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Acute-phase reaction induced by zoledronate and its effect on prognosis of patients with advanced non-small cell lung cancer

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ABSTRACT

Objectives: Zoledronate (ZOL) is usually used for prevention of skeletal-related events in cancer patients with bone metastases. The first administration of ZOL is occasionally associated with development of acute-phase reaction (APR), which is due to activation of γδ T cells. ZOL-related APR was associated with better overall survival (OS) of patients with non-small cell lung cancer (NSCLC) in our previous retrospective study. However, it remains to be clarified whether γδ T cells are more activated in patients who experienced ZOL-related APR, and whether γδ T cell activation is involved in prolongation of OS.

Materials and Methods: Twenty-three patients with advanced NSCLC were recruited between 2012 and 2014 in this study. We administered ZOL to participants with standard care. The patient characteristics, change in γδ T cell counts and cytokines, OS, and skeletal-related event-free survival were compared between patients with APR (APR group) and those without APR (non-APR group).

Results: Ten patients (43.5%) experienced a ZOL-related APR. The number of γδ T cells at baseline in the APR group was significantly higher than that in the non-APR group. Serum interleukin-6 and tumor necrosis factor-α in the APR group were significantly increased, but no change in the number of γδ T cells was observed after the first administration of ZOL in both groups. OS in the APR group was significantly longer than that in the non-APR group (median survival time: 23.1 vs. 14.5 months, $p < 0.01$).

Conclusion: We showed that APR is related to higher numbers of γδ T cells at baseline and increased cytokines after the first ZOL administration, but not to proliferative responses of γδ T cells. In addition, better OS was observed in the APR group. Therefore, the number of γδ T cells might be a prognostic marker in patients with NSCLC.

1. 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 result in several unfavorable skeletal-related events (SREs), including bone pain, pathological fractures, spinal cord compression, hypercalcemia, and the need for bone radiation. SREs have a negative effect on the quality of life (QOL) of cancer patients [3]. Zoledronate (ZOL), a nitrogen-containing bisphosphonate (N-BP), has been shown to reduce the incidence of SREs in cancer patients with bone metastases, including lung cancer [4]. In addition, some studies have shown that ZOL provides survival benefits in several types of cancer, including advanced lung cancer [5–7]; however, the significance of ZOL in promoting survival still remains controversial. Many theories and hypotheses have been presented regarding the mechanism of ZOL efficacy, including its direct antitumor activities [8] and

Abbreviations: CI, confidence internal; ECOG-PS, Eastern Cooperative Oncology Group-performance status; EGFR, epidermal growth factor receptor; HR, hazard ratio; N-BPs, nitrogen-containing bisphosphonates; NSCLC, non-small cell lung cancer; OS, overall survival; QOL, quality of life; SREs, skeletal-related events; ZOL, zoledronate; IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridization; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; ELISA, enzyme-linked immunosorbent assay; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; MST, median survival time; IPP, isopentenyl pyrophosphate; PD-1, programmed death-1; PD-L1, programmed death-ligand 1

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activation of γδ T cells, which are a small subset of T lymphocytes [9]. γδ T cells recognize non-peptide antigens in a major histocompatibility complex (MHC)-unrestricted manner, and play an active role, as components of innate immunity, in immunosurveillance against tumors as well as infections [10]. The first administration of ZOL is occasionally associated with the development of acute-phase reaction (APR), such as the development of fever. APR is reportedly due to the activation of γδ T cells [11], resulting in the release of interferon (IFN)- γ, interleukin (IL)-6, and tumor necrosis factor (TNF)-α [12]. We and Sunaga et al. reported that ZOL-related fever is associated with better overall survival (OS) in patients with advanced lung cancer [13,14]; however, it still remains to be clarified whether γδ T cells are more activated in patients who are experiencing ZOL-related APR, and whether γδ T cell activation is involved in the mechanism by which ZOL prolongs OS in patients with lung cancer.

We conducted a prospective study to investigate γδ T cell activation after the first ZOL administration and to clarify the association between ZOL-related APR and OS in patients with advanced non-small cell lung cancer (NSCLC).

2. Patients and methods

This study was a single institutional prospective observational study to investigate the change in γδ T cell activity by analyzing the number of γδ T cells in peripheral blood, as well as serum cytokines (IL-6 and TNF-α) that are released by stimulated γδ T cells before and after the first ZOL administration. The secondary objective of this study was to explore the predictive factors for APR, and to clarify the effect of APR on OS in patients with advanced NSCLC.

Participants were recruited at Tottori University Hospital in Japan, between August 2012 and August 2014. This study had ethical approval from the Institutional Review Board of Tottori University, and written informed consent was obtained from participants. We determined that a sample size of 24 would provide a power of 0.7 to reject the null hypothesis of no significant difference in the duration of OS between the two groups. This was based on an assumption of a ZOL-related APR hazard ratio of 0.35, which was observed in our previous retrospective study [13] with a two-sided p-value of 0.05, indicating statistical significance. Assuming that 10% of patients would withdraw during the study, we enrolled 26 patients in this study.

Eligible patients were 18 years of age or older with histologically or cytologically confirmed NSCLC and harboring bone metastases. All eligible patients were required to have an Eastern Cooperative Oncology Group-performance status (ECOG- PS) of 0–2 and adequate bone marrow reserve (leukocyte count > 3000 cells/μL, hemoglobin > 9.0 g/dL, and platelet count of > 10,000 /μL), renal function (creatinine < 1.5 mg/dL), and hepatic function (serum bilirubin < 1.5 mg/dL).

Patients were not eligible if they had uncontrolled symptomatic brain metastases, malignant pleuritis, malignant pericarditis, or an estimated life expectancy of ≤ 3 months.

We administered 4 mg of ZOL every 3 weeks to participants unless unacceptable side effects appeared, informed consent was withdrawn, or SREs occurred despite ZOL treatment. If SREs occurred during ZOL treatment, we proposed administering 120 mg of denosumab every 4 weeks as an alternative bone modifying drug.

Peripheral blood was obtained three times (before, 24–48 h after and 3–4 weeks after the first ZOL administration). The change in the number of γδ T cells was evaluated using the blood obtained before and 3 – 4 weeks after treatment. The change in IL-6 and TNF-α was evaluated by enzyme-linked immunosorbent assay (ELISA, R&D Systems. Minneapolis, MN, USA) using serum obtained before and 24 – 48 h after the first ZOL treatment.

The common manifestations of APR are flu-like symptoms (fever, arthralgia, muscle pain) or bone pain; the onset of APR is known to peak within 2 days after ZOL infusion and is short-lived [15]. Therefore, we defined APR as fever (> 37.5 ˚C), arthralgia, muscle pain, or bone pain that occurred within 2 days after the first ZOL administration, which did not persist for > 2 days.

Baseline characteristics, including age, sex, histology, smoking status, disease stage, ECOG-PS, driver oncogene, and the line of chemotherapy performed were collected.The patient characteristics, change in the number of γδ T cells and cytokines, OS, and SRE-free survival were compared between patients with APR (APR group) and those without APR (non-APR group).

The baseline characteristics were compared between the APR and non-APR groups using the Mann-Whitney test and Fisher's exact test for numerical and categorized data, respectively. Multiple regression analysis was used to explore the independent predictive factors for APR. The OS and SRE-free survival time were assessed using the Kaplan-Meier method and compared using the log-rank test. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using PASW Statistics 19 (IBM SPSS Statistics Somers, NY, USA).

3. Results

A total of 26 consecutive patients were enrolled between August 2012 and August 2014 in this study. Of these, 2 patients withdrew their consent and one patient was ineligible because he had small cell lung carcinoma. Of all patients originally enrolled, 23 were included in the analyses of this study.

The median follow-up time of patients was 15.8 months (range, 1.6–36.9 months). At data cut off, 20 of the 23 patients died of the disease, and 11 patients (48.8%) experienced SREs. The characteristics of all 23 patients are listed in Table 1. The ages of patients ranged from 38 to 84 years (median, 66 years), and 16 patients were men (69.6%). Of all 23 patients, 20 (87.0%) had adenocarcinoma, 2 (8.7%) had large cell carcinoma, and one patient (4.3%) had pleomorphic carcinoma. Twenty-one (91.3%) of patients had stage IV disease, and 2 (8.7%) had recurrent disease after surgery. Seventeen patients (73.9%) were smokers [current; n = 3 (13.0%), former; n = 14 (60.9%)], and 6 patients (26.1%) never smoked. The scores of ECOG-PS were 0–1 in 17 patients (73.9%) and 2 in 6 patients (26.1%). The epidermal growth factor receptor (*EGFR*) mutation status was tested in all patients, and 13 out of 23 (56.5%) were positive. In the 10 patients with wild type *EGFR*, the anaplastic lymphoma kinase (*ALK*) fusion gene was also tested by immunohistochemistry (IHC) or fluorescence *in situ* hybridization (FISH),

Table 1
Patient characteristics of all participants.

Patient characteristics (n = 23)	
Age, median (range)	66 (38 – 84)
sex	16 (69.6 %)
male	7 (20.4 %)
female	
histology	
adenocarcinoma	20 (87.0 %)
large cell carcinoma	2 (8.7 %)
pleomorphic carcinoma	1 (4.3 %)
Stage	
IV	21 (91.3 %)
Recurrent	2 (8.7 %)
Smoke	
Never	6 (26.1 %)
Former	14 (60.9 %)
current	3 (13.0 %)
ECOG-PS	
0–1	17 (73.9 %)
2	6 (26.1 %)
Driver oncogene	
EGFR mutation	13 (56.5 %)
ALK fusion	0
none	10 (43.5 %)