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Long-term impact of chemotherapy-induced ovarian failure on bone mineral density (BMD) in premenopausal breast cancer patients. The effect of adjuvant clodronate treatment

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Abstract

We present the 5-year results of the effect of adjuvant chemotherapy on bone mineral density (BMD) and the efficacy of clodronate in the prevention of bone loss in 73 premenopausal women with primary breast cancer. All patients were treated with cyclophosphamide, methotrexate, 5-fluorouracil (CMF) chemotherapy. The patients were randomised to oral clodronate 1600 mg daily for 3 years or to a control group. At 5 years, patients were divided into those with preserved menstruation and those with amenorrhoea. Changes in BMD correlated significantly with the menstrual function after chemotherapy. The change in the lumbar spine BMD at 3 and 5 years were +0.6 and −1.3% in the menstruating group and −7.5 and −10.4% in the amenorrhoeic group ($P=0.0001$ and 0.0001, respectively), and in femoral neck +1.7 and −0.3%, and −3.5 and −5.8% ($P=0.002$ and $P=0.001$, respectively). Three-year clodronate treatment significantly reduced the bone loss in the lumbar spine −3.0% compared with controls −7.4% at three years ($P=0.003$), but no significant difference was found in the femoral neck: −1.7% versus −2.8%, respectively ($P=0.86$). These differences between the study groups were still seen at 5 years: in the lumbar spine −5.8% versus −9.7% ($P=0.008$) and femoral neck −3.5% versus −5.1% ($P=0.91$). In conclusion, chemotherapy-induced ovarian failure in premenopausal women caused a temporary accelerated bone loss of the lumbar spine. Adjuvant clodronate treatment significantly reduced this bone loss. Two years after the termination of treatment, the bone loss was still significantly less in the clodronate group compared with the control group.

Keywords: Adjuvant chemotherapy, Amenorrhoea, Biphosphonates, Breast cancer, Clodronate, Postmenopausal osteoporosis

1. Introduction

Adjuvant chemotherapy significantly improves survival of premenopausal breast cancer patients [1]. In a majority of these patients, however, adjuvant chemotherapy causes ovarian failure and rapid bone loss which may increase the risk of osteoporosis later in life [2–6].

Biphosphonates have successfully been used in the treatment of osteoporosis. Biphosphonates prevent bone loss in patients with established osteoporosis [7–12]. Moreover, etidronate, risedronate and alendronate have been proven to reduce the risk of vertebral fractures in postmenopausal osteoporosis [10,13–16]. In breast cancer patients with bone metastases, biphosphonates reduce the risk of skeletal complications such as pain, pathological fractures and hypercalcaemia [17–23]. However, the role of adjuvant biphosphonate treatment in early stage breast cancer is still controversial [24–26].

We have previously reported that the 2-year-adjuvant clodronate treatment significantly reduced the bone loss in premenopausal early stage breast cancer patients who were treated with adjuvant chemotherapy [6]. In this paper we report (1) the long-term results of the impact of chemotherapy-induced ovarian failure on bone mineral density (BMD), (2) the effect of 3-year clodronate treatment and (3) the effect of its cessation on the bone mineral density at 5-years follow-up.

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2. Patients and methods

2.1. Patients

The study population consisted of 148 premenopausal newly diagnosed breast cancer patients without haematogenic metastases who were included in a trial of adjuvant clodronate. Eligible for the trial were patients with operable breast cancer and histologically-proven axillary metastases, T1-3 N1-2 M0, treated between May 1992 and July 1993 at the Helsinki University Hospital, Department of Oncology. Exclusion criteria were the following: (1) Karnofsky performance index below 70%; (2) other malignancies; (3) peptic ulcer or its symptoms; (4) creatinine over 150 umol/l; (5) pregnancy. In addition, patients with metastatic disease at the time of the BMD measurement or patients with bone metastases within 6 months after the BMD measurement were excluded from the analyses.

All patients underwent surgery with axillary evacuation and total mastectomy or breast-conserving resection and postoperative radiotherapy. Patients were treated with adjuvant chemotherapy which consisted of six cycles of cyclophosphamide (600 mg/m^2), methotrexate (40 mg/m^2) and 5-fluorouracil (600 mg/m^2) intravenously (i.v.) on day 1 with 3-weekly intervals (CMF). In addition, all patients were randomised to receive or not to receive oral clodronate (BonefosR, Leiras) 1600 mg daily for 3 years.

After chemotherapy, patients were divided into two groups according to menstrual status at 5 years of follow-up: patients who preserved menstruation (menstruating group) and patients who experienced menopause during the follow-up (amenorrhoea group). Amenorrhoea was defined as menstruation being absent for at least 6 months.

Of the 148 eligible premenopausal patients at entry, data from 75 patients were excluded from the 5-year analyses mainly due to metastatic disease (Table 1). Thus, only those 73 patients who were still disease-free at 5 years of follow-up were included in the analysis of BMD changes at 3 and 5 years. None of the patients included had previously used biphosphonates or calcitonin.

The pretreatment characteristics of patients in the menstruating and amenorrhoeic groups are given in Table 2. According to the pretreatment characteristics the groups were well balanced, except for the age of the patients: the patients in the amenorrhoeic group were significantly older than those in the menstruating group ($P<0.0001$). Characteristics of the patients in the clodronate and control groups are given in Table 3.

Table 1
Patients excluded from the analyses

Cause	Patients *n*
Metastatic disease	65
Inadequate systemic therapy	1
Gravidity	1
Discontinued follow-up	1
Previous breast cancer	1
Non-cancer death	1
Medication affecting bone metabolism[a]	5

[a] 3 patients on cortisone therapy, 1 patient on anticonvulsant medication and 1 patient on oestrogen therapy.

2.2. Methods

Informed consent was obtained from all participants. The study was approved by the Local Ethical Committee, at the Department of Oncology, at the Helsinki University Hospital. Staging investigations for breast cancer included clinical investigation, liver ultrasound, chest X-ray and bone scintigraphy. Basic laboratory tests before randomisation included a complete blood

Table 2
Pretreatment characteristics of the patients according to menstrual status[a]

Menstrual status at 5 years	Menstruating	Amenorrhoeic	*P* value
Patients (*n*)	19	51	
Patients (*n*) in:			
Clodronate group	7 (37%)	20 (39%)	
Control group	12 (63%)	31 (61%)	
Age (years)[b]	39 (37–42)	47 (46–48)	<0.0001
Weight (kg)[b]	64 (59–69)	65 (61–68)	NS
Height (cm)[b]	165 (162–168)	164 (162–166)	NS
Lumbar spine BMD (g/cm^2)[b]	1.02 (0.97–1.07)	1.02 (0.98–1.06)	NS
Femoral neck BMD (g/cm^2)[b]	0.82 (0.77–0.87)	0.85 (0.82–0.88)	NS
FSH (U/l)[c]	4.9 (0.4–9.7)	6.4 (1.8–81.8)	NS
LH (U/l)[c]	7.7 (0.2–61.1)	5.9 (0.7–75.9)	NS
Oestradiol (nmol/l)[c]	0.19 (0.02–0.97)	0.28 (0.02–3.58)	NS

[a] 3 patients had had a hysterectomy.
[b] Mean values (and 95% confidence interval)
[c] Median (and range)
BMD, bone mineral density; FSH, follicle stimulating hormone; LH, Luteinising hormone; NS = statistically non-significant.

count and sedimentation rate, liver enzymes (transaminase, alkaline phosphatase, 5-nucleotidase), serum creatinine, calcium and electrolytes. Patients were interviewed regarding menopausal status, medications and other diseases before randomisation and at 1, 2, 3 and 5 years after therapy. Bone scintigraphy and measurements of serum follicle stimulating hormone (FSH), luteinising hormone (LH) and oestradiol were performed before treatment and at 1, 2, 3 and 5 years. Clinical investigation and basic laboratory safety tests were repeated every 4–6 months with a radiological examination if necessary.

2.3. Bone densitometry

BMD (grams per square centimetre) was measured by dual-energy X-ray absorptiometry (DXA) using a Hologic QDR-1000 densitometer (Hologic, Inc., Waltham, MA, USA). BMD was measured at the lumbar vertebrae (L1–4) and at the femoral neck, femoral trochanter and Ward's triangle, intertrochanteric and total femoral area in the right femoral area before initiation of therapy and at 1, 2, 3 and 5 years. The coefficient of variation for precision of the BMD measurements in the lumbar vertebrae and femoral neck was 0.9 and 1.2%, respectively.

2.4. Statistical methods

BMD values are presented as percentages of the baseline value. The effect of chemotherapy and clodronate on changes in BMD at 1, 2, 3 and 5 years were tested by a repeated measures ANOVA model using the programs Statistical Package for the Social Science (SPSS) for Macintosh, with change from baseline BMD as a dependent variable and clodronate treatment and menopausal status as grouping variables. Other comparisons were made using the Mann–Whitney test or Wilcoxon matched pair test. 95% confidence intervals were calculated for the main outcome measures. The significance level was set at 0.01.

3. Results

During 1 year follow-up, 27 patients of 73 had developed permanent amenorrhoea, at 3 years this was 40 patients, and at 5 years 51 patients. 5 years after chemotherapy, 74% of the patients were permanently amenorrhoea. 3 patients had had a hysterectomy at entry and all of them had FSH of postmenopausal levels at 5 years. One patient had a hysterectomy during follow-up and her FSH level reached postmenopausal levels prior to the operation.

3.1. Effect of menstrual changes on BMD

Changes in BMD correlated significantly with menstrual function after chemotherapy at 5 years (in lumbar spine $P = 0.0001$; in femoral neck $P = 0.001$). Changes in BMD of the lumbar spine and femoral neck were −1.3 and −0.3% in the menstruating group, −10.4 and −5.8% in the amenorrhoea groupic respectively (Table 4). At 5 years, the amenorrhoeic patients were further divided into those who experienced amenorrhoea early, that is, during the first year after chemotherapy and those who developed menopause later during the follow-up period. It is of interest that bone loss at 5 years did not differ between these groups. The bone loss in the lumbar spine and femoral neck was

Table 3
Pretreatment characteristics of the patients in clodronate and control groups

Treatment group	Clodronate	Control	*P* value
Patients (*n*)	27	46	
Patients (*n*)			
Menstruating at 5 years	7 (26%)	12 (26%)	
Amenorrhoeic at 5 years	20 (74%)	31 (67%)	
Hysterectomised	0 (0%)	3 (7%)	
Age (years)[a]	45 (43–47)	45 (44–46)	NS
Weight (kg)[a]	64 (59–69)	65 (62–68)	NS
Height (cm)[a]	163 (161–165)	165 (163–167)	NS
Lumbar spine BMD (g/cm^2)[a]	1.02 (0.97–1.06)	1.01 (0.97–1.06)	NS
Femoral neck BMD (g/cm^2)[a]	0.81 (0.77–0.86)	0.85 (0.82–0.88)	NS
FSH (U/l)[b]	6.7 (2.3–48.9)	5.6 (0.4–81.8)	NS
LH (U/l)[b]	7.7 (2.6–61.1)	6.5 (0.2–75.9)	NS
Oestradiol (nmol/l)[b]	0.20 (0.02–1.16)	0.29 (0.02–3.58)	NS

[a] Mean values (and 95% confidence interval).
[b] Median (and range).
BMD, bone mineral density; FSH, follicle stimulating hormone; LH, Luteinising hormone; NS = statistically non-significant.

−10.4 and −5.1% in patients with an early onset of menopause and −10.5 and −6.5% in those with a later menopause at 5 years, respectively ($P=0.95$ and $P=0.26$, respectively).

3.2. Effect of clodronate treatment on BMD

Three-year clodronate treatment significantly reduced the bone loss in the lumbar spine −3.0% compared with controls −7.4% ($P=0.003$). In the femoral neck, no significant differences were found between the study groups: −1.7% versus −2.8% ($P=0.86$). At 5 years, 2 years after termination of treatment, the differences between the clodronate and control groups were still statistically significant in the lumbar spine, but not in the femoral neck ($P=0.008$ and $P=0.91$, respectively) (Table 5 and Fig. 1). The effect of clodronate on bone loss in the lumbar spine was seen in both menstruating and amenorrhoeic women (Table 6 and Fig. 2).

4. Discussion

As we have previously reported [6], adjuvant chemotherapy for breast cancer exposes premenopausal patients to early menopause and rapid bone loss especially in the lumbar spine. However, the bone loss rate is greatest during the first few years, getting slower thereafter.

In this present study, 74% of the women experienced menopause during the 5-year follow-up. In accordance with previous studies, women most prone to the onset of menopause after chemotherapy were those in their 40s, while women under 40 years of age had better preservation of menstruation. The changes in BMD were

Table 4
Percentile changes and 95% confidence intervals (95% CI) from baseline BMD of lumbar spine and femoral neck in menstruating and amenorrhoeic patients

	Menstruating		Amenorrhoeic		*P* value	
	3 years	5 years	3 years	5 years	3 years	5 years
Lumbar spine BMD	+0.6%	−1.3%	−7.5%	−10.4%	0.0001	0.0001
95% CI	−1.0 to 2.2%	−3.5 to 0.9%	−9.0 to−6.0%	−12.0 to −8.9%		
Femoral neck BMD	+1.7%	−0.3%	−3.5%	−5.8%	0.002	0.001
95% CI	−1.1 to 4.4%	−3.3 to 2.7%	−5.0 to −2.0%	−7.5 to −4.0%		

BMD. bone mineral density.

Table 5
Percentile changes and 95% confidence intervals (95% CI) from baseline BMD of lumbar spine and femoral neck in clodronate and control groups

	Clodronate		Control		*P*-value	
	3 years	5 years	3 years	5 years	3 years	5 years
Lumbar spine BMD	−3.0%	−5.8%	−7.4%	−9.7%	0.003	0.008
95% CI	−5.2 to −0.8%	−8.3 to −3.3%	−9.2 to −5.6%	−11.6 to −7.8%		
Femoral neck BMD	−1.7%	−3.5%	−2.8%	−5.1%	0.86	0.91
95% CI	−4.0 to 0.6%	−5.8 to −1.2%	−4.5 to −1.1%	−7.2 to −3.0%		

BMD, bone mineral density.

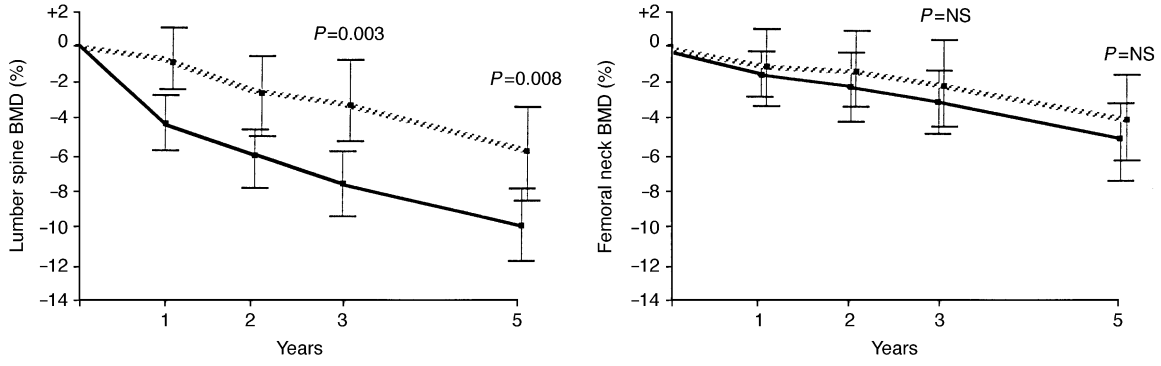

Fig. 1. Percentage bone mineral density (BMD) changes and 95% confidence intervals in the lumbar spine and femoral neck in the clodronate (dotted line) and control (bold line) groups.

significantly associated with menstrual function after chemotherapy [6]. The rate of bone loss was significantly less marked in women who continued menstruating after chemotherapy compared with women who experienced menopause. If menopause ensued early after chemotherapy, the rate of bone loss during the first 2 years appeared to be even larger than that found in longitudinal studies of natural menopause especially in the lumbar spine [6,27–30]. Similar rapid bone loss has also been demonstrated after oophorectomy in a longitudinal study of Genant and colleagues, in which lumbar spine bone density measured by quantitative computed tomography decreased 9.5% 2 years after oophorectomy [4]. Interestingly, the rate of bone loss related to chemotherapy-induced early menopause seemed to decrease from the first year of chemotherapy to the fifth year of follow-up. No difference in the BMD at 5 years was found between women who experienced menopause early after chemotherapy and those with a later onset of menopause.

3-year clodronate treatment significantly reduced the bone loss of the lumbar spine. In the femoral neck, no significant reduction of bone loss was seen by clodronate mainly due to the slower bone turnover rate in cortical than trabecular bone. The beneficial effect of clodronate was evident in both menstruating and amenorrhoeic women. However, in the rapid bone losers of the amenorrhoeic group, the bone-sparing effect of clodronate was only partial diminishing the rate of loss by 29–40%. In contrast, the less marked bone loss of the menstruating women was totally prevented by clodronate. In line with previous studies of alendronate [13–15], no acceleration of bone loss was observed after termination of clodronate. Following the discontinuation of treatment, both the clodronate and control patients lose bone mass at similar rates. However, 2 years after the termination of treatment, the total bone loss was significantly less in the clodronate than the control groups.

For the first time, in a prospective study, we were able to demonstrate that chemotherapy-induced ovarian failure in premenopausal women with breast cancer causes a temporary accelerated bone loss of the lumbar spine, which stabilises thereafter. Adjuvant clodronate treatment significantly reduces this bone loss in lumbar spine. The difference between the study groups was still evident 2 years after the termination of the clodronate treatment.

Table 6
Percentage changes and 95% confidence intervals (95% CI) from baseline BMD of the lumbar spine and femoral neck according to menstrual status and clodronate usage

	Clodronate		Control	
	3 years	5 years	3 years	5 years
Menstruating patients				
Lumbar spine BMD	+2.9%	+1.7%	−0.9%	−3.1%
95% CI	0.0 to 5.8%	−1.5 to 5.0%	−2.5 to 0.7%	−5.8 to −0.4%
Femoral neck BMD	+3.2%	+0.7%	+0.7%	−0.9%
95% CI	−2.1 to 8.5%	−5.5 to 6.8%	−3.0 to 4.3%	−4.7 to 3.0%
Amenorrhoeic patients				
Lumbar spine BMD	−5.1%	−8.4%	−9.0%	−11.8%
95% CI	−7.3 to −3.0%	−10.7 to −6.2%	−10.9 to −7.1%	−13.7 to −9.8%
Femoral neck BMD	−3.4%	−4.9%	−3.5%	−6.3%
95% CI	−5.7 to −1.2%	−7.2 to −2.7%	−5.5 to −1.5%	−8.8 to −3.8%

BMD, bone mineral density.

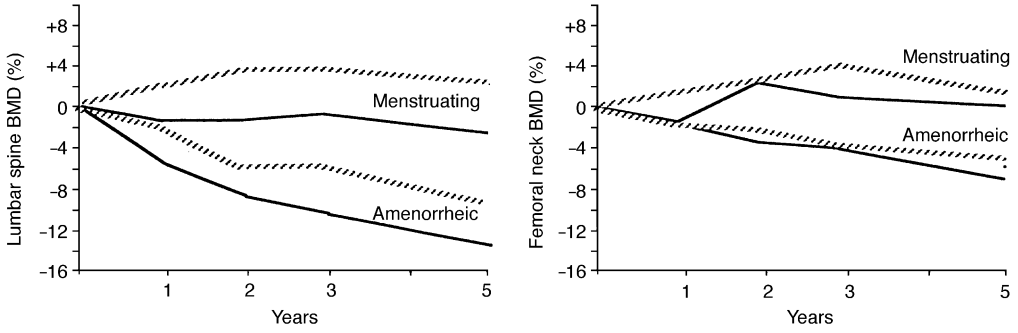

Fig. 2. Percentage bone mineral density (BMD) changes in the lumbar spine and femoral neck of the menstruating and amenorrhoeic patients in the clodronate (dotted line) and control (bold line) groups.

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