

## Interstitial Lung Disease after Pleurodesis for Malignant Pleural Effusion

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### Abstract

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**Objective** Pleurodesis is an effective therapy for malignant pleural effusion (MPE). While interstitial lung disease (ILD) has been regarded as a serious complication of pleurodesis, its clinicopathological characteristics have not been fully understood. This study was conducted to elucidate the incidence of ILD and the risk factors for ILD in patients who underwent pleurodesis to control MPE.

**Methods** The medical records of patients who underwent pleurodesis in Aichi Medical University between March 2008 and February 2013, the period before the approval of talc in Japan, were retrospectively analyzed.

**Results** A total of 84 patients underwent pleurodesis, all using OK-432. ILD occurred in 13 patients (15.5%). The development of ILD after pleurodesis was significantly associated with old age (odds ratio [OR]: 4.82, 95% confidence interval [CI]: 1.22-19.08) and epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) treatment (OR: 5.97, CI: 1.7-20.9). A multivariate analysis revealed that >67 years of age ( $p=0.01$ ) and EGFR-TKI treatment ( $p=0.02$ ) were significantly associated with the development of pleurodesis-related ILD. Among the patients who received both pleurodesis and EGFR-TKIs ( $n=23$ ), 8 patients developed ILD. All of these patients were receiving EGFR-TKI therapy at the time of pleurodesis or within 30 days after pleurodesis. In contrast, no cases of ILD were observed among the patients who stopped EGFR-TKIs before pleurodesis or started EGFR-TKIs at more than 30 days after pleurodesis.

**Conclusion** ILD seemed to be a frequent complication of pleurodesis in patients using OK-432, especially elderly patients and those who underwent pleurodesis while receiving EGFR-TKI therapy or who started EGFR-TKI therapy within 30 days after pleurodesis.

**Key words:** interstitial lung disease, pleurodesis, malignant pleural effusion, OK-432, epidermal growth factor receptor-tyrosine kinase inhibitor

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### Introduction

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Malignant pleural effusion (MPE) is a common complication in patients with advanced malignancies, especially lung cancer, and is associated with a dismal prognosis. Lung cancer, which is the most common metastatic tumor of the pleura, accounts for one-third of all MPEs (1). Tube drain-

age and pleurodesis with the intrapleural instillation of chemical agents to obliterate the pleural space and prevent fluid accumulation is an effective therapeutic approach for controlling MPEs (2). Various chemical agents have been used for pleurodesis. Talc, which is the standard sclerosing agent in many countries, has recently been approved for use in Japan. While the use of talc has been widely adopted since its approval in Japan in 2013, the most frequently used

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agent is a pulverized product of heat-killed *Streptococcus pyogenes* (OK-432) and tetracycline (3, 4). Pyrexia (10.5%) and pain (14.0%) are the most common complications of pleurodesis using talc (5). Acute respiratory distress syndrome (ARDS) and acute interstitial lung disease (ILD) are considered fatal complications of pleurodesis with talc. In previous studies, ARDS was observed in 5.9-9.0% of patients who underwent pleurodesis with talc (6-9). While ILD may occur after pleurodesis with OK-432, its clinicopathological characteristics have not been fully understood.

The present study investigated the incidence and risk factors for ILD in patients who underwent pleurodesis to control MPE during a period in which talc had yet to be fully introduced into clinical oncology practice.

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## Materials and Methods

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### Study design

The medical records of consecutive patients who underwent pleurodesis to control MPE at the Division of Respiratory Medicine and Allergology, Aichi Medical University School of Medicine between March 2008 and February 2013 were retrospectively analyzed. This retrospective observational study was approved by the institutional review board of Aichi Medical University School of Medicine.

### Pleurodesis

All patients underwent thoracic drainage using an indwelling chest tube after being diagnosed with MPE. The drainage tube was clamped after the removal of the effusion by thoracic drainage and the full expansion of the lung. After the instillation of OK-432 (0.2 Klinische Einheit units [KE]/kg, maximum 10 KE/body), OK-432 plus minocycline (MINO, 100 mg or 200 mg/body), OK-432 plus carboplatin (CBDCA, 300 mg/m<sup>2</sup>), or OK-432 plus MINO plus CBDCA, diluted in 100 mL of physiological saline, the tube was clamped, and the patient's position was rotated for 2 hours. The tube was then unclamped, allowed to drain, and suctioned at -10 mmHg. The tube was removed when the drainage volume decreased to ≤100 mL per day.

### The diagnosis of ILD

The medical charts of all patients were reviewed in detail, and all cases of respiratory insufficiency were examined to determine the onset, suspected cause, and outcome. Cases of acute ILD that occurred in the period between 1 year before and 1 year after pleurodesis were further investigated. Cases in which computed tomography (CT) was not performed, either before pleurodesis or when the patient's respiratory condition deteriorated, were excluded from the study.

The internationally accepted criteria for the diagnosis of ILD and a diagnostic algorithm developed from the American Thoracic Society/European Respiratory Society consensus statement were used (10, 11). Briefly, ILD is diagnosed based on the onset of clinical symptoms and signs; chest X-

ray and CT findings; laboratory tests including blood tests, microbiological cultures of sputum, blood, and urine; and fiberoptic bronchoscopy with bronchial lavage and transbronchial lung biopsy as necessary. Echocardiography and contrast-enhanced thoracic CT were performed to discriminate possible ILD from heart failure or other heart diseases and pulmonary embolism, respectively. Occasionally, broad-spectrum antibiotics and treatments for heart failure and/or pulmonary embolisms were administered to exclude a diagnosis. A lack of response to these treatments supported a diagnosis of ILD. All of the cases were independently reviewed by 2 experienced physicians (1 radiologist and 1 pulmonologist). When there was discordance regarding the review results, the reviewing physicians discussed the diagnosis until they reached an agreement (10, 11).

### Statistical analysis

Adverse events related to pleurodesis were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0. Fisher's exact test was used to compare categorical variables. The odds ratios (ORs) and accompanying 95% confidence intervals (CIs) of the categorical variables were estimated by a univariate analysis. Variables associated with pleurodesis-related ILD that had a p value of ≤0.25 in the univariate analysis were included in a multivariate logistic regression analysis.

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## Results

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From March 2008 to February 2013, 84 patients underwent pleurodesis to control MPE in the Division of Respiratory Medicine and Allergology, Aichi Medical University School of Medicine. The median age of the patients was 67 years; 68% of the patients were male, 67% were current or ex-smokers, 76% had lung cancer, and 14% had pre-existing ILD (Table 1). The 12 cases of pre-existing ILD were classified as usual interstitial pneumonia (UIP) pattern (n=1) and non-UIP pattern (n=11, including 5 patients with radiation pneumonitis). The histological types of the 64 lung cancer patients were adenocarcinoma (n=55, 85.9%), squamous cell carcinoma (n=5, 7.8%), and small cell carcinoma (n=4, 6.3%).

After pleurodesis, 13 patients (15.5%) developed ILD. Among the clinical factors, older age (>67 years) (OR: 4.82, 95% CI: 1.22-19.08) and the use of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) (OR: 5.97, 95% CI: 1.7-20.9) were significantly associated with the occurrence of ILD. ILD occurred after pleurodesis in 8 (35%) of the 23 patients who received EGFR-TKIs, while 5 patients (8%) of the 61 who did not receive EGFR-TKIs developed ILD (p=0.005). The incidence of ILD after pleurodesis among patients who were >67 years of age (25.6%) was significantly higher than the incidence in younger patients (6.7%) (Table 2). No other factors, including sex, pre-existing ILD, smoking history, performance

**Table 1. Patient Characteristics.**

		n	(%)
Total		84	(100)
Sex	Male	57	(68)
	Female	27	(32)
Age, median years (range)		67	(39-85)
Smoking status	Current smoker	8	(10)
	Ex-smoker	48	(57)
	Never smoker	28	(33)
Performance status	0-1	49	(58)
	2-4	35	(42)
Type of cancer	Lung cancer	64	(76)
	Gastrointestinal cancer	5	(6)
	Genitourinary cancer	10	(13)
	Head and neck cancer	2	(2)
	Sarcoma	1	(1)
	Cancer of unknown primary	2	(2)
Pre-existing ILD		12	(14)
Comorbidities	Diabetes mellitus	10	(12)
	Hypertension	23	(27)
	Coronary artery disease	7	(8)
	Cardiovascular disease	9	(11)
	Chronic obstructive pulmonary disease	7	(8)
	Liver cirrhosis	1	(1)
Sclerosing agents for pleurodesis	OK-432	52	(62)
	OK-432+MINO	22	(26)
	OK-432+CBDCA	7	(8)
	OK-432+MINO+CBDCA	3	(4)

ILD: interstitial lung disease, MINO: minocycline, CBDCA: carboplatin

**Table 2. Subgroup Analysis of Risk Factors for ILD after Pleurodesis (n=84).**

		ILD (+)	ILD (-)	Odds Ratio (95% CI)	p value
Total		13	71		
Sex	Male	8	49	1.39 (0.41-4.74)	0.75
	Female	5	22		
Age	67 or younger	3	42	4.82 (1.22-19.08)	0.03
	Older than 67	10	29		
Pre-existing ILD	Present	1	11	2.2 (0.26-18.68)	0.68
	Absent	12	60		
EGFR-TKI treatment	Yes	8	15	5.97 (1.7-20.9)	0.005
	No	5	56		
Smoking status	Ever smoker	8	48	1.3 (0.38-4.43)	0.75
	Never smoker	5	23		
Performance status	0,1	10	39	2.73 (0.69-10.78)	0.22
	2-4	3	32		
Agents for pleurodesis	OK-432	9	44	1.22 (0.34-4.37)	0.76
	OK432+(MINO or CBDCA or [MINO+CBDCA])	4	27		

ILD: interstitial lung disease, EGFR: epidermal growth factor receptor, TKI: tyrosine kinase inhibitor, MINO: minocycline, CBDCA: carboplatin

status (PS), and the sclerosing agents that were used for pleurodesis were associated with the development of pleurodesis-related ILD. We found no significant relationships between the occurrence of ILD and the dose of OK-432, the number of OK-432 instillations, or the success or

failure of pleurodesis: ILD occurred after pleurodesis in 2 of the 19 patients who underwent pleurodesis using less than 10KE of OK-432, while 11 of the 65 patients who received 10KE developed ILD (p=0.722). ILD developed in 1 of the 23 patients who underwent pleurodesis more than once, and

**Table 3. Multivariate Analysis of Risk Factors for ILD after Pleurodesis.**

Variable	Odds Ratio	95% CI	p value
Age (>67 / ≤67)	6.9	1.51-31.38	0.01
EGFR-TKI treatment (yes / no)	5.54	1.39-22.12	0.02
Performance status (0,1 / 2-3)	2.79	0.59-13.15	0.19

CI: confidence interval, EGFR: epidermal growth factor receptor, TKI: tyrosine kinase inhibitor

**Table 4. Characteristic of Patients who Developed ILD after Pleurodesis.**

No	Age	Sex	Type of cancer	Pre-existing ILD	Chemotherapy at ILD onset	Smoking status	PS	Site of ILD	CTCAE grade	Interval
1	69	Female	LC (ad)	Absent	EGFR-TKI (gefitinib)	Never	1	Bilateral	3	15
2	73	Male	LC (ad)	Absent	EGFR-TKI (gefitinib)	Ex-	1	Ipsilateral	5	22
3	51	Female	LC (ad)	Absent	EGFR-TKI (gefitinib)	Never	1	Ipsilateral	2	26
4	78	Female	LC (ad)	Absent	EGFR-TKI (gefitinib)	Ex-	1	Bilateral	4	187
5	61	Male	LC (ad)	Absent	EGFR-TKI (erlotinib)	Ex-	1	Ipsilateral	4	42
6	83	Male	LC (ad)	Absent	EGFR-TKI (gefitinib)	Ex-	1	Contralateral	5	88
7	71	Male	LC (ad)	Absent	EGFR-TKI (gefitinib)	Ex-	1	Bilateral	2	48
8	63	Female	LC (ad)	Absent	EGFR-TKI (erlotinib)	Never	3	Bilateral	3	57
9	80	Male	LC (ad)	Present	CBDCA+PTX	Never	3	Bilateral	1	90
10	78	Male	LC (ad)	Absent	VNR	Ex-	0	Bilateral	4	20
11	81	Male	LC (ad)	Absent	DTX	Ex-	1	Ipsilateral	1	147
12	77	Female	LC (ad)	Absent	-	Never	2	Ipsilateral	3	11
13	83	Male	LC (sm)	Absent	-	Ex-	1	Ipsilateral	1	60

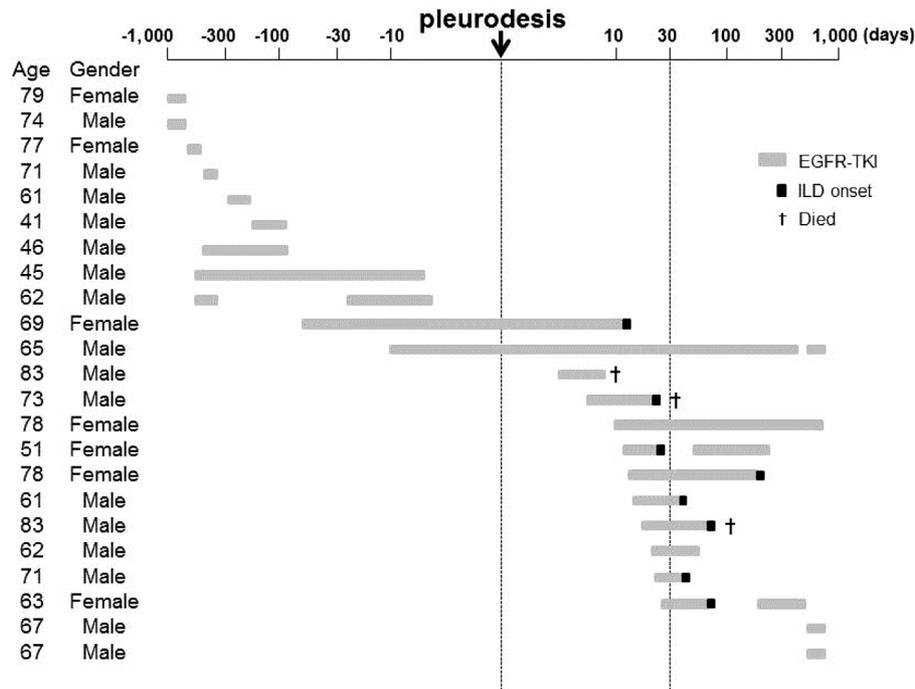
ILD: interstitial lung disease, PS: performance status, CTCAE: common terminology criteria for adverse events, Interval: interval between pleurodesis and ILD onset (days), LC (ad): lung cancer (adenocarcinoma), LC (sm): lung cancer (small cell carcinoma), EGFR: epidermal growth factor receptor, TKI: tyrosine kinase inhibitor, CBDCA: carboplatin, PTX: paclitaxel, VNR: vinorelbine, DTX: docetaxel, Never: never smoker, Ex-: ex-smoker, CTCAE grade 1: asymptomatic; clinical or diagnostic observations only; intervention not indicated, grade 2: symptomatic; medical intervention indicated; limiting instrumental activity of daily life (ADL), grade 3: severe symptoms; limiting self care ADL; oxygen indicated, grade 4: life-threatening respiratory compromise; urgent intervention indicated, grade 5: death

12 of the 61 patients who only underwent pleurodesis once ( $p=0.101$ ). ILD developed in 1 of the 10 patients in whom pleurodesis was not successful, and 12 of the 74 patients in whom it was successfully performed ( $p=0.101$ ). A multivariate analysis revealed that age, EGFR-TKI treatment, PS, old age ( $p=0.01$ ), and EGFR-TKI treatment ( $p=0.02$ ) were significantly associated with the development of pleurodesis-related ILD (Table 3).

All of the patients who developed ILD had lung cancer (Table 4). The median time from pleurodesis to the onset of ILD was 48 days (range, 11-187 days). Eleven patients were undergoing chemotherapy at the onset of ILD and, notably, 8 patients (61.5%) were receiving EGFR-TKI treatment. In 3 patients, bronchoalveolar lavage (BAL) was performed for the differential diagnosis of the infection and lymphangitis carcinomatosa. All BAL fluid showed a lymphocyte-dominant cell fraction in which the proportion of lymphocytes was >70%, and with negative bacterial culture and cytology results, supporting the diagnosis of ILD. ILD developed in the bilateral lungs of 6 patients, in the lung ipsilateral to the site of pleurodesis in 6 patients, and in the contralateral lung in 1 patient (Table 4). Two patients died of ILD after pleurodesis. Both patients were elderly male ex-

smokers with lung adenocarcinoma. One patient, who started gefitinib on the 18th day after pleurodesis, developed ILD on the 89th day after pleurodesis, and died on the 112th day after pleurodesis. The other patient started gefitinib on the 7th day after pleurodesis, developed ILD on the 23rd day after pleurodesis, and died on the 84th day after pleurodesis. One other patient died on the 9th day after pleurodesis with OK-432. He received gefitinib for 5 days (days 3-7 after pleurodesis). A postmortem examination revealed a massive gastrointestinal hemorrhage due to duodenal ulcers, right lung cancer invading the esophagus, MPE, and multiple liver metastases. There were no signs of ILD.

In this study, 23 patients received EGFR-TKI treatment. The patients who received EGFR-TKI treatment but ended it before pleurodesis ( $n=9$ ) or started EGFR-TKI at  $\geq 30$  days after pleurodesis ( $n=2$ ) did not develop ILD. Among the 12 patients who received EGFR-TKIs at the time of pleurodesis or within 30 days after pleurodesis, 8 developed ILD (67%, Figure). Six of the 9 (67%) patients who received gefitinib and 2 of the 3 (67%) patients who received erlotinib developed ILD. None of the patients who ended EGFR-TKIs before pleurodesis and none of the patients who started EGFR-TKIs at  $\geq 30$  days after pleurodesis developed ILD. The risk



**Figure.** ILD and pleurodesis in patients who were treated with EGFR-TKIs (n=23).

of ILD was significantly higher in patients who received EGFR-TKIs at the time of pleurodesis or within 30 days after pleurodesis (OR: 43.4, 95% CI: 2.05-920.41,  $p=0.004$ ).

## Discussion

In this retrospective analysis of 84 consecutive patients who underwent pleurodesis to control MPE, the incidence of ILD after pleurodesis was 15.5%. Two major risk factors for ILD were identified: EGFR-TKI therapy (odds ratios: 5.54) and older age at pleurodesis (odds ratio: 6.90). Overall, 61.5% of the patients who developed ILD after pleurodesis had undergone EGFR-TKI therapy, and 34.8% of patients who underwent EGFR-TKI therapy developed ILD after pleurodesis, suggesting a strong relationship between the onset of ILD and EGFR-TKI therapy in patients who received pleurodesis to control MPE. The relationship is significant. Notably, 66.7% of the patients who received EGFR-TKI therapy at the time of pleurodesis or within 30 days after pleurodesis, developed ILD; 2 (25%) of these patients died of ILD.

All of the patients in the current study received OK-432 as a sclerosing agent; some received additional minocycline and carboplatin. Pleurodesis-related ILD has been recognized to be a serious complication, and it has mostly been described in a small number of case reports, most of which were conference abstracts that were written in the Japanese language (Table 5). While no ILD was reported in the 34 patients who received OK-432 in a phase II trial of pleurodesis for MPE from non-small cell lung cancer (NSCLC) (4), Ishimoto reported that 3 cases of ILD (11.5%) occurred among 26 patients who underwent pleurodesis using OK-432 (Table 5). In total, pleurodesis-

related ILD was described in 18 patients in 8 reports, mostly with OK-432 (n=17), and 6 patients died of ILD (33%). One patient, who was undergoing gefitinib treatment at pleurodesis, developed fatal ILD. The high prevalence (15.5%) of ILD in the present study might be related with the use of EGFR-TKIs. Similarly to the report of Ishimoto et al., ILD occurred in 5 of the 61 (8%) patients who did not receive EGFR-TKIs. One of the risk factors for EGFR-TKI-related ILD is the reduced volume of the normal lung on CT (<50%) (10). We hypothesize that the chemical inflammation of the pleura and lung after pleurodesis using OK-432 may damage the normal lung and reduce its volume, increasing the risk of EGFR-TKI-related ILD.

ILD is a major adverse event of EGFR-TKI therapy. It is recognized that ILD is more common in Japan than in other countries. A large-scale prospective study on gefitinib-induced ILD in Japan revealed that the risk of developing acute ILD was mainly greater in the first 4 weeks after the initiation of gefitinib. The study further defined the risk factors, which include older age, poor PS, smoking, short duration after the diagnosis of NSCLC, reduced normal lung on CT, pre-existing ILD, and concurrent cardiac disease (10). Pleurodesis has not been reported as a risk factor for ILD in patients receiving EGFR-TKIs. Within the scope of our literature search, the current study is the first to report an association between pleurodesis-related ILD and the use of EGFR-TKIs. The present study failed to identify any significant risk factors (other than EGFR-TKI use and older age) for ILD, which may be attributable to the small sample size of the study. It should also be noted that none had pre-existing ILD among the patients who received EGFR-TKI therapy and developed ILD after pleurodesis. In the present study, the patients who were treated with EGFR-TKIs were

**Table 5. Reports of ILD after Pleurodesis.**

n	Pleural disease and cancer type	Sclerosis agents	Chemotherapy $\leq$ 30 days interval from pleurodesis	Outcome	reference
3*	MPE (3) LC (3)	OK-432 (3)	CBDCA+VP-16+VCR (1) NR (2)	Died (1) Improved (2)	[1][2]
4	MPE (3), PT (1) LC (3), NR (1)	CDDP+OK-432 (1), CDDP (1) DXR+OK-432 (1), OK-432 (1)	NR (4)	Died (2) Improved (2)	[3]
1	MPE (1) LC (1)	OK-432 (1)	NR (1)	Improved (1)	[4]
5	MPE (5) LC (5)	OK-432 (5)	Gefitinib (1) NR (4)	Died (2) Improved (3)	[5][6]
1	Chylothorax (1) LC (1)	OK-432 (1)	NR (1)	Died (1)	[7]
4	MPE (3), PT (1) LC (4)	OK-432 (4)	NR (4)	Improved (4)	[8]
18	MPE (15), PT (2) Chylothorax (1) LC (17), NR (1)	OK-432 (15) OK432 combined (2) CDDP (1)	CBDCA+VP-16+VCR (1) Gefitinib (1) NR (16)	Died (6) Improved (12)	

ILD: interstitial lung disease, MPE: malignant pleural effusion, LC: lung cancer, PT: pneumothorax, NR: not reported, DXR: doxorubicin, CBDCA: carboplatin, VP-16: etoposide, VCR: vincristine, ( ): no of patients, [1] Respiratory Molecular Medicine 1997; 1: 187-194 (in Japanese). Abstracts in Japanese from the meeting proceeding of [2] Japanese Journal of Lung Cancer 2001; 41: 547, [3] Annals of the Japanese Respiratory Society 1999; 37: 276, [4] Japanese Journal of Lung Cancer 2001; 41: 272, [5] Journal of the Japan Society for Respiratory Endoscopy 2010; 32: 198, [6] Japanese Journal of Lung Cancer 2008; 48: 558, [7] Japanese Journal of Lung Cancer 2011; 51: 282, [8] Annals of the Japanese Respiratory Society 2013; 2: 321. \*In 26 patients who underwent pleurodesis using OK-432, three developed ILD.

mostly never smokers or light smokers and had no underlying lung diseases, highlighting the potential risk of combining EGFR-TKI therapy and pleurodesis. Considering the effectiveness of EGFR-TKIs in the treatment of EGFR-mutant lung cancer, including patients with MPE (12), EGFR-TKI therapy alone (without pleurodesis), seems to be a preferable treatment option for reducing the risk of ILD. It is now widely accepted that EGFR-TKI alone (without pleurodesis) can prevent the recurrence of MPE (13). However, during the period of our retrospective study, it was not well known that MPE could be controlled by EGFR-TKI alone, and many patients underwent pleurodesis before starting treatment with EGFR-TKIs.

It was also shown that elderly patients ( $>67$  years) were at higher risk of ILD after pleurodesis. Older patients have been reported to be at a higher risk of ILD regardless of the administration of EGFR-TKI therapy or cytotoxic systemic chemotherapy in NSCLC (10), and after pleurodesis in pleural mesothelioma (14). Kudoh et al. also reported that the rate of mortality due to ILD was significantly higher in older patients ( $\geq 65$  years of age; OR: 4.49, 95% CI: 1.33-15.21). In the present study, 2 elderly patients, a 73-year-old man and an 83-year-old man (both of whom received EGFR-TKIs), died of ILD (Table 4 and Figure); thus, the mortality due to ILD after pleurodesis and EGFR-TKI therapy was 25%. The indications for pleurodesis need to be carefully considered, particularly for elderly patients.

In many countries, talc is used as the standard agent in sclerotherapy for MPE. This has recently been approved in Japan. The present study was conducted in our institute at the introduction of talc, to elucidate the incidence and clinical features of pleurodesis-related ILD. All of the cases in

this study received OK-432 as a sclerosing agent, and the results cannot directly be extrapolated to the potential risk of talc-related ILD in Japan. In many countries, acute ILD and ARDS are the most serious complications of pleurodesis using talc. Although acute ILD has been attributed to the talc particle size, the use of "graded" talc (in which most particles of  $<10 \mu\text{m}$  in size are removed), has been regarded as relatively safe (15, 16), cases of pleurodesis-related ILD have even been reported with graded talc (7, 17). Kuzniar et al. reported that the presence of peripheral edema, supplementary oxygen requirement, and chemotherapy within 14 days before pleurodesis were significant risk factors for acute ILD after surgical pleurodesis with talc (7). Considering the unexpectedly high prevalence of ILD in the present study, we suggest that patients who receive pleurodesis with talc should be closely monitored.

The present study is associated with some limitations, most of which are derived from the fact that it was a relatively small retrospective study that was performed in a single institute. The assessment of the clinical course before and after pleurodesis was restricted to a detailed chart review; accordingly, the information largely came from the records of clinical care. It was challenging to make a definitive diagnosis of acute ILD retrospectively when multiple differential diagnoses were raised. This was particularly evident in cases in which acute ILD had to be differentially diagnosed from pulmonary edema, lung infection, and lymphangitis carcinomatosa, because the patients' general conditions were often serious, and the clinical and laboratory examinations that are necessary to achieve an accurate diagnosis were therefore limited. However, several signs in high-resolution computed tomography (HRCT) may be helpful in

the discrimination of ILD: the dominance of pure ground glass opacities may correspond to diffuse alveolar damage, and suggest ILD, rather than lymphangitis carcinomatosa; and the appearance of the beaded sign or a beaded septum may suggest lymphangitis carcinomatosa (18). We believe that having 2 experienced physicians (1 pulmonologist and 1 diagnostic radiologist) independently review the radiological evaluations and chart records, and who could, when necessary discuss a diagnosis, meant that the cases were diagnosed as accurately as possible. The small sample size of this study was another limitation. A poor PS tended to be a risk factor for the development of ILD; however, it did not reach statistical significance. Third, the observations in this study were based on the experience at a single institute; thus, further studies are warranted to confirm the present findings in other settings.

In conclusion, despite the above-described limitations, the present study suggests the need for a cautious approach to pleurodesis, especially in elderly patients and patients receiving EGFR-TKIs.

#### Author's disclosure of potential Conflicts of Interest (COI).

Akihito Kubo: Honoraria, Chugai.

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