Difference in Benefit of Chemotherapy Between Small Cell Lung Cancer Patients with Interstitial Pneumonia and Patients with Non-small Cell Lung Cancer

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Abstract. *Background: It is not clear whether there is a difference in benefit of chemotherapy between small cell lung cancer (SCLC) patients with pre-existing idiopathic interstitial pneumonias (IIPs) and non-small cell lung cancer (NSCLC) patients with IIPs. Patients and Methods: We performed a retrospective study of the overall survival (OS) between advanced lung cancer patients with IIPs (n=28) and those without IIPs (n=145). Results: The OS in NSCLC patients with IIPs was shorter than in those without IIPs (median OS, 10.6 vs. 27.9 months, p=0.008) but the OS in SCLC patients with IIPs was not inferior to that of those without IIPs (12.7 vs. 14.8 months, p=0.835). Multivariate analysis showed that the small number of regimens increased the risk of mortality, instead of pre-existing IIPs. Conclusion: The continuation of chemotherapy in SCLC patients with IIPs made it possible to have a similar prognosis to that in those without IIPs.*

It has been reported that the incidence of lung cancer in Japanese patients with idiopathic interstitial pneumonias (IIPs) is approximately 6-17% (1) and, especially in patients with usual interstitial pneumonia (UIP), is higher than that of the general population with relative risk of 5.3 for prevalence of lung cancer mortality in a Japanese autopsy study (2). IIPs are a progressive pulmonary disease leading to respiratory failure and have a poor prognosis with a median survival time of 3-5 years from the time of diagnosis (3, 4). In addition, some patients develop an acute exacerbation (AE) of IIPs characterized by suddenly progressive and severe respiratory failure with new pulmonary infiltrates and pathological findings of diffuse alveolar damage (DAD) (5, 6). In lung cancer patients with IIPs, this fatal exacerbation occurs after chemotherapy with anticancer agents (1, 7) and pre-existing IIP has been reported to be a risk factor for drug-induced interstitial lung diseases (D-ILD) or an independent prognostic factor for poor survival (8-14). There exist lung cancer patients with IIPs who have best supportive care (BSC) alone without receiving standard chemotherapy to avoid the risk of developing AE of IIPs or D-ILD after chemotherapy.

On the other hand, it has been recently reported that the combination of platinum agents and etoposide (15, 16) in small cell lung cancer (SCLC) and the combination of platinum agents and vinorelbine (17), paclitaxel (18, 19), gemcitabine or pemetrexed (20) in non-small cell lung cancer (NSCLC) is feasible and effective as first-line chemotherapy for patients with pre-existing IIPs. In clinical practice, many patients with SCLC, as well as NSCLC, receive second-line chemotherapy or beyond. There is no report to evaluate whether the continuation of chemotherapy is associated with the outcome in lung cancer patients with IIPs. The purpose of the present retrospective study is to evaluate whether the continuation of chemotherapy improved the outcome in lung cancer patients with IIPs and whether there is a difference in benefit of chemotherapy between SCLC and NSCLC cases.

Patients and Methods

This retrospective study was approved by the Institutional Review Board, which decided that informed consent was not required for this study as it only involved examination of routine patient records and images. The data of 389 lung cancer patients (347 NSCLC cases and 42 SCLC cases) were retrospectively retrieved from the database of electronic medical records during the 5-year period from April 1, 2009 to March 31, 2014. Patients were diagnosed as having lung cancers using bronchoscopy and/or percutaneous needle biopsy at our institute and staged according to the guidelines of the Union Internationale Contre le Cancer (UICC) TNM classification of malignant tumors. Forty-three patients (11%) had IIPs at diagnosis for lung cancer. In

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Key Words: Small cell lung cancer, non-small cell lung cancer, idiopathic interstitial pneumonia, drug-induced interstitial lung disease, number of regimens.
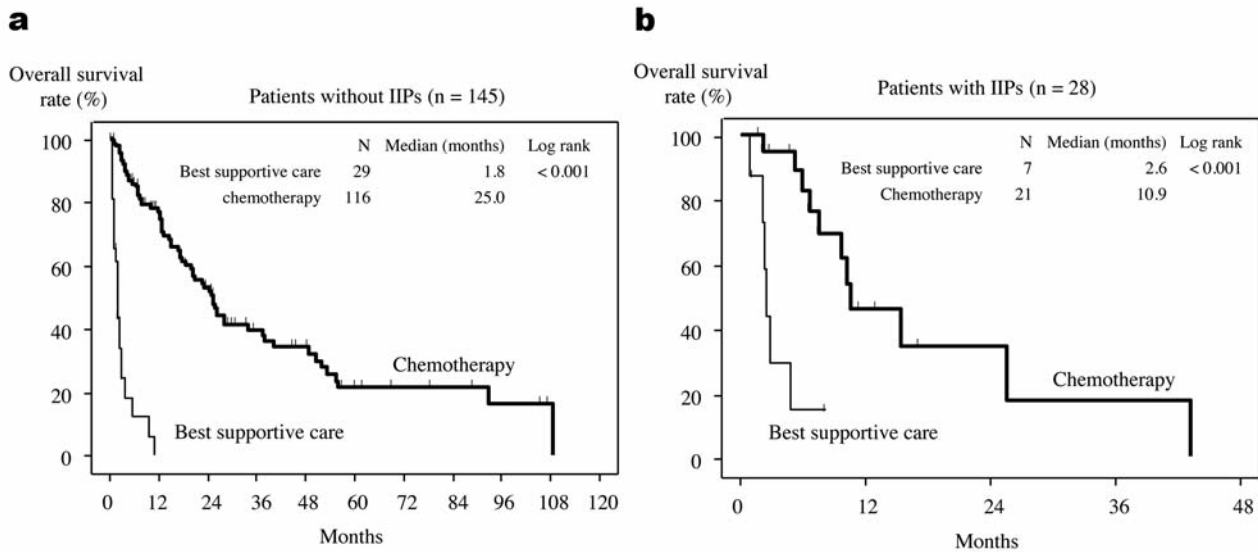
Figure 1. *Overall survival rate between chemotherapy and best supportive care in patients without (a) and with IIPs (b). IIPs, Idiopathic interstitial pneumonias.*
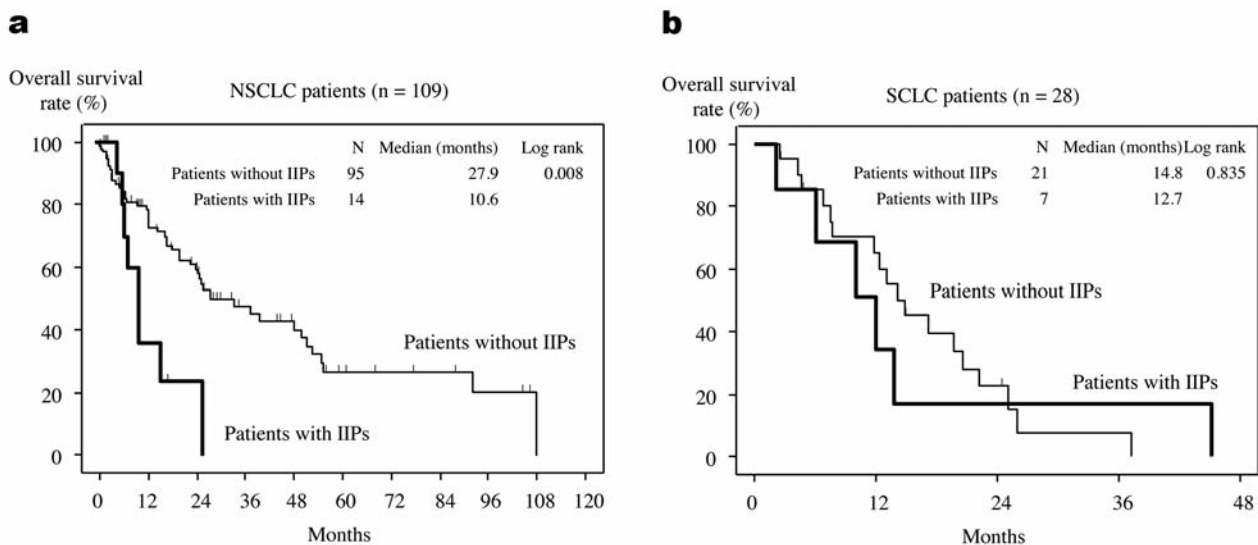

Figure 2. *Overall survival rates between NSCLC patients with and without IIPs (a) and SCLC with and without IIPs (b) after chemotherapy. IIPs, Idiopathic interstitial pneumonias; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.*

145 lung cancer patients who underwent surgery, 103 cases without postoperative recurrence and 14 recurred cases who received chemo-radiation or radiation therapy were excluded from this study. We also excluded 75 local advanced lung cancer patients who received chemoradiation or radiation therapy and 24 cases who did not have sufficient data to distinguish IIPs from miscellaneous diseases, such as pulmonary edema caused by heart failure, pulmonary hemorrhage or opportunistic infection disease. One-hundred seventy-three lung cancer patients who had first-line chemotherapy or beyond (without receiving thoracic radiation therapy) and who received BSC alone were included in this study. We divided those patients into 2 groups, patients with IIPs (n=28; 8 SCLC cases and 20 NSCLC cases) and

patients without IIPs (n=145; 25 SCLC cases and 120 NSCLC cases), and performed a retrospective study of the overall survival (OS) between the two groups.

A chest computed tomography (CT) scan test was performed at the end of one breath-hold and on supine image by a Brilliance 64 CT system (Philips, Tokyo, Japan) and examination parameters were 120 kV, 140 mA, 5-mm collimation and 10-mm-per rotation table speed. All evaluations in the present study were made at the same window setting (2,000–450 HU). The high-resolution CT (HRCT) images were assessed independently by both a radiologist and a respirologist and were evaluated according to the presence of IIPs. Diagnosis of IIPs was made according to An Official ATS/ERS/JRS/ALAT Statement:

Table I. *Patients' characteristics in lung cancer patients with IIPs and patients without IIPs.*

Characteristics	Unit	IIPs (+)	IIPs (−)	p
No. of patients		28	145	-
Age	year	76±8	74±12	0.347
Gender: men	no. (%)	23 (82)	92 (63)	0.088
Performance status: 0-1	no. (%)	18 (65)	97 (67)	0.959
Cigarette smoking: Yes	no. (%)	23 (82)	95 (66)	0.131
Blood tests				
White blood cell	×10² /µl	81±24	79±45	0.149
Lactate dehydrogenase	IU/l	276±146	265±231	0.293
C-reactive protein	mg/dl	2.3±3.7	2.3±3.6	0.385
KL-6	U/ml	1071±1210	838±1055	0.001
Pathological type of lung cancer				
Small cell carcinoma	no. (%)	6 (21)	25 (17)	0.793
Adenocarcinoma	no. (%)	12 (4 3)	96 (66)	0.033
Squamous cell carcinoma	no. (%)	8 (29)	25 (17)	0.279
Others	no. (%)	2 (7)	7 (5)	0.639
Clinical stage of lung cancer				
Stage III	no. (%)	9 (32)	20 (14)	0.035
Stage IV	no. (%)	18 (64)	102 (70)	0.678
Postoperative recurrence	no. (%)	1 (4)	23 (16)	0.131
Therapy for lung cancer				
Best supportive care	no. (%)	7 (25)	29 (20)	0.730
Chemotherapy	no. (%)	21 (75)	116 (80)	0.730
Platinum-based regimens	no. (%)	14 (50)	80 (55)	0.766
Pemetrexed and/or bevacizumab	no. (%)	7 (25)	52 (36)	0.371
EGFR-TKI	no. (%)	0	42 (29)	0.002
Median no. of regimens (range)	regimen	1 (1-3)	2 (1-11)	-
First-line therapy	no. (%)	12 (57)	45 (39)	0.183
Second-line therapy	no. (%)	4 (19)	29 (25)	0.317
Third-line therapy	no. (%)	5 (24)	14 (12)	0.532
Fourth-line therapy or beyond	no. (%)	0	28 (24)	0.002

D-ILD, Drug-induced interstitial lung disease; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; IIPs, idiopathic interstitial pneumonias.

"Idiopathic Pulmonary Fibrosis: Evidenced-based Guidelines for Diagnosis and Management" (21). The typical HRCT images of UIP were basal predominant, subpleural reticular abnormality with traction bronchiectasis and honeycombing without the presence of upper or mid-lung predominance, peribronchovascular predominance, extensive ground glass abnormality, profuse micronodules, discrete cysts, diffuse mosaic attenuation/air-trapping and consolidation in bronchopulmonary segments. Patients with IIPs who did not satisfy the definition of UIP were diagnosed as having non-UIP.

AE of IIPs are clinically defined when patients satisfy all of the following 4 conditions: (i) progressive dyspnea within the course of one month, (ii) new pulmonary infiltrates seen on chest radiograph and/or CT, (iii) decrease of arterial oxygen pressure (PaO$_2$) of 10 mmHg or more, (iv) the absence of infection, heart failure or pulmonary embolism (5, 6, 21, 22). In lung cancer patients without IIPs, there are many patterns of D-ILD, ranging from benign infiltrates to life-threatening acute respiratory distress syndrome, such as a fetal D-ILD caused by gefitinib in Japanese cases. In this

study, since it is very difficult to distinguish AE of IIPs from fetal D-ILD, we used the term 'D-ILD' when lung cancer patients with IIPs developed acute respiratory conditions that satisfied the above-mentioned definition of AE-IIPs after chemotherapy. Chemotherapy-related death was defined as death occurring within 4 weeks of the completion of treatment without clear evidence of any other cause of death or death obviously caused by treatment toxicity.

Measurements of white blood cells were performed using the XE-2100 system (Sysmex, Kobe, Japan). Serum levels of lactate dehydrogenase and C-reactive protein were measured using the AU680 biochemical analysis system (Beckman Coulter, Tokyo, Japan). Measurements of serum KL-6 were performed using an electrochemiluminescence immunoassay kit (EIDIA Co., Ltd., Tokyo, Japan; reference range <500 U/ml) following the manufacturer's instructions.

Statistical analysis was performed on a computer with a Stat View J 5.0 statistical program (Abacus Concepts Inc., City, CA, USA). Differences of clinical data and blood sample data between two independent samples were tested using the Mann-Whitney *U*-test. Analysis of categorical data was performed with the χ^2 test or Fisher's exact probability test. Single variable survival analyses were performed using the log rank test. Those variables with *p* values <0.05 on the univariable analysis were included in the Cox proportional-hazards model to be examined as prognostic factors of survival in lung cancer patients. Hazard ratio (HR) and corresponding 95% confidence intervals (CIs) were presented. The OS was estimated by the method of Kaplan and Meier. A two-tailed *p*-value of less than 0.05 was considered to indicate a statistically significant difference.

Results

Patients' characteristics (Table I). There was no difference in mean age, the percentage of cases with the Eastern Cooperative Oncology Group (ECOG) performance status (PS)≤1, smokers and the mean levels of white blood cell (WBC), lactate dehydrogenase (LDH) and C-reactive protein (CRP) between patients with IIPs and patients without IIPs; however, the percentage of men cases had a tendency to be higher (82 *vs*. 63%, *p*=0.088) and serum KL-6 levels was higher (1,071±1,210 *vs*. 838±1,055 U/ml, n=0.001) in patients with IIPs than in those without IIPs. In patients with IIPs, there were 11 cases with UIP and 17 cases with non-UIP. With regard to pathological type and clinical stage of lung cancer, there was no difference in the percentage of cases with SCLC, stage IV and postoperative recurrence between the two groups. Patients with IIPs had a lower percentage of cases with adenocarcinoma (43 *vs*. 66%, n=0.033) and a higher percentage of cases with stage III (32 *vs*. 14%, n=0.035) than patients without IIPs.

Anticancer agents and number of regimens of chemotherapy (Table I). The percentage of patients with IIPs who received BSC alone was 25% and 20% without IIPs. In 137 patients who received chemotherapy, there were no difference in the percentage of cases who received platinum-based chemotherapy and maintenance therapy using pemetrexed and/or bevacizumab between the two groups. Forty-two cases (29%) without IIPs

Table II. *Regimens of chemotherapy in lung cancer patients who developed D-ILD after chemotherapy.*

No.Pts	LC	No. of regimens								Survival after D-ILD (months)	Outcome
		1st	2nd	3rd	4th	5th	6th	7th	8th		
Lung cancer patients without IIPs (n=12)											
1 72F	AD	GEF								0.8	Dead
2 83F	AD	GEF								6.4	Alive
3 84M	AD	PEM								1.1	Dead
4 76F	AD	GEF	ERL							17.8	Alive
5 81F	AD	CBDCA+GEM	DTX							2.3	Dead
6 73F	AD	CDDP+PEM+BEV	DTX							1.7	Dead
7 50M	AD	CDDP+PEM	S-1	CBDCA+PTX	DTX					4.6	Dead
8 66M	SQ	CDDP+DTX	CBDCA+S-1	GEM	PTX					6.3	Dead
9 59M	AD	CDDP+PEM	DTX	CBDCA+PTX	GEM					2.0	Dead
10 66M	AD	CBDCA+PEM+BEV	S-1	GEM	VNR	DTX				0.8	Dead
11 66F	AD	CBDCA+PTX	GEF	PEM	ERL	GEM	S-1			10.5	Dead
12 83M	AD	CDDP+DTX	GEF	GEM	GEF	PEM	VNR	S-1	ERL	0.8	Dead
Lung cancer patients with IIPs (n=6)											
1 76M	SM	CBDCA+ETP								4.0	Alive
2 81M	SM	CBDCA+ETP								4.0	Dead
3 58M	SM	CBDCA+ETP								0.4	Dead
4 87M	SQ	DTX								3.5	Dead
5 77M	SQ	CDDP+GEM	VNR	S-1						0.7	Dead
6 37M	SM	CDDP+CPT-11	CBDCA+PTX	AMR						2.3	Dead

AD, Adenocarcinoma; AMR, amrubicin; BEV, bevacizumab; CBDCA, carboplatin; CDDP, cisplatin; CPT-11, irinotecan; D-ILD, drug-induced interstitial lung disease; DTX, docetaxel; ERL, erlotinib; ETP, etoposide; GEF, gefitinib; GEM, gemcitabine; LC, lung cancer; PEM, pemetrexed; Pts, patients; PTX, paclitaxel; SM, small cell lung cancer; SQ, squamous cell carcinoma; S-1, Tegafur, Gimeracil, Oteracil Potassium; VNR, vinorelbine.

tested positive for epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) in contrast to patients with IIPs. The median number of regimens for chemotherapy was one regimen in patients with IIPs (range=1-3) and two regimens in patients without IIPs (range=1-11). Twenty-eight cases (24%) of patients without IIPs had fourth-line chemotherapy or beyond, but none of patients with IIPs did.

Patients who developed D-ILD. Twelve cases in patients without IIPs (11 cases with adenocarcinoma, one case with squamous cell carcinoma) and 6 cases in patients with IIPs (4 cases with SCLC, two cases with squamous cell carcinoma) developed D-ILD with an incidence that had a tendency to be higher in patients with IIPs than in those without IIPs (29% *vs.* 10%, *p*=0.054). In patients without IIPs, 3 cases developed D-ILD in first-line chemotherapy, 3 cases in second-line and 6 cases in fourth-line or beyond. In patients with IIPs, 4 cases had D-ILD in first-line chemotherapy and 2 cases in third-line (Table II). The incidence of D-ILD was higher in patients with IIPs than in patients without IIPs in cases who patients received carboplatin (21% *vs.* 0%, *p*=0.003) or etoposide (50% *vs.* 0%, *p*=0.011), but not in cases where patients received other anticancer agents (Table III).

Prognosis. Seventeen cases (61%) of patients with IIPs and 89 cases (61%) of patients without IIPs have died. There was no difference in the percentage of cancer-related death (47 *vs.* 54%, *p*=0.610), chemotherapy-related death (7% *vs.* 2%, *p*=0.185) and other causes (7% *vs.* 5%, *p*=0.665) between the two groups. The OS was longer in patients who received chemotherapy than in patients who received BSC alone in both IIPs-negative(median survival time (MST), 25.0 *vs.* 1.8 months, *p*<0.001) and IIPs-positive patients (MST, 10.9 *vs.* 2.6 months, *p*<0.001) (Figure 1). In patients who received BSC alone (n=36), there was no difference in the OS between patients with and patients without IIPs (MST, 2.6 *vs.* 1.8 months, *p*=0.353).

When patients received chemotherapy (n=137), the OS was shorter in patients with IIPs than in patients without IIPs (MST, 10.9 *vs.* 25.0 months, *p*=0.043). In NSCLC cases (n=109), the OS was shorter in patients with than in patients without IIPs (MST, 10.6 *vs.* 27.9 months, *p*=0.008) (Figure 2a). In SCLC cases (n=28), the OS in patients with IIPs was not inferior to that in patients without IIPs (MST, 12.7 *vs.* 14.8 months, *p*=0.835) (Figure 2b). In patients with IIPs (8 cases with UIP and 13 cases with non-UIP who received chemotherapy), the OS had a tendency to be lower in UIP cases than in non-UIP cases (MST, 7.9 *vs.* 10.9 months, *p*=0.074).

Table III. *Incidence of D-ILD after chemotherapy between patients with IIPs and patients without IIPs.*

Suspected drug	Total	IIPs (+)	IIPs (–)	*p*-Value
Carboplatin	3/77 (4)	3/14 (21)	0/63 (0)	0.003
Pemetrexed	1/55 (2)	0/5 (0)	1/50 (2)	0.999
Gefitinib	2/32 (6)	0	2/32 (6)	-
Docetaxel	5/28 (18)	1/2 (50)	4/26 (15)	0.330
Paclitaxel	1/28 (4)	0/5 (0)	1/23 (4)	0.999
Amrubicin	1/24 (4)	1/4 (25)	0/20 (0)	0.166
Gemcitabine	1/23 (4)	0/1 (0)	1/22 (4)	0.999
Etoposide	3/23 (13)	3/6 (50)	0/17 (0)	0.011
S-1	2/23 (9)	1/1 (100)	1/22 (4)	0.087
Erlotinib	2/21 (10)	0	2/21 (10)	-
Total	18/137 (13)	6/21 (29)	12/116 (10)	

D-ILD, Drug-induced interstitial lung disease; IIPs, Idiopathic interstitial pneumonias; S-1, Tegafur, Gimeracil, Oteracil Potassium. Data represents the numbers of cases who developed D-ILD/the numbers of cases who received the suspected drug. Numbers in parentheses are the percentage.

Multivariate analysis of prognostic factors in lung cancer patients who received chemotherapy. In univariate analysis, ten variables associated with the OS time on the log rank tests are listed in Table IV. The Cox proportional-hazards model analysis showed that men gender, poor PS, SCLC, stage IV, absence of EGFR mutation, CRP levels (≥1.7 mg/dl) and the low number of chemotherapy regimens (<2 regimens) increased the risk of mortality. Although pre-existing IIPs and cigarette smoking did not affect the outcome, the occurrence of D-ILD had a tendency to be related to high mortality.

Discussion

When lung cancer patients with IIPs received BSC-alone, those patients died of cancer itself and not of other IIP-associated hazards, as there was no difference in the OS between patients without and patients with IIPs. Chemotherapy improved the outcome in lung cancer patients with IIPs, as well as in those without IIPs, but the OS was worse in cases with IIPs than in cases without IIPs because of the low number of chemotherapy regimens. When lung cancer patients with IIPs received chemotherapy, the MST of NSCLC patients was 10.6 months, significantly worse than that in those without IIPs; the MST of SCLC patients was 12.7 months that was not inferior to that in those without IIPs (Figure 2). It has been reported that in lung cancer patients with IIPs who received chemotherapy, MST is 5.8-10.6 months in NSCLC cases (11, 15-17, 20) and 8.7-10.7 months in SCLC cases (12, 16, 19). We suggest that the continuation of chemotherapy in SCLC patients with IIPs makes it

Table IV. *Multivariate analysis according to prognostic factors in lung cancer patients who received chemotherapy.*

	Univariate analysis (log rank test)	Multivariate analysis (Cox's proportional hazard model)		
	p-Value	Hazard ratio	95% confidence interval	*p*-Value
Pre-existing IIPs	<0.001	1.413	0.756-2.640	0.278
Gender (Women *vs*. Men)	0.020	0.517	0.271-0.986	0.045
Performance status (2-4 *vs*. 0-1)	<0.001	2.591	1.555-4.318	<0.001
Cigarette smoking (Yes *vs*. No)	0.028	0.600	0.293-1.228	0.169
Pathology (SCLC *vs*. NSCLC)	0.004	1.765	1.007-3.092	0.047
Clinical stage (IV *vs*. III)	0.003	2.302	1.339-3.960	0.002
EGFR mutation (Yes *vs*. No)	0.003	0.408	0.191-0.873	0.020
C-reactive protein (≥1.7 *vs*. <1.7 mg/dl)	0.001	1.918	1.141-3.227	0.014
D-ILD (Yes *vs*. No)	0.048	1.768	0.953-3.279	0.070
Number of regimens (≥2 *vs*. <2)	<0.001	0.263	0.152-0.454	<0.001

D-ILD, Drug-induced interstitial lung disease; EGFR, epidermal growth factor receptor; SCLC, small cell lung carcinoma; NSCLC, non-small cell carcinoma.

possible to have at least similar prognosis compared to that in those without IIPs.

It has also been reported that many anticancer agents including carboplatin and etoposide are feasible and effective as first-line chemotherapy for lung cancer patients with IIPs (15-20). On the other hand, there are some reports in which D-ILD occurs more frequently in lung cancer patients with IIPs when they receive docetaxel (23) or pemetrexed mono-therapy (24). Our results, however, showed that the use of carboplatin and etoposide increased the incidence of D-ILD in lung cancer patients with pre-existing IIPs but the use of other anticancer agents did not have a similar effect. The reason for this discrepancy was not clear in this study.

Men gender, cigarette smoking, pre-existing IIPs, poor PS and high levels of CRP have been reported to be a risk factor for D-ILD or an independent prognostic factor for poor survival (9-14). Our results showed that SCLC, the absence of EGFR mutation and the low number of chemotherapy regimens (<2 regimens) increased the risk of mortality instead of pre-existing IIPs or cigarette smoking as unfavorable prognostic factors. It is possible that the episode "D-ILD occurred more frequently in NSCLC patients with IIPs and made it difficult to continue chemotherapy" is related to poor

prognosis. On the other hand, no difference in prognosis was observed between SCLC patients with IIPs and in those without. The reason may be that SCLC patients do not have enough favorable prognosis to evaluate whether or not the number of regimens affects their outcome. In addition, our results also showed that the occurrence of D-ILD had a tendency to increase the risk of mortality. An early detection and treatment of D-ILD must be followed when administering anticancer agents to treat lung cancer patients with IIPs.

Our study has certain limitations. First, the sample size was small because this is a retrospective study at a single Institute. Secondly, almost all our patients were diagnosed as having IIPs using HRCT imaging and laboratory findings, but not using specimens obtained by surgical lung biopsy, except in postoperative recurrence cases. The best single-way to evaluate whether or not chemotherapy for lung cancer patients with IIPs improve their prognosis is to perform randomized prospective studies in patients who were pathologically diagnosed before chemotherapy (especially in patients with non-UIP). Nevertheless, even if their chemotherapy regimen has not been established, it is ethically unacceptable to randomly assign patients to receiving either chemotherapy or BSC alone. Also, for advanced lung cancer patients, there is no enough time to perform surgical lung biopsy before chemotherapy. It is, thus, important to let lung cancer patients with IIPs have an opportunity to receiving standard chemotherapy.

In conclusion, the continuation of chemotherapy in SCLC patients with IIPs made it possible to have at least similar prognosis compared to that in those without IIPs.

Conflicts of Interest

The Authors indicate no potential conflicts of interest.

References

1 Raghu G, Nyberg F and Morgan G: The epidemiology of interstitial lung disease and its association with lung cancer. Br J Cancer 91: S3-S10, 2004.

2 Matsushita H, Tanaka S, Saiki Y, Hara M, Nakata K, Tanimura S and Banba J: Lung cancer associated with usual interstitial pneumonia. Pathol Int 45: 925-932, 1995.

3 American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias: This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med 165: 277-304, 2002.

4 Katzenstein AL, Myers JL: Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. Am J Respir Crit Care Med 157: 1301-1315, 1998.

5 Kondoh Y, Taniguchi H, Kawabata Y, Yokoi T, Suzuki K and Takagi K: Acute exacerbation in idiopathic pulmonary fibrosis. Analysis of clinical and pathologic findings in three cases. Chest 103: 1808-1812, 1993.

6 Hyzy R, Huang S, Myers J, Flaherty K and Martinez F: Acute exacerbation of idiopathic pulmonary fibrosis. Chest 132: 1652-1658, 2007.

7 Minegishi Y, Takenaka K, Mizutani H, Sudoh J, Noro R, Okano T, Azuma A, Yoshimura A, Ando M, Tsuboi E, Kudoh S and Gemma A: Exacerbation of idiopathic interstitial pneumonias associated with lung cancer therapy. Intern Med 48: 665-672, 2009.

8 Camus P, Kudoh S, Ebina M: Interstitial lung disease associated with drug therapy. Br J Cancer 91: S18-S23, 2004.

9 Miyazaki K, Satoh H, Kurishima K, Nakamura R, Ishikawa H, Kagohashi K and Hizawa N: Interstitial lung disease in patients with small cell lung cancer. Med Oncol 27: 763-767, 2010.

10 Kenmotsu H, Naito T, Kimura M, Ono A, Shukuya T, Nakamura Y, Tsuya A, Kaira K, Murakami H, Takahashi T, Endo M and Yamamoto N: The risk of cytotoxic chemotherapy-related exacerbation of interstitial lung disease with lung cancer. J Thorac Oncol 6: 1242-1246, 2011.

11 Kinoshita T, Azuma K, Sasada T, Okamoto M, Hattori S, Imamura Y, Yamada K, Tajiri M, Yoshida T, Zaizen Y, Kawahara A, Fujimoto K and Hoshino T: Chemotherapy for non-small cell lung cancer complicated by idiopathic interstitial pneumonia. Oncol Lett 4: 477-4482, 2012.

12 Togashi Y, Masago K, Handa T, Tanizawa K, Okuda C, Sakamori Y, Nagai H, Kim YH and Mishima M: Prognostic significance of preexisting interstitial lung disease in Japanese patients with small-cell lung cancer. Clin Lung Cancer 13: 304-311, 2012.

13 Miyazaki K, Satoh H, Kurishima K, Nakamura R, Ishikawa H, Kagohashi K, Ohara G and Hizawa N: Impact of interstitial lung disease on survival for patients with non-small cell lung cancer. Anticancer Res 29: 2671-2674, 2009.

14 Song DH, Choi IH, Ha SY, Han KM, Lee JJ, Hong ME, Jeon K, Chung MP, Kim J and Han J: Usual interstitial pneumonia with lung cancer: clinicopathological analysis of 43 cases. Korean J Pathol 48: 10-16, 201.

15 Minegishi Y, Kuribayashi H, Kitamura K, Mizutani H, Kosaihira S, Okano T, Seike M, Azuma A, Yoshimura A, Kudoh S and Gemma A: The feasibility study of Carboplatin plus Etoposide for advanced small cell lung cancer with idiopathic interstitial pneumonias. J Thorac Oncol 6: 801-807, 2011.

16 Yoshida T, Yoh K, Goto K, Niho S, Umemura S, Ohmatsu H and Ohe Y: Safety and efficacy of platinum agents plus etoposide for patients with small cell lung cancer with interstitial lung disease. Anticancer Res 33: 1175-1179, 2013.

17 Okuda K, Hirose T, Oki Y, Murata Y, Kusumoto S, Sugiyama T, Ishida H, Shirai T, Nakashima M, Yamaoka T, Ohnishi T and Ohmori T: Evaluation of the safety and efficacy of combination chemotherapy with vinorelbine and platinum agents for patients with non-small cell lung cancer with interstitial lung disease. Anticancer Res 32: 5475-5480, 2012.

18 Shukuya T, Ishiwata T, Hara M, Muraki K, Shibayama R, Koyama R and Takahashi K: Carboplatin plus weekly paclitaxel treatment in non-small cell lung cancer patients with interstitial lung disease. Anticancer Res 30: 4357-4361, 2010.

19 Minegishi Y, Sudoh J, Kuribayasi H, Mizutani H, Seike M, Azuma A, Yoshimura A, Kudoh S and Gemma A: The safety and efficacy of weekly paclitaxel in combination with carboplatin for advanced non-small cell lung cancer with idiopathic interstitial pneumonias. Lung Cancer 71: 70-74, 2011.

20 Choi MK, Hong JY, Chang W, Kim M, Kim S, Jung HA, Lee SJ, Park S, Chung MP, Sun JM, Park K, Ahn MJ and Ahn JS: Safety and efficacy of gemcitabine or pemetrexed in combination with a platinum in patients with non-small-cell lung cancer and prior interstitial lung disease. Cancer Chemother Pharmacol *73*: 1217-1225, 2014.

21 Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE Jr, Kondoh Y, Myers J, Müller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL and Schünemann HJ; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management: Am J Respir Crit Care Med *183*: 788-824, 2011.

22 Collard HR, Moore BB, Flaherty KR, Brown KK, Kaner RJ, King TE Jr, Lasky JA, Loyd JE, Noth I, Olman MA, Raghu G, Roman J, Ryu JH, Zisman DA, Hunninghake GW, Colby TV, Egan JJ, Hansell DM, Johkoh T, Kaminski N, Kim DS, Kondoh Y, Lynch DA, Müller-Quernheim J, Myers JL, Nicholson AG, Selman M, Toews GB, Wells AU and Martinez FJ; Idiopathic Pulmonary Fibrosis Clinical Research Network Investigators: Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med *176*: 636-643, 2007.

23 Tamiya A, Naito T, Miura S, Morii S, Tsuya A, Nakamura Y, Kaira K, Murakami H, Takahashi T, Yamamoto N and Endo M: Interstitial lung disease associated with docetaxel in patients with advanced non-small cell lung cancer. Anticancer Res *32*: 1103-1106, 2012.

24 Kato M, Shukuya T, Takahashi F, Mori K, Suina K, Asao T, Kanemaru R, Honma Y, Muraki K, Sugano K, Shibayama R, Koyama R, Shimada N and Takahashi K: Pemetrexed for advanced non-small cell lung cancer patients with interstitial lung disease. BMC Cancer *14*: 508, doi: 10.1186/1471-2407-14-508, 2014.