Feasibility Study of Zoledronic Acid plus Cisplatin-Docetaxel as First-line Treatment for Advanced Non-small Cell Lung Cancer with Bone Metastases

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Abstract. *Background: This study evaluated the safety and efficacy of combined zoledronic acid, cisplatin and docetaxel in patients with non-small cell lung cancer (NSCLC) with bone metastases. Patients and Methods: Cisplatin 80 mg/m^2 and docetaxel 60 mg/m^2 with zoledronic acid 4 mg were given intravenously on day 1 every 3-4 weeks. The primary endpoint was feasibility of concomitant administration of zoledronic acid and cisplatin. Results: Thirty-five chemonaïve patients were enrolled. The median number of treatment cycles was four, and two or more cycles were administered in 29 (83%) patients without severe toxicity. No grade 3 or 4 renal toxicity was observed. The objective response rate was 29% and the 1-year survival rate was 37%. The pain score improved in 77% of the patients after six weeks. Conclusion: The combination of zoledronic acid, cisplatin and docetaxel is well-tolerated with acceptable renal toxicity, and has modest activity as a first-line treatment of NSCLC patients with bone metastases.*

Bone metastases are common in patients with solid tumors, affecting approximately 40% of patients with advanced non-small cell lung cancer (NSCLC). Historically, median survival after the diagnosis of bone metastases from NSCLC has been reported to be only six to seven months (1, 2). Patients with bone metastases frequently experience osteoclast-mediated bone destruction, resulting in clinically important complications such as fractures, the need for radiation therapy or bone surgery, spinal cord compression, or hypercalcemia of malignancy (HCM). These complications, collectively known as skeletal-related events (SREs), lead to pain and result in a significant negative impact on both the quality of life and survival (1, 3). SREs can eventually hamper adherence to therapy and significantly increase the overall costs of health care (4).

*Bis*phosphonates (BPs) are inhibitors of osteoclast-mediated osteolysis and have demonstrated utility in preventing SREs in patients with bone metastases (5-7). Among the BPs currently available, only zoledronic acid has demonstrated a delay in the onset and a reduction in the incidence of SREs when compared with a placebo, and exhibited a significant reduction of bone-related pain in patients with lung cancer with bone metastases (8, 9). An international expert panel recommends that for patients with NSCLC with bone metastases, zoledronic acid treatment must be considered as part of the treatment to prevent and delay the occurrence of further bone metastases and SREs and to relieve pain, where present (10, 11).

Platinum-based chemotherapy including cisplatin or carboplatin is considered as the standard first-line treatment for patients with advanced NSCLC (12). Pre-clinical data suggest that zoledronic acid may act by directly affecting tumor progression, possibly in synergy with anticancer agents such as cisplatin (13). Therefore, patients with NSCLC with bone metastases are candidates for combined zoledronic acid therapy given with anticancer agents. However, it is unknown whether administering zoledronic acid with cisplatin, which can be nephrotoxic, is feasible. Zoledronic acid can also result in renal deterioration. Based on these considerations, we conducted a feasibility study to evaluate the safety and efficacy of combined zoledronic acid, cisplatin and docetaxel administration in patients with NSCLC with bone metastases.

Patients and Methods

Patient eligibility. The present study enrolled chemonaïve patients with pathologically proven NSCLC with at least one bone metastasis. Patients were also required to be 20 to 75 years of age, have an Eastern Cooperative Oncology Group performance status of 0 or 1, and have adequate bone marrow reserve and organ function, including creatinine ≤1.2 mg/dl and creatinine clearance

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Key Words: Zoledronic acid, chemotherapy, cisplatin, renal toxicity, non-small cell lung cancer.

of 60 ml/min. Patients were not eligible if they had undergone prior treatment with a BP, had clinically symptomatic brain metastases, or had any other condition that could compromise protocol compliance. All patients were required to provide written informed consent before entry into the study. The study was approved by the Institutional Review Boards of the National Cancer Center. The trial has been registered under the number UMIN000000735.

Treatment plan. Cisplatin at 80 mg/m^2 and docetaxel at 60 mg/m^2 were administered intravenously on day 1 every 3-4 weeks. Patients also received an intravenous infusion of zoledronic acid of 4 mg over 15 min after the administration of chemotherapy on day 1. All patients received 2500 to 3000 ml of fluid for hydration and prophylactic antiemetic therapy consisting of a 5-hydroxytryptamine 3 receptor antagonist and a steroid. Patients receiving zoledronic acid also received calcium or vitamin D supplements if needed. Therapy was continued for up to four cycles unless the patient experienced unacceptable toxicity or had progressive disease (PD). Patients who completed or discontinued the study treatment could continue to receive zoledronic acid as maintenance treatment for prevention of SREs until unacceptable toxicity occurred. Any dose reduction in chemotherapy was based on the severity of a related toxicity, as graded by the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 (14). Study treatment was discontinued for any patients requiring a delay in study treatment for longer than three weeks or who had more than two dose reductions.

Baseline and treatment assessments. Pre-treatment evaluation included a medical history, a physical examination, vital signs, height and body weight, PS, complete blood count, biochemical studies, electrocardiogram, chest radiograph and computed-tomographic scan (CT), abdominal ultrasound or CT, brain magnetic resonance imaging (MRI) or CT, and bone scan. At least one bone metastasis was confirmed by diagnostic imaging with x-ray, CT or MRI before study entry. Objective tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) (15). Toxicity was graded based on the CTCAE version 3.0.

Pain was assessed using the Brief Pain Inventory (BPI) composite pain score at baseline and six weeks (16). Urinary *N*-telopeptide (NTX) and bone-specific alkaline phosphatase (BALP), as bone resorption markers, were evaluated at baseline and six weeks. SREs were defined as a pathological fracture, spinal cord compression, surgery or radiation therapy (RT) for bone, and HCM.

Statistical analysis. The primary objective of this study was to evaluate the feasibility of concomitant administration of zoledronic acid, cisplatin and docetaxel. Simon's minimax two-stage phase II study design was used to determine the sample size and decision criteria. The regimen would be considered feasible if two or more cycles of chemotherapy with combined zoledronic acid, cisplatin and docetaxel were completed in at least 80% of patients, and not feasible if the completion rate was ≤60%. The required number of patients was estimated to be 35, with a significance level of 0.05 and a statistical power of 80%. The secondary endpoints were toxicity, SREs, pain scores, best objective response, and overall survival (OS). The study participants were continuously monitored for serum creatinine increase, as a marker of decreased renal function. The mean change from baseline to six weeks in the Brief Pain Inventory (BPI) score and bone resorption markers was analyzed by the paired *t*-test. *p*-Values <0.05 were considered statistically significant. Two-sided statistical tests were used in all analyses.

Table I. *Patients' characteristics*.

Charactersitic	Patients (n=35) No.	%
Age, years		
Median	61	
Range	40-73	
Gender		
Female	10	29
Male	25	71
ECOG performance status		
0	3	9
1	32	91
Histology		
Adenocarcinoma	27	77
Squamous cell carcinoma	3	9
NOS	5	14
Metastatic sites		
Bone alone	12	34
Bone plus other organ*	23	66
Median (range) baseline serum creatinine, mg/dl	0.7 (0.5-0.9)	
Baseline mean BPI composite pain score	2.6	

*Lung 14; brain 11; liver 7; adrenal 4. ECOG, Eastern Cooperative Oncology Group; NOS, not other specified; BPI, Brief Pain Inventory.

Results

Between July 2007 and November 2009, 35 patients were enrolled in this study, and their characteristics are shown in Table I. Twenty-five (71%) patients were male, and 27 (77%) patients had adenocarcinoma. The median age was 61 years (range 40-73 years). All patients had normal serum creatinine levels.

All the patients underwent at least one cycle of chemotherapy with combined zoledronic acid, cisplatin and docetaxel. The median number of cycles per patient was four (range, 1-4). Two or more cycles were administered in 29 (83%; 95% confidence interval, 70.3% to 95.3%) patients, and four cycles in 19 patients (54%). The primary endpoint was met. Six patients had received only one cycle of treatment either because of toxicities (two patients with grade 3 allergic reaction due to docetaxel, one patient with grade 3 hypoalbuminemia, and one patient with grade 3 cardiac insufficiency), or PD (two patients). Twenty-three patients (66%) underwent maintenance therapy with zoledronic acid for a median of six cycles (range, 1-31).

The common adverse events associated with treatment are listed in Table II. Grade 3/4 neutropenia occurred in 63% of the patients in our study, but grade 3 febrile

Table II. *Adverse events (n = 35).*

Adverse event	CTCAE version 3.0			
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Leukocytes	20	29	43	3
Neutrophils	9	23	37	26
Hemoglobin	40	40	20	0
Platelets	14	6	0	0
Febrile neutropenia	-	-	3	0
Nausea	48	37	9	0
Vomiting	20	31	3	0
Anorexia	37	46	11	0
Fatigue	31	17	6	0
Alopecia	37	37	-	-
Allergic reaction	0	0	6	0
AST/ALT	49	6	8	0
Hypocalcemia	37	43	14	3
Creatinine	43	14	0	0

CTCAE, Common Terminology Criteria for Adverse Events; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

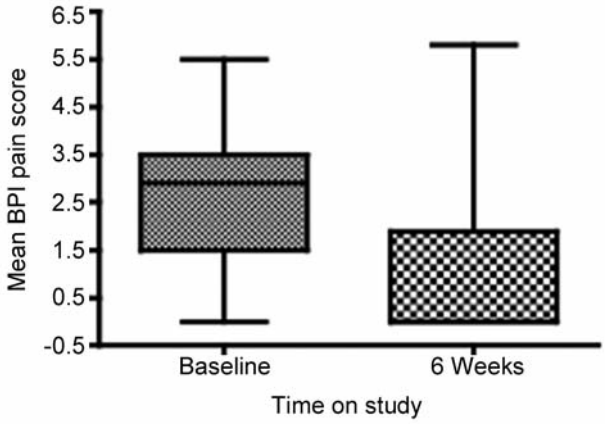

Figure 1. *Box plot for mean change from baseline in Brief Pain Inventory (BPI) composite pain scores. The mean BPI was 2.6±0.2 at baseline and 1.0±0.3 at 6 weeks (p<0.0001).*

neutropenia developed in only 3%. The majority of non-hematological toxicities were mild to moderate in severity. Grade 3/4 hypocalcemia was observed in six (17%) patients, but they were all asymptomatic. Osteonecrosis of the jaw was not observed. There were no treatment-related deaths. Serum creatinine increase as renal toxicity was reviewed in detail. Six patients had an increase in serum creatinine levels of >0.5 mg/dl from the baseline level. The median serum creatinine level was 0.7 (range, 0.5-0.9) mg/dl at baseline and 1.0 (range, 0.7-1.8) mg/dl at the end of the study. No patient developed grade 3 or 4 serum creatinine increase.

The proportion of patients who experienced at least one SRE was 29% (bone RT in six patients, bone RT plus spinal cord compression in two patients, spinal cord compression in one patient, and bone RT plus HCM in one patient). The median time to first SRE in the 10 patients with SRE was 5.3 months (range=4.6-16.1 months). The BPI composite pain score improved in 27 patients (77%) between baseline and six weeks (Figure 1). The mean BPI composite pain score was 2.6±0.2 at baseline and 1.0±0.3 at six weeks, demonstrating a statistically significant difference ($p<0.0001$). In bone resorption markers, the mean change from baseline to 6 weeks is shown in Figure 2. The baseline mean NTX was 72.1±12.6 nmol/mmol creatinine and 28.0±3.3 nmol/mmol at 6 weeks. This difference was statistically significant ($p=0.0004$). In contrast to this, the mean BALP level was 63.0±13.6 U/l at baseline and 58.3±16.4 at six weeks; there was no statistically significant difference ($p=0.82$).

There were 10 partial responses (PRs), 17 cancer of stable disease, and 8 PD among the 35 patients, and the overall response rate was 29%. The median follow-up time was 16 months. The median progression-free survival was 4 months, and the median OS was 8 months (range=2.1-41.4 months). The Kaplan–Meier curve for the OS is shown in Figure 3. The 1-year and 2-year survival rates were 37% and 26%, respectively. Twenty-seven patients (77%) underwent at least one subsequent chemotherapy. The epidermal growth factor receptor (*EGFR*) mutation status was analyzed in eight patients who had available tissue samples. *EGFR* mutations were detected in five tumor tissues (four deletions in exon 19 and one G719C point mutation in exon 18). Four out of five patients with *EGFR* mutation achieved PR with subsequent gefitinib or erlotinib treatment.

Discussion

To our knowledge, this is the first study to investigate the feasibility of concomitantly administering zoledronic acid with cisplatin-based chemotherapy for patients with advanced NSCLC with bone metastases. This study showed combined zoledronic acid, cisplatin and docetaxel to be safe, with acceptable renal toxicity. Hematological and non-hematological toxicities observed in our study were similar to those of a previous Japanese trial which assessed cisplatin and docetaxel without ZOL (17), although the number of patients in our study was not large. Neither grade 3 or 4 serum creatinine increase nor treatment-related deaths were observed. Furthermore, the BPI composite pain score improved in 77% of patients between baseline and six weeks. NTX levels were also reduced after six weeks in 97% of patients. We suggest that zoledronic acid plus a platinum-based chemotherapy, such as cisplatin and docetaxel, is suitable as the first-line treatment in clinical practice for patients with NSCLC with bone metastases at diagnosis.

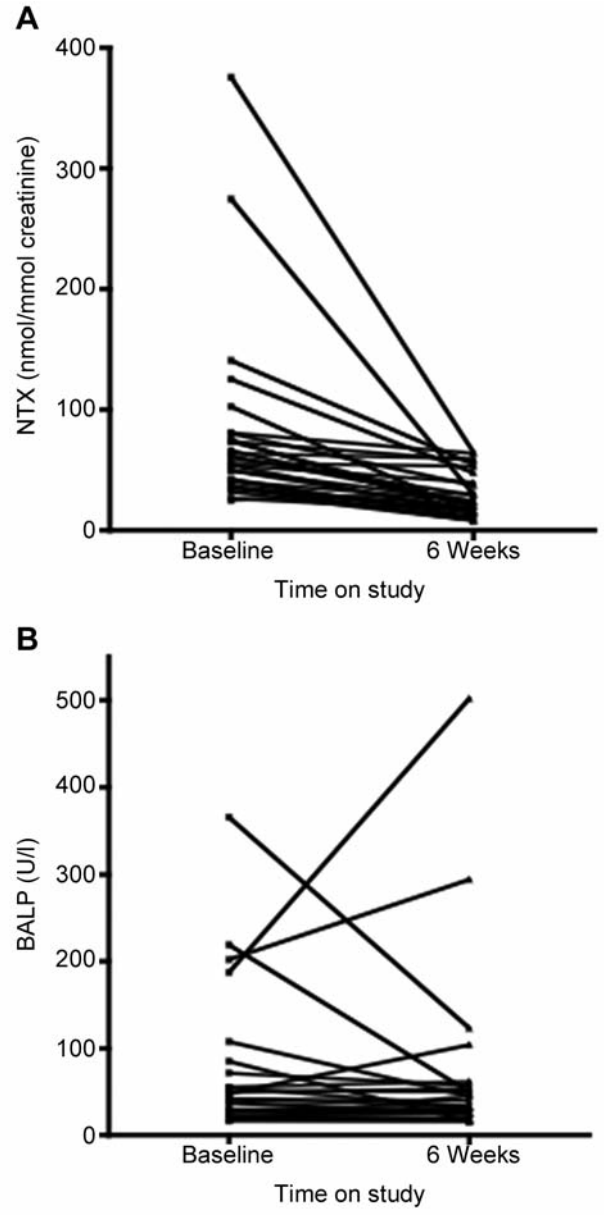

Figure 2. *Bone resorption markers at baseline and at 6 weeks. Urinary N-telopeptide (NTX) (A) and bone-specific alkaline phosphatase (BALP) (B). After 6 weeks, 97% of patients experienced a decrease of NTX level from baseline.*

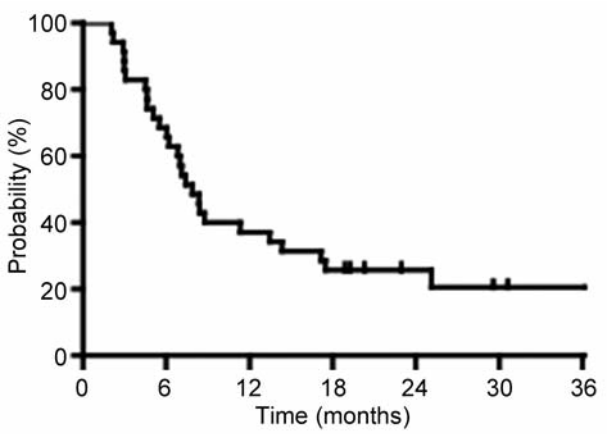

Figure 3. *Kaplan–Meier curve for overall survival. The 1-year and 2-year survival rates were 37% and 26%, respectively.*

Zoledronic acid has been suggested to have synergistic antitumor effects with chemotherapy, reduce angiogenesis, induce tumor-cell apoptosis, and activate anticancer immune responses (18, 19). Recently, several randomized controlled trials have been reported in patients with breast cancer, which evaluated the antitumor effect of zoledronic acid. The ABCSG-12 trials showed that the addition of zoledronic acid to endocrine therapy was associated with a 36% improvement in disease-free survival in pre-menopausal women with early-stage breast cancer (20). The subgroup analysis of the AZURE trial in patients with breast cancer who underwent neoadjuvant therapy, chemotherapy plus zoledronic acid showed a significant increase in pathological complete response compared with chemotherapy alone (21). One recent randomized phase II study of patients with stage IIIB or IV NSCLC without bone metastases evaluated the efficacy and safety of carboplatin and docetaxel with or without zoledronic acid. Although well-tolerated, this combination did not result in a significant improvement of disease progression or OS because the study was not powered to detect a difference in endpoints (22). Currently, a large phase III, international randomized prospective trial is underway, examining the efficacy of zoledronic acid in delaying or preventing bone metastasis in patients with stage III NSCLC.

Our results in the 35 patients with NSCLC with bone metastases indicated that the combination of zoledronic acid, cisplatin and docetaxel yielded an objective response rate of 29% and a median OS of 8 months, with a 1-year survival rate of 37%. The present study was unable to evaluate any survival benefit regarding the addition of zoledronic acid to chemotherapy, because this was a single-arm phase II study including only a small number of patients. However, the combination of zoledronic acid, cisplatin and docetaxel seems to have modest activity as a first-line treatment for patients with NSCLC with bone metastases, compared with historical data where the median OS after the diagnosis of bone metastases from NSCLC was only six to seven months (2).

The combination of zoledronic acid, cisplatin and docetaxel was demonstrated to be well-tolerated with acceptable renal toxicity and to have modest activity as a first-line treatment of patients with NSCLC with bone metastases. A larger randomized phase III trial is required to confirm the antitumor effects of zoledronic acid for NSCLC.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan. There are no other conflicts of interest for any of the contributors.

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Received May 7, 2012
Revised July 16, 2012
Accepted July 17, 2012