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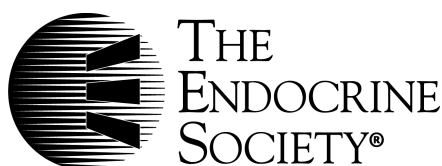
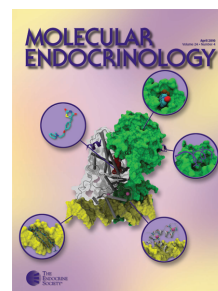
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Pamidronate in the Prevention of Chemotherapy-Induced Bone Loss in Premenopausal Women with Breast Cancer: A Randomized Controlled Trial

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Purpose: Mortality from breast cancer has decreased in large part because of adjuvant chemotherapy. Sequelae of therapy include ovarian failure and bone loss, loss that would increase these patients' risk of fracture with aging. In this study, we assessed the efficacy of pamidronate in preventing such loss.

Patients and Methods: The study was a 1-yr randomized, double-blind, placebo-controlled trial comparing pamidronate 60 mg iv every 3 months with placebo in 40 premenopausal women with newly diagnosed breast cancer. Bone mineral density (BMD) of the spine and hip and remodeling markers were monitored over 1 yr.

Results: Over half of the subjects became amenorrheic, and those who did were 4 yr older than those who did not ($P = 0.02$). The mean

difference in percent change in BMD at 12 months between the two treatment groups was 5.1% at the lumbar spine ($P = 0.002$) in the overall study group and 5% at the lumbar spine and 5.2% at the total hip in the amenorrheic subgroup ($P < 0.03$). Biochemical markers of bone remodeling did not differ between the two treatment groups, and treatment was well tolerated.

Conclusion: Chemotherapy-induced amenorrhea is common with ensuing bone loss at the spine and hip. Pamidronate prevented bone loss at the spine and hip and was well tolerated. (*J Clin Endocrinol Metab* 90: 3209–3214, 2005)

BREAST CANCER IS the second deadliest cancer in women. Over the last decade, breast cancer mortality for white women has dropped slightly by 6–8% (1, 2). In Western countries, this decrease in the mortality may be a result of early screening and adjuvant chemotherapy and early use of tamoxifen. It is most pronounced in young white women in their thirties, where the decline is estimated at 20% (1).

However, this improved mortality is not without any cost (3). In the majority of premenopausal patients with breast cancer, adjuvant chemotherapy induces early menopause, a strong predictor of accelerated bone loss. Indeed, it has been demonstrated that women who have premature menopause as a result of chemotherapy have bone mineral densities (BMDs) that are up to 14% lower than women who did not lose their periods (4). Furthermore, several recent prospective studies showed a bone loss at 1 yr varying from 4–8% in the spine and 2–4% at the hip in premenopausal women who became amenorrheic after receiving adjuvant chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil (5-FU) (CMF; Refs. 5–7). This issue is particularly relevant in the

Middle East where our group and others reported that an increasing proportion of women with breast cancer are premenopausal (8). Few are the studies that have addressed strategies to reverse this anticipated chemotherapy-induced bone loss (5, 6, 9). Such loss was only partially prevented by tamoxifen and minimized with the bisphosphonates risedronate or clodronate (5, 6). However, both studies used oral bisphosphonates, a regimen that may be associated with gastrointestinal side effects, an important consideration in cancer patients who may experience chemotherapy-induced nausea, vomiting, or gastrointestinal difficulties. This would jeopardize compliance with, and therefore the efficacy of, the therapy administered. Alternatively, iv bisphosphonates such as pamidronate and zoledronate have been shown to be safe and efficacious in reversing states of high turnover such as seen with hypercalcemia of malignancy or osteoporosis (10–13). The iv bisphosphonates can be easily administered in conjunction with the patient's chemotherapy regimen, are readily available in most parts of the world, are very well tolerated, and therefore ideally suited to prevent chemotherapy-induced bone loss (12, 13). To our knowledge, their efficacy in premenopausal women receiving chemotherapy for breast cancer was not demonstrated.

The primary objective of this investigation was to study the safety and efficacy of cyclical pamidronate in reducing chemotherapy-induced bone loss in premenopausal women with breast cancer. The secondary objective was to evaluate its efficacy in reducing bone turnover in such patients. Pam-

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Abbreviations: BMD, Bone mineral density; BMI, body mass index; CMF, cyclophosphamide, methotrexate, 5-FU; CV, coefficient of variation; FAC, 5-FU, adriamycin, cyclophosphamide; 5-FU, 5-fluorouracil.

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idronate was chosen for this trial because it was a readily available therapy for clinical use worldwide at the time the study was initiated (2000–2001).

Patients and Methods

Protocol

Our study was a prospective, randomized, double-blind, placebo-controlled trial, comparing the efficacy of cyclical iv administration of pamidronate, given as 60 mg iv in 500 ml dextrose in water over 2 h every 3 months (0, 3, 6, and 9 months) to placebo (500 ml dextrose in water) for 1 yr. Randomization was conducted by the chemotherapy nurse who administered the study drug pamidronate or placebo. Treatment assignment was based on the toss of a coin for the first patient, performed by the study nurse, and subsequently by alternating treatment assignment for the following study subjects. Patients received their treatment in the outpatient chemotherapy department. The dose and frequency for pamidronate administration was based on our experience using pamidronate in the prevention of bone loss; the dose was doubled in anticipation of the high remodeling due to ovarian failure (12). Based on the low calcium intake in this age group, as assessed in a population-based study (14), all subjects were advised to take a calcium/vitamin D supplement (500 mg calcium and 400 IU vitamin D/d). Subjects were reminded to take their supplement at their visits every 3 months. Information regarding intake of calcium and vitamin D from supplements was collected at baseline and at 12 months. Although only 25% of study subjects were taking a supplement of calcium and vitamin D at study entry, the proportion increased to 57% for calcium and 43% for vitamin D at 12 months.

The protocol was approved by the Research Committee and the Institutional Review Board of the American University of Beirut. All subjects signed informed consent.

Study subjects

Subjects were newly diagnosed premenopausal women with histologically proven, nonmetastatic breast cancer awaiting treatment with adjuvant chemotherapy. All subjects had a negative bone scan at study entry. The individual chemotherapeutic regimens were chosen by their oncologist and not dictated by the protocol. Exclusion criteria included any history of metabolic bone disease, history of having received any bisphosphonate or fluoride within a year of the start of the protocol, and history of intake of pharmacological amounts of any medications that can affect bone turnover (vitamin D, vitamin A, anabolic steroids, glucocorticoids, anticonvulsants, thiazides, or calcitonin). Also excluded were subjects with any history of allergy to bisphosphonates.

At screening, all subjects had a complete history, physical exam, and routine blood work with a complete blood count, liver function test, serum creatinine, a 25-OH vitamin D level, and a supersensitive TSH level. If eligible additional baseline studies included measurement of biochemical markers of bone remodeling, serum osteocalcin and CrossLaps, and BMD of the lumbar spine and total hip. Biochemical markers were measured at 3, 6, 9, and 12 months, and BMD measurements were repeated at 6 and 12 months of study entry. For each patient, markers were run in duplicate in the same assay at study completion.

Records of the caring oncologists were reviewed by the investigators after study completion for further follow-up on vital status and occurrence of metastatic disease. This information was available on 39 of 40 subjects with a mean follow-up of 2 ± 0.8 yr from study completion. These were exploratory analyses and not considered as primary end points.

Assays

Serum 25-OH vitamin D was measured by a competitive protein-binding assay using the Diasorin Incstar kit (Diasorin, Saluggia, Italy), with intra- and interassay coefficient of variation (CV) less than 13% at a serum concentration of 47 ng/ml. Serum TSH was measured by electrochemiluminescence immunoassay with intra- and interassay CV less than 8.6% for values between 0.003 and 0.07 μ U/ml (Roche, Minneapolis, MN). Serum osteocalcin levels were analyzed by immunoradiometric sandwich assay RIA, with intra- and inter-

assay CV less than 5% for values between 21.9 and 183.9 ng/ml (ELSA-osteokit, CIS Bio International, Gif-Sur-Yvette, France). Serum CrossLaps was determined by an ELISA, with intra- and interassay CV less than 6% for values between 1.7 and 3.5 nmol/liter (Osteometer Biotech, Herlev, Denmark).

BMD measurements

BMD of the lumbar spine (L1–L4) and the hip and total-body BMD, content, and body composition were performed at 0, 6, and 12 months using dual-energy x-ray absorptiometry. The study took place over 2 yr and overlapped with the transitioning in densitometers at our center. The first five subjects had their BMD measured at all time points on a Lunar DPX-L densitometer (Lunar, Madison, WI), nine subjects had their baseline BMD on a Lunar densitometer and their follow-up on a Hologic 4500 A densitometer (Hologic, Bedford, MA) including five who were randomized to treatment and four randomized to placebo, and 26 subjects had all their measurements on a Hologic 4500 A densitometer. A cross-calibration formula based on 72 subjects measured on both machines at the time of the transition allowed the expression of BMD in terms of Hologic units.

The results for percent changes in BMD both at the lumbar spine and total hip were evaluated using two approaches. In the first approach, percent changes in BMD were calculated as if all subjects had their BMD measured on the Hologic densitometer, using the cross-calibration formulas derived in our center (see below). In the second approach, actual percent changes in BMD were used in the 31 subjects who had their BMD on the same densitometer throughout the study, and calculated percent changes using conversion formulas were used in the nine subjects who transitioned from one machine to the other.

The mean values obtained with both methods, and the significance of the results, were identical, confirming the robustness of the study findings. The data shown under *Results* are based on the second approach.

The cross-calibration formulas derived were consistent with those published in the literature (15) and were as follows: total hip BMD Hologic $g/cm^2 = 0.968$ (total hip BMD Lunar g/cm^2) $- 0.031$ ($R^2 = 0.92$); lumbar spine L1–L4 Hologic $g/cm^2 = 0.835$ (lumbar spine Lunar g/cm^2) $+ 0.04$ ($R^2 = 0.92$). T-score for the lumbar spine and hip were calculated using the following formula: T-score = subject's BMD $-$ peak mean BMD/ SD of peak BMD. For the lumbar spine, peak BMD was provided by the densitometer software and is BMD for ages 20–29 yr. For the total hip, the following formula was used: total hip National Health and Nutrition Examination Study-based T-score = subject's BMD (on Hologic) $- 0.942/0.122$ (16). The precision of densitometry measurements at our center based on daily duplicates was $0.88 \pm 0.8\%$ at the lumbar spine ($n = 171$) and $0.83 \pm 0.7\%$ at the total hip ($n = 173$) for the period overlapping the study. These numbers are comparable to those we and others have previously published (17).

Statistical analyses

The main efficacy outcome was percent change in BMD at the lumbar spine and total hip, and the analyses performed were based on an intention to treat but essentially identical to per-protocol analyses as there was only one patient who dropped out during the 1-yr study because of the development of brain metastases and coma.

Differences between two groups were assessed by two-way ANOVA design with repeated measures (SAS version 8.02, Cary, NC). Because of the anticipated onset of amenorrhea in a large proportion of subjects, defined as complete loss of periods for at least 6 months from the start of treatment throughout the study duration, preplanned analyses included assessing the same end points in the subgroup of subjects who became amenorrheic while in the study.

The *t* tests were carried out using SPSS software, version 10.0 (SPSS, Chicago, IL). All results were expressed as mean (\pm *SD*) unless mentioned otherwise, two sided *P* values < 0.05 were considered as statistically significant.

Sample size calculation

Based on a 5% difference in BMD response at 1 yr between the two treatment arms, we anticipated that the protocol would require 20 pa-

tients per arm to prove the efficacy of pamidronate in preventing bone loss compared with placebo (power of 80%, $\alpha = 0.05$, and a dropout rate of 20%; GraphPad Instat, version 2.04a; Graphpad Software Inc., San Diego, CA). The 5% estimate was based on anticipated changes in lumbar spine BMD, the skeletal site that is most affected by estrogen deficiency in this population (5, 6).

Results

Clinical characteristics of study group

There were 40 subjects, 21 randomized to the pamidronate arm and 19 to placebo. Their mean age was 40 ± 6 yr, and they had a mean body mass index (BMI) of 27 ± 5 kg/m². As shown in Table 1, the subjects in the two treatment arms were comparable in all baseline characteristics including age, height, weight, BMI, percent lean mass, percent fat mass, baseline BMD both at the lumbar spine and hip, biochemical markers of bone remodeling, and treatment assignment. Patients received four to six cycles of chemotherapy depending on node status. Most patients (>80%) were prescribed a 5-FU, adriamycin, cyclophosphamide (FAC) regimen, 10% a cyclophosphamide, methotrexate, 5-FU (CMF) regimen, and 10–15% an anthracyclin (adriamycin or epirubicin) and cyclophosphamide (FAC-like) regimen by their oncologists (Table 1). Over two thirds were also started on tamoxifen at completion of the chemotherapy at a dose of 20 mg/d for a duration of 5 yr. This treatment was equally balanced between the two arms at study entry and by development of amenorrhea (see below). Over half of the patients became amenorrheic during the study, with no differences between the two treatment arms: 11 subjects in each of the pamidronate and placebo arms. The proportion of subjects on tamoxifen *vs.* no tamoxifen in the two subgroups was not

TABLE 1. Baseline characteristics of study participants

Characteristic	Pamidronate 60 mg (n = 21)	Placebo (n = 19)	P value
Age (yr)	40 (6)	40.5 (5)	0.8
Height (cm)	158 (7)	157 (7)	0.7
Weight (kg)	67 (15)	67 (12)	1.0
BMI (kg/m ²)	27 (5)	27 (4)	0.8
% Fat mass (kg)	25 (10)	24 (8)	0.8
Lean mass (kg)	40 (6)	40 (6)	0.9
Total hip BMD (g/cm ²)	0.84 (0.11)	0.89 (0.10)	0.2
T-score	-0.81 (0.92)	-0.45 (0.85)	0.2
Lumbar spine BMD (g/cm ²)	0.94 (0.14)	0.98 (0.10)	0.4
T-score	-1.12 (1.30)	-0.80 (0.88)	0.4
25-OH vitamin D [ng/ml, (nmol/liter)]	12.0 (11.5)	9.6 (6.4)	0.4
TSH mU/liter	1.6 (2.2)	1.7 (1.7)	0.9
Osteocalcin [ng/ml, (μ g/liter)]	20.4 (15.1)	18.0 (12.1)	0.6
CrossLaps (pmol/ml)	1.9 (2.2)	1.7 (2.0)	0.5
Tamoxifen [n (%)]	14 (67%)	14 (74%)	0.6
Stage [n (%)]			
I	2 (9%)	2 (11%)	
II	13 (62%)	9 (47%)	0.5
III	6 (29%)	8 (42%)	
Chemotherapy regimen [n (%)]			
FAC	16 (80%)	17 (84.2%)	
FAC-like regimens	2 (10%)	1 (5.3%)	0.8
CMF	2 (10%)	2 (10.5%)	

Data are expressed as mean (SD). FAC-like regimens contain an anthracyclin (adriamycin or epirubicin) and cyclophosphamide. The biochemical assays are reported in metric units (Système International). To change from metric to Système International, multiply 25-OH vitamin D by 2.496 and osteocalcin by 1.0.

significantly different by χ^2 . The mean age at study entry of women who became amenorrheic was 42 ± 5 yr and was 38 ± 5 yr in the women who did not become amenorrheic ($P = 0.02$).

BMD changes of the spine and hip at 6 and 12 months after study entry

Overall study group. As shown in Table 2 and Fig. 1, BMD stabilized at the lumbar spine in the pamidronate group and decreased in the placebo group, with a significant treatment effect at both the 6- and 12-month time points. Although the trend was similar at the total hip, a significant treatment effect was not achieved (Table 2 and Fig. 1).

Amenorrheic group. As shown in Fig. 2, BMD stabilized at the lumbar spine in the pamidronate group and decreased in the placebo group, with a significant treatment effect at both the 6- and 12-month time points. Similarly, at the total hip, BMD stabilized in the pamidronate group and decreased in the placebo group, with a treatment effect noted at 12 months and an almost significant effect at 6 months.

Nonamenorrheic group. There were no differences in percent change in BMD at either the lumbar spine or the total hip by treatment group at either time point in the nonamenorrheic subgroup ($P = 0.15$ at the lumbar spine; $P = 0.81$ at the hip at 12 months).

Markers of bone remodeling

Overall study group. There were no significant changes in the markers of bone remodeling markers as assessed by serum osteocalcin and of bone resorption markers as assessed by serum CrossLaps at any time point in either the pamidronate or placebo arm.

The mean values for serum osteocalcin at 6 and 12 months were 21.4 ± 10.4 and 22.3 ± 12.8 in the placebo group and 19.9 ± 13.5 and 21.6 ± 15.2 in the pamidronate group. The mean serum CrossLaps at 6 and 12 months were 2.1 ± 2.8 and 1.8 ± 2.4 in the placebo group and 2.2 ± 2.7 and 2.7 ± 5.1 in the pamidronate group. Similarly, subgroup analysis of patients who became amenorrheic revealed that the mean se-

TABLE 2. Percent changes in BMD in patients randomized to receive pamidronate or placebo during 1 yr

Site	Change in BMD (%)		Treatment effect		
	Pamidronate	Placebo	Mean	95% CI	P
Overall study group (n = 40)					
Lumbar spine					
6 months	1.8 (4.4)	-2.8 (2.6)	4.6	(2.2, 6.9)	0.000
12 months	1.9 (4.6)	-3.2 (5.0)	5.1	(-2.0, 8.2)	0.002
Total hip					
6 months	-0.2 (4.1)	-1.1 (2.6)	0.9	(-1.5, 3.3)	0.44
12 months	-0.3 (4.5)	-2.8 (4.0)	2.6	(-0.3, 5.5)	0.08
Amenorrheic group (n = 22)					
Lumbar spine					
6 months	1.1 (3.2)	-2.8 (3.2)	4.0	(1.0, 6.9)	0.01
12 months	0.95 (3.7)	-4.0 (5.8)	5.0	(0.6, 9.2)	0.03
Total hip					
6 months	1.5 (3.5)	-0.7 (1.1)	2.2	(-0.2, 4.6)	0.07
12 months	1.2 (3.0)	-4.0 (3.8)	5.2	(2.0, 8.3)	0.003

Data are expressed as mean (SD). CI, Confidence interval.

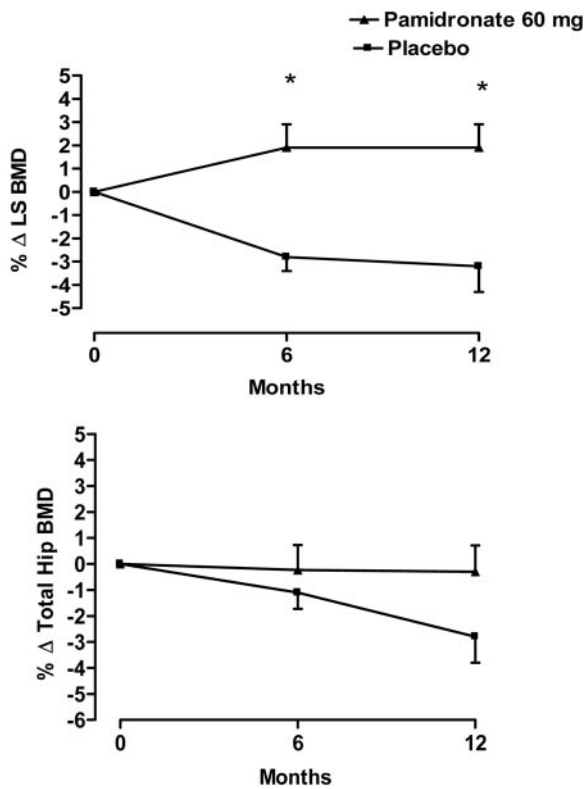


FIG. 1. Percent change (mean \pm SEM) in BMD at the lumbar spine (LS) (*top*) and total hip (*bottom*) in the overall study group by treatment. Subjects received pamidronate 60 mg or placebo infusion every 3 months for a total of four doses from study entry. *, Significant difference in percent change in BMD between the two arms by repeated-measures ANOVA. There was a significant treatment effect at the lumbar spine at 6 and 12 months ($P = 0.0003$).

rum osteocalcin at 6 and 12 months were 21.1 ± 10.1 and 22.1 ± 12.0 ng/ml in the placebo group and 23.8 ± 13.0 ng/ml in the pamidronate group. The mean serum Cross-Laps at 6 and 12 months were 2.3 ± 3.6 and 1.1 ± 0.9 pmol/ml in the placebo group and 1.4 ± 1.3 and 2.3 ± 3.4 pmol/ml in the pamidronate group. There were no differences in the markers of bone remodeling between the two treatment groups.

Follow-up events: metastasis and survival

All follow-up events were captured after the 1-yr study was completed. The mean follow-up duration from study entry was 2 ± 0.8 yr for patients in the placebo arm and 1.9 ± 0.8 yr for patients in the pamidronate arm ($P = 0.8$). Five patients developed metastases in the placebo arm: one in the contralateral breast, one to bone, one to liver and bone, one to bone and brain, and one to lung liver and bone. Three patients in the pamidronate group developed metastases: one to bone; one to liver, lung, and bone; and one to bone, adrenal, lung, and liver. There was no difference between the two treatment arms in the proportion of subjects who developed metastases in general or bone metastases in particular. Three patients died in the placebo arm and two in the pamidronate arm, with no difference in survival rates or time to death from study entry between the two groups.

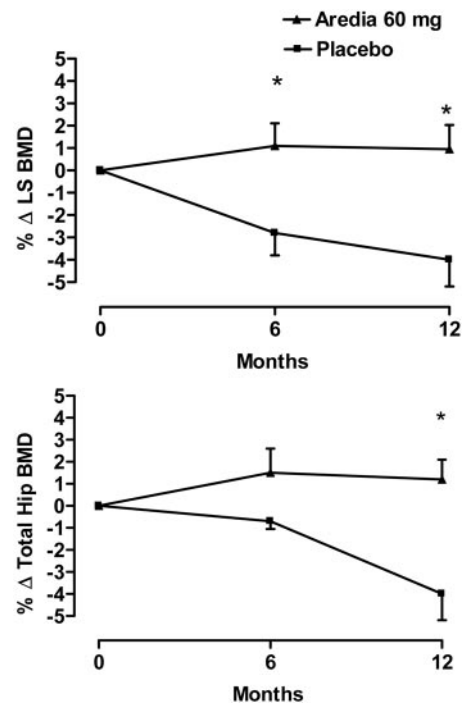


FIG. 2. Percent change (mean \pm SEM) in BMD at the lumbar spine (LS) (*top*) and total hip (*bottom*) in amenorrheic patients. Subjects received pamidronate 60 mg or placebo infusion every 3 months for a total of four doses from study entry. *, Significant difference in percent change in BMD between the two arms by repeated-measures ANOVA. There was a significant treatment effect at the lumbar spine at 6 and 12 months ($P = 0.0084$) and a significant treatment effect at the total hip at 12 months ($P = 0.026$).

Safety

No clinical symptoms of hypocalcemia were reported. Treatment was well tolerated; only one subject reported a flu-like syndrome that occurred with the first pamidronate infusion, which did not recur.

Discussion

Substantial bone loss takes place after chemotherapy in young premenopausal women with breast cancer. Bone loss was noted at the lumbar spine and hip, was more accentuated in the subgroup who became amenorrheic, and was prevented by cyclical administration of iv pamidronate.

Ovarian failure is a well recognized complication of chemotherapy in premenopausal woman (3, 5, 6, 7, 18, 19), occurring in a substantial proportion of patients, 40–70%, depending on the study (5, 7). Age is a significant predictor of ovarian failure in women receiving chemotherapy (5–7). In our study, women who developed amenorrhea were 42 yr old, on the average 4 yr older than those who did not. Ovarian failure has been shown to correlate with bone loss (5, 9), a loss that is most substantial at sites of high bone remodeling such as the lumbar spine (5–7). In the current study, bone loss at 12 months in the placebo arm averaged 3% at the lumbar spine and total hip in the overall study group and 4% at the lumbar spine and total hip in the amenorrheic subgroup. These values fell well within the reported decrements at these sites within a similar time frame (5–7, 9, 20, 21). These

decrements can be quite detrimental to skeletal health for the following reasons: first, they can be cumulative over 2–3 yr resulting in one half to a full SD decrease in BMD (9, 21); second, long-term follow-up suggests that they are not reversible (21). Furthermore, such decrements in BMD would be carried into older ages and are therefore anticipated to increase fracture risk with aging, with reported relative risks varying from 1.5–2.5 (22). Hence, there is a pressing need to evaluate therapies to prevent chemotherapy-induced bone loss in young women (3).

Few are the trials that have evaluated therapies to mitigate chemotherapy-induced bone loss in young women; the agents used were bisphosphonates (5, 6, 9, 20). Clodronate administered at a dose of 1600 mg daily failed to completely abolish bone loss at the lumbar spine in premenopausal women who became amenorrheic (5). Moreover, this bisphosphonate is not readily available worldwide. Oral risedronate administered at the dose of 30 mg cyclically prevented bone loss; however, it was used in women who were already 15 months past menopause (6). The iv bisphosphonates, such as zoledronate and pamidronate, are an attractive alternative circumventing gastrointestinal side effects, an important consideration in patients receiving chemotherapy where such side effects have been reported in up to 94% of patients (5). The iv agents may also have the additional advantage over oral bisphosphonates of preventing the occurrence of skeletal metastases, a benefit that has not been consistently demonstrated with the oral bisphosphonate clodronate (23, 24). Conversely, pamidronate was demonstrated to reduce skeletal events in patients with breast cancer and multiple myeloma (25, 26).

Tamoxifen, a commonly used therapy in breast cancer, seems to have a dichotomous effect on bone that is largely determined by the estrogen status of the patient. Indeed, it was shown to have a protective effect on bone in estrogen-deficient women (6, 27) but failed to do so in estrogen-replete subjects (20, 28). None of the studies had power to elucidate the effect of tamoxifen on bone when administered concomitantly with chemotherapy in young women (3, 5, 7). In this study, confounding was not a consideration because subjects on tamoxifen were equally distributed between the two treatment arms in the overall group and by amenorrheic status.

Bone remodeling markers measured right before the dose of pamidronate did not differ between the two treatment arms. This may be explained by the random timing of the blood draw and/or the dose of pamidronate used. Serum markers were not consistently measured in the morning and fasting state (29) and were drawn 3 months after the pamidronate dose, a time point that may have been well beyond their nadir. It is also possible that the dose of pamidronate used, in view of anticipated high remodeling caused by ovarian failure, was suboptimal. Indeed, our trial was not a dose-ranging/frequency study, and it is possible that higher or more frequent doses may have been more efficacious in reducing bone remodeling or in increasing bone density further. On the average, BMD was maintained or slightly increased, results that are similar or even superior to those reported with clodronate (5, 20) and comparable to those of oral risedronate in postmenopausal women (6). Although higher doses may have increased bone density further, this

may have been at the expense of unwarranted hypocalcemia. Furthermore, pamidronate was used in a preventive mode with the goal to maintain rather than to increase bone mass in premenopausal women with normal bone density at entry.

Other limitations that apply to our study as well as preceding ones (5, 6) include its relatively small sample size rendering it unable to address the putative deleterious effect of tamoxifen on bone in young premenopausal women and the anticipated protective effect of pamidronate on the occurrence of skeletal metastases (5–7), the latter being, however, purely exploratory analyses. These, however, can only be elucidated in large multicenter trials, such as the Cancer and Leukemia Cooperative Group and the National Adjuvant Surgical Bowel and Breast Cancer Project (30). Although all subjects were advised to take calcium and vitamin D, and did so upon questioning on follow-up visit, it is possible that the low vitamin D levels may have minimized the beneficial effect of the intervention on bone loss. Standard practice would have been to correct the hypovitaminosis D before starting bisphosphonate therapy, which was not done in order not to delay the start of chemotherapy. It is unlikely that the subjects had severe osteomalacia because none had bone pain, muscle weakness, or clinical hypocalcemia after pamidronate administration. However, bone histomorphometry data were not available to exclude osteomalacia in a definitive manner. Finally, the use of a cross-calibration formula when switching densitometers in one fourth of subjects may have confounded the results. However, as detailed in *Results*, despite the methodology used to calculate BMD changes over time, the results were quite robust in the overall group and in the amenorrheic subgroup.

Advantages of our study include its randomized, double-blind, placebo-controlled design and the fact that it established the efficacy of pamidronate in preventing bone loss in young women with an excellent safety profile. Indeed, only one patient in the pamidronate group experienced side effects, but they did not lead to her discontinuation from the study. Although we and other have reported a higher incidence of side effects in patients receiving pamidronate for osteoporosis (12), it is plausible that the low incidence reported herein is a result of the fact that cancer patients experience significant side effects from the chemotherapy itself, thus rendering ascertainment of side effects from pamidronate difficult. Pamidronate can be administered to young women receiving chemotherapy for breast cancer after a careful evaluation of its risk-benefit ratio, taking into consideration each patient's individual clinical profile.

In conclusion, iv pamidronate given at the dose of 60 mg every 3 months prevented chemotherapy-induced bone loss in young premenopausal women, was well tolerated, and is an attractive alternative in preserving skeletal health in such patients pending the results of large trials.

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