Bisphosphonates: Do We Know Their Role in Adjuvant Breast Cancer Treatment?

May 15, 2010 | Breast Cancer [1], Oncology Journal [2]
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Breast cancer is the most common noncutaneous cancer among women.[1] In 2009, an estimated 190,000 new cases occurred in the US. The 5-year survival rate for early-stage breast cancer has improved from approximately 63% in the early 1960s to almost 90% today, mainly as a result of early detection and treatment.[2] The improvement in survival from breast cancer treatments, however, which include chemotherapy, endocrine therapy, and/or ovarian ablation, does not come without the cost of potentially significant effects on bone mineral density (BMD).[3-5] The risk of having low bone mass increases significantly with age, as does the risk of developing breast cancer; consequently, the two diagnoses often overlap in the same individual. Additionally, women with breast cancer may be at increased risk for osteoporosis due to the effect on bone of certain anticancer therapies. Hence, some women with breast cancer may be at increased risk of osteoporosis.

Reeder and Brufsky review the role of adjuvant bisphosphonates in maintaining BMD in women with breast cancer.[6] They also address evolving data on the potential for adjuvant bisphosphonates to have an anticancer effect in this patient population. In their article, they enthusiastically highlight the possible positive benefit of adjuvant bisphosphonate use. To round out their discussion, additional studies are selectively highlighted here.

Brown et al investigated the effect on BMD of a 4-mg dose of zoledronic acid (Zometa) administered once to patients who were osteopenic at > 1 year following cancer therapy administered with curative intent.[7] Their results showed that lumbar spine BMD increased by a mean of 5.3% and the total hip BMD increased by a mean of 4.3% at 36 months. Similarly, Grey et al. generated data in postmenopausal women with osteopenia treated with one 5-mg dose of zoledronic acid. At 2 years there was a mean BMD increase of 5% in the lumbar spine and 2% in the hip.[8] These data raise the question of whether the doses used in clinical trials such as Z-FAST (Zometa-Femara Adjuvant Synergy Trial) are in excess of what is needed to maintain BMD. Perhaps more thought-provoking is that the Austrian Breast and Colorectal Cancer Study Group (ABCSG) trial ABCSG-12,[9] Z-FAST,[10] and the Cancer and Leukemia Group B (CALGB) study CALGB 79809[11] included women who may have had a normal BMD, and the osteoclast-inhibiting regimens used increased BMD. What are the implications of increasing BMD in a population with normal BMD, and how might such an effect alter risk of osteoporosis and/or atypical subtrochanteric femur fractures? To date, we have limited data to address this question. To determine whether adjuvant bisphosphonate therapy should become routinely incorporated into breast cancer care, either as an anticancer therapy or as prophylaxis against osteoporosis, we will need to formally address this concern. In addition, there are concerns about potential adverse events, such as osteonecrosis of the jaw, which was seen in approximately 0.7% of patients treated on the zoledronic acid arm of the adjuvant bisphosphonate study, AZURE (Adjuvant Zoledronic Acid to Reduce Recurrence).[12] The phase III placebo-controlled randomized clinical trials ARIBON (Effect of Oral Ibandronate on
Anastrozole-Induced Bone Loss), using ibandronate (Boniva),[13] and SABRE (Study of Anastrozole with the Bisphosphonate Risedronate), using risedronate (Actonel),[14] both stratified postmenopausal women with early-stage breast cancer receiving anastrozole (Arimidex) by their risk of fragility fracture. Those with a higher risk of osteoporotic fracture received open-label bisphosphonate therapy. Those with a lower risk of fracture were expectantly monitored on study. Women with an intermediate risk of osteoporotic fracture were randomized to receive bisphosphonate or placebo. In both studies, the arms receiving the oral bisphosphonate demonstrated a stabilized or increased BMD by approximately 0.6%-3% at 2 years. These data parallel what is expected in the management of low bone mass in general for postmenopausal women.[15] ARIBON and SABRE demonstrate that oral bisphosphonates administered at doses and intervals that are approved by the US Food and Drug Administration for prevention and/or treatment of postmenopausal osteoporosis are able to maintain or improve BMD in postmenopausal women with low bone mass who are being treated with an adjuvant aromatase inhibitor. ARIBON and SABRE are informative for postmenopausal women; however, the data regarding oral bisphosphonates for managing BMD in women experiencing chemotherapy-induced amenorrhea have been less predictable, as demonstrated by Hines et al, who found that weekly administration of adjuvant risedronate at a dose of 35 mg did not have a statistically significant impact on the rate of BMD loss at 1 year in this younger population.[16]

### TABLE 1

**Doses of Adjuvant Zoledronic Acid in Selected Clinical Trials**

ABCSG-12[9] and Z-FAST,[10] as discussed by Reeder and Brufsky, suggest that zoledronic acid at a dosage of 4 mg every 6 months may alter the risk of breast cancer recurrence. Longer term follow-up of these studies is of great interest, as are the results from other phase III studies investigating bisphosphonate effects on disease outcomes, including the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-34 trial (NCT00009945), the Southwest Oncology Group (SWOG) S0307 (NCT00127205) study, and the AZURE trial (NCT00072020). These three studies have completed accrual, but results have not been reported. These studies are using a variety of bisphosphonate regimens; the zoledronic acid regimens are outlined in Table 1. Other adjuvant bisphosphonate trials are ongoing, also with variability in the study designs and drug delivery. The article by Reeder and Brufsky brings several questions into the spotlight: Do bisphosphonates possess direct anticancer properties or does the predominant mechanism of action work through disturbing the bone microenvironment? If altering the bone microenvironment is critical to decreasing the risk of breast cancer metastases, what is the mechanism by which this occurs, and are there other agents that may be more effective in achieving this end? In addressing either BMD or recurrence risk, are there patients who may gain greater, or lesser, benefit from osteoclast inhibition? The majority of women diagnosed with breast cancer are expected to have an excellent outcome, so how will bone-targeting therapy further optimize this situation? What is the most advantageous drug, dose, scheduling, time of initiation, and duration of therapy? In addition, questions arise regarding cost-effectiveness, long-term toxicities, and effect on quality of life. The results of ongoing studies of adjuvant bisphosphonates in early breast cancer management are eagerly awaited, as are future studies addressing the many questions that remain with respect to use of these agents.

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**Financial Disclosure:** Dr. Barginear has no relationships to disclose. Dr. Van Poznak is a local PI of a phase III clinical trial for, and has received funding from, Novartis and Amgen.

**References**


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