Oral Clodronate and Reduction in Loss of Bone Mineral Density in Women With Operable Primary Breast Cancer

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Background: Women with primary breast cancer who receive systemic therapy may experience ovarian failure or early menopause, leading to a loss of bone mineral density (BMD). Loss of BMD may be reduced by use of bisphosphonates, compounds that inhibit the action of osteoclasts (cells that absorb or remove bone tissue). We have conducted a double-blind, randomized, two-center trial to evaluate BMD in women with primary breast cancer who were given the bisphosphonate clodronate (1600 mg/day orally) or placebo for 2 years. Methods: From August 31, 1990, through March 31, 1996, more than 300 eligible patients had been accrued, randomly assigned to study treatment, given the appropriate primary surgical care and systemic (chemotherapy and/or tamoxifen) therapy, and had completed follow-up for at least 1 year. BMD in the lumbar spine and in the hip, including the trochanteric area, was measured by use of dual-energy x-ray absorptiometry at the beginning of treatment and after 1 and 2 years of treatment. Changes in BMD were calculated as percent changes from the initial readings. Treatment effects for clodronate versus placebo (i.e., mean percent changes in BMD with clodronate minus mean percent changes in BMD with placebo) at 1 and 2 years for individual sites were calculated. Results: After 1 year, the treatment effects for clodronate versus placebo in the lumbar spine, the total hip, and the trochanter, respectively, were as follows: +2.38% (95% confidence interval [CI] = 1.36–3.41), +0.74% (95% CI = −0.13–1.60), and +1.29% (95% CI = 0.24–2.34). After 2 years, the corresponding treatment effects were +1.72% (95% CI = 0.12–3.34), +1.85% (95% CI = 0.51–3.20), and +2.30% (95% CI = 0.66–3.94), respectively. Conclusions: Oral clodronate appears to reduce the loss of BMD in patients who receive treatment for primary breast cancer. [J Natl Cancer Inst 1998;90:704–8]

Reduced bone density, with a subsequent risk of osteoporotic bone fractures, is likely to become an increasingly important clinical problem in the very large numbers of women treated for primary breast cancer. Premenopausal women who receive adjuvant chemotherapy may be at special risk of increased bone loss because of early menopause (1) or as a result of adjuvant ovarian ablation (2). Tamoxifen, although preventing bone loss in postmenopausal women by an agonistic estrogenic effect (3), appears to cause bone loss in premenopausal women, presumably by an antagonistic antiestrogenic effect on bone (4).

Use of estrogen replacement therapy has generally been considered unsafe in women who have had breast cancer (5), although the risk of activation of occult malignant disease has not been proven (6,7). There are clinical trials under way to evaluate the risks of using estrogen replacement therapy in patients with cancer and, in the meantime, its use to prevent bone loss should be restricted to these trials.

Bisphosphonates, such as clodronate and pamidronate, are agents that inhibit osteoclasts in bone and reduce bone turnover. Bisphosphonates are widely used in breast cancer to treat hypercalcemia (8). In women with metastatic breast cancer, clodronate has been shown to reduce the osteolytic complications of metastases, such as hypercalcemia, bone pain, and vertebral fracture (9). Furthermore, in patients with non-osseous metastases from breast cancer, clodronate will reduce the risk of developing bone metastases (10). In healthy women, bisphosphonates have been shown to be effective in reducing bone loss (11–13).

These observations encouraged us to undertake a double-blind clinical trial involving more than 1000 women treated for primary breast cancer. The clinical trial was designed to evaluate the effects of clodronate on the risk of developing bone metastases and, within this trial, to evaluate nonmetastatic changes in bone mineral density (BMD) in at least 300 patients. Herein, we report the sequential measurement of BMD in these patients.

Patients and Methods

The primary objective of the adjuvant clodronate trial is to evaluate the effect of clodronate on the incidence of bone metastases in patients with primary breast cancer. This multicenter, double-blind trial has accrued more than 1000 patients with histologically or cytologically confirmed primary operable breast cancer. These patients have been randomly assigned to receive orally four capsules per day of either 400 mg clodronate (Bonefos®; Leiras OY, Helsinki, Finland) (i.e., 1600 mg clodronate/day) or an identical placebo, to be taken over a 2-year period at least half an hour before or after eating, with recorded dose modifications and compliance.

Participants in the main trial were randomly assigned to receive clodronate or placebo within 6 weeks (later amended to 12 weeks) of primary diagnosis (histologic or cytologic). At the same time, most patients started systemic chemotherapy and/or endocrine therapy. Table 1 lists the characteristics of the 311 patients reported in this study who had repeat bone density measurements and indicates the types of systemic therapy they received. The chemotherapy used at the Royal Marsden Hospital (Sutton, Surrey, U.K.) was mainly a mitoxantrone and methotrexate (emtithomycin C) combination (clodronate group, 64 patients; placebo group, 64 patients; total = 65% of the patients treated). At the Tom Baker Cancer Centre, University of Calgary (Alberta, Canada), the combinations were either cyclophosphamide, methotrexate, and 5-fluorouracil (clodronate group, 10 patients; placebo group, 14 patients; total = 21% of the patients treated) or an anthracycline combination, such as doxorubicin and cyclophosphamide or epirubicin, cyclophosphamide, and 5-fluorouracil (clodronate group, 12 patients; placebo group, 13 patients; total = 22% of the patients treated at Calgary). The use and type of chemotherapy were evenly distributed between the clodronate and the placebo groups. Tamoxifen was given to most participants in the BMD study at the Royal Marsden Hospital (clodronate group, 98 patients; placebo group, 88 patients; total = 95% of patients treated).

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See "Notes" following "References.'"
The menopausal status of the participants was defined according to the date of their last menstrual period (LMP) and was categorized as premenopausal, perimenopausal, and postmenopausal. Patients who had a bilateral oophorectomy were classified as postmenopausal. Patients who had a hysterectomy without bilateral oophorectomy were classified according to their age (<50 years as premenopausal, from 50 to 54 years as perimenopausal, and ≥55 years as postmenopausal).

It was estimated that the BMD study needed 300 patients to detect clinically significant differences in BMD between the clodronate and the placebo groups. Unselected recruitment from the main trial to the BMD study began August 31, 1990, at the Royal Marsden Hospital and April 1, 1992, at Calgary (when dual-energy x-ray absorptiometry [DEXA] became available), and continued until March 31, 1996. Measurement of BMD was approved by the Royal Marsden Hospital and the Tom Baker Cancer Centre research ethics committees and was included in the information and consent mechanism for the main trial. All participants in the main trial were considered potentially eligible for the BMD study, subject to consent and to the limited availability of DEXA within the study period. During the recruitment period, a total of 703 patients were randomly assigned to receive clodronate or placebo in the main trial, and treatment allocation remained blinded throughout the study (clodronate, 350 patients; placebo, 353 patients). Among the 703 patients, 414 gave their consent for participation in the BMD study, and DEXA was available for baseline BMD measurements (clodronate group, 208 patients; placebo group, 206 patients).

At the time of this interim analysis, 328 patients (clodronate group, 167 patients; placebo group, 161 patients) had had follow-up BMD measurements. (DEXA was not always available, or participants did not always agree to repeat measurements.) Clinical records for 17 of the patients (clodronate group, 11 patients; placebo group, six patients) had not been included, leaving a total of 311 patients (clodronate group, 167 patients; placebo group, 161 patients) for inclusion in the analysis (Fig. 1).

All participants had operable breast cancer that was clinically staged as T1–T3 (14), and they had appropriate metastatic staging prior to primary treatment. The staging protocol included a clinical assessment, baseline blood tests (including routine hematology and biochemistry), and a chest x-ray. Other investigations, which included other radiologic examinations, bone scans, and magnetic resonance imaging, were undertaken if clinically indicated, and patients with evidence of metastases were excluded from the main trial and the BMD study. Estrogen receptor status was not available for the participants in this study.

BMD was assessed by DEXA, using an Hologic QDR 1000 densitometer (Vertec Scientific Ltd, Reading, U.K.), at the start of treatment and at 1 year and 2 years later. BMD measurements of the lumbar spine included the first through fourth lumbar vertebrae (L1–L4), with the exclusion of vertebrae affected by fracture or marked osteoarthritis on both the initial and the repeat scans. Measurements at the hip involved the total hip, including the trochanteric area. All bone density scans were analyzed at the Bone Metabolism Unit of the University of Sheffield by reviewers who were blinded to the randomly allocated treatment assignments. All clinical, prescribing, and investigative data have been monitored blindly by Leiras OY, according to U.S. Food and Drug Administration requirements. The data have been kept under annual review by an external data monitoring committee.

In a quality-control exercise, all of the BMD scans were reviewed, blinded to the randomly allocated treatment assignments. When the areas covered by the baseline scans and the follow-up scans were not within the limits of repeatability, those scans were identified for a later review and were excluded from the current analysis. In this way, data from 26 patients were excluded from the spinal analysis, and data from 29 patients were excluded from the hip analysis.

Toxic effects and adverse events related to drug therapy including chemotherapy, endocrine therapy, and clodronate/placebo treatment were recorded at outpatient clinics by use of standard data forms that were completed by the clinicians.

### Statistical Analysis

Analyses were based on the percent change in BMD from baseline in the spine and the hip (and the trochanter) at 1 and 2 years on an intent-to-treat basis by use of simple paired t tests.

The baseline BMD at each of the sites was checked for normality by use of the Shapiro–Wilk test. Bone densities were found to be normally distributed. After adjustment for outlier values, the per-
cent changes were also shown to follow a normal distribution (Shapiro–Wilk test), and parametric statistics were used in the analysis. Mean percent changes were calculated for various subgroups, and differences were assessed by means of the paired t test and by analysis of variance. All reported P values are two-sided. The treatment effect was defined as the difference in the mean percent change between the clodronate and the placebo groups.

Results

Of the 1079 patients (clodronate group, 538 patients; placebo group, 541 patients) entered in the bone metastasis trial, a total of 311 (clodronate group, 156 patients; placebo group, 155 patients) had repeat bone density measurements carried out within the first 2 years of follow-up. The median age, height, weight, and menopausal status were well matched for both treatment groups and for both recruiting centers (Table 1). The type of primary adjuvant or neoadjuvant systemic treatment was well matched between the clodronate and the placebo treatment groups, but substantial differences existed between the two recruiting centers, reflecting differences in breast cancer treatment protocols at the two hospitals.

For all patients at 1 year, the placebo group had a loss of 2.2% in BMD in the lumbar spine, whereas the clodronate group had a small gain of 0.18%, giving a treatment effect for clodronate of +2.38% (95% confidence interval [CI] 1.36–3.41; P < .001) (Table 2). At 1 year, in the trochanter, patients who received placebo had a mean loss of 0.74% in BMD, whereas patients who received clodronate had a mean gain of 0.55%, giving a treatment effect of +1.29% (95% CI = 0.24–2.34; P = .02) (Table 2). After 2 years, the treatment effect for clodronate in spinal BMD was +1.72% (95% CI = 0.12–3.34; P = .04); in hip BMD, it was +1.13% (95% CI = 0.51–3.20; P = .01); in trochanteric BMD, it was +2.30% (95% CI = 0.66–3.94; P = .007) (Table 2). These results indicated an overall treatment effect for clodronate in preventing loss of BMD in patients after primary treatment for breast cancer (Table 2).

Analysis of changes in BMD for all subgroups of patients, either by center, menopausal status, or adjuvant treatment with tamoxifen or placebo, showed a similar beneficial treatment effect for clodronate (Table 3).

Premenopausal and perimenopausal women on placebo were at increased risk of loss of BMD, especially in the first year, and clodronate appeared to be effective in minimizing this loss (Table 3). Although most patients were receiving adjuvant chemotherapy and tamoxifen, the total number of patients was small. Therefore, it is not possible to undertake treatment subgroup analyses in premenopausal and postmenopausal women.

Apart from an increased incidence of diarrhea, toxicity related to clodronate medication was very low compared with the toxicity for other treatments, as evi-

<table>
<thead>
<tr>
<th>Site</th>
<th>Change in BMD</th>
<th>Treatment effect for clodronate*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Clodronate</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>Mean 95% CI†</td>
<td>P‡</td>
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<tr>
<td>Lumbar spine</td>
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<tr>
<td>1 y</td>
<td>0.18% −2.20%</td>
<td>2.38% 1.36–3.41 &lt; .001</td>
</tr>
<tr>
<td>2 y</td>
<td>−0.16% −1.88%</td>
<td>1.72% 0.12–3.34 .04</td>
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<tr>
<td>Total hip</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 y</td>
<td>0.40% −0.34%</td>
<td>0.74% −0.13–1.60 .09</td>
</tr>
<tr>
<td>2 y</td>
<td>1.13% −0.72%</td>
<td>1.85% 0.51–3.20 .008</td>
</tr>
<tr>
<td>Trochanter</td>
<td></td>
<td></td>
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<tr>
<td>1 y</td>
<td>0.55% −0.74%</td>
<td>1.29% 0.24–2.34 .02</td>
</tr>
<tr>
<td>2 y</td>
<td>0.67% −1.63%</td>
<td>2.30% 0.66–3.94 .007</td>
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*See “Patients and Methods” section for details on calculating treatment effect.
†Two-sided.
‡CI = confidence interval.
Premature termination of medication between the two treatment groups was not significant in the incidence of premature termination of medication between the two treatment groups. There was no statistically significant difference in the incidence of premature termination of medication between the two treatment groups.

In conclusion, we have confirmed in this trial that the use of clodronate is safe and effective in preventing bone loss in patients who have been treated for primary operable breast cancer. The extent of this clinical problem of bone loss has not yet been fully evaluated. However, it is likely that there will be an increase in the risk of osteoporosis with future improvements in systemic therapy for breast cancer, together with a likely increase in the loss of BMD due to wider use of current cancer treatments. The cost benefits of widespread use of bisphosphonates as an intervention for patients receiving systemic treatment for primary breast cancer will need to be evaluated.

Discussion

In healthy postmenopausal women, both clodronate and another bisphosphonate (i.e., alendronate) have been shown to reduce the loss of BMD (11,12). With alendronate, this reduction in loss of BMD was associated with a 50% reduction in the risk of vertebral and nonvertebral osteoporotic fractures (13). Whether this treatment would be similarly effective in premenopausal and postmenopausal women who have had breast cancer and were receiving adjuvant chemotherapy and/or tamoxifen was unknown. In postmenopausal women receiving tamoxifen, clodronate has been reported to cause an increase in BMD (15). Therefore, we established a study to measure BMD by DEXA in an unselected subgroup of patients from a large trial involving women with primary operable breast cancer.

The main results from this trial indicate that patients treated for primary operable breast cancer have evidence of bone loss, as estimated by DEXA measurements of BMD. Premenopausal patients were at increased risk of bone loss, presumably because most of these women were receiving adjuvant chemotherapy, with the associated development of ovarian failure and early menopause. Furthermore, many patients received tamoxifen, which has an antiestrogenic effect on bone in premenopausal women, causing a loss of BMD (4). In premenopausal patients in this study, clodronate significantly reduced the loss of BMD at 1 year, although this effect did not persist at 2 years.

Our results confirm similar findings from another small study (16) that demonstrated that clodronate will reduce the loss of BMD caused by ovarian failure following adjuvant chemotherapy in premenopausal women with primary breast cancer. A similar result has been reported for another bisphosphonate, risedronate (17).

In contrast, postmenopausal patients on placebo in our study had relatively little bone loss, probably because most of these women were receiving adjuvant tamoxifen, which has been shown to reduce bone loss in postmenopausal women (3). In postmenopausal women on clodronate, there was a statistically significant increase in spinal BMD at 1 and 2 years.

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References


Notes

Editor’s note: E. McCloskey is currently conducting research sponsored by Leiras OY, the manufacturer of Bonefos®, which is the form of clodronate used in this study. K. Rosenqvist is a clinical research associate manager in the Clinical Research Department of Leiras OY. J. Kanis is currently conducting research on bisphosphonates that is sponsored in part by pharmaceutical companies.

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