The Role of Bisphosphonates in Early Breast Cancer

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Abstract
Clinical trials are investigating the use of bisphosphonates in patients with early (nonmetastatic) breast cancer. Results from trials of clodronate are generally encouraging but somewhat contradictory. Of the three trials published to date, two reported that clodronate had beneficial effects on both bone metastases and survival. In contrast, the third trial reported that clodronate had no effect on metastases and a negative effect on survival. Small studies of adjuvant pamidronate and zoledronic acid also produced promising data, but these need to be reproduced in a large-scale, randomized trial setting before clinically meaningful conclusions can be drawn. A number of adjuvant trials are in progress to further evaluate the role of oral clodronate and i.v. zoledronic acid and to examine the effects of the newer bisphosphonate,ibandronate (oral formulation), in this setting. One of these trials is the joint Southwest Oncology Group/Intergroup/National Surgical Adjuvant Breast and Bowel Project trial, which is designed to compare the efficacy and safety of all three of these bisphosphonates in approximately 6,000 women with early breast cancer. Patient preference for oral or i.v. therapy will also be assessed. The Oncologist 2006;11(suppl 1):13–19

Introduction
In patients with breast cancer, the most common site for distant metastasis is bone [1]. The resulting metastatic bone disease (MBD) can cause a number of debilitating sequelae, including bone pain, fractures, and spinal cord compression. All of these conditions reduce the quality of life for the patient and have wider implications for the patient’s family and health care providers.

A number of therapeutic options are currently available to treat the symptoms of MBD. These include analgesics for relieving bone pain, radiotherapy, surgery, and bisphosphonates. Bisphosphonates are used to reduce the risk of patients experiencing a skeletal-related event (SRE) and to alleviate bone pain, thereby improving quality of life. The precise mechanism of pain relief is unknown, but it is likely that a reduction in tumor-induced bone resorption is a factor.

A large amount of preclinical evidence suggests that bisphosphonates may also have direct effects against tumors. These include inhibition of tumor cell adhesion to bone, tumor growth, and angiogenesis [2–4]. These findings have raised considerable interest in the prospect of bisphosphonates being studied earlier in the course of breast cancer, in the adjuvant setting. Evidence from the five clinical studies published to date on the use of adjuvant bisphosphonates has been conflicting and inconclusive, and therefore a number of new trials are in progress to clarify the effects of these agents on the incidence of bone recurrence and overall survival of patients with early breast cancer.

This manuscript reviews some of the preclinical evidence supporting the potential use of adjuvant bisphosphonate therapy and discusses the results obtained so far in clinical trials. This paper also presents the design, aims, and objectives of a new adjuvant study, the Southwest Oncology Group (SWOG)/Intergroup/National Surgical Adjuvant Breast and Bowel Project (NSABP) S0307 trial.
ABNORMAL BONE REMODELING RESULTING FROM BONE METASTASIS
During the process of bone homeostasis, bone is constantly remodeled by the actions of osteoclasts, which are involved in bone resorption, and osteoblasts, which form new bone [5]. When a patient has MBD, this normally balanced process becomes unregulated, leading to abnormal bone growth with lesions that can result in debilitating clinical sequelae.

Much of the skeletal damage caused by metastases occurs through increased osteoclast activity, probably through a mechanism known as “the vicious cycle” [6]. Osteoclast activity and proliferation are stimulated by a variety of factors secreted by malignant cells, including parathyroid hormone-related protein (PTHrP), prostaglandin-E, transforming growth factors, tumor necrosis factor, and interleukins. This process is further compounded through the actions of bone-derived growth factors and cytokines that are released during the process of bone resorption. These can attract cancer cells to the bone surface and stimulate their growth and proliferation, thereby exacerbating the destructive effects on the bones.

Effective management of MBD is therefore essential to minimize the risk for SREs, relieve pain, and generally improve the quality of life of affected patients. Therapeutic options for this include antineoplastic therapy (chemotherapy or hormonal therapy), radiotherapy, surgery, analgesics, and bisphosphonates.

BISPHOSPHONATES IN MBD
Bisphosphonates are used as a supportive therapy in cancer patients with MBD to prevent SREs and relieve pain. Four bisphosphonates are currently available for the treatment of MBD: oral clodronate (Bonefos®, Schering AG, Berlin; and Osta®; F. Hoffmann-La Roche Ltd., Basel, Switzerland), i.v. pamidronate (Aredia®; Novartis Pharmaceuticals Corporation, East Hanover, NJ), i.v. zoledronic acid (Zometa®; Novartis Pharmaceuticals Corporation), and oral or i.v. ibandronate (Bondronat®; F. Hoffmann-La Roche Ltd.).

Oral clodronate and i.v. pamidronate have demonstrated efficacy in patients with metastatic cancers and are widely used [7–9]. The newer bisphosphonates, i.v. zoledronic acid and i.v. and oral ibandronate, have also proven to be effective in the treatment and prevention of SREs [10–12]. Although all four agents have demonstrated efficacy in metastatic cancer, their potential in the adjuvant setting is not yet fully established.

PRECLINICAL RATIONALE FOR ADJUVANT USE
A number of preclinical studies suggest that bisphosphonates have direct antitumor effects in addition to their ability to reduce osteoclast-mediated bone resorption. These effects include prevention of tumor cell adhesion to bone, induction of tumor cell apoptosis, antagonism of growth factors, and antiangiogenic effects. Smaller tumors may be more susceptible to change in the bone microenvironment than larger tumors, suggesting that bisphosphonate treatment should start as early as possible for those patients with cancers that are associated with metastasis to bone [13].

Results from in vitro studies of bisphosphonates provide evidence that they are able to inhibit the adhesion of breast and prostate tumor cells to bone matrix [2, 14] and to inhibit tumor cell invasion [15]. Furthermore, ibandronate is able to inhibit the growth of fully established metastases and reduce the rate of growth in animal models of MBD [3].

Bisphosphonates also have antiangiogenic properties, observed in both in vitro and in vivo studies. Angiogenesis is essential for the metastasis and continued growth and survival of solid tumors. In one study of antiangiogenic effects, endothelial cells were treated with bisphosphonates in vitro, and the incidence of capillary-like tube formation was reduced [16]. In the same study, ibandronate and zoledronic acid were also able to reduce the effect of testosterone-induced revascularization in the prostate gland of castrated rats.

In another study, Fromigue and colleagues [17] found that bisphosphonates were able to antagonize the effects of bone growth factors on the survival of human breast cancer cells in vitro. Direct antitumor effects were also found in two further in vitro studies of bisphosphonates. Senaratne and colleagues [18] reported that all of the bisphosphonates studied, including zoledronic acid, pamidronate, and clodronate, significantly reduced the viability of three human breast cancer cell lines and induced apoptotic changes in both the nucleus and cell morphology. Apoptotic effects were also observed in an in vitro study of the effects of ibandronate on human breast cancer cells [19].

There is also evidence that there may be synergistic effects between bisphosphonates and some chemotherapeutic and hormonal agents. Jagdev and colleagues [20] found such effects when zoledronic acid was used in combination with paclitaxel. Exposing breast cancer cell lines to the combination resulted in a 4–5 fold greater rate of apoptosis when compared with zoledronic acid exposure alone. Moreover, Neville-Webbe et al. [21] showed that the synergistic interaction was drug sequence dependent. Maximal levels of apoptosis were achieved when cells were treated with paclitaxel followed by zoledronic acid, rather than the reverse sequence or simultaneous treatment [21]. Similarly, ibandronate in combination with taxoids inhibited the adhesion to and invasion of bone by human breast carcinoma cells (Fig. 1) [22]. A recent in vitro study also found additive effects between ibandronate and the antiestrogens 4-hydroxytamoxifen and fulvestrant in estrogen receptor-positive breast cancer cell lines [23].
Adjuvant Clinical Trial Data

Unfortunately, the clear-cut antitumor effects of bisphosphonates observed in preclinical studies have not been reproduced in the clinical setting to date. Data from clinical trials of adjuvant bisphosphonate therapy suggest that their use in this setting may be beneficial, but data have been inconsistent across trials. There are three published adjuvant trials of clodronate [21, 24–28] and two separate trials of pamidronate [29] and zoledronic acid [30]. Key results from these trials are discussed here and presented in Table 1 [24–28, 31].

Clodronate

Results obtained from randomized, placebo-controlled clinical trials of adjuvant clodronate suggest that it may increase overall survival for patients with breast cancer. In a single-center trial of 302 women with primary breast cancer, patients received either postoperative treatment with oral clodronate (1,600 mg) for 2 years or no treatment [24]. After a 3-year follow-up, patients in the adjuvant clodronate group had a significantly lower incidence of bone metastases than those in the untreated control group ($p = .044$). There was a longer overall survival time in the clodronate group ($p < .002$) [32].

A 10-year (103 months ± 12 months) follow-up study of 290 of the original patients found that the significantly longer disease-free survival was not maintained, but that clodronate still improved overall survival ($p = .002$); 79.6% of clodronate-treated patients survived compared with 59.3% of patients who received placebo [25].

Adjuvant oral clodronate was also assessed in a 2-year, randomized, placebo-controlled trial in 1,069 women with primary operable breast cancer [27]. Clodronate resulted in a significantly lower incidence of bone metastasis, by 45% during the first 2 years ($p = .031$) and by 31% during the 5-year study period ($p = .043$) compared with placebo. There was also a significantly longer overall survival time compared with placebo ($p = .047$). After a 10.5-year follow-up, oral clodronate was still found to significantly improve overall survival ($p = .048$) [28].

In contrast, a third trial did not find a clinical benefit for the use of adjuvant oral clodronate in patients with nodal-positive breast cancer [26]. In a 5-year, randomized, open-label trial of clodronate given for 3 years, the incidence of bone metastases was not lower in the clodronate-treated patients than in patients in the no bisphosphonate control arm. Furthermore, both overall and disease-free survival times were significantly shorter in women treated with clodronate compared with those who received placebo. After a 10-year follow-up, no significant difference in survival was seen between patients who received clodronate and those who received placebo, but disease-free survival was shorter in the clodronate group [31].

**Table 1.** Clinical trials of adjuvant clodronate therapy in breast cancer published to date

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Placebo controlled</th>
<th>Duration of follow-up</th>
<th>Bone metastases</th>
<th>Disease-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diel et al. [24]</td>
<td>302</td>
<td>No</td>
<td>53 mos</td>
<td>$\downarrow$ ($p = .044$)</td>
<td>$\uparrow$ ($p = .002$)</td>
<td></td>
</tr>
<tr>
<td>Jaschke et al. [25]</td>
<td>103 mos</td>
<td></td>
<td></td>
<td>($p = .770$)</td>
<td>($p = .01$)</td>
<td></td>
</tr>
<tr>
<td>Saarto et al. [26, 31]</td>
<td>299</td>
<td>No</td>
<td>5 yrs, 10 yrs</td>
<td>($p = .27$), ($p = .35$)</td>
<td>($p = .007$), ($p = .01$)</td>
<td></td>
</tr>
<tr>
<td>Powles et al. [27, 28]</td>
<td>1,069</td>
<td>Yes</td>
<td>5 yrs, 10.5 yrs</td>
<td>$\downarrow$ ($p = .043$)</td>
<td>$\uparrow$ ($p = .047$)</td>
<td></td>
</tr>
</tbody>
</table>

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The results of this last trial are concerning, but they are most likely explained by a randomization bias. Significantly more patients with estrogen receptor (ER)- and progesterone receptor-negative breast cancer were randomized to the clodronate group than the placebo group and this may explain the results. Furthermore, ER-negative patients in the study did not receive adjuvant chemotherapy, and this is now known to be a beneficial treatment for these patients.

**Pamidronate**
Kokufu and colleagues [29] assessed the effects of pamidronate in a small \((n = 90)\), nonrandomized study of patients with high-risk breast cancer (four or more positive nodes). Results published after a median follow-up of 5.4 years showed that patients who received adjuvant pamidronate had a significantly lower incidence of bone metastases \((p = .008)\) and a significantly higher rate of metastasis-free survival \((p = .035)\). Although encouraging, this study was small and the clinical significance of the findings remains to be confirmed in larger randomized trials.

**Zoledronic Acid**
The effects of adjuvant zoledronic acid therapy have been studied in a randomized, open-label study of 40 patients with recurrent solid tumors who did not present with bone metastases at baseline [30]. After 12 months of treatment, significantly more patients in the zoledronic acid group were free from bone metastases than patients in the control group \((60\% \text{ vs. } 10\%; p < .0005)\). This difference between groups remained significant after 18 months \((20\% \text{ vs. } 5\% \text{ for placebo}; p = .0002)\).

**The S0307 Trial Design**
Several trials are currently evaluating the role of adjuvant i.v. zoledronic acid, oral clodronate, and oral ibandronate (Table 2). In addition to these, the S0307 trial is designed to assess the efficacy of bisphosphonates in reducing the incidence of bone metastases. It is a 3-year, joint SWOG/Inter-group/NSABP trial in 6,000 women with breast cancer.

The trial was initiated at the end of 2005 and is due to end in 2015. After 3 years of treatment, patients will be followed up for an additional 3 years. Enrolled patients will randomly receive one of three adjuvant bisphosphonate regimens, in addition to standard systemic therapy (Fig. 2) [33].

The trial will enroll female patients with histologically confirmed stage I, II, or III nonmetastatic breast cancer who are receiving standard adjuvant therapy. Entry criteria are standard, but a new feature in this trial is a requirement for a pretrial dental examination for identification of periodontal disease and exposed bone; this is in an effort to reduce any potential risk factors for osteonecrosis of the jaw or maxilla.

**Efficacy and Safety Assessments**
The primary efficacy end point is disease-free survival. Secondary end points include overall survival, distribution of sites of first recurrence, and adverse events. Substudies will include serum/tumor markers (PTHrP and crosslinked N-telopeptides of type I collagen \([\text{NTX}]\)) and other relevant markers of bone turnover and potential predictors of bone recurrence.

Tolerability of oral and i.v. bisphosphonate therapy and patient preference for either administration route are other interesting end points in the trial. There are safety concerns associated with the use of oral and i.v. bisphosphonates. Tolerability is an important consideration with oral therapies because adverse events such as gastrointestinal side effects can result in poor patient compliance. Gastrointestinal side effects have been reported by patients using oral clodronate [27, 34]. The relatively large size of the capsule can limit patient compliance [35]. In contrast, oral ibandronate, a more potent bisphosphonate with a smaller pill size than clodronate (50 mg

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**Table 2. Ongoing adjuvant bisphosphonate trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Primary cancer</th>
<th>Treatment regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-34</td>
<td>3,300</td>
<td>Stage I/II breast cancer</td>
<td>Clodronate (1,600 mg/day) vs. placebo for 3 yrs</td>
</tr>
<tr>
<td>AZURE</td>
<td>3,300</td>
<td>Stage II/III breast cancer</td>
<td>Adjuvant therapy, with or without zoledronic acid (4 mg) for 5 yrs</td>
</tr>
<tr>
<td>Coleman et al. [42]</td>
<td>3,300</td>
<td>Early breast cancer</td>
<td>i.v./oral ibandronate with or without capecitabine (six cycles) for 2 yrs</td>
</tr>
<tr>
<td>ICE</td>
<td>1,400</td>
<td>Early breast cancer</td>
<td>Epirubicin, paclitaxel, and cyclophosphamide with or without ibandronate or epirubicin, paclitaxel, cyclophosphamide, and capecitabine with or without ibandronate</td>
</tr>
<tr>
<td>GAIN</td>
<td>3,000</td>
<td>Node-positive breast cancer</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AZURE, Adjuvant zoledronic acid to reduce recurrence; GAIN, German Adjuvant Intergroup Node-Positive study; ICE, Ibandronate with or without Capecitabine in elderly patients with Early breast cancer; NSABP, National Surgical Adjuvant Breast and Bowel Project.
vs. 1,600 mg), has to date not been associated with a high incidence of gastrointestinal adverse events. It appears to be at least as effective as i.v. ibandronate in preventing SREs in the metastatic setting [36, 37]. The 50-mg tablet taken once a day is relatively small (1 cm). Good compliance with oral regimens means patients can have the benefits of therapy without making frequent hospital visits for i.v. bisphosphonates.

By its very nature, patient compliance with i.v. bisphosphonates is high, but side effects of pyrexia and ophthalmic and renal toxicity with aminobisphosphonates have been reported [38, 39]. In contrast, oral bisphosphonates are rarely associated with renal toxicity. In the S0307 trial, renal function will be monitored in compliance with product labeling. Zoledronic acid (4 mg) will be administered monthly for 6 months then every 3 months for 2.5 years.

Another safety issue that may result from treatment with certain bisphosphonates is osteonecrosis of the jaw and maxilla [40, 41]. To date, most reports of osteonecrosis of the jaw and maxilla have been associated with zoledronic acid and pamidronate [41]. Although aminobisphosphonates constitute by far the majority of reported cases, all classes of bisphosphonate may be associated with this serious toxicity. Duration of bisphosphonate therapy and dental treatment, particularly extractions, are also associated with a higher risk of osteonecrosis of the jaw.

The primary statistical comparison will be a log-rank test of all three treatments (two-sided) with an overall significance level of 0.04. The trial is designed to detect superiority to clodronate as the standard of care, assuming a disease-free survival rate of 80% at a 5-year follow-up for patients who received clodronate. Two interim analyses will be performed after one third and two thirds of defined events have occurred.

**Summary**

Although the use of bisphosphonates as effective therapy for patients with hypercalcemia and pain and for the prevention of skeletal complications is well established, their use in the adjuvant setting is still under clinical trial assessment. A number of well-designed, randomized clinical trials of bisphosphonate therapy for early-stage breast cancer are currently under way. NSABP B-34, assessing oral clodronate versus placebo, will provide additional evidence for efficacy in the adjuvant therapy of breast cancer. The advent of newer bisphosphonates, such as oral ibandronate, means that bone resorption can be inhibited using more potent agents. Trials such as S0307 will compare three commonly used bisphosphonates, assessing their relative efficacy in the prevention of metastatic spread to bone in early breast cancer. It will also attempt to differentiate among three different bisphosphonates in terms of safety and patient preference for oral versus i.v. treatment.

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**Disclosure of Potential Conflicts of Interest**

A. H. G. P. has acted as a consultant for Schering AG, Berlex, Roche, AstraZeneca, Pfizer, and Ortho-Biotech.
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