

Emerging role for bisphosphonates in cancer management

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Bisphosphonates have become commonly used for preventing and treating osteoporosis [1] and, more recently, to reduce the risk of skeletal related events in cancer patients with bone metastases [2,3]. After initial clinical observations suggested bisphosphonates could favorably influence the course of breast cancer patients with bone metastases [4], both preclinical and clinical studies have aggressively addressed this issue. At present, a series of full-scale randomized clinical trials, planned to involve nearly 25,000 breast cancer patients, are underway to evaluate the role of bisphosphonates and other bone-targeted agents as potential additions to adjuvant therapy management [5]. Most recently, interest in the potential of bisphosphonates to influence breast cancer incidence as a component of primary prevention strategies have emerged as well [5].

In a series of articles in this journal, leaders in this field provide reviews and commentaries on the preclinical science in this area, the current clinical evidence and the definitive information which should emerge in the proximate future regarding the expanding role of bisphosphonates in breast cancer patient management.

Doctor's Lipton, Costa, and Coleman present current evidence regarding bone marker use to guide anti-resorptive therapy targeting bone [6]. They present data that urinary N-telopeptide of type I collagen (NTX) levels before and during bisphosphonate therapy pro-

vide information regarding risk of skeletal related event development, bone disease progression and death in patients with bone metastases from breast cancer [7, 8]. In addition, they outline ongoing studies evaluating bone markers to guide duration of anti-resorptive therapies, an area of importance given the increasing effectiveness of systemic therapy for breast cancer patients with disseminated disease. Finally, they look to the future and discuss the potential utility of bone markers in early breast cancer.

Michael Gnant steps back to provide a board view of anti-cancer activity of bisphosphonates and breast cancer [9]. He reviews the “seed versus soil” role of the bone microenvironment in supporting metastases and potentially facilitating drug resistance. Preclinical studies supporting biologically based, likely mechanisms of action are outlined. He reviews the clinical trials evaluating oral clodronate and the adjuvant trials evaluating zoledronic acid. These include the Austrian Breast Cancer Study Group (ABCSSG) – 12 trial [10], the trials evaluating early versus delayed zoledronic acid use and the AZURE trial [11] evaluating a more intensive zoledronic acid schedule in breast cancer patients with high risk early stage disease receiving chemotherapy or chemo-endocrine therapy.

Doctor's Li and Rugo [12] discuss trials integrating bisphosphonate use and their impact on the emerging efficacy marker of disseminated tumor cells in early stage breast cancer patients. While still controversial, disseminated tumor cells in the bone marrow has been associated with increased breast cancer recurrence, distant metastases, and death from breast cancer when followed in early stage breast cancer patients [13]. In three

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phase II randomized trials in patients with early stage breast cancer, bisphosphonate use has been associated with either a statistically significant or borderline significant favorable influence on reducing the percentage of disseminated tumor cells. Finally, the authors look to the future and outline the status of several new agents with different mechanisms of action which also may target the bone microenvironment.

Doctor Vera Hirsh expands the discussion by asking whether bisphosphonates may have an anticancer role in lung cancer patients in addition to their influence on skeletal morbidity [14]. Since bone metastases are common in several tumor types, perhaps it is not surprising that investigators have examined the influence of anti-resorptive agents in diseases other than breast cancer. Initial clinical observations in lung cancer recall issues regarding bone turnover markers discussed by Lipton and colleagues. As one example, patients with non-small cell lung cancer with elevated baseline NTX levels were at greater risk of skeletal related events and death compared to patients with normal NTX levels [15,16].

Finally Nananda Col and I address the issue of the potential for bisphosphonates to play a role in primary breast cancer prevention [5]. We outline the results of the available adjuvant breast cancer trials evaluating bisphosphonates and provide our own perspective on the significance of the findings and include two meta-analyses of the available results. In the first, all results are entered in an intent-to-treat fashion. In this analyses the overall odds ratio was 0.82 for the risk of disease recurrence events favoring zoledronic acid however, this was not statistically significant. A second post-hoc analysis was based on the hypothesis that bisphosphonate may be effective only in a non-stimulated bone environment (either in postmenopausal women or premenopausal women receiving GNRH analog use). When the meta-analyses is run incorporating only the postmenopausal AZURE participants, the overall odds ratio of 0.71 was statistically significant [5].

Observational studies regarding bisphosphonate use in women without cancer and the associated influence on breast cancer incidence must be interpreted with caution as bisphosphonates are prescribed for women with low bone mineral density (BMD) and women with low BMD are at lower breast cancer risk [17]. Thus, it is imperative that this likely confounding variable be adequately controlled for to avoid "confounding by indication". In our analyses from the Women's Health Initiative we were fortunate to have BMD assessment in 10,418 women of our total of 154,768 participants.

We then were able to correlate the BMD difference in this population with a validated hip fracture predictive score which did not require BMD determination and used the hip fracture predictive score to make individual adjustments for potential BMD differences in the larger WHI cohort [18]. Against this background we found a statistically significant 32% lower incidence of breast cancer in bisphosphonate users. Perhaps the most intriguing finding was that the association appeared to be similar for both estrogen receptor positive and estrogen receptor negative breast cancers. This poses the question, could bisphosphonates be the long sought after intervention which could reduce estrogen receptor negative breast cancer incidence? Other observational study reports variously were able to control or estimate BMD differences in bisphosphonate users and non-users are discussed.

In several of the presentations authors touch upon and/or review the ongoing full-scale adjuvant breast cancer trials evaluating anti re-absorptive agents including bisphosphonates and denosumab. The promising ABCSG-12 results for zoledronic acid use were seen in a population of hormone receptor positive, premenopausal women treated with GNRH analogs and hormonal therapy [10]. In contrast, in the AZURE trial no overall effect of zoledronic acid was seen in a population which included both pre and postmenopausal, largely node-positive patients receiving adjuvant chemotherapy where hormone therapy use was not precisely defined [11]. Based on the results of these two studies one could question whether bisphosphonates might play a role only in a low bone activity environment or only in women with hormone receptor positive breast cancer. One study which will most closely mimic the ABCSG-12 design is sponsored by the National Cancer Institute, Naples. HOBEO is a phase III study in premenopausal patients with hormone receptor positive breast cancer randomized to adjuvant triptorelin and tamoxifen or letrozole plus zoledronic acid. Whether the sample size of 1,050 will be sufficient to address this issue remains to be seen [19].

A program initiated by the Southwest Oncology Group is comparing three bisphosphonates (zoledronate, clodronate, ibandronate) in women receiving standard therapy for stage I-III breast cancer. The enrollment of 5,400 is reasonable but the absence of a no bisphosphonate control could complicate interpretation [19]. The long awaited NSABP B-34 trial evaluating clodronate with or without chemotherapy and/or hormonal therapy in 3,323 stage I and II breast cancer [19] is scheduled for presentation at the 2011 San

Antonio Breast Cancer Symposium. The GAIN study will compare two chemotherapy regimens with a second randomization to oral ibandronate 50 mg/day or placebo for two years. A total of 3,024 patients have been recruited and safety data has been presented [20].

Given the substantial differences in study designs of the ongoing studies evaluating bisphosphonates in an adjuvant setting, definitive findings could emerge or, alternatively, if relatively low bone activity is required for bisphosphonate effect, perhaps only subgroups from these large trials will demonstrate bisphosphonate efficacy. Such a case could pose difficulties for clinicians and regulators in determining the optimal role, if any, for such therapy as a standard component of adjuvant breast cancer patient management.

Finally, the high frequency of bisphosphonate use in many Western countries now for the prevention in therapy of osteoporosis would likely preclude the feasibility of a full-scale primary prevention trial. However, concerns which have emerged regarding the safety of long term bisphosphonate use in such populations [21, 22] and the emerging importance of specific fracture prediction models with higher accuracy than reliance on BMD testing alone [23] suggest that in the future bisphosphonate use may decline in the general population opening the door to placebo controlled primary prevention trials.

This special issue discussing bisphosphonates as potential cancer therapy provides clinicians and investigators with the up-to-date background allowing them to put the emerging clinical results in prospective.

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