A Randomized, Placebo-Controlled Trial of Zoledronic Acid in Patients With Hormone-Refractory Metastatic Prostate Carcinoma

Fred Saad, Donald M. Gleason, Robin Murray, Simon Tchekmedyian, Peter Venner, Louis Lacombe, Joseph L. Chin, Jeferson J. Vinholes, J. Allen Goas, Bee Chen

For the Zoledronic Acid Prostate Cancer Study Group

Background: **Bone metastases are a common cause of morbidity in patients with prostate carcinoma. We studied the effect of a new bisphosphonate, zoledronic acid, which blocks bone destruction, on skeletal complications in prostate cancer patients with bone metastases.** ***Methods:*** **Patients with hormone-refractory prostate cancer and a history of bone metastases were randomly assigned to a double-blind treatment regimen of intravenous zoledronic acid at 4 mg (N = 214), zoledronic acid at 8 mg (subsequently reduced to 4 mg; 8/4) (N = 221), or placebo (N = 208) every 3 weeks for 15 months. Proportions of patients with skeletal-related events, time to the first skeletal-related event, skeletal morbidity rate, pain and analgesic scores, disease progression, and safety were assessed. All statistical tests were two-sided.** ***Results:*** **Approximately 38% of patients who received zoledronic acid at 4 mg, 28% who received zoledronic acid at 8/4 mg, and 31% who received placebo completed the study. A greater proportion of patients who received placebo had skeletal-related events than those who received zoledronic acid at 4 mg (44.2% versus 33.2%; difference = –11.0%, 95% confidence interval [CI] = –20.3% to –1.8%; *P* = .021) or those who received zoledronic acid at 8/4 mg (38.5%; difference versus placebo = –5.8%, 95% CI = –15.1% to 3.6%; *P* = .222). Median time to first skeletal-related event was 321 days for patients who received placebo, was not reached for patients who received zoledronic acid at 4 mg (*P* = .011 versus placebo), and was 363 days for those who received zoledronic acid at 8/4 mg (*P* = .491 versus placebo). Compared with urinary markers in patients who received placebo, urinary markers of bone resorption were statistically significantly decreased in patients who received zoledronic acid at either dose (*P* = .001). Pain and analgesic scores increased more in patients who received placebo than in patients who received zoledronic acid, but there were no differences in disease progression, performance status, or quality-of-life scores among the groups. Zoledronic acid at 4 mg given as a 15-minute infusion was well tolerated, but the 8-mg dose was associated with renal function deterioration.** ***Conclusion:*** **Zoledronic acid at 4 mg reduced skeletal-related events in prostate cancer patients with bone metastases. [J Natl Cancer Inst 2002;94:1458–68]**

Prostate carcinoma is one of the most common cancers in men worldwide *(1,2).* Bone is a preferred, and sometimes the only, site for prostate cancer metastases, which occur in more than 80% of men with advanced prostate cancer *(3,4).* In addition to bone metastases, bone loss resulting from previous orchiectomy or hormonal therapies that lower or block androgen activity may contribute to an increased risk of fracture, pain, and other skeletal complications *(5–8).* Complications from bone metastases are a major cause of morbidity in patients with prostate carcinoma, causing pain, spinal cord compression, pathologic fractures, and abnormalities in serum calcium levels *(9).* Patients with hormone-refractory metastatic prostate cancer are particularly prone to incapacitating progressive bone disease *(10).* Antineoplastic treatment options are limited for patients at this stage of the disease, especially those who are elderly and may have additional complicating medical conditions. Radiation therapy and surgery are commonly used for the treatment of localized bone metastases, whereas bone-seeking radionuclides can be helpful in the management of pain from widespread symptomatic bone metastasis *(11).* Hemibody irradiation can also provide relief from pain associated with extensive bone involvement, but the high incidence of side effects may adversely affect quality of life *(12).*

Prostate cancer bone metastases characteristically appear on radiographs as areas of increased bone density, suggesting excessive bone formation by osteoblasts as the predominant reaction to metastatic tumor. However, biochemical and histomorphometric studies indicate that osteolysis, excessive bone destruction, is also present in prostate cancer bone metastases *(9,10,13–15).* Thus, bisphosphonates, pyrophosphate analogs that block bone destruction, may be useful for the treatment of patients with osteoblastic metastases as well as those with osteolytic metastases. Pamidronate, a second-generation bisphosphonate, is an effective treatment for metastatic bone disease in patients with multiple myeloma or breast cancer *(16,17),* tumors characterized by primarily osteolytic metastases. However, re-

Affiliations of authors: F. Saad, Centre Hospitalier de l'Université de Montréal, Hôpital Notre-Dame, Montréal, Quebec, Canada; D. M. Gleason, Advanced Clinical Therapeutics, Tucson, AZ; R. Murray, Division of Hematology and Medical Oncology, Peter MacCallum Cancer Institute, East Melbourne, Victoria, Australia; S. Tchekmedyian, Pacific Shores Medical Group, Long Beach, CA; P. Venner, Cross Cancer Center, Edmonton, Alberta, Canada; L. Lacombe, CHUQ-Hôtel-Dieu de Quebec, Quebec, Quebec, Canada; J. L. Chin, London Health Sciences Centre, London, Ontario, Canada; J. J. Vinholes, Irmandade de Santa Casa de Misericordia de Porto Alegre, Rio Grande do Sul, Brazil; J. A. Goas, B. Chen, Novartis Pharmaceuticals Corporation, East Hanover, NJ.

Correspondence to: Fred Saad, M.D., Uro-Oncology Clinic, Centre Hospitalier de l'Université de Montréal, Hôpital Notre-Dame, 1560 Rue Sherbrooke East, Montréal, Quebec, Canada H2L 4M1 (e-mail: fred.saad@ssss.gouv.qc.ca).

See "Notes" following "References."

sults from a placebo-controlled phase III trial of pamidronate at 90 mg did not show a reduction in skeletal-related events in men with metastatic prostate cancer and bone pain *(18)*. In a phase III placebo-controlled trial of another bisphosphonate, oral clodronate, at 2080 mg daily, men with prostate cancer who were beginning or responding to hormonal therapy slightly increased the time to new symptomatic bone lesions ($P = .08$) [*(19)*; D. Dearnaley: personal communication].

Zoledronic acid, a new nitrogen-containing bisphosphonate, has been evaluated in phase I trials in patients with a variety of cancers and bone metastases *(20,21)*. In an earlier comparative phase III trial *(22)*, a 4-mg infusion of zoledronic acid was as effective as a 90-mg infusion of pamidronate in reducing skeletal complications in patients with multiple myeloma or breast cancer. In the present study, a randomized, placebo-controlled, phase III trial in men with hormone-refractory prostate cancer, we evaluated zoledronic acid to determine its effectiveness and safety in reducing skeletal-related events associated with metastatic bone disease.

METHODS

Protocol, Assignment, and Blinding

Patient enrollment and study treatment took place from June 1998 through January 2001. Eligibility for the double-blind study required prostate cancer patients to have a documented history of bone metastases and to have had three consecutive increasing serum prostate-specific antigen (PSA) measurements while on hormonal therapy. The serum PSA measurements were taken at least 2 weeks apart, with the third measurement being greater than or equal to 4 ng/mL and taken within 8 weeks of visit 1 (the screening visit). Other eligibility requirements for the study included serum testosterone levels within the castrate range (<50 ng/dL), past or current objective evidence of bone metastasis (defined as more than three foci of increased activity on a bone scan), and an Eastern Cooperative Oncology Group (ECOG) performance status *(23)* of 0, 1, or 2. Antineoplastic therapy at the time of study entry or during the trial was at the discretion of the treating physician, except that initiation of cytotoxic chemotherapy at the time of study entry was grounds for exclusion. Patients were excluded from the study if they had bone pain requiring strong narcotic therapy, were receiving cytotoxic chemotherapy (with the exception of estramustine), had received radiation therapy within 3 months, had received any previous bisphosphonate treatment, or if they had severe cardiovascular disease, refractory hypertension, symptomatic coronary artery disease, a serum creatinine of more than 3.0 mg/dL (265 μmol/L) or a corrected (for albumin) serum calcium of less than 8.0 mg/dL or greater than 11.6 mg/dL. All patients provided written informed consent. At each site, the study investigations were initiated only after approval by an institutional review board. The study was conducted in accordance with the Declaration of Helsinki, including amendments, concerning medical research in humans, Directive 91/507/EEC (European Community Rules Governing Medicinal Products), and U.S. 21 Code of Federal Regulations dealing with clinical studies.

At the screening visit, written informed consent was obtained, a medical history was taken, and a physical examination was performed. Tumor measurements were taken directly or from radiographs, the ECOG performance status was assessed, and venous blood was drawn for a serum chemistry panel, complete blood count, PSA level, and serum bone alkaline phosphatase, testosterone, and parathyroid hormone levels. A routine urinalysis was performed and a morning second-void urine specimen was collected for urine chemistries (N-telopeptide, pyridinoline, deoxypyridinoline, and creatinine). A 12-lead electrocardiogram was performed in the 2 weeks before visit 2 (randomization and first study treatment). A radionuclide bone scan and bone survey films, including a chest x-ray, were obtained within 30 days before visit 2. The bone survey included films of the lateral skull, cervical spine, thoracic spine, lumbar spine, chest, pelvis, and upper and lower extremities.

Assignment and Blinding

The 643 patients who met the inclusion criteria after the screening visit were randomly assigned to treatment according to a computer-generated list of randomization numbers provided to each center.

Patients were randomly assigned to receive treatment with zoledronic acid (Zometa®; Novartis Pharma AG, Basel, Switzerland/Novartis Pharmaceuticals Corp., East Hanover, NJ) at 4 mg or 8 mg or placebo once every 3 weeks for 20 cycles (15 months). Initially, each treatment consisted of a 5-minute 50-mL intravenous infusion, but this was amended to a 15-minute 100-mL infusion in June 1999 to increase renal safety. A subsequent protocol amendment in June 2000 reduced the dose of the zoledronic acid 8-mg treatment arm to 4 mg because of renal toxicity. All patients also received a 500-mg calcium supplement and 400–500 IU of vitamin D daily. Pain management, including analgesics, radiation therapy, or other treatment, was at the discretion of the treating physician.

Our study was a double-blind study. The pharmacist at each participating center was responsible for maintaining the blinding of the study. At each study drug treatment visit, patients received a 100 mL-infusion of normal saline with or without study drug to maintain the blinding of the study. Zoledronic acid in 100 mL of normal saline is a clear, colorless solution. Treatment assignments were revealed to study personnel and any other persons involved in study conduct or monitoring only after the last patient had completed the last study visit, all data had been entered into the database, any inconsistencies in the data had been reconciled, and the database had been closed to any further changes.

Efficacy Variables

The primary efficacy variable was the proportion of patients having at least one skeletal-related event. Skeletal-related events were prospectively defined as pathologic bone fractures (vertebral or nonvertebral), spinal cord compression, surgery to bone, radiation therapy to bone (including the use of radioisotopes), or a change of antineoplastic therapy to treat bone pain. Surgery to bone events included procedures to set or stabilize pathologic fractures or areas of spinal cord compression and procedures to prevent an imminent fracture or spinal cord compression. Radiation therapy to bone events included radiation for pain relief, to treat or prevent pathologic fractures, or to treat or prevent spinal cord compression. Follow-up bone scans were done 6 and 15 months after enrollment, and follow-up bone surveys were done every 3 months. All radiologic assessments were reviewed by a central radiologist, who was blinded to treatment assignment. If multiple vertebral or nonvertebral fractures were detected in the films from a particular visit, only one event was

included in the count of the total number of skeletal-related events. A new vertebral compression fracture was defined as a decrease in total, anterior, or posterior vertebral height of at least 25% from baseline.

Secondary efficacy variables included time to the first skeletal-related event, skeletal morbidity rate, proportion of patients with individual skeletal-related events, time to disease progression, objective bone lesion response, bone biochemical markers, and quality-of-life parameters. In the present study, the skeletal morbidity rate was defined as the number of skeletal-related events divided by the time at risk in years. Only one event was counted in any 3-week interval, to avoid multiple counts of possibly interdependent skeletal-related events. Tumor response criteria for the determination of disease progression were modified from National Prostate Cancer Project criteria *(24).* The objective response in bone was assessed by the central radiologist, according to modified criteria of the International Union Against Cancer *(25).* By these criteria, bone metastases less than 2 cm in greatest diameter were considered evaluable, whereas those measuring at least 2 cm in greatest diameter were considered measurable. A complete response consisted of resolution of all osteoblastic metastases and complete recalcification of all osteolytic metastases. A partial response consisted of resolution of some but not all osteoblastic metastases or a decrease of at least 50% in the size of measurable osteoblastic metastases and a decrease of at least 30% in the size of evaluable osteoblastic metastases, or at least partial recalcification of one or more osteolytic metastases and no new bone metastases (osteolytic or osteoblastic) or progression of any bone metastasis.

Urine specimens (from a morning second-void) and a venous blood sample were collected to measure biochemical markers of bone metabolism in all patients 1 month after enrollment and then every 3 months. Urinary N-telopeptide/creatinine ratio, urinary pyridinoline/creatinine ratio, and urinary deoxypyridinoline/creatinine ratio assess bone breakdown products and therefore reflect bone resorption activity, whereas serum bone-specific alkaline phosphatase is an indicator of osteoblast activity, reflecting bone formation. A central laboratory (Mayo Medical Laboratories, Rochester, MN) performed measurements of urine and serum biochemical markers of bone metabolism for all patients.

Quality-of-life parameters included a pain score assessed with the Brief Pain Inventory (BPI) *(26),* analgesic scores, ECOG performance status, and two quality-of-life questionnaires: Functional Assessment of Cancer Therapy-General (FACT-G), version 4 *(27)* and EURO Quality of Life EQ-5D (EURO QOL) *(28).* The BPI questionnaire was completed by the patient, and the analgesic score was assessed by the investigator every 6 weeks after enrollment. The FACT-G and EURO QOL questionnaires were completed by the patient, and ECOG status was assessed by the investigator every 3 months after enrollment. The pain score, as assessed on the BPI, was a composite of four pain scores (worst pain, least pain, average pain of the last 7 days, and pain right now) and was the primary efficacy variable for the quality-of-life assessments. An increase in score indicated increased pain. Analgesic scores were recorded by the investigator on the basis of the type of pain medication administered (0 = none, 1 = minor analgesics, 2 = tranquilizers and antidepressants, 3 = mild narcotic, 4 = strong narcotic) and were a modification of a Radiation Therapy Oncology Group analgesic score *(29).* An increase in ECOG performance status or a decrease in FACT-G or EURO QOL scores indicated worsening patient status.

Safety

Safety was assessed by evaluating all adverse events throughout the study and by evaluating serial laboratory tests, which included a complete blood count with differential and platelet count at 3 weeks and then every 3 months, and a serum chemistry panel every 3 weeks. After the amendment to reduce the 8-mg dose of zoledronic acid to 4 mg, serum creatinine was measured before the next dose of study medication was administered. Renal function was assessed by reviewing all renal adverse events and creatinine values. In addition, the incidence of renal function deterioration, defined as a change from baseline serum creatinine of greater than or equal to 0.5 mg/dL (if the baseline value was <1.4 mg/dL) or of greater than or equal to 1.0 mg/dL (if the baseline value was $\geqslant$1.4 mg/dL), was assessed within each treatment group and by infusion duration (5 or 15 minutes). A Data Safety Monitoring Board and a Renal Advisory Board, each consisting of clinical experts not participating in this trial, monitored safety during the study. A higher incidence of renal function deterioration in the group of patients receiving zoledronic acid at 8 mg led to a recommendation by these boards to switch this group to 4 mg. Therefore, this group of patients is hereafter referred to as the zoledronic acid 8/4 mg group.

Statistical Methods

The trial was designed to have 80% power to detect a 16% difference in the proportion of patients receiving zoledronic acid at 4 mg or placebo who reported any skeletal-related event during the 15 months of the trial, with an overall type I error rate of 0.05 (two-sided). Because the 8-mg dose was decreased to 4 mg, the statistical plan was amended before study completion and unblinding to specify the comparison of zoledronic acid at 4 mg to placebo as the primary study analysis.

Statistical analyses were performed on the intent-to-treat population, which included all randomly assigned patients. For all efficacy variables, the primary endpoint was the analysis at 15 months. All tests of statistical significance were two-sided. The proportions of patients with skeletal-related events were compared between the treatment groups using the Cochran–Mantel–Haenszel test *(30).* Times to the first on-study occurrence of a skeletal-related event or renal function deterioration were compared between the treatment groups using survival analysis methods, including Kaplan–Meier product-limit estimates, and Cox regression *(31).* Data for patients who died or discontinued study participation but had no events before death or discontinuation were included as a censored observation at the time of departure from the study. The last scheduled evaluation visit was at 15 months (420 days). Due to schedule variations, the last evaluation visit occurred at up to 450 days for some patients.

The primary analysis for the quality-of-life parameters was done on the change from baseline in the BPI pain score at 15 months. For patients who died or discontinued study participation, the last BPI pain score data were carried forward to subsequent time points. Changes from baseline in mean (least squares) pain scores, FACT-G total scores, and EURO QOL-5D scores were compared between the treatment groups using analysis of covariance *(32),* with the baseline value as a covari-

ate. Changes from baseline in analgesic use and performance status were compared between the treatment groups using the Cochran–Mantel–Haenszel test, with modified ridit scores *(33)*. Analyses were not adjusted for multiple significance testing. The statistical software package used for the analyses was SAS/STAT®, version 6.12 (SAS Institute, Cary, NC).

RESULTS

Participant Flow and Follow-up

A total of 643 patients were randomly assigned to receive zoledronic acid at 4 mg (N = 214), zoledronic acid at 8/4 mg (N = 221), or placebo (N = 208) (Fig. 1). Three patients, one assigned to the zoledronic acid-at-4-mg group and two assigned to the zoledronic acid-at-8/4-mg group, never received study drug. These patients were analyzed in their randomization group for efficacy but were not included in safety analyses. In addition, one patient who was assigned to the zoledronic acid-at-8/4-mg group incorrectly received zoledronic acid at 4 mg for the duration of the study. This patient was included in the zoledronic acid-at-8/4-mg group for the efficacy analysis and the zoledronic acid-at-4-mg group for the safety analysis.

Approximately 38% of patients who received zoledronic acid at 4 mg, 28% of those who received zoledronic acid at 8/4 mg, and 31% who received the placebo completed the study (Fig. 1). The most common reasons given for not completing the study were withdrawal of consent, adverse events, and death, all of which were most common in the zoledronic acid-at-8/4-mg group. For those who received the placebo, unsatisfactory therapeutic effect was also a common reason given for not completing the study.

Duration of study treatment was evaluated in each treatment group. There was no statistically significant difference in the mean (± standard deviation) duration of exposure to the study treatment among the various groups: 9.4 ± 5.8 months in the zoledronic acid-at-4-mg group, 8.8 ± 5.3 months in the zoledronic acid-at-8/4-mg group, and 9.0 ± 5.4 months in the placebo group. Of the patients in the safety analysis, there were 98 (45.8%) patients in the zoledronic acid at 4 mg group, 77 (35.3%) patients in the zoledronic acid-at-8/4-mg group, and 77 (37.0%) patients in the placebo group who received at least 12 months of study drug.

The proportions of patients assigned to treatment after the infusion duration was increased to 15 minutes were similar across treatment groups: 45.3% in the zoledronic acid-at-4-mg group, 42.7% in the zoledronic acid-at-8/4-mg group, and 40.4% in the placebo group. The majority (76%) of patients in the zoledronic acid-at-8/4-mg group received only 8-mg infusions because they had completed the study or discontinued participation in the study before the dose was reduced.

Demographic and disease characteristics were generally similar among the three treatment groups (Table 1). More than 90% of the patients were older than 60 years, and few had metastatic disease at sites other than bone and/or lymph nodes. More than 90% of the patients in each group had an ECOG performance status of 0 or 1. More patients in the zoledronic acid groups than in the placebo group had a baseline serum creatinine of greater than or equal to 1.4 mg/dL.

Skeletal-Related Events

During the study, at least one skeletal-related event occurred in 92 (44.2%) patients who received placebo and 71 (33.2%) patients who received zoledronic acid at 4 mg (difference = –11.0%, 95% CI = –20.3% to –1.8%; P = .021) (Table 2). At least one skeletal-related event occurred in 85 (38.5%) patients who received zoledronic acid at 8/4 mg (difference = –5.8%, 95% CI = –15.1% to 3.6%, P = .222 versus placebo). Compared with patients who received the placebo, fewer patients who received zoledronic acid at 8/4 mg (22.1% versus 14.9%, P = .054) and statistically significantly fewer patients who received zoledronic acid at 4 mg experienced a fracture (22.1% versus 13.1%, P = .015). Similarly, compared with patients who received the placebo, fewer patients who received zoledronic acid at 8/4 mg (29.9% versus 34.6%, P = .300) and statistically significantly fewer patients who received zoledronic acid at 4 mg (25.7%, P = .048 versus placebo) experienced any

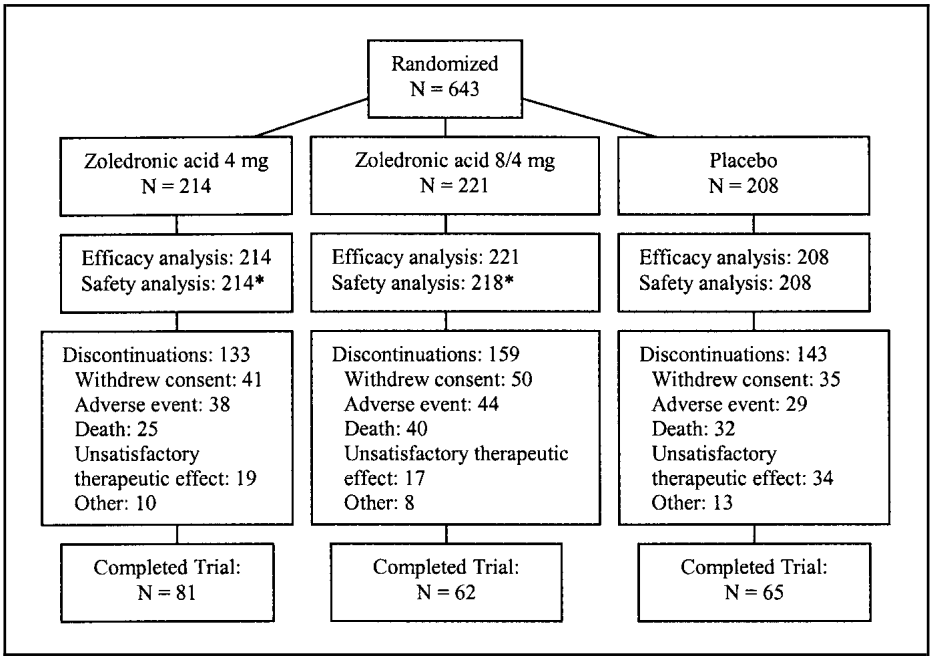

Fig. 1. CONSORT diagram. * Three patients, one randomly assigned to receive zoledronic acid at 4 mg and two randomly assigned to receive zoledronic acid at 8/4 mg, never received the study drug and were not included in the safety analysis. One patient randomly assigned to receive zoledronic acid at 8/4 mg incorrectly received 4 mg; this patient was included in the 8/4-mg group for efficacy and in the 4-mg group for safety analysis.

Table 1. Baseline demographic and disease characteristics of patients with metastatic prostate cancer enrolled in a randomized, placebo-controlled phase III trial of zoledronic acid*

Characteristic	Treatment group		
	Zoledronic acid		
	4 mg (N = 214)	8/4 mg (N = 221)	Placebo (N = 208)
Age, y			
Mean ± SD	71.8 ± 7.9	71.2 ± 8.0	72.2 ± 7.9
Median	72.0	72.0	73.0
>60 years, n (%)	195 (91.1)	202 (91.4)	193 (92.8)
Race/ethnicity, n (%)			
Caucasian	178 (83)	186 (84)	173 (83)
Black	24 (11)	19 (9)	19 (9)
Other	12 (6)	16 (7)	17 (8)
Weight, kg			
Mean ± SD	82.8 ± 14.2	82.1 ± 14.4	83.4 ± 16.1
ECOG status, n (%)†			
0	85 (39.7)	99 (44.8)	93 (44.7)
1	112 (52.3)	103 (46.6)	97 (46.6)
⩾2	17 (7.9)	18 (8.1)	18 (8.7)
Missing	0	1 (0.5)	0
Site of metastases at baseline, n (%)			
Bone	212 (99.1)	219 (99.1)	205 (98.6)
Distant lymph nodes	29 (13.6)	19 (8.6)	15 (7.2)
Lung	6 (2.8)	4 (1.8)	5 (2.4)
Liver	1 (0.5)	5 (2.3)	1 (0.5)
No. of bone metastases			
Mean ± SD	4.2 ± 2.5	4.1 ± 2.5	4.2 ± 2.6
Prostate-specific antigen, ng/mL			
Mean ± SD	276.5 ± 737.1	350.9 ± 1148.9	211.1 ± 464.9
Median	81.7	88.2	61.0
Previous skeletal-related event, n (%)	66 (30.8)	71 (32.1)	78 (37.5)
Time since diagnosis, mo‡			
Mean ± SD	62.2 ± 43.5	67.6 ± 43.8	66.6 ± 46.9
Median	51.8	61.3	56.9
Time since first bone metastases, mo‡			
Mean ± SD	23.8 ± 26.1	25.8 ± 31.4	28.4 ± 30.7
Median	16.1	16.1	17.8
Brief Pain Inventory score§			
Mean ± SD	2.0 ± 2.0	2.5 ± 2.1	2.1 ± 2.0
Median	1.8	2.3	1.8
Pain at baseline, n (%)	140 (72.5)	158 (79.4)	140 (73.3)
Baseline serum creatinine, n (%)			
<1.4 mg/dL	173 (80.8)	170 (76.9)	170 (81.7)
⩾1.4 mg/dL	41 (19.2)	48 (21.7)	33 (15.9)
Missing	0 (0.0)	3 (1.4)	5 (2.4)
Baseline hemoglobin, n (%)			
<12 g/dL	67 (31.3)	69 (31.2)	51 (24.5)
⩾12 g/dL	141 (65.9)	148 (67.0)	152 (73.1)
Missing	6 (2.8)	4 (1.8)	5 (2.4)

*N = total number of patients included in analysis; n = number of patients; SD = standard deviation.

†ECOG = Eastern Cooperative Oncology Group criteria *(23)*.

‡28 days in a month.

§Brief Pain Inventory score *(26)* was the primary efficacy variable for the quality-of-life assessments.

skeletal-related event other than fracture. With the exception of changes in antineoplastic treatment, individual nonfracture skeletal-related events (radiation therapy to bone, surgery to bone, and spinal cord compression) also occurred less frequently in patients who received either dose of zoledronic acid than in those who received placebo.

Two additional efficacy variables associated with skeletal-related events were assessed. The difference in the time to the first occurrence of any skeletal-related event between patients who received zoledronic acid at 4 mg and those who received placebo was statistically significant ($P = .011$; Fig. 2). The time to the first skeletal-related event was not reached for patients who received zoledronic acid at 4 mg and was, therefore, considered as at least 420 days (based on the fact that the estimated event rate was <50% at day 420, the end of treatment), whereas the median time to the first skeletal-related event was 321 days for patients who received placebo. The median time to the first skeletal-related event for patients who received zoledronic acid at 8/4 mg was 363 days, not statistically significantly different from that of patients who received placebo ($P = .491$).

The mean skeletal morbidity rates for all skeletal-related events combined and for each individual type of skeletal-related event were lower for patients who received zoledronic acid at 4 mg or at 8/4 mg than for those who received the placebo, with the exception of changes in antineoplastic therapy, which occurred more frequently for those who received zoledronic acid at 8/4 mg than for those in the other groups (Table 3).

Bone Lesions

We next evaluated the objective bone metastasis response. No complete responses in bone were observed among the 524 patients with evaluable bone metastasis data (174 patients who received zoledronic acid at 4 mg, 175 patients who received zoledronic acid at 8/4 mg group, and 175 patients who received placebo). Partial responses were observed in nine (5.2%) patients from the zoledronic acid-at-4-mg group, in six (3.4%) patients from the zoledronic acid-at-8/4-mg group, and in eight (4.6%) patients from the placebo group. Bone metastases were stable (radiographically unchanged) in 47 (27%) patients who received zoledronic acid at 4 mg, 46 (26%) patients who received zoledronic acid at 8/4 mg, and 35 (20%) patients who received placebo. The median time to radiographic progression of bone lesions was similar (87–92 days) among all three groups of patients.

Biochemical Markers of Bone Metabolism

Several biochemical markers of bone metabolism were measured in urine and serum samples from patients enrolled in the study. Urinary markers of bone resorption (N-telopeptide-, pyridinoline-, and deoxypyridinoline-to-creatinine ratios), which reflect bone resorption, were statistically significantly decreased in patients who received zoledronic acid at either 4 mg or at 8/4 mg ($P = .001$ versus placebo at 15 months for each comparison, except $P = .002$ for pyridinoline-to-creatinine ratio in the 4-mg group versus placebo). The N-telopeptide-to-creatinine ratio, a measure of bone resorption, decreased approximately 70% within 1 month after treatment with zoledronic acid at 4 mg (95% CI = –72.6% to –66.3%) or zoledronic acid at 8/4 mg

Table 2. Proportions of metastatic prostate cancer patients with skeletal-related events up to month 15 in a randomized, placebo-controlled phase III trial of zoledronic acid*

Skeletal-related events	No. of patients in treatment group (%)			Difference (95% CI) between 4-mg and placebo groups†	*P*	Difference (95% CI) between 8/4-mg and placebo groups	*P*
	Zoledronic acid						
	4 mg (N = 214)*	8/4 mg (N = 221)	Placebo (N = 208)				
All skeletal-related events	71 (33.2)	85 (38.5)	92 (44.2)	−11.1 (−20.3 to −1.8)	.021	−5.8 (−15.1 to 3.6)	.222
All pathologic fractures	28 (13.1)	33 (14.9)	46 (22.1)	−9.0 (−16.3 to −1.8)	.015	−7.2 (−14.5 to 0.2)	.054
Vertebral fractures	8 (3.7)	17 (7.7)	17 (8.2)	−4.4 (−8.9 to 0.1)	.053	−0.5 (−5.6 to 4.6)	.852
Nonvertebral fractures	22 (10.3)	22 (10.0)	33 (15.9)	−5.6 (−12.0 to 0.8)	.092	−5.9 (−12.2 to 0.4)	.065
Radiation therapy to bone	49 (22.9)	53 (24.0)	61 (29.3)	−6.4 (−14.8 to 1.9)	.136	−5.3 (−13.7 to 3.0)	.201
Surgery to bone	5 (2.3)	6 (2.7)	7 (3.4)	−1.0 (−4.2 to 2.1)	.514	−0.7 (−3.9 to 2.6)	.770
Spinal cord compression	9 (4.2)	11 (5.0)	14 (6.7)	−2.5 (−6.9 to 1.8)	.256	−1.8 (−6.2 to 2.7)	.434
Change in antineoplastic treatment	10 (4.7)	18 (8.1)	14 (6.7)	−2.1 (−6.5 to 2.4)	.362	1.4 (−3.6 to 6.4)	.570

*N = total number of patients included in analysis; CI = confidence interval.

†*P* values (two-sided) for between-treatment analysis are from the Cochran–Mantel–Haenszel test, with modified ridit score *(30)*.

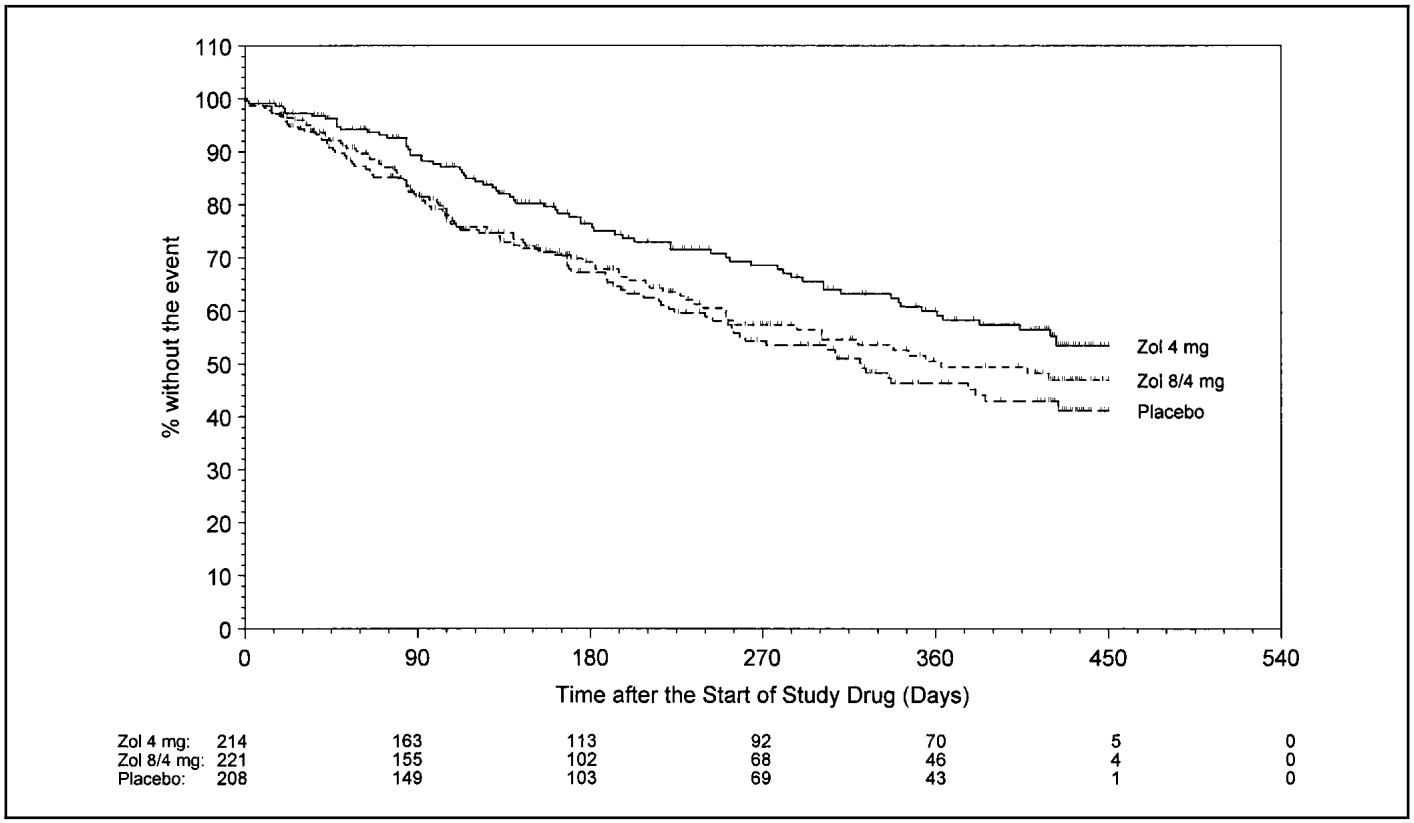

Fig. 2. Kaplan–Meier estimates of event rates for time to the first on-study skeletal-related event for all intent-to-treat patients with metastatic prostate cancer randomly assigned to receive zoledronic acid at 4 mg, zoledronic acid at 8/4 mg, or placebo. The number of patients at risk at each time point is shown in the table below the graph. Percentage of patients (95% confidence interval [CI]) without a skeletal-related event at 90 days: zoledronic acid at 4 mg, 90.9% (95% CI = 86.8% to 94.9%); zoledronic acid at 8/4 mg, 83.3% (95% CI = 78.2% to 88.4%); placebo, 83.5% (95% CI = 78.4% to 88.7%); at 270 days: zoledronic acid at 4 mg, 70.0% (95% CI = 63.0% to 76.9%); zoledronic acid at 8/4 mg, 58.0% (95% CI = 50.5% to 65.6%); placebo, 57.3% (95% CI = 49.7% to 64.8%); at 450 days: zoledronic acid at 4 mg, 55.1% (95% CI = 46.9% to 63.4%); zoledronic acid at 8/4 mg, 46.8% (95% CI = 38.2% to 55.4%); placebo, 42.8% (95% CI = 34.4% to 51.2%). At the last study evaluation (450 days), *P* value (two-sided) from Cox regression *(31)* = .011 for zoledronic acid at 4 mg versus placebo and *P* = .491 for zoledronic acid at 8/4 mg versus placebo.

(95% CI = –75.9% to –69.5%) and remained suppressed (Fig. 3, A). Serum bone alkaline phosphatase, a measure of bone formation activity by osteoblasts, increased statistically significantly more by the end of the study in patients who received the placebo (33.7%, 95% CI = 21.1% to 56.3%) than in patients who received zoledronic acid at 4 mg (0.7%, 95% CI = –9.9% to 14.3%; *P* = .001) or at 8/4 mg (5.6%, 95% CI = –7.8% to 24.1%; *P* = .003) (Fig. 3, B). By the end of the study, levels of serum parathyroid hormone, a regulator of calcium homeostasis, increased statistically significantly more in patients who received zoledronic acid at 4 mg (81.8%, 95% CI = 56.3% to 111.1%; *P* = .001) or at 8/4 mg (90%, 95% CI = 57.9% to 126.7%; *P* = .001) than in patients who received the placebo (17.1%, 95% CI = 3.3% to 27.5%) (Fig. 3, C).

Table 3. Skeletal morbidity rate up to month 15 in patients with metastatic prostate cancer enrolled in a randomized, placebo-controlled, phase III trial of zoledronic acid*

Skeletal morbidity rate†	Skeletal morbidity rates* (95% CI) in treatment groups			*P*‡	
	Zoledronic acid				
	4 mg (N = 214)	8/4 mg (N = 221)	Placebo (N = 208)	4 mg versus placebo	8/4 mg versus placebo
All skeletal-related events	0.80 (0.57 to 1.03)	1.06 (0.77 to 1.35)	1.49 (1.03 to 1.94)	.006	.143
All pathological fractures	0.21 (0.11 to 0.31)	0.21 (0.13 to 0.28)	0.45 (0.27 to 0.63)	.009	.042
Vertebral fractures	0.04 (0.01 to 0.08)	0.10 (0.05 to 0.14)	0.16 (0.04 to 0.28)	.048	.818
Nonvertebral fractures	0.17 (0.08 to 0.27)	0.11 (0.06 to 0.16)	0.31 (0.17 to 0.46)	.071	.048
Radiation therapy to bone	0.44 (0.27 to 0.60)	0.64 (0.40 to 0.87)	0.88 (0.48 to 1.28)	.084	.208
Surgery to bone	0.03 (0.00 to 0.07)	0.05 (0.00 to 0.10)	0.06 (0.01 to 0.11)	.509	.766
Spinal cord compression	0.14 (0.00 to 0.28)	0.10 (0.04 to 0.17)	0.23 (0.04 to 0.42)	.247	.443
Change in antineoplastic treatment	0.10 (0.02 to 0.18)	0.22 (0.06 to 0.38)	0.12 (0.04 to 0.21)	.364	.531

*Data are the mean and 95% confidence interval (CI); N = total number of patients included in analysis.

†Skeletal morbidity rate was defined as the number of skeletal-related events divided by the time at risk in years.

‡*P* values (two-sided) for between-treatment analysis are from Cochran–Mantel–Haenszel test, with modified ridit score *(30)*.

Quality of Life

Quality of life was assessed with several measures. Mean pain scores (range = 0–10) increased from baseline in all three groups at every 3-month interval, with one exception at 3 months where the zoledronic acid groups had a slight decrease from baseline (Fig. 4). The mean increase from baseline in pain score at 15 months was 0.88 (95% CI = 0.61 to 1.15) for patients who received the placebo compared with 0.58 (95% CI = 0.29 to 0.87) for patients who received zoledronic acid at 4 mg (P = .134 versus placebo) and 0.43 (95% CI = 0.16 to 0.70) for patients who received zoledronic acid at 8/4 mg (P = .026 versus placebo). Analgesic scores (range = 0–4) were also increased slightly more from baseline at every time point for patients who received the placebo than for patients who received either dose of zoledronic acid. However, the differences in analgesic scores were not statistically significant. The mean ECOG performance scores increased from baseline to the last measurement, with no statistically significant difference among the three groups. The total FACT-G quality-of-life and the EURO-QOL scores decreased from baseline to the last measurement, with no statistically significant differences among the three groups.

Adverse Events

The most common adverse events that occurred during the trial are shown in Table 4. Fatigue, anemia, myalgia, fever, and lower-limb edema occurred in at least 5% more patients in both of the zoledronic acid groups than in the placebo group. Similar proportions of patients who received zoledronic acid at 4 mg (9.8%), zoledronic acid at 8/4 mg (12.4%), and placebo (10.1%) discontinued the study drug because of a serious adverse event. Eight patients—four (2.0%) from the zoledronic acid-at-4-mg group and four (1.9%) from the zoledronic acid-at-8/4-mg group—experienced grade 3 or 4 hypocalcemia. Thirty-eight patients—nine (4.6%) each from the zoledronic acid-at-4-mg and placebo groups and 20 (9.7%) from the zoledronic acid-at-8/4-mg group—had grade 3 or 4 decreases in hemoglobin concentration.

Fourteen patients—seven (3.3%) in the zoledronic acid-at-4-mg group, five (2.3%) in the zoledronic acid-at-8/4-mg group, and two (1.0%) in the placebo group—had grade 3 serum creatinine increases, but no patient had a grade 4 increase. With the 15-minute infusion regimen, renal function deterioration occurred in 15.2% of patients who received zoledronic acid at 4 mg, in 20.7% of patients who received zoledronic acid at 8/4 mg, and in 11.5% of patients who received placebo. Kaplan–Meier estimates of time to first renal function deterioration were determined. Compared with patients who received placebo, patients who received zoledronic acid at 4 mg had a relative risk ratio of 1.07 (95% CI = 0.46 to 2.47; P = .882), indicating comparable risk, whereas patients who received zoledronic acid at 8/4 mg had a relative risk ratio of 1.76 (95% CI = 0.79 to 3.93, P = .165). Comparison between the patients who received zoledronic acid at 4 mg with those who received zoledronic acid at 8/4 mg revealed a relative risk ratio of 1.63 (95% CI = 0.80 to 3.30, P = .176).

Outcome

We also assessed the median time to cancer progression and found it to be 84 days for patients in each treatment group. There were no statistically significant differences between patients who received zoledronic acid and those who received placebo regarding the percent change from baseline serum PSA within 30 days of progression of disease, indicating that zoledronic acid had no apparent effect on the secretion, clearance, or measurement of PSA. The median time of survival was 464 days for patients who received placebo, 546 days for patients who received zoledronic acid at 4 mg (P = .091 versus placebo), and 407 days for patients who received zoledronic acid at 8/4 mg (P = .386 versus placebo).

Discussion

For patients with hormone-refractory metastatic prostate cancer, the clinical course is often painful and debilitating, with few therapeutic options. To date, chemotherapy for patients with hormone-refractory metastatic prostate cancer has produced, at best, modest palliative and biochemical responses with no proven survival advantage *(34)*. Furthermore, chemotherapy treatments do not specifically address the bone complications often associated with metastatic prostate cancer. Treatment with bisphosphonates is a new approach to management of metastatic bone disease in patients with prostate cancer.

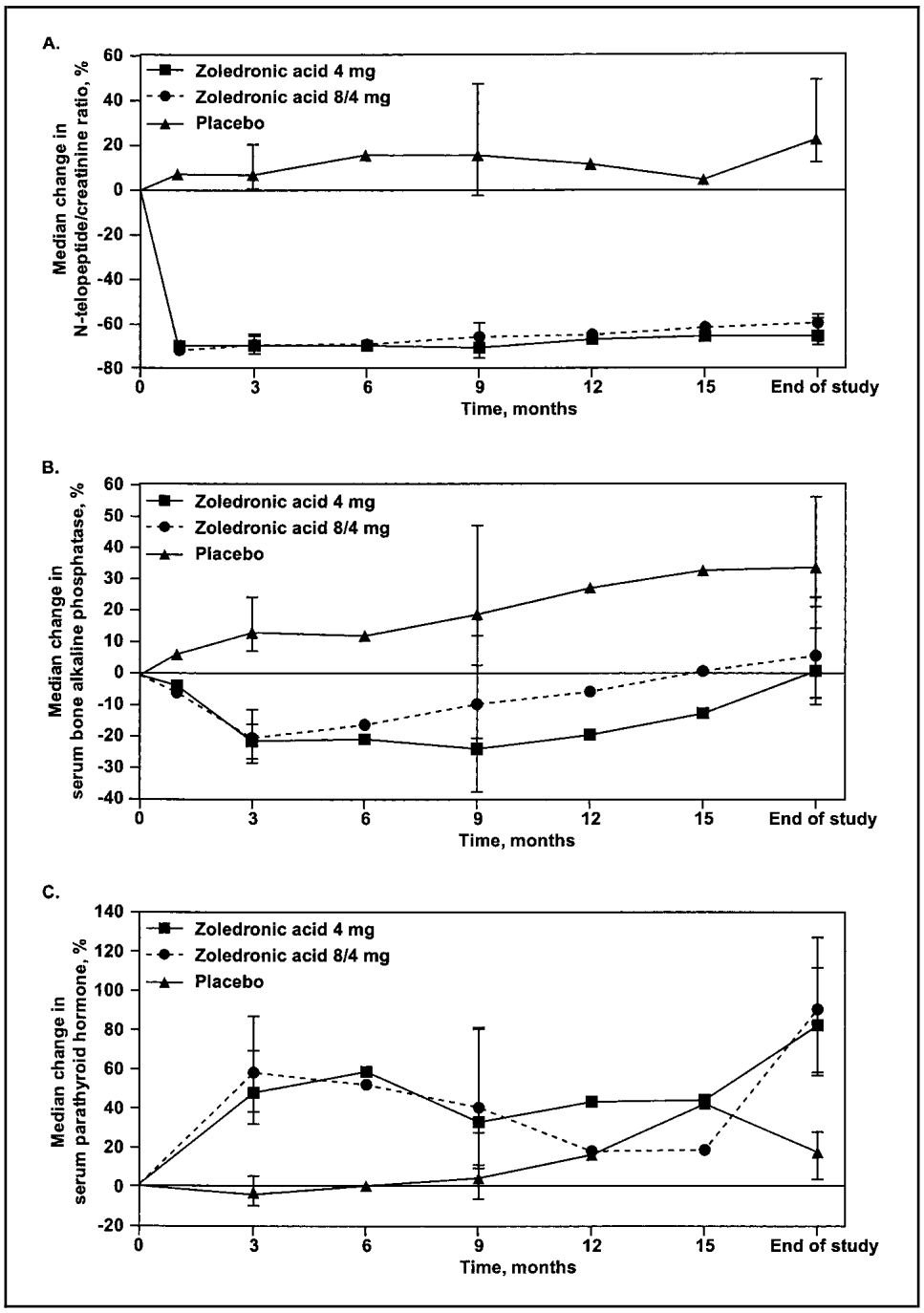

Fig. 3. Median change from baseline (percent) values for urinary N-telopeptide-to-creatinine ratio (**A**), serum bone alkaline phosphatase (**B**), and serum parathyroid hormone (**C**), all measures of bone metabolism, in patients with metastatic prostate cancer enrolled in a randomized, placebo-controlled phase III trial of zoledronic acid. Error bars show 95% confidence intervals for median percent change at 3 months, 9 months, and at the end of the study. At the last visit, all *P* values (two-sided) from Cochran–Mantel–Haenszel test with modified ridit score *(33)* = .001 for the difference between each zoledronic acid group and placebo, with the exception that *P* = .003 for the difference in serum bone alkaline phosphatase between zoledronic acid at 8/4 mg and placebo.

In this study, prostate cancer patients with bone metastases who received zoledronic acid, a new bisphosphonate, given as a 4-mg infusion, had fewer skeletal-related events than those who received the placebo. Furthermore, the median time to the first skeletal-related event was statistically significantly longer and the skeletal morbidity rate was statistically significantly lower for patients who received zoledronic acid at 4 mg than for those who received the placebo. Therefore, all three major study outcomes concerning skeletal-related events were superior for patients who received zoledronic acid at 4 mg than for patients who received placebo.

It was surprising to note that the efficacy outcomes for patients who received the higher 8/4-mg dose of zoledronic acid were intermediate between those who received the 4-mg dose of zoledronic acid and those who received the placebo and did not reach statistical significance when compared with placebo. The analysis of the data for patients in the 8/4-mg zoledronic acid group is complicated by both the change in dose from 8 mg to 4 mg, prompted by safety concerns, and the higher discontinuation rate compared with that for patients in the 4-mg group. Although there were some minor differences in the patient prognostic factors collected at baseline, the differences do not seem adequate to explain the difference in outcome. With the regimen used in this study, it is possible that the 4-mg dose of zoledronic acid may already be exerting a maximal effect on bone cells. The similar effects of the two doses on the biochemical markers of bone metabolism support this hypothesis.

The proportion of patients with pathologic fractures and the skeletal morbidity rate for such fractures in patients in the zoledronic acid-at-4-mg group were each statistically significantly

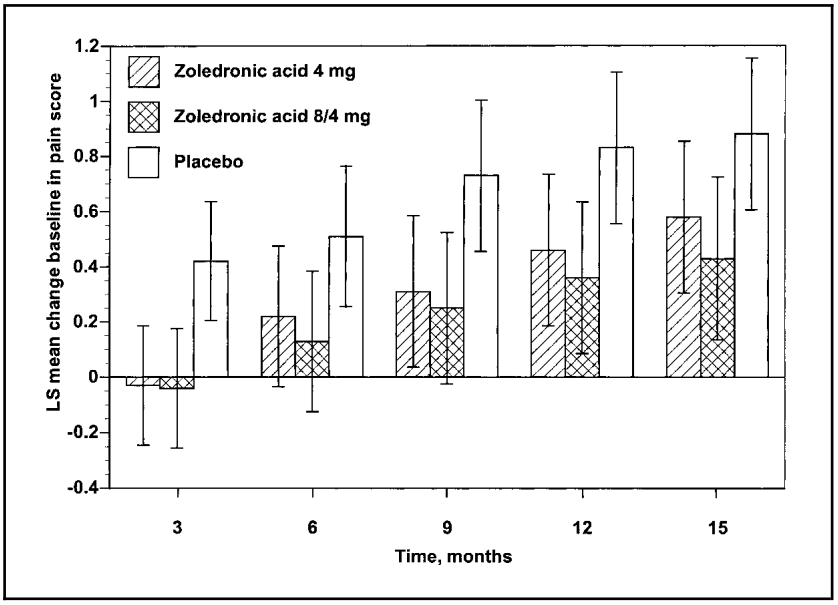

Fig. 4. Mean (least squares [LS]) change from baseline value of the Brief Pain Inventory *(26)* pain score. Error bars show 95% confidence intervals for the least squares mean change. At 15 months, *P* value (two-sided) from analysis of covariance *(32)* with the baseline value as a covariate = .134 for zoledronic acid at 4 mg versus placebo and .026 for zoledronic acid at 8/4 mg versus placebo.

Table 4. Most frequent adverse events by treatment group in patients with metastatic prostate cancer enrolled in a randomized, placebo-controlled phase III trial of zoledronic acid

	No. of patients with adverse events in treatment group (%)		
	Zoledronic acid		
Adverse event*	4 mg (N = 214)	8/4 mg (N = 218)	Placebo (N = 208)
Bone pain	108 (50.5)	133 (61.0)	127 (61.1)
Nausea	77 (36.0)	115 (52.8)	77 (37.0)
Constipation	72 (33.6)	85 (39.0)	72 (34.6)
Fatigue	70 (32.7)	67 (30.7)	53 (25.5)
Anemia	57 (26.6)	60 (27.5)	37 (17.8)
Myalgia	53 (24.8)	53 (24.3)	37 (17.8)
Vomiting	46 (21.5)	64 (29.4)	43 (20.7)
Weakness	45 (21.0)	50 (22.9)	40 (19.2)
Anorexia	43 (20.1)	55 (25.2)	36 (17.3)
Fever	43 (20.1)	48 (22.0)	27 (13.0)
Edema, lower limb	41 (19.2)	48 (22.0)	27 (13.0)
Dizziness	38 (17.8)	22 (10.1)	24 (11.5)
Diarrhea	36 (16.8)	35 (16.1)	32 (15.4)
Weight decrease	36 (16.8)	38 (17.4)	26 (12.5)

*Original adverse event terms are coded into standard adverse event dictionary terms for database entry. N = number of patients included in analysis.

lower than in the placebo group. If this difference were primarily the result of asymptomatic fractures diagnosed only on the vertebral radiographs, the clinical relevance of treatment with zoledronic acid might be diminished. However, nonvertebral fractures, which are generally accompanied by acute clinical symptoms and which were more common in each group than vertebral fractures, also occurred in fewer patients treated with zoledronic acid at 4 mg than in those treated with the placebo. Furthermore, only one fracture was counted within a given 3-week period, decreasing the likelihood that asymptomatic fractures skewed the overall study results.

There were no differences in measures of tumor progression or overall survival between patients in the zoledronic acid and placebo groups, despite the differences in skeletal-related events. The low completion rate in this study, with only about one third of the patients completing the planned 15 months of study treatment, is not surprising given a median time to progression of disease of 84 days for each treatment group and a median survival of approximately 15 months (placebo group). An ongoing phase III trial *(35)* evaluating earlier use of zoledronic acid in men with prostate cancer will help address the question of whether interventions at an earlier time point may hold more potential with regard to altering overall disease outcomes.

Studies with two other bisphosphonates, pamidronate and clodronate, have evaluated effects on bone metastases in patients with prostate cancer *(18,19)*. A recent trial comparing pamidronate with placebo in patients with prostate cancer metastatic to bone was unable to show a difference in the proportions of patients with skeletal-related events *(18)*. That study, however, included fewer patients and shorter treatment duration than our current trial. In a study of adjuvant oral clodronate, the time to development of symptomatic bone metastases in 311 men with prostate cancer was 23.6 months in those who received clodronate compared with 19.3 months in those who received placebo ($P = .08$) [*(19)* and Dearnaley D: personal communication, May 2002]. Dose reduction from adverse events, primarily gastrointestinal, was required statistically significantly more often with clodronate than with the placebo ($P<.001$). These results with clodronate cannot be directly compared with the results of our zoledronic acid study because of differences in study populations and endpoints. However, the clodronate study results indicate a need for better tolerated bisphosphonates for the treatment of prostate cancer patients.

Because of age and previous hormonal therapy, many patients in our study are likely to have entered the trial with generalized bone loss, which can predispose patients to fractures. Smith et al. *(36)* observed an 8.5% decrease in trabecular bone mineral density of the lumbar spine after approximately 1 year of leuprolide therapy in men with advanced or recurrent prostate cancer, suggesting that this common hormonal therapy may contribute to such bone loss. Whether the effects of zoledronic acid in this study are the result of an antiosteoporotic effect on the general skeleton rather than on bone metastases is unknown. Although a decrease in the number of fractures may be observed

when bisphosphonates are used to treat osteoporosis in men *(37),* it is unlikely that an antiosteoporotic effect would have an important impact on radiation therapy to bone, surgery to bone, or spinal cord compression events for men with metastatic prostate cancer. Compared with uninvolved areas of the skeleton, bone metastases have greatly increased bone metabolism and bisphosphonates preferentially accumulate in areas of high bone metabolism. Although zoledronic acid may have a positive effect on inhibition of bone loss from the overall skeleton, its primary site of action in the patients enrolled in this study is more likely to be at the site of metastasis to bone.

A marked decrease in urinary biomarkers of bone resorption after treatment of patients with zoledronic acid, but not with placebo, indicates inhibition of active osteolysis. Although osteoblastic lesions are characteristic of prostate cancer, an osteolytic component has been confirmed in several reports *(13,38, 39).* Bone resorption markers such as N-telopeptide and C-telopeptide have been noted to be higher in patients with osteoblastic disease than in patients with osteolytic disease *(15).* A decrease in bone resorption markers has been associated with a clinical response to treatment in prostate cancer patients with bone metastases *(14,40).* Serum bone alkaline phosphatase levels, an indicator of osteoblastic activity, showed little change in patients who received zoledronic acid but increased in those who received placebo. Although the biology of osteoblasts in prostate cancer is still not well understood, our observation indicates that such cells may retain at least some sensitivity to regulation, whether direct or, more likely, indirect, within the bone microenvironment. The change in urinary and serum markers of bone metabolism, therefore, clearly indicates that, compared with placebo, zoledronic acid affected bone metabolism.

Pain relief is an important goal in patients with metastatic prostate cancer. The current study demonstrates a modest but consistent effect on pain, which reached statistical significance at 15 months in patients who received the high zoledronic acid dose. It is important to note that this study was not primarily designed to assess pain, and that many confounding factors, including use of radiation therapy for bone pain, make pain and analgesic scores difficult to interpret. Several smaller, open-label studies with earlier bisphosphonates have described an analgesic effect on bone pain *(41–45),* but this effect has not been previously confirmed in randomized, controlled trials. Etidronate disodium, a first-generation bisphosphonate, was ineffective in palliating pain in a randomized, double-blind, placebo-controlled trial in 57 patients with metastatic prostate cancer *(46).* Similarly, two double-blind, placebo-controlled trials of the bisphosphonate clodronate in patients with prostate cancer and bone metastases found no statistically significant difference in pain relief *(47,48).* Therefore it is encouraging that, in this placebo-controlled study, patients treated with zoledronic acid, which is more potent than earlier bisphosphonates, had less of an increase in pain than patients receiving placebo.

The flu-like symptoms (fever, myalgia) that occur with other bisphosphonates *(49)* were also observed in patients who received zoledronic acid. As in our study with zoledronic acid, renal impairment reported in patients treated with other bisphosphonates appears to be related to dose and the rate of infusion *(49).* When the 4-mg dose of zoledronic acid was given over 15 minutes, however, the risk of renal function deterioration was not different from that with placebo.

In summary, patients with metastatic prostate cancer who received a 15-minute intravenous infusion of zoledronic acid (4 mg) given every 3 weeks had fewer skeletal-related events than did patients who received placebo. At the recommended dose and regimen, the benefit-to-risk ratio is acceptable for patients with hormone-refractory prostate cancer metastatic to bone. Ongoing studies evaluating earlier intervention, before the development of bone metastases, are a rational next step to further define the optimal therapeutic role of zoledronic acid for patients with prostate cancer.

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NOTES

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In addition to 162 patients enrolled in this trial by the authors, 481 patients were enrolled by another 136 centers, including 64 in the United States, 15 in Argentina, 10 in Australia, nine in Canada, six each in France and Brazil, five each in Germany and the United Kingdom, four in New Zealand, three in Italy, two each in Chile and Switzerland, and one each in Austria, Belgium, Peru, Sweden, and Uruguay.

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