

# Oral Bisphosphonates as Adjuvant Therapy for Operable Breast Cancer

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**Abstract** Bone is the most common site of metastatic spread from primary operable breast cancer, causing pain, fractures, and hypercalcemia. This spread depends on the release of osteolytic substances by the cancer cells, which activate osteoclasts to cause bone resorption. The osteoclasts also release growth factors that can act back on the cancer cells to activate growth. This vicious circle thereby facilitates the growth of metastases in bone, thus making this a preferential site for relapse. Agents, such as the bisphosphonates, which block osteoclast function, have been shown to reduce the progression of established bone metastases. The oral bisphosphonate clodronate (1,600 mg/d) is effective for treatment of patients with bone metastases. When used as adjuvant therapy, given to patients with operable breast cancer for 2 years, clodronate has been reported to significantly reduce the risk of bone metastases during the 2-year study period [19 clodronate patients versus 35 placebo patients; hazard ratio (HR), 0.546;  $P = 0.03$ ] and 5-year study period (51 clodronate patients versus 73 placebo patients; HR, 0.692;  $P = 0.04$ ) with a significant reduction in mortality (HR, 0.768;  $P = 0.048$ ). This benefit, together with the low toxicity and safety of clodronate, supports its use as additional adjuvant therapy for patients with primary breast cancer. Further, similarly designed trials are under way to establish the optimal duration of therapy, the efficacy in stage I disease, and the relative potential of other bisphosphonates, particularly the more powerful aminobisphosphonates, such as ibandronate and zoledronate.

## Background

Bone is the most common site of metastatic relapse from breast cancer (1). The pathophysiologic process whereby metastases from breast can so easily develop in a structure as solid as bone depends on a precise mechanism that involves the release of agents from cancer cells in the bone marrow, which can activate osteoclasts and cause osteolysis (2–5). Identification of the agents involved in tumor-induced bone osteolysis has established a remarkable vicious circle between cancer cells and osteoclasts whereby the cancer cells release osteolytic agents, such as parathyroid hormone-related protein, which activate osteoclasts to cause osteolysis. These activated osteoclasts release growth factors, such as transforming growth factor- $\beta$ , which cause cancer cell replication and tumor growth in bone, thereby making bone a preferential site of metastatic development (6, 7). Antiosteolytic agents, including nonsteroidal anti-inflammatory drugs and bisphosphonates, which inhibit osteoclast activity (8), have been shown to prevent the development of bone metastases in rats and rabbits (4, 7,

9–12). Unfortunately, early clinical trials using nonsteroidal anti-inflammatory drugs failed to show clinical benefit, apart from pain relief.

These data provided the basis for trials of bisphosphonates in patients with bone metastases from breast cancer to prevent the complications of hypercalcemia and bone pain and the need for palliative radiotherapy. Several placebo-controlled trials have now reported that oral clodronate will reduce the skeletal complications in patients with bone metastases from breast cancer. Oral clodronate significantly reduced these bone events, such as onset of bone pain, the frequency of hypercalcemic events, and the incidence of fractures, and prolonged the time to the first bone event ( $P = 0.006$ ; refs. 13–15). There was a similar reported reduction in the incidence of bone events using i.v. pamidronate (16, 17). Oral clodronate has also been used in a small trial of patients with metastatic or advanced breast cancer but with no evidence of bone metastases and shown to reduce the incidence of subsequent bone metastases and bone events (18). The results from all these metastatic trials encouraged the use of these drugs in patients with operable breast cancer to attempt to prevent the development of bone metastases.

## Adjuvant Clodronate Trials

The first of the adjuvant clodronate trials was started in 1989. The trial design was double blind and placebo controlled, and involved 1,069 patients with primary operable breast cancer. The participants were randomized to receive oral clodronate (1,600 mg/d) 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 additionally when clinically indicated.

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The final analysis showed that oral clodronate significantly reduced the risk of bone metastases during the 2-year study period [19 clodronate patients versus 35 placebo patients; hazard ratio (HR), 0.546;  $P = 0.03$ ] and 5-year study period (51 clodronate patients versus 73 placebo patients; HR, 0.692;  $P = 0.04$ ). This reduction was predominantly seen in patients with stage II and III disease. There was also a significant reduction in mortality (HR, 0.768;  $P = 0.048$ ; ref. 19).

An analysis of the incidence of skeletal-related events in the 51 clodronate patients and 73 placebo patients who developed bone metastases was also done to estimate the clinical benefit of early treatment. Choice of treatment for these patients at relapse was at the discretion of the investigator; however, it was general practice to use a bisphosphonate when bone metastases occurred. The results of this analysis showed that the clodronate patients were less likely to have metastatic bone events (fractures, hypercalcemia, and bone irradiation) even when corrected for the fewer numbers, indicating a probable spillover benefit for these patients even if they had relapsed in bone.

With regard to relapse at other sites in this trial, there was no evidence of a significant decrease in nonosseous metastatic relapse in patients randomized to the clodronate group (112 clodronate patients versus 128 placebo patients;  $P = 0.26$ ) or in the subgroup of visceral metastases (89 clodronate patients versus 106 placebo patients;  $P = 0.25$ ). Furthermore, there was an overall significant reduction in mortality (98 clodronate patients versus placebo 129 patients;  $P = 0.048$ ). In this trial, oral clodronate (1,600 mg/d) was well tolerated, with no significant toxicity apart from mild to moderate diarrhea (20).

In a subset of 498 patients (243 clodronate patients and 255 placebo patients), the bone mineral density was measured by dual X-ray absorptiometry (Hologic QDR1000, Bedford, MA) at entry into the trial and annually for 5 years thereafter. For the 1st and 2nd years, while undergoing treatment, oral clodronate (1,600 mg/d) protected against cancer treatment-induced loss of spine and hip bone mineral density. After the discontinuation of use of clodronate, rates of bone loss returned after ~1 year to the rate of bone loss in placebo-treated women. The women randomized to clodronate still had a significantly greater bone mineral density at 5 years than those treated with placebo (21, 22).

The results of another small, randomized, open-label study of oral clodronate involving 299 patients with operable breast cancer have been published, reporting no reduction in the incidence of skeletal metastases (23), although there was a reduction in the incidence of new bone metastases in the clodronate arm ( $P = 0.04$ ). However, there was a reported increased incidence of visceral metastasis and a reduction in overall survival for patients randomized to clodronate versus placebo. These negative findings are not in keeping with the preclinical data or the results of the large, blinded, placebo-controlled trial described herein and may be related to a significant imbalance in prognostic factors caused by the randomization process. In particular, there were significantly more patients with estrogen receptor-negative cancers in the clodronate group. This imbalance was compounded by these receptor-negative patients receiving endocrine therapy rather than chemotherapy as systemic therapy. It is therefore difficult to make definitive conclusions from this small, unbalanced, open, non-placebo-controlled study.

A further small, randomized, open-label study with oral clodronate involving 302 women with newly diagnosed primary breast cancer has also been reported. These patients had operable breast cancer but also had micrometastases detected in their bone marrow at the time of primary diagnosis (10, 24). The patients were randomly assigned to receive oral clodronate (1,600 mg/d) or no clodronate during a 2-year treatment period. All patients received standard adjuvant therapies, including surgery, radiotherapy, endocrine therapy, and/or chemotherapy. The two arms were well balanced with respect to prognostic factors during the 3-year follow-up period; patients who received oral clodronate had an ~50% reduction in the incidence of bone metastases (8% versus 17% with placebo;  $P = 0.003$ ) and a significantly longer bone metastasis-free survival ( $P < 0.001$ ) compared with those receiving standard treatment. A later analysis still confirmed a significant reduction in overall survival for clodronate patients, although the significant reduction in disease-free survival no longer persisted (25).

## Discussion

Based on extensive preclinical data indicating that the development of bone metastases depends on cancer cells producing osteolytic agents that facilitate the growth and invasion in bone, randomized clinical trials have consistently shown that use of antiosteolytic bisphosphonates will reduce the occurrence of the bone events of fractures, hypercalcemic episodes, and pain. These agents are now in common clinical use for patients with bone metastases.

The clinical data reviewed herein indicate that the addition of the oral bisphosphonate clodronate (1,600 mg/d) for 2 years to standard adjuvant therapy for patients with primary operable breast cancer probably reduces the occurrence of metastatic relapse in bone during the first 5 years after primary diagnosis. This reduction was most pronounced during the 2-year treatment period but persisted throughout the 5-year study period. Although one adjuvant study, a small open study, indicated a negative effect on relapse and survival, the data from the large, double-blind randomized trial summarized herein indicate that it is unlikely that this is real and that the negative result probable relates to an imbalance in the randomization process in this study.

In all of these trials, oral clodronate was generally well tolerated. This safety profile is supported by >260,000 patient-years of marketing experience in 26 countries of clodronate used for treatment of hypercalcemia and bone lysis.

Three randomized, double-blind trials are now planned or under way evaluating the use of adjuvant bisphosphonates. The National Surgical Adjuvant Breast and Bowel Project B34 trial is evaluating oral clodronate (1,500 mg/d) versus placebo for 3 years. Accrual of 3,323 patients is now complete. The AZURE trial is comparing i.v. zoledronate versus control, and accrual of 3,360 patients is also complete. Finally, the S0307 Intergroup/National Surgical Adjuvant Breast and Bowel Project trial plans to accrue 6,000 patients randomized to oral ibandronate versus i.v. zoledronate versus oral clodronate.

## Conclusions

The results from the only large, randomized, double-blind, placebo-controlled trial of an adjuvant bisphosphonate

indicate that the addition of oral clodronate (1,600 mg/d) for 2 years to standard adjuvant breast cancer therapy can significantly reduce the occurrence of bone metastases during a 5-year period. This benefit, together with the low toxicity and substantial safety of clodronate, supports its use as additional adjuvant therapy for patients with primary breast cancer, particularly those at high risk of metastatic relapse. The results from further similarly designed trials are needed to confirm these observations and investigate the optimal duration of therapy, the efficacy in stage I disease, and the relative potential of other bisphosphonates, particularly the more potent aminobisphosphonates, such as ibandronate and zoledronate.

## Open Discussion

**Dr. Bruland:** How do you think bone marrow aspiration with either immunomagnetic tumor cell isolation or cyto-keratin staining will influence or confound the stage distribution versus the tumor biology?

**Dr. Powles:** We did a trial ~20 years ago where we did bone marrow aspirates on a large number of patients. About 50% of the patients had micrometastases in the bone marrow. In the 15-year follow-up study, 60% of the patients who had positive bone marrow relapsed and 40% hadn't relapsed. In those who didn't have a positive marrow, it was the other way around. So, in fact, it was no better than axillary staging.

**Dr. Bruland:** Both the publication of the German group and also a paper from our institution show a strong negative prognostic effect in stage I breast cancer patients of cyto-keratin positivity.

**Dr. Powles:** That will happen, but you would think that 100% would relapse. However, you find that 20% of the population have cells in their bone marrow and only 60% of them 15 years later with no treatment have relapsed.

**Dr. Lipton:** What do you think is going on here? Is the drug killing tumor cells or is the drug covering the surface of bone? What is that implying for intravenous zoledronic acid versus an oral low-dose daily drug?

**Dr. Powles:** I assume that we are blocking the osteoclasts and that interaction is critical for the development of bone metastases.

**Dr. Lipton:** Will high doses of zoledronic acid once a month accomplish the same thing that a low dose of a bisphosphonate would?

**Dr. Coleman:** In the AZURE study, we're giving large doses of bisphosphonates to women who may never get recurrence. If we don't see an effect with that amount of bisphosphonate, then we can assume that there is something special about clodronate.

**Dr. Rogers:** Certainly, *in vitro* clodronate has very little effect on tumor cells in terms of apoptosis and proliferation and doesn't have the same sorts of effects that the nitrogen bisphosphonates have, for example, *in vitro*.

**Dr. Powles:** I will be very surprised if the aminobisphosphonates don't work as well as clodronate.

**Dr. Guise:** It's hard to say without doing a comparison. I don't know if the levels you get from a daily oral dose of bisphosphonate are levels that would be clinically significant to kill tumor cells at other sites.

**Dr. Weilbaecher:** Isn't there a method of obtaining macrophages in mice by giving them clodronate to accelerate the macrophages?

**Dr. Rogers:** You can eliminate macrophages effectively using liposomal clodronate. It's a cytotoxic agent through the formation of this ATP metabolite.

**Dr. Coleman:** Assuming that clodronate is working in your study as a resorption inhibitor, have you looked at patients who have very rapid bone resorption by virtue of chemotherapy-induced menopause or who are naturally in those early postmenopausal years? Are these the women with the fast bone resorption that you think might be driving the metastatic process?

**Dr. Powles:** No, but that's an excellent idea.

**Dr. Coleman:** One of the reasons we've pushed the dose of bisphosphonates so high is that we want to have the drug there for at least 10 years.

**Dr. Powles:** The issue with the bisphosphonates is that they seem to be independent of other treatments. Although you've only got a 20% or 15% residual relapse rate after adjuvant chemo and/or endocrine therapy, it looks like it will be effective on that 15%. The other issue is women's health and bone loss caused by breast cancer treatment.

**Dr. Smith:** It may be that the baseline metabolic state of bone predicts risk of developing bone metastases. Did your trial control for osteoporosis at baseline? In other words, did you exclude patients with osteoporosis?

**Dr. Powles:** No, we did not.

**Dr. Smith:** Do you worry that the concurrent changes in patterns of care such that women are being screened for osteopenia and osteoporosis and treated will diminish the treatment effect? You'll be eliminating the patients who were most likely to have benefited in these trials?

**Dr. Weilbaecher:** It's not standard of care right now, but soon it may be. We're not getting baseline bone densities, even though arguably maybe we should.

**Dr. Coleman:** We are excluding women who are already taking a bisphosphonate from our study. Clearly, some will develop osteoporosis during the study and presumably most will be in the control arm. They obviously get whatever is the appropriate registered treatment for bone loss in their country. The hope is that there is something different between a background osteoporosis dose of bisphosphonate and a cancer therapeutic dose. Otherwise, we might as well just use clodronate.

**Dr. Smith:** So the women in the AZURE trial, for example, didn't have baseline DEXA scans.

**Dr. Coleman:** No, they don't.

**Dr. Berenson:** We have preclinical data showing that COX-2, in combination with bisphosphonates, can really wipe out the myeloma. Has anybody thought about using bisphosphonates with COX-2 in breast cancer or prostate cancer?

**Dr. Weilbaecher:** There are some prevention data indicating that there might be a role for COX inhibition for prevention of breast cancer, but I would offer an alternative view on this. We found in our genetically targeted  $\beta_3$  integrin knockout mice, which lack functional platelet coagulation so the platelets cannot aggregate, that we can prevent bone metastasis in those mice. If we took wild-type mice and gave them an inhibitor of  $\alpha_{2B}\beta_3$ -induced platelet aggregation, we could block bone metastasis. I offer an alternative hypothesis that if you went to a strict COX-2

inhibitor, you might not see as strong an effect on breast cancer prevention and metastasis because nonselective COX1/2 inhibitors like aspirin or indomethacin decrease platelet aggregation in addition to effects on cellular proliferation.

**Dr. Berenson:** There are data to suggest that celecoxib's effects were independent of COX-2 in other models. Whether that's true in myeloma, we don't know. Regarding osteoporosis, in the ovariectomized models, you're clearly showing more of a tendency to develop worse bone metastasis. Are those patients going to be more likely to be prevented from having bone metastasis than those that come in with normal bone density? Has anybody approached that in breast cancer?

**Dr. Coleman:** Presumably because of tumor-derived growth factors from the primary, there has been a systemic effect on bone. Therefore, you did have a very high incidence of osteoporosis.

**Dr. Berenson:** How does that play out with the bone density of women at risk of breast cancer?

**Dr. Guise:** There are other preclinical data showing that platelets are important for bone metastases and that may involve lysophosphatidic acid receptors, which act on the cancer cells to stimulate production of IL-8. There is a long

connection of thromboembolic events associated with metastasis, which is an important connection.

**Dr. Body:** Coming back to the *in vitro* work, it is true that clodronate does not inhibit cancer cell growth much. Quite surprisingly, we found that, when breast cancer cells are cultured in a steroid-free medium, which could be viewed as an *in vitro* model for aromatase inhibitor action, there was a marked stimulation of their growth. Moreover, there was an apparent link with the estrogen receptor. Maybe, this is just a lab observation without any clinical meaning but maybe it is relevant when using aromatase inhibitors in conjunction with clodronate.

**Dr. Weilbaecher:** Did you say that the aromatase inhibitors increase estrogen receptor levels?

**Dr. Body:** No, we published, in British Journal of Cancer that, in a steroid-free medium, clodronate increased the growth of breast cancer cells and that these *in vitro* conditions could be viewed as a model for the activity of aromatase inhibitors, which block estrogen production. Moreover, we have several arguments to claim that this action of clodronate on the growth of breast cancer cells occurred indirectly through the estrogen receptor.

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