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COMMENTARIES

Can Bisphosphonates Really Reduce the Risk of Recurrences in Early Breast Cancer?

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Commentary on: Eidtmann H, de Boer R, Bundred N, Llombart-Cussac A, Davidson N, Neven P, von Minckwitz G, Miller J, Schenk N, Coleman R. Efficacy of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36-month results of the ZO-FAST Study. *Ann Oncol*. 2010 Nov;21(11):2188-94.

Aromatase inhibitors (*e.g.*, letrozole, anastrozole, exemestane) are used as adjuvant endocrine therapy in patients with hormone-responsive early breast cancer with efficacy superior to selective estrogen receptor modulators (*e.g.*, tamoxifen), but with increased bone loss and higher risk of fracture. In the ZO-FAST study, Eidtmann *et al*. (1) investigated the effect of the bisphosphonate zoledronic acid (4 mg every 6 months) on prevention of bone loss in postmenopausal women with hormone receptor-positive early breast cancer (n = 1,065) who were due to receive letrozole (2.5 mg daily) for 5 years and who had a starting T-score of ≥ -2 for bone mineral density (BMD). Patients were randomly assigned to receive immediate zoledronic acid or delayed zoledronic acid at a dosing regimen of 4 mg every 6 months for 5 years. Women in the immediate group were given the bisphosphonate at the start of letrozole therapy while women in the delayed group were only given zoledronic acid if their T score fell below -2, or if there was a clinical or asymptomatic fracture at 36 months. Immediate zoledronic acid was found to be effective in preserving BMD during endocrine therapy, increasing the percentage change from baseline in lumbar spine BMD to + 4.39% (95% CI = 3.69% to 5.11%; P < 0.0001) at 36 months. In contrast, the 36-month mean percentage change in the delayed group was - 4.9% (95% CI = -5.54% to -4.25%; P < 0.0001). Although this trial was designed to evaluate zoledronic acid prevention of bone loss as a primary endpoint, Eidtmann *et al*. also assessed disease recurrence and survival as a secondary endpoint. The authors found that patients receiving immediate zoledronic acid had a 41% reduction in the risk of having a disease-free survival (DFS) event (disease recurrence or death) compared to patients receiving delayed zoledronic acid (HR = 0.59; 95% CI = 0.36 to 0.96; P = .0314). Importantly, patients receiving immediate zoledronic acid not only experienced numerically fewer bone metastases compared with patients who received delayed zoledronic acid (9 vs. 17), but also a reduced number of local (2 vs. 10) and distant recurrences (20 vs. 30). Adverse events were similar between immediate and delayed groups. In conclusion, the results of this study first show that zoledronic acid effectively prevents cancer treatment-induced bone loss in postmenopausal women receiving the aromatase inhibitor letrozole for breast cancer. They also suggest, based on secondary endpoints, that the bisphosphonate zoledronic acid has anticancer effects. This *Commentary* reviews the strength of the evidence for this conclusion.

There is a growing body of preclinical evidence that bisphosphonates may exhibit direct and indirect anticancer activities in addition to their established bone-protective activities (2). Potential anticancer mechanisms of action of bisphosphonates

include inhibition of adhesion, migration and invasion of cancer cells; induction of cancer cell death; inhibition of tumor angiogenesis; and activation of the immune system against cancer cells (2). The anticancer activity of zoledronic acid in the preclinical setting has been translated recently to the bedside in a large phase III clinical trial in patients with early breast cancer (ABCSG-12) (3). The ABCSG-12 trial accrued 1,803 premenopausal women with early-stage breast cancer receiving ovarian suppression (goserelin) plus hormonal therapy (tamoxifen or anastrozole) alone or in combination with zoledronic acid (4 mg every 6 months) for 3 years (3). The addition of zoledronic acid to endocrine therapy resulted in a reduction of 36% (P = 0.01) in the relative risk of disease progression when compared with endocrine therapy alone (3). Interestingly, as observed in the ZO-FAST study (1), the reduced risk of recurrence upon adjuvant therapy with zoledronic acid was not limited to bone sites, but was also seen at extraskeletal sites and in the contralateral breast (3). Moreover, the 62-month analysis of ABCSG-12 showed that the benefits of combining zoledronic acid with adjuvant endocrine therapy persists (HR = 0.68; P = 0.008) long after completion of therapy (> 2 years post-treatment) (4). Similarly, the DFS benefit with immediate zoledronic acid at 36 months' follow-up in the ZO-FAST study was recently reported as being maintained at 60 months with a reduction of recurrences both in and outside bone (HR = 0.66 vs. delayed zoledronic acid; P = 0.034) (5). This anticancer effect of zoledronic acid was also reported in a companion trial of ZO-FAST, the Z-FAST trial, which examined as a primary endpoint the effect of zoledronic acid on prevention of bone loss induced by letrozole in postmenopausal women with hormone receptor-positive early breast cancer (n = 602) (6). The 12-month analysis of Z-FAST demonstrated fewer disease recurrences in immediate patients compared with delayed patients (1 vs. 6; P = 0.056). A numerically lower rate of disease recurrence at 36 months' follow-up was still observed in immediate patients compared to delayed patients. However, this DFS benefit did not reach statistical significance (9 vs. 16; P = 0.127) (6).

The reasons why adjuvant zoledronic acid treatment significantly improved disease-related outcomes in the ABCSG-12 and Z-ZO-FAST trials are unknown. In these trials, the bisphosphonate was administered over long treatment intervals (every 6 months) and the anticancer effect of zoledronic acid in the ABCSG-12 trial was maintained for at least 2 years post-treatment (4). Although bisphosphonates exhibit direct antitumor activities in animal models of cancer and metastasis (2), the long-lasting effect of zoledronic acid in ABCSG-12 with respect to DFS rather militate in favor of indirect antitumor mechanisms. For example, the clinical use of a bisphosphonate early in the disease course, in order to prevent cancer treatment-induced bone loss, might alter the release of factors from the bone matrix that are required for the seeding and growth of cancer cells in the bone marrow. We have recently studied the antitumor effect of a structural analog of the bisphosphonate risedronate, NE-58051, which has a bone mineral affinity similar to that of risedronate, but a 3,000-fold lower bone antiresorptive activity *in vivo* (7). *In vitro*, both compounds directly inhibited breast cancer cell proliferation. *In vivo*, we found that NE-58051 (in contrast to risedronate) did not inhibit breast cancer bone metastasis formation nor skeletal tumor burden, indicating that the antitumor effect of bisphosphonates was achieved mainly through inhibition of osteoclast-mediated bone resorption (7). Indeed, by inhibiting bone resorption, zoledronic acid may deprive cancer cells of bone-derived growth factors (*e.g.*, transforming growth factor-β) that are required for tumor growth and metastasis formation (8). Bisphosphonates also inhibit the release of ionic calcium from bone mineral during bone resorption (2). The calcium-sensing receptor (CaSR) facilitates the retention of hematopoietic stem cells in the osteoblastic niche (9) and extracellular ionic calcium promotes the localization of CaSR-expressing cancer cells in bone (10). Zoledronic acid, by inhibiting the release of ionic calcium from bone mineral, could therefore regulate the

retention of cancer cells in the bone marrow. These findings (7-10) are in line with the observation that zoledronic acid plus standard therapy significantly reduces the prevalence of disseminated tumor cells (DTCs) in the bone marrow from patients with early-stage breast cancer (11;12). Residual DTCs from a primary breast cancer can lay dormant in the bone marrow for extended periods of time before developing into bone lesions or mobilizing to cause disease recurrence at other distant sites (13). Thus, the effect of zoledronic acid on inhibition of breast cancer recurrences at skeletal and nonskeletal sites in the ZO-FAST and ABCSG-12 studies might be attributable to its effect on the DTCs, by blocking their retention in the bone marrow. Zoledronic acid might also interfere with circulating tumor cells (CTCs) in the bloodstream. There is an association between the presence of CTCs and an increased risk of relapse in breast cancer patients (14). Interestingly, recent preclinical evidence suggests that CTCs can recolonize their tumors of origin (15). This process called “tumor self-seeding” could explain, for instance, the local recurrences in breast cancer (15). In the ABCSG-12 and ZO-FAST studies, patients receiving zoledronic acid experienced fewer locoregional recurrences compared with patients who received hormonal therapy alone (15 vs. 29 at 62 months in the ABCSG-12 trial and 5 vs. 12 at 60 months in the ZO-FAST trial) (4;5). Zoledronic acid might therefore inhibit local recurrences, potentially by blocking the tumor self-seeding of CTCs. Increased cancer surveillance via activation of the cytotoxicity of $V\gamma9V\delta2$ T cells could represent another potential mechanism through which zoledronic acid exhibits anticancer activity. There is some clinical evidence that a monthly treatment with zoledronic acid induces a significant expansion of $V\gamma9V\delta2$ T cells in breast and prostate cancer patients with bone metastases (2). However, it is not known whether a longer treatment interval (every 6 months) with the bisphosphonate also induces a sustained $V\gamma9V\delta2$ T cell expansion in patients. Other potential antitumor mechanisms are most likely to occur. For example, there is evidence that bone marrow-derived endothelial cell progenitors and macrophages provide a suitable microenvironment (pre-metastatic niche) within host organs, such as the lungs, before the arrival of the first tumor cells (16). Zoledronic acid has some antiangiogenic activies *in vitro* and *in vivo* (2). Moreover, bisphosphonate treatment (zoledronic acid, pamidronate) of tumor-bearing mice induces a profound reduction in $CD11b^+$ macrophages infiltrating mammary or cervical carcinoma lesions (2). It is therefore conceivable that the carry-over effect of zoledronic acid on inhibition of breast cancer recurrences at skeletal and nonskeletal sites in the ABCSG-12 and ZO-FAST studies might be attributable not only to its effect on DTCs/CTCs, by blocking their seeding and/or survival in the bone marrow, but also by directly perturbing the recruitment of endothelial cell progenitors and macrophages from the bone marrow.

These data obtained in the ABCSG-12 and Z-ZO-FAST trials support the adjuvant use of bisphosphonates early in the clinical management of breast cancer. However, these intriguing results need to be weighed against recent data obtained in the AZURE trial, which were presented at the 33rd Annual San Antonio Breast Cancer Symposium in December of 2010 (17). The AZURE trial recruited 3,360 women with stage II/III breast cancer to determine whether treatment with zoledronic acid in addition to standard therapy improves disease-related outcomes. The addition of zoledronic acid to standard therapy unexpectedly failed to lower the risk of breast cancer recurrences. However, in a pre-planned analysis based on menopausal status, a benefit in DFS (HR = 0.76; $P < .05$) and overall survival (HR = 0.71; $P = .017$) was seen with zoledronic acid in women who were postmenopausal for more than 5 years before study entry (17). Nevertheless, Novartis withdrew its applications for approval of Zometa to prevent the recurrence of breast cancer in the U.S. and Europe.

This subgroup analysis with postmenopausal women in the AZURE trial and the results obtained in the ABCSG-12

and Z-ZO-FAST trials all strongly suggest that zoledronic acid may prevent breast cancer recurrences at multiple sites, especially when endogenous levels of estrogens are low. As discussed above, bone marrow-derived cells (endothelial progenitor cells, macrophages) contribute to the formation of metastases by providing a suitable environment for cancer cells (16). Interestingly, estrogens can influence lung metastasis formation in animals, by mobilizing bone marrow-derived endothelial progenitor cells to the pre-metastatic niche (18). In the absence of estrogens, endothelial progenitor cells might therefore be more sensitive to the inhibitory effects of zoledronic acid, leading to inhibition of angiogenesis in distant relapses. Alternative inhibitory mechanisms may be involved as well. For example, bone marrow-derived mesenchymal stem cells enhance primary tumor growth of the estrogen receptor-positive, hormone-dependent breast carcinoma cell line MCF-7 in mice (19). Zoledronic acid could conceivably interfere directly with the tumor growth-supportive functions of bone marrow-derived mesenchymal cells.

In addition to the anticancer effects of zoledronic acid reported for clinical trials in women receiving adjuvant therapy for early breast cancer (1,3-5), three recent epidemiological studies showed that current use of bisphosphonates in healthy postmenopausal women for the treatment of osteoporosis was associated with a 30% reduced risk of breast cancer (20-22). The biological significance of these findings clearly warrants further investigation. However, these studies highlight the importance of identifying mechanisms that, under estrogen deprivation, are responsible for the anticancer activity of zoledronic acid. It will help to define patients with early breast cancer who could benefit from adjuvant bisphosphonate therapy.

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