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Effect of oral clodronate on bone mass, bone turnover and subsequent metastases in women with primary breast cancer

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ABSTRACT

Breast cancer treatments have been associated with accelerated bone loss and increased osteoporosis risk. In a subgroup analysis of a randomised, double-blind, placebo-controlled study, we compared the changes in spine and total hip bone mineral density (BMD) and biochemical markers of bone turnover in women with primary breast cancer who had received standard therapy plus either oral clodronate 1600 mg/d ($n = 419$) or placebo ($n = 432$) for 2 years. After 2 years, spine BMD was 1.92% higher in patients who received clodronate instead of placebo ($P < 0.0001$) and total hip BMD was 1.29% higher ($P = 0.002$ versus placebo). Patients who received clodronate had a median 26% reduction in levels of serum N-terminal pro-peptide of type I procollagen (PINP) – a marker of bone turnover – after 2 years of therapy. This compares with a median 5% increase in patients who received placebo ($P < 0.0001$). Effects on BMD, but not biochemical markers, persisted for up to 3 years post-treatment. Early changes in PINP were associated with changes in BMD and the likelihood of developing bone metastases. This study shows the use of oral clodronate during primary breast cancer treatment is associated with reduced bone turnover and protection against bone metastases.

1. Introduction

The propensity of breast cancer to spread to bone, resulting in significant clinical morbidity, is well recognised and has led to the established use of bisphosphonates to ameliorate skeletal complications in women with metastatic disease.[1] Additional evidence suggests that earlier use of bisphosphonates (i.e. from around the time of initial breast cancer diagnosis) can decrease the incidence of bone metastases and may improve survival.[2–4] There is growing recognition that breast cancer survivors have increased risk of developing osteoporosis, a skeletal disorder associated with risk of bone fractures.[5,6]

Osteoporosis results from the interaction between breast cancer treatments, endocrine function and normal bone cells. For example, a prospective study of normal healthy subjects and newly diagnosed breast cancer patients in whom baseline and incident vertebral fractures were detected by standardised lateral spine radiographs,[5] showed that whilst the prevalence of vertebral fractures was similar in both groups at baseline, the incidence of vertebral fractures over 3 years was markedly increased in breast cancer patients (5.4%)

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compared with controls (1.5%; age-matched relative risk = 4.7; $P < 0.0001$).[5] A similar but less marked increase in the incidence of largely non-vertebral fractures was also observed in the Women's Health Initiative Observational Study (WHI-OS), which compared over 5000 breast cancer survivors with a reference population of over 80,000 women and found that breast cancer survivors had a 28% increased risk of non-hip fracture after adjustment for age, years since menopause, weight and ethnicity.[6]

Bisphosphonates are established as first line therapy in the treatment of post-menopausal and secondary osteoporosis. This class of drugs significantly improves spine bone mineral density (BMD) and decreases fracture risk at both vertebral and non-vertebral sites.[7–12] More recently, studies have demonstrated that using oral clodronate upon diagnosis of breast cancer can significantly decrease the risk of developing skeletal metastases.[2–4] The ability of oral clodronate to significantly reduce the occurrence of bone metastases during a 2-year treatment period and significantly reduce mortality during approximately 5-year follow-up period has been demonstrated in a large, double-blind, multicentre trial.[3,4] Results from a sub-analysis of this large trial demonstrated that oral clodronate significantly reduced the loss of BMD during the 2 years of treatment.[13] The objective of the current analysis was to evaluate the effect of oral clodronate treatment on spine and hip BMD during the 2-year treatment period and during 3 years of post-treatment follow-up, and to examine the relationship between early changes in BMD or bone turnover markers and incident tumour metastases, in a subgroup of that larger population.

2. Patients and methods

2.1. Study design

The overall trial design and participants have been previously described (ISRCT83688026).[3,4] Briefly, this double-blind, multicentre, randomised, placebo-controlled study evaluated the long-term effect of adjuvant oral clodronate (BONEFOS®, Bayer Schering Pharma Oy, Finland) 1600 mg/d for 2 years on the incidence of bone and other metastases and on long-term survival in women with primary operable breast cancer. Of the 1069 patients enroled in the main study, 851 (79.6%) had measurements of BMD and/or biochemical markers and were included in the present analysis. In accordance with the Declaration of Helsinki, all patients provided informed consent prior to participation.

If relapse or bone metastases occurred, study medication (oral clodronate or placebo) was discontinued, and patients received appropriate local or systemic therapies according to the treatment protocols of the individual study centre. Analyses of treatment effects on BMD and bone turnover were on intent-to-treat basis; patients were not excluded if study medication was discontinued.

2.2. BMD measurements

In a subset of 516 patients, BMD was measured by dual energy X-ray absorption at baseline and annually for up to 5 years thereafter. BMD measurements were made at the lumbar spine (L1–L4) and the hip (total and sub-regions including the femoral neck, trochanter, intertrochanter and Wards areas) using Hologic QDR1000 densitometers (Hologic Inc., Bedford, MA) at each study centre. The BMD data were collected centrally at the study centre in Sheffield, using appropriate quality control procedures and identifying any scans that required review and/or re-analysis under blinded conditions. Changes in spinal BMD were only examined in vertebrae deemed not to have developed incident deformities, progressive osteoarthritis or metastases during follow-up.

2.3. Biochemical marker measurements

Serum and urine samples were collected from 566 women (227 of whom were also included in the BMD subgroup analysis) for assessments of bone turnover at baseline and at annual intervals up to 3 years. Assessments included assays for serum bone-specific alkaline phosphatase (BSAP) and the amino-terminal pro-peptide of type I procollagen (PINP), as markers of increased bone formation. Serum levels of the carboxyterminal telopeptide of type I collagen (ICTP) and fasting urine levels of the amino-terminal telopeptide of type I collagen (NTx) were measured, as markers of bone resorption. Concentrations of serum PINP and ICTP were determined using radioimmunoassay kits (Orion Diagnostica Oy, Espoo, Finland). The intra- and inter-assay coefficients of variation (CV) for these assays ranged from 2–9%. BSAP isoenzyme was determined using a kit from Boehringer Mannheim (Mannheim, Germany), in which the isoenzyme was precipitated by lectin and the activity was calculated from total and residual alkaline phosphatase activity. Intra- and inter-assay CVs were 4% and 5%, respectively. Finally, fasting excretion of cross-linked NTx in urine was analysed using Osteomark® enzyme-linked immunosorbent assay (Ostex International, Seattle, Washington) and related to creatinine excretion.

For the purpose of this analysis, serum PINP was chosen as the primary biochemical variable due to its robustness, reflected in lack of significant diurnal variation and good durability during long-term storage, thawing and refreezing.[14] It was used to examine correlations between biochemical responses and changes in BMD and the development of bone metastases. Assuming a CV of 7%, the least significant change at the 95% level for serum PINP was estimated to be 20% (2.8 times the CV).[15] Using this threshold and the percentage changes between baseline and 1 year, women were classified as 'responsive' (>20% decrease in PINP), 'stable' (<20% change in PINP), or 'progressive' (>20% increase in PINP) with respect to bone turnover.

2.4. Statistical analysis

Comparability of treatment groups at baseline and other time points was assessed using a multi-way ANOVA for continuous variables and a chi-squared test for categorical variables. For changes in BMD over time, comparisons were made using General Linear Model (GLM)-repeated measures analysis, with treatment and menopausal status as factors. Analyses for the medication and follow-up periods were conducted separately.

3. Results

Patient demographics and baseline clinical characteristics in terms of age, weight and menopausal status were similar in the treatment groups (Table 1). In the BMD subgroup, clodronate-treated patients had slightly lower hip and spine BMD at baseline than placebo-treated patients, but, these differences were not statistically significant. In the biochemical marker subgroup, median values for all four markers were similar in both groups (Table 1).

3.1. *Effect of clodronate on changes in spine and hip BMD*

During the 2-year treatment period, mean BMD of the lumbar spine was maintained in patients receiving oral clodronate (mean change, 0.06%; 95% confidence interval [CI], –0.72% to 0.73%) but decreased significantly in those receiving placebo (mean change, –1.87%; 95% CI, –2.52% to –1.22%) so that spine BMD was 1.92% higher with clodronate than with placebo (95% CI, 0.99% to 2.86%; $P < 0.0001$; Fig. 1). Similarly, during the same 2-year period, mean total hip BMD was maintained in patients receiving oral clodronate (mean change, 0.52%; 95% CI, –0.07% to 1.11%) but decreased significantly in those receiving placebo (mean change, –0.77%; 95% CI, –1.24% to –0.30%). Total hip BMD was 1.29% higher with clodronate (95% CI, 0.50% to 2.28%; $P = 0.002$; Fig. 2). Similar effects were observed at all the hip sub-regions including the femoral neck (Table 2). In the placebo group, the greatest loss of spine BMD occurred during the first year with a more linear pattern of loss at the hip (Figs. 1 and 2).

The ability of oral clodronate to prevent bone loss during the 2 years of treatment was observed in both premenopausal and post-menopausal women, with no significant interaction between menopausal status and the ability of clodronate to prevent bone loss ($P = 0.477$ for the interaction). At the hip, total BMD in premenopausal women receiving placebo decreased significantly at 2 years, whilst oral clodronate therapy decreased bone loss by 69% (–1.84% ± 0.36% versus –0.57% ± 0.38%, respectively; $P = 0.008$ between groups). By con-

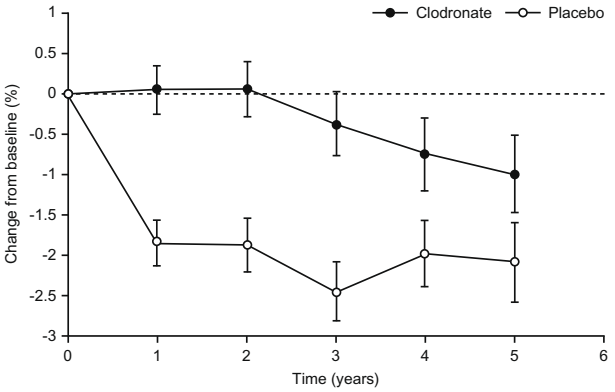

Fig. 1 – Effect of oral clodronate on lumbar spine bone mineral density during treatment and follow-up compared with placebo. During the 2-year treatment period, mean BMD of the lumbar spine was maintained in patients who received oral clodronate, whilst it decreased significantly in patients who received placebo ($P < 0.0001$). Following discontinuation of treatment, bone loss occurred in both groups. *P* values for differences at 2 years and 5 years were $P < 0.0001$ and $P = 0.11$.

Table 1 – Patient baseline demographic and clinical characteristics.

Characteristic	Clodronate ($n = 419$)	Placebo ($n = 432$)
Age (years)	52.9 ± 10.3	52.8 ± 10.3
Height (cm)	161.9 ± 5.9	161.4 ± 6.2
Weight (kg)	67.4 ± 12.6	67.2 ± 12.1
BMI (kg/m^2)	25.7 ± 4.9	25.9 ± 4.8
Premenopausal (%)	49.9	48.1
Disease stage(%)		
I	28.4	27.3
II	56.3	56.0
Other	15.3	16.7
BMD study		
N	111	116
Spine BMD (g/cm^2)	0.98 ± 0.15	0.99 ± 0.14
Total hip BMD (g/cm^2)	0.89 ± 0.14	0.91 ± 0.13
Biochemical marker study		
N	276	283
BSAP (μg/mL)	8.54 ± 3.53	8.39 ± 3.69
PINP (μg/L)	39.5 ± 24.9	38.3 ± 24.0
ICTP (μg/L)	3.74 ± 1.34	3.72 ± 1.27
NTx (nmol/mmol) creatinine[a]	57.2 ± 23.9 (44)	61.4 ± 28.7 (40)

Data are mean ± standard deviation, unless otherwise stated; BMD, bone mineral density; BSAP, bone-specific alkaline phosphatase; ICTP, carboxyterminal telopeptide of type 1 collagen; NTx, amino-terminal telopeptide of type 1 collagen; PINP, amino-terminal pro-peptide of type 1 collagen.

[a] Numbers of patients with urine NTx measurements shown in parentheses.

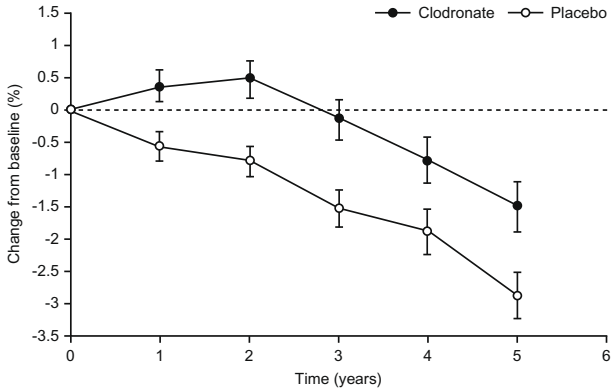

Fig. 2 – Effect of oral clodronate on hip bone mineral density during treatment and follow-up compared with placebo. During the 2-year treatment period, mean BMD of the total hip was maintained in patients who received oral clodronate, whilst it decreased significantly in patients who received placebo ($P = 0.004$). Following discontinuation of treatment, bone loss occurred in both groups. *P*-values differences between groups at 2 years and 5 years were $P = 0.002$ and $P = 0.009$.

trast, in post-menopausal women, hip BMD remained stable in women who received placebo whilst oral clodronate increased BMD significantly from baseline compared with placebo (0.19% ± 0.30% versus 1.34% ± 0.43%, respectively; $P = 0.078$ between groups). At the spine, significant BMD loss occurred in premenopausal women in both treatment groups ($P < 0.001$ compared to baseline for both), but the decrease was 36% less in the oral clodronate group (–2.54% ± 0.43% versus –3.95% ± 0.45%, $P = 0.004$ between groups). No significant change in spine BMD was observed in post-menopausal women who received placebo, but treatment with oral clodronate significantly increased BMD (0.05% ± 0.40% versus 2.09% ± 0.42%; $P < 0.001$ between groups).

Following cessation of treatment and during the 3-year follow-up period, BMD decreased in both treatment groups at all sites studied (Table 2, Figs. 1 and 2); although the rate of decrease in spine BMD appeared greater in women who had received clodronate compared with those who did not, the rates were not statistically significantly different between the groups at the spine ($P = 0.057$) or total hip ($P = 0.851$). Patients treated with oral clodronate continued to have higher mean BMD than those treated with placebo (Table 2, Figs. 1 and 2). At the end of 5 years, BMD remained greater at the spine (mean difference, 1.10%; 95% CI, –0.26% to 2.46%; $P = 0.11$) and was significantly higher at the total hip (mean difference, 1.40%; 95% CI, 0.34% to 2.45%; $P = 0.009$) and hip sub-regions apart from the intertrochanter region (Table 2) in women treated with clodronate.

3.2. *Effect of oral clodronate on markers of bone turnover*

During 2 years of therapy, serum PINP concentrations decreased by a median 26% with oral clodronate and increased by a median 5% with placebo ($P < 0.0001$ between groups; Fig. 3a). The effect of oral clodronate on serum PINP was largely offset by the end of the first year post-treatment and values at 3 years were similar to those in the placebo group (Fig. 3a).

A similar pattern of change was observed for urinary NTx (Fig. 3b) although post-baseline paired samples for analysis of fasting urinary excretion of NTx were only available for 74 women. Treatment with oral clodronate was associated with a significantly greater decrease in urine NTx compared with placebo (Fig. 3b). The effect of oral clodronate on urinary NTx was largely offset by the end of the first year post-treatment with median decreases similar to those in the placebo group at this time. Serum bone alkaline phosphatase activity increased significantly from baseline in both groups, but the increase was significantly greater in the placebo group, consistent with a greater increase in bone turnover (Fig. 3c). As with urinary NTx and serum PINP, the values were very similar in both groups at 3 years. Changes in serum ICTP were relatively small and similar in both treatment groups. For example, the median decreases by 1 year were –7.5% and –8.1% for oral clodronate and placebo, respectively ($P > 0.05$).

Table 2 – Mean changes in BMD by hip sub-regions.

Hip sub-region	Clodronate Mean (95% CI)	Placebo Mean (95% CI)	Difference Mean (95% CI)	*P*-value
Femoral neck				
2 years	0.03 (–0.67, 0.73)	–1.42 (–2.04, –0.81)	1.45 (0.53, 2.38)	0.002
5 years	–2.35 (–3.27, –1.43)	–4.05 (–4.88, –3.22)	1.70 (0.46, 2.94)	0.007
Trochanter				
2 years	0.36 (–0.29, 1.01)	–1.43 (–1.99, –0.86)	1.78 (0.92, 2.64)	0.000
5 years	–1.35 (–2.18, –0.51)	–3.13 (–3.97, –2.29)	1.78 (0.60, 2.96)	0.003
Intertrochanter				
2 years	0.51 (–0.18, 1.21)	–0.37 (–0.88, 0.15)	0.88 (0.02, 1.74)	0.045
5 years	–1.02 (–1.89, –0.15)	–2.03 (–2.79, –1.27)	1.00 (–0.15, 2.16)	0.087
Ward's area				
2 years	1.27 (–0.11, 2.66)	–0.86 (–1.95, 0.22)	2.13 (0.39, 3.88)	0.017
5 years	–1.72 (–3.15, –0.28)	–4.31 (–5.62, –3.00)	2.60 (0.66, 4.54)	0.009

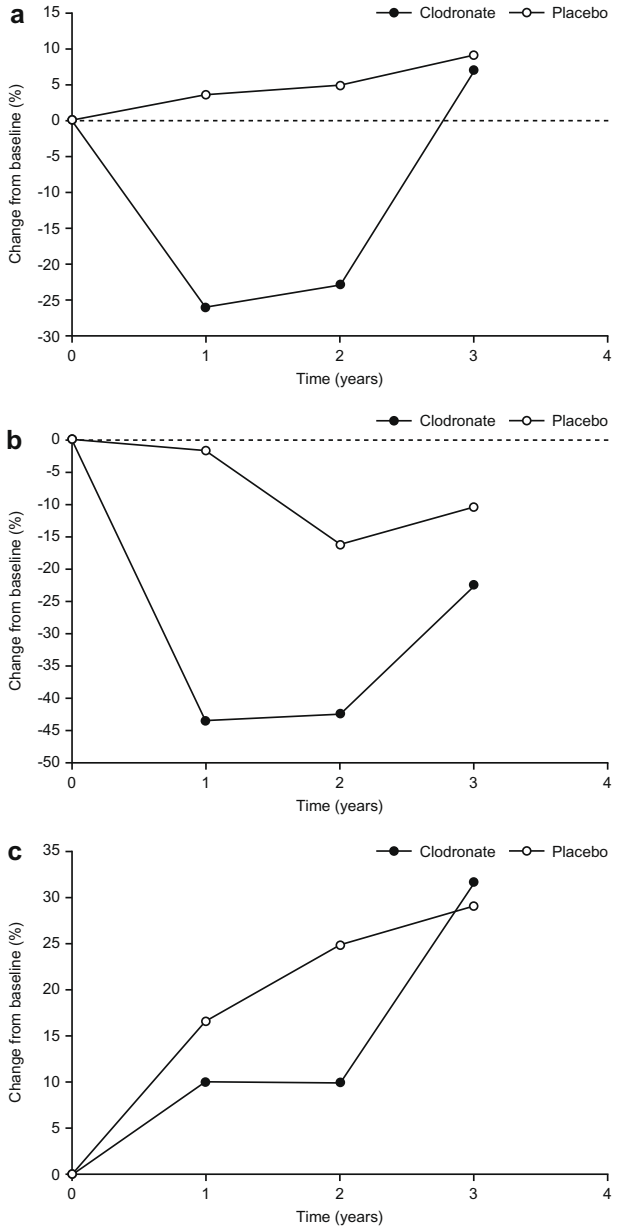

Fig. 3 – Median percentage changes from baseline in serum PINP (3a), fasting urine NTx (3b), and serum BSAP (3c) during treatment and at 1 year post-treatment. During the 2 years of therapy, patients who received oral clodronate had significantly decreased serum PINP concentrations as well as significantly greater decreases in urine NTx, and significantly lower increases in BSAP than patients who received placebo.

3.3. *Bone density and bone turnover at diagnosis of breast cancer and subsequent incidence of bone metastases*

In women randomised to the placebo group who subsequently developed metastases, there were no significant differences in spine BMD, hip BMD or biochemical markers of bone resorption and formation at study entry (Tables 3 and 4). Similar results were obtained if all patients, including those assigned to clodronate, were included in the analysis.

Table 3 – Comparison of baseline BMD in women assigned to the placebo group who developed or remained free from bone metastases.

Women who developed bone metastases, mean (SD)[a]	
Spine (g/cm^2)	1.00 ± 0.14 (39)
Total hip (g/cm^2)	0.99 ± 0.14 (39)
Women who remained free from bone metastases, mean (SD)[a]	
Spine (g/cm^2)	0.99 ± 0.14 (219)
Total hip (g/cm^2)	0.91 ± 0.14 (225)

IQ – Interquartile range; BMD – bone mineral density.
[a] Numbers in parentheses represent the numbers of patients for whom samples were evaluable.

Table 4 – Comparison of baseline serum biochemical markers in women assigned to the placebo group who developed/remained free of bone metastases.

Women who developed bone metastases, median (IQ range)[a]	
Serum PINP (μg/L)	35.5, 27–51 (38)
Serum BSAP (μg/m)	8.0, 6–9 (38)
Serum ICTP (μg/L)	3.8, 3.0–4.6 (38)
Women who remained free from bone metastases, median (IQ range)[a]	
Serum PINP (μg/L)	34.0, 24–47 (245)
Serum BSAP (μg/m)	8.0, 6–10 (245)
Serum ICTP (μg/L)	3.6, 2.9–4.3 (245)

BSAP, bone-specific alkaline phosphatase; ICTP, carboxyterminal telopeptide of type 1 collagen; IQ, Interquartile range; PINP, amino-terminal pro-peptide of type 1 collagen.
[a] Numbers in parentheses represent the numbers of patients for whom samples were evaluable.

The number of urine samples for NTx measurement was too small to be interpretable.

3.4. *Oral clodronate therapy, biochemical response and relationship to changes in BMD and bone metastases*

The proportion of women classified as 'responsive' was significantly higher (55% versus 31%; $P < 0.0001$) during oral clodronate therapy, whilst the number classified as 'progressive' was significantly lower (23% versus 41%, $P < 0.0001$; Fig. 4). The effect of oral clodronate was observed in both premenopausal and post-menopausal women (Fig. 4). There were significant differences in spine BMD changes across the three groups: women who responded to therapy with oral clodronate experienced a significant improvement in spine BMD at 2 years compared to women who had stable or progressive bone turnover (ANOVA, $P < 0.001$; $R = 0.49$; Fig. 5). A similar pattern was observed for total hip BMD at 1 year, but the difference did not reach statistical significance (mean percentage change,+1.13,+1.38, and –0.21 in the responsive, stable, and progressive groups, respectively; $P = 0.400$).

Finally, in the 230 women with paired measurements at baseline and 1 year, there was a significant relationship between changes in PINP and the subsequent development of bone metastases (Fig. 6). The incidence of metastases was sig-

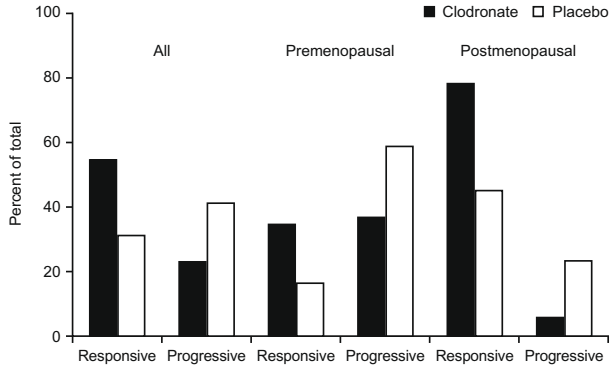

Fig. 4 – Response and progression in bone turnover as judged at 1 year based on changes in serum PINP. In the clodronate group, significantly more women were responsive to treatment ($P < 0.0001$).

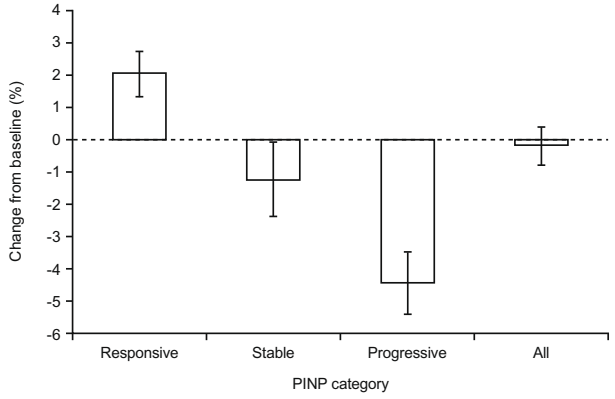

Fig. 5 – Changes in spine bone mineral density at 2 years in the categories of PINP changes at 1 year in women who received oral clodronate. Women who were responsive to therapy, judged by PINP, experienced a significant improvement in BMD of the spine at 2 years compared with women who had stable or progressive bone turnover ($P < 0.001$).

nificantly higher in women in the progressive group at 1 year (11/53, 20.8%) than in women who were responsive (8/126, 6.3%) or who were stable (4/51, 7.8%; $P = 0.011$). As underlying bone metastases may contribute to increases in PINP, the analysis was repeated following exclusion of women who had bone metastases within 2 years of diagnosis. The relationship between PINP progression and the development of bone metastases persisted (Fig. 6), with the incidence in the progressive group being 17.6% compared with 5.2% in the other groups combined ($P = 0.015$).

4. Discussion

The results from this study indicate that patients with breast cancer who received oral clodronate experienced maintenance of, or increase in, BMD at the spine and hip during 2 years of treatment compared with those receiving placebo.

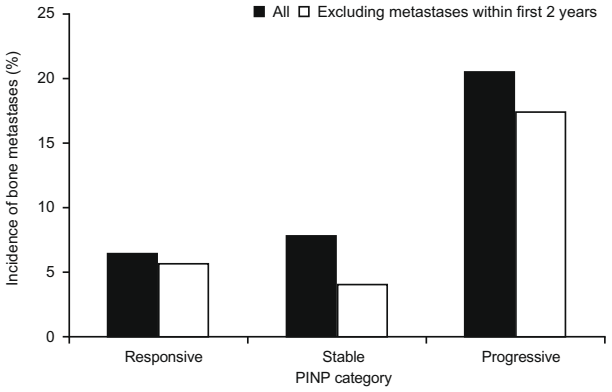

Fig. 6 – Changes in PINP at 1 year in women who received oral clodronate and the incidence of bone metastases over 5 years of follow-up. The incidence of bone metastases was significantly higher in women with progression at 1 year than in women responsive treatment or with stable disease ($P = <0.02$ for both comparisons).

As expected, bone loss was most marked in premenopausal women as judged by changes in BMD and bone turnover markers at 1 year. Though not recorded in the present study, this largely relates to a disruption or cessation of ovarian function, with bone loss secondary to oestrogen deficiency;[16] however, a direct effect of chemotherapy on bone cannot be excluded. Similar treatment effects have been noted in pre- and post-menopausal women treated with clodronate 1600 mg daily.[17,18] In addition, prevention of bone loss and increased BMD have been reported with oral risedronate in premenopausal women[19] and with intravenous zoledronate in pre- and post-menopausal women undergoing ovarian suppression and/or aromatase inhibition, respectively.[20,21]

When treatment was discontinued, patients treated with oral clodronate experienced decreases in spine and hip BMD similar to patients previously treated with placebo. Although BMD decreased during the 3 years of follow-up, women who were previously treated with oral clodronate still had higher BMD at 5 years than those treated with placebo. These data suggest the absence of a "rebound" increase in bone loss when clodronate was discontinued, confirmed by the changes observed in the biochemical markers of bone turnover, particularly serum PINP and urinary NTx levels. These data are consistent with a relatively early offset of treatment with clodronate on bone turnover which may have implications for clinical practise. Firstly, the optimal duration of therapy may be longer than used in this study and should perhaps be in line with the duration of most other adjuvant therapies. The ongoing National Surgical Adjuvant Breast and Bowel Project (NSABP) study B34 (Clodronate With or Without Chemotherapy and/or Hormonal Therapy in Treating Women With Stage I or Stage II Breast Cancer) will examine 3 years of oral clodronate use. Secondly, the offset reflects a degree of control over the suppression of bone turnover, an aspect that may assume greater importance given recent concerns about potential over-suppression of bone turnover[22,23] and the apparent association of potent bisphosphonate use with serious side effects such as osteonecrosis of the jaw.[24–27]

This study has addressed, for the first time, the interaction between bone mass and/or bone turnover at diagnosis and the subsequent risk of skeletal metastases, thus examining the "soil" component of Paget's "seed and soil" hypothesis.[28] *In vitro* and *in vivo* studies have demonstrated attraction of tumour cells by products of bone resorption and enhanced metastatic disease in the presence of localised stimulation of bone turnover.[29,30] Our study suggests that bone metabolism at the time of breast cancer diagnosis, judged by bone mass and turnover markers, is not significantly associated with the subsequent risk of bone metastasis. There is, however, an apparent relationship between changes in bone turnover within the first year and subsequent bone metastases. Changes in serum PINP over the first year have previously been shown to correlate with changes in BMD in pre- and post-menopausal women.[31] Our study confirms these observations but also suggests a relationship between early changes in bone turnover, assessed by PINP, and the subsequent development of bone metastases. If confirmed, the use of PINP as a marker of bone turnover would support the targeting and benefit of early use of bisphosphonates rather than waiting until bone metastases have occurred.

In conclusion, adding oral clodronate to standard adjuvant therapy in primary breast cancer reduces bone turnover and thus appears to protect the skeleton from metastases. Because longer treatment with oral clodronate may provide greater protection against bone loss, further investigation is warranted to determine the optimum duration of treatment. Serum PINP has the potential to be a marker of response to therapy and possibly provide early detection of skeletal metastases but needs to be compared to other modalities including tumour markers and bone scans.

Role of the funding source

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Conflict of interest statement

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