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Non-small Cell Lung Cancer Patients with *EML4-ALK* Fusion Gene Are Insensitive to Cytotoxic Chemotherapy

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Abstract. *Background: Although patients with the echinoderm microtubule-associated protein-like 4–anaplastic lymphoma kinase gene (EML4-ALK) re-arrangement and epidermal growth factor gene EGFR mutations have proven sensitive to specific inhibitors, there is currently no consensus regarding the sensitivity of non-small cell lung cancer (NSCLC) patients with such mutations to cytotoxic chemotherapy. Patients and Methods: The responses to first-line cytotoxic chemotherapy were retrospectively compared between advanced or postoperative recurrent patients with non-squamous NSCLC who harbor the EML4-ALK fusion gene (ALK^+), EGFR mutation ($EGFR^+$), or neither abnormality (wild-type). Results: Data for 22 ALK^+, 30 $EGFR^+$, and 60 wild-type patients were analyzed. The ALK^+ group had a significantly lower response rate than the other two groups. Progression-free survival was significantly shorter in the ALK^+ cohort compared to the $EGFR^+$ ($p<0.001$) and wild-type cohorts ($p=0.0121$). Conclusion: NSCLC patients with the EML4-ALK fusion gene might be relatively insensitivite to cytotoxic chemotherapy.*

Lung cancer is one of the most common causes of death worldwide (1). Non-small cell lung cancer (NSCLC) is the most prevalent histological type, accounting for almost 80% of all lung neoplasms. Its refractoriness to chemotherapy means that little major progress has been made in the treatment of advanced or recurrent NSCLC until recently, though the discovery of driver mutations is now changing the conventional treatment.

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Somatic mutations in the epidermal growth factor receptor gene (*EGFR*) have been shown to correlate with clinical response to the tyrosine kinase inhibitor (TKI), gefitinib (2). The results of randomized phase III studies indicated that progression-free survival (PFS) was significantly longer in patients who received gefitinib compared to those who received cytotoxic chemotherapy (3, 4). The echinoderm microtubule-associated protein-like 4–anaplastic lymphoma kinase (*EML4-ALK*) fusion gene was identified in NSCLC in 2007 (5), since then small-molecule inhibitors targeting *EML4-ALK* have been developed and have shown impressive efficacy in patients with lung adenocarcinomas harboring the *EML4-ALK* fusion gene (6).

In this context, it is becoming increasingly important to consider the genetic status, such as *EGFR* mutations and *EML4-ALK* rearrangements, when selecting chemotherapies for NSCLC. Cisplatin-containing regimens are still important to the treatment of postoperative-recurrent or advanced NSCLC, though the sensitivity of NSCLCs with gene mutations to such cytotoxic chemotherapies remains unclear. Some studies (7-9) have investigated the response of NSCLC patients with *EGFR* mutations or the *EML4-ALK* fusion gene to cytotoxic chemotherapy, but the results remain controversial. The present study aimed to evaluate the efficacy of cytotoxic chemotherapy in NSCLC with driver-gene mutations.

Patients and Methods

This retrospective study enrolled 428 patients with advanced or recurrent non-squamous NSCLC treated with first-line cytotoxic chemotherapy, excluding patients treated with molecular-targeted drugs such as EGFR-TKIs or ALK inhibitors, at the Kyushu Cancer Center between April 2009 and March 2012. Only patients who met the following inclusion criteria were registered: (i) screened for both *EGFR* mutation and *EML4-ALK* fusion gene status; (ii) not treated with any investigational drug and not registered on any other clinical study as first-line chemotherapy (Figure 1). Patients were classified into three groups: patients with the *EML4-ALK* fusion gene but

without *EGFR* mutation (*ALK*$^+$); patients with EGFR mutation but without EML4-ALK fusion gene (*EGFR*$^+$); patients with neither *EML4-ALK* fusion gene nor *EGFR* mutation (wild-type). Written informed consent was obtained from all patients and the study was approved by the hospital ethics committee. The present study also conformed to the provisions of the Declaration of Helsinki.

Detection of EGFR mutations and EML4-ALK rearrangements. Tumor specimens were grossly dissected by a pathologist. Genomic DNA was extracted and purified from formalin-fixed paraffin-embedded tissues. *EGFR* mutations were detected using the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method (10). *ALK* re-arrangements, were detected by fluorescence *in situ* hybridization, immunohistochemistry or reverse transcription-polymerase chain reaction, according to previous reports (11).

Treatment response. Imaging studies, including chest computed tomography scans, were performed after every two cycles of treatment (or sooner if needed) to evaluate response and document disease progression. Responses were classified according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Treatment response was defined as the best response recorded during the period from the start of treatment to the time of disease progression or treatment discontinuation. Treatment responses were evaluated according to RECIST, and were defined as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD).

Statistical analysis. Associations among clinical characteristics and treatment responses between two subgroups were analyzed by χ^2 or Fisher's exact tests. PFS was defined as the time elapsed between treatment initiation and tumor progression or death from any cause, and was calculated using the Kaplan–Meier method. The log-rank test was used to obtain *p*-values for univariate survival analysis, with appropriate adjustment for multiplicity. A *p*-value <0.05 was considered statistically significant. Statistical analysis was performed using JMP pro 9.0 (SAS Institute INC., Cary, NC, USA).

Results

Patients' characteristics. The demographic and clinical characteristics of patients are summarized in Table I. The median age of the patients at study entry was 58.5 years (range, 27-75 years). The majority of patients were female (64.3%), had a performance status of 0 (76.7%), had adenocarcinoma (96.4%), were a current or former smoker (60.7%), and had clinical stage IV disease (79.5%). *ALK*$^+$ patients (median age, 53 years) were significantly younger than *EGFR*$^+$ (median age, 65 years; $p<0.001$) and wild-type patients (median age, 61 years; $p<0.001$). No patients had both an *EGFR* mutation and *EML4-ALK* rearrangement. Genetic status was strongly related to smoking history ($p<0.001$) and sex ($p=0.0109$).

Clinical response to cytotoxic chemotherapy according to genetic subtype of NSCLC. Treatment response was evaluated in all patients (Table II). Out of the 112 patients who met the inclusion criteria and were analyzed, none (0%) had CR, 47 patients (42.0%) had PR, 39 (34.8%) had SD and 26 (23.2%) had PD. The overall response rate (RR) was 42.0% (95% confidence interval (CI)= 33.6-51.6%). The RRs in the three cohorts were 18.1% in the *ALK*$^+$ cohort, 53.3% in the *EGFR*$^+$, and 45.0% in the wild-type cohort. The RR in the *ALK*$^+$ cohort was significantly lower than in the other two cohorts ($p=0.0198$ for *EGFR*$^+$ cohort, $p=0.0225$ for wild-type cohort), but there was no significant difference in RR between the *EGFR*$^+$ and wild-type cohorts. There were no patients in the *EGFR*$^+$ cohort with PD.

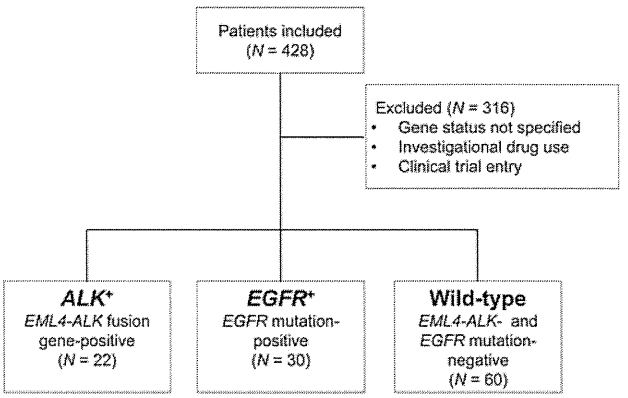

Figure 1. *Criteria for patient selection. Patients were grouped into three cohorts according to genetic status.*

We also analyzed the correlation between chemotherapy regimen and clinical response (Figure 2). We classified the different types of chemotherapy and evaluated the influence of genetic status on sensitivity to cytotoxic chemotherapy according to the presence and type of gene abnormalities. Chemotherapy was classified into platinum doublet, platinum doublet-plus-bevacizumab, and others. 'Others' included patients who were treated by single-agent therapy, including three patients treated with docetaxel and three with pemetrexed. The combination of platinum doublet and bevacizumab achieved relatively good responses among patients in the *EGFR*$^+$ and wild-type cohorts, while relatively few *ALK*$^+$ patients achieved a partial response.

Some studies have suggested that the *ALK* fusion gene is a sensitivity biomarker for pemetrexed (12, 13), and pemetrexed-containing regimens were thus analyzed in detail in this cohort (Figure 3). However, only 22% of patients in the *ALK*$^+$ cohort achieved a partial response with a pemetrexed-containing regimen, which was still lower than in the other cohorts. There was no significant difference in response to pemetrexed-containing regimens between the *ALK*$^+$ and wild-type cohorts ($p=0.438$).

Analysis of PFS according to genetic status. PFS curves of sub-groups according to genetic status are shown in Figure 4.

Table I. *Characteristics and patients' genetic statuses.*

Variable	Total (N=112)	*ALK*+ (N=22)	*EGFR*+ (N=30)	Wild (N=60)	
Gender					
Male	40 (35.7%)	8 (36.4%)	11 (36.7%)	39 (65.0%)	p=0.0109
Female	72 (64.3%)	14 (63.6%)	19 (63.3%)	21 (35.0%)	
Age	58.5 (27-75)	53 (27-70)	65 (39-75)	61 (28-75)	p<0.001
Performance status					
0	86 (76.7%)	15 (68.2%)	21 (70.0%)	50 (83.3%)	p=0.4900
1	22 (19.6%)	6 (27.3%)	8 (36.4%)	8 (13.3%)	
2	4 (3.6%)	1 (4.5%)	1 (5.0%)	2 (3.3%)	
Histology					
Adenocarcinoma	108 (96.4%)	22 (100%)	29 (96.7%)	57 (98.0%)	p=0.5556
Non-adenocarcinoma	4 (3.8%)	0 (0%)	1 (3.3%)	3 (5.0%)	
Smoking history					
Never	44 (39.3%)	15 (68.2%)	17 (56.7%)	12 (20.0%)	p<0.001
Current or Former	68 (60.7%)	7 (31.8%)	13 (43.3%)	48 (80.0%)	
Clinical Stage					
IIIA	4 (3.5%)	2 (9.1%)	1 (3.3%)	1 (1.67%)	p<0.001
IIIB	3 (2.7%)	0 (0%)	0 (0%)	3 (5.0%)	
IV	89 (79.5%)	14 (63.5%)	29 (95.6%)	46 (76.7%)	
Recurrence*	16 (14.3%)	6 (27.3%)	0 (0%)	10 (16.7%)	

*Postoperative recurrence.

Table II. *Clinical response to first-line chemotherapy according to genetic status.*

Response	Total	*ALK*+	*EGFR*+	Wild
CR	0	0	0	0
PR	47 (42.0%)	4 (31.8%)	16 (53.3%)	27 (45.0%)
SD	39 (34.8%)	7 (31.8%)	14 (46.7%)	18 (30.0%)
PD	26 (23.2%)	11 (50%)	0	15 (25.0%)

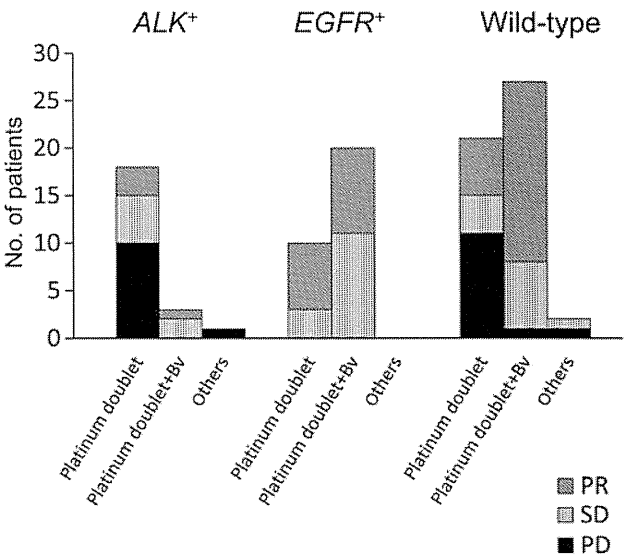

Figure 2. *First-line chemotherapy regimens and best responses among the three cohorts. Vertical axis indicates number of patients. Bv, bevacizumab.*

The median PFS times were 105 days for the *ALK*+ cohort (95%CI=57-161 days), 154 days for the wild-type cohort (95%CI=101-227 days) and 186 days for the *EGFR*+ cohort (95%CI=149-330 days) after a median follow-up period of 173.1 days (range=11-768 days). PFS was significantly shorter in the *ALK*+ cohort compared with the wild-type (p=0.0121) and *EGFR*+ cohorts (p<0.001). There was no significant difference between the wild-type and *EGFR*+ cohorts according to survival analysis, though PFS tended to be higher in the *EGFR*+ cohort compared with the wild-type cohort (p=0.091) (Figure 4).

Discussion

We investigated the efficacy of cytotoxic chemotherapy in patients with NSCLC with driver-gene mutations, including *EGFR* mutations and *EML4-ALK* gene fusion. The results suggest that NSCLC patients with the *EML4-ALK* fusion gene may be more resistant to conventional cytotoxic chemotherapy than those with *EGFR* mutations or with neither abnormality, while patients with *EGFR* mutations showed a relatively good response to cytotoxic chemotherapy. In contrast to the results of a previous report, NCSLC patients with the *EML4-ALK* fusion gene did not have a better response to pemetrexed than other cohorts.

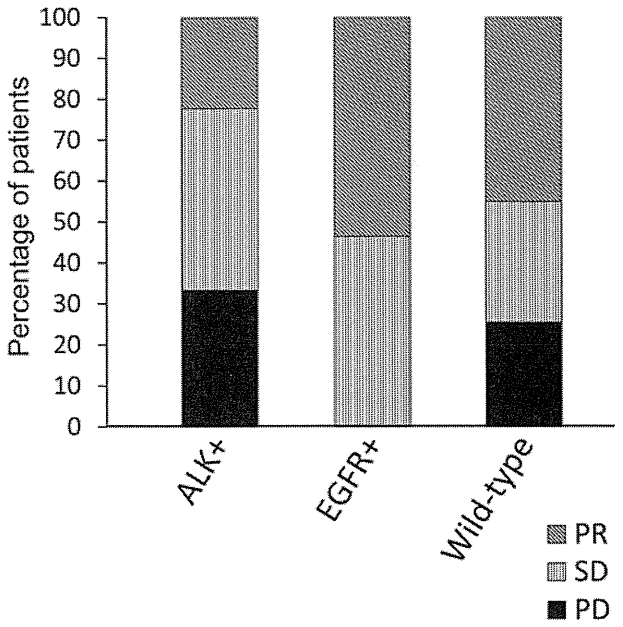

Figure 3. *Proportion of best response to pemetrexed. Data for pemetrexed-containing regimens were extracted from Figure 2 and re-analyzed in terms of sensitivity.*

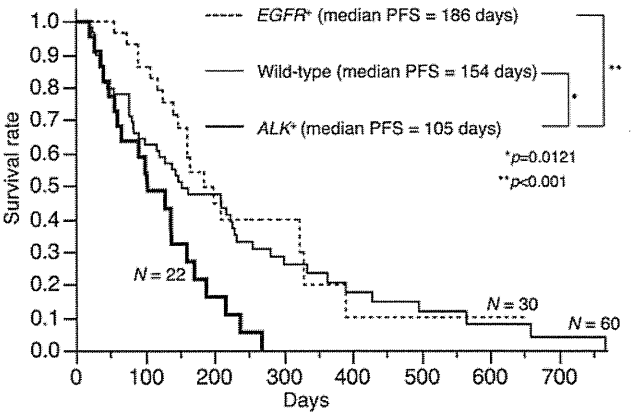

Figure 4. *Kaplan–Meier survival curve of progression-free survival (PFS) for patients in the three cohorts. The thick line indicates ALK+ cohort, thin line indicates wild-type cohort, broken line indicates EGFR+ cohort.*

Our data suggest that patients with the *EML4-ALK* fusion gene show increased resistance to cytotoxic chemotherapy, which may translate into a poor prognosis for NSCLC patients harboring this re-arrangement. Recent reports have indicated an association between NSCLC prognosis and the *ALK* fusion gene. Although different opinions have been expressed (14), the *ALK* rearrangement is generally thought to be associated with a poorer prognosis (8, 15).

Our current results suggest the existence of a relationship between driver-gene mutation and chemosensitivity. Previous studies have reported that *EGFR* mutation status could be a biomarker of response to cytotoxic chemotherapy (7, 16, 17), as is suggested by the tendency identified in our study. However, our results demonstrated that *ALK*$^+$ NSCLC was more resistant to cytotoxic chemotherapy than *EGFR*$^+$ and wild-type tumors. This is in contrast to the results of Takeda *et al.* (9), who found similar overall survival rates in wild-type and *ALK*$^+$ NSCLC patients in terms of first-line chemotherapy, or those of Lee *et al.* (8), who found no differences in PFS after first-line chemotherapy, irrespective of genetic status. There are several possible explanations for these discrepancies. These studies, including the present one, were subject to limitations, such as a retrospective design, single-institution study, small *EML4-ALK* cohort size, or selection bias in that not all patients were examined for *EGFR* and *EML4-ALK* gene status. Moreover, the different outcomes may have been attributable to effects of *EML4-ALK* variants or racial variation on sensitivity to cytotoxic chemotherapy. More recently, Shaw *et al.* reported a RR of only 7% with docetaxel in second-line chemotherapy in *ALK*$^+$ patients (18), indicating the refractory nature of *ALK*$^+$ cancer. However, the effects of the *EML4-ALK* fusion gene on the response of patients with NSCLC to cytotoxic chemotherapy remain controversial, and further prospective studies or meta-analyses are needed to clarify the predictive value of gene mutation status for cytotoxic chemotherapy.

The mechanism responsible for the relationship between *EML4-ALK* and chemosensitivity remains unclear. Some studies have reported that the *EML4-ALK* fusion gene was predictive of a favorable response to pemetrexed in NSCLC (12, 13). They suggested that the increase in sensitivity to pemetrexed was the result of activation of the folate-pathway enzyme 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/inosine monophosphate cyclohydrolase, and inhibition of the DNA-synthesis enzyme thymidylate synthase, rendering *ALK*$^+$ carcinoma more sensitive to pemetrexed (12, 18, 19), in contrast with the results of the current study. This discrepancy could be caused by differences among *ALK* variants in terms of their effects on sensitivity to cytotoxic chemotherapy. Heuckmann *et al.* showed that different *ALK* fusion variants had different protein stabilities, with consequent effects on sensitivity to *ALK* inhibitors (20). It is possible that this phenomenon could also impact on the effects of cytotoxic chemotherapy. Further basic studies are required to investigate these speculations.

Despite the need for further studies, the current results suggest that gene-mutation status should be considered when choosing for an appropriate chemotherapeutic regimen in patients with NSCLC. Yamashita *et al.* and Kalikaki *et al.*

reported that NSCLC patients with EGFR mutations were sensitive to chemotherapy (17, 21). The result of the NEJ002 study might thus infer that NSCLC patients with *EGFR* mutations could be treated with EGFR-TKIs after cytotoxic chemotherapy (22). In contrast, if NSCLC patients with *ALK* rearrangements are resistant to cytotoxic chemotherapy, as suggested by our results, they might progress during the course of first-line chemotherapy, and could thus miss the opportunity to be treated with ALK inhibitors. Shaw *et al.* (23) reported that *EML4-ALK*$^+$ patients treated with the ALK inhibitor crizotinib had a more favorable prognosis than those without crizotinib. The administration of cytotoxic agents as first-line chemotherapy should, therefore, be carefully planned and discussed in patients with NSCLC with *EML4-ALK* rearrangements.

In conclusion, through the present study we report an association between the *EML4-ALK* fusion gene and insensitivity to cytotoxic chemotherapy in NSCLC. Our results suggest that *EML4-ALK*$^+$ patients might be more insensitive to cytotoxic chemotherapy than patients with *EGFR* mutations or those with neither abnormality. *EML4-ALK* re-arrangement and *EGFR*-mutation status might be useful predictive biomarkers for the efficacy of cytotoxic chemotherapy.

Conflicts of Interest

The Authors have declared no conflicts of interest.

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Phase II study of zoledronic acid combined with docetaxel for non-small-cell lung cancer: West Japan Oncology Group

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Key words

Chemotherapy, docetaxel, non-small-cell lung cancer, phase II, zoledronic acid

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The aim of this open-label, multicenter, randomized phase II trial was to evaluate the efficacy and safety of zoledronic acid in combination with docetaxel in previously treated patients with non-small-cell lung cancer (NSCLC) and bone metastases. In this study, patients randomly received docetaxel (60 mg/m^2) with (group DZ) or without (group D) zoledronic acid every 21 days. There were 50 patients in each group, and the primary endpoint was progression-free survival. In an efficacy analysis of 94 patients (DZ, 48; D, 46), the median progression-free survival was 2.7 months (95% confidence interval [CI], 1.5–3.5 months) for the DZ group and 2.6 months (95% CI, 1.5–3.4 months) for the D group (stratified log-rank test, $P = 0.89$). The median overall survival was 10.4 months (95% CI, 7.0–15.8 months) for the DZ group and 9.7 months (95% CI, 6.1–12.5 months) for the D group (stratified log-rank test, $P = 0.62$). There were no clinically relevant differences in the frequencies of grade 3 or 4 adverse events between the two groups. No treatment-related deaths occurred in the DZ group. Zoledronic acid combined with docetaxel was well tolerated but did not meet the primary endpoint of demonstrating a longer progression-free survival in advanced NSCLC patients with bone metastases compared with docetaxel alone. This trial was registered with the University Hospital Medical Information Network (UMIN000001098).

Lung cancer is the leading cause of cancer death worldwide and non–small-cell lung cancer (NSCLC) accounts for more than 80% of all cases of lung cancer.[1] For individuals with advanced NSCLC, first-line treatment with platinum-based chemotherapy offers only a moderate improvement in survival and quality of life over best supportive care (BSC) alone.[2,3] Second-line treatment with docetaxel, despite a low tumor response rate, is a standard treatment option on the basis of phase III studies comparing docetaxel with ifosfamide, vinorelbine or BSC alone.[4,5] Thus, there is a need for new treatment options to prolong the survival of patients with advanced NSCLC. Approximately 30–40% of patients with NSCLC develop bone metastases, which often cause skeletal-related events (SRE) such as pathologic fracture, spinal cord compression, or the need for palliative radiation or surgery to the bone.[6] SRE are associated with decreased quality of life, increased health-care costs and poor survival; therefore, it is clinically imperative to prevent SRE during the treatment of advanced NSCLC.[7–10]

Zoledronic acid, a nitrogen-containing bisphosphonate, significantly delays the appearance of SRE and reduces the incidence of SRE compared with a placebo in patients with cancer and bone metastases, including those with NSCLC.[11,12] Furthermore, several preclinical and clinical studies provide evidence supporting the use of zoledronic acid for the treatment of patients with advanced NSCLC.[13–16] The inclusion of zoledronic acid in chemotherapy regimens has an additive and/or synergistic antitumor effect on NSCLC cell lines and may prolong survival and delay disease progression in patients with advanced NSCLC.[17–19] However, whether the inclusion of zoledronic acid in such regimens has clinically meaningful survival benefits in patients with NSCLC and bone metastases is uncertain. Therefore, we

conducted this study to evaluate the efficacy and safety of zoledronic acid in combination with docetaxel in previously treated patients with NSCLC and bone metastases.

Patients and Methods

Study design. We conducted an open-label, multicenter, randomized phase II study in Japan. The study protocol was approved by the West Japan Oncology Group (WJOG) Protocol Review Committee and the institutional review board of each participating institution. This trial was registered with the University Hospital Medical Information Network (UMIN000001098).

Eligibility criteria. Patients were required to be histologically or cytologically diagnosed with NSCLC and bone metastases (at least one bone metastasis that had not been treated with radiation therapy) and to have had previous treatment with one or two chemotherapy regimens. Other inclusion criteria included an age of ≥20 years, Eastern Cooperative Oncology Group performance status of 0–2, measurable disease, no history of chemotherapy with docetaxel, no history of prior treatment with zoledronic acid, adequate baseline organ function (leukocyte count ≥3500/mm^3; absolute neutrophil count ≥2000 /mm^3; hemoglobin ≥9.0 g/dL; platelet count ≥100 000/mm^3; total bilirubin ≤2.0 mg/dL; aspartate aminotransferase and alanine aminotransferase [ALT] levels ≤100 IU/L; creatinine clearance, ≥30 mL/min; and SpO_2 under room air, ≥90%). Written informed consent was obtained from all patients. Patients were ineligible if they had active concomitant malignancy, third-space fluid collection requiring drainage, radiographic signs of interstitial pneumonia or pulmonary fibrosis, active SRE at the time of registration, hypercalcemia requiring prompt treatment, active periodontal disease or severe comorbidities (active infectious disease, severe heart disease, uncontrolled diabetes mellitus, gastrointestinal bleeding, intestinal paralysis, bowel obstruction or psychiatric disease), or a history of drug allergy. Patients receiving systemic steroid medication and pregnant or breast-feeding women were also excluded.

Treatment. Equal numbers of patients randomly received 60 mg/m^2 docetaxel intravenously for 1 h with (DZ group) or without (D group) intravenous zoledronic acid for 15 min. Random assignment was stratified by institution, gender and performance status (0–1 or 2). The dose of zoledronic acid for each patient was based on his or her creatinine clearance (>60 mL/min, 4 mg; 50–60 mL/min, 3.5 mg; 40–49 mL/min, 3.3 mg; 30–39 mL/min, 3.0 mg). Zoledronic acid was administered to patients in the DZ group immediately after docetaxel administration. Patients were treated every 3 weeks until their disease progressed, toxicity became intolerable or they refused additional treatment. The dose of docetaxel was decreased to 50 mg/m^2 if any of the following was observed: leukocyte count <1000/mm^3, platelet count <25 000/mm^3, grade 3 febrile neutropenia or grade 3 nonhematological toxicity (with the exception of hyponatremia, hypocalcaemia and alopecia). In cases of grade 4 nonhematological toxicity or continued toxicity requiring a second dose reduction, the protocol treatment was terminated. Other criteria for protocol treatment termination included use of excluded concomitant therapy and physician recommendation.

Patients received full supportive care as required, including transfusion of blood products. Granulocyte colony-stimulating factor was administered as needed. There was no restriction on subsequent chemotherapy after disease progression in this study.

Evaluation. Patient assessment, including physical examination, complete blood count and biochemistry, was performed every 1–2 weeks. Bone markers and levels of urinary N-terminal telopeptide of type I collagen (NTX) and serum C-terminal telopeptide of type I collagen (I-CTP) were evaluated every 4 weeks. SRE included pathologic fracture, spinal cord compression and need for palliative radiation or surgery to the bone, and were assessed every 6 weeks.

Patients who received one or more protocol treatment were evaluated for safety during treatment. Adverse events were recorded and graded using the Common Terminology Criteria for Adverse Events, Version 3.0. The Response Evaluation Criteria in Solid Tumors guideline version 1.0 was used to evaluate tumor response.[20] Computed tomography was performed at baseline and every 6 weeks. A complete response (CR) or a partial response (PR) was confirmed at least

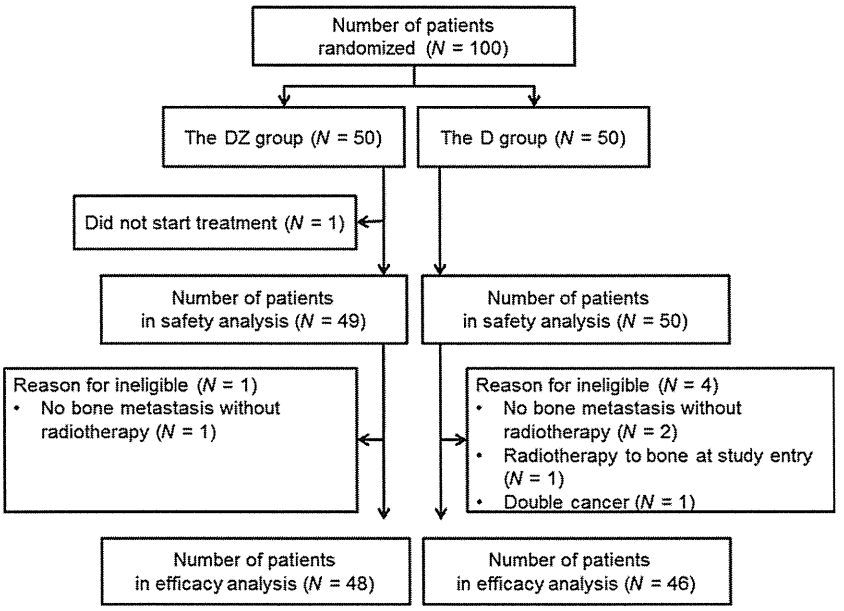

Fig. 1. Patient disposition. D, docetaxel alone; DZ, docetaxel with zoledronic acid.

4 weeks after the first documentation of the response. Stable disease (SD) was defined as either sufficient tumor shrinkage to qualify as a CR or a PR or sufficient increase in tumor mass to qualify as progressive disease (PD) after at least 6 weeks. Progression-free survival (PFS) was defined as the time from patient registration to objective tumor progression or patient death. Patients whose disease had not progressed at the time of termination of protocol treatment were assessed until progression or death was documented. SRE-free survival was defined as the time from patient registration to the appearance of SRE or the death of the patient. Patients who had not experienced SRE at the time of termination of protocol treatment were assessed until SRE or death was documented. Overall survival (OS) was defined as the time from patient registration to death from any cause. All patients were followed up for 1 year after the last patient had enrolled.

Study endpoints and statistical analyses. The primary endpoint in this study was PFS. The secondary endpoints included OS, overall response rate (ORR), SRE rate, SRE-free survival and safety. This randomized phase II study was designed to detect a 1-month improvement in PFS, with an assumed PFS of 2 months in the D group and 3 months in the DZ group, with a two-sided alpha error of 20% and a power of approximately 80%. A total of 100 patients were registered over 2 years with a 1-year follow-up period after the last enrollment. Survival curves were estimated using the Kaplan–Meier method and compared by log-rank test. Fisher's exact test was used for categorical data. All analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics. From May 2007 to March 2010, 100 patients from 15 Japanese institutions were enrolled in this study: 50 patients were randomly assigned to the DZ group and 50 to the D group (Fig. 1). Patient demographics and baseline disease characteristics were well-balanced between the two treatment groups (Table 1). While one patient in the DZ group did not receive any protocol treatment, 99 patients (49 for DZ and 50 for D) were assessable for safety. In the DZ group 1 patient and in the D group 4 patients were ineligible, and 94 patients (48 for DZ and 46 for D) were included in the efficacy analysis (Fig. 1). The median number of treatment cycles was three for the DZ group (range, 1–19 cycles) and three for the D group (range, 1–17 cycles). The median number of administered doses of zoledronic acid was 3 (range, 1–19), with a median drug exposure of 12.0 mg (range, 3.5–76.0 mg). Reasons for going off protocol included disease progression (37 for DZ and 33 for D), patient refusal (eight for DZ and eight for D), unacceptable toxicity (two for DZ and five for D) and others (two for DZ and four for D).

Safety. Adverse events for the 99 patients included in the safety analysis are summarized in Table 2. The occurrence of adverse events was similar in the two groups, with the exception of any grade of hypocalcemia (76% *vs* 30%) and pyrexia (39% *vs* 10%), which were more frequent in the DZ group compared with the D group. One patient in the DZ group experienced periodontal disease, but no cases of osteonecrosis of the jaw (ONJ) were observed in either group. The most common adverse events worse than grade 3 were leukopenia (63% and 56% for DZ and D, respectively), neutropenia (78% and 80% for DZ and D, respectively), febrile neutropenia (4% and 12% for DZ and D, respectively) and elevated ALT level (27% and 30% for DZ and D, respectively). There were no clinically relevant differences in the frequencies of adverse events of grade 3 or higher between the two groups. The protocol treatment was terminated in seven patients because of unacceptable toxicity levels, including grade 3 nail change ($N = 1$) and grade 2 periodontal disease ($N = 1$) in the DZ group, and required a second dose reduction because of grade 4 leukopenia ($N = 1$) or grade 3 febrile neutropenia ($N = 1$), grade 4 infection ($N = 1$), grade 3 allergic reaction ($N = 1$) and grade 1 pneumonitis ($N = 1$) in the D group. No treatment-related deaths were observed in the DZ group, while two treatment-related deaths were observed in the D group (infection, $N = 1$; gastrointestinal perforation, $N = 1$).

Efficacy. For the 94 patients included in the efficacy analysis, the ORR was 8% for the DZ group (CR, $N = 0$; PR, $N = 4$;

Table 1. Patient demographics and baseline disease characteristics

Characteristic	DZ group ($N = 50$)		D group ($N = 50$)	
	Number	%	Number	%
Age, years				
Median	62		63	
Range	34–77		45–79	
Sex				
Female	19	38	18	36
Male	31	62	32	64
ECOG performance status				
0–1	47	94	47	94
2	3	6	3	6
Smoking status				
Smoker	19	38	15	30
Never smoked	31	62	35	70
Histological subtype				
Adenocarcinoma	39	78	38	76
Squamous cell carcinoma	5	10	7	14
Others	6	12	5	10
Number of prior chemotherapies				
1	34	68	39	78
2	15	30	11	22
No data	1	2	0	0
Number of bone metastases				
Single	11	22	12	24
Multiple	39	78	38	76
Prior SRE				
No	41	82	42	84
Yes	8	16	8	16
No data	1	2	0	0
Urinary NTX				
High level (≥64 nmol/mmol creatinine)	20	40	22	44
Normal level (<64 nmol/mmol creatinine)	23	46	22	44
No data	7	14	6	12
Serum I-CTP				
High level (≥4.5 ng/mL)	35	70	35	70
Normal level (<4.5 ng/mL)	8	16	9	18
No data	7	14	6	12

D, docetaxel alone; DZ, docetaxel with zoledronic acid; ECOG, Eastern Cooperative Oncology Group; I-CTP, C-terminal telopeptide of type I collagen; NTX, N-terminal telopeptide of type I collagen; SRE, skeletal-related event.

Table 2. Summary of adverse events (CTCAE)

Adverse event	DZ group (N = 49)				D group (N = 50)			
	All		≥Grade 3		All		≥Grade 3	
	Number	%	Number	%	Number	%	Number	%
Leukopenia	45	92	31	63	47	94	28	56
Neutropenia	45	92	38	78	46	92	40	80
Anemia	33	67	3	6	31	62	3	6
Thrombocytopenia	2	4	0	0	5	10	0	0
Elevated ALT level	24	49	13	27	21	42	15	30
Elevated AST level	19	39	4	8	16	32	3	6
Elevated creatinine level	7	14	1	2	13	26	2	4
Hypercalcemia	2	4	0	0	8	16	1	2
Hypocalcemia	37	76	3	6	15	30	0	0
Febrile neutropenia	2	4	2	4	6	12	6	12
Infection	13	27	5	10	5	10	3	6
Sensory neuropathy	12	24	2	4	11	22	1	2
Fatigue	33	67	2	4	33	66	2	4
Anorexia	30	61	2	4	30	60	1	2
Nausea	20	41	1	2	23	46	0	0
Vomiting	8	16	1	2	8	16	0	0
Allergic reaction	3	6	0	0	2	4	1	2
Gastrointestinal perforation	0	0	0	0	1	2	1	2
Pyrexia	19	39	0	0	5	10	0	0
Periodontal disease	1	2	0	0	0	0	0	0

ALT, alanine transaminase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events, version 3.0; D, docetaxel alone; DZ, docetaxel with zoledronic acid.

SD, N = 18; PD, N = 25; not evaluable, N = 1) and 4% for the D group (CR, N = 0; PR, N = 2; SD, N = 20; PD, N = 23; not evaluable, N = 1). The difference in ORR between the two groups was not statistically significant (P = 0.88). Median PFS was 2.7 (95% CI, 1.5–3.5) months for the DZ group and 2.6 (95% CI, 1.5–3.4) months for the D group (stratified log-rank test, P = 0.89; Fig. 2a). Median OS was 10.4 (95% CI, 7.0–15.8) months for the DZ group and 9.7 (95% CI, 6.1–12.5) months for the D group (stratified log-rank test, P = 0.62; Fig. 2b). No remarkable difference in PFS (Fig. 3a) or OS (Fig. 3b) was observed according to demographic characteristics (number of bone metastases, prior SRE, baseline urinary NTX and baseline serum I-CTP).

For the 94 patients included in the efficacy analysis, the cumulative incidence rates of an SRE at 3, 6, 9 and 12 months were 17%, 20%, 27% and 30%, respectively, for the DZ group, and 16%, 27%, 39% and 39%, respectively, for the D group (Fig. 4a). Median SRE-free survival was 7.2 (95% CI, 4.9–10.7) months for the DZ group and 6.0 (95% CI, 4.4–8.5) months for the D group (stratified log-rank test, P = 0.84). In subset analyses of the SRE rate according to baseline bone marker levels (Fig. 4b), the cumulative incidence rates of SRE at 12 months were 44% for the DZ group (N = 19) and 48% for the D group (N = 19) in patients with high baseline urinary NTX levels, 24% for the DZ group (N = 29) and 30% for the D group (N = 27) in patients with normal or unknown baseline urinary NTX levels, 43% for the DZ group (N = 34) and 38% for the D group (N = 32) in patients with high baseline serum I-CTP levels, and 7% for the DZ group (N = 14) and 37% for the D group (N = 14) in patients with normal or unknown baseline serum I-CTP levels.

Discussion

This is the first prospective, randomized, phase II study to evaluate the efficacy and safety of zoledronic acid in combination with docetaxel in previously treated advanced NSCLC

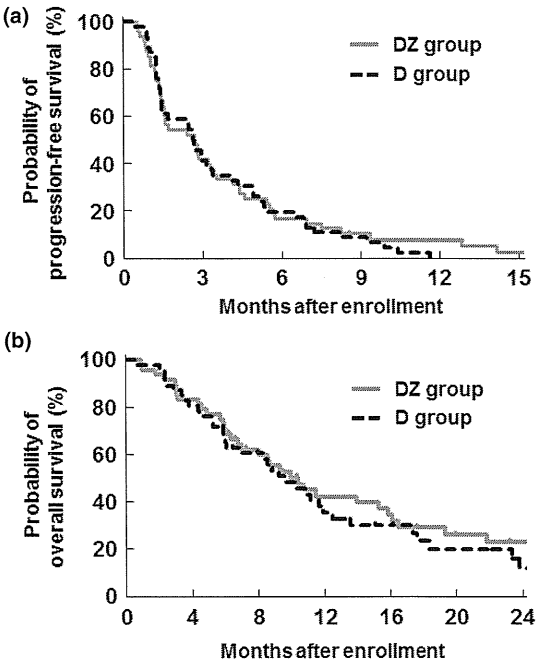

Fig. 2. (a) Progression-free survival and (b) overall survival in the DZ and D groups. D, docetaxel alone; DZ, docetaxel with zoledronic acid.

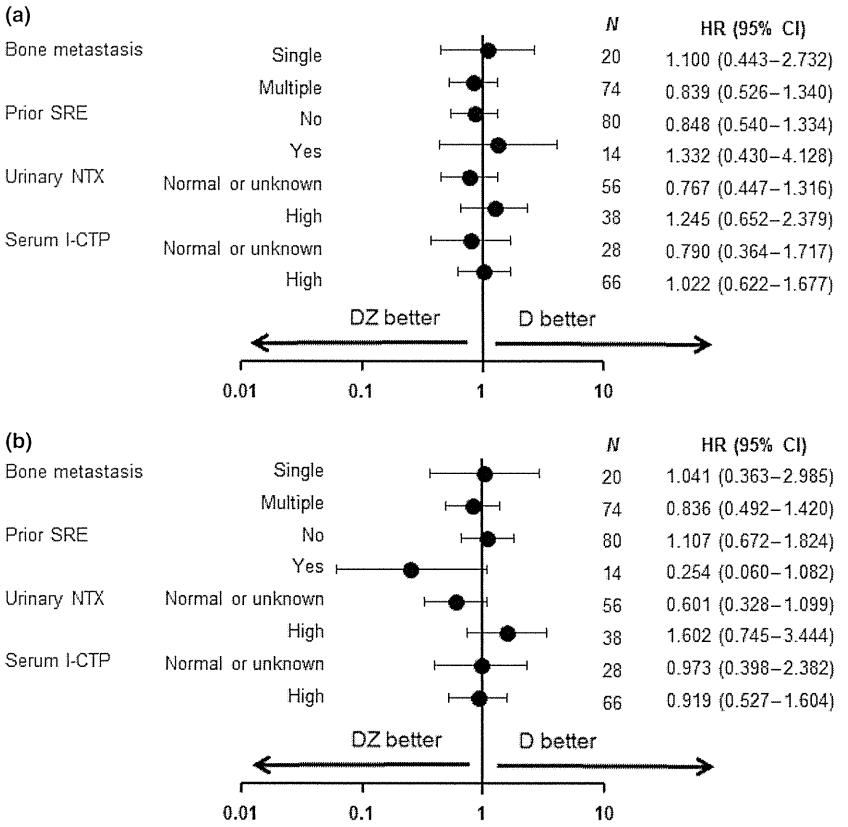

Fig. 3. (a) Subgroup analyses of hazard ratio for progression-free survival and (b) overall survival in the DZ and D groups. D, docetaxel alone; DZ, docetaxel with zoledronic acid; I-CTP, C-terminal telopeptide of type I collagen; NTX, N-terminal telopeptide of type I collagen; SRE, skeletal-related event.

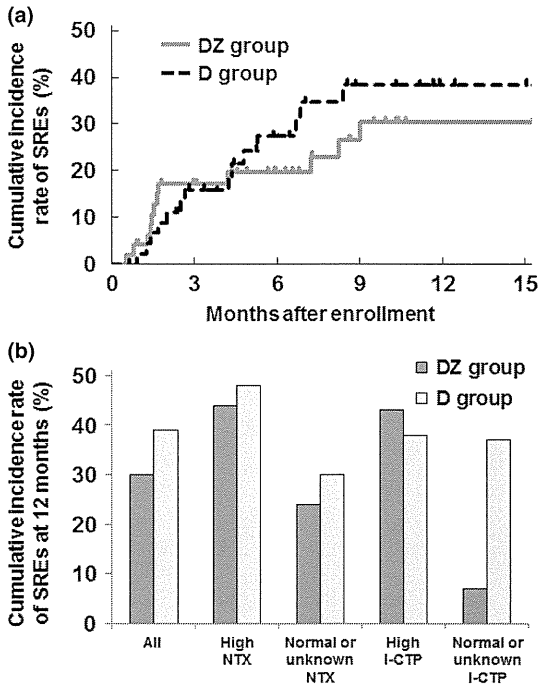

Fig. 4. (a) Cumulative incidence rate of SRE in the DZ and D groups. (b) Subgroup analyses of SRE rate according to baseline bone marker levels in the DZ and D groups. D, docetaxel alone; DZ, docetaxel with zoledronic acid; I-CTP, C-terminal telopeptide of type I collagen; NTX, N-terminal telopeptide of type I collagen; SRE, skeletal-related event.

patients with bone metastases. The similarity in the median PFS and OS of patients in the DZ and D groups suggests that the combination of zoledronic acid and docetaxel might not provide survival benefits to patients with NSCLC and bone metastases compared with docetaxel alone. In a previous randomized phase III study, a subgroup analysis of patients with NSCLC ($N = 382$) revealed that zoledronic acid significantly reduced the risk of a first on-study SRE compared with a placebo. However, there was no significant difference in OS between the two groups (median 187 days for zoledronic acid *vs* 157 days for placebo; $P = 0.539$).[11,12,14] Two randomized studies in which zoledronic acid was combined with standard treatment also showed no survival benefits for patients with NSCLC who had no bone involvement.[21,22] These results are consistent with our observation that zoledronic acid failed to prolong the survival of NSCLC patients with bone metastases. In a recent subgroup analysis of a randomized phase III study, denosumab significantly improved OS, whereas zoledronic acid did not. This analysis was conducted on a group of 811 patients with lung cancer and bone metastases (median 8.9 *vs* 7.7 months for denosumab and zoledronic acid, respectively; hazard ratio for death, 0.80; 95% CI, 0.67–0.95; $P = 0.01$) and 702 patients with NSCLC and bone metastases (median 9.5 *vs* 8.0 months for denosumab and zoledronic acid, respectively; hazard ratio for death, 0.78; 95% CI, 0.65–0.94; $P = 0.01$).[23,24] Denosumab, a human anti-RANKL monoclonal antibody, is a potential anticancer therapy for patients with NSCLC and bone metastases and should be evaluated further in future studies.

For patients with NSCLC and bone metastases, increased SRE risk correlated with a history of SREs, multiple bone metastases, and bone turnover markers.[25–27] Significantly high levels of urinary NTX, a sensitive bone resorption marker, were also associated with increased SRE risk and poor survival prognosis.[27] In agreement, the cumulative incidence rates of SRE were high in patients with high baseline urinary NTX levels in our study. A retrospective analysis of a phase III study revealed that zoledronic acid significantly reduces the risk of death compared with a placebo in 144 patients with NSCLC and high baseline NTX levels (hazard ratio for death, 0.65; 95% CI, 0.45–0.95; $P = 0.025$).[15] In our study, for 38 patients (19 for DZ and 19 for D) with NSCLC and high baseline NTX levels, the median OS was 8.6 months for the DZ group and 11.2 months for the D group (hazard ratio for death, 1.60; 95% CI, 0.75–3.44). Therefore, combination treatment with zoledronic acid and docetaxel did not improve OS in previously treated patients with NSCLC and bone metastases in addition to high baseline NTX levels. However, the number of patients in our study was small; as such, this study was not powered to detect differences in secondary variables, and statistical testing was performed for exploratory purposes.

The most common severe toxicities in the present study were leukopenia, neutropenia, febrile neutropenia and elevated ALT levels, which were similar in the two groups. No treatment-related deaths were observed in the DZ group. Although hypocalcemia and pyrexia were more frequent in the DZ group than in the D group, they were mild and manageable in most cases. A possible reason for the high incidence of hypocalcemia in this study was underuse of calcium supplements and vitamin D. Prophylactic oral administration of daily calcium supplements and vitamin D should be considered during treatment with zoledronic acid. No patient experienced ONJ in this study, although it may be argued that the duration of zoledronic acid treatment was too short for this to occur. No additional adverse events were observed in the present study compared with previous studies.[11,12,23,24]

The present study demonstrated the safety and tolerability of the combination of zoledronic acid and docetaxel but did not meet the primary endpoint of PFS in advanced NSCLC patients with bone metastasis. Based on these results, we abandoned assessment of the survival benefits of adding zoledronic acid to docetaxel treatment in a larger phase III study. There are potential limitations to our study. First, we used an open-label study design despite the use of PFS as the primary endpoint. Second, the sample size of the present study was relatively small. Third, we did not collect data regarding post-study treatment with zoledronic acid. New treatment options are still needed to prolong the survival of advanced NSCLC patients with bone metastasis.

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症 例

頭皮原発血管肉腫の肺転移により続発性気胸を生じた1例

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要 旨

頭皮原発血管肉腫の肺転移は，続発性気胸を高率に引き起こすことが知られている．症例は83歳，男性．80歳時，頭皮原発血管肉腫の診断にて皮膚科で手術療法，放射線療法，化学療法をうけ，寛解したが，20ヵ月後に薄壁空洞型の肺転移を認めた．その数日後に左気胸をきたし，当科へ紹介となった．胸腔ドレーンを留置したが，エアリークの改善なく，胸腔鏡補助下左上葉切除術を施行した．免疫組織化学的にCD31陽性であり，頭皮原発血管肉腫の肺転移巣と診断された．短期間で気胸の再発を認め，エアリークが持続したため，2回目の手術を行った．残存する左下葉に多発する薄壁の小嚢胞性病変を認め，その数ヵ所よりエアリークを認めた．小嚢胞を一部楔状切除し，被覆術を行った．小嚢胞も病理学的に頭皮原発血管肉腫の肺転移と診断された．気胸は治癒したが，原病の進行による呼吸不全のため術後36日に死亡した．本疾患の肺転移による気胸は難治性であり，若干の文献的考察を加えて報告する．

索引用語：頭皮原発血管肉腫，続発性気胸，肺転移，薄壁空洞
angiosarcoma of the scalp, secondary pneumothorax, lung metastasis, thin-walled cavity

はじめに

軟部組織肉腫は全悪性疾患の1%以下の頻度とされるが，血管肉腫は軟部組織肉腫の中でも約2%の頻度で，非常に稀な疾患である．血管肉腫は皮膚，心臓，乳房などさまざまな場所に発生し，肺転移を起こしやすい．その中で，頭皮に発生した血管肉腫は，他部位に発生した血管肉腫と異なり，特殊な形態の肺転移を起こしやすく，続発性気胸を引き起こすことが多いとされている．

今回我々は，頭皮原発血管肉腫の術後20ヵ月後に発症した肺転移から，続発性気胸に至った症例を経験したので，文献的考察を踏まえて報告する．

症 例

患 者：83歳，男性．

主 訴：胸部違和感．

既往歴：慢性腎臓病，高尿酸血症，虫垂炎手術歴．

家族歴：特記事項なし．

生活歴：喫煙歴なし．

現病歴：2010年11月初旬に転倒し右前頭部を打撲した．その部位に結節が出現し急速に増大したため，12月に当院皮膚科初診．初診時前頭部右側に19 mm×19 mmの表面が潰瘍化し，血痂を付着した結節を認めた．結節の周囲には5 cm×5 cmの範囲に境界不明瞭な紫紅色斑が散在していた(Fig. 1)．CT検査ではリンパ節転移と遠隔転移を認めなかった．2011年1月，結節周囲の境界不明瞭な紫紅色斑を含めた腫瘍をSafety margin 5 cmで一部骨膜上で切除された．病理結果は血管肉腫の診断であり，断端陰性であった．術後はweekly docetaxel療法(40 mg/日)計38回投与と放射線照射140 Gy/70 frが施行された．2012年8月のCT検査で左肺上葉S^3に28 mm，S^5に10 mmの嚢胞性病変を認め，肺転移が疑われ，その8週間後のCT検査で左肺S^3 38 mm，S^5 27 mmいずれの嚢胞性病変も増大が認められた(Fig. 2A，B)．2012年10月に左胸部違和感を主訴に近医を受診したところ，胸部単純X線検査で左気胸の診断となり，当院へ

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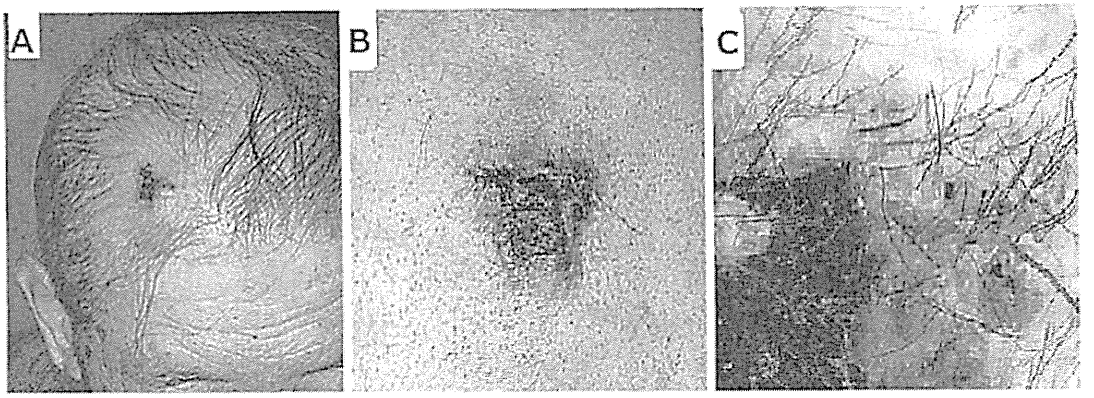

Fig. 1　At the initial visit, there was a wine-colored nodule with poorly-marginated macula at the right front of the head. The tumor size was 19×19 mm. (A, B). Dermoscopy findings revealed a stream-like area at the center of the nodule surrounded by a pink to purple color gradation (C).

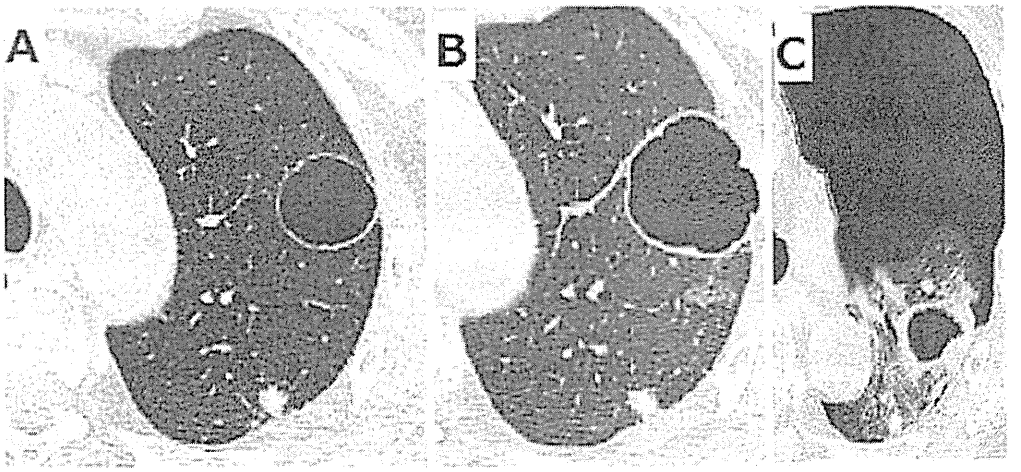

Fig. 2　A chest CT scan shows a subpleural thin-walled cyst at the left upper lobe (A). There was a gound glass appearance around the cyst revealing the hemorrhage of tumor vessels. The cyst had grown significantly larger 2 months later (B). A CT scan shows left pneumothorax (C).

紹介受診となった．

入院時現症：身長 161 cm，体重 54 kg，血圧 159/94 mmHg，脈拍 102/分　整，体温 35.8℃，SpO2 92%（room air）．

血液生化学検査：赤血球 $284\times10^4/\mu l$，Hb 10.0 g/dl，CRP 1.13 mg/dl と貧血と軽度の炎症所見を認めた．また，BUN 21.64 mg/dl，クレアチニン 1.37 mg/dl と軽度の腎機能障害を認めた．

入院時胸部 CT 所見：左気胸を認め，左肺 S^3，S^5 の嚢胞性病変はいずれも縮小しており，その破裂が気胸の原因と考えられた．縦隔気腫，皮下気腫は認めなかった．また，少量の左胸腔の液体貯留を認めた（Fig. 2C）．

入院後経過：入院後，胸腔ドレーンを挿入した．エアリークを認め，入院後5日経過してもエアリークの改善なく，X線検査でも肺の拡張は十分に得られず，胸膜癒着術も困難であったため，手術を行う方針とした．

手術所見：胸腔鏡で胸腔内を観察すると，癒着，胸水，播種性病変は認めなかった．左 S^3 の嚢胞壁は穿孔しており，同部が気胸の原因であった（Fig. 3A）．S^5 の病変は暗赤色の嚢胞性病変として観察された（Fig. 3B）．下葉に病変は認められず，胸腔鏡補助下に左上葉切除を施行し，両病変を摘出した．

病理組織学的所見：腫瘍細胞は核の大小不同，不整形核，明瞭な核小体を有する異型細胞であり，上皮様の形

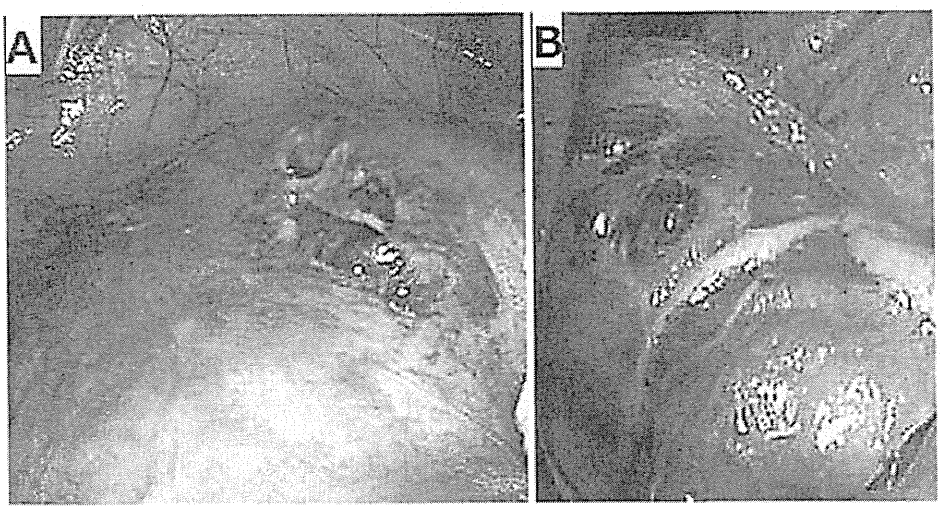

Fig. 3 The tumor wall at S3 was ruptured (A). The tumor, located at a lingular segment, showed a thin-walled and dark red colored cyst (B).

態や紡錘様の形態を呈しながらびまん性，浸潤性に嚢胞辺縁に散在していた．頭皮原発巣と同様の異形細胞であり，これらの異形細胞は免疫組織学にてCD31陽性，CD34陰性であり，頭皮原発血管肉腫の肺転移巣と診断した（Fig. 4）．

術後経過：術後はエアリークを認めず術翌日に胸腔ドレーンを抜去し，術後13日目に自宅退院となった．

退院後初診（術後26日）の胸部X線検査で左気胸の再発を認めたが，無症状であった．CTでも左気胸を確認したが，新規の肺転移，嚢胞性病変は認めなかった（Fig. 5）．入院のうえ，胸腔ドレーンを挿入し，エアリークを確認した．胸水は淡血性で約500 mlの排液を認めたが，胸水細胞診は陰性であった．エアリークは改善なく，ドレナージでは十分な拡張を得られず，再入院から7日目に再び手術を行った．

手術所見（2回目）：胸腔鏡で胸腔内を観察すると，前回切開創を中心に，下葉と壁側胸膜との広範な癒着を認めたため，第5肋間で開胸を行った．左肺下葉に多発する薄壁の小嚢胞性病変を認め，その数ヵ所よりエアリークを認めた（Fig. 6）．前回手術した上葉気管支断端に異常は認めなかった．小嚢胞を一部楔状切除し，残りはフィブリン糊とポリグリコール酸（PGA）シートを用いて臓側胸膜を広範囲に被覆した．

病理組織学的所見（2回目手術標本）：肺胞組織と線維性肥厚と毛細血管の増生を伴う胸膜が認められる．その中に腫大した核と明瞭な核小体を有する異型細胞が散在しており，1回目手術時の標本の腫瘍細胞と類似していた．免疫染色でも異型細胞はCD31陽性，CD34陰性と前回同様の結果であり，頭皮原発血管肉腫の肺転移巣と診断した．腫瘍細胞は穿破した嚢胞部分のみならず，穿破していない嚢胞部分にも存在していた．

2回目術後経過：術後3日目にエアリークは消失し，術後8日目に胸腔ドレーンを抜去した．術後21日目のPET-CTにて，両肺にFDG集積を認めた．左胸腔内には血性胸水と考えられる液体貯留を認めた．また，第2腰椎に圧迫骨折とFDG集積を認め，血管肉腫の腰椎転移による病的骨折と考えられた．術後30日のX線検査では左胸腔の液体貯留は増加し，縦隔の右方偏移を認めた．その後，呼吸状態は徐々に悪化し，術後36日に呼吸不全で死亡した．

考　察

血管肉腫は軟部組織腫瘍の2%という稀な悪性腫瘍である．心臓，肝臓，乳房，皮膚，頭部などに発生し，60%は皮膚から発生する[1,2]．皮膚の血管肉腫は主に高齢者に発症し，頭頸部，特に頭皮に生じやすいという特徴があり，他部位に発生する血管肉腫とは区別されてきた．水上らの報告によると，国内の血管肉腫症例の平均生存期間は19.5ヵ月で，5年生存率は9%と非常に予後の悪い疾患である[3]．血管肉腫は肺に転移しやすい傾向があり[1,3,4]，Tateishiらの報告によると，肺に転移した血管肉腫は画像上，多発結節が63%，多発薄壁空洞病変が21%，

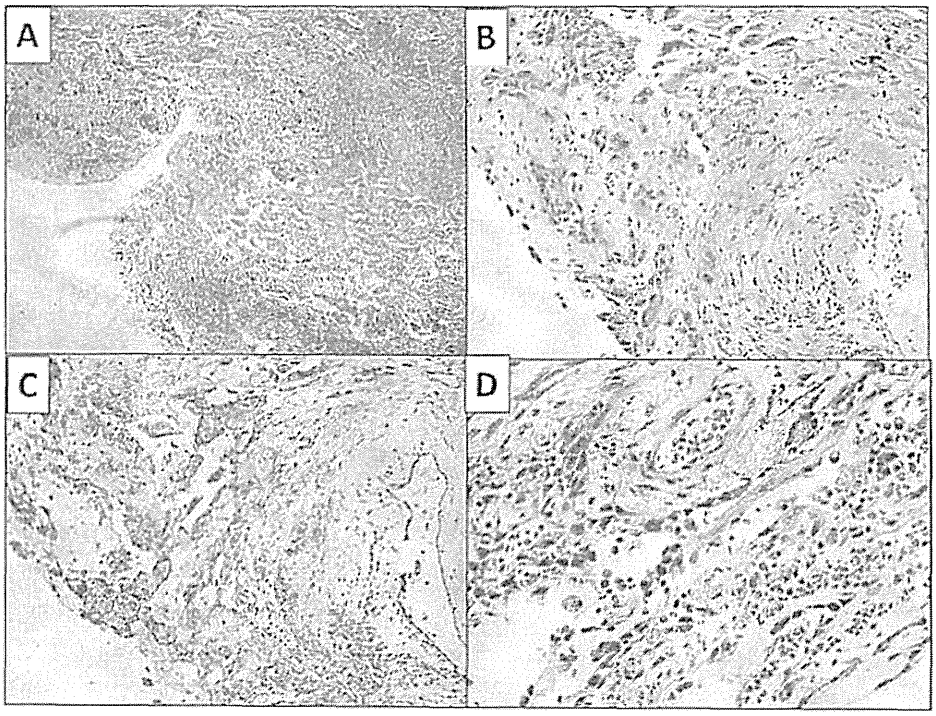

Fig. 4　Histopathologic findings of the specimen in the left S3 resected at the first operation showed atypical epithelioid cells and spindle cells involving lung parenchyma along the periphery of the cyst (A HE ×100, B HE ×400). Tumor cells showed positive immunostaining for CD 31 (C). The tumor at the lingular segment showed the same findings (D HE ×400).

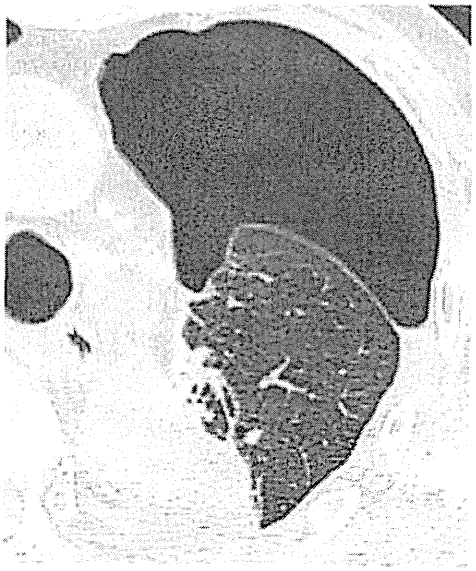

Fig. 5　A chest CT scan at the second pneumothorax shows collapse of the residual left lung, leading to atelectasis.

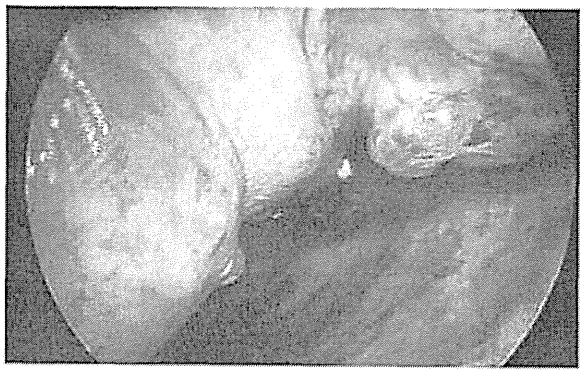

Fig. 6　At the second operation, many tiny cysts were observed in the left lower lobe, and some of them caused pneumothorax.

孤立性結節が8%とされている．また，病変の周囲にすりガラス陰影を伴うものが42%存在する[1]．この中で続発性気胸を生じるのは多発薄壁空洞病変のみである．空洞病変を形成する機序としては（1）腫瘍性病変の乏血性

壊死[1,6]，(2)以前から存在していた嚢胞壁に腫瘍細胞が浸潤する[1,6]，(3)肺胞壁に腫瘍細胞が浸潤し，チェックバルブ機構で空洞性病変を形成する[1,6]，(4)血管肉腫に特徴的な洞様血管吻合を呈する，血液貯留の嚢胞性病変を形成しながら腫瘍細胞が増殖する[1]といったものが考えられている．

Kitagawaらは95症例の血管肉腫の剖検例を頭部血管肉腫と非頭部血管肉腫の2群に分けて検討している．頭部原発が35%であり，気胸は頭部血管肉腫群でのみ見られ，その31%に生じている．また，血管肉腫の肺転移は血胸や血性胸水を起こし，その多くは両側性に発症することが知られており[7,8]，血胸や無気肺などの肺合併症も頭部血管肉腫群で多かった[5]．後藤らは頭部血管肉腫による続発性気胸10症例を解析しており，頭部血管肉腫の診断から初回気胸までの平均期間は19.4ヵ月であり，また気胸発症後の平均生存期間は約4ヵ月と短く，予後不良と報告している[9]．

2回目の手術時に認めた多発の肺転移は非常に興味深い．頭部血管肉腫の肺転移は薄壁空洞壁が破裂することで気胸を生じるが，それと同時に腫瘍細胞が胸腔内に播種されると予想される．本症例の2回目の気胸の原因は，初回手術時には認められていなかった多発薄壁空洞病変が原因であり，播種による形成が疑われた．しかし，肉腫細胞は特徴的であるにも関わらず，胸水細胞診では腫瘍細胞は認めなかった．病理標本でも肉腫細胞は胸膜表面にはなく，胸膜直下に存在しており，播種とは考えにくかった．むしろ一旦肺転移が起こると急速に肺転移が進展，多発する特性を有すると考えられる．多発した胸膜直下の転移巣は薄壁空洞化し，極めて破裂しやすく，難治性気胸となると考えられる．本症例をみる限り，空洞病変を形成する機序としては，腫瘍の乏血壊死，既存の嚢胞壁への腫瘍浸潤，血液の貯留する嚢胞病変の形成，との考え方は否定的である．血管肉腫をはじめとする間葉系腫瘍は，胸膜直下への転移が多いという傾向が認められる．機序は不明であるが，何らかのきっかけで一気に胸膜直下への多発転移が惹起され，肺胞レベルのチェックバルブ機構により急速に嚢胞が拡大することにより，薄壁胸膜が破裂すると考えるのが妥当である．骨肉腫でも肺転移巣の破裂で気胸が起こることが報告されている[10]が，骨肉腫では薄壁空洞を形成することは稀で，腫瘍壁の壊死により破綻し，気胸になると考えられる．血管肉腫と骨肉腫では，同じ間葉系の腫瘍でも肺転移の性状と進展および気胸の形成過程は異なる．これらの点を呼吸器外科医は十分に認識すべきである．

皮膚原発血管肉腫に対する標準的な治療方針は未だ確立されていないが，外科的切除，放射線療法，化学療法，分子標的療法，免疫療法の組み合わせの集学的治療が重要だと考えられている[3]．皮膚原発血管肉腫の化学療法としては，MAID療法(Mesna，Adriamycin，Ifosfamide，Dacarbazine)やタキサン系薬剤の他，近年では，海外の症例報告において分子標的薬である抗vascular-endothelial growth factor (VEGF) 抗体であるbevacizumab，VEGF受容体を含むマルチキナーゼ阻害薬であるsorafenibなどの有効性が報告されており[11-13]，特にタキサン系薬剤との併用で効果的であったという症例報告が多いため[11,13]，今後は皮膚原発血管肉腫において化学療法，分子標的療法が中心になると考えられる．

その一方で，その特異な形態の肺転移から続発性気胸に至ると，有効的な治療は現時点で存在せず，気胸が引き金となった呼吸不全が死因となることも少なくない．胸膜癒着術や外科的切除が行われているが，効果は少なく，再発気胸に対しても，胸腔ドレナージおよび胸膜癒着術を繰り返し行うことしか生存期間を延長しない[9]．すなわち気胸のコントロールが，頭部血管肉腫肺転移の重要な課題である．今回の症例では，保存的治療では肺の拡張が十分得られず，胸膜癒着術の効果も期待できない程度の重度のエアリークが長期にわたり持続していた状況であったため，やむを得ず外科的治療を選択した．腫瘍はS^3とS^5に存在しており，いずれもサイズが大きかったため，マージンを考慮しても，部分切除は不可能であり，左上葉切除を行った．2回目の手術に関しても，胸腔ドレーン挿入が長期となり，保存的改善は見込めず，患者にとって非常に強いストレスとなっていたため，インフォームドコンセントを行ったうえで，手術を選択した．

肺転移巣の外科的切除を行ったが，初回手術からわずか1ヵ月余りで多発肺転移を認め，その延命効果はほとんどなかったと言える．ただし，胸腔ドレーンを抜去することができ，一時的ではあったが自宅退院ができたことは，姑息的治療として評価してもよいと考える．

結　語

今回我々は頭部血管肉腫の肺転移による続発性気胸を経験した．初回手術から1ヵ月で新規肺転移巣による気胸再発を来しており，気胸初回発生から2ヵ月で死亡し

た．難治性の予後不良の疾患であるが，気胸のコントロールが課題である．

利益相反

本論文について申告する利益相反はない．

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