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OUR EXPERIENCE WITH ZOLEDRONIC ACID IN THE TREATMENT OF PATIENTS WITH NON-SMALL CELL LUNG CANCER AND BONE METASTASES

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ABSTRACT:

Objective: Bone metastases occur in 30- 40% of patients with lung cancer. The aim of this study was to assess the efficacy and safety of Zoledronic acid, a third generation biphosphonates, in patients with non- small cell lung cancer and bone metastases. **Methods:** Among May 2004 and December 2008 fifty three consecutive patients with inoperable non- small cell lung cancer and bone metastases was evaluated. Zoledronic acid was administered at dose 4 mg every 3- 4 weeks as rapid intravenous infusion. All patients were treated with combination chemotherapy too. **Results:** After the treatment with Zoledronic acid was observed significant reduction of serum calcium level. Serum alkaline phosphatase also decreases but not significantly. With regard of clinical efficacy 36 of patients stabilized or reduced their needs for analgesic treatment. No grade 4 side effects were recorded. **Conclusion:** Zoledronic acid as rapid intravenous infusion is safe and convenient in the treatment of patients with non- small cell lung cancer and bone metastases.

Key words: Zoledronic acid, Non- small cell lung cancer, Bone metastases

INTRODUCTION

Lung cancer is the most common cancer worldwide (1) and non- small cell lung cancer (NSCLC) is the most prevalent form of lung cancer (2, 3). Advanced NSCLC is often highly symptomatic (4), and an estimated 30 to 40% of patients develop bone metastases (5). The high prevalence of bone metastases in stage IV non- small cell lung cancer /NSCLC/ patients contributes substantially to the burden of the disease, while treatment innovations have provided little hope for improvement in overall survival. Bone metastases can cause considerable skeletal morbidity, including severe bone pain, pathologic fractures, spinal cord compression and hypercalcemia of malignancy and may result in functional impairment and loss of mobility. These skeletal- related events are the result of the resorption of mineralized bone by osteoclasts. The management of skeletal complications is typically a multimodal endeavor involving surgery, radiation therapy, analgesics and more recently administration of biphosphonates (BP) (6). BPs are inhibitors of bone resorption and have been extensively used in the oncology setting for the treatment and prevention or palliation of skeletal complications associated with osteolytic lesions in patients with solid tumors and bone metastases.

Zoledronic acid is new, highly potent, nitrogen-containing BP that has demonstrated superior efficacy for the treatment of hypercalcemia of malignancy compared with Pamidronic acid. Recently, it has been reported that Zoledronic acid offers greater convenience and is as effective and well tolerated as Pamidronic acid in the treatment of bone metastases from breast cancer or multiple myeloma (7,8). Zoledronic acid has also demonstrated activity in the treatment of bone metastases in patients with advanced lung cancer and other solid tumors (9).

The aim of this study was to assess the efficacy and safety of intravenous infusion of Zoledronic acid in the setting of patients with NSCLC and bone metastases.

PATIENTS AND METHODS

Fifty three consecutive patients with advanced or metastatic morphologically proven stage IV NSCLC entered the study. Eligibility criteria included adult patients age 18-75 years, World Health Organization (WHO) performance status 0 to 2, life expectancy >12 weeks, adequate bone marrow function (absolute granulocyte count > $1,5x10^9$/L, platelet count > $140x10^9$/L) as well as normal renal (serum creatinine level < 1,5 мmol/L) and hepatic function (serum bilirubin level < 21 мmol/L), at least one bone metastases, documented by plain radiography or bone scan. Patients were excluded if they had a history of severe cardiovascular cardiac disease, hypertension refractory to treatment, symptomatic coronary artery disease or symptomatic brain metastases, presence of active infections, renal or hepatic dysfunction, and pregnancy.

Pre- treatment evaluation included a complete medical history and physical examination, laboratory test (hematology and standard biochemistry), chest radiographs,

electrocardiogram (ECG). Bone lesion sites were assessed by physical evaluation and plain radiography of the areaor bone scan. During treatment, a physical examination, an ECG, a blood- cell count with differential, platelet count and standard biochemical assessment (including serum creatinine, urea, sodium, potassium, calcium, transaminases, total bilirubin, total proteins, albumin and lactate dehydrogenase) preceded each cycle. Furthermore, the patient's temperatures, pulse rates and arterial blood pressures were monitored at the beginning and end of infusion, as well as 2 hours following completion.

Zoledronic acid 4 mg was diluted in 100 ml normal saline 0,9% and administered on a patient in a rapid, 15- min intravenous infusion with repetition every 3 or 4 weeks depending on the patient's chemotherapy sessions. 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%.

Chemotherapy schedule consist of: Gemcitabine 1250 mg/m2 by intravenous infusion day 1 and 8 and cis- Platinum 80 mg/m2 with hydratation on day 1 with repetition every 21-28 days depending on hematological toxicity.

Serum creatinine clearance were performed every six courses. The patient's analgesic treatment was recorded during each visit and any changes were evaluated according to the WHO three- step analgesic ladder (10). 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 patient's 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 plain radiography and if necessary, bone scans every 6 months, while the clinical benefit was assessed during each visit by recording any changes in analgesic treatment.

The statistical evaluation of the reported parameters was conducted through the use of the Wilcoxon test for pair differences. The results were considered statistically significant if $p < 0,05$ level.

RESULTS

Between May 2004 and December 2008 from a total of 53 patients who were diagnosed with stage IV NSCLC with bone metastases and undergoing treatment in Department of Chemotherapy, Oncological center, UMHAT "Dr G. Stranski", Medical University- Pleven, entered the study. Some patient's characteristics are present on table 1. All 53 patients (41 men, 12 women) had available parameter values for baseline, 1st, 3rd and 6th cycles. The group had a median age of 66,9 years (range 43- 74 years). With regard to the performance status of the 53 patients: 8, 28 and 17 patients had a PS of 0 (15,1%), 1 (52,8%) and 2 (32,1 %), respectively. Five patients had hypercalcemia, while the remaining were normocalcemic. All patients were evaluated for toxicity and efficacy. A total of 278 infusions were administered to 53 patients with a median of 5 infusions per patient (range 4- 9) and a mean follow-up period of 14 months (range 6-12 months).

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 or creatinine levels did not increase significantly and no changes were detected in patient temperatures or blood pressures. The most commonly observed adverse events were bone pain, nausea, anemia, vomiting, dyspnea and constipation (Table 3). No grade 4 serious adverse effects were recorded.

After the first administration of Zoledronic acid, serum calcium levels notably decreased from a mean value of 2,72 mmol/l to 2,26 mmol/l, a difference of statistical significance ($p=0,01$). Even after 6 months, these levels remained significantly lower. The mean values of the main parameters studied, including baseline and after 6 months following Zoledronic acid infusion, are provided in Table 2. The observed reductions in serum alkaline phosphatase levels were not statistically significant. Seven of the patients included in the study needed bone radiation (one before Zoledronic acid administration and six after, due to pain). The remainder of the 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 all group of 53 patients on Zoledronic acid, nineteen (35,9 %) patients reduced their need, 21 (39,6%) patients did not necessitate any adjustments throughout the treatment and 13 (24,5%) patients required increased doses for skeletal bone pain, respectively (Figures 1 and 2).

Concerning the number of bone lesions evaluated through consecutive plain radiography or bone scans, twenty- six patients (49%) maintained the same number of bone lesions, while 6 patients (11,3%) presented significant improvements. Twenty- one patients (39,7%) demonstrated bone disease progression with an increase in the number of lesions, as detected by bone scans. However, only 11 of these patients (20,75%) required an increase in their analgesic medication.

DISCUSSION

The natural history of bone metastases in patients with solid tumors shows that these patients have a poor prognosis. The skeletal complications from bone metastases result in significant pain and impaired mobility for patients. Zoledronic acid is biphosphonate that have broad efficacy in the treatment of bone metastases from all malignancies, including lung carcinoma. 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 rapid administration was investigated.

In our study we demonstrate that the 15-min infusion of Zoledronic acid at a dose 4 mg was safe and effective, since none of our patient's vital signs or renal functions deviated from the normal levels throughout the ttreatment. Zoledronic acid was well tolerated. Adverse effects included bone pain, nausea, anemia, vomiting, dyspnea and constipation. These events were primarily mild to moderate in severity. No dead due to serious adverse effects was observed. Our observations are 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 (11). 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 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 (11,12). Finally, these results conform to similar studies utilizing other BPs, such as Pamidronate, that demonstrated clinical benefits in cancer patients with osteolytic lesions (11,12). 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 (13-15). 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.

In summary, 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 patients with bone metastases. The recommended administration schedule could improve patient acceptability by simplifying the management and reducing the need for safety monitoring and treatment of adverse effects. Finally, the established clinical benefits may decrease the metastatic bone disease burden on healthcare systems and oncology units.

Table 1. Patient characteristics

Patient characteristics	Number of patients- 53
Age (years)	43 - 74
Sex	
Males	41 (73,3%)
Females	12 (26,7%)
Performance status WHO	
0	8 (15,1%)
1	28 (52,8%)
2	17 (32,1%)
Histology	
Squamous	34 (64,1%)
Adenocarcinoma	12 (24,7%)
Large- cell	5 (9,4%)
Other	2 (3,8%)
Primary therapy	
Chemotherapy	39 (73,6%)
Radiotherapy	9 (16,9%)
Chemo- radiotherapy	5 (9,5%)
Number of bone metastases	
1	15 (30,2%)
2	12 (24,6%)
>2	24 (45,2%)

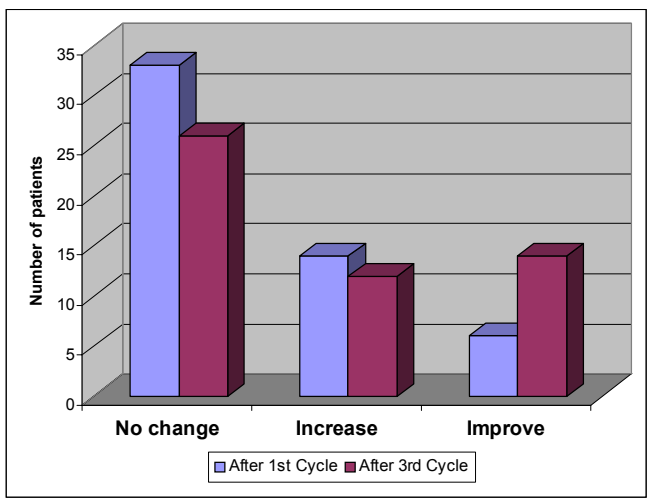
Table 2. Mean value of parameters studied

Parameter studied	Referent values	Baseline	After treatment
Serum creatinine (м/l)	44- 134	93,7	88,4
Blood urea nitrogen mmol/l	1,7- 8,2	5,9	6,1
Alanine aminotransferase U/l	<40	29,3	26,7
Alkaline phosphatese U/l	< 280	136,5	114,4
Serum calcium mmol/l	2,2- 2,55	2,72	2,26

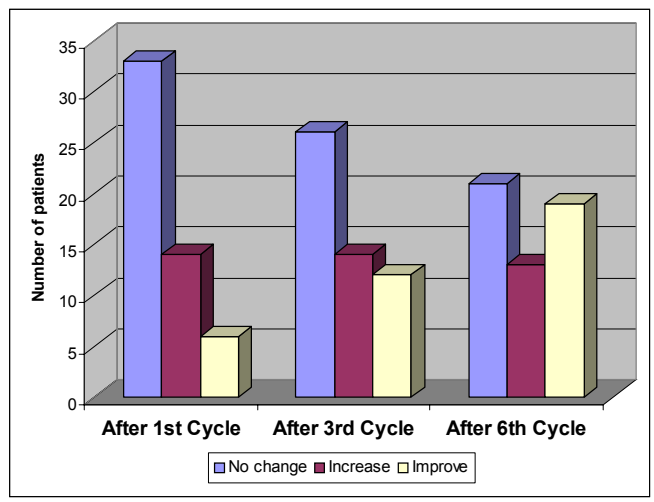
Table 3. Most frequently adverse events observed (all grades)

Adverse event	Number of patients	%
Bone pain	21	39,6
Nausea	16	30,1
Vomiting	9	16,8
Dyspnea	8	15,0
Anemia	11	20,7
Constipation	14	26,4
Pyrexia	9	16,9
Weakness	16	30,1
Headache	8	15,0
Others	19	35,8

Figure 1. Pain changes over three treatment cycles.



Fgure 2. Pain changes over six treatment cycles.



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