

Safety and Pain Palliation of Zoledronic Acid in Patients with Breast Cancer, Prostate Cancer, or Multiple Myeloma Who Previously Received Bisphosphonate Therapy

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ABSTRACT

An open-label study conducted in community centers assessed the safety of zoledronic acid 4 mg intravenously over 15 minutes every 3-4 weeks as treatment of bone metastases in patients with multiple myeloma, breast cancer, or prostate cancer with and without previous bisphosphonate exposure. Adverse events (AEs), pain, and quality-of-life (QOL) scores were recorded, and serum creatinine (SCr) levels were measured before each infusion. Of 638 patients, 415 patients (65%) had received prior bisphosphonate therapy. Fatigue, nausea, and arthralgia were the most frequent AEs. Nausea was more common in bisphosphonate-naïve patients. SCr levels increased notably in 6.6% of patients: 7.7% of patients who received prior bisphosphonate therapy and 4.5% of bisphosphonate-naïve

patients. Treatment was delayed because of SCr-level increases in 1.4% of patients with prior bisphosphonate exposure and 0.4% of bisphosphonate-naïve patients. SCr-level increases and treatment delays did not correlate with duration of prior bisphosphonate therapy. There was a trend towards more treatment discontinuations in patients with prior bisphosphonate exposure compared with bisphosphonate-naïve patients. Pain scores decreased from baseline; total QOL scores remained constant. The results of this study suggest that, with proper SCr-level monitoring, cancer patients with bone metastases who have previously received intravenous bisphosphonate treatment can be safely converted to zoledronic acid therapy. *The Oncologist* 2004;9:687-695

INTRODUCTION

In 65%-75% of patients with advanced breast or prostate cancer and 70%-95% of patients with multiple myeloma, bone metastases are a common cause of morbidity [1, 2]. The activation of osteoclasts by cancer cells that have migrated to the bone microenvironment causes increased resorption of

mineralized bone, resulting in cortical bone destruction [1]. As potent inhibitors of osteoclast activity, bisphosphonates are effective agents in the treatment of metastatic bone lesions, decreasing both the symptoms (e.g., bone pain) and complications (e.g., pathologic fracture, spinal cord compression, hypercalcemia) associated with metastatic bone disease

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[1, 2]. Zoledronic acid (Zometa[®]; Novartis Pharmaceuticals Corporation; East Hanover, NJ), a new highly potent, heterocyclic, nitrogen-containing bisphosphonate, has a more convenient administration schedule and is at least as or more effective than pamidronate (Aredia[®], Novartis), the previous i.v. bisphosphonate of choice for treatment of bone metastases in patients with breast cancer or multiple myeloma [1, 3, 4]. Zoledronic acid is the only bisphosphonate proven effective in the treatment of bone metastases in patients with advanced prostate cancer and other solid tumors [3, 5, 6].

In clinical trials of zoledronic acid, the most common bisphosphonate-related adverse events (AEs) were bone pain, nausea, and fatigue [7]. The incidence of renal dysfunction was similar in patients receiving zoledronic acid 4 mg over 15 minutes and patients receiving pamidronate 90 mg over 2 hours; the incidence was higher in patients receiving zoledronic acid 4 mg or 8 mg over 5 minutes [1, 3, 7]. Therefore, adhering to current zoledronic acid administration guidelines (i.e., administration of 4 mg by i.v. infusion over no less than 15 minutes) is important to minimize the development of renal dysfunction [7].

Before Food and Drug Administration (FDA) approval of zoledronic acid, many cancer patients with bone metastases received pamidronate. Many of these patients are now treated with zoledronic acid. Approximately one-third of patients treated with i.v. bisphosphonates still receive pamidronate, although many may be candidates for conversion to zoledronic acid. Data regarding the safety of zoledronic acid in patients with a history of significant exposure to bisphosphonate therapy are limited; phase III trials evaluating zoledronic acid in cancer patients with bone metastases excluded this patient population [1, 3-5]. Therefore, an evaluation of the safety of zoledronic acid in patients who received prior i.v. bisphosphonate therapy is warranted and will support the clinical rationale for converting appropriate patients to zoledronic acid.

This article reports the results of a community-based study of zoledronic acid (4 mg through a 15-minute infusion) in patients with breast cancer, prostate cancer, or multiple myeloma and bone metastases; most of these patients received prior bisphosphonate therapy. The objectives of the study were to assess: A) overall and renal safety; B) changes in pain scores from baseline; C) quality of life (QOL); and D) infusion duration. Results were analyzed according to tumor type and history of bisphosphonate therapy.

MATERIALS AND METHODS

Patients

Ambulatory adult patients (≥ 18 years of age) with at least one cancer-related bone lesion detected by conventional

radiography or bone scan and either Durie-Salmon stage III multiple myeloma or biopsy-proven breast or prostate cancer were enrolled in the study. The study protocol required all patients to have an FDA-approved indication for treatment with zoledronic acid; therefore, patients with prostate cancer were included only if their disease had progressed after receiving one or more hormone therapy regimens. All patients had a baseline Eastern Cooperative Oncology Group performance status of ≤ 2 .

Patients were excluded if they had abnormal renal function defined as either a serum creatinine (SCr) level that was at least 1.5 times above the upper limit of normal or a calculated creatinine clearance value of ≤ 60 ml/min, a corrected serum calcium level < 8.0 mg/dl (i.e., 2.0 mmol/l), or symptomatic brain metastases. Previous bisphosphonate treatment was permitted.

Planned enrollment was approximately 500 patients to allow sufficient statistical power for analyses of pain, QOL, and safety parameters. The study was approved by the institutional review boards of the participating institutions and conducted in compliance with international guidelines regulating patient safety. Informed consent was obtained from each patient before enrollment.

Study Design and Treatment

This open-label, prospective, multicenter study was conducted at 90 community-based medical centers in the United States. Patients received an infusion of zoledronic acid 4 mg i.v. over 15 minutes every 3-4 weeks for six doses. The study included no control group. Administration delays were required for notable changes in SCr level, defined as an increase of ≥ 0.5 mg/dl for patients with a normal baseline SCr level (i.e., < 1.4 mg/dl), an increase of ≥ 1.0 mg/dl in patients with an abnormal baseline SCr level (i.e., ≥ 1.4 mg/dl), or a doubling of any SCr level. For patients with a notable increase in SCr, the next dose was withheld until the SCr level returned to within 10% of the baseline SCr level.

Patients were instructed to take a calcium supplement (500 mg) and a multivitamin tablet containing vitamin D (400-500 IU) once daily for the study duration. The study allowed concomitant treatment with all standard antineoplastic therapies, radiation therapy for skeletal and nonskeletal tumor sites, use of standard cytokines or colony-stimulating factors for prevention or treatment of chemotherapy-induced cytopenias and corticosteroids for prevention or treatment of chemotherapy-induced nausea and vomiting, treatment of spinal cord compression or other recognized cancer syndromes, and administration of other marketed therapies. Therapies that affect osteoclast activity, such as calcitonin, mithramycin, gallium nitrate, or a bisphosphonate other than the study drug, were not permitted.

Assessments

Before each infusion, patients were assessed for any AE occurring since the last infusion. All AEs were monitored and graded by the investigator using the National Cancer Institute's Common Toxicity Criteria, version 2.0. Serious AEs were defined as untoward events that: A) were fatal or life threatening; B) required inpatient hospitalization or prolongation of existing hospitalization; C) caused persistent or significant disability or incapacity; D) constituted a congenital anomaly or birth defect; or E) were medically significant because they jeopardized the patient or required medical or surgical intervention to prevent one of the previously listed serious AEs. SCr levels were evaluated at baseline, within 2 weeks of each infusion, and at the final study visit (i.e., 4 weeks after the last zoledronic acid infusion). Physical examinations, routine monitoring of hematology parameters and blood chemistries, and other laboratory tests were conducted according to the clinical practice at each institution.

Pain assessments were conducted at baseline, before each infusion, and at the final study visit using a 100-mm visual analog scale (VAS). QOL was assessed at baseline and before infusions at visits 2 and 6 using the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire [8]. At each study visit, study personnel recorded the duration of infusion.

Statistical Analysis

Safety analyses of all patients who received at least one dose of study medication were summarized according to tumor type, prior exposure to bisphosphonate therapy, and duration of prior bisphosphonate therapy. Pain, QOL, and infusion-duration parameters were evaluated for the intent-to-treat (ITT) population, defined as all patients who received at least one dose of study medication and had at least one post-baseline pain score recorded. The change from baseline pain score was analyzed using paired *t*-tests. Kaplan-Meier estimates were used to assess time to development of pain for patients who reported no pain upon study entry. Chi-squared analysis was used to compare the incidences of notably increased SCr levels and treatment delays and discontinuations because of increased SCr levels.

RESULTS

Patients

All 638 patients enrolled in the study were assessable for safety. Of these patients, 613 (96.1%) were assessable for pain, QOL, and infusion time (ITT population). All study visits were completed by 472 patients (74%); 166 patients (26%) discontinued therapy prematurely. The most common reasons

for therapy discontinuation were AEs (6.4%), death (6.3%), serious AEs (3%), withdrawal of consent (4.9%), abnormal laboratory values (3%), and lack of follow-up (2.5%). Discontinuation reasons and rates were similar among all cancer types.

Overall, 77.4% of patients received all six infusions, including 78% of patients with breast cancer, 75.3% of patients with prostate cancer, and 78.3% of patients with multiple myeloma. Table 1 shows baseline demographic and disease characteristics. The mean baseline pain score was 28.1 mm (maximum score = 100 mm), with approximately 75% of patients reporting pain at study entry.

A total of 415 patients (65%) had received prior bisphosphonate therapy: one hundred ninety-six of these patients (47.2%) had received more than 6 but less than 24 months of prior treatment, and 110 (26.5%) had received at least 24 months of prior treatment. Most patients (95.4%) with prior exposure to bisphosphonates had received pamidronate. Three patients (0.7%) had received zoledronic acid, 8 patients (1.9%) had received both pamidronate and zoledronic acid, 7 patients (1.7%) had received alendronate, and in 2 patients (0.3%) the specific prior bisphosphonate received was unknown.

Overall Safety

Fatigue, nausea, and arthralgia were the most common AEs (Table 2). The incidence of these events did not vary significantly among tumor types. Nausea was mild in most cases, with grade 1/2 nausea occurring in 12.5% of patients. No cases of osteonecrosis were reported. Of 225 serious AEs in 96 patients, only one was suspected to be related to zoledronic acid (described in **Renal Safety** section). Grade 3 AEs occurred in 169 patients (26.5%); 79 patients (12.4%) experienced grade 4 AEs. Only 12 (4.8%) of the grade 3 or 4 AEs were suspected to be related to zoledronic acid. One death, unrelated to zoledronic acid, caused by renal failure and disseminated intravascular coagulation occurred in an 81-year-old patient with prostate cancer with a history of coronary artery disease, deep vein thrombosis, and hydronephrosis. Renal failure in this patient was attributed to underlying disease, diuretics, and previous cisplatin therapy.

Fatigue was the most common AE in patients with prostate cancer and multiple myeloma; nausea was the most common AE in patients with breast cancer. Dyspnea and vomiting were more common in patients with breast cancer than in patients with multiple myeloma or prostate cancer. Nausea was more common in patients with no prior bisphosphonate exposure (20% versus 12%); however, the incidence of other acute-phase reactions, such as arthralgia and fever, did not differ based on prior bisphosphonate exposure nor did the overall incidence of other AEs (Table 2).

Table 1. Baseline demographics and disease characteristics				
Characteristic	Myeloma n = 129	Breast n = 355	Prostate n = 154	All patients n = 638
Mean age, year ± SD	66.4 ± 11	60 ± 13	72.6 ± 9	64.3 ± 13
Gender, n (%)				
Male	79 (61)	7 (2)	154 (100)	240 (38)
Female	50 (39)	348 (98)	0	398 (62)
Race, n (%)				
White	97 (75)	307 (86.5)	124 (81)	528 (83)
Black	20 (15)	23 (6.5)	22 (14)	65 (10)
Asian	2 (2)	4 (1)	2 (1)	8 (1)
Other	10 (8)	21 (6)	6 (4)	37 (6)
Prior BP therapy, n (%)	108 (84)	278 (78)	29 (19)	415 (65)
Duration of prior BP therapy, n (%) [*]				
0-6 months	31 (29)	61 (22)	13 (45)	105 (25)
>6-24 months	52 (48)	132 (47.5)	12 (41)	196 (47)
>24 months	25 (23)	81 (29)	4 (14)	110 (26.5)
Metastatic sites, n (%)				
1	75 (58)	169 (48)	84 (54.5)	328 (51)
2	44 (34)	106 (30)	50 (32.5)	200 (31)
≥3	10 (8)	80 (22)	20 (13)	110 (17)
Baseline pain score, mean ± SD	29.4 ± 27	27.2 ± 25	29 ± 28	28.1 ± 26
Pts with baseline pain (VAS ≥5 mm), n (%)	100 (77.5)	259 (73)	102 (66)	461 (72)
Baseline score in pts with baseline pain, mean ± SD	36.9 ± 25	35.4 ± 23.5	41.3 ± 26	37 ± 24

*Percentage calculated according to number of patients with history of bisphosphonate therapy; duration of prior bisphosphonate therapy unknown in four patients.

SD = standard deviation; BP = bisphosphonate

Adverse event, n (%)	Patients, n (%)				
	Prior BP therapy[†]			Total (n = 415[†])	No prior BP therapy (n = 223)
	0-6 months (n = 105)	>6-24 months (n = 196)	>24 months (n = 110)		
Any AE	84 (80)	149 (76)	80 (73)	316 (76)	177 (79)
Fatigue	22 (21)	30 (15)	16 (14.5)	70 (17)	41 (18)
Nausea	18 (17)	16 (8)	16 (14.5)	51 (12)	45 (20)
Arthralgia	15 (14)	25 (13)	9 (8)	49 (12)	28 (13)
Dyspnea	12 (11)	16 (8)	11 (10)	39 (9)	18 (8)
Bone pain	13 (12)	19 (10)	5 (4.5)	37 (9)	25 (11)
Pyrexia	11 (10.5)	17 (9)	8 (7)	37 (9)	14 (6)
Back pain	9 (9)	14 (7)	12 (11)	35 (8)	16 (7)
Constipation	13 (12)	14 (7)	4 (4)	31 (7.5)	18 (8)

^{*}AEs included in table occurred in at least 10% of patients in any of the subgroups listed.

[†]Duration of prior BP therapy unknown for four patients

BP = bisphosphonate.

Renal Safety

During the study, 6.6% of patients had one or more SCr levels that met protocol criteria for a notably increased SCr level from that of baseline (Table 3). Although the incidence of notable SCr level increases was slightly higher among patients with prior exposure to bisphosphonates compared with patients with no prior bisphosphonate exposure (7.7% and 4.5%, respectively), the difference was not statistically significant, $p = 0.31$ (Table 3). The development of a notable SCr level increase was slightly higher in patients receiving more than 6 months of prior bisphosphonate therapy compared with patients receiving 6 months or less of prior bisphosphonate therapy (Table 3). The maximum changes in SCr level were similar in patients with and without prior bisphosphonate exposure and in patients within each tumor type. Changes in SCr levels, from baseline to final visit, were not influenced by duration of prior bisphosphonate therapy. The timing of first notable SCr level increase was consistent across infusions 2 through 6 (5-7 patients per infusion); however, a higher number of patients ($n = 13$) first experienced a notable elevation in SCr level at the posttreatment final visit.

Of the seven patients (1.1%) that had a protocol-specified treatment delay because of a notable SCr level increase, six patients (1.4%) had received prior bisphosphonate therapy and one patient (0.4%) was bisphosphonate naïve,

$p = 0.25$ (Table 3). Treatment delays because of a notable SCr level increase did not correlate with the duration of prior bisphosphonate therapy or vary among tumor types (Table 3). The overall rate of discontinuation due to SCr level increases was 3.1%. There was a trend toward more treatment discontinuations because of SCr level increases in patients with prior bisphosphonate exposure compared with patients with no prior bisphosphonate exposure (4.1% and 1.3%, respectively, $p = 0.06$) (Table 3). Fifteen of 17 patients (88.2%) with prior bisphosphonate exposure who discontinued zoledronic acid because of SCr level increases had received more than 6 months of bisphosphonate treatment. Of note, protocol violations occurred in 16 patients who should have undergone dose delay because of a notably increased SCr level.

Only one serious renal AE was suspected to be related to the study drug. A 74-year-old patient with prostate cancer developed grade 2 renal failure, concomitant congestive heart failure, and pneumonia 42 days after beginning the study and subsequently discontinued study medication because of poor medical condition. This patient had no history of bisphosphonate therapy.

Pain Scores

Of the 613 patients in the ITT population, 461 (75%) reported pain at baseline (VAS pain score, ≥ 5 mm). At every

Table 3. Notable SCr-level increase and treatment delay/discontinuation for SCr-level increases^a

Parameter	Notable SCr increase, <i>n</i> (%)	Treatment delay for SCr increase, <i>n</i> (%) ^c	Treatment discontinuation for SCr increase, <i>n</i> (%)
History of BP therapy			
No prior therapy (<i>n</i> = 223)	10 (4.5)	1 (0.4)	3 (1.3)
Prior therapy (<i>n</i> = 415)	32 (7.7) ^b	6 (1.4) ^d	17 (4.1) ^e
Months of prior BP therapy ^f			
0-6 months (<i>n</i> = 105)	7 (6.7)	3 (2.9)	2 (1.9)
>6-24 months (<i>n</i> = 196)	16 (8.2)	1 (0.5)	7 (3.6)
>24 months (<i>n</i> = 110)	9 (8.2)	2 (1.8)	8 (7.3)
Tumor type			
Breast (<i>n</i> = 355)	22 (6.2)	4 (1.1)	13 (3.7)
Multiple myeloma (<i>n</i> = 129)	10 (7.8)	2 (1.6)	4 (3.1)
Prostate (<i>n</i> = 154)	10 (6.5)	1 (0.6)	3 (1.9)
All types (<i>n</i> = 638)	42 (6.6)	7 (1.1)	20 (3.1)

^aNotable SCr-level increases defined as ≥ 0.5 mg/dl if baseline < 1.4 mg/dl; ≥ 1 mg/dl if baseline ≥ 1.4 mg/dl; or any doubling of SCr level from baseline.

^b $p = 0.12$

^cProtocol violations occurred in 16 patients who did not have treatment delayed for notable SCr-level increase.

^d $p = 0.25$

^e $p = 0.06$

^fDuration of prior bisphosphonate therapy unknown for 4 patients.

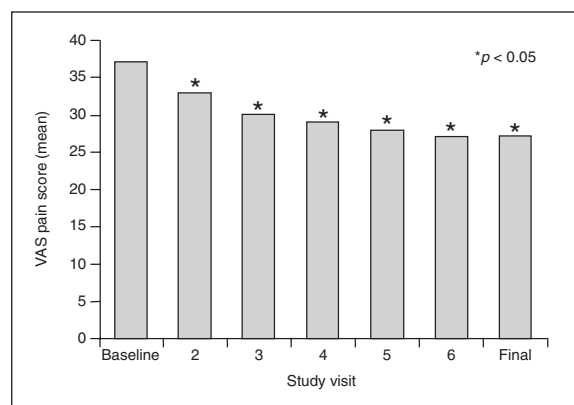


Figure 1. Mean VAS pain scores: patients with pain at baseline.
*Significant reductions ($p < 0.05$) from baseline VAS pain score.

visit, these patients experienced a statistically significant decrease in mean pain scores compared with baseline pain scores (Fig. 1). For each tumor type, patients experienced reductions in pain scores at every visit, with the change in pain scores from baseline statistically significant in one or more assessments for each tumor type (Table 4). Patients

with multiple myeloma and breast cancer experienced a significant reduction in pain scores from baseline scores in at least four of the six visits, whereas patients with prostate cancer experienced a significant reduction in pain scores from baseline at visit 2 only (Table 4). In the ITT population, mean VAS pain scores decreased from baseline scores at all assessments after the second visit, with statistically significant reductions at visits 4 ($p = 0.05$) and 5 ($p = 0.03$). Of the 152 patients (25%) who were pain free at baseline, the median time to development of pain, using Kaplan-Meier analysis, was estimated to be 168 days.

QOL Scores

Total mean FACT-G scores remained constant from baseline to visits 2 and 6 for the ITT population (Fig. 2). Total mean FACT-G scores also remained constant for each cancer type. Of the four subscale scores that comprise the total FACT-G score (physical, functional, emotional, social well-being), mean physical well-being scores improved significantly from baseline to infusion visit 2 ($p = 0.03$) as did mean emotional well-being scores ($p < 0.001$). Emotional well-being scores also improved significantly

Table 4. Change from baseline in mean VAS pain scores in patients with baseline pain*

Visit	Myeloma (n = 100)	Breast (n = 259)	Prostate (n = 102)	All patients (n = 461)
Infusion 2				
n	94	255	100	449
Mean \pm SD	33.3 \pm 27	32.8 \pm 24.5	34.7 \pm 25	33.3 \pm 25
Mean change \pm SD	-2.7 \pm 28	-2.6 \pm 25	-6.7 \pm 27.5 [†]	-3.5 \pm 26 [†]
Infusion 3				
n	91	235	92	418
Mean \pm SD	30.9 \pm 24	27.8 \pm 23	33.8 \pm 26.5	29.8 \pm 24
Mean change \pm SD	-4.3 \pm 24.5	-7.4 \pm 24 [†]	-5.6 \pm 31	-6.3 \pm 26 [†]
Infusion 4				
n	93	225	87	405
Mean \pm SD	27.7 \pm 22	27.9 \pm 24	34.9 \pm 29	29.4 \pm 25
Mean change \pm SD	-7.6 \pm 21 [†]	-6.9 \pm 26 [†]	-4.4 \pm 33	-6.5 \pm 26.5 [†]
Infusion 5				
n	84	215	79	378
Mean \pm SD	24.9 \pm 23	26.4 \pm 23	34.7 \pm 29	27.8 \pm 24.5
Mean change \pm SD	-9.7 \pm 26 [†]	-8.1 \pm 26 [†]	-5.6 \pm 32.5	-8 \pm 28 [†]
Infusion 6				
n	77	204	74	355
Mean \pm SD	25.3 \pm 21	25.1 \pm 23	33.3 \pm 29	26.8 \pm 24
Mean change \pm SD	-8.3 \pm 25 [†]	-8.6 \pm 27 [†]	-6.1 \pm 35	-8 \pm 28 [†]
Final visit				
n	75	221	72	368
Mean \pm SD	24.6 \pm 23	26 \pm 24	33.2 \pm 29	27.2 \pm 25
Mean change \pm SD	-7.7 \pm 27 [†]	-7.1 \pm 26 [†]	-5.6 \pm 34	-6.9 \pm 28 [†]

*Patients with baseline VAS score ≥ 5 mm were considered to have pain at baseline.

[†] $p < 0.05$

SD = standard deviation

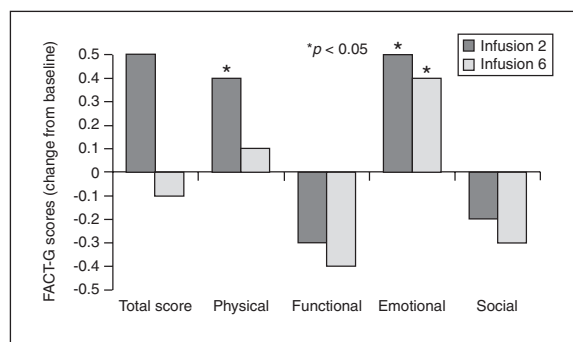


Figure 2. Change from baseline FACT-G scores ($p < 0.05$).

from baseline to visit 6 ($p = 0.02$). Functional and social well-being scores decreased from baseline at both assessments; these differences were not statistically significant.

Infusion Time

The mean infusion duration for the 3,374 infusions administered during the study was 17 minutes (range, 5-75 minutes), with the mean infusion duration for each visit varying only slightly throughout the study. Infusions of ≤ 14 minutes occurred during only 3% of the infusions, demonstrating strict adherence to the protocol and prescribing information for zoledronic acid (i.e., administration of 4 mg by i.v. infusion over no less than 15 minutes) [7].

DISCUSSION

The results of this open-label study demonstrate the safety of zoledronic acid as treatment of bone metastases secondary to multiple myeloma, breast cancer, or prostate cancer in patients with or without prior bisphosphonate exposure. In this study, 65% of patients received prior bisphosphonate therapy, primarily with pamidronate. Because patients receiving previous bisphosphonate therapy were excluded from the phase III trials evaluating zoledronic acid as treatment for bone metastases, the results of this study demonstrating the safety of zoledronic acid in patients previously exposed to bisphosphonates are both timely and clinically relevant.

Zoledronic acid was generally well tolerated in this study, with 77% of patients completing all six infusions. AEs reported were similar to AEs experienced by patients in other trials evaluating i.v. bisphosphonate therapy [1, 3-5, 7]. With the exception of a higher incidence of nausea in bisphosphonate-naïve patients, the incidence of AEs did not differ based on history of prior bisphosphonate treatment. The overall incidence of AEs in this trial was lower than the incidence noted in the integrated safety analysis presented in the zoledronic acid package insert [7]. Bone pain occurred in only 8.9%-11.2% of patients [7].

Zoledronic acid displayed renal safety, with 6.6% of patients developing a notable increase in their SCr level, and only 1.1% of patients requiring a treatment delay due to an increased SCr level. Furthermore, only 3.1% of patients discontinued therapy because of a change in SCr level. These very low rates of treatment delay and discontinuation, in patients receiving anticancer therapy, indicate that the overall SCr-level increases in this study were minor and manageable.

Patients with multiple myeloma experienced a slightly higher incidence of notable SCr-level increases compared with patients with breast or prostate cancer. This finding is not surprising given the underlying, disease-related renal dysfunction in many patients with multiple myeloma. Despite the higher incidence of notable SCr-level increases in patients with multiple myeloma, these patients did not experience substantially higher rates of treatment delay or discontinuation compared with patients with breast or prostate cancer. More patients who received prior bisphosphonate therapy had treatment discontinued because of increased SCr level than patients with no prior bisphosphonate exposure (Table 3). Even though this difference approached statistical significance ($p = 0.06$), the statistical power of the study to detect this difference was low given the small number of these events.

The duration of prior bisphosphonate therapy did not significantly affect the incidence of notable SCr level increases or treatment delays due to SCr level increases. Rates of treatment discontinuation due to SCr-level changes increased proportionally according to duration of prior bisphosphonate therapy (Table 3); however, the rate of discontinuation in the most heavily exposed patient population (i.e., >24 months of previous bisphosphonate therapy) was only 7.3%, suggesting that most patients with prior bisphosphonate exposure receiving zoledronic acid will not require therapy interruption from renal complications.

The rate of notable SCr-level increases in this study ($\leq 8.2\%$ for all patient subgroups) compares favorably with the rate of notable SCr-level increases in the phase III trials evaluating zoledronic acid in patients without exposure to prior bisphosphonates (8.8%-15.2% of patients with multiple myeloma, breast cancer, or prostate cancer) [7]. In previous clinical trials evaluating the use of zoledronic acid as treatment for bone metastases, the duration of infusion was changed from 5 minutes to 15 minutes because of a high incidence of SCr-level increase observed in patients receiving 5-minute infusions. The study protocol did not permit prolongation of the 15-minute infusion time in patients who experienced elevated SCr levels, although this will be the focus of a separate study. The current study represents the largest experience with zoledronic acid administered as a 15-minute infusion in a community setting. This study

demonstrates that the safety profile of zoledronic acid is better or comparable to that observed previously and not influenced substantially by prior bisphosphonate exposure. The low overall incidence of renal AEs also demonstrates that, with proper SCr-level monitoring as recommended in the manufacturer's prescribing information, zoledronic acid is safe in patients with or without a history of prior bisphosphonate treatment.

Both pamidronate and zoledronic acid have been shown to decrease the incidence and/or severity of bone pain in some patients with bone metastases, although a number of factors other than bisphosphonate therapy may have contributed to this decrease, such as a response to antitumor therapy or the use of pain medications and/or other supportive care therapies [1, 3, 5, 9-11]. In this study, pain scores in patients receiving zoledronic acid decreased from baseline at each assessment, suggesting that zoledronic acid may help manage pain resulting from osteoclastic bone destruction and does not increase the incidence or severity of bone pain in patients with bone metastases. Statistically significant, albeit modest, reductions in mean pain scores compared with baseline scores occurred more often in patients with multiple myeloma or breast cancer than patients with prostate cancer. Nonetheless, mean pain scores in patients with prostate cancer did not increase at any assessment. A more rigorous and comprehensive pain and opioid assessment may have provided greater insight into the role of zoledronic acid for the palliation of bone pain.

Several trials assessing the safety and efficacy of bisphosphonate therapy in cancer patients with bone metastases have also included an assessment of QOL [3, 5, 9-11]. Because many factors other than bisphosphonate therapy influence QOL in these patients (i.e., AEs associated with anticancer therapy, underlying disease progression), the results of these trials have been inconsistent [3, 5, 9-11]. In some trials, QOL scores were similar in patients receiving bisphosphonates or placebo; in other trials, bisphosphonate-treated patients had less of a reduction in QOL scores compared with placebo-treated patients [3, 5, 9-11]. In this study, overall QOL remained stable. Patient-reported measures of physical and emotional well-being improved, whereas measures of functional and social well-being declined. The decline in functional and social well-being

may have been related to the course of the underlying disease, concomitant administration of chemotherapy or radiation therapy, or other comorbid medical conditions or life situations. Although a variety of factors influence QOL measurements at any given time, our study results suggest that zoledronic acid therapy does not adversely affect overall QOL.

CONCLUSIONS

Zoledronic acid 4 mg administered as a 15-minute infusion every 3-4 weeks was well tolerated in patients with bone metastases from multiple myeloma, breast cancer, or prostate cancer, including patients who had significant prior exposure to bisphosphonates. With proper SCr-level monitoring, patients with bone metastases who have received prior bisphosphonate therapy can be safely converted to zoledronic acid. Although there was a trend towards more treatment discontinuations because of increased SCr level in patients with prior bisphosphonate exposure and with an increased duration of prior bisphosphonate therapy, the incidence of treatment discontinuations in these patients was still low. Overall, administration of zoledronic acid is safe in patients who have previously received a bisphosphonate.

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