

# Zoledronic Acid Delays the Onset of Skeletal-Related Events and Progression of Skeletal Disease in Patients with Advanced Renal Cell Carcinoma

Allan Lipton, M.D.<sup>1</sup>

Ming Zheng, Ph.D.<sup>2</sup>

John Seaman, Pharm.D.<sup>2</sup>

<sup>1</sup> Department of Medicine, Milton S. Hershey Medical Center, Hershey, Pennsylvania.

<sup>2</sup> Novartis Pharmaceuticals Corporation, East Hanover, New Jersey.

The authors gratefully acknowledge the participation of investigators from Argentina, Australia, Austria, Belgium, Brazil, Canada, France, Germany, Italy, New Zealand, Poland, Switzerland, the United Kingdom, and the United States.

Allan Lipton has 200 shares of Novartis stock in a retirement account and has received honoraria from Novartis Pharmaceuticals Corporation

Ming Zheng and John Seaman are both employed by Novartis Pharmaceuticals Corporation

Address for reprints: Allan Lipton, M.D., Department of Medicine, Milton S. Hershey Medical Center, P.O. Box 850 H-46, Hershey, PA 17033; Fax: (717) 531-5076; E-mail: alipton@psu.edu

Received April 11, 2003; accepted May 13, 2003.

**BACKGROUND.** The objective of this study was to assess the efficacy and safety of zoledronic acid in patients with bone metastases secondary to renal cell carcinoma (RCC).

**METHODS.** A retrospective subset analysis of patients with RCC enrolled in a multicenter, randomized, placebo-controlled study of zoledronic acid was performed. Patients were randomized to receive zoledronic acid (4 or 8 mg as a 15-minute infusion) or placebo with concomitant antineoplastic therapy every 3 weeks for 9 months. The primary efficacy analysis was the proportion of patients with one or more skeletal-related events (SREs), which were defined as pathologic fracture, spinal cord compression, radiation therapy, or surgery to bone. Secondary analyses included time to first SRE, skeletal morbidity rate (events per year), disease progression, and multiple event analysis.

**RESULTS.** In this subset of 74 patients with RCC, zoledronic acid (4 mg) was found to significantly reduce the proportion of patients with an SRE (37% vs. 74% for placebo;  $P = 0.015$ ). Similarly, zoledronic acid significantly reduced the mean skeletal morbidity rate (2.68 vs. 3.38 for placebo;  $P = 0.014$ ) and extended the time to the first event (median not reached vs. 72 days for placebo;  $P = 0.006$ ). A multiple event analysis demonstrated that the risk of developing an SRE was reduced by 61% compared with placebo (hazard ratio of 0.394;  $P = 0.008$ ). The median time to progression of bone lesions was significantly longer for patients who were treated with zoledronic acid ( $P = 0.014$  vs. placebo). Zoledronic acid appeared to be well tolerated; the most common adverse events in all treatment groups included bone pain, nausea, anemia, and emesis.

**CONCLUSIONS.** Zoledronic acid (4 mg as a 15-minute infusion) demonstrated significant clinical benefit in patients with bone metastases from RCC, suggesting that further investigation of zoledronic acid in this patient population is warranted.

*Cancer* 2003;98:962-9. © 2003 American Cancer Society.

**KEYWORDS:** bisphosphonate, bone, renal cell carcinoma (RCC), neoplasm metastasis.

Skeletal involvement is common in patients with renal cell carcinoma (RCC). The incidence of RCC has been increasing steadily over the last 2 decades,<sup>1</sup> and it has been estimated that bone metastases will develop in approximately 30% of patients with RCC.<sup>2</sup> Bone metastases cause considerable skeletal morbidity, including bone pain, pathologic fractures, spinal cord compression, and hypercalcemia of malignancy (HCM).<sup>3</sup> It has been reported that approximately 81% of patients with RCC and bone metastasis require radiotherapy, 42% experience a long-bone fracture, and 29% require orthopedic surgery or develop HCM at some point during the course of their

disease.<sup>2</sup> Unfortunately, bone metastases rarely respond to systemic treatment for RCC, which includes primarily interferon- $\alpha$  and interleukin-2.

Bisphosphonates have been used extensively in the treatment of patients with HCM and in the prevention of skeletal complications associated with bone metastases in patients with breast carcinoma and multiple myeloma.<sup>4–8</sup> However, studies of patients with solid tumors other than breast carcinoma or prostate carcinoma have been limited. Most clinical trials of bisphosphonates only enrolled patients with bone metastases from breast carcinoma or prostate carcinoma.<sup>5–7</sup>

Recently, the results of a Phase III, placebo-controlled study demonstrated the efficacy of zoledronic acid (ZOMETA®; Novartis Pharma AG, Basel, Switzerland/Novartis Pharmaceuticals Corporation, East Hanover, NJ) in patients with a wide variety of solid tumors, including lung carcinoma (small cell and non-small cell) and RCC.<sup>9</sup> In that study, zoledronic acid (4 mg as a 15-minute infusion) prolonged the time to first skeletal event (not including HCM) by 2 months ( $P = 0.023$ ) and reduced the percentage of patients who experienced skeletal-related events (SREs). Because of the poor prognosis of patients with metastatic RCC and their limited treatment options, a retrospective analysis was performed to assess the benefit of zoledronic acid in this subset of patients. The analyses presented herein parallel those performed in the original report of the study and include multiple analyses of SREs, time to progression of bone disease, overall survival, and the safety and tolerability of zoledronic acid compared with placebo.

## MATERIALS AND METHODS

### Patients

All patients had at least one site of bone metastasis and an Eastern Cooperative Oncology Group (ECOG) performance status  $\leq 2$ . Patients with liver metastases, total bilirubin  $> 2.5$  mg/dL at screening, serum creatinine  $> 3.0$  mg/dL, or symptomatic brain metastases were excluded. Patients also were excluded if they had received another bisphosphonate within 30 days of receiving zoledronic acid or if they had a diagnosis of severe cardiovascular disease, hypertension refractory to treatment, or symptomatic coronary artery disease within 6 months of randomization. Written informed consent was obtained from all patients. The study enrolled 773 patients with lung carcinoma and a variety of other solid tumors.<sup>9</sup> A subset of 74 patients with RCC was included in this retrospective analysis. The original Phase III study was approved by the Institutional Review Boards of the respective institutions and was conducted in

compliance with international guidelines regulating patient safety.

### Study Design and Treatment

Patients were randomized to receive zoledronic acid (4 mg or 8 mg) or placebo every 3 weeks for 9 months. Initially, patients received zoledronic acid as a 5-minute infusion in 50 mL of infusate. However, the infusion time was increased to 15 minutes, and the infusion volume was increased to 100 mL to prevent renal-related, adverse events.<sup>9</sup> Subsequently, the 8-mg zoledronic acid dose was reduced to 4 mg (8/4-mg group). Serum creatinine was monitored during the 2 weeks before each dose of study drug. All patients received daily calcium supplements (500 mg) and a multivitamin tablet containing vitamin D (400–500 IU) throughout the study.

Before the first study treatment, a complete physical examination was performed, and a medical history was taken. Tumor assessment, bone scans, and bone surveys also were performed before treatment and were assessed along with ECOG performance status at 3 months, 6 months, and 9 months. SREs and adverse events were recorded at each visit every 3 weeks.

### Statistical Analysis

The primary efficacy analysis in the original study was the percentage of patients with at least 1 SRE during the 9 months on study. SREs were defined as pathologic fracture, spinal cord compression, radiation therapy to bone, or surgery to bone. For all efficacy variables analyzed, zoledronic acid (4 mg) was compared with placebo. No efficacy conclusions were drawn from the 8/4-mg group. The proportions of patients who had SREs were compared between treatment groups using the Cochran–Mantel–Haenszel test.

Other efficacy variables that were compared between treatment groups for the retrospective analysis included the annual incidence of skeletal complications (skeletal morbidity rate, defined as the number of SREs per year), time to first SRE, time to progression of bone metastases, and overall survival. The number of SREs and progression of bone lesions were assessed centrally by a radiologist who was blinded to the treatment and to the clinical course of patients. Time to event and overall survival were analyzed using the Kaplan–Meier method and the log-rank test. A multiple event analysis was performed using the Andersen–Gill approach.<sup>10</sup> For time to event and skeletal morbidity rate analyses, SREs that occurred within 21 days (21-day window) of the previous event were excluded from the SRE analysis, unless otherwise noted. Pain

**TABLE 1**  
**Primary Tumor Demographics for Patients in Each Treatment Group**

Primary tumor site	No. of patients (%)		
	Zoledronic acid		Placebo (n = 247 patients)
	4 mg (n = 254 patients)	8/4 mg (n = 265 patients)	
Lung carcinoma <sup>a</sup>	124 (48.8)	134 (50.6)	123 (49.8)
Other			
Renal cell carcinoma	27 (10.6)	28 (10.6)	19 (7.7)
Unknown primary	15 (5.9)	14 (5.3)	14 (5.7)
Head and neck	6 (2.4)	7 (2.6)	4 (1.6)
Thyroid	2 (0.8)	5 (1.9)	4 (1.6)
Other	80 (31.5)	77 (29)	83 (33.6)

<sup>a</sup> Lung carcinoma includes both small cell and nonsmall cell lung carcinoma.

was assessed by using Brief Pain Inventory composite scores.<sup>11</sup> After consulting with the Renal Advisory Board, changes in renal function were assessed using change from baseline serum creatinine levels. Elevated serum creatinine was defined as an increase  $\geq 0.5$  mg/dL if baseline values were  $< 1.4$  mg/dL, an increase  $\geq 1.0$  mg/dL if baseline values were  $\geq 1.4$  mg/dL, or any increase  $\geq 2$  times the baseline serum creatinine value. The time to first serum creatinine increase was analyzed using the Kaplan-Meier method and the log-rank test.

## RESULTS

### Patients

This clinical trial enrolled patients with bone lesions secondary to lung carcinoma and with a variety of solid tumors other than breast carcinoma or prostate carcinoma. Primary tumor demographics are presented by treatment group in Table 1. A total of 74 patients with RCC were enrolled in the study. Patient demographics and baseline disease characteristics of the subset of patients with RCC are summarized in Table 2. In general, patient demographics and baseline disease characteristics were balanced among treatment groups. The median age was approximately 64 years for each treatment group. The median time from initial diagnosis to study entry was comparable for the 4-mg zoledronic acid group (25.5 months) and the other groups (22.7 for the 8/4-mg zoledronic acid group and 21.2 months for the placebo group). However, the majority of patients (78–95%) in all groups had good performance status (ECOG performance status, 0–1). Most patients (63–79%) had one to three bone lesions and had previously experienced an SRE at study entry. One-half to two-thirds of patients had

normal baseline serum creatinine levels before they received study treatment.

### Efficacy

Figure 1A shows that the percentage of patients who experienced an SRE was reduced significantly for the 4-mg zoledronic acid group (37%) compared with the placebo group (74%;  $P = 0.015$ ). This 50% reduction is striking considering that many more patients in the placebo arm of the RCC subset developed an SRE (74%) compared with the overall study population (44%).<sup>9</sup> Similarly, the annual incidence of skeletal complications, or *skeletal morbidity rate*, was reduced from a mean of 3.38 events per year for patients in the placebo group to 2.68 events per year ( $P = 0.014$ ) for patients who were treated with 4 mg of zoledronic acid (Fig. 1B). The most common SREs were radiation therapy to bone and pathologic fracture; reductions in the incidence of each SRE were achieved with zoledronic acid (Table 3). Similar results were observed for the 8/4-mg zoledronic acid group; however, no efficacy conclusions were drawn from that treatment arm. The median time to first skeletal complication was not reached for the 4-mg zoledronic acid group, compared with a median of 72 days to first skeletal complication for patients in the placebo group ( $P = 0.006$ ) (Fig. 2). The extension in time to first pathologic fracture for patients in the 4-mg zoledronic acid group also was significant (median not reached vs. 168 days for the placebo group;  $P = 0.003$ ) (Fig. 3). Finally, the multiple event analysis (Fig. 4) revealed that there was a significant reduction (61%) in the risk of developing an SRE for patients in the 4-mg zoledronic acid group compared with the placebo group (hazard ratio, 0.394;  $P = 0.008$ ).

Analysis of the best radiographic bone lesion response at month 9 indicated that 7% of patients in the 4-mg zoledronic acid group achieved a partial response compared with no responses in the placebo group (Table 4). Bone lesions progressed in only 22% of patients who received zoledronic acid (4 mg) compared with 53% of patients who received placebo. It is noteworthy that the time to progression of bone lesions (Fig. 5) was significantly longer in patients who received zoledronic acid (4 mg) compared with patients who received placebo (median, 256 days vs. 89 days, respectively;  $P = 0.014$ ). In the overall study population, although the time to progression of bone lesions was longer for patients who received 4 mg zoledronic acid (median, 145 days), the increase did not achieve statistical significance compared with patients who received placebo (median, 109 days;  $P = 0.340$ ).<sup>9</sup> In patients with RCC, the median overall survival showed a trend toward favoring zoledronic

**TABLE 2**  
**Patient Demographics and Baseline Disease Characteristics by Treatment Group**

Characteristic	Zoledronic acid		Placebo (n = 19 patients)
	4 mg (n = 27 patients)	8/4 mg (n = 28 patients)	
Median age (yrs)	64	64	65
Sex (%)			
Male	18 (67)	24 (86)	17 (89)
Female	9 (33)	4 (14)	2 (11)
Primary therapy (%)			
Immunotherapy <sup>a</sup>	17 (63)	17 (61)	9 (47)
Hormonal therapy	1 (4)	1 (4)	1 (5)
Median time from initial diagnosis to study entry (months) <sup>b</sup>	25.5	22.7	21.2
ECOG performance status (%)			
≤ 1	21 (78)	24 (86)	18 (95)
≥ 2	5 (19)	4 (14)	1 (5)
Median BPI composite pain score	4.3	3.9	3.3
No. of lesions at study entry (%)			
Unknown	1 (4)	1 (4)	1 (5)
1-3	21 (78)	22 (79)	12 (63)
4-6	4 (15)	3 (11)	4 (21)
7-9	1 (4)	2 (7)	2 (11)
Previous SRE (%)			
Yes	22 (81)	23 (82)	18 (95)
No	5 (19)	5 (18)	1 (5)
Baseline serum creatinine (%)			
Normal (< 1.4 mg/dL)	17 (63)	16 (57)	9 (47)
Abnormal (≥ 1.4 mg/dL)	10 (37)	12 (43)	10 (53)

ECOG: Eastern Cooperative Oncology Group; BPI: Brief Pain Inventory (scale, 0-10); SRE: skeletal-related event.

<sup>a</sup> Denotes interferon-based and/or interleukin-based immunotherapy with or without additional chemotherapeutic agents.

<sup>b</sup> Twenty-eight days in a month.

acid (295 days for the 4-mg zoledronic acid group vs. 216 days for the placebo group;  $P = 0.179$ ) but did not achieve statistical significance compared with placebo (Fig. 6).

### Safety

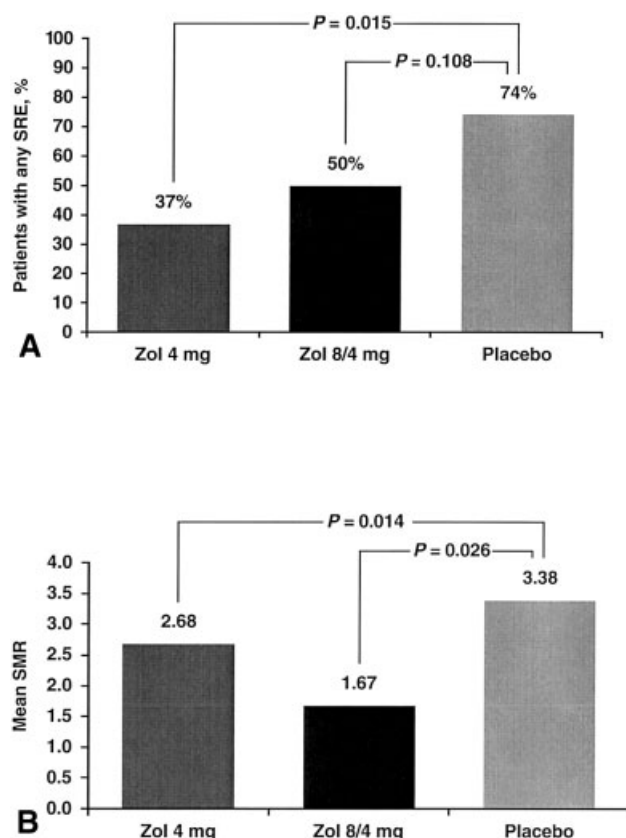
The most commonly reported adverse events (all grades) in all treatment groups were bone pain, nausea, anemia, fatigue, emesis, and pyrexia (Table 5). The proportion of patients who had episodes of nausea, fatigue, emesis, and pyrexia was greater in the 4-mg zoledronic acid treatment group compared with the placebo group. Serious adverse events were reported by 48% of patients in the 4-mg zoledronic acid group compared with 68% of patients in the placebo group. The most frequently reported, serious adverse events, regardless of relation to study drug, were malignant neoplasm, bone pain, dehydration, dyspnea, and pneumonia.

Renal adverse events, which are known to be associated with intravenous (i.v.) bisphosphonates, were followed closely. Before and after the change in infu-

sion time (from 5 minutes to 15 minutes), the numbers of patients who experienced renal adverse events in the 4-mg zoledronic acid group and the placebo group were similar: Two patients in the placebo group had a renal-related adverse event compared with no patients in the 4-mg zoledronic acid group. After the 15-minute infusion amendment, 2 patients in the 4-mg zoledronic acid group experienced a renal-related adverse event, compared with 3 patients in the placebo group. The overall renal-related adverse events across the 9-month study duration are shown in Table 6.

### DISCUSSION

This retrospective analysis of 74 patients with RCC who were enrolled in a large, randomized, Phase III study of zoledronic acid in patients with bone metastases from a variety of solid tumors demonstrated that zoledronic acid (4 mg as a 15-minute infusion) provided a significant treatment benefit for patients with RCC. Zoledronic acid significantly reduced the percentage of patients who had SREs, and the effects were



**FIGURE 1.** Zoledronic acid (Zol) reduced (A) the percentage of patients who experienced at least one skeletal-related event (SRE) and (B) the annual incidence of skeletal-related events. SMR: skeletal morbidity rate.

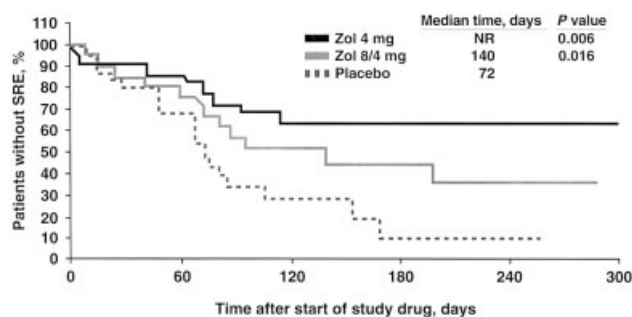
**TABLE 3**  
Total Number of Skeletal-Related Events

SRE	No. of SREs			
	With 21-day window		Without 21-day window <sup>a</sup>	
	Zoledronic acid 4 mg	Placebo	Zoledronic acid 4 mg	Placebo
Any SRE	15	20	20	35
Radiation to bone	8	9	11	12
Pathologic fracture	4	11	4	16
Vertebral	1	4	1	5
Nonvertebral	3	9	3	11
Surgery to bone	3	4	3	4
Spinal cord compression	1	3	2	3

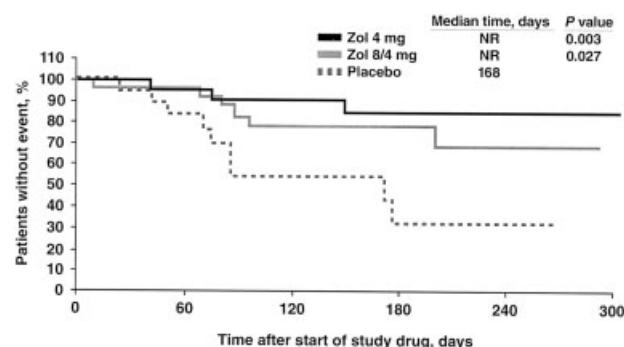
SRE: skeletal-related event.

<sup>a</sup> Events that occurred within 21 days of a prior event were counted.

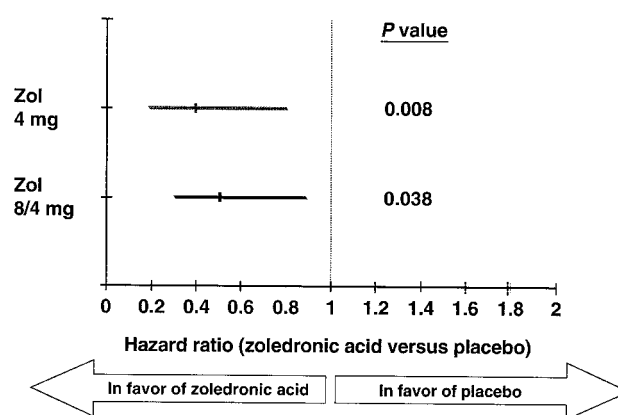
consistent across all types of SREs. Compared with the study's overall patient population, the proportions of patients with RCC who had SREs (74% for the placebo group) was nearly 2-fold greater (44% for the entire



**FIGURE 2.** Zoledronic acid (Zol) significantly delayed the time to first skeletal-related event (SRE). NR: not reached.



**FIGURE 3.** Zoledronic acid (Zol) significantly delayed the time to first pathologic fracture. NR: Not reached.



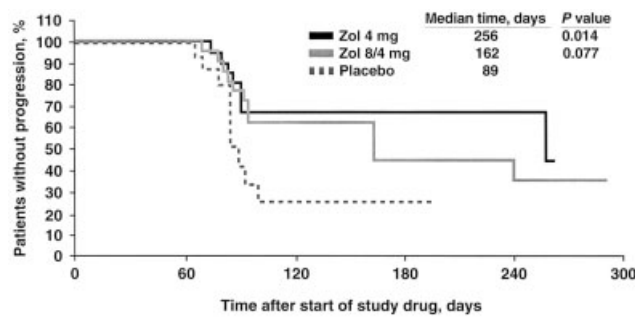
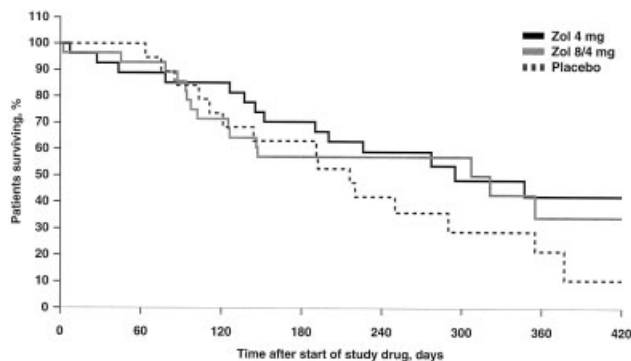
**FIGURE 4.** Patients who were treated with zoledronic acid (Zol) had a reduced risk of developing skeletal complications (Andersen-Gill multiple event analysis hazard ratio  $\pm$  95% confidence interval).

patient population),<sup>9</sup> suggesting that patients with RCC who have bone metastases are at greater risk of developing SREs compared with patients who have other types of solid tumors. The benefit of zoledronic acid in patients with RCC also was demonstrated clearly in the median time to first SRE and the time to first pathologic fracture, both of which increased sig-

**TABLE 4**  
Best Bone Lesion Response up to Month 3

Response	No. of patients (%)		
	Zoledronic acid		Placebo
	4 mg (n = 27 patients)	8/4 mg (n = 28 patients)	(n = 19 patients)
PR	2 (7)	5 (18)	0 (0)
No change	11 (41)	4 (14)	4 (21)
Progression	6 (22)	9 (32)	10 (53)
Not evaluable	8 (30)	10 (36)	5 (26)

PR: partial response.

**FIGURE 5.** Zoledronic acid (Zol) significantly delayed the progression of bone lesions compared with placebo.**FIGURE 6.** This plot shows Kaplan–Meier estimates of survival for patients who were treated with zoledronic acid (Zol) versus placebo.

nificantly in patients who were treated with zoledronic acid. Furthermore, in the analysis of multiple SREs, patients who received zoledronic acid were at a significantly reduced risk (61%) of developing an SRE. The multiple event analysis accounted for the time to first SRE in addition to the time to subsequent SREs and, thus, is a more accurate measure of treatment effect than conventional endpoints, such as the proportion of patients or the time to first SRE.

It is noteworthy that patients with RCC who re-

**TABLE 5**  
Most Frequently Reported Adverse Events (All Grades) in  $\geq 15\%$  of Patients by Treatment Group Regardless of Relation to Study Drug

Adverse event	Zoledronic acid					
	4 mg (n = 27 patients)		8/4 mg (n = 28 patients)		Placebo (n = 19 patients)	
	No.	%	No.	%	No.	%
Bone pain	14	52	11	39	12	63
Nausea	14	52	10	36	6	32
Emesis	9	33	10	36	5	26
Fatigue	9	33	6	21	3	16
Pyrexia	8	30	8	29	3	16
Anorexia	7	26	3	11	2	11
Anemia	7	26	5	18	6	32
Dyspnea	6	22	5	18	3	16
Arthralgia	6	22	7	25	4	21
Rigors	6	22	3	11	2	11
Edema lower limb	6	22	2	7	2	11
Constipation	5	19	5	18	7	37
Cough	5	19	2	7	3	16
Hypocalcemia	5	19	0	0	0	0
Weakness	4	15	4	14	5	26
Dehydration	4	15	6	21	2	11
Abdominal pain	4	15	5	18	0	0
Paresthesia	4	15	2	7	3	16
Dyspepsia	3	11	6	21	0	0
Aggravated malignant neoplasm	3	11	2	7	3	16
Myalgia	3	11	4	14	4	21
Diarrhea	2	7	6	21	3	16
Weight decrease	2	7	6	21	2	11
Pneumonia	1	4	5	18	1	5
Confusion	0	0	4	14	4	21

ceived zoledronic acid also showed significant response in bone lesions. The median time to bone lesion progression was prolonged significantly, and the number of patients who had a partial response or stable bone disease was greater in the zoledronic acid group compared with the placebo group. However, overall survival was similar for the placebo group and the zoledronic acid group.

The median survival for patients with advanced RCC is  $< 1$  year, and the 5-year mortality rate is nearly 100%.<sup>12</sup> Metastasis to bone has been identified as an independent prognostic variable that is predictive of poor survival in patients with metastatic RCC.<sup>13</sup> During their short survival, the majority of patients with RCC who have bone metastases will experience a skeletal complication, such as a fracture, that may be accompanied by debilitating pain. The current standard of care for patients with metastatic RCC includes surgical approaches and immunotherapy.<sup>14–16</sup> Immunotherapy with interferon or high-dose bolus interleukin-2 has achieved response rates from 15% to 20%.<sup>17</sup>

**TABLE 6**  
**Renal-Related Adverse Events after 9 Months of Treatment Regardless of Study Drug Relation (after 15-minute Infusion Amendment)**

Adverse event	No. of patients (%)		
	Zoledronic acid		Placebo (n = 15 patients)
	4 mg (n = 18 patients)	8/4 mg (n = 21 patients)	
Hyperuricemia	1 (5.6)	0 (0.0)	0 (0.0)
Hematuria	0 (0.0)	1 (4.8)	1 (6.7)
Renal failure, NOS	1 (5.6)	0 (0.0)	0 (0.0)
Blood creatinine increased	0 (0.0)	2 (9.5)	0 (0.0)
Difficulty in micturition	0 (0.0)	0 (0.0)	1 (6.7)
Hematuria present	0 (0.0)	1 (4.8)	0 (0.0)
Obstructive uropathy	0 (0.0)	1 (4.8)	0 (0.0)
Oliguria	0 (0.0)	0 (0.0)	1 (6.7)
Acute renal failure	0 (0.0)	1 (4.8)	0 (0.0)
Total patients	2 (11.1)	4 (19.0)	3 (20.0)

NOS: not otherwise specified.

Unfortunately, immunotherapy does not treat metastatic bone disease effectively.<sup>13</sup> This retrospective analysis demonstrated that zoledronic acid may provide a significant clinical benefit in patients with RCC. Further investigation will be required to determine whether the effects of zoledronic acid on the progression of bone disease can translate into an overall survival benefit. These results also suggest that patients with RCC may be good candidates for inclusion in investigations of zoledronic acid's antitumor effects or its ability to prevent bone metastases.

Zoledronic acid (4 mg as a 15-minute i.v. infusion every 3 weeks) was tolerated well by patients with RCC. The clinical adverse event profile for patients who were treated with zoledronic acid was similar to that for patients who received placebo and was consistent with the patterns observed in the larger Phase III patient population<sup>9</sup> and in clinical trials of other i.v. bisphosphonates.<sup>5,7</sup> Adverse events with a greater incidence in the zoledronic acid treatment arms compared with the placebo arm included nausea, anemia, pyrexia, emesis, and dyspnea. The administration of i.v. bisphosphonates has been associated with decreased renal function.<sup>18</sup> In the current analysis, the renal safety profile of zoledronic acid (4 mg as a 15-minute infusion) was similar to placebo. In fact, the rate of adverse renal events in patients who received 4 mg zoledronic acid was lower compared with the placebo group. Although the 8-mg dose of zoledronic acid administered as a 15-minute infusion appeared to be tolerated well in this subset analysis, that dose was associated in the entire patient population with

an increased incidence of rising serum creatinine levels and is not recommended.

Significant clinical benefits from zoledronic acid treatment were demonstrated in this retrospective subgroup analysis of patients with RCC and bone metastases. To our knowledge, the current analysis is the first to demonstrate a statistically significant clinical benefit in this patient population. The results of this analysis support an expanded role for zoledronic acid in the treatment of patients with bone metastases secondary to RCC and encourage the exploration of zoledronic acid treatment in patients with RCC.

## REFERENCES

1. Ries LAG, Eisner MP, Kosary CL, et al. SEER cancer statistics review, 1973–1999. Bethesda: National Cancer Institute, 2000. Available from URL: [http://seer.cancer.gov/csr/1973\\_1999/](http://seer.cancer.gov/csr/1973_1999/) [accessed March 3, 2003].
2. Zekri J, Ahmed N, Coleman RE, Hancock BW. The skeletal metastatic complications of renal cell carcinoma. *Int J Oncol.* 2001;19:379–382.
3. Coleman RE. Skeletal complications of malignancy. *Cancer.* 1997;80:1588–1594.
4. Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol.* 2001;19:558–567.
5. Hortobagyi GN, Theriault RL, Porter L, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. *N Engl J Med.* 1996;335:1785–1791.
6. Lipton A, Theriault RL, Hortobagyi GN, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. *Cancer.* 2000;88:1082–1090.
7. Berenson JR, Lichtenstein A, Porter L, et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. *N Engl J Med.* 1996;334:488–493.
8. Rosen LS, Gordon D, Kaminski M, et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a Phase III, double-blind, comparative trial. *Cancer J.* 2001;7:377–387.
9. Rosen LS, Gordon D, Tchekmedyian S, et al. 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. *J Clin Oncol.* In press.
10. Andersen PK, Gill RD. Cox's regression model for counting processes: a large sample study. *Ann Stat.* 1982;10:1100–1120.
11. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore.* 1994;23:129–138.
12. Clark JI, Gaynor ER, Martone B, et al. Daily subcutaneous ultra-low-dose interleukin 2 with daily low-dose interferon- $\alpha$  in patients with advanced renal cell carcinoma. *Clin Cancer Res.* 1999;5:2374–2380.

13. Kankuri M, Pelliniemi TT, Pyrhonen S, Nikkanen V, Helenius H, Salminen E. Feasibility of prolonged use of interferon-alpha in metastatic kidney carcinoma: a Phase II study. *Cancer*. 2001;92:761-767.
14. Godley P, Kim SW. Renal cell carcinoma. *Curr Opin Oncol*. 2002;14:280-285.
15. Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med*. 2001;345:1655-1659.
16. Mickisch GH, Garin A, van Poppel H, de Pijck L, Sylvester R. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. *Lancet*. 2001;358:966-970.
17. Glaspy JA. Therapeutic options in the management of renal cell carcinoma. *Semin Oncol*. 2002;29(Suppl 7):41-46.
18. Zojer N, Keck AV, Pecherstorfer M. Comparative tolerability of drug therapies for hypercalcaemia of malignancy. *Drug Safety*. 1999;21:389-406.