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Rarpid Infusion of Ibandronate in Lung Cancer Patients with Bone Metastases

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Abstract. *Background: The high prevalence of bone metastases in stage IV non-small cell lung cancer (NSCLC) patients contributes substantially to the burden of the disease by resulting in significant skeletal morbidity. Ibandronate is a new generation of bisphosphonates (BPs) with demonstrated clinical benefit in breast and prostate cancer patients with bone metastases. Patients and Methods: In 32 patients with newly diagnosed non-small cell lung cancer and bone metastases, 4 mg of ibandronate were administered, as a rapid 20-minute intravenous infusion every 3-4 weeks. Results: A total of 189 infusions were administered over a 24-month period during which a statistically significant decrease in calcium serum levels (p=0.03) was observed. The serum levels of alkaline phosphatase (ALP) were also decreased but not significantly. With regard to clinical efficacy, 24 of our patients stabilized or reduced their need for analgesic treatment. The reduced time of infusion (20 min vs. 2 h) did not correlate with any side-effects, including vital sign deterioration and renal dysfunction. Conclusion: The rapid infusion of ibandronate in lung cancer patients with bone metastases is a safe and convenient procedure that may be administered in a day clinic setting.*

Bisphosphonates (BPs) are potent osteoclast-mediated osteolysis inhibitors that constitute an established treatment for bone metabolism disorders, such as Paget's disease and osteoporosis. When used in the setting of malignant bone disease, it has been demonstrated that BPs, administered in a more intense dosing, delay and prevent skeletal complications, while also treating malignant hypercalcemia. The intravenous administration of BP has been the standard of care in patients with bone lesions from multiple myeloma or secondary, solid malignancy bone metastases, such as those found in breast and prostate cancers. With regard to safety, intravenous administration is generally well-tolerated in long-term use, while the development of more potent, second- and third-generation BPs has greatly improved the convenience (due to the shorter infusion time) and clinical activity of these agents (1, 2).

Ibandronate is a third generation, highly potent nitrogen-containing BP that affects bone mineralization by slowing the formation of hydroxyapatite. It is also a very potent osteoclast inhibitor that seems to prevent bone resorption and hypercalcemia. While the exact action mechanism is not fully understood, BPs may alter proton pump function or impair the release of acid hydrolases (3). When compared with the use of other BPs in pre-clinical studies, ibandronate appears more potent than alendronate and pamidronate (4). Clinical trials with breast cancer patients demonstrated that ibandronate is effective in reducing bone resorption in normocalcemic and hypercalcemic patients, though the effectiveness appears to be dose-dependent (4-7).

With regard to administration, most investigators suggest the 2-h infusion. However, although this approach has proven safe, it causes considerable discomfort to patients and further burdens oncology units and day clinics. This study was conducted in order to evaluate the safety and efficacy of the 20-minute intravenous administration of ibandronate in non-small cell lung cancer (NSCLC) patients with bone metastases.

Patients and Methods

Eligibility criteria. Patients aged ≤75 years, with histologically or cytologically confirmed NSCLC were included in this study. Other

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Key Words: Analgesic therapy, bisphosphonates, hypercalcaemia, lung cancer.

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 ≤1.0 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 h of enrolment 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.

Patients treatment. Ibandronate 4 mg was administered diluted in 250ml normal saline 0.9% and administered on an out-patient basis in a rapid, 20-min intravenous infusion every 3 or 4 weeks depending on and coinciding with the patients' chemotherapy sessions. In 28-day and 21-day cycles, ibandronate was administered every 4 and 3 weeks, respectively. Treatment was continued in the absence of disease progression in the bones, 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. The safety of ibandronate use was assessed by physical examination, full blood count and complete biochemical profiling prior to each infusion as well as by monitoring patients' vital signs before, after and 2 h following administration completion. Efficacy was ascertained by measuring calcium and alkaline phosphatase (ALP) serum levels on the first, second and sixth infusion. Bone lesions were evaluated with bone scans every 6 months while the clinical benefit was assessed during each visit by recording any changes in analgesic treatment.

Table I. *Patient characteristics (total number n=32).*

	No of patients
Gender	
Male	27
Female	5
Histopathological type	
Adenocarcinoma	14
Squamous cell carcinoma	14
Large cell carcinoma	4
Performance Status (ECOG)	
0	6
1	21
2	5

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).

Results

Between June 2000 and July 2001, a total of 32 patients (27 men and 5 women), diagnosed with NSCLC with bone metastases and undergoing treatment in the Oncology Unit, Third Department of Medicine at Sotiria General Hospital, Athens, Greece, were enrolled in the study. The patients had a median age of 66 years (range 47-75 years). With regard to performance status, 6 patients had a PS of 0 (6/32, 19%), 21 patients had a PS of 1 (21/32, 66%) and 5 patients had a PS of 2 (5/31, 15%). Seven patients (7/32, 22%) had hypercalcemia, while the remaining 25 (25/32, 78%) were normocalcemic. All patients were evaluated for toxicity and efficacy. A total of 512 infusions were administered to 32 patients with a median of 16 infusions per patient (range 5-29) and a mean follow-up period of 14 months (range 4-24 months). The patients' characteristics are shown in Table I.

Toxicity. As a rapid, 20-min infusion, the administration of ibandronate was well tolerated by all patients. The reduced 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 ibandronate, serum calcium levels were notably decreased from a mean value of 11.01 mg/dl to 9.017 mg/dl, a deference of statistical significance ($p=0.03$). Even after 6 months, these levels remained significantly reduced. The mean, main parameter values that we evaluated before as well as 1 and 6 months following ibandronate infusion are provided in Table II. The

Table II. *Mean values of the main parameters studied.*

	BEFORE 1st BP administration	BEFORE 2nd BP administration	AFTER 6 cycles of BP administration
S.Creatinine (mean, mg/dl)	0.793 (SD: 0.220)	0.775 (SD:0.206) $p=0.755$	0.736 (SD:0.203) $p=0.328$
BUN (mean, mg/dl)	39.28 (SD:16.73)	34.28 (SD:13.69) $p=0.218$	38.60 (SD:15.47) $p=0.879$
ALT (mean, U/L)	37.83 (SD:24.15)	32.41 (SD:16.70) $p=0.325$	31.84 (SD:21.90) $p=0.345$
ALP (mean, U/L)	300.3 (SD:200.4)	296.5 (SD:202.8) $p=0.943$	259.9 (SD:254.3) $p=0.521$
Ca^{2+} (mean, mg/dl)	11.01 (SD:0.67)	9.017 (SD:0.64) $p=0.03$	8.972 (SD:0.782) $p=0.04$

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

observed reductions in serum ALP levels were not statistically significant. None of the patients included in the study developed any skeletal-related or 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, 5 patients (5/32, 16%) reduced their need, 19 patients (19/32, 59%) did not necessitate any adjustments throughout the study and only 8 patients (8/32, 25%) required increased doses for skeletal bone pains while in treatment with ibandronate. Concerning the number of the bone lesions as evaluated through consecutive bone scans, 16 patients (16/32, 50%) maintained the same number of bone lesions, while 2 patients (2/32, 6%) presented significant improvements. Fourteen patients (14/32, 43%) demonstrated bone disease progression with an increase in the number of lesions, as detected by bone scans. However, only 8 of these patients (8/14) required an increase in their analgesic medication.

Discussion

Bones represent a preferred metastatic site for many solid tumors, including NSCLC. The complications associated with 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 stage IV NSCLC patients contributes substantially to the burden of the disease, while treatment innovations have provided hope for improvement in their overall survival. BPs are the current standard of care for preventing skeletal complications associated with bone metastases (8). 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 (9).

Ibandronate, 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 turn-over and, if not removed from circulation through bone absorption, is excreted unchanged by the kidneys. The most serious toxicity observed from its application, nephrotoxicity, is clearly dose-dependent and associated with the intravenous infusion rate (10).

Several trials have addressed the issues of optimal dosing and administration scheduling as well as the efficacy of ibandronate use in solid malignancies, mainly those associated with breast and prostate cancers. In a randomized double blind trial, patients were given three different doses (2, 4 and 6 mg) of ibandronate as a single 2-h intravenous infusion. The observed calcium levels were normalized in 50%, 76% and 77% of the patients that were given 2 mg, 4 mg and 6 mg, respectively (6). Based on this trial, the 4 mg ibandronate dose was chosen for our study.

Initial administration of early BP's (more than 4 hours) was based on the 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 results from the shared BP backbone, it was expected that third generation, more potent BPs, such ibandronate could be administered more rapidly (more than 2 h), at therapeutic doses, without significant nephrotoxicity risk. Nevertheless, due to the frequent, repeated scheduling of BP administration, a 2-h infusion may cause significant discomfort to patients and considerably overload day clinics. Hence, the safety of a more rapid administration was investigated. We were able to demonstrate that a 20-min infusion of ibandronate was safe, since none of our patients' vital signs or renal functions deviated from normal levels throughout the trial. Our observation is in accordance to those of similar studies that applied third generation BPs, like zolendronic acid, risedronate and clondronate. It seems that as these newer BPs are more potent osteoclast inhibitors

than older agents, *i.e.* aledronate and pamidronate and, as a result, can be administered more rapidly at therapeutic doses, without significant nephrotoxicity risk (11). 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.

In our study, ibandronate 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 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 health care resources by limiting the need for analgesics and bone radiotherapy. Our data are in accordance with previous observations demonstrating that ibandronate decreased resorption markers in a dose-dependent fashion and effectively increased bone density in postmenopausal osteoporotic women (10, 11). Finally, these results conform to similar studies utilizing other BPs, such as pamidronate and zolendronic acid, that demonstrated clinical benefits in cancer patients with osteolytic lesions (10, 11).

Several resent studies 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 (12-14). It is possible that the new generation bisphosphonates like ibandronate also possess antineoplastic properties. Pre-clinical 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 20-min instead of the 2-h intravenous administration of ibandronate provides an important, safe and effective alternative to existing bisphosphonate options for metastatic bone disease management in NSCLC patients. The recommended administration schedule could improve patient acceptability by simplifying the management and reducing the need for safety monitoring and adverse effect treatment. Furthermore, its established clinical benefits may decrease the metastatic bone disease burden on health care 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 patients with bone metastases.

References

1 Lipton A: Toward new horizons: the future of bisphosphonate therapy. The Oncologist *9*: 38-47, 2004.

2 Coleman RE: Bisphosphonates: clinical experience. The Oncologist *9*: 14-27, 2004.

3 Sahni M, Guenther HL, Fleisch H, Collin P and Martin TJ: Bisphosphonates act on rat bone resorption through the mediation of osteoblasts. J Clin Invest *91*: 2004-2011, 1993.

4 Ralston SH, Thiebaud D, Herrmann Z, Steinhauer EU, Thürlimann E, Walls J *et al*: Dose- response study of ibandronate in the treatment of cancer associated hypercalcaemia. Br J Cancer *75*: 295-300, 1997.

5 Burckhardt P: Ibandronate in oncology. Cancer *80*: 1696-1698, 1997.

6 Pechestorfer M, Herrmann Z, Body JJ, Manegold C, Degardin M, Clemens MR *et al*: Randomized phase II trial comparing different doses of bisphosphonate ibandronate in the treatment of hypercalcaemia of malignancy. J Clin Oncol *14*: 268-276, 1996.

7 Syrigos KN, Michalaki V, Mitromaras A, Pliarchopoulou F, Katirtzoglou N, Antonaki E *et al*: Safety and efficacy of the new bisphosphonate ibandronate in the management of bone metastasis following rapid infusion. In Vivo *16*: 361-364, 2002.

8 Heidenreich A and Ohlmann CH: Ibandronate: its pharmacology and clinical efficacy in the management of tumor-induced hypercalcemia and metastatic bone disease. Expert Rev Anticancer Ther *4*: 991-1005, 2004.

9 Pecherstorfer M: Efficacy and safety of ibandronate in the treatment of neoplastic bone disease. Expert Opin Pharmacother *5*: 2341-2350, 2004.

10 Berenson JR: Recommendations for zoledronic acid treatment of patients with bone metastases (review). Oncologist *10(1)*: 52-62, 2005.

11 Cameron D: Patient management issues in metastatic bone disease. Semin Oncol *31*: 79-82, 2004.

12 Aparicio A, Gardner A, Tu Y, Savage A, Berenson J and Lichtenstein A: *In vitro* cytoreductive effects on multiple myeloma cells induced by bisphosphonates. Leukemia *12*: 220-229, 1998.

13 Lee MV, Fong MV, Singer FR and Guenette RS: Bisphosphonates treatment inhibits the growth of prostate cancer cells. Cancer Res *61*: 2602-2608, 2001.

14 Diel IJ, Solomayer EF, Costa SD, Gollan C, Goerner R, Wallwiener D *et al*: Reduction in new metastases in breast cancer with adjuvant chodronate treatment. N Engl J Med *339*: 357-363, 1998.

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