Bisphosphonates in Breast Cancer: A Triple Winner?

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We know that bisphosphonates prevent or delay skeletal-related events in breast cancer metastatic to bone, prevent or treat bone loss in patients receiving adjuvant aromatase inhibitor therapy, and decrease bone recurrences and breast cancer–related deaths when used in the adjuvant setting in postmenopausal women with early-stage breast cancer.

The medical management of a patient with cancer involves three essential components: prevention of cancer-related morbidity, management of the side effects of anticancer therapy, and most importantly, control of tumor growth. Bisphosphonates are effective on all three of these fronts, as highlighted in the review by Drs. Blanchette and Pritchard.[1] However, despite years of research on the role of bisphosphonates in breast cancer, several important questions remain unanswered.

Various types of bisphosphonates (clodronate, pamidronate, ibandronate, and zoledronate) help prevent skeletal-related events (SREs) in patients with metastatic disease—e.g., pathological fractures, bone pain, and hypercalcemia of malignancy. All bisphosphonates are superior to placebo at delaying or preventing SREs in patients with metastatic breast cancer.[2] However, intravenous zoledronate, administered every 3 to 4 weeks, seems to be the most efficacious, compared with intravenous pamidronate and oral ibandronate.[3,4] In addition, subcutaneously administered denosumab, a monoclonal antibody against the receptor activator of nuclear factor kappa-B ligand (RANKL), a mediator of osteoclast formation and differentiation, was found to be superior to intravenous zoledronate at reducing SREs in patients with breast cancer metastatic to bone.[5] Denosumab may also be a better treatment choice than zoledronic acid in patients with renal insufficiency, since it is not renally eliminated.

Recent research on the effectiveness of bisphosphonates at preventing breast cancer–related morbidity in bone has focused on dosing interval. The ZOOM trial, which compared the standard every-4-weeks administration of intravenous zoledronate against an every-12-weeks schedule after an initial year of monthly treatment, had significant flaws in methodology, making it difficult to interpret the study conclusion of noninferiority for the longer dosing interval.[6] Although preliminary results from the OPTIMIZE-2 trial using intravenous zoledronate suggest that the longer every-12-weeks dosing interval may be noninferior to the every-4-weeks schedule, we agree with the conclusion of Drs. Blanchette and Pritchard that final publication of the OPTIMIZE-2 trial and the Cancer and Leukemia Group B (CALGB) 70604 trial (ClinicalTrials.gov identifier: NCT00869206) may help shed light on the question of the optimal dosing interval in the management of breast cancer metastatic to bone.[7] We also agree with their conclusion that the overall duration of bisphosphonate treatment should be based on an individualized assessment of risks and benefits. Another potential indication for the use of bisphosphonates in breast cancer is the prevention of bone loss due to adjuvant anti-estrogen therapy with aromatase inhibitors. Clinical trials have found that the use of bisphosphonates (clodronate, risedronate, ibandronate, zoledronate) and denosumab have prevented reduction in lumbar spine bone mineral density (BMD; a surrogate marker for osteoporosis and osteoporotic fracture), whereas aromatase inhibitor therapy in the absence of these drugs has invariably resulted in bone loss.[2,8] The recently published MA.27B trial confirmed that early-stage breast cancer patients who have significant osteopenia or osteoporosis can be safely given adjuvant aromatase inhibitors as long as they are also receiving bisphosphonates.[9] One key question remains unresolved: Should zoledronate be used in an upfront manner (along with adjuvant aromatase inhibitor therapy) or in a delayed manner (treatment initiated only if a patient becomes osteopenic or develops a pathologic fracture)? Three randomized trials in early-stage breast cancer patients receiving adjuvant aromatase inhibitors have investigated this question and found that the mean difference in lumbar spine BMD significantly favored upfront use compared with delayed initiation.[10-12] However, we do not yet know whether such an effect on BMD will translate into the clinically meaningful benefit of reductions in osteoporotic fractures. If not, upfront use may unnecessarily subject patients with normal BMD to the potential adverse effects of bisphosphonate therapy.
Finally, a potential beneficial role of bisphosphonates in the adjuvant treatment of breast cancer may help determine whether to initiate upfront treatment with this class of medication. If bisphosphonates have an anti-tumor effect as well, upfront use of these agents might warrant serious consideration. The bone marrow microenvironment is a possible site where breast cancer cells may be able to lie dormant and evade adjuvant systemic treatment.[13] These dormant cancer cells may subsequently escape the bone marrow and either metastasize to other organ sites or start proliferating within the bone. Several large randomized clinical trials have evaluated the role of aminobisphosphonates in reducing the risk of breast cancer recurrence and death.[2] Menopausal status was found to significantly influence the effect of bisphosphonates on breast cancer recurrence. Meta-analysis of individual patient-level data, led by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG), showed a significant decrease in bone recurrences and breast cancer–related death in postmenopausal patients who received adjuvant bisphosphonate treatment compared with those who did not receive such treatment.[14]

For the practicing oncologist, the EBCTCG meta-analysis may raise more questions than it answers. According to the meta-analysis results, bisphosphonates may be a useful adjunct to adjuvant systemic therapy for preventing breast cancer-related deaths in the subset of women who are postmenopausal.[15] The type of bisphosphonate required to produce this effect, as well as the dosing interval and duration of therapy, remains unclear. Most of the larger clinical trials have used intravenous zoledronate, and we agree that this medication could be used at an every-6-months interval for 3 to 5 years, as in Austrian Breast and Colorectal Cancer Study Group Trial 12 and the Z-FAST/ZO-FAST series of trials.[11,12,16]

The safety and tolerability of bisphosphonates have been extensively investigated and are well summarized by Blanchette and Pritchard.[1] The most common side effects are bone pain and fever. With appropriate use of preventive dentistry, the rates of osteonecrosis of the jaw are less than 1%. [17] The risk of hypocalcemia, the other major adverse effect of this medication class, can be reduced by concurrent use of calcium and vitamin D supplements.[18] The risk of acute renal failure is slight, although we recommend modifying the dosage in the presence of renal insufficiency and avoiding bisphosphonate therapy altogether if creatinine clearance is < 30 mL/min.[18]

In summary, we know that bisphosphonates prevent or delay SREs in breast cancer metastatic to bone, prevent or treat bone loss in patients receiving adjuvant aromatase inhibitor therapy, and decrease bone recurrences and breast cancer–related deaths when used in the adjuvant setting in postmenopausal women with early-stage breast cancer. Bisphosphonates could well be “triple winner” medications in breast cancer.

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**References:**


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