Safety and Efficacy of Zoledronic Acid Rapid Infusion in Lung Cancer Patients with Bone Metastases: A Single Institution Experience

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Abstract. *Zoledronic acid (Zometa™, Novartis, Basel, Switzerland) is a new generation of bisphosphonates (BPs) with demonstrated clinical benefit in breast and prostate cancer patients with bone metastases. The safety and efficacy of intravenous zoledronic acid in lung cancer patients was assessed. In 86 patients with newly diagnosed non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC) and bone metastases, 4 mg of zoledronic acid was administered with rapid 15-minute intravenous infusion every 3-4 weeks. A total of 414 infusions were administered over a 24-month period during which a statistically significant decrease in serum calcium levels (p=0.03) was observed. Serum alkaline phosphatase (ALP) also decreased but not significantly. With regard to clinical efficacy, 55 of our patients stabilized or reduced their need for analgesic treatment. No significant side-effects, including fever, hemodynamic instability and renal dysfunction, were seen. We conclude that the rapid infusion of zoledronic acid is safe and convenient for lung cancer patients even after the 3rd and 6th months follow-up.*

Bones represent a preferred metastatic site for many solid tumors, including non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Worldwide, it is estimated that the 5-year prevalence of bony metastatic disease, as a complication of lung cancer, is in the order of 1,394,000 cases, with an estimated incidence of 30-65% (1). Bone metastases often result in significant skeletal morbidity, such as severe bone pain, pathological fractures, spinal cord compression and hypercalcemia. The high prevalence of bone metastases in SCLC and in stage IV disease of NSCLC patients contributes substantially to the burden of the disease, while treatment innovations have provided little hope for improvement in overall survival.

Bisphosphonates (BPs) are the current standard of care for preventing skeletal complications associated with bone metastases (2, 3). BPs, have been shown to significantly reduce the incidence of any skeletal-related or bone events in patients with bone metastases. Hence, the role of BP therapy in oncology is expanding to fill the emerging need for maintaining bone health throughout the continuum of cancer patient care (4). Zoledronic acid, one of the newer BPs, is an osteoclast inhibitor that prevents bone resorption. It binds to those bones that have a high rate of bone turnover and, if not removed from circulation through bone absorption, is excreted unchanged by the kidneys. The most serious toxicity observed from its application is nephrotoxicity (5).

Several trials have addressed the issues of optimal dosing and administration scheduling, as well as the efficacy of zoledronic acid use in solid malignancies. In a randomized double-blind trial including patients with skeletal metastases from lung cancer and other solid neoplasms, two different doses of 4 and 8 mg (later reduced to 4 mg) of zoledronic acid were given as a single 15-min intravenous infusion. The observed skeletal-related events (SREs), including hypercalcemia, were lower for the two treatment groups, 97/257 (38%) and 93/260 (35%), respectively, as compared with the placebo group 117/250 (47%). Moreover, the dose of 4 mg was safer for patients, with fewer side-effects than that of 8 mg (6). Based on this trial, the 4 mg zoledronic acid dose was chosen for our study.

In contrast to other BPs, such as pamidronic acid which is administered over a two-hour infusion session in an outpatient setting, zoledronic acid provides a more rapid solution with similar or better effects. This also provides a lesser burden on outpatient clinics in addition to more

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convenience to patients. We evaluate the safety and efficacy of this rapid infusion of zoledronic acid in the setting of patients with non-small and small cell lung cancer with bone metastases.

Patients and Methods

Patient eligibility criteria. Patients aged ≤75 years, with histologically or cytologically confirmed NSCLC or SCLC were included in this study. Other eligibility criteria included age >18 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2, life expectancy ≥12 weeks, at least one bone metastasis documented by bone scan and plain radiography (situated outside previously irradiated locations), normal renal (serum creatinine ≤1.4 x upper limit) and hepatic (bilirubin ≤1.5 x upper normal limit, serum glutamate oxaloacetate transaminase (SGOT), and serum glutamate pyruvate transaminase (SGPT) ≤2.5 x upper normal limit) functions.

Patients were excluded if they had a history of cardiac disease (uncontrolled hypertension, unstable angina, congestive heart failure, second- or third-degree heart block, myocardial infarction within the previous year and cardiac ventricular arrhythmias requiring medication), renal or hepatic dysfunction, or an active infection of the urinary tract. Females of childbearing potential had to have a negative serum or urine pregnancy test within 48 hours of enrollment and had to take adequate contraceptive measures during the study. Pregnant or lactating women were excluded. The study was approved by the local hospital review board and ethics committee and conducted in accordance to the Helsinki Declaration. All patients gave their written, informed consent to participate in the study.

Treatment plan. Pre-treatment evaluation included a complete medical history and physical examination, laboratory tests (hematology and standard biochemistry), chest radiographs, electrocardiogram (ECG) and an isotopic whole-body bone scan. Bone lesion sites were assessed by physical evaluation and plain radiography of the area. During treatment, a physical examination, an ECG, a blood-cell count with differential, platelet count and standard biochemical assessment (including serum creatinine, urea (BUN), sodium, potassium, calcium, transaminases, total bilirubin, total proteins, albumin and lactate dehydrogenase) preceded each cycle. Furthermore, the patients' temperatures, pulse rates and arterial blood pressures were monitored at the beginning and end of infusion, as well as 2 hours following completion. The two-hour mark was chosen on the basis that a rapid biphasic elimination of the drug from the systemic system occurs at 1.87 hours (ZOMETA package insert. Zoledronic acid prescribing information. East Hanover, NJ Novartis Pharmaceutical Corporation, 2003).

Patient treatment. Zoledronic acid 4 mg was administered diluted in 100 ml normal saline 0.9% and administered on an outpatient basis in a rapid, 15-min intravenous infusion every 3 or 4 weeks depending on and coinciding with the patients' chemotherapy sessions. In 21-day and 28-day cycles, zoledronic acid was administered every 3 and 4 weeks, respectively. Treatment was discontinued in the presence of deterioration of patient performance status and unacceptable toxicity, *i.e.* creatinine levels above the upper normal limit or reduction of serum creatinine clearance >25%.

Follow-up and evaluation. Serum creatinine clearance and bone scans were performed every six months. The patients' analgesic treatment was recorded during each visit and any changes were evaluated according to the WHO three-step analgesic ladder (7). The safety of zoledronic acid use was assessed by physical examination, full blood count and a complete biochemical profile prior to each infusion as well as by monitoring patients' vital signs before, immediately after and 2 hours following administration completion. Efficacy was ascertained by measuring calcium and alkaline phosphatase (ALP) serum levels on the first, third and sixth infusion. Bone lesions were evaluated in size, intensity and number, with bone scans every 6 months, while the clinical benefit was assessed during each visit by recording any changes in analgesic treatment.

Statistical analysis. The statistical evaluation of the reported parameters was conducted through the use of the Wilcoxon test for pair differences: $p<0.05$ (SPSS statistical program v. 8.0, Win 2000, Win XP v.8, Athens, Greece).

Results

Between January 2004 and December 2005, from a total of 124 patients who were diagnosed with NSCLC or SCLC with bone metastases and undergoing treatment in the Oncology Unit, Third Department of Medicine at Sotiria General Hospital, Athens, Greece, 86 patients were enrolled in the study. All 86 patients (72 men, 14 women) had available parameter values for baseline, 1st and 3rd cycles, and 52 of them (48 men, 4 women) had available parameter values for baseline, 1st, 3rd and 6th cycles. The group of 86 patients had a median age of 63.6 years (range 35-75 years) and the group of 52 patients had a median age of 64 years (range 35-75 years). With regard to the performance status of the 86 patients: 56, 27 and 3 patients had a PS of 0 (56/86, 65.1%), 1 (27/86, 31.4%) and 2 (3/86, 3.4%), respectively. From the group of 52 patients, the PS was the following: 34, 16 and 2 patients had a PS of 0 (34/52, 65.4%), 1 (16/52, 30.8%) and 2 (2/52, 3.8%), respectively. Three patients had hypercalcemia, while the remaining were normocalcemic. All patients were evaluated for toxicity and efficacy. A total of 414 infusions were administered to 86 patients with a median of 5 infusions per patient (range 3-18) and a mean follow-up period of 18 months (range 4-18 months). The patients' characteristics are shown in Table I.

Toxicity. The administration of the rapid, 15-min infusion of zoledronic acid was well tolerated by all patients. The infusion time did not correlate with any changes in vital signs or renal dysfunction. Serum urea (BUN) or creatinine levels did not increase significantly and no changes were detected in patient temperatures or blood pressures.

Efficacy. After the first administration of zoledronic acid, serum calcium levels notably decreased from a mean value of 9.472 mg/dl to 9.127 mg/dl, a difference of statistical

Table I. *Patient characteristics.*

	No. of patients (total number=86)
Gender	
Male	72
Female	14
Histopathological type	
Non-small cell lung cancer	74
Small cell lung cancer	12
Performance status (ECOG)	
0	63
1	20
2	3

Table II. *Mean value of the main parameters studied (n=86 patients).*

	Before 1st BP administration	After 3 cycles of BP administration
SC (mean, mg/dl)	0.936	0.886
BUN (mean, mg/dl	39.720	40.070
ALT (mean, U/L)	26.730	41.870
ALP (mean, U/L)	127.650	113.510
Ca^{2+} (mean, mg/dl)	9.472	9.107

SC: serum creatinine, BUN: blood urea nitrogen, ALT(SGPT): alanine aminotransferase; ALP: alkaline phosphatase, Ca^{2+}: serum calcium.

Table III. *Mean value of the main parameters studied (n=52 patients).*

	Before 1st BP administration	After 3 cycles of BP administration	After 6 cycles of BP administration
SC (mean, mg/dl)	0.960	0.937	0.929
BUN (mean, mg/dl	40.270	37.269	41.654
ALT (mean, U/L)	27.920	29.173	28.712
ALP (mean, U/L)	114.710	89.038	86.308
Ca^{2+} (mean, mg/dl)	9.387	9.110	9.081

SC: serum creatinine, BUN: blood urea nitrogen, ALT(SGPT): alanine aminotransferase, ALP: alkaline phosphatase, Ca^{2+}: serum calcium.

significance ($p=0.01$). Even after 6 months, these levels remained significantly lower. The mean values of the main parameters studied, including at 1 and 6 months following zoledronic acid infusion, are provided in Tables II and III. The observed reductions in serum ALP levels were not statistically significant. Five of the patients included in the study needed bone radiation (one before zoledronic acid administration and four after, due to pain). The remainder of the 81 patients developed neither any skeletal-related nor any direct bone event, such as pathological fractures, spinal cord compression, bone radiation, or surgery and malignancy-related hypercalcemia. Regarding the analgesic effect as it pertains to analgesic treatment of the two cohorts of 86 and 52 patients on zoledronic acid, 7 (7/86, 8.1%) and 3 (3/52, 5.8%) patients reduced their need, 50 (50/86, 57%) and 31 (31/52, 59.6%) patients did not necessitate any adjustments throughout the study and 30 (30/86, 34.8%) and 18 (18/52, 34.6%) patients required increased doses for skeletal bone pain, respectively (Figures 1 and 2). Concerning the number of bone lesions evaluated through consecutive bone scans, 36 patients (36/86, 42%) maintained the same number of bone lesions, while 6 patients (6/86, 7%) presented significant improvements. Forty-three patients (43/86, 43%) demonstrated bone disease progression with an increase in the number of lesions, as detected by bone scans. However, only 30 of these patients (30/43) required an increase in their analgesic medication.

Discussion

Initial administration of first generation BP's (up to 4 hours) was based on reports of renal failure that resulted from therapy and was attributed to the precipitation of insoluble calcium BP complexes in the renal tubule. Since the described renal dysfunction resulted from the shared BP backbone, it was expected that third generation, more potent BPs, such zoledronic acid could be administered more rapidly, at therapeutic doses, without significant nephrotoxic risks. Nevertheless, due to the frequent, repeated scheduling of BP administration, a 2-hour infusion may cause significant discomfort to patients and considerably overload outpatient clinics. Hence, the safety and effectiveness of a more rapid administration was investigated.

We were able to demonstrate that the 15-min infusion of zoledronic acid was safe and effective, since none of our patients' vital signs or renal functions deviated from the normal levels throughout the trial. Our observation is in accordance with those of similar studies that applied third generation BPs such as risedronate and clondronate. It appears that these newer BPs are more potent osteoclastic inhibitors than their older counterparts, *e.g.* aledronate and pamidronate and, as a result, can be administered more rapidly at therapeutic doses without significant nephrotoxic risk (8). Our observation concurs with a more convenient ibandronate administration on an outpatient basis, rendering the entire procedure more patient-friendly without compromising safety, while also alleviating the resource burden on oncology units (9).

In our study, zoledronic acid rapidly relieved moderate to severe metastatic bone pain, improving the patient's quality of life and functioning. It also provided an effective, long-term relief from metastatic bone pain, since in most of the patients

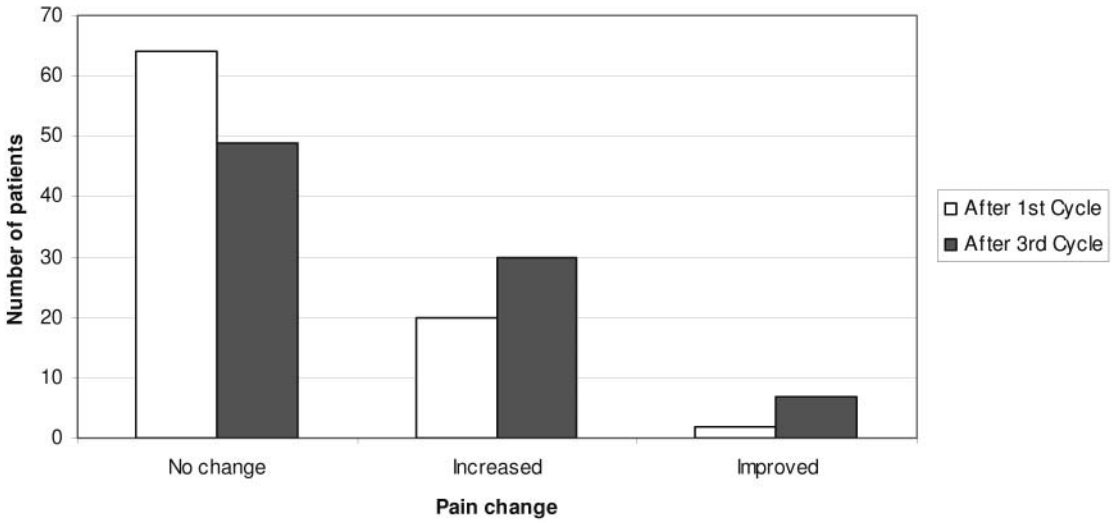

Figure 1. *Pain changes over three treatment cycles (n=86 patients).*

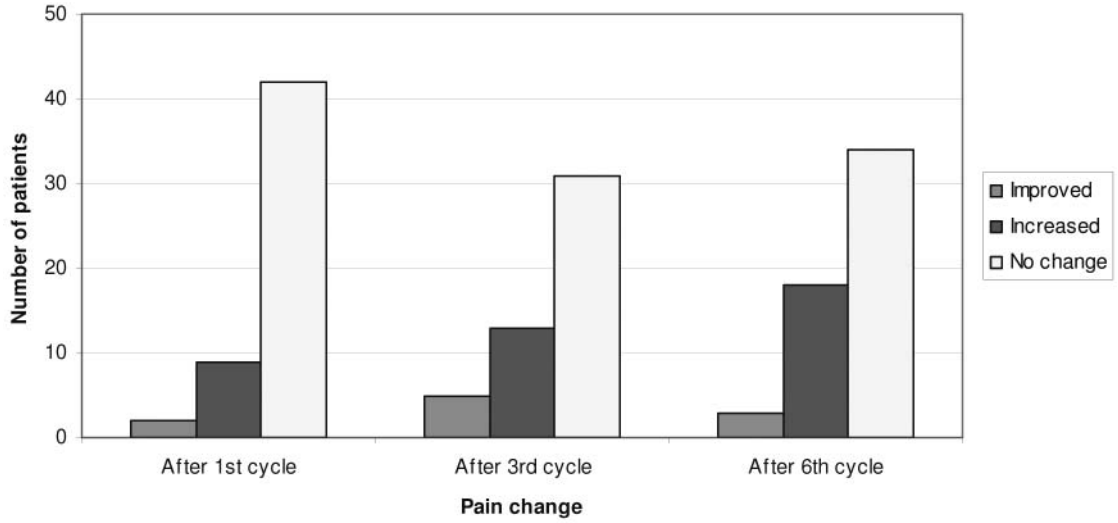

Figure 2. *Pain changes over six treatment cycles (n=52 patients).*

studied, the effect was permanent and no analgesic treatment increase or modification was needed, despite bone disease progression. This clinical benefit may reduce the burden of metastatic bone disease on healthcare resources by limiting the need for analgesics and bone radiotherapy. Our data are in accordance with previous observations demonstrating that zoledronic acid decreased resorption markers in a dose-dependent fashion and effectively increased bone density in postmenopausal osteoporotic women (5, 8). Finally, these results conform to similar studies utilizing other BPs, such as pamidronate, that demonstrated clinical benefits in cancer patients with osteolytic lesions (5, 8).

Several recent studies have established that various bisphosphonates induce *in vitro* and *in vivo* osteoclast apoptosis, while others raised the intriguing possibility that they may also be capable of interfering with the growth and survival of metastatic cancer cells in the bone (10-12). It is possible that the new generation bisphosphonates like zoledronic acid also possess antineoplastic properties. Preclinical and preliminary clinical results suggest that BPs may provide additional benefits beyond their current applications. As a result, clinical trials are currently investigating the efficacy of BPs in the adjuvant setting to prevent the development of

bone metastases in patients with solid malignancies, or to avert cancer treatment-induced bone loss. The results of these trials will certainly broaden the potential clinical applications of BPs in oncology.

In conclusion, the investigated 15-min intravenous administration of zoledronic acid provides an important, safe and effective alternative to existing bisphosphonate options for metastatic bone disease management in NSCLC and SCLC patients. The recommended administration schedule could improve patient acceptability by simplifying the management and reducing the need for safety monitoring and treatment of adverse effects. Furthermore, its established clinical benefits may decrease the metastatic bone disease burden on healthcare systems and oncology units. Finally, the suggested administration mode could be used in the future design of large, randomized trials to evaluate the clinical benefits and probable antineoplastic properties of ibandronate in NSCLC and SCLC patients with bone metastases.

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