Negative Impact of Coexisting Interstitial Lung Disease on Clinical Outcomes in Small-cell Lung Cancer Patients

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Abstract. *Background/Aim:* The impact of interstitial lung disease (ILD) on the clinical outcome of patients with small-cell lung cancer (SCLC) is not fully understood. The aim of this study was to investigate the impact of ILD on treatment and survival outcomes of SCLC patients. *Patients and Methods:* A retrospective analysis was performed on the clinical outcomes of SCLC patients, treated with chemotherapy, with or without ILD ([ILD group (n=16) and non-ILD group (n=51)]). *Results:* Median PFS and OS were significantly shorter in the ILD group than in the non-ILD group (median PFS, 184 vs. 290 days, $p=0.008$; median OS, 236 vs. 691 days, $p<0.001$). Multivariate analysis revealed that coexisting ILD was an independent predictive factor of PFS (hazard ratio [HR]=2.06; 95% confidence interval [CI]=1.01-4.18; $p=0.046$) and OS (HR=3.29; 95%CI=1.53-7.08; $p=0.002$). *Conclusion:* Coexisting ILD might be a negative predictive factor of PFS and OS of SCLC patients treated with chemotherapy.

Small-cell lung cancer (SCLC) accounts for approximately 13% of primary lung cancer cases and is categorized as limited disease (LD)-SCLC and extensive disease (ED)-SCLC based on treatment options. Standard-care for LD-SCLC and ED-SCLC is chemoradiotherapy and platinum combined chemotherapy, respectively. Despite a high sensitivity to initial chemotherapy and radiotherapy, most patients with SCLC develop tumor relapse and have dismal prognosis (1, 2).

Interstitial lung disease (ILD) is characterized by inflammation and fibrosis of alveoli, distal airways, and septal

interstitium of lungs, and typical computed tomography (CT) findings of ILD include an interstitial shadow reflecting thickened septa, reticulation, areas of decreased attenuation, ground-glass opacities, and honeycombing (3). ILD, particularly idiopathic pulmonary fibrosis (IPF), is a risk factor for lung cancer; previous studies reported that lung cancer incidence in patients with IPF ranged from 13-20.4%, which is higher than that in the general population (4-6). Evaluation of the causes of death in IPF patients revealed that acute exacerbation (AE) and chronic respiratory failure account for 64% of the deaths, whereas lung cancer alone accounts for 11% of the deaths (7).

AE is a serious obstacle in the treatment of lung cancer patients with ILD. The incidence rates of AE induced by chemoradiotherapy, radiotherapy, and chemotherapy in patients with concomitant ILD and lung cancer were 42.9%, 16.7%, and 20-26.6%, respectively (8, 9). Moreover, mortality due to AE of ILD (AE-ILD) due to chemotherapy was reported to range from 29-50% (9-12). Thus, treatment strategies for lung cancer patients with ILD should be distinct from those in non-ILD patients.

In lung cancer patients with ILD, the rates of non-small-cell lung cancer (NSCLC) and SCLC were reported to be 62.5-63.3% and 30.2-36.5%, respectively (10, 12). Several retrospective studies of NSCLC patients showed that the presence of ILD was a poor prognostic factor and a negative predictive factor for response to chemotherapy (13-16). However, the clinical impact of ILD in patients with SCLC treated with chemotherapy remains unclear. Therefore, we conducted a retrospective study to investigate the clinical features of SCLC patients with ILD and assess the impact of coexisting ILD on clinical outcomes including therapeutic response and prognosis.

Patients and Methods

Patients. Between April 2006 and March 2016, 87 SCLC patients were diagnosed at Kumamoto University Hospital. Among these, 72

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Key Words: Small-cell lung cancer, interstitial lung disease, chemotherapy, acute exacerbation.

Table I. Patient characteristics.

	Non-ILD (n=51)		ILD (n=16)		p-Value
	n	%	n	%	
Age, years					
Median (range)	67 (45-85)		71 (56-83)		0.955
<65	17	33.3	4	25.0	
≥65	34	66.7	12	75.0	
Gender					
Male	43	84.3	14	87.5	0.755
Female	8	15.7	2	12.5	
Smoking					
Yes	48	94.1	15	93.8	0.957
No	3	5.9	1	6.3	
PS					
0-1	46	90.2	13	81.3	0.336
≥2	5	9.8	3	18.8	
LDH, U/l					
Median (range)	233 (153-567)		245 (147-1070)		0.407
<240	29	56.9	8	50.0	
≥240	22	43.1	8	50.0	
Stage					
LD	32	62.7	7	43.8	0.179
ED	19	37.3	9	56.3	
ILD					
UIP pattern	-	-	12	75.0	-
Non-UIP pattern	-	-	4	25.0	
Treatment					
Chemoradiotherapy	29	56.9	1	6.3	<0.001
Chemotherapy	22	43.1	15	93.8	
Regimen					
Platinum + VP-16	42	82.3	16	100	0.196
Platinum + CPT-11	8	15.7	0	0	
Other	1	2.0	0	0	

ILD: Interstitial lung disease; PS: Eastern Cooperative Oncology Group performance status; LDH: lactate dehydrogenase; LD: limited disease; ED: extensive disease; UIP: usual interstitial pneumonia; VP-16: etoposide; CTP-11: irinotecan.

patients received first-line chemotherapy except for 12 and 3 patients who received best supportive care (BSC) and radiotherapy alone, respectively. After the exclusion of 5 patients who were lost to follow-up within the first 3 months after diagnosis due to transfer to another hospital, the remaining 67 patients were included in this retrospective study. The patients were divided into the ILD (n=16) and non-ILD (n=51) groups according to the diagnosis at the time of inclusion. The following baseline and clinical characteristics were reviewed and compared between the groups: age, sex, smoking status, Eastern Cooperative Oncology Group performance status (PS), serum lactate dehydrogenase (LDH), stage (LD or ED), type of treatment (chemoradiotherapy or chemotherapy alone), and specific chemotherapeutic regimens. The institutional review board of Kumamoto University Hospital approved of this study (IRB-number 1451).

Diagnosis of ILD and AE of ILD. ILD diagnosis and classification as usual interstitial pneumonia (UIP) or non-UIP were based on the international consensus statement of the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT). UIP

pattern was defined by the following four features: subpleural and basal predominance, reticular abnormality, honeycombing with or without traction bronchiectasis, and absence of features listed as inconsistent with UIP pattern. AE-ILD was also based on the ATS/ERS/JRS/ALAT consensus statement as follows: subjective worsening of dyspnea within the past month; evidence of worsening of partial pressure of oxygen in arterial blood; new radiographic alveolar infiltrates; and absence of an alternative explanation including infection, pulmonary embolism, pneumothorax, worsening of malignant tumor, and heart failure (17). All CT scans were evaluated by 2 independent pulmonologists (K.A. and K.S.).

Outcome parameters and statistical analysis. Best overall response was assessed by the Response Evaluation Criteria in Solid Tumors version 1.1 (18). Overall response rate (ORR) was defined as the percentage of patients with complete response and partial response. Progression-free survival (PFS) was defined as the time from start of first-line chemotherapy to disease progression or death from any cause or last follow-up. Overall survival (OS) was defined as the time from the start of first-line chemotherapy to death from any cause or last follow-up.

Table II. Treatment and chemotherapeutic regimen for patients with LC-SCLC and ED-SCLC.

	LD-SCLC patients				<i>p</i> -Value	ED-SCLC patients				<i>p</i> -Value
	Non-ILD (n=32)		ILD (n=7)			Non-ILD (n=19)		ILD (n=9)		
	n	%	n	%		n	%	n	%	
Treatment										
Chemoradiotherapy	27	84.4	1	14.3	<0.001	2	10.5	0	0	0.312
Chemotherapy	5	15.6	6	85.7		17	89.5	9	100.0	
Regimen										
Platinum + VP-16	31	96.9	7	100.0	0.636	11	57.9	9	100.0	0.021
Platinum + CPT-11	0	0	0	0		8	42.1	0	0	
Others	1	3.1	0	0		0	0	0	0	

LD: Limited disease; ED: extensive disease; ILD: interstitial lung disease; chemo: chemotherapy; RT: radiotherapy; VP-16: etoposide; CPT-11: irinotecan.

Fisher exact test and the chi-squared test were used for comparison of categorical variables between the 2 groups. PFS and OS were calculated by the Kaplan–Meier method and compared by the log-rank test. To evaluate the clinical impact of ILD on PFS and OS, multivariate analysis was performed using the Cox regression model. Clinical variables that were previously known to exert clinical and prognostic influence on SCLC were included in the multivariable analysis (1, 19, 20). All *p*-values <0.05 were considered to indicate statistical significance. All statistical analyses were performed by Statistical Package for the Social Science (version 23.0; IBM, Armonk, NY, USA).

Results

Patient characteristics. Demographic and clinical patient characteristics are shown in Table I. There were no significant differences in age, sex, smoking status, PS, serum LDH, and stage between the 2 groups, although the proportion of those receiving chemoradiotherapy was significantly lower in the ILD than in the non-ILD group (6.3% vs. 56.9%; *p*<0.001). Additionally, the proportion of LD-SCLC patients receiving chemoradiotherapy was lower in the ILD than in the non-ILD group (14.3% vs. 84.4%; *p*<0.001, Table II). All patients with ILD had platinum and etoposide (VP-16), and ED-SCLC patients in the non-ILD group had a significantly higher rate of treatment with irinotecan (CPT-11) than those in the ILD group (42.1% vs. 0%; *p*=0.021, Table II). In the ILD group, 2 patients had connective tissue disease-associated ILD, including 1 patient with rheumatoid arthritis, polymyositis, and sclerosis and 1 patient with mixed connective tissue disease and rheumatoid arthritis, whereas the remaining 14 patients were diagnosed with idiopathic interstitial pneumonia (IPF, *n*=11; non-IPF, *n*=3). Evaluation of CT scans revealed that UIP and non-UIP patterns were present in 12 and 4 patients, respectively. Among those with the non-UIP CT pattern, 1 and 3 patients had cellular non-specific and fibrotic interstitial pneumonia patterns, respectively.

Response to first-line chemotherapy. ORR of first-line chemotherapy is shown in Table III. ORR was significantly lower in the ILD than in the non-ILD group (50.0% vs. 84.3%; *p*=0.005). ORR for both LD- and ED-SCLC patients tended to be lower in the ILD than in the non-ILD group (LD-SCLC, 71.4% vs. 93.8%, *p*=0.078; ED-SCLC, 33.3% vs. 68.4%, *p*=0.080).

Survival analysis. Median follow-up was 391 days (range=43–2,485 days). Median PFS was significantly shorter in the ILD than in the non-ILD group (184 vs. 290 days, *p*=0.008, Figure 1A). Median PFS for both the LD-SCLC and ED-SCLC patients tended to be lower in the ILD than in the non-ILD group (LD-SCLC, 236 vs. 303 days, *p*=0.174, Figure 1B; ED-SCLC, 143 vs. 217 days; *p*=0.023, Figure 1C). Median OS was also shorter in the ILD than in the non-ILD group (236 vs. 691 days; *p*<0.001, Figure 1D). Median OS for both the LD- and ED-SCLC patients was shorter in the ILD than in the non-ILD group (LD-SCLC, 347 vs. 935 days, *p*=0.049, Figure 1E; ED-SCLC, 203 vs. 441 days; *p*<0.001, Figure 1F).

Subsequent chemotherapy. The proportion of second-line chemotherapy tended to be lower in the ILD than the non-ILD group (43.8% vs. 64.7%, *p*=0.136, Table IV). Among the second-line chemotherapy regimens, 17 (33.3%) and 16 (31.4%) of the 51 patients in the non-ILD group received platinum-based combination chemotherapy and amrubicin, respectively, whereas 3 (18.8%) and 2 (31.4%) of the 16 patients in the ILD group received topotecan and paclitaxel, respectively. The proportion of third-line chemotherapy was significantly lower in the ILD than in the non-ILD group (41.2% vs. 6.3%, *p*=0.009). Among the third-line chemotherapy regimens, 12 (23.5%) and 6 (11.8%) patients received amrubicin and topotecan, respectively, in the non-ILD group, whereas only 1 patient in the ILD group received paclitaxel.

Table III. Response to first-line chemotherapy.

	All patients		<i>p</i> -Value	LD-SCLC patients		<i>p</i> -Value	ED-SCLC patients		<i>p</i> -Value
	Non-ILD (n=51)	ILD (n=16)		Non-ILD (n=32)	ILD (n=7)		Non-ILD (n=19)	ILD (n=9)	
CR	11	3		11	3		0	0	
PR	32	5		19	2		13	3	
SD	3	5		0	2		3	3	
PD	4	2		1	0		3	2	
NE	1	1		1	0		0	1	
ORR	84.3%	50.0%	0.005	93.8%	71.4%	0.078	68.4%	33.3%	0.080

LD: Limited disease; ED: extensive disease; ILD: interstitial lung disease; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE: not evaluable; ORR: overall response rate.

Table IV. Subsequent chemotherapy.

	Non-ILD (n=51)		ILD (n=16)		<i>p</i> -Value
	n	%	n	%	
Second-line chemotherapy	33	64.7	7	43.8	0.136
Platinum doublet	17	33.3	3	18.8	
AMR	16	31.4	0	0	
TOP	0	0	2	12.5	
CPT-11	0	0	0	0	
PTX	0	0	2	12.5	
Third-line chemotherapy	21	41.2	1	6.3	0.009
Platinum doublet	1	0	0	0	
AMR	12	23.5	0	0	
TOP	6	11.8	0	0	
CPT-11	1	0	0	0	
PTX	1	0	1	6.3	

LD: Limited disease; ED: extensive disease; ILD: interstitial lung disease; chemo: chemotherapy; AMR: amrubicin; TOP: topotecan; CPT-11: irinotecan; PTX: paclitaxel.

Predictive factors of PFS and OS. Multivariate analysis of PFS performed to evaluate the clinical impact of coexisting ILD (Table V) showed that ED-stage (hazard ratio [HR], 1.82; 95% confidence interval [CI]=1.03-3.23, $p=0.040$) and coexisting ILD (HR, 2.06; 95%CI=1.01-4.18, $p=0.046$) were independent negative predictive factors. Multivariate analysis for OS showed that poor PS (≥ 2) (HR=3.27; 95%CI=1.18-9.03, $p=0.023$), ED-stage (HR=2.03; 95%CI=1.09-3.78, $p=0.026$), and coexisting ILD (HR=3.29; 95%CI=1.53-7.08; $p=0.002$) were negative prognostic factors.

AE of ILD. Among the 16 patients with coexisting ILD, 5 (31.3%) experienced AE of ILD during the entire study period from the start of chemotherapy. Table VI summarizes the characteristics and clinical outcomes of

Table V. Multivariate analysis for PFS and OS.

Variable	PFS		OS	
	HR (95%CI)	<i>p</i> -Value	HR (95%CI)	<i>p</i> -Value
Age, years				
≥ 65	0.83 (0.47-1.48)	0.526	1.03 (0.53-1.97)	0.937
<65	Ref		Ref	
Gender				
Male	0.80 (0.35-1.85)	0.605	0.75 (0.29-1.93)	0.549
Female	Ref		Ref	
PS				
≥ 2	1.44 (0.53-3.89)	0.472	3.27 (1.18-9.03)	0.023
0-1	Ref		Ref	
LDH, U/l				
≥ 240	1.49 (0.84-2.64)	0.169	1.26 (0.65-2.42)	0.493
<240	Ref		Ref	
Stage				
ED	1.82 (1.03-3.23)	0.040	2.03 (1.09-3.78)	0.026
LD	Ref		Ref	
ILD				
ILD	2.06 (1.01-4.18)	0.046	3.29 (1.53-7.08)	0.002
Non-ILD	Ref		Ref	

PFS: Progression-free survival; OS: overall survival; HR: hazard ratio; 95%CI: 95% confidence interval; PS: Eastern Cooperative Oncology Group performance status; LDH: lactate dehydrogenase; LD: limited disease; ED: extensive disease; ILD: interstitial lung disease; Ref: reference.

these patients. All 5 patients who developed AE of ILD had UIP pattern. Additionally, 4 patients had IPF. Regarding treatment, 3, 1, and 1 patient received platinum plus VP-16, topotecan, and paclitaxel, respectively. All 5 patients received steroid therapy, including 1 patient who was administered steroid pulse therapy with methylprednisolone. Two patients with AE-ILD died within 2 weeks after the onset of AE, only 1 patient received subsequent chemotherapy after AE, and the remaining 2 patients received BSC.

Figure 1. Kaplan–Meier survival curves for progression-free survival (PFS) and overall survival (OS) of patients with small-cell lung cancer (SCLC) with or without interstitial lung disease (ILD). PFS in all patients (A), those with limited disease (LD)-SCLC (B), and those with extensive disease (ED)-SCLC (C). OS in all patients (D), those with LD-SCLC (E), and those with ED-SCLC (F).

Table VI. Acute exacerbation of patients with interstitial lung disease.

Case	Gender	Age, years	UIP/non-UIP	Regimen	Treatment line	Outcome of AE	OS after AE (days)	Subsequent therapy
1	M	56	UIP	CDDP+VP-16	1st line	Recovery	225	PTX
2	M	59	UIP	TOP	2nd line	Death	11	(-)
3	M	72	UIP	PTX	2nd line	Recovery	76	BSC
4	F	74	UIP	CBDCA+VP-16	1st line	Death	12	(-)
5	M	77	UIP	CBDCA+VP-16	1st line	Recovery	28*	BSC

ILD: Interstitial lung disease; UIP: usual interstitial pneumonia pattern; AE: acute exacerbation; M: Male; F: Female; CDDP: cisplatin; CBDCA: carboplatin; VP-16: etoposide; TOP: topotecan; PTX: paclitaxel; BSC: best supportive care. *Censored due to transfer to hospital.

Discussion

The present study demonstrated that 23.9% of SCLC patients treated with chemotherapy had concomitant ILD and that there were no significant differences in the characteristics between those with ILD and without ILD. The ORR, PFS, and OS rates were significantly worse in the ILD group than in the non-ILD group, and multivariate analyses revealed that coexisting ILD was a negative predictive factor for PFS and OS in SCLC patients treated with chemotherapy.

Several retrospective studies showed that 9.0%-24.3% of NSCLC patients were complicated with ILD at diagnosis (12, 16). In the current study, the proportion of ILD in SCLC patients (23.9%) was similar to that reported in previous studies on NSCLC (12, 16). SCLC is strongly associated with smoking, which is also a recognized risk factor for several ILD types such as respiratory bronchiolitis-ILD, desquamative interstitial pneumonitis, IPF, and combined pulmonary fibrosis and emphysema (1, 21, 22). Since ILD is a relatively common complication in SCLC patients, establishment of an optimal treatment strategy for patients with SCLC and coexisting ILD is critical.

The present study showed that ORR in patients with ILD was lower than that in those without ILD and that coexisting ILD was a negative predictive factor, suggesting that ILD might be associated with resistance to chemotherapy. Kanaji *et al.* similarly reported that NSCLC patients with ILD had lower response rates to chemotherapy/molecular target therapy when compared with those without ILD. (16) Multiple cytokines and growth factors including vascular endothelial growth factor (VEGF) and transforming growth factor β (TGF- β) were shown to be associated with pulmonary fibrosis (23, 24). Previous studies showed that VEGF mRNA expression and TGF- β concentration in bronchoalveolar lavage fluid of IPF patients were elevated compared to those without IPF (25-27). VEGF is a major regulator of angiogenesis that is essential for tumor progression and metastasis (28, 29). TGF- β was shown to play an important role in epithelial-mesenchymal transition, which is associated with chemoresistance (30). Although we did not evaluate VEGF and TGF- β in bronchoalveolar lavage fluid of

SCLC patients with ILD, these abundant tumor-promoting and chemoresistance factors in ILD patients might be associated with lower response and shorter PFS.

This analysis showed that coexisting ILD was a negative prognostic factor in SCLC patients treated with chemotherapy. Togashi *et al.* reported that median OS was significantly shorter in SCLC patients with coexisting ILD than those without coexisting ILD (10.7 vs. 17.8 months) and that coexisting ILD was a negative prognostic factor, consistent with the present study (19). Possible factors associated with worse prognosis in SCLC patients with ILD are lower frequency of chemoradiotherapy and subsequent chemotherapy. First, a meta-analysis evaluating thoracic radiotherapy for LD-SCLC found that chemoradiotherapy for LD-SCLC significantly prolonged survival compared with chemotherapy alone (31). In the present study, the proportion of chemoradiotherapy in the ILD group (only 1 in 7 LD-SCLC patients) was significantly lower than that in the non-ILD group. One possible reason for the lower chemoradiotherapy rate in the ILD group is physicians' avoidance of chemoradiotherapy for SCLC patients with ILD due to concerns regarding AE of ILD being precipitated by chemoradiotherapy. Second, the proportion of patients receiving subsequent chemotherapy beyond first-line chemotherapy tended to be lower in the ILD than in the non-ILD group. A randomized phase III trial comparing topotecan with BSC showed that topotecan prolonged survival in the second-line setting (32). Additionally, several agents such as amrubicin and CPT-11 were reportedly effective as salvage therapy for recurrent SCLC patients (33-35). However, amrubicin and CPT-11 are contraindicated for ILD patients in Japan, due to the high risk of AE. Since the selection of chemotherapeutic regimens in Japanese SCLC patients with ILD is limited, further development of effective and safe treatments for patients with ILD is needed.

Several retrospective studies showed that the incidence of AE-ILD in lung cancer patients with ILD receiving chemotherapy was 20%-26.6%, (8, 9) and that the mortality of AE-ILD was remarkably high between 29% and 50% (9-12). In this study, 5 (31%) of the 16 SCLC patients with ILD

experienced AE and 2 (40%) patients died of AE-ILD, consistent with previous reports (8-12). Moreover, all 5 patients with AE-ILD had the UIP pattern, including 4 patients diagnosed with IPF. Since AE-ILD is a life-threatening adverse event, strategies for prevention of AE-ILD during chemotherapy should be developed for patients with ILD. For example, nintedanib is a tyrosine kinase inhibitor that targets multiple receptors including fibroblast growth factor, platelet-derived growth factor, and VEGF. A recent analysis of data pooled from the TOMORROW and INPLUSIS trials comparing nintedanib to placebo in IPF patients showed that the HR of time to first AE was 0.53 (95%CI=0.34-0.83; $p=0.0047$) in favor of nintedanib and that the proportion of patients with AE was lower in the nintedanib group than in the placebo group (4.6% vs. 8.7%) (36). To evaluate whether nintedanib prolongs time to AE of IPF, a currently ongoing randomized trial is comparing nintedanib combined with carboplatin plus nab-paclitaxel with carboplatin plus nab-paclitaxel alone for patients with NSCLC and IPF (37). Therefore, SCLC patients with ILD might benefit from chemotherapy plus nintedanib.

The present study has several limitations. First, this was a retrospective single-center study including only Japanese patients. AE of Japanese patients with IPF were reported to be more frequent than in other ethnic groups (7, 17). Second, potential clinical factors affecting prognosis such as pulmonary function and serum Krebs von den Lungen-6 (KL-6) levels were not evaluated. A decline in forced vital capacity of >10% within 6 months and baseline serum KL-6 level of >1,000 U/ml were reported as sensitive predictors of OS (38, 39). Further large-sized studies including other ethnic groups and ILD prognostic factors are warranted to elucidate the clinical significance of coexisting ILD in SCLC.

In conclusion, the present study showed that coexisting ILD might be a negative predictive factor of ORR, PFS, and OS in SCLC patients treated with chemotherapy. Moreover, the incidence of AE-ILD was higher in SCLC patients with ILD. Thus, SCLC patients with ILD might require distinctive treatment strategies compared with those without ILD.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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