

**Major P, Lortholary A, Hon J, Abdi E, Mills G, Menssen HD, Yunus F, Bell R, Body J, Quebe-Fehling E, Seaman J. 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.**

Hypercalcemia of malignancy (HCM) is another syndrome that is often referred to as an oncologic emergency. It is common in cancer patients, occurring in approximately 10-20% of cases.

Bisphosphonates are the most commonly used agents to treat hypercalcemia of malignancy and in addition, may prevent skeletal complications. Which bisphosphonate should be used as the first line of defense and what is the data behind its efficacy and safety? In this article, the authors used two identical, concurrent, parallel, multicenter, randomized, double-blind, double-dummy trials to compare the efficacy and safety of zoledronic acid and pamidronate for treating hypercalcemia of malignancy. Patients with moderate to severe HCM [ $> \text{ or } = 12.0 \text{ mg/dL}$ ] were treated with a single dose of zoledronic acid (4 or 8 mg) via 5-minute infusion or pamidronate (90 mg) via 2-hour infusion. Clinical end points included rate of complete response by day 10, response duration, and time to relapse. 287 patients were randomized and evaluated for safety; 275 were evaluated for efficacy. Both doses of zoledronic acid were superior to pamidronate in the treatment of HCM. The complete response rates by day 10 were 88.4% ( $P = .002$ ), 86.7% ( $P = .015$ ), and 69.7% for zoledronic acid 4 mg and 8 mg and pamidronate 90 mg, respectively. Normalization of calcium occurred by day 4 in approximately 50% of patients treated with zoledronic acid and in only 33.3% of the pamidronate-treated patients. The median duration of complete response favored zoledronic acid 4 and 8 mg over pamidronate 90 mg with response durations of 32, 43, and 18 days, respectively. Conclusion: Zoledronic acid is superior to pamidronate; 4 mg is the dose recommended for initial treatment of HCM and 8 mg for relapsed or refractory hypercalcemia.

# Zoledronic Acid Is Superior to Pamidronate in the Treatment of Hypercalcemia of Malignancy: A Pooled Analysis of Two Randomized, Controlled Clinical Trials

By P. Major, A. Lortholary, J. Hon, E. Abdi, G. Mills, H.D. Menssen, F. Yunus, R. Bell, J. Body, E. Quebe-Fehling, and J. Seaman

**Purpose:** Two identical, concurrent, parallel, multicenter, randomized, double-blind, double-dummy trials were conducted to compare the efficacy and safety of zoledronic acid and pamidronate for treating hypercalcemia of malignancy (HCM).

**Patients and Methods:** Patients with moderate to severe HCM (corrected serum calcium [CSC]  $\geq$  3.00 mmol/L [12.0 mg/dL]) were treated with a single dose of zoledronic acid (4 or 8 mg) via 5-minute infusion or pamidronate (90 mg) via 2-hour infusion. A protocol-specified pooled analysis of the two parallel trials was performed. Clinical end points included rate of complete response by day 10, response duration, and time to relapse.

**Results:** Two hundred eighty-seven patients were randomized and evaluated for safety; 275 were eval-

uated for efficacy. Both doses of zoledronic acid were superior to pamidronate in the treatment of HCM. The complete response rates by day 10 were 88.4% ( $P = .002$ ), 86.7% ( $P = .015$ ), and 69.7% for zoledronic acid 4 mg and 8 mg and pamidronate 90 mg, respectively. Normalization of CSC occurred by day 4 in approximately 50% of patients treated with zoledronic acid and in only 33.3% of the pamidronate-treated patients. The median duration of complete response favored zoledronic acid 4 and 8 mg over pamidronate 90 mg with response durations of 32, 43, and 18 days, respectively.

**Conclusion:** Zoledronic acid is superior to pamidronate; 4 mg is the dose recommended for initial treatment of HCM and 8 mg for relapsed or refractory hypercalcemia. *J Clin Oncol* 19:558-567. © 2001 by American Society of Clinical Oncology.

**H**YPERCALCEMIA OF malignancy (HCM) is the most common life-threatening metabolic complication of malignancy, affecting approximately 10% to 20% of patients with advanced cancer.<sup>1</sup> The incidence of HCM varies widely by cancer type but occurs most frequently in patients with multiple myeloma and carcinomas of the lung, breast, kidney, and head and neck.<sup>2-4</sup> A retrospective study of cancer-associated hypercalcemia reported that median survival was 30 days in patients treated with antihypercalcemic therapy.<sup>5</sup> Clinical symptoms of HCM such as nausea, vomiting, and altered mental status are distressing and diminish quality of life in the later stages of cancer progression. HCM can also lead to renal failure.

Patients with or without bone metastases can develop HCM. Hypercalcemia is mediated by soluble factors secreted by tumor cells and the immune system, such as parathyroid hormone-related protein (PTHrP), prostaglandins, and cytokines. These factors stimulate excess bone resorption and release of calcium from the bone matrix. As a result, patients experience bone loss, weakened bone structure, and elevated circulating calcium levels.<sup>1,6-8</sup> PTHrP also stimulates increased renal reabsorption of calcium, resulting in further increases in serum calcium levels.

Bisphosphonates are potent inhibitors of bone resorption and are the most effective therapy for HCM. Pamidronate (Aredia®; Novartis Pharmaceuticals Corporation, East Hanover, NJ) at a dose of 60 to 90 mg administered via 4-hour intravenous (IV) infusion is one of the most commonly used treatments of HCM. In studies investigating a variety of doses (30 to 90 mg) and schedules of pamidronate, complete response (CR) rates of 40% to 100% were observed within 7 days after intensive IV fluid hydration, and median duration of response ranged from 11 days to 3 to 4 weeks.<sup>9-16</sup>

Zoledronic acid (ZOMETA®; Novartis Pharmaceuticals Corporation) is a new-generation, nitrogen-containing bisphosphonate that has been shown in preclinical studies to be more potent than currently available bisphosphonates, including pamidronate.<sup>17</sup> Zoledronic acid was 850-fold more effective than pamidronate at inhibiting the induction of hypercalcemia in rats, and 40- to 100-fold more potent

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From the Hamilton Regional Cancer Centre, Hamilton, Ontario, Canada; Centre Paul Papin, Angers, France; Comprehensive Cancer Institute, Huntsville, AL; Bendigo Hospital, Bendigo, and Andrew Love Cancer Centre, Geelong, Australia; Feist-Weiller Cancer Center, Shreveport, LA; Medizinische Klinik III, Universitätsklinikum Benjamin Franklin, Freie Universität Berlin, Berlin, Germany; Boston Cancer Group, Memphis, TN; Institut Jules Bordet, Brussels, Belgium; and Novartis Pharma, Basel, Switzerland.

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Address reprint requests to Pierre P. Major, MD, Hamilton Regional Cancer Center, 699 Concession St, Hamilton L8V 5C2, Canada; email pierre.major@hrcc.on.ca.

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than pamidronate in inhibiting calcium release induced by a variety of activators of bone resorption in an in vitro calvaria assay.<sup>17</sup>

A recent multicenter, phase I, dose-finding trial demonstrated that zoledronic acid at doses of 0.02 and 0.04 mg/kg (equivalent to 1.2 and 2.4 mg in a 60-kg patient) normalized corrected serum calcium (CSC) in 19 of 20 hypercalcemic cancer patients.<sup>18</sup> Adverse events included transient hypophosphatemia in seven patients, transient hypocalcemia in three patients, and mild fever in 10 patients treated at the highest dose levels. Other phase I trials in patients with bone metastases or multiple myeloma demonstrated that zoledronic acid at doses ranging from 0.1 to 16 mg via rapid infusion was well tolerated<sup>19,20</sup> and that doses  $\geq 2$  mg effectively suppressed markers of bone resorption.<sup>20</sup> These studies also showed that 4 to 8 mg of zoledronic acid was more effective with respect to suppressing markers of bone resorption than lower doses, suggesting that these dose levels might be more effective in the treatment of HCM.

Two identical, concurrent, parallel, multicenter, randomized, double-blind, double-dummy trials were conducted to investigate the clinical efficacy of zoledronic acid (4 and 8 mg) versus 90 mg of pamidronate in the treatment of moderate to severe HCM. The results of a protocol-specified pooled analysis of the data from these two trials are presented here.

PATIENTS AND METHODS

Patients

Patients  $\geq 18$  years of age with histologic or cytologic confirmation of cancer and severe HCM, defined as baseline CSC  $\geq 3.00$  mmol/L (12.0 mg/dL), were eligible. Patients who had a history of allergic reaction or sensitivity to bisphosphonates or who were treated with bisphosphonates for hypercalcemia within 90 days or for other complications within 30 days of study entry were excluded, as were patients who exhibited serum creatinine more than 4.5 mg/dL (400  $\mu$ mol/L) or who were treated with calcitonin within 72 hours, with mithramycin or with a newly initiated antineoplastic cytotoxic chemotherapy or hormone therapy within 7 days, with gallium nitrate within 14 days, or with any investigational drug within 30 days of study entry. In addition, patients who were severely dehydrated, could not tolerate IV hydration, or suffered from hyperparathyroidism, adrenal insufficiency, vitamin D intoxication, milk alkali syndrome, sarcoidosis or other granulomatous disease, or multiple endocrine neoplasia syndromes were not eligible. All patients provided written informed consent before entry onto the study.

Treatment

Patients were randomized to treatment with either a single dose of zoledronic acid (4 or 8 mg) via a 5-minute IV infusion or pamidronate (90 mg) via a 2-hour IV infusion (Fig 1). Bisphosphonate therapy was administered simultaneously with IV hydration (ie, 500 mL of IV fluids over 4 hours). Patients received 250 mL of IV fluids before infusion of study drug. The remaining portion of the required IV hydration was administered as part of a double-dummy infusion, which maintained

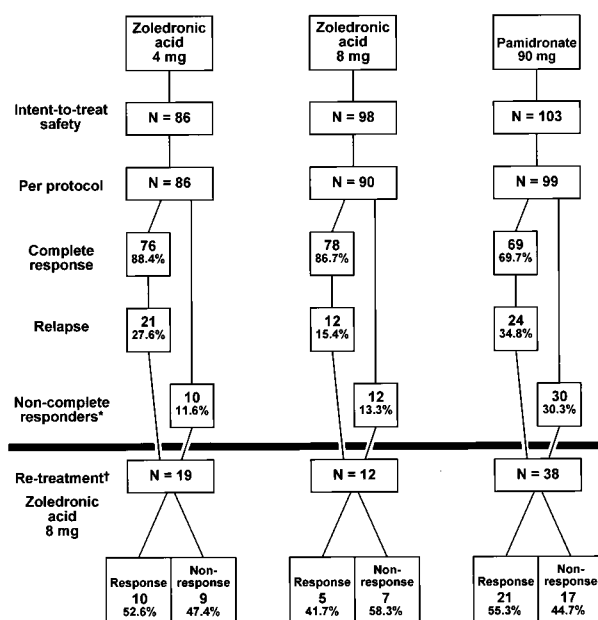


Fig 1. Patient randomization, disposition, and response summary. \*Inclusion of refractory patients, partial responders, and other non-complete responders. †The number of patients re-treated excludes those who discontinued or died.

the double-blind nature of the trial. That is, each patient received either a 5-minute IV infusion of zoledronic acid, then a 2-hour IV infusion of saline, and finally a 2-hour infusion of fluids, or a 5-minute IV infusion of saline, then a 2-hour IV infusion of pamidronate, and finally a 2-hour infusion of fluids.

Patients who were refractory to initial therapy or who relapsed up to 56 days after initial treatment with either zoledronic acid or pamidronate were re-treated with a single dose of 8 mg of zoledronic acid via 5-minute infusion and were followed-up for 28 days.

Study Design and Schedule

Two identical, concurrent, parallel, multicenter, randomized, double-blind, double-dummy trials were conducted at centers in the United States/Canada and Europe/Australia. One day before administration of study drug, a complete physical examination including urinalysis was performed, and venous blood was drawn for serum chemistry, including CSC, PTHrP levels, complete blood cell counts with differential and platelet counts, and other parameters. If the patient met the eligibility criteria, vital signs were monitored, IV hydration was initiated, and the study drug was administered. Venous blood was drawn for serum chemistry, including CSC, on days 4, 7, 10, 14, 17, 21, 24, and 28 and weekly thereafter, up to day 56. The following concomitant therapies were permitted during the study: standard antineoplastic therapies (including cytotoxic agents, biologic response modifiers, hormonal agents, or corticosteroids) and cytokines.

Patients were followed-up for 56 days or until relapse, defined as CSC  $\geq 2.90$  mmol/L (11.6 mg/dL). If CSC was not lower than baseline (day 1 value) by at least 0.05 mmol/L (0.2 mg/dL) on day 4 or 0.25 mmol/L (1.0 mg/dL) on day 7, or day 10 CSC was  $\geq 2.90$ mmol/L, then re-treatment with 8 mg of zoledronic acid was initiated for refractory

disease. Once a patient experienced relapse, re-treatment was initiated for relapsing disease.

For re-treatment of relapsed or refractory disease, CSC was monitored on re-treatment days 1, 4, 7, 10, 14, 21, and 28. If the re-treatment baseline CSC was not lowered by at least 0.05 mmol/L (0.2 mg/dL) on day 4 or 0.25 mmol/L (1.0 mg/dL) on day 7, then treatment of the patient was discontinued. The remaining patients were followed-up until day 28 or relapse.

Patients were evaluated for CR, defined as normalization of CSC to  $\leq 2.70$  mmol/L (10.8 mg/dL) by day 10. Other clinical end points evaluated were time to relapse of HCM, defined as the number of days from the date of infusion to the last CSC less than 2.90 mmol/L (11.6 mg/dL); duration of response, defined as the number of days from the onset of CR to the last CSC less than 2.90 mmol/L (11.6 mg/dL); duration of CR, defined as the number of days from the onset of CR to the last CSC  $\leq 2.70$  mmol/L (10.8 mg/dL); and efficacy of re-treatment for relapsed or refractory HCM. Safety and tolerability of zoledronic acid were assessed by review of clinical findings, adverse events, vital signs, routine blood chemistries, hematologic values, and urinalysis.

### Statistical Methods

**Sample size.** Using a 10% one-sided equivalence range and a one-sided .025 significance level, 90 patients per treatment group were required to show zoledronic acid 4 mg or 8 mg is at least as effective as 90 mg pamidronate with 80% power. The expected response rate was 90% for the pamidronate 90 mg group and 92% for the 4 mg or 8 mg zoledronic acid groups. A closed test procedure was applied. Zoledronic acid 4 mg was to be declared noninferior to pamidronate 90 mg only if zoledronic acid 8 mg was also declared noninferior.

**Analysis populations.** The primary efficacy analyses were performed on the eligible per-protocol population. The per-protocol population consisted of all randomized patients who received the IV infusion and satisfied the admission criteria for HCM. Cancer patients were considered to have HCM if their CSC was  $\geq 3.00$  mmol/L (12.0 mg/dL) within 1 day before study drug infusion. An intent-to-treat analysis was also performed.

**Methodology.** The primary analysis was performed on the CR rate by day 10, based on the 95% confidence interval (normal approximation to the binomial) of the differences in the proportion of patients who had a CR in the zoledronic acid and the pamidronate groups. Once noninferiority was confirmed, analyses to investigate the superiority of zoledronic acid compared with 90 mg of pamidronate were performed.<sup>21</sup>

The percentage of patients who had a CR by day 10 was analyzed using the Cochran-Mantel-Haenszel test, controlling for the baseline CSC level (CSC  $<$  or  $\geq 3.4$  mmol/L [13.6 mg/dL]). Patients were considered to have a CR once the CSC was  $\leq 2.70$  mmol/L (10.8 mg/dL), regardless of whether the CSC increased to a higher level on subsequent days. Patients who did not achieve a CR (or who died or discontinued the study without a CR) before day 10 were considered nonresponders. The proportions of patients who achieved a CR by day 4 and day 7 were also analyzed.

Between-treatment comparisons were performed on the change from baseline in CSC at days 4, 7, and 10 using analysis of covariance. For missing CSC values, the last CSC observation available (including baseline) was carried forward.

Time to relapse curves were drawn using the Kaplan-Meier method and were analyzed using Cox regression, with baseline CSC group included as a covariate. All patients who did not achieve a CR had their time to relapse set to zero (and not censored). For all other patients with a CR, the actual time to relapse was calculated as the duration in days

between the date of infusion and the last available CSC less than 2.90 mmol/L (11.6 mg/dL). Patients who died after a CR was achieved (but before documentation of relapse) were assumed to have relapsed on the day the last calcium value was obtained. All other complete responders who discontinued or completed the study without documented relapse were censored on the last day on which a CSC value was obtained.

Duration of CR was calculated using rules similar to time to relapse, except that the durations were based on the day of onset of the CR rather than the start date of the infusion. Durations were calculated only for the subset of patients who had a CR. No formal analyses were planned or performed on durations because the analyses would be biased; any differences that could be attributed to treatment effect would be confounded with the actual number of patients who responded.

For re-treatment of relapsed or refractory patients, the per-protocol population consisted of all patients who received the IV infusion of zoledronic acid 8 mg and whose baseline CSC was  $\geq 2.75$  mmol/L (11.0 mg/dL). The same clinical end points as the initial phase were summarized. However, patients who were complete responders but discontinued or completed the 28-day follow-up without documented relapse were counted as having a relapse on the last day a calcium value was obtained.

## RESULTS

### Patient Demographics and Baseline Clinical Characteristics

A total of 287 patients were randomized in the combined trials: 138 and 149 patients at the United States/Canada and European/Australian centers, respectively. Of these, 275 patients were eligible for the efficacy analysis (ie, per-protocol population): 86 patients in the zoledronic acid 4-mg dose group, 90 patients in the zoledronic acid 8-mg dose group, and 99 patients in the pamidronate 90-mg dose group. Demographic and baseline clinical characteristics were generally comparable between treatment groups (Table 1). Approximately 60% of patients were male, and approximately 80% were Caucasian. The proportion of patients with a breast or hematologic malignancy was greater in the zoledronic acid 4-mg group than in the zoledronic acid 8-mg or pamidronate 90-mg group.

### CR Rate

In the primary day 10 analysis, 88.4% ( $P = .002$ ) and 86.7% ( $P = .015$ ) of patients in the 4- and 8-mg zoledronic acid dose groups, respectively, achieved a CR, compared with 69.7% of patients in the pamidronate 90-mg group (Fig 2). By day 7, the proportion of patients with a CR in the zoledronic acid 4- and 8-mg groups was also significantly greater than the proportion of patients in the pamidronate 90-mg group. The zoledronic acid 8-mg group also had significantly more complete responders by day 4. There was no significant difference in the proportions of patients with CR between the zoledronic acid 4- and 8-mg dose groups.

**Table 1. Patient Demographics and Baseline Clinical Characteristics by Treatment Group**

	Zoledronic Acid 4 mg (n = 86)		Zoledronic Acid 8 mg (n = 90)		Pamidronate 90 mg (n = 99)		Total (n = 275)		Re-Treatment Zoledronic Acid 8 mg (n = 69)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
<b>Sex</b>										
Male	46	53.5	60	66.7	56	56.6	162	58.9	42	60.9
Female	40	46.5	30	33.3	43	43.4	113	41.1	27	39.1
<b>Race</b>										
White	73	84.9	70	77.8	76	76.8	219	79.6	54	78.3
Black	11	12.8	15	16.7	17	17.2	43	15.6	13	18.8
Asian		0	2	2.2	1	1.0	3	1.1		—
Other	2	2.3	3	3.3	5	5.1	10	3.6	2	2.9
<b>Age, years</b>										
Mean	60.0		58.7		59.0		59.2		58.3	
Median	60.50		61.00		61.00		61.00		61.0	
Range	33-84		21-84		25-87		21-87		33-84	
< 65 years	52	60.5	59	65.6	67	67.7	178	64.7	47	68.1
≥ 65 years	34	39.5	31	34.4	32	32.3	97	35.3	22	31.9
<b>Cancer group</b>										
Breast/hematologic	40	46.5	26	28.9	31	31.3	97	35.3	24	34.8
Other	46	53.5	64	71.1	68	68.7	178	64.7	45	65.2
<b>Baseline CSC</b>										
Mean, mmol/L	3.49		3.42		3.49		3.47		3.17	
Range, mmol/L	3.02-4.71		3.00-4.68		3.00-5.16		3.00-5.16		2.75-4.23	
Mean, mg/dL	13.96		13.67		13.95		13.86		12.67	
Range, mg/dL	12.08-18.84		12.00-18.72		12.00-20.64		12.00-20.64		11.00-16.9	
<b>Primary cancer site</b>										
Lung	15	17.4	25	27.8	23	23.2	63	22.9	18	26.1
Breast	22	25.6	14	15.6	15	15.2	51	18.5	11	15.9
Multiple myeloma	9	10.5	5	5.6	9	9.1	23	8.4	8	11.6
Head and neck	9	10.5	9	10.0	12	12.1	30	10.9	8	11.6
Renal	9	10.5	10	11.1	11	11.1	30	10.9	8	11.6
Unknown	2	2.3	1	1.1	4	4.0	7	2.5	2	2.9
Hematologic	9	10.5	7	7.8	7	7.1	23	8.4	5	7.2
Other	11	12.8	19	21.1	18	18.2	48	17.5	9	13.0
<b>Bone metastases</b>										
No	37	43.0	40	44.4	54	54.5	131	47.6	40	58.0
Yes	49	57.0	50	55.6	45	45.5	144	52.4	29	42.0
<b>Baseline PTHrP</b>										
≤ 2 pmol/L	62	72.1	59	65.6	65	65.7	186	67.6	41	59.4
> 2 pmol/L	20	23.3	25	27.8	24	24.2	69	25.1	23	33.3
<b>Use of loop diuretics, days 1-10</b>										
No	64	74.4	66	73.3	78	78.8	208	75.6	58	84.1
Yes	22	25.6	24	26.7	21	21.2	67	24.4	11	15.9
<b>Prior use of bisphosphonates in past year</b>										
No	77	89.5	86	95.6	91	91.9	254	92.4	63	91.3
Yes	9	10.5	4	4.4	8	8.1	21	7.6	6	8.7
<b>Blood urea nitrogen/creatinine ratio</b>										
Median	18.8		17.4		15.6		16.9		17.0	
<b>Time since cancer diagnosis</b>										
< 1 month	20	23.3	23	25.6	24	24.2	67	24.4	8	11.6
1-< 6 months	8	9.3	19	21.1	22	22.2	49	17.8	26	37.7
6-< 12 months	17	19.8	8	8.9	15	15.2	40	14.5	10	14.5
≥ 12 months	41	47.7	40	44.4	38	38.4	119	43.3	25	36.2

Mean CSC levels at days 4, 7, and 10 were significantly lower ( $P \leq .05$ ) in patients treated with 4 or 8 mg of zoledronic acid than in patients treated with 90 mg of pamidronate (Fig 3). Onset of normalization of CSC occurred by day 4 in approx-

imately one half of the patients treated with zoledronic acid (45.3% for zoledronic acid 4 mg and 55.6% for zoledronic acid 8 mg), whereas only 33.3% of the pamidronate 90-mg patients had CSC normalization by day 4.

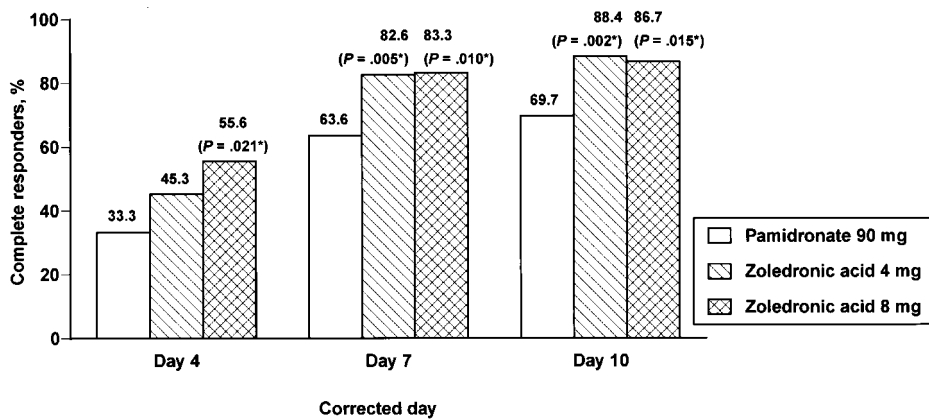


Fig 2. Percent of patients achieving a CR (CSC  $\leq$  2.7 mmol/L [10.8 mg/dL]). \*Statistical significance versus pamidronate. Corrected day: day 4 = days 2-5; day 7 = days 6-8, day 10 = days 9-11.

The number of patients with a CR by day 10 was similar for patients with baseline CSC less than 3.4 or  $\geq$  3.4 mmol/L (13.6 mg/dL) (Table 2). CR rates by day 10 were also similar within each treatment group regardless of baseline PTHrP level, baseline blood urea nitrogen/creatinine ratio, age, race, sex, or cancer type. CR rates in the zoledronic acid groups were also similar regardless of whether patients had bone metastases. However, in the pamidronate group, only 61% of patients without bone metastases compared with 80% of patients with bone metastases achieved a CR by day 10.

#### Duration of CR, Time to Relapse

The median time to relapse in patients treated with 4 or 8 mg of zoledronic acid was 30 ( $P = .001$ ) and 40 days ( $P =$

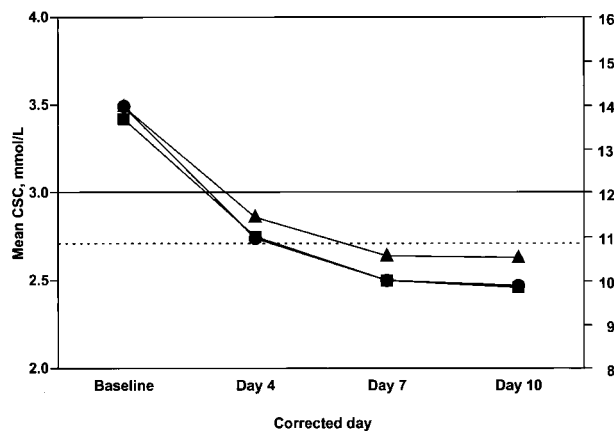


Fig 3. CSC mean at baseline and days 4, 7, and 10 after treatment of hypercalcemia with (●) zoledronic acid 4 mg, (■) zoledronic acid 8 mg, or (▲) pamidronate 90 mg. If calcium value is missing, then last value is carried forward. Corrected day: see Fig 2 legend. Corrected days 4, 7, and 10, zoledronic acid 4 mg versus pamidronate,  $P = .005$ ,  $.001$ , and  $.001$ , respectively; for zoledronic acid 8 mg versus pamidronate,  $P = .051$ ,  $.003$ , and  $.001$ , respectively.

.007), respectively, compared with 17 days in the pamidronate group (Fig 4). The time-to-relapse analysis was a protocol-specified analysis; because this analysis reflects both the length of response and the proportion of patients responding, it magnifies the difference in favor of the zoledronic acid group because of the higher response rate in this group compared with pamidronate. In patients in whom normal serum values were achieved, the median duration of CR in patients treated with 4 mg or 8 mg of zoledronic acid was 32 and 43 days, respectively, compared with 18 days in the pamidronate group (Fig 5).

#### Re-Treatment With Zoledronic Acid

Seventy patients who relapsed after having achieved a CR or were refractory to initial treatment with zoledronic acid or pamidronate were re-treated with zoledronic acid 8 mg, but only 69 patients were evaluated for efficacy. Demographics for this population were similar in most respects to the entire study population (Table 1). The mean baseline CSC level for the re-treatment group was 3.17 mmol/L (12.67 mg/dL) before re-treatment, compared with 3.52 mmol/L (14.08 mg/dL) before initial treatment with zoledronic acid or pamidronate. Approximately 33% of patients had baseline levels of PTHrP greater than 2 pmol/L. Fifteen patients (22%) had refractory HCM.

After re-treatment with 8 mg of zoledronic acid, mean CSC values decreased from 3.17 mmol/L at baseline to 2.71 mmol/L at day 10, and 36 patients (52%) achieved a CR by day 10. The median duration of CR was 10.5 days, and the median duration of response was 15 days. The median time to relapse was 8 days.

#### Safety

The most common adverse events (fever, anemia, nausea, constipation, and dyspnea) occurred with similar frequency among the zoledronic acid 4- and 8-mg groups and the

**Table 2. Complete Response Rate Day 10 of Initial Treatment for Selected Subgroups**

Subgroup	Zoledronic Acid 4 mg		Zoledronic Acid 8 mg		Pamidronate 90 mg	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Baseline CSC						
< 3.4 mmol/L	39	87	54	90	38	78
≥ 3.4 mmol/L	37	90	24	80	31	62
Bone metastases						
Present	44	90	42	84	36	80
Absent	32	87	36	90	33	61
PTHrP level						
≤ 2 pmol/L	55	89	53	90	48	74
> 2 pmol/L	17	85	19	76	17	71
Blood urea nitrogen/creatinine ratio						
≤ 20	40	87	47	87	47	71
> 20	32	89	30	86	21	66

pamidronate 90-mg group (Table 3). Adverse events suspected to be drug-related included fever, hypophosphatemia, and asymptomatic hypocalcemia. Renal adverse events were reported somewhat more frequently in the zoledronic acid groups than in the pamidronate 90-mg group. Two patients in the zoledronic acid 8-mg group and one patient in the pamidronate 90-mg group developed grade 4 serum creatinine values: Two patients developed grade 3 creatinine changes in the zoledronic acid 4-mg group and three patients each in the zoledronic acid 8 mg and pamidronate 90-mg group (Table 4).

Two other serious adverse events were observed: one patient in the zoledronic acid 4-mg group experienced confusion and hallucination, and one patient in the pamidronate 90-mg group developed thrombocytopenia. No treatment-related deaths occurred.

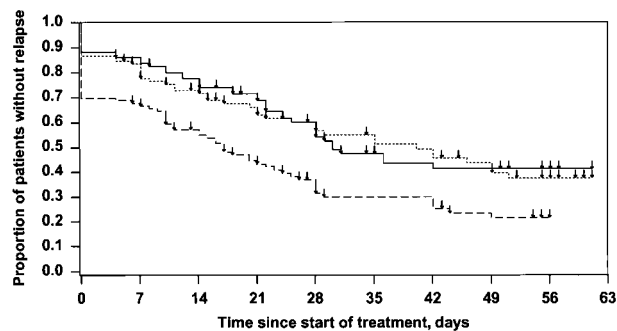
**DISCUSSION**

This study represents the largest prospective, randomized, comparative, clinical trial ever conducted between two

bisphosphonates in HCM or other disease states. The efficacy data demonstrate that a new heterocyclic nitrogen-containing bisphosphonate, zoledronic acid, administered as a single 5-minute IV infusion of 4 mg or 8 mg, is superior to 90 mg of pamidronate in the treatment of moderate to severe HCM. CSC normalized within 4 to 10 days in a significantly greater proportion of patients treated with either the 4- or 8-mg dose of zoledronic acid than with 90 mg of pamidronate. Furthermore, mean CSC was lower for patients treated with zoledronic acid than with pamidronate at each posttreatment evaluation. Of equal importance, patients treated with zoledronic acid maintained a clinically acceptable CSC level for a significantly longer time than patients treated with the current standard therapy of 90 mg of pamidronate. The prolonged response time as well as the much shorter infusion time with zoledronic acid both represent additional important treatment advances for these terminally ill patients.

The 4-mg dose of zoledronic acid was as effective as the 8-mg dose in the HCM population as a whole. Subgroup analysis showed zoledronic acid to be equally effective regardless of sex, age, tumor type, presence or absence of bone metastases, or serum level of PTHrP. The 8-mg dose of zoledronic acid normalized calcium by day 4 in a slightly greater proportion of patients and was associated with a longer duration of response and time to relapse. However, these differences may be of minor clinical significance for the individual patient. Furthermore, patients in these clinical trials had quite high mean CSC levels, with several patients having values of 4.5 to 5.0 mmol/L (18 to 20 mg/dL). Because many patients in clinical practice may have less severe hypercalcemia, it seems prudent to recommend the lower dose of 4 mg as initial therapy in most patients, with the 8-mg dose reserved for patients requiring re-treatment.

The 52% re-treatment response rate observed in patients with relapsed or refractory HCM, although not as impres-



**Fig 4. Kaplan-Meier estimation of time to relapse of hypercalcemia after treatment with (—) zoledronic acid 4 mg (median, 30 days), (---) zoledronic acid 8 mg (median, 40 days), or (· · ·) pamidronate 90 mg (median, 17 days). Arrows denote censored time. Zoledronic acid 4 mg versus pamidronate, *P* = .001; zoledronic acid 8 mg versus pamidronate, *P* = .007.**

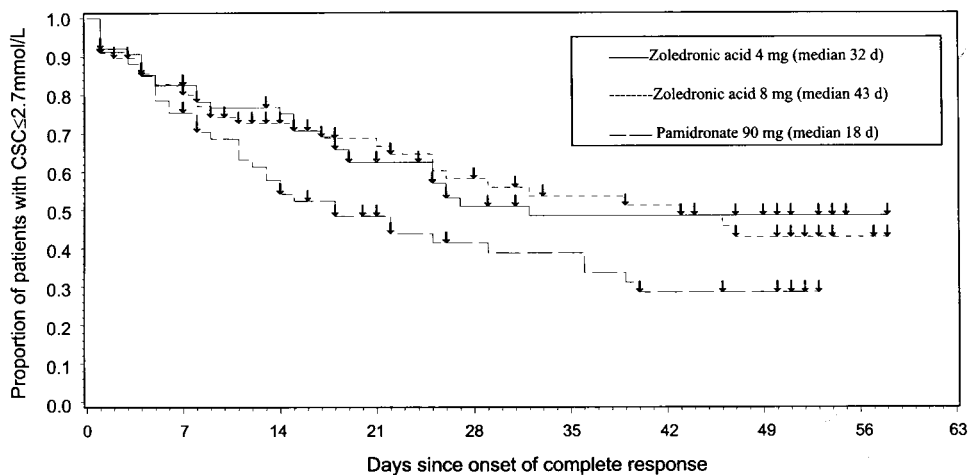


Fig 5. Kaplan-Meier estimation of the median duration CR. Median duration of CR for 4 and 8 mg of zoledronic acid and 90 mg of pamidronate are shown in the box.

sive as the effect of initial therapy, is still meaningful in this patient population. Diminished responsiveness of HCM to re-treatment with bisphosphonates has been suggested by other trials with small numbers of re-treated patients.<sup>22,23</sup>

The response rate of 69.7% observed with 90 mg of pamidronate in these trials was lower than expected. In earlier HCM trials, 90 mg of pamidronate was reported to normalize CSC in up to 100% of patients.<sup>14,24,25</sup> Changes in cancer treatment and differences in study design may be among the factors contributing to this difference. The previous studies evaluated only 10 to 20 patients at the 90-mg dose, and baseline CSC levels were lower than the 3.49 mmol/L (13.95 mg/dL) in the pamidronate group in the current trials. Earlier studies with pamidronate also required up to 48 hours of

hydration before bisphosphonate treatment, and the degree of hypercalcemia required for study entry as well as the definition of response varied from study to study. The large number of patients and centers participating in the trials reported here, as well as the fact that response rates were similar between studies, support the validity of the results for pamidronate as well as zoledronic acid.

Although not as extensively tested as pamidronate or zoledronic acid, other aminobisphosphonates have been evaluated in HCM. The response rates reported with ibandronate in a recent trial were lower than those achieved with zoledronic acid. Among 147 patients with a median baseline CSC of 3.4 mmol/L, 76% and 77% of patients achieved normocalcemia with 4 and 6 mg of ibandronate, respective-

Table 3. Number of Patients With Most Frequent Adverse Events (> 15%)

	Zoledronic Acid 4 mg		Zoledronic Acid 8 mg		Pamidronate 90 mg		Re-Treatment Zoledronic Acid 8 mg	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Patients studied								
Total no. of patients studied	86	100	98	100	103	100	70	100
Total no. of patients with any adverse event	81	94.2	94	95.9	95	92.2	50	71.4
Adverse events								
Fever	38	44.2	34	34.7	34	33.0	11	15.7
Anemia	19	22.1	27	27.6	18	17.5	8	11.4
Nausea	25	29.1	21	21.4	28	27.2	8	11.4
Constipation	23	26.7	19	19.4	13	12.6	5	7.1
Dyspnea	19	22.1	18	18.4	20	19.4	6	8.6
Confusion	11	12.8	15	15.3	13	12.6	4	5.7
Insomnia	13	15.1	15	15.3	10	9.7	2	2.9
Vomiting	12	14.0	15	15.3	17	16.5	5	7.1
Hypokalemia	10	11.6	12	12.2	16	15.5	4	5.7
Diarrhea	15	17.4	10	10.2	17	16.5	8	11.4
Abdominal pain	14	16.3	7	7.1	13	12.6	7	10.0

NOTE. Adverse events are sorted in descending frequency, as reported in the zoledronic acid 8-mg column.

**Table 4. Number of Patients With Common Toxicity Criteria Grade 3 or 4 Serum Creatinine Values**

	Zoledronic Acid 4 mg (n = 86)		Zoledronic Acid 8 mg (n = 96)		Pamidronate 90 mg (n = 100)		Re-Treatment Zoledronic Acid 8 mg (n = 68)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Serum creatinine								
Grade 3	2	2.3	3	3.1	3	3.0	1	1.5
Grade 4		0	2	2.1	1	1.0	1	1.5

ly.<sup>26</sup> Response was dependent on ibandronate dose, severity of hypercalcemia, and tumor type, with patients with breast cancer and hematologic tumors having a better response than patients with other tumor types. Single doses of 5, 10, or 15 mg of alendronate sodium resulted in an overall CR rate of 74% in 41 patients with an initial CSC of at least 2.88 mmol/L (11.5 mg/dL).<sup>23</sup> The highest response rate of 90% was achieved with 15 mg, but only 10 patients received this dose.

The safety profile of zoledronic acid was similar to that of pamidronate. The adverse events that were commonly reported are not unexpected in patients with advanced cancer, and the frequency of each type of adverse event was generally similar among the zoledronic acid 4- and 8-mg and pamidronate 90-mg groups. Hypocalcemia and hypophosphatemia were somewhat more common after zoledronic acid treatment than treatment with pamidronate, presumably because of the more potent pharmacologic activity of zoledronic acid.

Zoledronic acid has demonstrated a lower nephrotoxic potential than pamidronate in two short-term rat models.<sup>27</sup> However, bisphosphonates have been associated with impairment of renal function.<sup>28</sup> Therefore, monitoring of renal function should be routine practice, particularly when patients have underlying or concomitant illnesses associated

with renal function impairment or have decreased renal function before treatment or receiving the higher 8-mg dose.

Pamidronate has demonstrated long-term effectiveness for treatment of bone metastases in large trials in patients with multiple myeloma or breast cancer.<sup>29,30</sup> Because zoledronic acid has even greater pharmacologic effects on bone, a number of phase III trials are underway or are being initiated to investigate the activity of zoledronic acid in treatment of cancer patients with bone metastases. Preclinical data have also suggested that zoledronic acid may have antitumor activity.<sup>31-36</sup> These studies provide the clinical rationale for trials investigating the potential of zoledronic acid to prevent bone metastases in patients with breast and prostate cancer.

In conclusion, IV zoledronic acid provides a more effective and more convenient treatment for HCM than pamidronate, while maintaining a similar safety profile. Given that pamidronate has been the standard of care for HCM until now, it is likely that zoledronic acid will replace it as first-line therapy.

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#### APPENDIX

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