# Practical Considerations in Bone Metastases in Breast Cancer

*a report by*
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Progress in the management of breast cancer through the use of endocrine therapy and chemotherapy has proven beneficial for patients with relapsed metastatic disease, and the adjuvant use of such therapy has resulted in reduced relapse rates and improved survival for patients with operable breast cancer. This, combined with recent evidence of the benefits of aromatase inhibitor therapy in both early and advanced breast cancer, will continue to have a substantial impact on the evolving management of this disease. The mechanism of actions of both chemotherapy and endocrine therapy is based on the direct effect of the drugs on the proliferation and survival of cancer cells.

A completely different additional approach is to use drugs with an effect on a normal host tissue, which could control the development of the cancer. For example, bone, a common site for the development of metastases, is a good potential target because the development of bone metastases depends on the ability of cancer cells to produce substances that activate osteoclasts causing osteolysis, thereby facilitating the growth of the cancer in the bone. The activated osteoclasts in turn release growth factors that are able to promote cancer cell proliferation in the bone marrow, further encouraging metastatic development in the bones and possibly elsewhere in the body.[1] Use of agents that inhibit osteoclasts could prevent the development of bone metastases and this benefit would be added to the proven benefits of anticancer agents such as endocrine therapy and chemotherapy.[2]

## Management of Patients with Bone Metastases

The use of bisphosphonates to treat patients with bone metastases was established over 15 years ago with clear evidence of reduced bone events, such as the incidence of fractures, and hypercalcaemia and the requirement for radiotherapy. Controlled studies have confirmed that bisphosphonate therapy such as clodronate has a significant success rate in treating tumour-induced hypercalcaemia and in ameliorating bone pain.[3–6] Thus, bisphosphonates are currently considered the standard of care for patients with breast cancer who have been diagnosed with bone metastases or bone destruction.[7,8]

The safety profile for the non-aminobisphosphonate clodronate is excellent, with no identified significant toxicity based on data from over 260,000 patient years of experience in 69 countries where this drug is licensed for treatment of hypercalcaemia and osteolysis. Clodronate has been established as well tolerated overall after long-term use in primary breast cancer patients, with no cases of oesophageal perforation, in comparison with the increased frequency of oesophagitis that has been reported for oral pamidronate and alendronate.[9] Furthermore, no cases of osteonecrosis of the jaw have been reported with the use of clodronate, in marked contrast to the growing numbers of cases reported with intravenous pamidronate and zoledronate.[10–12] In contrast to the aromatase inhibitors, which have the safety concern of documented loss of bone mineral density in patients with breast cancer,[13] clodronate has been shown to prevent bone loss and improve bone mineral density in breast cancer patients.[14–16]

## Adjuvant Therapy to Prevent Bone Metastases

The therapeutic benefit for patients with metastatic disease, together with experimental data showing that bisphosphonates block osteolysis by inhibiting osteoclast activity,[17] encouraged the start of a large, placebo-controlled, multicentre adjuvant trial of the oral bisphosphonate clodronate for prevention of bone metastases in patients with primary operable breast cancer in 1989.[18] This was followed by two other smaller trials in 1990.[19,20]

In the Powles trial, 1,069 women with primary operable breast cancer were randomised to receive either oral clodronate 1,600mg daily or placebo for two years as an addition to standard adjuvant therapy.[18,21] The primary outcome was the time to development of bone metastases after five years of follow-up and the secondary outcome was overall survival. Over this five-year follow-up, in the entire study population (stage 1–3 patients) clodronate significantly reduced the risk of bone metastases by

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*Figure 1: Risk of Bone Metastases During the Five-year Study Period in Stage II/III Patients[21]*

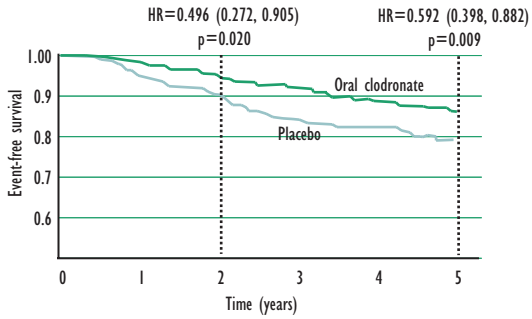
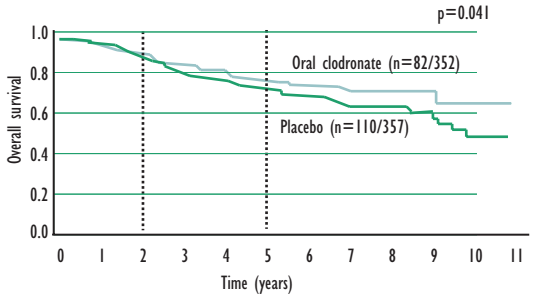



*Figure 2: Risk of Mortality During the Five-year Study Period in Stage II/III Patients[21]*




31% (51 versus 73 patients, p=0.043 ). For stage 2/3 patients, in whom most events occurred, the reduction was also significant, with the risk of bone metastases development reduced by 41% (39 versus 64 patients, p=0.009) in patients treated with clodronate compared with the risk in those treated with placebo (see *Figure 1*). In addition, in the overall population (stage 1–3), patients randomised to clodronate had a significant 23% reduction in mortality (p=0.048) and there was a 26% reduction in mortality reported for stage II/III patients (p=0.041), as shown in *Figure 2*. Furthermore, in a subset of patients where bone mineral density was evaluated, a prevention of the loss of bone mineral density was reported during the two-year medication period, indicating an anti-osteolytic effect of the drug.[16]

To address the possibility that the use of bisphosphonates as adjuvant therapy could have compromised treatment after relapse, the incidence of skeletal-related events (fractures, hypercalcaemia, bone radiation or surgery) in the patients who developed bone metastases during this trial was also investigated and reported. The choice of treatments for patients who relapsed in bone was at the discretion of the treating oncologist; however, it was not necessary for the code to be unblinded and bisphosphonate therapy could be used as clinically indicated. Over the five-year study period there were 29 (5.5%) bone events in the 51 clodronate patients who relapsed compared with 53 (9.8%) bone events in the 73 placebo patients who relapsed (p=0.01).[22] Notably, the 51 clodronate patients survived longer than the 73 placebo patients, indicating that there may be a spillover benefit for patients who had previously received clodronate. Although not a planned analysis, these results suggest that early use of bisphosphonates may be better than waiting until the bone metastases have occurred.

The findings from the Powles study are similar to those reported from a small randomised open-label study by Diel et al., involving 302 women with newly diagnosed primary breast cancer, in whom disseminated isolated tumour cells had been detected in the bone marrow.[19,23,24] The patients were treated by standard breast and axillary surgery, plus radiotherapy if indicated, plus appropriate adjuvant endocrine therapy, and/or chemotherapy if indicated. They were also randomised to receive either two years of oral clodronate 1,600mg/day or not, and the randomisation was well balanced for prognostic factors. Over the three-year follow-up period, 8% of the clodronate patients developed bone metastases compared with 17% of controls (p=0.003), and the patients treated with clodronate achieved significantly longer bone metastasis-free survival (p=0.001) compared with those receiving standard treatment. Furthermore, there was a significant reduction in the incidence of visceral metastases (p=0.001) and improved overall survival (p=0.001) in the clodronate patients compared with the control group.[24]

The third trial evaluating adjuvant clodronate is a randomised non-blinded study that randomised 299 women with primary operable breast cancer to 1,600mg of oral clodronate versus no bisphosphonate for three years.[20] The latest report for this trial[25] showed no reduction in the incidence of skeletal metastases, although there was a reduction in the incidence of bone as the site of the first metastases (p=0.03) in the clodronate arm. The authors also reported a negative effect of oral clodronate on visceral metastasis-free and overall survival, particularly in oestrogen receptor (OR)-negative breast cancer patients. However, there was a significant imbalance in the distribution of OR and progesterone receptor (PR) status between the two arms, with significantly more OR- and PR-negative patients in the clodronate arm (25 randomised to clodronate versus 10 to control, p=0.03). Furthermore, these OR-negative patients were treated with anti-oestrogen therapy instead of chemotherapy, contrary to current standard practice. The reported increased mortality was no longer significant when this imbalance in OR and PR was corrected.

Overall, the three trials have a measure of agreement in that the large, double-blind placebo-controlled Powles trial clearly shows benefit for clodronate with a significant reduction in the incidence of bone metastases and improved survival for patients on

clodronate, supported by the Diel trial with almost identical results. The unbalanced Saarto trial shows comparable results with these two trials when corrected for the imbalance in randomisation for oestrogen and progesterone receptor.

Confirming the excellent safety profile for oral clodronate, in all of these trials oral clodronate was very well tolerated with no significant side effects apart from mild to moderate diarrhoea in approximately 10% to 15% of patients.[9] This side effect was manageable, did not require discontinuation of therapy and thus was not a clinical problem.

## Implications for Current Practice

Although questions such as the optional duration of therapy and efficacy in stage 1 disease remain to be answered, the overall data from the recent clinical trials demonstrate that oral clodronate, when added to standard adjuvant therapy, reduced the risk for bone metastases and improved overall survival of patients with primary breast cancer. This evidence, together with the outstanding safety for the drug and the prevention of loss of bone mineral density, strongly support the use of this drug for adjuvant therapy for patients with operable breast cancer, particularly for patients with a relatively bad prognosis, such as those with stage 2/3 disease. Further trials are in progress that will evaluate the use of bisphosphonates as adjuvant therapy, such as the National Surgical Adjuvant Breast and Bowel Project (NSABP) B34 trial. This is a placebo-controlled trial in which oral clodronate 1,600mg/day is to be administered for three years to patients with operable breast cancer, predominantly stage 1 disease. This will provide clarification of benefit in stage 1 disease, which is known to have a lower risk of recurrence and death than stage 2/3. Although the NSABP trial completed accrual in 2004 with 3,323 patients enrolled, results from this trial are not expected to be available until 2009. In addition, other trials are being initiated using nitrogen-containing bisphosphonates, one of which has clodronate as the control arm, although these results will not be available for many years.

## Conclusions

In the author's opinion, the evidence reviewed in this article, particularly the survival benefit reported in a large, randomised trial, at this time strongly supports the expanded licensing of this drug for use as adjuvant therapy to prevent bone metastases in patients with stage 2/3 primary operable breast cancer, and the results of on-going trials to determine its role in stage I patients are eagerly awaited. In addition, the body of literature continues to support the continued use of bisphosphonates in the management of bone metastases and the maintenance of healthy bone tissue in patients with advanced disease. Further, the positive effects of oral clodronate on bone mineral density may make it an even more valuable addition to therapy in light of the growing use of aromatase inhibitors, with the added convenience of an oral administration well-suited to use in otherwise healthy patients. Overall, the evidence regarding the efficacy of bisphosphonate therapy in breast cancer both for the management of patients with bone metastases and in the prevention of bone metastases is solid. Further, clodronate holds a unique position in terms of established safety and convenience, making this bisphosphonate an important component of the management of patients with breast cancer because of its highly favourable benefit–risk ratio. ■

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