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Editorial

EDITORIAL

Bisphosphonate Choice as Adjuvant Therapy for Breast Cancer: Does it Matter?

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Tumor microenvironment is critical to the growth of breast cancer cells in bones. Excessive activity of osteoclasts, induced by a low-estrogen state, result in the production of growth factors that promote growth of cancer cells. Bisphosphonates induce apoptosis of osteoclasts, and consequently, alter the premetastatic niche in bones (1). The seminal trial by Diel et al. in 1998 demonstrated that clodronate reduced the incidence of bone metastases in women with early-stage breast cancer and bone marrow positive for circulating tumor cells (2). Subsequent clinical trials of bisphosphonates as adjuvant therapy for breast cancer conducted over the past 20 years have shown mixed results (3).

The Early Breast Cancer Clinical Trials Group (EBCCTG) conducted a meta-analysis composed of individual patient data on 18 766 women derived from 26 randomized adjuvant bisphosphonate trials in breast cancer (4). In postmenopausal women, there were highly statistically significant reductions with the addition of bisphosphonates at 10 years for bone recurrence (relative risk [RR] = 0.72, 95% confidence interval [CI] = 0.60 to 0.86, 6.6% vs 8.8%; two-sided $P = .0002$) and for breast cancer mortality (RR = 0.82, 95% CI = 0.73 to 0.93, 14.7% vs 18.0%; two-sided $P = .002$). Bisphosphonates demonstrated this benefit independent of the type or schedule of bisphosphonate use, estrogen receptor status, axillary lymph node involvement, or the use of adjuvant chemotherapy.

With this background, the SWOG 0307 (S0307) trial, examining the worth of clodronate, ibandronate, or zoledronic acid to improve disease-free survival (DFS) in women with early-stage breast cancer (EBC), is now presented in the Journal (5). Women with stages I–III EBC (n = 6097) were randomly assigned to 3 years of oral clodronate (1600 mg daily), oral ibrandronate (50 mg daily), or intravenous zoledronic acid (ZA; 4 mg monthly for 6 months, then 4 mg every 3 months for 2.5 years). DFS at 5 years was 87.6% in the clodronate arm, 87.4% in the ibandronate arm, and 88.3% in the ZA arm ($P = .49$). Overall survival at 5 years was 92.6% in the clodronate arm, 92.9% in the ibandronate arm, and 92.6% in the ZA arm ($P = .50$). No differences were seen between all three agents based on age or tumor subtypes. Grade 3 or 4 toxicities were seen in 8.3% of patients on clodronate, 10.5% of patients on ibandronate, and 8.8% of patients on ZA. Osteonecrosis of the jaw was seen in 0.36% of patients on clodronate, 0.77% of patients on ibandronate, and 1.26% of patients on ZA.

Three questions arise from this study. First, there was unfortunately no placebo fourth arm to the trial. In a trial of this size, this could have helped further confirm the worth of bisphosphonates seen in other individual trials and in the EBCCTG meta-analysis. However, in 2006, when S0307 was initiated, one smaller randomized trial of clodronate vs placebo had demonstrated a DFS benefit to clodronate in EBC, so the lack of a placebo arm in S0307 is understandable (6).

Second, there was a lower than expected event rate in S0307, likely due to better systemic adjuvant therapies available to these patients with EBC over the past 10 years, as well as because of patient selection in the trial (33% of patients in S0307 had stage I EBC, and 50% had node-negative EBC). This is outstanding news for our patients with EBC, but S0307 may have therefore lacked the statistical power to determine true differences between the three agents. However, the excellent and near identical efficacy seen with all three agents in this large, randomized clinical trial suggest that cost, patient access, and patient preference should be the determining factors as to which bisphosphonate to use in this setting.

Finally, questions of dosing frequency as well as length of bisphosphate use remain partially unanswered by S0307. Three years of bisphosphonates appear sufficient in S0307 to obtain an excellent clinical result. However, the EBCCTG meta-analysis suggests that a less dose-intensive regimen of ZA (every 6 months) may be as efficacious in terms of DFS and OS as the more intensive regimen of ZA used in S0307 (4). The recently completed SUCCESS A trial suggests that 2 years of ZA is as

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efficacious as 5 years in terms of DFS in EBC (7). Taken together, these studies suggest that a recommendation of 2–3 years of either an oral bisphosphonate (clodronate or ibandronate daily) or ZA at a dose of 4 mg intravenously every 6 months is reasonable.

Should every woman with EBC receive a bisphosphonate? S0307 does not answer this question. Studies of biomarkers of bisphosphonate efficacy in this setting have been lacking, other than to suggest that postmenopausal women with EBC appear to derive most of the benefit. Recent data examining amplification of the *MAF* gene on chromosome 16 as a biomarker for ZA efficacy in preventing recurrence in women with EBC in the AZURE trial are interesting in this regard (8), and we look forward to further analyses of *MAF* amplification in other large trials of bisphosphonates in EBC such as the National Surgical Adjuvant Breast and Bowel Project protocol B-34 (9).

The relative as well as absolute reductions in the risk of breast cancer death at 10 years with the use of bisphosphonates in postmenopausal women (18% relative reduction, 3.3% absolute reduction) are similar to the benefit seen with anthracycline polychemotherapy vs a CMF regimen as well as about 50% of the benefit seen with the addition of polychemotherapy vs no chemotherapy (10). Bisphosphonates, in one form or another, are generic and relatively inexpensive in most regions of the world (for example, in India, the price of one dose of zoledronate ranges from $10 to $30). Major guideline organizations such as the American Society of Clinical Oncology and Cancer Care Ontario have endorsed the use of adjuvant bisphosphonates in EBC (11).

So why are bisphosphonates not more widely used as adjuvant therapy for EBC? In high-income countries, where 5- to 10-year survival rates from breast cancer are greater than 85%, the incremental benefit from routine clinical use of adjuvant bisphosphonates may seem marginal. At a recent St Gallen Consensus Conference, despite the fact that the previous conference "strongly endorsed" the use of adjuvant bisphosphonates in postmenopausal women with breast cancer (12), 40% of the panelists stated that they do not routinely use them in their clinical practice, and 36% of the panelists stated that they do not use them in younger women who have suppressed ovarian function (13).

In low- to middle-income countries, however, the 5- to 10-year survival rates from EBC still hover around 50%–60%, and inexpensive interventions to reduce this mortality are needed. Given their low cost, relatively modest toxicity, and survival benefit, widespread use of adjuvant bisphosphonates for early-stage postmenopausal breast cancer, especially in resource-constrained areas of the world, has great potential to further reduce breast cancer mortality worldwide and therefore be a resounding success for global oncology.

Notes

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The authors disclose the following conflicts of interest: Adam Brufsky is a consultant for Novartis and for Amgen.

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