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Development of fever following first administration of zoledronate as a prognostic factor in advanced non-small cell lung cancer patients with bone metastases

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Abstract. Nitrogen-containing bisphosphonates (N-BPs), which are usually used for the treatment of advanced cancer with bone metastasis, occasionally cause fever following the first administration. However, it is unclear as to how the development of fever following the first administration of N-BP is associated with clinical outcome. The aim of the present study was to determine the prognostic value of the development of fever following the first administration of N-BP in advanced non-small cell lung cancer patients with bone metastases. The present study reviewed the data of 46 patients with advanced non-small cell lung cancer who were administered zoledronate (ZOL), an N-BP, for bone metastasis, between March 2009 and March 2011 in the Department of Medical Respirology at Tottori University Hospital. Clinicopathological factors were evaluated using univariate and multivariate analyses, and these factors were compared between the fever and non-fever groups. Of the 46 patients, 15 (32.6%) developed fever following the first administration of ZOL. No significant differences were observed in the clinicopathological characteristics between the two groups. The overall survival in the fever group was significantly longer compared with the non-fever group (median survival time: 33.4 vs. 15.7 months, P=0.04), and the development of fever following the first ZOL administration was independently associated with longer overall survival. The development of fever following the first ZOL administration was an independent prognostic factor in advanced non-small cell lung cancer patients with bone metastases. Thus, ZOL-associated fever may be a predictive factor for an undefined, survival-promoting effect of ZOL.

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Abbreviations: CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group-performance status; EGFR, epidermal growth factor receptor; HR, hazard ratio; N-BPs, nitrogen-containing bisphosphonates; Sq, squamous cell carcinomas; NSCLC, non-small cell lung cancer; OS, overall survival; QOL, quality of life; SRE, skeletal-related events; ZOL, zoledronate

Key words: nitrogen-containing bisphosphonates, survival time, prognosis, prognostic indicator, non-small cell lung cancer

Introduction

Lung cancer is the leading cause of cancer-related death worldwide (1), and bone metastases occur in 20-30% of patients with lung cancer (2). Bone metastases reduce the quality of life (QOL) of cancer patients by causing pain or skeletal-related events (SREs) such as pathological fractures, spinal cord compression, and hypercalcemia. Nitrogen containing bisphosphonates (N-BPs) are widely used to prevent SREs in cancer patients with bone metastases (3,4). Preclinical studies have demonstrated the *in vitro* anticancer activity of N-BPs in multiple myeloma (5). In particular, the N-BP zoledronate (ZOL) has demonstrated survival benefits in premenopausal women with early-stage breast cancer and in previously untreated patients with multiple myeloma (6,7). However, the survival benefit of ZOL in patients with cancer, including lung cancer, remains unclear.

N-BPs inhibit osteoclastic bone resorption by blocking farnesyl-pyrophosphate-synthase, an enzyme in the mevalonate pathway. The first administration of intravenous N-BPs is occasionally associated with the development of fever, which is due to the activation of γδ T cells, resulting in the release of interferon-γ, interleukin-6, and tumor necrosis factor-α (8,9). γδ T cells, a small subset of T lymphocytes, play an active role in immunosurveillance against tumors as well as infections, as components of innate immunity (10).

Therefore, we hypothesized that the development of fever after the first administration of N-BPs would be associated with the survival of patients with cancer. The aim of this retrospective study was to estimate the prognostic value of fever development after the first ZOL administration (ZOL-related fever) in advanced or recurrent non-small cell lung cancer (NSCLC) patients with bone metastases.

Patients and methods

Materials. We retrospectively reviewed the data of patients who received a diagnosis of advanced or recurrent NSCLC between March 2009 and March 2011 at Tottori University Hospital in Japan and who received ZOL therapy for bone metastases. This retrospective study was approved by our institutional human research committee. The onset rate of ZOL-related fever is known to peak within the first 2 days after ZOL infusion and is short lived (11). Therefore, ZOL-related fever was defined as fever (>37.5˚C) that occurred within 2 days after the first ZOL administration and that did not persist for >2 days. Fever treated with antibiotics was not regarded as ZOL-related fever.

Methods and statistical analysis. The exclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 2-4 at diagnosis, and no data concerning fever after the treatment with ZOL, even if records of ZOL administration were available. We collected clinicopathological data such as age, sex, smoking history, ECOG-PS, disease stage, histological type, epidermal growth factor receptor (*EGFR*) mutation status, the time from the first ZOL administration to first SRE, and overall survival (OS) from the time of diagnosis of advanced disease or recurrence. The characteristics of patients with ZOL-related fever (fever group) were compared with those of patients without ZOL-related fever (non-fever group) by using the Mann-Whitney test and Fisher's exact test for numerical and categorized data, respectively. The OS and the time to first SRE were assessed using the Kaplan-Meier method and compared using the log-rank test. Multivariate testing was performed using Cox regression analysis with adjustments for factors that tended to be associated with OS (P<0.3), such as smoking history, histological type, *EGFR* mutation status, PS, and ZOL-related fever.

P<0.05 was considered statistically significant. Statistical analyses were performed using PASW Statistics 19 (IBM SPSS Statistics, Somers, NY, USA).

Results

A total of 62 patients with advanced or recurrent NSCLC who were administered ZOL therapy were screened. Of these, 16 patients were excluded because of the lack of data concerning ZOL-related fever, and 46 patients were included in this retrospective study. The median follow-up time of patients was 15.7 months (range, 4.2-107.3 months). The patient characteristics for all 46 patients are listed in Table I. The age of patients ranged from 47 to 86 years (median age, 65 years), with 30 (63.2%) men. Of the 46 patients, 37 (80.4%) had non-squamous cell carcinomas (non-Sq) (adenocarcinoma; n=36, large cell carcinoma; n=1), and 6 had Sq. Thirty-seven (80.4%) patients had stage IV disease, and 7 (15.2%) had stage IIIB disease. The remaining 2 (4.3%) patients had recurrent disease after surgery. *EGFR* mutation status was tested in 39 of the 46 patients and was positive in 16 (34.8%) patients. Seven patients had unknown *EGFR* mutation status, and all of these 7 patients were diagnosed with Sq (n=6) or large cell carcinoma (n=1). All 16 patients harboring *EGFR* mutations received EGFR-tyrosine kinase inhibitors at least once. Twenty-nine patients (80.5%) were former or current smokers.

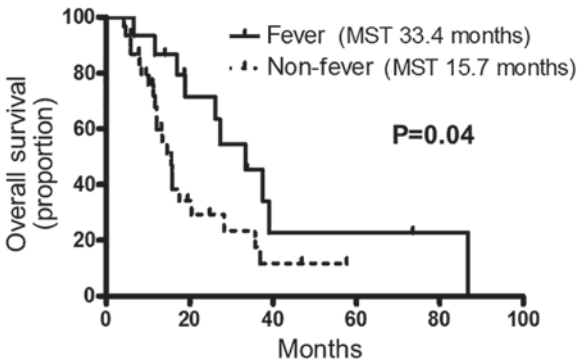

Figure 1. Kaplan-Meier curves of overall survival in the fever (n=15) and non-fever groups (n=31). MST, median survival time.

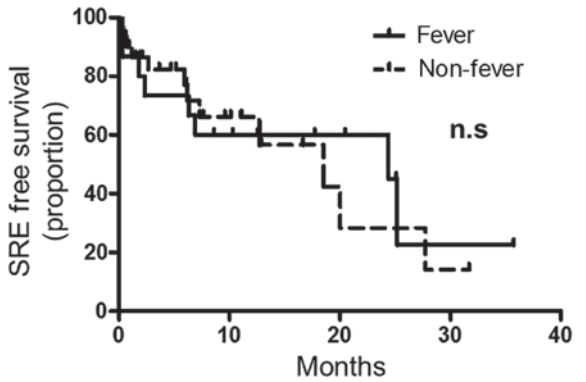

Figure 2. Kaplan-Meier curves of the time to first skeletal-related events in the fever (n=15) and non-fever groups (n=31). n.s., not significant.

Patient characteristics including age, sex, *EGFR* mutation status, ECOG-PS, and smoking history were compared between the two groups (Table I). Compared with patients in the non-fever group, the patients in the fever group tended to be younger (median age, 62 vs. 66 years) and female (53.3 vs. 29.0%), with a higher prevalence of ECOG-PS score 0 (33.3 vs. 16.1%), but these differences were not significant.

Of the 46 patients, 15 (32.6%) experienced ZOL-related fever after the first ZOL administration. To elucidate whether ZOL-related fever was associated with clinical outcome, we compared OS and time to the first SRE between the two groups. As shown in Fig. 1, the OS of fever group was significantly longer than that of the non-fever group (median survival time: 33.4 vs. 15.7 months, P=0.04) with a hazard ratio (HR) [95% confidence interval (CI)] of 0.46 (0.22-0.97). In addition, the median time to first SRE was 24.4 months in the fever group and 18.5 months in the non-fever group, with no significant difference between the two groups [HR (95% CI) 1.3 (0.91-1.73), P=0.88] (Fig. 2).

Positive *EGFR* mutation status [HR (95% CI) 0.41 (0.20-0.86), P=0.016], non-Sq histology [HR (95% CI) 0.24 (0.07-0.80), P=0.02], no smoking history [HR (95% CI) 0.37 (0.20-0.80), P=0.001], and female sex [HR (95% CI) 0.46 (0.22-0.95), P=0.036] were significantly associated with longer OS (Table II). In addition, multivariate analysis performed to test whether ZOL-related fever was an independent prognostic factor revealed that the presence of ZOL-related fever [HR (95% CI) 0.37 (0.16-0.83), P=0.02] and the absence of smoking

Table I. Patient characteristics.

Characteristics	Total	Fever	Non-fever	P-value
No. of patients	46	15	31	
Age in years, median (range)	65 (47-86)	62 (47-78)	66 (48-86)	0.13
Sex				0.33
Female	16 (34.8%)	7 (46.7%)	9 (29.0%)	
Male	30 (63.2%)	8 (53.3%)	22 (71.0%)	
Disease stage				0.69
IIIB	7 (15.2%)	3 (20%)	4 (12.9%)	
IV	37 (80.4%)	11 (73.3%)	26 (83.9%)	
Recurrent	2 (4.3%)	1 (6.7%)	1 (3.2%)	
Histological type				0.45
Squamous cell carcinoma	9 (19.6%)	4 (26.7%)	5 (16.1%)	
Non-squamous cell carcinoma	37 (80.4%)	11 (73.3%)	26 (83.9%)	
EGFR mutation status				0.74
Positive	16 (34.8%)	6 (40%)	10 (32.2%)	
Negative or unknown	30 (65.2%)	9 (60%)	21 (67.8%)	
ECOG-PS score				0.26
0	17 (37.0%)	5 (33.3%)	5 (16.1%)	
1	29 (63.0%)	10 (66.7%)	26 (83.9%)	
Smoking history				0.52
Never smoker	10 (21.7%)	7 (46.7%)	10 (32.2%)	
Former or current smoker	36 (78.3%)	8 (53.3%)	21 (67.8%)	

ECOG-PS, Eastern Cooperative Oncology Group-performance status; EGFR, epidermal growth factor receptor.

Table II. Univariate and multivariate analyses of overall survival.

	Univariate analysis			Multivariate analysis		
Variable	HR	95% CI	P-value	HR	95% CI	P-value
Age (>70 vs. ≤70 years)	1.4	0.62-3.2	0.42	-	-	-
ECOG-PS score (0 vs. 1)	0.88	0.4-2.1	0.79	-	-	-
Sex (female vs. male)	0.46	0.22-0.95	0.04	0.27	0.04-1.64	0.16
Histology (non-Sq vs. Sq)	0.24	0.07-0.80	0.02	0.44	0.15-1.2	0.12
EGFR mutation status (positive vs. negative or unknown)	0.41	0.20-0.86	0.02	0.44	0.18-1.1	0.08
Smoking history (never smoker vs. former or current smoker)	0.37	0.20-0.80	<0.01	0.13	0.20-0.85	0.03
The presence of ZOL-related fever (yes vs. no)	0.46	0.22-0.97	0.04	0.37	0.16-0.83	0.02

CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group-performance status; EGFR, epidermal growth factor receptor; HR, hazard ratio; Sq, squamous cell carcinomas; ZOL, zoledronate.

history [HR (95% CI) 0.13 (0.20-0.85), P=0.03] were significant independent prognostic factors (Table II). The presence of *EGFR* mutation tended to be associated with better OS [HR (95% CI) 0.44 (0.15-1.2), P=0.12], although this finding was not statistically significant.

Discussion

In the present study, we compared the characteristics of patients in the fever group with those of patients in the non-fever group in order to identify predictors of ZOL-related fever. Reid *et al*

reported that young age and female sex are predictors of the development of fever after ZOL administration in patients with osteoporosis (11). In our study, although patients in the fever group tended to be younger than those in the non-fever group, with a greater percentage of women, these differences were not significant. Further large-scale studies are necessary to confirm whether such characteristics are predictors of ZOL-related fever in patients with cancer.

We compared the OS between the fever group and non-fever group in NSCLC patients treated with ZOL. Although there were no significant differences in patient characteristics between the two groups, the OS in the fever group was significantly longer than that in the non-fever group. This indicates that ZOL-related fever is an important prognostic indicator in advanced or recurrent NSCLC patients with bone metastases. To the best of our knowledge, this is the first report of an association between ZOL-related fever and clinical outcome in patients with cancer. As the time to the first SRE was not significantly different between the two groups, the difference in OS between the two groups is likely not attributable to the preventive effect of ZOL on SREs.

In addition to ZOL-related fever, a positive *EGFR* mutation status, non-Sq histology, no smoking history, and female sex were significantly associated with longer OS. These characteristics are known prognostic factors in patients with NSCLC, and are strongly associated with the presence of *EGFR* mutation (12-14). Owing to the emergence of EGFR tyrosine kinase inhibitors, the survival of NSCLC patients with *EGFR* mutation is better than that of patients without *EGFR* mutation (13). We performed multivariate analyses to exclude confounding influences, and the results revealed that ZOL-related fever is independently associated with better OS in advanced NSCLC patients with bone metastases.

Two hypotheses may explain the association between ZOL-related fever and improved OS. First, patients in the fever group may have superior immunocompetence than those in the non-fever group, resulting in better prognosis, and ZOL administration results in the development of fever depending on the immunocompetence of the patient. In other words, ZOL-related fever is a prognostic factor regardless of any beneficial clinical effects of ZOL. Second, patients in the fever group alone may benefit from favorable effects of ZOL other than SRE inhibition. Thus, ZOL-related fever is a predictive factor for an undefined, survival-promoting effect of ZOL.

ZOL-related fever is associated with the activation of γδ T cells, which recognize non-peptide antigens in a major histocompatibility complex-unrestricted manner (15). γδ T cells have demonstrated cytotoxicity against a variety of cell lines *in vitro*, including peripheral blood mononuclear cells from patients with NSCLC (16). Immunotherapies utilizing γδ T cells are currently under development and have been shown to be safe and feasible (17-19). Such therapies could offer invaluable alternatives for cancer treatment in the future. Thus, it is possible that ZOL-related fever is a predictive factor for an additional survival-improving effect of ZOL, and that γδ T cells were activated to a greater extent by ZOL in the fever group, resulting in the activation of cancer immunity and improved OS. However, further study is necessary to clarify the mechanism by which ZOL prolongs OS and to confirm whether γδ T cells are activated after ZOL administration in the fever group. In this regard, we are conducting a prospective observational study to confirm the reproducibility of the correlation between ZOL-related fever and OS and to clarify the precise mechanism of ZOL-related fever development in patients with advanced NSCLC.

In conclusion, the development of ZOL-related fever was independently correlated with better OS in advanced or recurrent NSCLC patients with bone metastases. ZOL-related fever is a predictive factor for an undefined, survival-promoting effect of ZOL.

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