A Phase I Dose-ranging Trial of Monthly Infusions of Zoledronic Acid for the Treatment of Osteolytic Bone Metastases

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ABSTRACT

Bisphosphonates are potent inhibitors of bone resorption and provide a therapeutic benefit for patients with bone metastases. Zoledronic acid is a highly potent, nitrogen-containing bisphosphonate. In the present trial, we assessed the safety and tolerability of increasing doses of zoledronic acid and its effects on urinary markers of bone resorption in cancer patients with bone metastases. Fifty-nine cancer patients with bone metastases were enrolled sequentially into one of 8 treatment groups in the core protocol. Each patient received a 5-min i.v. infusion of 0.1, 0.2, 0.4, 0.8, 1.5, 2, 4, or 8 mg zoledronic acid monthly for 3 months. Patients were monitored for clinical findings, adverse events, electrocardiograms, markers of bone resorption, as well as routine hematology, blood chemistries, and urinalysis. Thirty patients who demonstrated a radiographic response to treatment or stable disease in the core protocol were enrolled in a humanitarian extension protocol and continued to receive monthly infusions. Zoledronic acid was well tolerated at all dose levels. Adverse events reported by >10% of patients included skeletal pain, nausea, fatigue, upper respiratory tract infection, constipation, headache, diarrhea, and fever. Three patients in the core protocol and one patient in the extension protocol experienced grade 3 skeletal pain, “flu-like” symptoms, or hypophosphatemia, which were possibly related to treatment; all recovered completely. Adverse events were reported with similar frequency across all of the dosage groups. Zoledronic acid resulted in sustained, dose-dependent decreases in urinary markers of bone resorption. Zoledronic acid was safe and well tolerated and demonstrated potent inhibition of bone resorption.

INTRODUCTION

Patients with bone metastases are at increased risk for skeletal-related events, including bone pain, hypercalcemia, pathological fractures, and spinal cord compression (1–3). Osteolytic bone destruction results from the biochemical interactions between metastatic tumor cells and the bone microenvironment (4, 5). The secretion of tumor-associated humoral and paracrine factors, such as parathyroid hormone-related protein, stimulate osteoclast-mediated bone resorption without an accompanying increase in bone formation (1, 4–8). Bisphosphonates have emerged as an important class of drugs that inhibit both normal and pathological bone resorption and that have had a major impact on the treatment of metastatic bone disease (9–30).

Bisphosphonates are analogues of PP, and differ from one another based on their substituted side chains (27). They can be segregated into two distinct pharmacological classes [i.e., nitrogen-containing (amino) and non-nitrogen-containing bisphosphonates] based on their molecular mechanism of action (31). Nitrogen-containing bisphosphonates, including alendronate, ibandronate, pamidronate, and zoledronic acid, inhibit protein prenylation, which inhibits osteoclast function and induces apoptosis in osteoclasts as well as myeloma and breast cancer cells in vitro (32–36). Non-nitrogen-containing bisphosphonates, such as clodronate and etidronate, are metabolized intracellularly to cytotoxic, nonhydrolyzable analogues of ATP.

Preclinical studies have demonstrated that nitrogen-containing bisphosphonates are at least 100-fold more potent than non-nitrogen-containing bisphosphonates with respect to their ability to inhibit bone resorption in vitro (35). Zoledronic acid (1-hydroxy-2-imidazol-1-yl-phosphonoethyl bisphosphonic acid; Zometa, Novartis Pharmaceuticals Corporation, East Hanover, NJ) is a new-generation heterocyclic nitrogen-containing bisphosphonate (Fig. 1). In preclinical studies, zoledronic acid demonstrated more potent inhibition of osteoclast-mediated bone resorption than any bisphosphonate tested (37). In several in vitro and in vivo model systems that surveyed indices of bone resorption, zoledronic acid was 100 to 850 times more potent than pamidronate (37, 38). Zoledronic acid has also been shown to preserve bone mass, architecture, and strength in estrogen-deficient animals without adversely affecting bone mineralization (39, 40). Moreover, zoledronic acid has demonstrated lower nephrotoxic potential than pamidronate in two short-term rat models (41). These in vivo and in vitro data demonstrated that zoledronic acid is highly potent and has the largest therapeutic ratio of any bisphosphonate tested with respect to the desired inhibition of bone resorption versus
unwanted renal toxicity and inhibition of bone mineralization (38, 41, 42).

A Phase I, multicenter, dose-finding study in patients with hypercalcemia of malignancy demonstrated that zoledronic acid via 30-min i.v. infusion at doses of 0.02 and 0.04 mg/kg (i.e., 1.2 and 2.4 mg, respectively, for a 60-kg individual) was safe and well tolerated, and both doses effectively normalized corrected serum calcium (42). The only adverse events were transient hypophosphatemia and hypocalcemia in a small minority of patients and transient mild fever in 30% of patients. On the basis of this favorable safety profile, subsequent clinical trials have used shorter infusion times.

Zoledronic acid has also been investigated in patients with bone metastases and has been shown to dramatically suppress biochemical markers of bone resorption (43, 44). Several urinary markers of bone resorption, especially NTX (45–48). In cancer patients with lytic bone disease, suppression of NTX correlated with a reduction in fracture risk and a significant reduction in bony disease progression (46). NTX appears to be the most sensitive indicator of bone resorption compared with other urinary bone markers (e.g., hydroxyproline, DPD, and PYD; Ref. 48).

In the present study, zoledronic acid was administered to advanced cancer patients with osteolytic bone metastases. The objectives were to assess the safety and tolerability of increasing doses of zoledronic acid when administered as a 5-min IV infusion monthly for 3 months, to determine the safety and tolerability of extended (>3 months) zoledronic acid therapy, and to determine the effects of zoledronic acid on urinary markers of bone resorption.

PATIENTS AND METHODS

Patients. Cancer patients with evaluable osteolytic metastatic disease were eligible for the study if they were ≥18 years of age, had a life expectancy of ≥6 months, experienced no systemic change of cancer treatment within 8 weeks of study entry, and exhibited ECOG performance status of ≤2. All of the patients provided written informed consent before entry into the study. Patients with evaluable osteolytic bone metastases were excluded for the following reasons: radiation therapy within 3 months of study treatment; scheduled orthopedic surgery or radiation therapy to treat problems related to metastatic bone lesions within 14 days of study treatment; skeletal complications (e.g., pathological fracture, spinal cord compression) within 14 days of study treatment; prior allergic reaction or sensitivity to bisphosphonates; ECOG performance status of 3 or 4; clinically significant ascites, brain metastases, or abnormal electrocardiogram; chronic treatment with corticosteroids; previous therapy with calcitonin and/or mithramycin within 14 days of study treatment; or prior treatment with a bisphosphonate within 90 days or with other investigational drug within 30 days of study treatment.

Study Design and Treatment. This was a multicenter, open-label, dose-ranging, safety trial of short-duration, multiple IV infusions of zoledronic acid in advanced cancer patients with osteolytic bone metastases. Patients were sequentially enrolled into one of eight treatment groups and received a 5-min IV infusion of 0.1, 0.2, 0.4, 0.8, 1.5, 2, 4, or 8 mg zoledronic acid monthly for 3 cycles in the core protocol. Patients were enrolled into the first three treatment groups (0.1, 0.2, or 0.4 mg) without an intervening period of observation. Enrollment into the higher-dose groups (≥0.8 mg) occurred only after at least three patients receiving the current highest dose completed the 1-week follow-up after the third infusion without grade 3 or 4 treatment-related toxicity, as defined by the National Cancer Institute’s Common Toxicity Criteria. If at least two patients exhibited grade 3 or 4 toxicity, then the next lowest-dose level would be considered the maximum tolerated dose. After completion of the 3-month core protocol, patients with radiographic evidence of a complete or partial bone lesion response, or stable disease, and an ECOG performance status of ≤2 were eligible for a humanitarian extension protocol and continued to receive monthly zoledronic acid infusions at the same dose level received during the core protocol. Treatment duration was not specified in the extension trial but continued until the treating physician judged that further therapy was no longer in the patient’s best interest, an adverse event resulted in discontinuation, the patient withdrew consent, or death.

The following concomitant therapies were permitted during the study: standard antineoplastic therapies, including cytotoxic chemotherapeutic agents, hormonal agents, and biological response modifiers; standard radiation therapy to treat extraskel-etal and/or skeletal tumor sites; standard cytokines or colony-stimulating factors; and acute or subacute doses of corticosteroids to treat spinal cord compression, or for treatment for nausea and vomiting. Prohibited medications included those expected to affect osteoclast activity (e.g., other bisphosphonates, calcitonin, mithramycin, gallium nitrate, and so forth). No patients received any prohibited medications during the study.

Assessment of Safety and Efficacy. Safety was evaluated by review of clinical findings, adverse events, vital signs, routine blood chemistries, hematological values, chest radiographs, urinalysis, and electrocardiogram data. Patients who had their zoledronic acid treatments extended beyond 3 months were assessed for safety only. The severity of adverse events was graded according to the National Cancer Institute’s Common Toxicity Criteria. Treatment-emergent adverse events or worsening adverse events (i.e., deterioration of a medical condition present in a less serious form at study entry) were recorded at each subsequent visit.
Efficacy was assessed by weekly measurement of urinary markers of bone resorption. Two-hour fasting urine samples were analyzed for calcium:creatinine ratio, hydroxyproline:creatinine ratio, NTX:creatinine ratio, PYD:creatinine ratio, and DPD:creatinine ratio. Serum osteocalcin, pain score, analgesic score, and ECOG performance status were also evaluated on a weekly basis. Assessment of pain and analgesic use was conducted using previously described methods (49). Pain scores reflect the patient’s perception of pain during the week before each study visit. The severity of pain was rated on a scale of 0 (no pain) to 3 (severe pain). The frequency of pain was rated on a scale of 0 (none) to 3 (constant). Pain score was calculated by multiplying the severity by the frequency. The analgesic score was calculated as the average daily dose of analgesic in morphine-equivalent milligrams. Bone lesion response was visualized by plain radiography at study end and assessed by a central radiologist using International Union Against Cancer (UICC) criteria.

**Statistical Methods.** Descriptive summary statistics were used to evaluate efficacy variables, including bone marker resorption data, pain score, analgesic consumption, and ECOG performance status. All of the patients who received the study drug were included in the efficacy analysis.

**RESULTS**

**Patient Demographics and Baseline Clinical Characteristics.** Fifty-nine patients were enrolled: 6 patients in the 0.4-mg dose group; 7 patients each in the 0.1-, 0.2-, 0.8-, 4-, and 8-mg dose groups; 8 patients in the 2-mg dose group, and 10 patients in the 1.5-mg dose group. Table 1 summarizes patient demographics and baseline clinical characteristics by treatment group. The majority (>95%) of patients were >40 years of age, and the majority of patients had multiple myeloma (61%) or breast cancer (32%). All of the patients had evidence of lytic lesions, although a minority of patients also showed mixed or osteoblastic lesions, with the majority of patients showing 2 lytic lesions. Treatment groups were well balanced for baseline clinical characteristics and laboratory values, including baseline bone markers (Table 2), except that the 0.8-mg dose group exhibited a higher mean serum osteocalcin level (17.2 ng/ml) compared with other groups (range, 4.3–9.2 ng/ml). However, urinary bone markers in the 0.8-mg dose group were comparable with other groups. All of the patients in all of the treatment groups experienced skeletal pain or at least one skeletal complication at or before study entry.

**Safety Profile.** During the 3-month core protocol, at least one adverse event was experienced by 54 (92%) of 59 patients, whether treatment related or not. The most commonly reported adverse events were skeletal pain (20 patients), nausea (14 patients), fatigue (12 patients), upper respiratory tract infection (10 patients), constipation (9 patients), headache (9 patients), diarrhea (8 patients), and fever (7 patients). Adverse events that were considered possibly related to treatment occurred in 24 (41%) of 59 patients. The most common treatment-related adverse events were skeletal pain, nausea, fever, rigores, and stomatitis, and the majority of these were mild to moderate in

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<table>
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<th>Zoledronate, mg</th>
<th>Patients studied</th>
<th>Sex, M/F</th>
<th>Age, yr</th>
<th>Origin</th>
<th>Cancer diagnosis</th>
<th>Number/type lesions</th>
<th>Pain score</th>
<th>ECOG PS</th>
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<td>Blastic</td>
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<td>6</td>
<td>2/4</td>
<td>3–40</td>
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<td>Multiple myeloma</td>
<td>Mixed</td>
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<td>1</td>
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*NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; PS, performance status.
Table 2  Mean baseline bone marker variables by treatment group

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<tr>
<th>Zoledronate, mg</th>
<th>Patients studied</th>
<th>Calcium (mg/mg)</th>
<th>Hydroxyproline (mg/mg)</th>
<th>PYD (pmol/mmol)</th>
<th>DPD (pmol/mmol)</th>
<th>NTX (pmol/mmol)</th>
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<td>(n = 10)</td>
<td>(n = 6)</td>
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<tr>
<td>4</td>
<td>6</td>
<td>8.4</td>
<td>9.2</td>
<td>6.8</td>
<td>17.2</td>
<td>7.3</td>
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Table 3  Most common treatment-related adverse events, number of patients (%)

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<th>Zoledronate, mg</th>
<th>Patients studied</th>
<th>Skeletal pain</th>
<th>Nausea</th>
<th>Fever</th>
<th>Rigors</th>
<th>Stomatitis</th>
<th>Fatigue</th>
<th>Influenza-like symptoms</th>
<th>Moniliasis</th>
<th>Conjunctivitis</th>
<th>Eye complaints</th>
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<tr>
<td>0.2</td>
<td>7</td>
<td>6 (10)</td>
<td>3 (5)</td>
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<tr>
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<tr>
<td>0.8</td>
<td>5</td>
<td>2 (33)</td>
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severity (Table 3). No apparent relationship was observed between the dose of zoledronic acid and either the frequency or the severity of any adverse event. No unexpected adverse events were observed, and there were no grade 3 or 4 abnormalities in hematological values, liver enzymes, or serum creatinine.

Severe (i.e., grade 3) adverse events were experienced by 14 (24%) of 59 patients. In three patients, these adverse events were considered possibly related to treatment, including two patients with increased bone pain (one patient in the 0.1-mg dose group and one patient in the 4-mg dose group), and one patient in the 0.8-mg dose group with severe “flu-like” symptoms. All three of the patients recovered completely. These events are consistent with an acute-phase reaction that is commonly associated with nitrogen-containing bisphosphonates. At any dose level, there was no more than one grade 3/4 treatment-related toxicity; thus, the maximum tolerated dose was not reached in this study.

Four deaths occurred during the study, but none were treatment related. Three patients, one each in the 0.8-mg, 1.5-mg, and 4-mg treatment groups, died from events related to cancer progression, and one patient in the 8-mg treatment group died because of a cerebrovascular accident secondary to hemorrhagic brain metastases.

**Extension Protocol.** After completion of the 3-month core protocol, 30 (51%) of 59 patients with radiographic evidence of a complete or partial bone lesion response or of stable disease had their treatment extended by enrollment in the extension protocol. A minimum of 1 dose was received during the extension protocol; the maximum was 56 doses. All of the patients treated on the extension protocol reported at least one adverse event during both core and extension protocols. These included skeletal pain (21 patients), fatigue (15 patients), upper respiratory tract infection (15 patients), anorexia (13 patients), anemia (13 patients), diarrhea (14 patients), and nausea (14 patients). The most common treatment-related adverse events were skeletal pain (five patients) and fever (two patients). Other adverse events possibly related to the treatment included anorexia, fatigue, hypocalcemia, hypophosphatemia, and rigors; these were reported by 1 patient each. There was no apparent relationship between zoledronic acid dose and either the frequency or the severity of any adverse event during the extension protocol. Sixteen patients experienced cancer progression.

In the course of the extension protocol, 16 grade 3 and 1 grade 4 adverse events were experienced by 10 (33%) of 30 patients. One event was possibly related to treatment. One patient treated with 4 mg of zoledronic acid experienced grade 3 hypophosphatemia but recovered within 8 days. All of the other serious adverse events were considered not related to the study drug by the investigators.

Seven patient deaths occurred during the extension protocol; none of the deaths was treatment related. Four patients, each in the 0.1-, 0.8-, 2-, and 8-mg treatment groups, died from disease progression. One patient in the 1.5-mg group died of gastrointestinal bleeding, and one patient in the 8-mg group died of respiratory failure secondary to disease progression. One patient died as a result of suicide. This patient had moved out of the area with rapidly progressive disease that was unresponsive to all of the therapeutic maneuvers and had been off this study for 6 months at the time of his suicide.

**Effect of Zoledronic Acid on Urinary Bone Markers.** A dose-dependent decrease in all of the urinary markers of bone resorption was observed (Figs. 2 and 3). Doses of zoledronic acid ≥0.2 mg substantially suppressed urinary markers of bone resorption, including PYD, DPD, calcium, and hydroxyproline.
creatinine ratios, whereas 0.1 mg zoledronic acid had little or no effect on these markers (Fig. 2). Urinary levels of NTX were substantially suppressed even at the lowest dose; however, doses ≥0.8-mg had a greater effect compared with lower doses (Fig. 3). In the 0.1- to 0.4-mg dose groups, mean maximum NTX levels were decreased 40–60% compared with 70–80% below baseline in the 0.8- to 4.0-mg dose groups. In the 8-mg dose group, the mean maximum decrease in NTX excretion was >80% below baseline. As shown in Fig. 4, PYD and DPD levels decreased rapidly in the higher-dose groups (≥1.5 mg) and continued to decrease in most dosage groups, reaching a maximum level of suppression only after approximately 5 weeks. Suppression of PYD and DPD was most rapid in the 8-mg dose group (Fig. 2), and this dose produced the greatest sustained decrease at study end (40 and 55% below baseline for PYD and DPD, respectively). The data for the 0.2-, 0.8-, and 4-mg dose groups exhibited substantial scatter over the duration of the study and are not represented in Fig. 4. In general, urinary markers of bone resorption were increasingly suppressed as both the time and the dose increased.

**Secondary Efficacy End Points.** Analysis of pain score, analgesic use, ECOG performance status, response of lytic lesions, and serum osteocalcin levels did not demonstrate any consistent trend or dose-response relationship. There was no detectable trend for improvement or worsening of pain score in any dose group or between dose groups. This is attributable in part to the varying amounts of analgesic medication used during the trial. The 0.8-mg dose group exhibited a consistent decrease in analgesic use and a stable or slight decrease in median pain score at 28, 56, and 84 days from initial treatment. Patients in the 8-mg-dose group also reported decreases in pain but also noted increased analgesic use. The 8-mg group had the highest mean baseline pain score. At study end, ECOG performance status remained unchanged or worsened in all of the treatment groups except the 0.1-mg group.

Lytic bone lesion response was assessed in 48 of 59 patients in the core protocol, and 29 (60%) of 48 patients showed no change in lytic lesions during the study. Eight (17%) patients exhibited a partial response (two patients in the 0.1-mg dose group, three patients in the 0.8-mg dose group, and one patient each in the 1.5-, 2-, and 4-mg dose groups). Eight (17%) patients experienced mixed progression (i.e., one or more osteolytic lesions showed signs of recalcification, whereas new lesions appeared and/or one or more lesions progressed). Three (6%) patients were considered failures in terms of lesion response.

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*Fig. 2* Suppression of urinary markers of bone resorption by increasing doses of zoledronic acid. Levels of suppression are expressed as the mean maximum percentage decrease from baseline. ▲, PYD; ●, DPD; ■, Ca; ○, HO-Pro (hydroxyproline).

*Fig. 3* Urinary PYD:creatinine and DPD:creatinine ratios at the indicated times after zoledronic acid treatment. Levels of suppression are expressed as the median percentage difference from baseline.

*Fig. 4* Mean maximum decrease from baseline in NTX:creatinine ratio by dose of zoledronic acid. ●, 0.1 mg; ■, 0.4 mg; ▲, 1.5 mg; ●, 2 mg; ○, 8 mg.
DISCUSSION

Bisphosphonates are potent inhibitors of normal and pathological bone resorption and have been shown to significantly reduce skeletal morbidity in patients with osteolytic bone disease. In the present Phase I trial, the safety and efficacy of zoledronic acid, a new-generation heterocyclic nitrogen-containing bisphosphonate, was assessed in advanced cancer patients with bone metastases. Zoledronic acid was safe and well tolerated at all of the dose levels tested, and the maximum tolerated dose was not reached. The nature, frequency, and severity of commonly reported adverse events were similar in all of the treatment groups and were consistent with an acute-phase response. Laboratory assessments indicated that multiple doses of zoledronic acid up to 8 mg, via 5-min infusion, were not associated with hematological, hepatic, or renal toxicity. There was a tendency, however, for patients receiving doses of zoledronic acid up to 8 mg, via 5-min infusion, to develop mild, reversible, asymptomatic hypercalcemia or hypophosphatemia. Grade 3 or 4 treatment-related toxicity occurred in 1 patient in any dose group. There were no unexpected adverse events, and no apparent relationship was observed between dose level and the frequency or severity of any adverse event. Furthermore, all of the adverse events were comparable with those typically associated with other bisphosphonates (1, 9, 50, 51).

The finding that infusion of up to 8 mg zoledronic acid via 5-min IV infusion was not associated with any measurable renal toxicity is consistent with preclinical studies indicating that zoledronic acid has a low nephrotoxic potential compared with other bisphosphonates (41). In contrast, 90 mg of pamidronate requires a more prolonged infusion time (2–4 h), in part, to minimize the potential nephrotoxicity that was observed in animal studies, including focal proximal tubular necrosis, decreased creatinine clearance, and increased enzynuria (52, 53). This is consistent with the observation that the nephrotoxicity associated with bisphosphonates is related to the rate of infusion, not the antiresorptive potency of the drug. Bisphosphonates are pharmacologically distinct with respect to their ability to inhibit bone resorption but have similar pharmacokinetic properties, including comparable absorption, distribution, and elimination characteristics (54). In general, infusion of bisphosphonates at a rate greater than ~1 mg/min is associated with an increased risk of nephrotoxicity. The 5-min infusion time of zoledronic acid is more convenient than the 2-h minimum required for pamidronate and is more suited to outpatient therapy.

Because osteolytic lesions are associated with increased bone resorption, patients often have elevated levels of calcium and other elements of the bone matrix in the serum and urine. Newer markers include several breakdown products of type I collagen, including NTX, PYD, and DPD (55–58). These by-products of bone resorption provide useful surrogate markers to monitor bone metabolism, treatment response, and disease progression (58–60). Recent studies suggest that these bone markers may predict the rate of bone loss and the potential for fracture in patients with lytic bone disease (46, 58, 61, 62). In particular, reductions in urinary NTX excretion were highly correlated with reduced risk of fractures and bony disease progression (46). A >50% increase in NTX excretion predicted disease progression in 78% of cases (47). These studies suggest that NTX is a sensitive indicator of bone resorption that can predict clinical outcome.

In the present study, several sensitive markers of bone resorption were used to monitor the effects of zoledronic acid on bone metabolism. In general, multiple monthly doses of zoledronic acid resulted in sustained, dose-dependent decreases in urinary NTX, PYD, DPD, hydroxyproline, and calcium:creatinine ratios. Although there was no clear treatment-related improvement in clinical outcome in this Phase I trial, the observed decreases in bone resorption markers would be expected to result in clinically significant decreases in skeletal morbidity with longer duration of treatment and follow-up.

In breast cancer patients with bone metastases and advanced multiple myeloma patients treated with 90 mg of pamidronate, urinary calcium:creatinine and hydroxyproline:creatinine ratios were reduced from baseline by ~27–32% and 20–33%, respectively (1, 9, 50, 51). In the present study, zoledronic acid at doses ranging from 0.2 to 8 mg induced 76–92% mean maximum decreases in calcium excretion and 29–50% decreases in hydroxyproline excretion. This suggests that zoledronic acid is 10- to 100-fold more potent than pamidronate with respect to the inhibition of bone resorption in patients with bone metastases. Other Phase I and II studies have also demonstrated that zoledronic acid dramatically reduced bone resorption markers in patients with hypercalcemia of malignancy and bone metastases (42, 43).

In conclusion, zoledronic acid was safe and well tolerated and demonstrated potent inhibition of bone resorption. The substantial suppression of bone resorption markers, particularly NTX excretion observed in this study, is expected to translate into reductions in the incidence of skeletal complications in patients with bone metastases. Furthermore, preclinical studies suggest that zoledronic acid may produce additional therapeutic benefits by inducing apoptosis of tumor cells (31, 32, 34, 63, 64). Currently, Phase III randomized trials are under way to compare the efficacy of zoledronic acid with pamidronate in patients with bone metastases.

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REFERENCES

Zoledronic Acid for Osteolytic Bone Metastases


A Phase I Dose-ranging Trial of Monthly Infusions of Zoledronic Acid for the Treatment of Osteolytic Bone Metastases
