MEETING REPORT

Treatment recommendations for the use of bone-targeted agents in 2011—report from the 6th Annual Bone and the Oncologist New Updates meeting

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ABSTRACT

The 6th annual Bone and the Oncologist New Updates conference was held in Ottawa, Ontario, April 14–15, 2011. This meeting traditionally focuses on innovative research into the mechanisms and consequences of treatment-induced and metastatic bone disease. This year, the multidisciplinary audience was polled to produce “treatment recommendations for the use of bone-targeted agents.” In addition, the meeting report itself outlines some of the key topics presented on adjuvant bisphosphonate use and the role of bone-targeted agents in the settings of metastatic and cancer-therapy-induced bone loss.

KEY WORDS

Cancer, bone health, bone metastases, bone-targeted agents

1. INTRODUCTION

Since 2005, the annual Bone and the Oncologist New Updates (BONUS) meetings—a day to day-and-a-half conference consisting of keynote national and international speakers—have covered a range of bone issues pertinent to health care professionals in oncology. The topics covered have ranged from normal bone function to the effects of cancer and cancer therapies on normal bone and metastatic bone disease. A major part of BONUS has also been to focus on the wealth of research experience in Canada and to generate real and exciting hypotheses that will shape future basic, translational, and clinical research.

The 6th annual BONUS conference (April 14–15, 2011) brought together clinicians, basic scientists, and others interested in the effects of cancer and its treatment on bone health. Controversial topics about the adjuvant use of bisphosphonates to prevent breast cancer recurrences and about the role and clinical significance of bone biomarkers were discussed. This year there was also a drive to produce “treatment recommendations for the use of bone-targeted agents in 2011,” using input from the multidisciplinary audience. The results should be viewed as treatment recommendations rather than treatment guidelines, because by its very nature, the production of a guideline requires a full systematic review of the topic.

2. SESSIONS

2.1 Status of Adjuvant Bisphosphonate Treatment for Breast Cancer in 2011

Presenter: Alexander Paterson MD, Department of Oncology, Tom Baker Cancer Centre, University of Calgary, Calgary, AB

Bisphosphonates have become a cornerstone of care for patients with metastatic bone disease and for the treatment and prevention of cancer treatment–related bone loss. Some population data also suggest that bisphosphonates may reduce breast cancer risk\(^1,2\). Several adjuvant trials of oral clodronate, pamidronate, and zoledronic acid are ongoing, and some results have already been presented or published (or both).

2.1.1 Studies That Have Been Presented or Published

The Austrian Breast and Colorectal Cancer Study Group (ABCSG) trial 12 was a randomized open-label phase III trial for premenopausal patients with stage I/II estrogen receptor–positive disease who did not receive adjuvant chemotherapy. All patients received chemical ovarian suppression with goserelin (a luteinizing hormone–releasing hormone analog) and were then randomized in a 2×2 factorial design to tamoxifen or to anastrozole with or without zoledronic acid. Data from that trial showing that zoledronic acid ameliorated bone loss associated with chemical castration has been known for several years\(^3\). After 62 months of follow-up, disease-free survival (DFS) was also significantly superior in the zoledronic acid treatment group, with a hazard ratio (HR) of 0.68 [95% confidence interval (CI): 0.46 to
0.91] and a reduction in all types of relapses⁴. There was, however, no significant difference in overall survival between the groups.

Despite those promising results, the study has a number of uncertainties and limitations. The small number of events (137 in 1803 patients) is a major limitation when trying to determine whether the treatment benefit occurred mostly in bone or at other sites of recurrence. Second, few patients received chemotherapy, making the applicability of the results to the North American setting problematic. The effect of zoledronic acid was observed at 3 years (after treatment with that agent had stopped), and it was more pronounced in the anastrozole group, suggesting that, in the adjuvant setting, a low-estrogen environment may be particularly important for bisphosphonate therapy to have an effect.

The large phase iii AUREZ study randomized 3300 stage ii/iii breast cancer patients to standard therapy with or without an additional intensive regimen of zoledronic acid⁵. Disease-free and overall survival were similar in both groups. Only when a preplanned subgroup analysis by menopausal status was performed was a significantly superior outcome in the treatment group observed, in agreement with the results of ARCSG 12. The AUREZ finding again suggests that the effect of zoledronic acid appears only in the presence of a low-estrogen environment. However, there are clearly concerns with the definition of menopause used in the study (5 or more years since menopause or age greater than 60 years), which is not a generally recognized definition.

In another study, oral clodronate led to an improvement in bone mineral density (BMD) and to a reduction in the incidence of bone metastasis (HR: 0.69; p = 0.04), which translated into an improvement in overall survival (HR: 0.76; p = 0.048) after 5 years of follow-up⁶. The trial design was double-blind and placebo-controlled, and 1069 patients with primary operable breast cancer were involved. The participants were randomized to receive oral clodronate (1600 mg daily) or placebo for 2 years in conjunction with standard treatment for primary breast cancer. All patients were assessed for bone metastases at 2 and 5 years and when clinically indicated.

The phase iii randomized trials ZO-FAST, Z-FAST, and E-ZO-FAST were planned in similar manner to assess BMD and risk of fracture among postmenopausal women with early breast cancer receiving adjuvant letrozole⁷–⁹. In all those studies, patients were randomized to receive treatment with zoledronic acid immediately or only after a documented decrease in BMD or a clinical fracture. Immediate zoledronic acid improved BMD and increased DFS in a pooled analysis of ZO-FAST and Z-FAST; however, improvement in DFS was not seen in E-ZO-FAST¹⁰. A limitation of the studies is that the primary endpoint was defined as a change in BMD, and the evaluation of DFS was performed in a subsequent analysis.

In postmenopausal women, production of estrogen decreases. Low estrogen leads to increased bone turnover and resorption, and it is possible that bisphosphonates are most effective in that microenvironment. Overall data from adjuvant trials suggest that the anticancer activity of zoledronic acid may be expressed through its effects on age- or estrogen-dependent changes to the bone microenvironment. Several observational studies suggest that women taking oral bisphosphonates for osteoporosis have a significantly lower risk for breast cancer, but those observations are confounded by the known association of low bone mass and reduced breast cancer risk¹¹–¹⁴.

Estrogen undoubtedly has an important role in bone metabolism: it suppresses bone resorption, accelerates osteoclast apoptosis, suppresses proinflammatory cytokines and interleukins in marrow and inhibits RANKL (receptor activator of nuclear factor κB ligand) and osteoblast and stromal secretion of transforming growth factor β—all of which reduce the activity or number of functional osteoclasts. Estrogen enhances bone formation by inhibiting apoptosis of osteoblasts and by leading to increased secretion of transforming growth factor β, bone morphogenetic protein, and insulin-like growth factor 1. Consequently, declining levels of estrogen cause upregulation of T cells, interleukin 6, tumour necrosis factor α, and RANKL, decreasing bone density and increasing turnover markers¹²–¹⁵. After presentation of the latter results, and regardless of populations that may potentially benefit from adjuvant zoledronic acid and the presence of mechanisms for potential bisphosphonate benefit, Novartis withdrew their U.S. Food and Drug Administration application for approval of adjuvant zoledronic acid.

2.1.2 Ongoing Trials
The B-34 study by the National Surgical Adjuvant Breast and Bowel Project is investigating outcomes in early breast cancer patients who, in addition to standard therapy, are receiving oral clodronate or placebo for 3 years. Patient accrual is complete, and initial results were presented at San Antonio in 2011. For the entire study population, no difference was observed between arms in progression-free survival, recurrence-free interval, bone-metastasis free interval, or overall survival. However, in a subgroup analysis, women 50 years of age and older who received clodronate experienced improvements in recurrence-free interval and in bone and non-bone metastasis-free interval, but not in overall survival¹⁶.

The Southwest Oncology Group 0307 randomized open-label study was designed to determine the relative efficacy of zoledronic acid (4 mg every 4 weeks for 6 months, then every 3 months for 2.5 years) and the oral agents ibandronate (50 mg daily for 3 years) and clodronate (1600 mg daily) for the prevention of bone metastasis in stages i–iii breast cancer patients. The study is fully accrued, with

The humanized antibody to RANKL, denosumab, has been investigated in clinical trials not only for the prevention of osteoporosis but also for patients with bone metastasis. A recent publication by Stopeck et al. showed denosumab to be superior to zoledronic acid in both delaying and preventing skeletal-related events (SREs), without any effect on survival17. Denosumab is also currently being studied in the D-CARE trial, which started in 2010 and which remains open to accrual. Patients are being randomized to subcutaneous denosumab or placebo and then followed for DFS and bone metastasis–free survival (http://clinicaltrials.gov/ct2/show/NCT01077154). Although these exciting results may offer patients a new treatment option that lacks an association with infusion reactions or renal toxicity and that is easy and quick to administer, no survival benefit has been associated with the use of these agents.

To summarize, the evidence for the use of bisphosphonates as adjuvant therapy for the prevention of bone metastasis in women with breast cancer is still controversial. It is possible that certain subgroups (for example, older postmenopausal women or younger women receiving ovarian suppressive therapy) may have some benefit in DFS; however, more evidence is required.

2.2 Optimizing Bisphosphonate Therapy for Breast Cancer Patients in 2011

**Presenter:** Eitan Amir MB PhD, Division of Hematology and Oncology, Princess Margaret Hospital, University of Toronto, Toronto, ON

2.2.1 Cancer Therapy–Induced Bone Loss

Bone loss caused by chemotherapy, hormonal therapy, and radiotherapy for cancer can lead to fractures and reduce quality of life18–20. Clinical guidelines have been developed for the prevention and treatment of aromatase inhibitor–associated bone loss in postmenopausal women with breast cancer21. According to current recommendations, BMD should be assessed in patients initiating or receiving aromatase inhibitors, and other risk factors for osteoporosis should also be assessed. Patients with a T score greater than –2.0 and no additional risk factors are advised to start physical activity, calcium and vitamin D supplementation, risk-factor monitoring, and annual BMD evaluations. For patients with risk factors or a T score less than –2.0, the addition of bisphosphonates to previous interventions is recommended, as is monitoring of BMD.

A number of oral22, intravenous3–9, and subcutaneous23 agents have a role in the management of cancer treatment–related bone loss. The various agents and routes of administration have different advantages and limitations. For example, subcutaneous administration results in better compliance than oral treatment does, but it demands the involvement of additional health care providers. Oral bisphosphonates are generally well-tolerated and have a good safety profile. On the other hand, for oral bisphosphonates and for denosumab, data on the efficacy of those agents in reducing fractures caused by cancer treatment–related bone loss are limited, and the long-term safety of denosumab is not yet known.

To summarize, the optimal agent for the prevention and treatment of cancer treatment–related bone loss is still not fully established. Another unresolved issue is the optimal way in which risk and treatment response can be evaluated in cancer therapy–induced bone loss. Measurement of BMD does not have a strict correlation with fracture risk; it assesses bone characteristics quantitatively, but not qualitatively. Better risk-prediction models are required.

2.2.2 Metastatic Disease

In metastatic bone disease, bisphosphonates are effective in reducing the incidence and delaying the onset of SREs such as fractures, spinal cord compression, hypercalcemia, and the need for radiation or surgery to bone. Such SREs can result in bone pain, significant morbidity, and loss of patient autonomy. These sequelae ultimately lead to decreased survival and increases in health care costs and resources for breast cancer patients.

A number of questions about the use of bone-targeted therapies in practice remain unanswered, including when to start, the optimal duration of treatment, the best agent to use, and the best management of the side effects of treatment. Our group has been involved in the development of innovative strategies to individualize therapy according to patient risk.

Although treatment guidelines recommend that bisphosphonates be started in all breast cancer patients with bone involvement24–26, the inter-patient variability in SRE risk is significant27. In lower-risk patients, SREs are infrequent, and the impact of treatment is unknown. In higher-risk patients, appropriate bone-targeted therapy may provide good bone control, but the worst-risk group (high frequency of bone events despite optimal therapy) needs new and effective interventions. Reducing the frequency of intravenous bisphosphonate administration in patients at lower risk of skeletal complications has several potential advantages. First, it could reduce the incidence of cumulative dose-related side effects such as renal impairment and osteonecrosis of the jaw. In addition, reducing the frequency of intravenous
bisphosphonate infusions would reduce drug costs and the number of visits that patients must make to the infusion unit for treatment.

A number of ongoing trials have set out to determine individualized approaches. Several phase III trials are comparing the efficacy and safety of standard with less-frequent regimens of bisphosphonate treatment in low-risk patients. The NCT00375427 trial, comparing a 4-week with a 12-week schedule of zoledronic acid for the prevention and delay of \texttt{sre} (primary endpoint: annual overall skeletal morbidity rate), has already completed, with preliminary and equivalent results emerging on the ClinicalTrials.gov Web site (http://clinicaltrials.gov/ct2/show/NCT00375427). The NCT00320710 study is also comparing treatment every 4 with every 12 weeks, the primary endpoint being the \texttt{sre} rate. That study is still recruiting patients (http://clinicaltrials.gov/ct2/show/NCT00320710).

Several different regimens of zoledronic acid infusion were assessed in the Bismarck trial (NCT00458796), in which the standard arm received a 4-week schedule, and depending on serum N-telopeptide levels, the experimental arms received zoledronic acid every 3–4, 8–9, or 15–16 weeks for 24 months. That study is now closed, having failed to reach its accrual target (http://clinicaltrials.gov/ct2/show/NCT00458796). The Cancer and Leukemia Group is conducting a randomized phase III trial studying two different schedules (4 weeks vs. 12 weeks) of zoledronic acid and comparing their efficacy in the treatment of patients with metastatic breast cancer, metastatic prostate cancer, or multiple myeloma with bone involvement (http://clinicaltrials.gov/ct2/show/NCT00869206).

A small pilot study (38 patients) titled \texttt{REFORM}, with a biomarker-based primary endpoint, set out to determine if women at low risk of \texttt{sre} gain benefits from less-frequent administration of bisphosphonates (every 12 weeks) that are similar to the benefits from a standard 3- to 4-weekly regimen. Serum C-telopeptide was chosen as the biomarker for the study because blood levels of that marker were found to correlate with survival in patients with bone metastasis for those with bone metastasis for those. Patients entered the study after receiving a minimum of 3 cycles of monthly pamidronate. Groups were well balanced for age, duration of previous bisphosphonates, and baseline telopeptide levels. Pamidronate was given for 1 year. Preliminary results show that the proportion of patients remaining in the low-risk telopeptide group at 48 weeks was similar in both groups (73\% vs. 68\%, \(p = 0.64\)). In all patients not maintaining telopeptides in the low-risk range, there was evidence of concurrent systemic progression. The \texttt{sre} rate was similar in the two groups. A gradual increase in telopeptide levels was noted in the 12-weekly group during follow-up. The conclusions of the authors were that, in women with low-risk bone metastases, 12-weekly intravenous bisphosphonate appears to be noninferior to 3- to 4-weekly treatment in patients with stable systemic disease. Although the absolute increase in telopeptide levels in the 12-weekly arm raises concern about a possible increase in late \texttt{sre}s for those on de-escalated therapy, that finding requires further study in a larger randomized study.

2.3 In Search of Consensus

**Presenters:** Nathaniel Bouganim MD, Division of Medical Oncology, The Ottawa Hospital Cancer Centre, University of Ottawa, Ottawa, ON; Alexander Paterson MD, Department of Oncology, Tom Baker Cancer Centre, University of Calgary, Calgary, AB; and the bonus 6 audience

Numerous guidelines and recommendations address the treatment of bone metastasis in cancer patients. According to the guidelines, bisphosphonates have a role in the treatment of bone metastasis and in the prevention of \texttt{sre}s in cancer patients. A number of questions related to the treatment of bone metastasis are unresolved, including the timing of treatment initiation, the duration of treatment, the optimal agent, and the management of treatment-related adverse events. We therefore decided to poll the meeting audience for their opinions about whether there was a consensus on a range of scenarios in the metastatic (Table i), cancer therapy–induced bone loss (Table ii), and adjuvant (Table iii) settings.

3. SUMMARY

The bonus meetings strive to bring together people interested in bone disease. This gathering continues to be an excellent forum to foster research and wide multidisciplinary interaction. We extend our thanks to all who made the 6th meeting such a success, including our pharmaceutical sponsors. We will use the feedback from the conference to make further program changes before organization begins for a 2012 meeting!

4. CONFLICT OF INTEREST DISCLOSURES

MC has received honoraria from Amgen and Novartis. AP has received honoraria from Amgen and Novartis. None of the other authors has any financial conflicts of interest to disclose.

5. REFERENCES


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<thead>
<tr>
<th>Question</th>
<th>Issues in the literature</th>
<th>Consensus reached?</th>
<th>Consensus statement</th>
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<tbody>
<tr>
<td>Should bone-targeted agents be started in patients with metastatic disease but with no bone metastases?</td>
<td>Bisphosphonates should not be administered to women with no bone metastases outside the scope of a clinical trial. Clearly, these agents can be given in patients at high risk of fragility fracture secondary to osteoporosis.</td>
<td>Yes</td>
<td></td>
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<td>Should bone-targeted agents be started in all patients with bone metastases?</td>
<td>Treatment recommendations vary for patients with merely radiologic evidence of bone destruction to patients who are symptomatic; some of the recommendations limit treatment delivery to patients whose life expectancy exceeds 3–6 months.</td>
<td>Yes</td>
<td>All breast cancer patients with bone metastases should probably be treated with a bone-targeted agent</td>
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<td>For how long should bone-targeted agents be continued?</td>
<td>Optimal duration of therapy is unclear. Although the benefits are largely based on trials providing 2 years of therapy, some of the guidelines support prolonged treatment until a decline in patient’s performance status is noted.</td>
<td>Yes</td>
<td>Treatment should be continued until evidence of a substantial decline in the patient’s performance status appears.</td>
</tr>
<tr>
<td>Which bone-targeted agent should be used?</td>
<td>Pamidronate, zoledronic acid, clodronate, and recently, denosumab have all been recommended in guidelines.</td>
<td>No</td>
<td>Given the lack of a documented survival benefit for any one of these bone targeted agents, the data are insufficient to support the use of one agent over the other.</td>
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<td>How should the dose of a bone-targeted agent be adjusted in patients with renal dysfunction?</td>
<td>In cases of renal dysfunction, treatment should be given according to the ASCO 2011 guidelines.</td>
<td>Yes</td>
<td>In patients with an estimated creatinine clearance exceeding 60 mL/min, no change in dose, infusion time, or interval is required; creatinine should be monitored with each intravenous bisphosphonate dose.</td>
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<td>Should you stop bone-targeted therapy in a patient who requires dental work?</td>
<td>ADA and ASCO 2011 guidelines state that dental work should be completed before bone targeted agents are started and that, during therapy, invasive dental procedures that involve manipulation of the jaw bone or periosteum should be avoided.</td>
<td>No</td>
<td>Evidence on the risk of osteonecrosis of the jaw is limited in patients on bisphosphonates who have invasive dental work. Nevertheless, try to avoid extractions, root canals, and ill-fitting dentures if possible.</td>
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<tr>
<td>Should bone-targeted agents be switched after a skeletal-related event on another agent?</td>
<td>Studies have used surrogate markers to reflect the risk for skeletal-related events.</td>
<td>No</td>
<td>Currently no double-blind data with appropriate endpoints support such action.</td>
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**ASCO** = American Society of Clinical Oncology; **ADA** = American Dental Association.
TABLE II  Treatment with bone-targeted agents in the setting of cancer therapy–induced bone loss

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<th>Consensus statement</th>
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<tr>
<td>What is standard care for patients about to start an aromatase inhibitor?</td>
<td>According to ASCO recommendations32, bone mineral density should be measured in patients initiating or receiving aromatase inhibitor therapy. Risk factors for fragility fracture have to be assessed.</td>
<td>Yes</td>
<td>Patients with a T-score equal to or higher than –2.0, with no additional risk factors, are advised to use physical activity, calcium and vitamin D supplementation, and monitoring of risk factors and bone mineral density once or twice yearly. For patients with risk factors or a T-score lower than –2.0, the addition of bisphosphonates or denosumab is recommended.</td>
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ASCO = American Society of Clinical Oncology.

TABLE III  Treatment with bone-targeted agents in the adjuvant setting

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<td>Should patients receive adjuvant bone-targeted therapies?</td>
<td>Many!</td>
<td>Yes</td>
<td>Outside of a clinical trial, bone-targeted agents should not be given to patients as an adjuvant (that is, anticancer) treatment. Zoledronic acid every 6 months can be considered in premenopausal patients not receiving chemotherapy, per the Austrian Breast and Colorectal Cancer Study Group trial 124.</td>
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