

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Breast Cancer In Focus

Bisphosphonates as Adjuvant Therapy

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H&O What is the mechanism of action of bisphosphonates in breast cancer?

CS A significant proportion of women with breast cancer will develop skeletal metastases. Bisphosphonates reduce skeletal complications related to bone metastases such as pain, pathologic fractures, use of radiation, hypercalcemia, and spinal chord compression.¹ Bisphosphonates are specific inhibitors of osteoclast-mediated bone resorption. When tumors metastasize to the bone, osteoclast activation ensues, resulting in increased bone resorption. Bone resorption, in turn, releases growth factors and cytokines from the bone matrix that promote tumor growth, creating a “vicious cycle.”² Bisphosphonates break this vicious cycle by inhibiting osteoclast-mediated bone resorption; this allows new bone formation and “healing” to occur within bone metastases and indirectly inhibits tumor growth by decreased release of growth factors and cytokines.

Bisphosphonates also directly inhibit tumor growth in human breast cancer cell lines and breast cancer xenografts.³ The mechanism(s) of the antitumor effect are not fully understood, but inhibition of the cellular processes of adhesion—invasion and apoptosis—have been demonstrated. In addition, the bone marrow contains disseminated tumor cells (DTCs) in early stage breast cancer,⁴ and treatment with zoledronic acid (Zometa, Novartis), a third generation nitrogen-containing bisphosphonate, reduces these DTCs.⁵

The largest trial that looked at zoledronic acid in the adjuvant setting is the recent Austrian Breast Cancer Study Group (ABCSSG) Trial 12.⁶ Over 1,800 premenopausal women were treated the gonadotropin-releasing hormone agonist (GnRH) goserelin and were then randomized to

either tamoxifen or an aromatase inhibitor; half of the women were also treated with intravenous (IV) zoledronic acid every 6 months for 3 years versus a no treatment control. Results showed that women who received zoledronic acid had statistically significantly fewer recurrences than those who did not receive zoledronic acid (hazard ratio for disease-free survival [DFS] was 0.64; 95% CI 0.46–0.91; $P=.01$; absolute improvement in DFS of 3.2%) However, zoledronic acid did not improve overall survival. In addition, in a small neoadjuvant chemotherapy trial where women were randomized to receive zoledronic acid or no treatment, a higher pathologic complete response rate, smaller residual tumors, and a lower mastectomy rate were observed in those that received zoledronic acid.⁷

Larger randomized trials such as the NSAPB B34, in which women with early breast cancer received adjuvant chemotherapy and were randomized to either oral clodronate or placebo, or the AZURE trial, in which women received adjuvant endocrine or chemotherapy and were randomized to receive either zoledronic acid or a no treatment control, are completed but as yet not reported. Based on the available data, I would take a cautious approach and not provide zoledronic acid routinely to reduce the risk of recurrence until the data is available from these larger trials.

H&O What factors are involved when deciding whether to administer adjuvant bisphosphonates?

CS Treatment for early stage breast cancer may cause bone loss that will translate into higher risks of subsequent osteopenia and osteoporosis in some women. For example, premenopausal women receiving adjuvant chemotherapy may develop ovarian failure or early menopause^{8,9}; likewise, postmenopausal women receiving aromatase inhibitors have decreased estrogen levels.¹⁰ Estrogen deprivation causes bone loss; bisphosphonates including zoledronic acid, which are indicated for postmenopausal women to prevent and treat osteoporosis, are likewise used in women with early-stage breast cancer, according to published guidelines.^{11,12} It is important to remember that smoking cessation, reduction of alcohol consumption, increase in physical activity (particularly in weight bearing exercise), and taking adequate amounts of daily calcium and vitamin D not only promote bone health in breast cancer survivors but also contribute

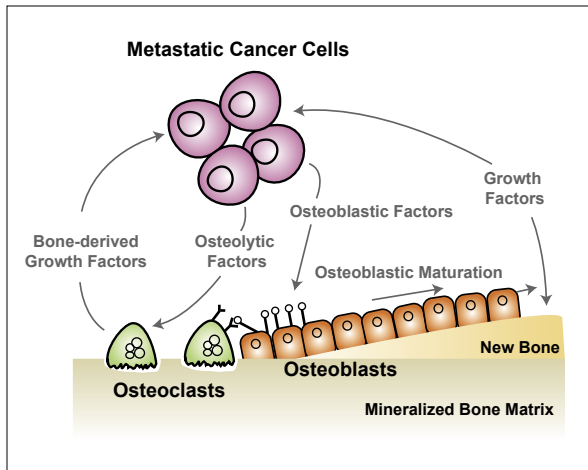


Figure 1. The “vicious cycle” of osteolytic metastases.

Data from Guise et al. *Clin Can Res.* 2006;12(20):6214s.

to overall health. Thus, bisphosphonates are standard treatments to treat and prevent osteoporosis in breast cancer survivors, but their role in preventing recurrence is less clear.

H&O Are there any risks associated with bisphosphonate treatment?

CS There are 2 major side effects associated with zoledronic acid. The first is renal insufficiency, and there are monitoring guidelines in the drug package insert that detail dose reductions on the basis of elevations of creatinine. Osteonecrosis of the jaw (ONJ) is an emerging problem that seems to depend on the dosing frequency (monthly) and duration (in excess of 3 years) of treatment in individuals receiving zoledronic acid for palliation of skeletal metastases.^{11,12} Although there is some uncertainty in whether having a major dental procedure during bisphosphonate treatment is causal or merely associated with the development of subsequent osteonecrosis,¹³ in most studies, dental surgery has emerged as a potential predisposing factor. This has led to the recommendation to have dental screening, and if necessary dental extractions, periodontal surgery, and dental implants, prior to starting IV bisphosphonates.^{14,15} Less is known about oral bisphosphonates and ONJ, but cases have been very rarely reported.¹⁶ However, when zoledronic acid is used for the treatment of osteopenia/osteoporosis or in the ABCSG trial 12 with schedules of every 3 or 6 month dosing for durations of 3 years or less, no cases of osteonecrosis have been observed.

H&O What are some current studies evaluating adjunct bisphosphonates?

CS SWOG-S0307 (Clinical Trials Support Unit [CTSU] web site: www.ctsu.org) entitled “Phase III Randomized Study of Adjuvant Zoledronate versus Clodronate versus

Ibandronate in Women With Resected Primary Stage I-III Adenocarcinoma of the Breast” is based on a premise that bisphosphonates will prevent recurrence and is attempting to identify which bisphosphonate is optimal vis-à-vis efficacy to reduce recurrence and side effects. This trial includes 4,500 women who are receiving adjuvant endocrine, chemotherapy, or both, and who will be randomized to either IV zoledronic acid monthly for 6 months and every 3 months for 2.5 years or oral clodronate or ibandronate daily for 3 years. The primary endpoint is disease recurrence. In addition, there are several ongoing European trials evaluating ibandronate in combination with adjuvant chemotherapy.

H&O What are our next steps with bisphosphonates?

CS I would not be surprised if in the next few years, there are sufficient data from the completed and ongoing randomized trials that establish bisphosphonates as a component of adjuvant therapy to reduce recurrence rates in addition to preventing bone loss. Defining the optimal drug and schedule of administration, identifying the women who are more or less likely to benefit from bisphosphonates, and whether these drugs will improve survival, are our next priorities.

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