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EFFICACY OF PAMIDRONATE IN REDUCING SKELETAL COMPLICATIONS IN PATIENTS WITH BREAST CANCER AND LYTIC BONE METASTASES

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ABSTRACT

Background Bisphosphonates such as pamidronate disodium inhibit osteoclast-induced bone resorption associated with cancer that has metastasized to bone.

Methods Women with stage IV breast cancer who were receiving cytotoxic chemotherapy and had at least one lytic bone lesion were given either placebo or pamidronate (90 mg) as a two-hour intravenous infusion monthly for 12 cycles. Skeletal complications, including pathologic fractures, the need for radiation to bone or bone surgery, spinal cord compression, and hypercalcemia (a serum calcium concentration above 12 mg per deciliter [3.0 mmol per liter] or elevated to any degree and requiring treatment), were assessed monthly. Bone pain, use of analgesic drugs, performance status, and quality of life were assessed throughout the trial.

Results The efficacy of treatment was evaluated in 380 of 382 randomized patients, 185 receiving pamidronate and 195 receiving placebo. The median time to the occurrence of the first skeletal complication was greater in the pamidronate group than in the placebo group (13.1 vs. 7.0 months, $P=0.005$), and the proportion of patients in whom any skeletal complication occurred was lower (43 percent vs. 56 percent, $P=0.008$). There was significantly less increase in bone pain ($P=0.046$) and deterioration of performance status ($P=0.027$) in the pamidronate group than in the placebo group. Pamidronate was well tolerated.

Conclusions Monthly infusions of pamidronate as a supplement to chemotherapy can protect against skeletal complications in women with stage IV breast cancer who have osteolytic bone metastases. (N Engl J Med 1996;335:1785-91.)

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BONE metastases occur in most women with advanced breast cancer. The destruction of bone in these lesions results from osteoclast-induced bone resorption that may be stimulated by osteoclast-activating factors released by tumor cells.^{1,2} Cytotoxic chemotherapy or hormone therapy is the preferred treatment for symptomatic bone disease, but progressive skeletal destruction ultimately leads to increased pain, immobility, and deterioration in the quality of life.

Bisphosphonates are potent inhibitors of osteoclastic bone resorption and are effective in treating cancer-related hypercalcemia.^{3,4} Pamidronate disodium, a second-generation bisphosphonate, inhibits the resorption of bone at doses that do not affect bone mineralization.⁵ The results of several open-label trials suggest that pamidronate may reduce skeletal complications⁶⁻¹⁰ and biochemical markers of bone resorption^{9,10} in patients with bone lesions due to metastatic breast cancer.⁶⁻¹⁰ At least half the patients treated with intravenous pamidronate at

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TABLE 1. CHARACTERISTICS OF THE PATIENTS WITH ADVANCED BREAST CANCER AND SKELETAL DISEASE WHO COULD BE EVALUATED, ACCORDING TO STUDY GROUP.*

CHARACTERISTIC	PAMIDRONATE (N = 185)	PLACEBO (N = 195)
Age — yr	57±12	56±12
Stratum — no. of patients (%)†		
1	121 (65)	128 (66)
2	64 (35)	67 (34)
Estrogen- and progesterone-receptor status — no. of patients (%)		
Positive for either or both	116 (63)	120 (62)
Other	69 (37)	75 (38)
Metastases in addition to bone — no. of patients (%)		
Lung	25 (14)	30 (15)
Liver	30 (16)	29 (15)
Brain	6 (3)	1 (1)
Other	18 (10)	27 (14)
None, bone only	115 (62)	117 (60)
Time from primary diagnosis to bone metastases — yr	4.3±4.6	3.8±4.5
Time from bone metastases to study entry — yr	1.9±2.5	1.6±1.7
Bone lesions ≥1 cm in diameter — no. of patients (%)		
1 lesion	80 (43)	82 (42)
2 lesions	69 (37)	71 (36)
≥3 lesions	36 (19)	42 (22)
Skeletal complications during the 3 mo before study entry — no. of patients (%)		
Need for radiation	41 (22)	57 (29)
Fracture	30 (16)	35 (18)
Pain score — no. of patients (%)‡		
0	31 (17)	27 (14)
1–3	74 (40)	76 (39)
4–9	80 (43)	92 (47)
No. of prior chemotherapy regimens — no. of patients (%)		
0 or 1	84 (45)	80 (41)
2 or 3	87 (47)	104 (53)
≥4	14 (8)	11 (6)
No. of prior hormone treatments — no. of patients (%)		
0 or 1	90 (49)	102 (52)
2 or 3	77 (42)	77 (39)
≥4	18 (10)	16 (8)
ECOG performance score — no. of patients (%)		
0	34 (18)	30 (15)
1	87 (47)	98 (50)
2	37 (20)	52 (27)
3	27 (15)	15 (8)

*Plus-minus values are means ±SD. ECOG denotes Eastern Cooperative Oncology Group.

†Patients were stratified before randomization according to whether they had ECOG performance-status scores of 0 or 1 (stratum 1) or 2 or 3 (stratum 2).

‡Pain was scored by multiplying the severity of pain by the frequency of pain, with each of these measures graded from 0 to 3. Thus, a score of 0 denoted no pain, whereas a score of 9 denoted severe, constant pain.

regular intervals, ranging from weekly to every three months, had relief of bone pain and evidence of healing or stabilization of lytic bone lesions. In one of these studies, a 90-mg dose of pamidronate administered every four weeks was more effective than lower doses in reducing pain.⁹ Even a single 90-mg dose of intravenous pamidronate relieved pain effectively in approximately half of patients with progressive bone metastases of breast cancer.¹¹ We conducted a randomized, double-blind study to compare monthly infusions of pamidronate (90 mg) with placebo (5 percent dextrose in water) for the prevention of skeletal complications in patients with such metastases. The drug was given in addition to chemotherapy.

METHODS

Patients

We enrolled women with stage IV breast cancer who were receiving cytotoxic chemotherapy and had at least one predominantly lytic, metastatic bone lesion at least 1 cm in diameter. Patients were enrolled at 97 study sites (constituting the Protocol 19 Aredia Breast Cancer Study Group) in the United States, Canada, Australia, and New Zealand from January 1991 through March 1994. All the patients had Eastern Cooperative Oncology Group (ECOG) scores for performance status¹² of 0 to 3 at the time of enrollment and an estimated life expectancy of at least nine months. In each patient, the presence of a lytic lesion that could be evaluated was confirmed by the central radiologist.

Patients were ineligible for the study if they had a skeletal complication (a pathologic fracture, the need for radiation to bone or bone surgery, or spinal cord compression due to vertebral collapse) or a corrected serum calcium concentration (corrected for serum albumin concentration) above 12.0 mg per deciliter (3.0 mmol per liter) during the two weeks before enrollment, a serum creatinine concentration above 2.5 mg per deciliter (220 μmol per liter), ascites or a serum total bilirubin concentration above 2.5 mg per deciliter (43 μmol per liter), or a New York Heart Association (NYHA) ranking¹³ of class III or IV. Patients were also excluded from the study if they were treated with a bisphosphonate (except as part of the study) during the 60 days before enrollment or at any time during the trial or if they had been treated for bone pain with radiation, corticosteroids (except as part of the patient's chemotherapeutic regimen), calcitonin, or pliamycin during the 2 weeks before enrollment. If a bone lesion had been treated with radiation during the three months before enrollment, it was disqualified from evaluation in this study. During the trial, the chemotherapy regimen (but not the study drug) received by an individual patient could be changed or discontinued at the discretion of the attending oncologist.

Study Design

Before randomization, eligible patients were stratified according to their ECOG scores for performance status, so that stratum 1 contained patients with scores of 0 or 1 and stratum 2 contained patients with scores of 2 or 3. Within each stratum the patients were randomly assigned (in equal numbers) to receive either 90 mg of pamidronate disodium (Aredia, Ciba-Geigy, Summit, N.J.; administered in 250 ml of 5 percent dextrose in water) or placebo (250 ml of 5 percent dextrose in water), administered 12 times as a two-hour infusion at intervals of four weeks, although the patients were allowed to receive the study drug every three weeks if they were receiving chemotherapy on a three-week schedule. A site-specific, computer-generated randomization list was provided in advance to the study pharmacist at each site, who prepared the medication within 24 hours before

its use. Other study personnel, as well as the patients and investigators, remained unaware of the treatment assignments.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics review board at each institution. All the patients provided written informed consent. The results obtained during the 12 cycles of treatment are reported here. Several patients required up to 14 months for the assessment of skeletal complications to be completed because of delays in the infusion of the 12 cycles of study drug related to the scheduling of chemotherapy.

Study Assessments

At each monthly visit, patients were evaluated for the occurrence of skeletal complications, including pathologic fractures, spinal cord compression with vertebral compression fracture, the need for surgery to treat or prevent pathologic fractures or spinal cord compression, or the need for radiation to bone. Patients were also assessed for hypercalcemia, defined as a documented corrected serum calcium concentration above the normal range that required treatment or a corrected serum calcium concentration of 12 mg per deciliter (3.0 mmol per liter), with or without treatment. The assessments at 3, 4, 6, 9, 10, and 12 months included evaluations of bone pain and analgesic-drug use, as previously described¹⁴; determinations of ECOG performance status; scoring on the Spitzer quality-of-life index¹⁵; and physical examination.

Radiographic surveys of the skeleton were performed before entry into the study and after 3, 6, and 12 cycles of treatment. Of the pathologic fractures observed in the study, 46 percent were in the ribs, 41 percent were vertebral, 7 percent were in the long bones, and 6 percent were pelvic. Twenty-one percent of patients had at least one vertebral fracture, 19 percent had at least one rib fracture, 7 percent had at least one fracture of a long bone, and 4 percent had at least one pelvic fracture. The response of bone lesions was assessed by the central radiologist according to a modification of the criteria of the International Union against Cancer for the classification of patients with breast cancer,¹⁶ with recalcification used as a marker of the healing of osteolytic lesions. Pathologic fractures were not considered evidence of progressive disease in bone. A vertebral fracture was defined as a loss of at least 25 percent of vertebral-body height between evaluations. The central radiologist evaluated all x-ray films and was unaware of each patient's treatment regimen.

Studies performed in the clinical laboratory before study entry and periodically during treatment included a complete blood count, with differential and platelet count; serum chemical analysis; measurements of serum bone alkaline phosphatase (after 6 and 12 cycles of treatment) and serum carcinoembryonic antigen (after 2, 4, 6, 9, and 12 cycles); and urinalysis. Two-hour urine samples were collected in fasting patients before study entry and after 6 and 12 cycles for the determination of calcium, hydroxyproline, and creatinine concentrations. Data on efficacy and safety were analyzed for the 12 months of the trial, and each patient was followed for survival until the patient's death, the last date of contact or loss to follow-up, or February 1, 1995, whichever occurred first.

Statistical Analysis

Kaplan-Meier estimates of the time from randomization to the first occurrence of a skeletal complication were calculated for each study group; the log-rank test was used for comparisons between groups. The proportions of patients who had a first skeletal complication by the end of 3, 6, 9, and 12 cycles of treatment (up to 126, 210, 294, and more than 400 days, respectively) were estimated from the Kaplan-Meier curves of the time to the first event. In addition, the actual proportion of patients in each study group who had a skeletal complication by the end of 3, 6, 9, and 12 cycles was calculated as the cumulative number of patients who had an event by the end of that time period divided by the total number of patients in the study group. The chi-square test was used to compare these proportions between groups.

Changes from base line in bone pain, scores for the use of an-

algesic drugs, ECOG performance status, and the quality-of-life index and percent changes from base line in serum concentrations of carcinoembryonic antigen and bone metabolic markers were compared between groups by the Wilcoxon rank-sum test. The chi-square test was used to compare the response rates of bone lesions on the basis of radiologic assessments. Kaplan-Meier estimates of the time from randomization until death (with the data censored as of February 1, 1995) were calculated for each study group, and the groups were compared by the log-rank test. All tests were two-sided. Primary analyses of the aggregate data were planned after 12 cycles.

RESULTS

We enrolled 382 women in the study; 185 women were randomly assigned to receive pamidronate, and 197 to receive placebo. All the patients were included in the safety assessments and analyses of survival. Two patients in the placebo group did not have bone metastases that could be evaluated, and they were excluded from all the efficacy analyses.

The clinical features at entry into the study were similar in the two groups (Table 1). There were no differences between the groups in the number of prior chemotherapy regimens or hormonal treatments, the use of analgesic drugs, or quality-of-life scores (data not shown). During the trial, 23 percent of the pamidronate group and 22 percent of the placebo group received megestrol acetate; 19 and 21 percent, respectively, received tamoxifen; and 6 and 4 percent received aminoglutethimide. The chemotherapy regimens and hormonal treatments used in the two groups were similar at study entry and throughout the trial. Specifically, there was no difference between the groups in the percentage of patients who were treated with doxorubicin-containing regimens or tamoxifen.

Forty-eight percent of the patients completed all 12 cycles of pamidronate or placebo. The most common reasons for premature discontinuation of the study treatment were adverse clinical side effects, death, and refusal to continue therapy; all these reasons were equally distributed between the groups. The mean duration of participation in the study was 9.6 months in the pamidronate group and 8.9

TABLE 2. PATIENTS IN THE STUDY GROUPS ACCORDING TO THE DURATION OF THEIR PARTICIPATION.

NO. OF MONTHS IN STUDY	PAMIDRONATE (N = 185)	PLACEBO (N = 197)*
	no. of patients (% of group)	
0 to <3	14 (8)	19 (10)
3 to <6	22 (12)	39 (20)
6 to <9	32 (17)	29 (15)
9 to <12	18 (10)	26 (13)
≥12	99 (54)	84 (43)

*The two patients who were enrolled in the study but excluded from the efficacy analyses because they did not have bone metastases that could be evaluated are included here.

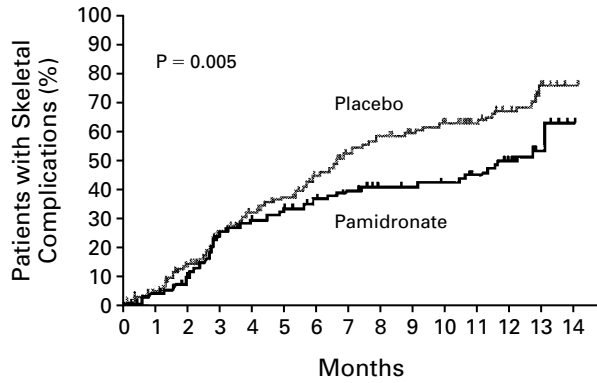


Figure 1. Kaplan–Meier Estimates of the Time to the First Skeletal Complication.

months in the placebo group. Table 2 shows the duration of participation in the trial. The median duration of follow-up in the assessments of efficacy (regarding skeletal complications) and safety was 11.9 months in the pamidronate group and 10.2 months in the placebo group. In the survival analyses, the median duration of follow-up was 25.7 months in the pamidronate group and 27.8 months in the placebo group. Six patients were lost to follow-up.

Skeletal Complications

The median time to the first skeletal complication (Fig. 1) was significantly less in the placebo group than in the pamidronate group (7.0 vs. 13.1 months, $P=0.005$ by the log-rank test). The times to the

TABLE 3. SKELETAL COMPLICATIONS AFTER THE COMPLETION OF 3, 6, 9, AND 12 CYCLES OF TREATMENT.

TYPE OF COMPLICATION	PATIENTS WITH A COMPLICATION			KAPLAN–MEIER ESTIMATES OF THE PROPORTION WITH A COMPLICATION		
	PAMIDRONATE (N=185)	PLACEBO (N=195)	P VALUE*	PAMIDRONATE (N=185)	PLACEBO (N=195)	P VALUE†
	no. (%)			%		
All skeletal complications‡						0.005
3 cycles	50 (27)	59 (30)	0.49	29	34	
6 cycles	65 (35)	91 (47)	0.02	39	54	
9 cycles	68 (37)	102 (52)	0.002	41	63	
12 cycles	79 (43)	110 (56)	0.008	62	75	
Pathologic fracture, nonvertebral						0.01
3 cycles	24 (13)	29 (15)	0.59	14	17	
6 cycles	31 (17)	47 (24)	0.08	19	29	
9 cycles	34 (18)	51 (26)	0.07	21	33	
12 cycles	37 (20)	59 (30)	0.02	25	62	
Pathologic fracture, vertebral						0.49
3 cycles	26 (14)	16 (8)	0.07	15	9	
6 cycles	35 (19)	24 (12)	0.08	21	15	
9 cycles	36 (19)	33 (17)	0.52	22	23	
12 cycles	42 (23)	37 (19)	0.37	38	30	
Radiation to bone						0.001
3 cycles	21 (11)	30 (15)	0.25	12	17	
6 cycles	28 (15)	48 (25)	0.02	17	29	
9 cycles	30 (16)	61 (31)	0.001	18	40	
12 cycles	36 (19)	65 (33)	0.002	24	44	
Surgery on bone						0.01
3 cycles	5 (3)	8 (4)	0.45	3	5	
6 cycles	5 (3)	12 (6)	0.10	3	8	
9 cycles	6 (3)	17 (9)	0.02	4	12	
12 cycles	7 (4)	19 (10)	0.02	14	29	
Hypercalcemia						0.02
3 cycles	2 (1)	11 (6)	0.02	1	7	
6 cycles	9 (5)	15 (8)	0.26	6	9	
9 cycles	10 (5)	22 (11)	0.04	7	15	
12 cycles	11 (6)	24 (12)	0.03	8	17	

*P values were determined by the unadjusted Pearson chi-square test.

†P values were determined by the log-rank test.

‡Hypercalcemia was not included among the skeletal complications studied here.

first nonvertebral pathologic fracture ($P=0.01$), the first radiation treatment of bone ($P=0.001$), and the first bone surgery ($P=0.01$) were also shorter in the placebo group, as was the time to the first episode of hypercalcemia ($P=0.02$). The proportion of patients who had any skeletal complication and the proportion who received radiation treatment of bone were significantly lower in the pamidronate group than in the placebo group after 6, 9, and 12 cycles of treatment (Table 3). The proportion of patients who required bone surgery was significantly smaller in the pamidronate group than in the placebo group after 9 cycles of treatment, and the proportion with new nonvertebral pathologic fractures was significantly smaller after 12 cycles. There were no significant differences between the groups in the proportion of patients with new vertebral pathologic fractures (Table 3) or new pathologic fractures of any type, vertebral and nonvertebral combined (data not shown). The proportion of patients with hypercalcemia was significantly lower in the pamidronate group than in the placebo group after 3, 9, and 12 cycles of treatment. Spinal cord compression with vertebral compression fracture developed in only 2 percent of the patients in each treatment group.

Radiologic Assessment

Eighty-five percent of the patients had radiologic assessments both at base line and subsequently. Of the patients who could be evaluated radiologically, a significantly higher proportion in the pamidronate group had complete or partial responses than in the placebo group (33 percent vs. 18 percent, $P=0.001$).

Quality-of-Life Variables

The patients in the pamidronate group had decreases from base line in bone pain after three, six, and nine cycles of treatment (Fig. 2), whereas the patients in the placebo group had progressive worsening of bone pain. At the final measurement, the pain scores were increased from base line in both groups, but the increase was significantly greater in the placebo group. A similar pattern was observed for analgesic-drug use (data not shown). Among the patients with pain at base line, significantly more in the pamidronate group had decreased pain scores at the last measurement than in the placebo group (44 percent vs. 32 percent, $P=0.03$). In both groups, ECOG performance scores and Spitzer quality-of-life scores worsened from base line to the end of the study, with significantly more worsening in ECOG performance scores in the placebo group ($P=0.03$).

Metabolic Markers of Tumor and Bone

There were no differences between the groups in the change from base line in serum concentrations of carcinoembryonic antigen; at the final measure-

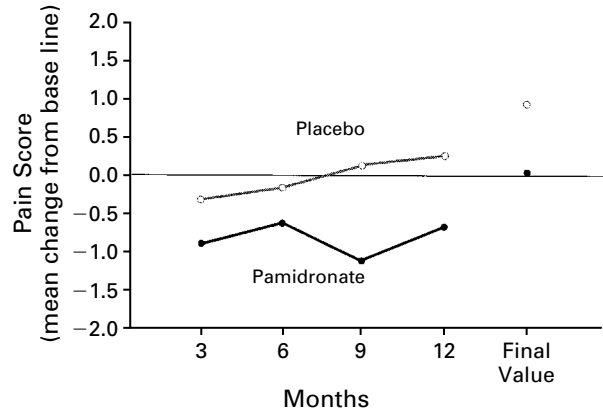


Figure 2. Mean Changes in the Pain Scores of Patients with Pain at Base Line.

“Final values” were calculated from the last scores obtained after base line for each patient, whether the patient completed the study or not. The differences between the groups both at nine months and in the final measurement were statistically significant ($P\leq 0.05$).

TABLE 4. MEDIAN PERCENT CHANGE FROM BASE LINE AT THE LAST STUDY MEASUREMENT.*

VARIABLE	PAMIDRONATE		PLACEBO	
	NO. OF PATIENTS	PERCENT CHANGE	NO. OF PATIENTS	PERCENT CHANGE
Urinary hydroxyproline:creatinine	113	-33	108	-6
Urinary calcium:creatinine	114	-28	108	+25
Serum bone alkaline phosphatase	113	-41	106	-1

* $P<0.001$ for the difference between groups for each variable shown.

ment, the median increase in both groups was 40 percent. Changes in serum and urinary markers of bone resorption and formation at the final measurement are shown in Table 4. The median decreases from base line in the measures of bone resorption — the ratio of the urinary hydroxyproline concentration to the creatinine concentration and the ratio of the urinary calcium concentration to the creatinine concentration — were both significantly greater in the pamidronate group, as was the decrease from base line in serum concentrations of bone alkaline phosphatase, a marker of bone formation.

Adverse Events

The infusions of pamidronate were well tolerated. The incidence of adverse clinical side effects and toxic effects of chemotherapy was similar in the two study groups. Three patients in the pamidronate group were withdrawn from the study because of

pamidronate-related toxicity: one patient was hospitalized because of increased weakness, fatigue, and dyspnea; one was hospitalized because of symptomatic hypocalcemia (serum calcium, 7.2 mg per deciliter [1.8 mmol per liter]); and one refused further therapy because of severe bone pain after each infusion. No patients in the placebo group were withdrawn because of placebo-related toxicity.

Outcome

Overall survival was not significantly affected by pamidronate. The median estimate of survival was 14.8 months in the pamidronate group and 14.2 months in the placebo group.

DISCUSSION

Besides analgesic drugs, radiotherapy, and surgery, there is currently no specific treatment for cancer-related bone disease other than the hormonal therapy or chemotherapy directed against the cancer. In metastatic breast cancer, chemotherapy is normally reserved for patients with hormone-resistant disease. In these patients, response rates in bone are generally lower than the overall response rates to chemotherapy.¹⁷⁻²³ A survey of data on bone responses from several studies of chemotherapy in patients with advanced breast cancer suggests that the response rates range from 0 to 30 percent.²⁴

In our study, monthly infusions of pamidronate as a supplement to chemotherapy significantly reduced the incidence of complications of lytic bone metastases in patients with advanced breast cancer and delayed the onset of the complications. Overall morbidity from skeletal causes was reduced by the end of six cycles of treatment, but the effects of pamidronate became more evident with successive treatments. The occurrence of episodes of hypercalcemia was reduced after 3 cycles of treatment, the need for radiation to bone was reduced after 6 cycles, the need for surgery on bone was reduced after 9 cycles, and the occurrence of nonvertebral pathologic fractures was reduced after 12 cycles. For all these events, the time to the first occurrence was significantly greater in the pamidronate group.

Other than spinal cord compression, which occurred in only a few patients, the only skeletal complications whose incidence was not reduced by pamidronate treatment were pathologic vertebral fractures. In a study of patients with stage III multiple myeloma, pamidronate administered monthly for nine cycles (in addition to antimyeloma treatment) reduced the rates of both vertebral and nonvertebral fractures.²⁵ The lack of effect of pamidronate on vertebral fractures in our trial may be due to the aggressiveness of the osteolytic bone process in patients with breast cancer.

There were significant initial decreases in pain and narcotic scores in the pamidronate group, but not in the placebo group, confirming the early palliative ef-

fect previously observed in patients with skeletal metastases.²⁵⁻²⁷ By the final measurement, pain scores increased in both groups, but they increased significantly more in the placebo group. However, the proportion of patients who required radiation therapy of bone lesions remained significantly smaller in the pamidronate group. Most patients undergoing radiation therapy received it for the relief of bone pain. The effect of pamidronate on bone pain may partly explain the fact that there was significantly less worsening of ECOG performance scores in the group receiving the drug. A similar effect was seen in the multiple myeloma trial.²⁵

Since there was no difference in survival between the two groups, pamidronate does not appear to affect the underlying metastatic disease.^{25,27} This is also suggested by the fact that the groups did not differ with respect to serum carcinoembryonic antigen concentrations.

We conclude that monthly infusions of pamidronate are an effective supplement to chemotherapy for the reduction of skeletal complications and the relief of symptoms associated with lytic bone lesions due to metastatic breast cancer. Pamidronate is safe and well tolerated as palliative treatment of osteolytic bone metastases.

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APPENDIX

In addition to the authors, the following principal investigators of the Protocol 19 Aredia Breast Cancer Study Group participated in this study. *United States* — N. Abramson, Jacksonville, Fla.; T. Beck, Boise, Idaho; S. Berlin, Gloucester, Mass.; R. Berris, Denver; R. Bordoni, Atlanta; E. Braud, Springfield, Ill.; R.J. Brooks, Tucson, Ariz.; R. Burningham, Portland, Oreg.; J. Congdon, Everett, Wash.; J. Craig, Shreveport, La.; F.J. Cummings, Providence, R.I.; D. Decker, Royal Oak, Mich.; A. Desai, Philadelphia; T. Dobbs, Knoxville, Tenn.; P. Eisenberg, Greenbrae, Calif.; J. Feldmann, Mobile, Ala.; W. Fintel, Salem, Va.; S. Flamm-Honig, Washington, D.C.; P.J. Flynn, Minneapolis; S. George, Rancho Mirage, Calif.; I. Gill, Riverside, Calif.; D. Glover, Philadelphia; F. Gonzalez, Columbia, S.C.; W. Gradishar, Chicago; W. Grosh, Charlottesville, Va.; G. Gross, Tyler, Tex.; G. Harman, Lackland, Tex.; J. Harris, Fargo, N.D.; J. Hueser, Columbia, Mo.; H.S. Jhangiani, Fountain Valley, Calif.; S. Jones, Dallas; C. Kardinal, New Orleans; A. Kaufman, Sellersville, Pa.; A. Keller, Tulsa, Okla.; R. Kerr, Austin, Tex.; J. Kessler, Hampton, Va.; W. Kincaid, Johnson City, Tenn.; J. Lamon, Poway, Calif.; I. Lerner, St. Paul, Minn.; J. Link, Long Beach, Calif.; A. Lipton, Hershey, Pa.; J. Long, Travis Air Force Base, Calif.; J. Mailliard, Omaha, Nebr.; D. Miller, Summit, N.J.; J. Moore, Tulsa, Okla.; R. Navari, Birmingham, Ala.; B. Needles, St. Louis; D. Osborn, Olympia, Wash.; C.K. Osborne, San Antonio, Tex.; T. Panella, Knoxville, Tenn.; M. Perry, Columbia, Mo.; K. Pendergrass, Kansas City, Mo.; E. Pollard, Corpus Christi, Tex.; P.G. Rausch, Frederick, Md.; S. Richman, Miami; R. Rudolph, Seattle; J. Sandbach, Austin, Tex.; M. Sangosse, Newark, N.J.; H. Sher, Jacksonville, Fla.; G. Smith, Santa Rosa, Calif.; J. Sparano, Bronx, N.Y.; R. Stoltz,

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