xgeva, Amgen)

was found to be superior to zoledronic acid in 3 head-to-head comparisons (1 in breast cancer, 1 in prostate cancer, and 1 in other solid tumors and multiple myeloma). So, in the past 20 years, we went from two-thirds of patients having an SRE to approximately one-quarter of patients having an SRE.

Both zoledronic acid and denosumab are approved for treatment-induced bone loss and for the treatment of metastatic disease arising from all solid tumors. Zoledronic acid is approved for multiple myeloma, but denosumab is not.

H&O How do you identify which patients are at increased risk of bone complications?

AL Currently, all people with bone metastasis are at risk. However, we know that people with bone pain are at higher risk and that people with high bone marker resorption (although no longer widely used clinically) are much more likely to have skeletal events and die sooner than people with bone metastases and low levels of n-telopeptide bone marker. There needs to be a lot more research to determine which patients are more likely to develop SREs and how soon they may develop them.

Bone mineral density is used to measure the density of bone to determine who is going to get osteoporosis and who is more likely to fracture, and bone scan is used to diagnose bone metastasis. However, there is no commonly used test to predict who is going to get SREs. We have conducted retrospective studies on some older pamidronate and zoledronic acid trials and found that high marker patients are more likely to have SREs, but this finding has not translated into routine clinical usage.

H&O What is the optimal timing of initiating treatment for possible skeletal complications?

AL Retrospective data from the zoledronic acid trials show that in breast cancer and prostate cancer, the earlier the initiation of therapy, the better the effect. Starting patients with bone metastases on therapy at the time of diagnosis or before they have pain appeared to result in better outcomes compared to waiting to start therapy until they felt pain. The current dogma is to start people on a bone treatment at the time of diagnosis of bone metastasis.

H&O What are some important studies that have been recently presented?

AL There have been 5 recently reported studies. Three of these studies were conducted in metastatic disease comparing denosumab to zoledronic acid in breast cancer, prostate cancer, other solid tumors, and myeloma. All 3 studies consistently showed that denosumab was superior to zoledronic acid in terms of delaying the time of the first SRE. In men with prostate cancer, the median time to an SRE was 21 months with denosumab and 17 months with zoledronic acid. In patients with breast cancer, the median time to an SRE was 27 months with zoledronic acid and 32 months with denosumab.

In the last few weeks, findings from the other 2 trials, which were performed in the adjuvant setting, have been reported. Data from the first of the 2 trials (the AZURE [Adjuvant Zoledronic Acid to Reduce Recurrence] trial) were reported at the 2010 San Antonio Breast Cancer Symposium by Dr. Robert Coleman. The AZURE trial comprised 3,360 patients from 174 centers in England who were randomized to receive adjuvant chemotherapy and/or endocrine therapy plus or minus zoledronic acid at 4 mg intravenously every 3–4 weeks for 6 doses to prevent recurrent disease. The findings showed that adjuvant zoledronic acid did not improve disease-free survival or overall survival in stage II/III breast cancer patients. There was, however, an interesting subgroup of patients—women 5 years postmenopause—who had significant benefit from zoledronic acid. Because the study missed its primary endpoint, Novartis has withdrawn its application for zoledronic acid in the adjuvant setting. The second adjuvant trial was conducted in men with localized prostate cancer with rising prostate-specific antigen levels and at risk of developing metastatic disease. The press release detailing the findings of this study stated that denosumab significantly delayed the time to recurrent disease by approximately 4.5 months. A survival advantage has not yet been reported, but it is still early.

So, we have seen 2 adjuvant studies, one positive and one negative, and we have seen 3 metastatic studies all favoring denosumab over zoledronic acid.

H&O Are there any significant treatment-related toxicities?

AL Zoledronic acid is associated with renal failure and risk of osteonecrosis of the jaw. Denosumab does not cause renal failure, and has been reported to cause osteonecrosis of the jaw at a similar rate to zoledronic acid. Denosumab causes less acute-phase reactions than zoledronic acid.

H&O What can cancer patients do to manage their bone health?

AL Many thousands of women, especially those with breast cancer, are getting adjuvant aromatase inhibitors, and many thousands of men with localized prostate

cancer are receiving androgen deprivation therapy. These people need to be aware that when they start treatment that reduces their hormone levels, they need to measure their baseline bone mineral density and baseline vitamin D level, and they should have regular monitoring because of the possibility of becoming osteopenic or osteoporotic. Both men and women receiving aromatase inhibitor treatment and androgen deprivation therapy have an increased risk of fracture, and, therefore, intervening with calcium and vitamin D and possibly an oral or intravenous bisphosphonate or denosumab is suggested.

Suggested Readings

Coleman RE, Thorpe HC, Cameron D, et al. Adjuvant Treatment with Zoledronic Acid in Stage II/III Breast Cancer. The AZURE Trial (BIG 01/04). Paper presented at the 2010 San Antonio Breast Cancer Symposium; Friday, December 10, 2010; San Antonio, Texas.

Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol*. 2010;28:5132-5139.

Fizazi, K, Carduccin, MA, Smith, MR, et al. A randomized phase III trial of denosumab versus zoledronic acid in patients with bone metastases from castration resistant prostate cancer. *J Clin Oncol (*ASCO Annual Meeting Abstracts). 2010;28:Abstract 4507.