Zoledronic Acid Versus Placebo in the Treatment of Skeletal Metastases in Patients With Lung Cancer and Other Solid Tumors: A Phase III, Double-Blind, Randomized Trial—The Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group

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Purpose: **To assess the efficacy and safety of zoledronic acid in patients with bone metastases secondary to solid tumors other than breast or prostate cancer.**

Patients and Methods: **Patients were randomly assigned to receive zoledronic acid (4 or 8 mg) or placebo every 3 weeks for 9 months, with concomitant antineoplastic therapy. The 8-mg dose was reduced to 4 mg (8/4-mg group). The primary efficacy analysis was proportion of patients with at least one skeletal-related event (SRE), defined as pathologic fracture, spinal cord compression, radiation therapy to bone, and surgery to bone. Secondary analyses (time to first SRE, skeletal morbidity rate, and multiple event analysis) counted hypercalcemia as an SRE.**

Results: **Among 773 patients with bone metastases from lung cancer or other solid tumors, the proportion with an SRE was reduced in both zoledronic acid groups compared with the placebo group (38% for 4 mg and 35% for 8/4 mg zoledronic acid *v* 44% for the placebo group; *P* = .127 and *P* = .023 for 4-mg and 8/4-mg groups, respectively). Additionally, 4 mg zoledronic acid significantly increased time to first event (median, 230 *v* 163 days for placebo; *P* = .023), an important end point in this poor-prognosis population, and significantly reduced the risk of developing skeletal events by multiple event analysis (hazard ratio = 0.732; *P* = .017). Zoledronic acid was well tolerated; the most common adverse events in all treatment groups included bone pain, nausea, anemia, and vomiting.**

Conclusion: **Zoledronic acid (4 mg infused over 15 minutes) is the first bisphosphonate to reduce skeletal complications in patients with bone metastases from solid tumors other than breast and prostate cancer.**

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IT HAS been estimated that approximately 30% to 65% of patients with metastatic lung cancer will develop bone metastases,[1,2] and median survival from the time patients develop bone metastases is less than 6 months.[2] Bone metastases cause considerable skeletal morbidity, including bone pain, pathologic fractures, spinal cord compression, and hypercalcemia of malignancy (HCM).[1] These skeletal-related events (SREs) are the result of the resorption of mineralized bone by osteoclasts. Bisphosphonates have been used extensively in the treatment of HCM and in the prevention or palliation of skeletal complications associated with osteolytic lesions in breast cancer and multiple myeloma. However, studies in patients with other solid tumors have been limited.

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Zoledronic acid (ZOMETA; Novartis Pharma AG, Basel, Switzerland/Novartis Pharmaceuticals Corporation, East Hanover, NJ) is a new, highly potent, nitrogen-containing bisphosphonate that has demonstrated superior efficacy for the treatment of HCM compared with pamidronate, the current standard treatment.[3] Recently, it has been reported that zoledronic acid offers greater convenience and is as effective and well tolerated as pamidronate in the treatment of bone metastases from breast cancer or multiple myeloma.[4,5] Zoledronic acid has also demonstrated activity in the treatment of bone metastases in patients with advanced prostate cancer.[6]

Despite improvements in the primary treatment of lung cancer and other solid tumors, SREs continue to complicate the clinical course for many patients. However, the efficacy of bisphosphonates for the treatment of bone metastases in this population has not been demonstrated in well-controlled trials. Therefore, a phase III, multicenter, randomized, placebo-controlled trial was initiated to investigate the effectiveness of zoledronic acid in the treatment of patients with bone metastases secondary to solid tumors other than breast or prostate cancer.

PATIENTS AND METHODS

Patients

Adult patients (≥18 years of age) with bone metastases secondary to lung cancer and other solid tumors not including breast or prostate cancer were eligible. All patients were required to have at least one site of bone metastasis

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and an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2. Patients were excluded if they had liver metastases with total bilirubin level higher than 2.5 mg/dL at screening, serum creatinine level higher than 3.0 mg/dL, or symptomatic brain metastases. Patients were also excluded if they had more than a single exposure to a bisphosphonate within 30 days, a diagnosis of severe cardiovascular disease, hypertension refractory to treatment, symptomatic coronary artery disease, or pregnancy within 6 months of random assignment. The study was approved by the institutional review boards of the respective institutions and was conducted in compliance with international guidelines regulating patient safety. All patients provided written informed consent.

Treatment

Patients were randomly assigned in a double-blind fashion to receive zoledronic acid (4 or 8 mg) or placebo every 3 weeks for 9 months. Initially, patients received zoledronic acid via 5-minute infusion in 50 mL of infusate; however, due to concerns over renal safety, a protocol amendment in June 1999 changed the infusion time to 15 minutes and increased the volume of the infusion to 100 mL (195 patients were accrued before this amendment). A subsequent amendment to the protocol in June 2000, implemented because of concerns over decreased renal tolerability at the higher dose level, required patients originally randomly assigned to receive 8 mg zoledronic acid to instead receive 4 mg zoledronic acid; this arm is hereafter referred to as the 8/4-mg arm. All patients were accrued before this amendment, and 198 patients (75%) in the 8/4-mg group had completed or discontinued study treatment and received only the 8-mg dose; however, 67 patients (25%) were still receiving treatment and were switched to the lower dose. Thereafter, serum creatinine was monitored within 2 weeks before each subsequent dose of the study drug. All patients received daily calcium supplements (500 mg) and a multivitamin tablet containing vitamin D (400 to 500 U) throughout the study.

Study Design and Schedule

To ensure adequate enrollment of patients with tumor types other than non–small-cell lung cancer (NSCLC), patients were stratified according to tumor type (NSCLC or other solid tumor) before random assignment.

Before the first study treatment, a complete physical examination was performed, and a medical history was taken, which included history of SREs, antineoplastic history, and ECOG performance status. Tumor assessment, bone scan, and bone survey were performed before treatment. Pain was assessed using the Brief Pain Inventory (BPI) composite pain score[7] and an analgesic score (measured on a scale of 0 to 4). Tumor assessment, bone scan and survey, and ECOG performance status were assessed at 3, 6, and 9 months. Skeletal-related events and adverse events were recorded at each visit every 3 weeks. Pain and analgesic scores were assessed every 6 weeks.

Statistical Analysis

The primary efficacy analysis was the proportion of patients with at least one SRE during the 9 months on study. Skeletal-related events included pathologic fracture, spinal cord compression, radiation therapy to bone, or surgery to bone. HCM was not included in the definition of SREs for purposes of the primary efficacy analysis, because the efficacy of zoledronic acid in the treatment of HCM has been established.[3] However, because HCM is a clinically important event, secondary efficacy analyses are reported with and without HCM as a skeletal event to evaluate the overall benefit of zoledronic acid. For all efficacy variables analyzed, comparisons of 4 mg zoledronic acid versus placebo were used to assess the effectiveness of zoledronic acid. Therefore, all efficacy conclusions are based on the recommended 4-mg dose of zoledronic acid. The proportion of patients with an SRE was compared between treatment groups using the Cochran-Mantel-Haenszel test stratified by lung cancer and other solid tumors.

Secondary efficacy analyses of SREs included time to first SRE, the skeletal morbidity rate (defined as the number of SREs per year), and a multiple event analysis. A preplanned multiple event analysis was performed using the Andersen-Gill method,[8] and the robust estimate of variance was used to compute *P* values. For the skeletal morbidity rate and multiple event analysis, a 21-day event window was used for counting SREs, such that any event occurring within 21 days of a previous event was not counted. This ensured that potentially interdependent events, such as surgery to repair a fracture, occurring within 21 days of a previous event were not counted as separate SREs. Other secondary efficacy variables included change from baseline in BPI composite pain score, analgesic use, ECOG performance status, best bone lesion response, time to progression of bone lesions, changes from baseline in biochemical markers of bone resorption, time to progression of overall disease, and survival. Quality of life was measured using the Function Assessment of Cancer Therapy – General (FACT-G) instrument, and analyzed using a random effect pattern mixture model.

Time to first SRE, time to progression of bone metastases, time to overall disease progression, and overall survival were compared between treatment groups using the Kaplan-Meier method and the log-rank test. For time to first SRE and progression of bone lesions, a patient who discontinued the study treatment (including discontinuation due to death) without an event was censored at the time of discontinuation. For time to progression of overall disease, death due to progression of disease was counted as an event.

Skeletal morbidity rate and change from baseline in analgesic use, performance status, and biochemical markers of bone resorption were compared between treatment groups using the Cochran-Mantel-Haenszel test stratified by lung cancer and other solid tumors. The mean change from baseline BPI composite pain score was compared between treatment groups using analysis of covariance, with baseline value as a covariate, and treatment and stratum as factors. Time to first serum creatinine increase was analyzed using the Kaplan-Meier and log-rank tests.

The study was designed to have 80% power to detect a 16% difference in the proportion of patients having an SRE during the first 9 months of the study (assuming a 48% incidence of SREs in the placebo group and a 32% incidence in either zoledronic acid group). Taking into account the variance included in the intent-to-treat patient population, with an overall type I error rate of 0.05 (two-sided), the sample size was determined to be 600 patients. However, because the cumulating blinded data indicated that many patients died without experiencing an SRE and the overall event rate was lower than expected, the protocol was amended to enroll 700 patients in the study, to have 80% power to detect a 14% difference in the proportion of patients having an SRE (assuming a 38% incidence of SREs in the placebo group and 24% incidence in either zoledronic acid group). There was no interim analysis and no blinding was broken during the course of amendment. A data safety monitoring board and a renal safety board were involved in the review of the data to ensure safe and appropriate study conduct.

RESULTS

Patients

A total of 773 patients with osteolytic, osteoblastic, or mixed bone metastases from solid tumors other than breast or prostate cancer were enrolled in the study. As indicated in Table 1, 257 patients were randomly assigned to receive 4 mg zoledronic acid, 266 to receive 8/4 mg zoledronic acid, and 250 to receive placebo. A total of seven patients did not receive study medication for a variety of reasons, such as errors in issuing randomization numbers. These patients were included in the intent-to-treat efficacy analyses but not in the safety analyses because they did not receive treatment. Approximately 25% of patients completed 9 months of therapy, and the median duration of treatment was 4 months. Reasons for discontinuation are presented in Table 1.

Patient and baseline disease characteristics for the assessable patients are shown in Table 2. Approximately 50% of patients had NSCLC, 10% of patients had renal cell carcinoma, and 8% of patients had small-cell lung cancer. Median age was approximately 63 years. The majority (approximately 80%) of patients

Table 1. Patient Disposition by Treatment Group

Criterion	Zoledronic Acid 4 mg		Zoledronic Acid 8/4 mg		Placebo	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Randomized	257	—	266	—	250	—
Assessable for safety	254	—	265	—	247	—
Completed	68	27	65	25	63	25
Discontinued	186	73	200	75	184	75
Reasons for discontinuation						
Death	66	26	75	28	66	27
Adverse event(s)	49	19	65	25	51	21
Patient withdrew consent	44	17	35	13	40	16
Insufficient efficacy	18	7	14	5	20	8
Protocol violation	4	2	0	0	0	0
No longer required study drug	2	1	1	< 1	4	2
Lost to follow-up	2	1	4	2	0	0
Administrative problems	1	< 1	1	< 1	1	< 1

were being treated with chemotherapy and had an ECOG performance status of ≤ 1. In all treatment groups, the median baseline BPI composite pain score was approximately 3.3, and approximately 90% of patients had normal serum creatinine levels (<1.4 mg/dL) at baseline. Approximately two thirds of the patients had experienced an SRE before study entry.

SREs

The primary end point, which excluded HCM, did not reach statistical significance for comparison of 4 mg zoledronic acid versus placebo (38% *v* 44%; $P = .127$), but it was statistically significant for the comparison of 8/4 mg zoledronic acid versus placebo (35% *v* 44%; $P = .023$). However, in the analysis of all

Table 2. Patient and Baseline Disease Characteristics by Treatment Group

Characteristic	Zoledronic Acid 4 mg (n = 254)		Zoledronic Acid 8/4 mg (n = 265)		Placebo (n = 247)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Median age, years	64		62		64	
Sex						
Male	158	62	186	70	159	64
Female	96	38	79	30	88	36
Type of cancer						
NSCLC	124	49	134	51	120	49
SCLC	17	7	22	8	19	8
Renal cell carcinoma	27	11	28	11	19	8
Cancer unknown primary	18	7	16	6	17	7
Head and neck	6	2	7	3	4	2
Thyroid	2	1	5	2	4	2
Other	60	24	53	20	64	26
Primary therapy						
Chemotherapy	207	82	212	80	197	80
Hormonal therapy	3	1	1	< 1	2	1
Median time from initial diagnosis, months*	3.8		2.4		2.5	
ECOG performance status						
≤ 1	211	83	218	82	215	87
≥ 2	42	17	45	17	32	13
Median BPI composite pain score	3.5		3.3		3.3	
Previous SRE						
Yes	166	65	180	68	179	73
No	88	35	85	32	68	27
Baseline serum creatinine						
Normal (< 1.4 mg/dL)	233	92	232	88	220	89
Abnormal ($\geq$ 1.4 mg/dL)	18	7	33	13	25	10

Abbreviations: NSCLC, non–small-cell lung cancer; SCLC, small-cell lung cancer; ECOG, Eastern Cooperative Oncology Group; BPI, Brief Pain Inventory; SRE, skeletal-related event.

*Twenty-eight days in a month.

Table 3. Proportion of Patients Experiencing Individual Skeletal-Related Events by Treatment Group

Skeletal-Related Event	Zoledronic Acid 4 mg (n = 257)		Zoledronic Acid 8/4 mg (n = 266)		Placebo (n = 250)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Radiation to bone	69	27	70	26	81	32
Pathologic fracture	40	16	31	12	53	21
Vertebral	20	8	13	5	30	12
Nonvertebral	26	10	21	8	29	12
Surgery to bone	11	4	14	5	9	4
Spinal cord compression	7	3	7	3	10	4
Hypercalcemia of malignancy	0	0	2	1	8	3
Any skeletal-related event	97	38	93	35	117	47

skeletal events (including HCM), 4 mg zoledronic acid significantly reduced the proportion of patients with an event as compared with the placebo group (38% *v* 47%; $P = .039$). Similarly, 35% of patients treated with 8/4 mg zoledronic acid had an event ($P = .006$ compared with the placebo group). Table 3 summarizes the proportion of patients with each individual type of SRE. The most common SREs were radiation to bone and pathologic fracture. A treatment benefit was observed across all event types; in particular, no patients treated with 4 mg zoledronic acid developed HCM compared with 8 patients (3%) in the placebo group ($P = .004$). Compared with the placebo group, patients in the 8/4-mg group experienced significant decreases in HCM ($P = .044$), pathologic fracture ($P = .003$), and vertebral fracture ($P = .004$).

Zoledronic acid also significantly extended the median time to first SRE by more than 2 months compared with placebo (Fig 1). Median time to first SRE (excluding HCM) was 230 days for 4 mg zoledronic acid versus 163 days for placebo ($P = .023$); median time to first SRE (including HCM) was 230 days versus 155 days for placebo ($P = .007$). When this analysis was performed excluding HCM, and using only the first 700 enrolled patients (planned enrollment), the results were similar ($P = .020$). A Cox regression stratified analysis adjusting for previous SRE experience showed that this comparison remained statistically significant ($P = .028$). The median time to first event was not reached for individual SREs. However, the time to first pathologic fracture was significantly longer in patients treated with 4 mg zoledronic acid compared with the placebo group (first quartile, 238 *v* 161 days; $P = .031$). Likewise, the time to first vertebral fracture and the time to first radiation therapy were significantly longer ($P = .05$) in the 4-mg group. Because patient survival in this study was short (approximately 6 months), time to first SRE was also performed including death as an event. Results were similar as reported earlier: for patients treated with 4 mg zoledronic acid, the median time to first event (excluding HCM, including death) was 136 days versus 93 days for the placebo group ($P = .039$). For each analysis, event rates were similar in the 4-mg and 8/4-mg groups.

The skeletal morbidity rate for all events (SREs excluding HCM) was lower among patients treated with either 4 mg zoledronic acid (mean ± SD, 2.24 ± 9.12; $P = .069$) or 8/4 mg zoledronic acid (mean ± SD, 1.55 ± 3.8; $P = .005$) compared with the placebo group (mean ± SD, 2.52 ± 5.11). The skeletal morbidity rate (the number of events per year; including HCM) was significantly lower among patients treated with either 4 mg zoledronic acid (mean ± SD, 2.24 ± 9.12; $P = .017$) or 8/4 mg zoledronic acid (mean ± SD, 1.59 ± 3.8; $P = .001$) compared with the placebo group (mean ± SD, 2.73 ± 5.29). The skeletal morbidity rate for each type of SRE was lower in the zoledronic acid treatment groups compared with the placebo group except for surgery to bone and spinal cord compression.

A multiple event analysis using the Andersen-Gill approach demonstrated a significant 27% risk reduction for multiple events, in favor of 4 mg zoledronic acid (hazard ratio = 0.732;

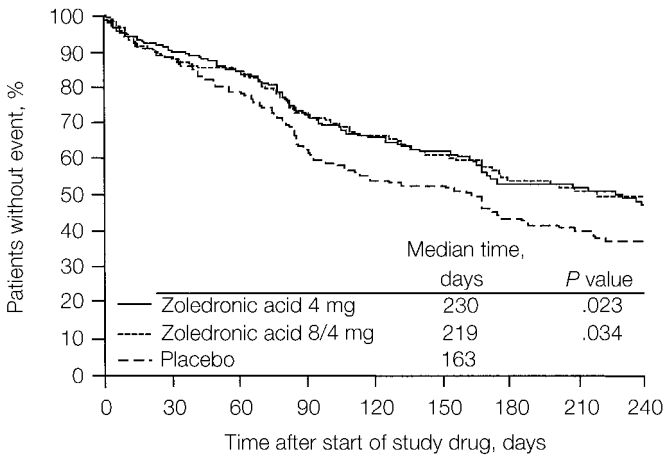

Fig 1. Kaplan-Meier estimates of time to first skeletal-related event (not including hypercalcemia of malignancy).

Table 4. Hazard Ratio of Occurrence of SREs in Patients Treated With 4 mg Zoledronic Acid Compared With Patients Treated With Placebo, Based on the Multiple Event Analysis*

Stratum	SRE (not including HCM)		SRE (including HCM)	
	Hazard Ratio	Robust *P*	Hazard Ratio	Robust *P*
Lung cancer	0.729	.061	0.706	.036
Other solid tumors	0.737	.136	0.696	.071
Total	0.732	.017	0.701	.006

Abbreviations: SRE, skeletal-related event; HCM, hypercalcemia of malignancy.
*Andersen-Gill method.

$P = .017$; Table 4). The results were similar when HCM was included in the analysis.

Substrata Analysis of SREs

Because the trial was powered for the primary end point, subset analyses were not expected to detect statistically significant differences. Nevertheless, findings in both the NSCLC and other solid tumor strata suggested a consistent treatment benefit with respect to occurrence of SREs and time to first SRE compared with the placebo group. The proportion of patients with an SRE was not significantly different for patients in the NSCLC stratum treated with 4 mg zoledronic acid versus placebo (42% *v* 45%; $P = .557$); however, there was a trend toward a longer time to first event (median 171 *v* 151 days; $P = .188$) for patients treated with 4 mg zoledronic acid. In the other solid tumor stratum, 4 mg zoledronic acid substantially reduced the proportion of patients with an SRE (33% *v* 43%; $P = .110$) and extended the time to first event (median, 314 *v* 168 days; $P = .051$) compared with placebo. Notably, the multiple event analysis demonstrated a 27% reduction in the risk of skeletal events in favor of 4 mg zoledronic acid among patients in both the NSCLC cancer and other solid tumor strata, versus the placebo group (Table 4). When patients were grouped according to the radiologic appearance of their bone lesions, 4 mg zoledronic acid demonstrated consistent reductions in SREs among patients with osteolytic and osteoblastic bone metastases (data not shown).

Pain, Analgesic Use, and ECOG Performance Status

Other efficacy end points included the change from baseline in BPI composite pain score, analgesic score, and ECOG performance status. The mean BPI composite pain score increased slightly from baseline to month 9 for all three treatment groups, indicating increases in pain. However, the mean composite pain score decreased among patients in the 4-mg zoledronic acid group who had pain at baseline. Mean analgesic score and ECOG performance status also increased from baseline to month 9 for all three treatment groups, indicating increases in analgesic use and decreases in functional capacity due to progressive disease. There were no statistically significant differences between zoledronic acid and placebo with respect to any of these global quality-of-life outcomes. Changes in FACT-G scores were also comparable between treatment groups.

Bone Lesion Response and Time to Progression of Bone Lesions

Analysis of best radiographic bone lesion response at month 9 indicated a partial response in 8% of patients treated with 4 mg zoledronic acid versus 4% of placebo-treated patients. Bone lesions progressed in 33% and 36% of patients treated with 4 mg zoledronic acid or placebo, respectively. The time to progression of bone lesions was longer in patients treated with 4 mg zoledronic acid (median, 145 days; $P = .340$) and in patients treated with 8/4 mg zoledronic acid (median, 238 days; $P = .009$) compared with the placebo group (median, 109 days).

Bone Markers

All markers of bone metabolism, including *N*-telopeptide, pyridinoline, and deoxypyridinoline creatinine ratios, as well as serum bone alkaline phosphatase, decreased from baseline to study end in patients treated with zoledronic acid. Suppression of bone markers was similar in the 4-mg and 8/4-mg groups, and differences in the median percent change from baseline between the zoledronic acid treatment groups and the placebo group were statistically significant at each time point. At study end, the *N*-telopeptide to creatinine ratio was reduced 55% below baseline in patients treated with 4 mg zoledronic acid, compared with an 11% increase in the placebo group ($P < .001$). Similar results were observed with other bone markers, including pyridinoline to creatinine ratio ($P < .001$) and deoxypyridinoline to creatinine ratio ($P < .001$). Parathyroid hormone was increased from baseline in all treatment groups, though patients treated with zoledronic acid experienced a greater increase in parathyroid hormone compared with the placebo group. Alkaline phosphatase, a marker for bone formation, decreased from baseline by 12% in patients treated with 4 mg zoledronic acid, compared with a 2% increase in the placebo group ($P < .01$).

Time to Disease Progression and Overall Survival

The median time to overall disease progression was 89 days in patients treated with 4 mg zoledronic acid, compared with 84 days in patients treated with placebo ($P = .117$). The median time to death was similar in both treatment groups, with a median of 203 days for patients treated with 4 mg zoledronic acid, compared with 183 days for the placebo group ($P = .623$).

Safety

The most commonly reported adverse events (all grades) in all treatment groups were bone pain, nausea, anemia, vomiting, constipation, dyspnea, and fatigue (Table 5). The proportion of patients having nausea, vomiting, and dyspnea was higher in the 4-mg zoledronic acid treatment group compared with the placebo group. The proportion of patients experiencing bone pain, however, was higher in the placebo group compared with either zoledronic acid treatment group. Serious adverse events affected similar proportions of patients in all treatment groups. The most frequently reported serious adverse events, regardless of relation to study drug, were anemia, dehydration, aggravated malignant neoplasm, and dyspnea, and these were similar across the treatment groups.

Renal adverse events, which are known to be associated with intravenous (IV) bisphosphonates, were reviewed in greater detail. Decreased renal function was defined as a change from baseline serum creatinine of $\geq$ 0.5 mg/dL for patients with normal baseline serum creatinine and $\geq$ 1.0 mg/dL for patients with abnormal baseline serum creatinine or at least two times baseline value. Before the implementation of the 15-minute infusion amendment, the proportion of patients with decreased renal function was substantially higher in the zoledronic acid treatment groups compared with the placebo group (Table 6), with a hazard ratio of 3.8 by Kaplan-Meier analysis. However,

Table 5. Most Frequently Reported Adverse Events (all grades) in ≥ 15% of Patients by Treatment Group Regardless of Relationship to Study Drug

Adverse Event	Zoledronic Acid 4 mg (n = 254)		Zoledronic Acid 8/4 mg (n = 265)		Placebo (n = 247)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Bone pain	129	51	130	49	145	59
Nausea	116	46	106	40	83	34
Anemia	94	37	82	31	82	33
Vomiting	91	36	83	31	71	29
Constipation	85	34	76	29	89	36
Dyspnea	83	33	90	34	65	26
Fatigue	79	31	78	29	72	29
Pyrexia	67	26	70	26	56	23
Weakness	66	26	67	25	65	26
Anorexia	58	23	60	23	62	25
Edema of lower limb	56	22	53	20	49	20
Aggravated malignant neoplasm	54	21	67	25	56	23
Cough	47	19	44	17	38	15
Diarrhea	43	17	48	18	44	18
Headache	42	17	36	14	26	11
Insomnia	42	17	38	14	30	12
Dehydration	40	16	48	18	41	17

after the implementation of the 15-minute infusion-time amendment, the proportion of patients with decreased renal function was not significantly different between the 4-mg zoledronic acid and placebo groups (10.9% *v* 6.7%). Notably, for patients randomized after the infusion-time amendment (n = 578), there was no significant difference in time to first episode of decreased renal function between the 4-mg zoledronic acid and placebo groups (hazard ratio, 1.57; $P = .228$). Therefore, the infusion-time amendment substantially reduced the excess risk of increased serum creatinine compared with placebo.

DISCUSSION

In this trial, zoledronic acid (at the recommended dose of 4 mg via a 15-minute infusion every 3 weeks in addition to standard antineoplastic therapy) demonstrated a consistent reduction of skeletal morbidity across multiple end points compared with placebo in patients with lung cancer and a variety of other solid tumors, though the primary end point (proportion of patients with an SRE at 9 months) did not reach statistical significance. However, the end-of-study difference in the proportion of patients with an SRE, only provides a snapshot of the true difference because of the shorter-than-expected survival in both groups of patients. Importantly, analysis of time to first SRE showed an early and continued separation of the event curves, and the median time to the first event was significantly extended by more than 2 months in patients treated with zoledronic acid. In this population of patients with a median survival of only 6 months, time to first SRE is a meaningful measure of treatment effect because it accounts for the timing of events and patient discontinuations. Only approximately one fourth of the patients in each treatment group completed the study, because of rapid disease progression in this end-stage population.

Table 6. Proportion of Patients With Serum Creatinine Increase by Baseline Serum Creatinine and Treatment Group

Baseline Serum Creatinine	Zoledronic Acid 4 mg		Zoledronic Acid 8/4 mg		Placebo	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Prior to protocol amendment						
Normal*	7/55	13	5/47	11	3/50	6
Abnormal†	3/6	50	2/8	25	0/4	0
Total	10/61	16.4	7/55	12.7	3/54	5.6
After protocol amendment						
Normal*	17/154	11	19/160	12	10/143	7
Abnormal†	1/11	9	2/21	10	1/20	5
Total	18/165	10.9	21/181	11.6	11/163	6.7

NOTE. "Prior to" and "After protocol amendment" indicates those patients treated before or after, respectively, the amendment to 15-minute infusion of zoledronic acid.

*Normal baseline serum creatinine was defined as < 1.4 mg/dL, and serum creatinine increase was defined as a change from baseline ≥ 0.5 mg/dL or at least two times baseline value.

†Abnormal baseline serum creatinine was defined as ≥ 1.4 mg/dL, and serum creatinine increase was defined as a change from baseline ≥ 1.0 mg/dL or at least two times baseline value.

The proportion of patients with an SRE and time to first SRE are both conservative end points, used in previous multicenter studies of other bisphosphonates.[9] However, the skeletal morbidity rate and multiple event analysis may more accurately reflect the degree of skeletal morbidity commonly seen in these patients because they capture information on all SREs occurring after the first event. In this trial, the skeletal morbidity rate was significantly lowered in patients treated with zoledronic acid compared with the placebo group when HCM was included in the analysis. Moreover, the multiple event analysis demonstrated a significant and consistent reduction in the risk of skeletal complications in the overall patient population and in both stratification groups. Although not reported here, two other multiple event analysis methods (Wei-Lin-Weissfeld, and Prentice, Williams, and Peterson) confirm these results.[10,11] These results are particularly striking given the heterogeneous nature of the patient population and the advanced stage of disease. Moreover, the median duration of exposure to zoledronic acid was only approximately 4 months. Aside from all these statistical considerations, the weight of the evidence from all end points suggests the clinical benefit of zoledronic acid.

Markers of bone turnover were all significantly suppressed in patients treated with zoledronic acid compared with placebo, confirming the pharmacologic activity on surrogate bone markers. There is no objective evidence, however, based on changes in bone resorption markers or time to event analyses, that 8 mg zoledronic acid is more effective than 4 mg.

This is the first large randomized trial to demonstrate a treatment benefit for bisphosphonate therapy in patients with lung cancer and other solid tumors. The true clinical impact of this therapy is difficult to measure in terms of the improved quality of life for patients who are able to maintain their independence longer and suffer fewer debilitating and painful skeletal complications. Pathologic fractures can be particularly problematic, often requiring hospitalization and surgical intervention.

Zoledronic acid (4 mg via 15-minute infusion every 3 weeks) was well tolerated. The clinical adverse-event profile for patients treated with zoledronic acid was similar to that of patients treated with placebo and was consistent with that of other IV bisphosphonates.[12,13] Adverse events with a higher incidence in the zoledronic acid groups, compared with the placebo group, included nausea, anemia, pyrexia, vomiting, and dyspnea. However, these events were primarily mild to moderate in severity. Furthermore, there was no difference in the incidence of reported serious adverse events between treatment groups.

Although bisphosphonates are generally well tolerated, impaired renal function has been associated with the IV administration of these drugs as a class.[14] The renal safety profile of 4 mg zoledronic acid (via 15-minute infusion) was consistent with that of other IV bisphosphonates. Among patients receiving 15-minute infusions, there was no significant difference between the 4-mg zoledronic acid and placebo groups in time to first episode of decreased renal function, with a hazard ratio of 1.57. Therefore, infusion of 4 mg zoledronic acid via 15-minute infusion is associated with only a slightly greater risk of increased serum creatinine compared with placebo. In a large phase III trial in patients with breast cancer and multiple myeloma, 4 mg zoledronic acid via 15-minute infusion was associated with a similar risk of serum creatinine increase compared with 90 mg pamidronate disodium via 2-hour infusion (risk ratio, 1.0).[5] The 8-mg dose of zoledronic acid, however, has been associated with an increased incidence of renal function deterioration, even when administered via 15-minute infusion, and should not be used.

In summary, zoledronic acid has demonstrated clinical utility in the treatment of HCM[3] and bone metastases in patients with breast cancer or multiple myeloma[5] and prostate cancer.[15] The current study is the first to demonstrate the efficacy of a bisphosphonate across multiple end points of clinical significance in patients with bone metastases secondary to lung cancer and other solid tumors. The results of this trial support an expanded role for zoledronic acid in the treatment of patients with solid tumors and bone metastases.

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The acknowledgment is included in the full text version of this article only, available on-line at www.jco.org.
It is not included in the PDF version.

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