

A feasibility study of zoledronic acid combined with carboplatin/nedaplatin plus paclitaxel in patients with non-small cell lung cancer with bone metastases

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ABSTRACT

Aims and background. Although zoledronic acid (ZOL) has been reported to inhibit bone metastasis from lung cancer, the optimum chemotherapy regimen in combination with ZOL has not yet been determined.

Methods and study design. Eighteen patients having non-small cell lung cancer (NSCLC) with bone metastasis who received carboplatin/nedaplatin plus paclitaxel combined with ZOL (4 mg every 28 days) were enrolled to investigate the feasibility of this treatment. The efficacy was evaluated by the percentage of patients at 9 months who were receiving radiation therapy, the time to first radiation treatment, and quality of life. Adverse effects were also evaluated.

Results. Only 3 among 18 patients received radiation therapy for bone metastases during the 9 months of the study. ZOL seems to prolong the median time to the first radiation treatment and maintain the quality of life regarding pain and activity status. No patients discontinued the treatment, although grade 3 or 4 treatment-related adverse effects occurred in 8 patients.

Conclusions. ZOL combined with carboplatin/nedaplatin plus paclitaxel is an effective and tolerable treatment for NSCLC with bone metastases.

Introduction

The skeleton is one of the most common sites of metastasis for non-small cell lung cancer (NSCLC), and approximately 30% to 40% of patients with advanced NSCLC develop bone metastases¹. Among patients with cancer of unknown primary origin, more than 50% of those who present with bone metastases were revealed to have a lung primary cancer at autopsy². Bone metastases cause considerable skeletal-related events (SREs), including bone pain, pathological fractures, spinal cord compression, and hypercalcemia of malignancy, which result in a significant negative impact on the quality of life (QOL) and survival of cancer patients³.

Zoledronic acid (ZOL: ZOMETA®; Novartis Pharma AG, Basel, Switzerland / Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA) is a bisphosphonate used for the prevention or palliation of skeletal complications associated with bone metastases. Rosen *et al.*⁴ reported that ZOL significantly extended the time to the first SRE and reduced the risk of developing SREs compared with the placebo group among patients with bone metastases from lung cancer or other solid tumors. Based on these available data and the published safety precautions, the use of ZOL in combination

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with chemotherapy is recommended for patients suffering from lung cancer with bone metastases⁵.

However, there have been only a few reports describing the optimum chemotherapy regimen in combination with ZOL for the treatment of NSCLC. In fact, the chemotherapy regimen used in combination with ZOL in the above study by Rosen *et al.* was not specified. Moreover, the effect of adding ZOL to chemotherapy on QOL has not yet been investigated in detail. Since chemotherapy using carboplatin (CBDCA)/nedaplatin (254-S) plus paclitaxel (PAC) is considered to be one of the standard regimens, and the most frequently used regimen for NSCLC in Japan^{6,7}, we conducted a clinical study to examine the feasibility of combined treatment with ZOL and CBDCA/254-S plus PAC for NSCLC patients with bone metastases. In addition, the effect of this treatment on QOL in these patients was evaluated.

Patients and methods

Patient selection

Eighteen NSCLC patients treated between September 2007 and September 2009 at the Juntendo University Hospital and Showa University Hospital were enrolled in this prospective study. The study subjects were consecutively registered according to the following inclusion criteria: histologically or cytologically confirmed advanced NSCLC with at least one site of bone metastasis; measurable or assessable disease; Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 ; adequate organ function including a white blood cell count (WBC) $>3000/\text{mm}^3$, hemoglobin $>9 \text{ g/dL}$, platelet count $>100,000/\text{mm}^3$, serum creatinine $<2 \text{ mg/dL}$, serum AST and ALT levels less than 2.5 times the upper normal limit, serum bilirubin $<2.5 \text{ mg/dL}$, and an adjusted serum calcium level within 8 to 12 mg/dL. The exclusion criteria were as follows: more than a single administration of a bisphosphonate within 30 days; complicated with severe cardiovascular disease; pregnancy; or planning invasive dental treatment.

Treatment methods

CBDCA AUC = 6 was administered on day 1 along with weekly PAC, 70 mg/m^2 on days 1, 8, and 15, or 254-S, 80 mg/m^2 on day 1 along with PAC, 90 mg/m^2 on days 1, 8, and 15 every 4 weeks, and each 4-week treatment schedule was designated as 1 cycle. ZOL (4 mg) was intravenously administered on day 8 for both regimens. These treatments were repeated for 4 to 6 cycles. Dose reduction, omission and discontinuation of the anti-cancer drugs were all based on the judgments of the respective physicians-in-charge. The therapy was continued until disease progression, the appearance of intolerable toxicity, or withdrawal of consent. ZOL was administered until the occurrence of a serious adverse ef-

fect. Complete blood count and biochemistry examinations were repeated at least once a week after the initial evaluation.

Evaluation of SREs, toxicity and QOL

Radiation therapy was performed in cases of the incidence of spinal cord compression, for prevention of fractures, and in cases where there was poor control of pain despite administration of analgesics. The patients were evaluated to determine these SREs by physical examination, x-ray, CT and MRI. The efficacy of combined treatment with ZOL and CBDCA/254-S plus PAC was evaluated by the incidence of patients who received radiation therapy to bone and the time to first radiation treatment during the 9 months of the study. QOL scores were collected at regularly scheduled visits before and after each cycle of ZOL administration by using the quality of life questionnaire for cancer patients treated with anti-cancer drugs (QOL-ACD) and the lung cancer symptom scale (LCSS). The QOL-ACD and LCSS consist of 22 and 9 items, respectively. The questions on the QOL-ACD are grouped into 5 functional categories (daily life activity, physical condition, psychological condition, social attitude, and face scale). The questions in the LCSS are grouped into 2 categories: major lung cancer symptoms (appetite, cough, dyspnea, fatigue, hemoptysis, and pain) and summation items (symptomatic distress, activity status, and overall QOL). Adverse effects were evaluated until 4 weeks after the last administration of chemotherapy or until the patient's death, according to the common terminology criteria for adverse events (CTCAE) version 3.0. Ethics committee study approval was obtained from each institution, and written informed consent was obtained from all patients.

Statistical methods

The differences between the study and control groups were assessed using unpaired *t*-tests and the Mann-Whitney *U*-test for continuous outcomes. The time to first radiation treatment was compared using the Kaplan-Meier method. Statistical significance was defined as $P \leq 0.05$. All analyses were performed using the StatView software program, version 5.0.

Results

Eighteen patients (13 men and 5 women) were enrolled in this study between September 2007 and September 2009 (data not shown). The median age was 67.5 years (range, 35-78 years). Their ECOG performance status for ZOL was 0 for four (22.2%), 1 for twelve (66.7%) and 2 for two patients (11.1%). The median number of cycles of CBDCA/254-S plus PAC therapy was 4 cycles (1-6 cycles), and the median number of administrations of ZOL was 4 (1-8 times).

Only 3 of the 18 patients (16.7%) received radiation therapy for bone metastases during the 9 months of the study. The reasons for radiation therapy were a pathological fracture of the femur and poor control of pain due to bone metastasis in the pelvis and rib. Seventeen other patients who were diagnosed with NSCLC with bone metastases at diagnosis and treated with the same chemotherapy regimen without ZOL from 2007 to 2009 at Juntendo University Hospital were analyzed as a control group. These patients met the inclusion criteria but refused to enter the study. The incidence of patients receiving radiation therapy was significantly reduced by the addition of ZOL to chemotherapy compared with the chemotherapy-only control group (16.7% vs 70.6%, $P = 0.0013$, data not shown). ZOL also significantly extended the median time to the first radiation treatment in comparison with the control group (160.5 days vs 111.5 days, $P = 0.027$, 95% CI, 0.07-0.94) (Figure 1). As for QOL assessment, there were no significant differences in each QOL domain score and the overall QOL in the QOL-ACD between the ZOL and control groups. With regard to the LCSS, there were no significant differences in appetite, fatigue, cough, dyspnea, or hemoptysis scores between the groups, while the pain score for the ZOL group was better than that for the control group (Figure 2A). Moreover, the activity status score for the ZOL group was higher than that for controls (Figure 2B). The adverse effects are listed in Table 1. Grade 3 or 4 treatment-related adverse effects occurred in 8 of the patients in both groups. There were no significant differences in adverse effects between the groups. No osteonecrosis of the jaw or treatment-related death occurred and no patients discontinued the chemotherapy because of adverse effects in the study group.

Discussion

Patients with bone metastases are at high risk of developing SREs, particularly pathological fractures and

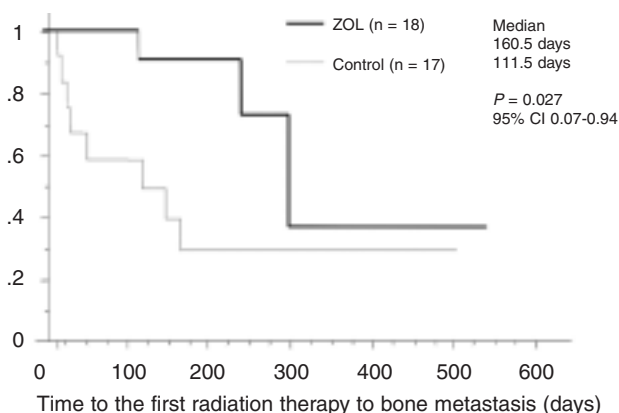


Figure 1 - Kaplan-Meier estimates of time to first radiation treatment for affected bones. The solid line indicates the zoledronic acid group (ZOL), the dotted line the control group.

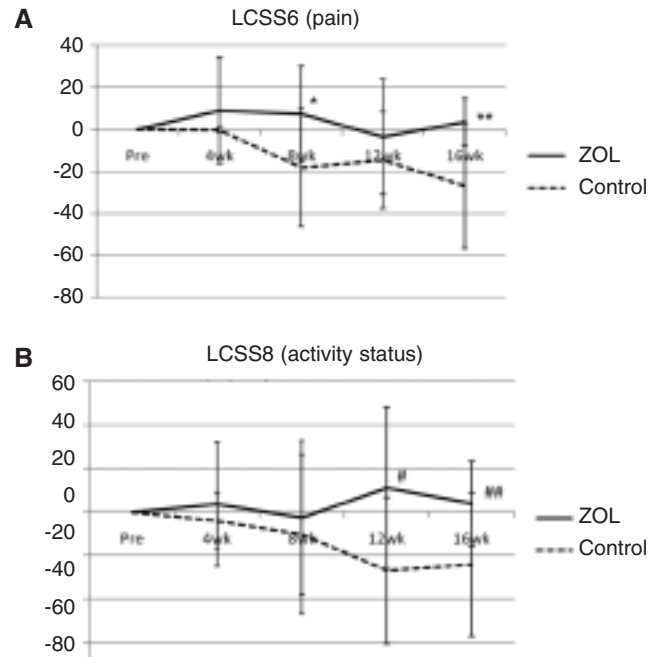


Figure 2 - Time courses of Lung Cancer Symptom Scale (LCSS) items 6 (pain, A) and 8 (activity status, B). The LCSS 6 score at 8 weeks after the start of treatment was significantly higher in the ZOL group than in the control group (* $P = 0.0256$). At 16 weeks the LCSS 6 score showed a trend towards being higher in the ZOL group than the control group (** $P = 0.0795$). The LCSS 8 score at 12 weeks after the start of treatment was significantly higher in the ZOL group than the control group (# $P = 0.0375$). At 16 weeks the LCSS 8 score of the ZOL group showed a trend towards being higher than that of the control group (** $P = 0.0658$). The solid lines indicate the ZOL group, the dotted lines the control group. ZOL, zoledronic acid.

the need for palliative radiation therapy. Furthermore, the first SRE increases the risk of developing subsequent SREs⁸. These SREs cause a significant negative impact on both QOL and survival; the median survival for patients with bone metastasis is <6 months³. In addition, Hirsh *et al.*⁹ reported that patients with metastatic bone disease from lung cancer who developed SREs had a 50% shorter survival compared with patients who did not develop SREs. Therefore, prevention of the first SRE is important for the treatment of these patients.

ZOL is a potent inhibitor of bone resorption and has proven effective for the prevention of SREs in patients with bone metastases of a variety of solid tumors^{4,10-12}. However, few previous reports have demonstrated the feasibility of combined treatment with ZOL and platinum plus PAC in patients with lung cancer. In this study, we demonstrated the feasibility of combined treatment with ZOL and platinum plus PAC in patients with advanced NSCLC. We do not know whether PAC-containing regimens are truly the most appropriate regimen. Lu *et al.*¹³ revealed that there was a synergistic inhibitory activity of ZOL and PAC on bone metastasis in nude mice. They showed that ZOL enhanced the efficacy of PAC synergistically by reducing the incidence of

Table 1 - Adverse effects

Grade	Zoledronic acid (n = 18)				No. of patients with grade ≥ 3	Control (n = 17)				No. of patients with grade ≥ 3
	1	2	3	4		1	2	3	4	
Hematological					5					3
Neutropenia	-	3	2	-	2	3	2	2	1	3
Anemia	1	2	2	-	2	1	2	-	-	0
Thrombocytopenia	2	-	1	-	1	-	1	-	-	0
Nonhematological					3					5
Nausea/vomiting	3	1	-	-	0	6	-	3	1	4
Constipation	1	-	-	-	0	-	-	-	-	0
Fatigue	1	-	-	1	1	-	-	-	-	0
Fever	-	1	-	-	0	-	-	-	-	0
Infection	-	-	2	-	2	-	-	-	-	0
Mucositis	1	-	-	-	0	-	-	-	-	0
ALP	1	-	-	-	0	-	-	-	-	0
ALT/AST	1	1	-	-	0	2	-	-	-	0
Creatinine	-	-	-	-	0	-	-	-	1	1
Necrosis of the jaw	-	-	-	-	0	-	-	-	-	0

bone metastasis from lung cancer, and prolonged survival in a mouse model of NSCLC with a high potential for metastasis to bone. Moreover, Michailidou *et al.*¹⁴ recently revealed that combining ZOL with PAC caused minimal effects on the normal microvasculature *in vivo*, suggesting that this combination therapy does not seem to be associated with deleterious microvascular side effects. In fact, adverse effects of grade 3 or 4 occurred in 8 patients, respectively, in the ZOL and control groups. There were no significant differences in the number of chemotherapy cycles given or the incidence of grade 3 or 4 toxicity between study and control groups (Table 1). Moreover, this incidence was similar to that of adverse effects due to CBDCA plus PAC without ZOL¹⁵. We did not observe any of the common adverse effects of bisphosphonates such as bone pain, renal dysfunction, or osteonecrosis of the jaw, another reported serious adverse effect of ZOL. Additionally, no patients discontinued chemotherapy because of these adverse effects. Therefore, ZOL appears to be well tolerated for the treatment of NSCLC with bone metastasis in combination with CBDCA/254-S plus PAC, without resulting in a significant increase in serious toxicities. Rosen *et al.*⁴ have reported that ZOL combined with chemotherapy reduced skeletal complications in patients with bone metastases from lung cancer and other solid tumors. In their study of 773 patients, of whom more than 50% had lung cancer, they reported that the hazard ratio of occurrence of SREs in patients with lung cancer treated with 4 mg ZOL calculated by multiple event analysis was 0.706. Although this result is consistent with our results, the data were drawn from subset analysis for the lung cancer population. With regard to the chemotherapeutic regimen, they did not mention the specific cytotoxic

drugs that were combined with ZOL in their study. Recently, Pandya *et al.*¹⁶ have reported a randomized phase II study of ZOL in combination with docetaxel and CBDCA in patients with unresectable stage IIIB or stage IV NSCLC, but could not show an inhibitory effect of the addition of ZOL to chemotherapy on disease progression. In Japan, 3 phase II studies to demonstrate the efficacy and safety of ZOL combined with chemotherapy (ZOL + docetaxel/cisplatin, ZOL + doxorubicin, or ZOL + vinorelbine) in patients with unresectable NSCLC are ongoing. However, the results of these studies have not yet been reported. Taken together, PAC-containing chemotherapy seems to be appropriate to be combined with ZOL in patients with NSCLC and bone metastases.

We also revealed that ZOL combined with CBDCA/254-S plus weekly PAC improved pain (LCSS item 6) and activity status (LCSS item 8) scores. We further analyzed a variety of QOL and LCSS scores to reveal the efficacy of ZOL in combination with PAC plus CBDCA/254-S in NSCLC patients with bone metastases. Unfortunately, there were no significant differences in overall QOL domain scores (daily life activity, physical condition, psychological condition, social attitude, and face scale) in the QOL-ACD between the study and control groups. Furthermore, the overall QOL in the LCSS (item 9) was also not improved by the addition of ZOL to chemotherapy. These results are similar to those reported by Rosen *et al.*⁴. These results suggest that the addition of ZOL to chemotherapy can effectively prevent the incidence of SREs and decrease pain, resulting in improvement of activity status, but may not be sufficient to improve overall QOL.

In conclusion, the feasibility of ZOL in combined treatment with CBDCA/254-S plus PAC was examined

in this study. ZOL combined with CBDCA/254-S plus PAC for patients with NSCLC with bone metastases inhibited the SREs and maintained the QOL in terms of pain and activity status. Additionally, no serious adverse effects were observed by combination use of ZOL with CBDCA/254-S plus PAC. Our results suggest that combined treatment of ZOL with CBDCA/254-S plus PAC would be an acceptable therapeutic option for patients with NSCLC with bone metastases. However, further large-scale studies are necessary to confirm these results because of the small sample size of this study.

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