

Safety and Efficacy of Platinum Agents plus Etoposide for Patients with Small Cell Lung Cancer with Interstitial Lung Disease

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Abstract. *Background:* The safety and efficacy of combination of platinum agents plus etoposide for patients with small cell lung cancer (SCLC) with pre-existing interstitial lung disease (ILD) is uncertain. *Patients and Methods:* Fifty-two patients received platinum agents plus etoposide as first-line chemotherapy for SCLC with pre-existing ILD. The clinical characteristics, treatment outcome and survival of these patients were retrospectively reviewed. *Results:* During first-line chemotherapy, only one (2%) out of the 52 patients developed an acute exacerbation of ILD. The median number of treatment cycles was four. The overall response rate was 69%. The median progression-free survival period was 4.5 months. The median survival time was 9.4 months. Thirty-three patients (63%) received at least one subsequent chemotherapy regimen, and five of these patients developed acute exacerbation of ILD. *Conclusion:* The combination of platinum agents plus etoposide is feasible and effective in SCLC patients with pre-existing ILD, compared with regimens after second-line chemotherapy.

Small cell lung cancer (SCLC) accounts for 15% to 20% of all lung cancer cases (1). SCLC is characterized by rapid growth and widespread metastatic disease, and most patients have extensive disease at the time of diagnosis. SCLC is significantly sensitive to chemotherapy or radiation therapy, and therefore systemic chemotherapy is recognized as a standard treatment (2). The standard chemotherapy regimen for SCLC patients is the combination of platinum agents plus

etoposide or platinum agents plus irinotecan, which is the most frequently used combination and yields a median survival period of approximately 9-12 months in clinical trials (3, 4).

Pre-existing interstitial lung disease (ILD) is one of the most common complications in patients with lung cancer. ILD, also known as diffuse parenchymal lung disease, is a diverse group of pulmonary disorders classified together because of similar clinical, radiographical, physiological, and pathological features (5). In patients with cancer, pre-existing ILD is considered to be a risk factor for acute exacerbation, which is a fatal complication of treatments such as chemotherapy, surgery, and radiation therapy (6, 7). The incidence of lung cancer in patients with ILD is reported to be 20-30% and is higher than that in the general population (8). Kudoh *et al.* reported recently that pre-existing ILD was confirmed to be an important determinant of the development of the acute exacerbation of ILD after chemotherapy for patients with advanced non-small cell lung cancer (NSCLC) (6). However, few reports exist on the association between pre-existing ILD and the safety and efficacy of chemotherapy in patients with SCLC. Whether chemotherapy for patients with SCLC with pre-existing ILD is feasible remains unclear because patients with severe complications, such as pre-existing ILD, have been excluded from most prospective clinical trials.

In this retrospective study, we investigated the safety and efficacy of the combination of platinum agents plus etoposide as a first-line chemotherapy for patients with SCLC with preexisting ILD.

Patients and Methods

Between January 2001 and December 2009, a total of 557 consecutive patients were diagnosed as having SCLC at the National Cancer Center Hospital East. Overall, 52 (11%) of these patients had pre-existing ILD and received first-line chemotherapy. The clinical characteristics, treatment outcome, and survival of these patients were retrospectively reviewed using data obtained from

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Key Words: Interstitial lung disease, small cell lung cancer, chemotherapy, cisplatin, carboplatin, etoposide, acute exacerbation.

Table I. *Patients' characteristics.*

Characteristic	N	%
Number of patients	52	
Age (years)		
Median (range)	71 (50-85)	
Gender		
Male	50	96
Female	2	4
Performance status		
0/1	9/37	88
2/3	5/1	12
Smoking status		
Never smoker	0	0
Current/former	25/27	100
Brinkman index median (range)	1050 (315-2940)	
Clinical stage		
Limited disease	29	56
Extensive disease	23	44

their medical records. The patients were staged according to the staging system of the Veterans Administration Lung Cancer Study Group as limited disease (LD) or extensive disease (ED) (9). In this study, two independent pulmonologists (T.Y. and K.Y.) who had no knowledge of the patients' outcome diagnosed pre-existing lung conditions based on pre-treatment chest computed tomography (CT) findings obtained before first-line chemotherapy. Pre-treatment conventional CT or high-resolution CT (HRCT) films of the chest were used in our analysis. Pre-existing ILD was diagnosed when diffuse ground-glass opacity, peripheral reticular opacity, and consolidation without segmental distribution and a honeycomb pattern were detected in bilateral lung fields on the chest X-ray and CT findings. The acute exacerbation of ILD was diagnosed based on the chest X-ray and/or CT findings, which showed newly-developed diffuse pulmonary opacities, physical findings, and serum levels of markers of damaged pneumocytes [*i.e.* lactate dehydrogenase (LDH), C-reactive protein (CRP), Krebs von den Lungen-6 (KL-6)] and the lack of a response to antibiotics. Patients with pulmonary infection, pneumothorax, pulmonary embolism, or heart failure were excluded.

The objective tumor response was assessed according to the Response Evaluation Criteria Solid Tumor (RECIST) (10). The objective response rate (ORR) was calculated as the total percentage of patients with a complete response (CR) or a partial response (PR). Toxicity was graded using the Common Terminology Criteria for Adverse Events (CTCAE), ver. 3.0 (11). A univariate analysis was performed to identify risk factors for the acute exacerbation of ILD in patients with SCLC with pre-existing ILD. All the variables were analyzed using the Fisher's exact test. Multivariate analyses were performed using logistic regression. A clinical evaluation of progression-free survival (PFS) was measured from the start of the first-line chemotherapy to the identifiable time for progression. The overall survival (OS) was measured as the period from the start of first-line chemotherapy until death from all causes. The PFS and OS were plotted using the Kaplan-Meier method. All the p-values were two-sided, and a level of 5% was considered statistically significant, unless otherwise specified.

Table II. *Treatment outcome of first-line chemotherapy in 52 patients with small cell lung cancer with pre-existing Interstitial Lung Disease.*

	N	%
Number of patients	52	
First-line chemotherapy regimen		
Carboplatin plus etoposide	22	42
Cisplatin plus etoposide	30	58
Number of cycles (1/2/3/4)	8/6/6/32	15/12/12/61
Objective response		
CR	1	
PR	35	
SD	9	
PD	3	
NE	4	
Overall response rate (LD/ED)		72/65

CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; LD, limited disease; ED, extensive disease.

Results

Patients' characteristics. The pre-treatment characteristics of the patients are shown in Table I. The median age at the time of first-line chemotherapy for SCLC was 71 years (range=50-85 years), 96% of them were men, and 88% had an Eastern Cooperative Oncology Group performance status (PS) of 0 or 1. All the patients were current or former smokers. None of the patients had histologically-confirmed interstitial pneumonia. Overall, 56% of the patients had LD and 44% had ED. As the first-line chemotherapy, 22 (42%) out of the 52 patients received carboplatin plus etoposide, and 30 (58%) patients received cisplatin plus etoposide (every 3 to 4 weeks). In the three cases, radiation therapy was performed after four cycles of chemotherapy. After progression, 33 patients received second-line chemotherapy. Subsequent chemotherapy regimens were amrubicin in 17 patients, cisplatin plus irinotecan in nine, irinotecan in six, carboplatin plus etoposide in five, topotecan in four, the combination of irinotecan, cisplatin plus etoposide in two, and carboplatin plus paclitaxel in one patient.

Treatment efficacy. Table II summarizes the treatment outcome of first-line chemotherapy. Regarding treatment delivery, the median number of administered cycles was four (range=1-4). Overall, 32 (61%) of the patients completed all four of the planned cycles. The treatment was discontinued because of progressive disease (PD) in seven patients, toxicity in nine, and other reasons in four patients. The ORR was 69% (72% in LD and 65% in ED, respectively), comprising of one CR and 35 PR. The response was not evaluable in four patients because of death before the first

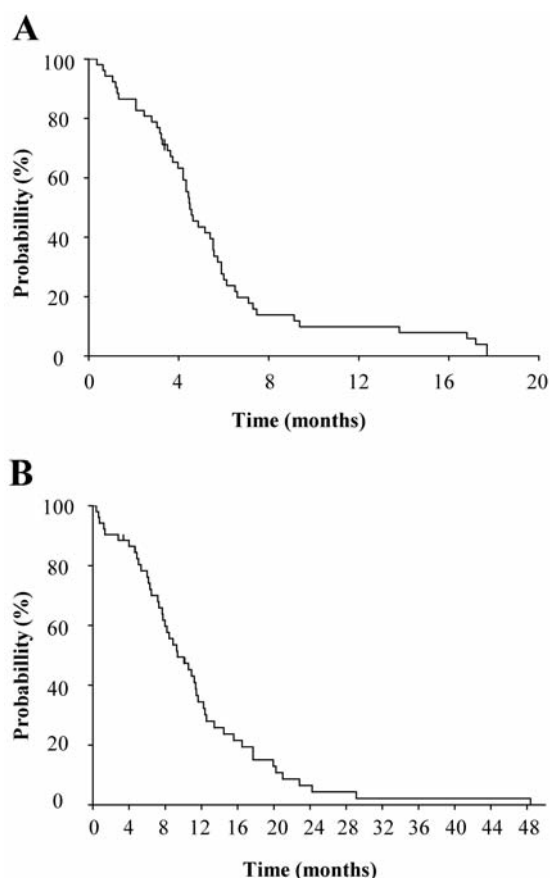


Figure 1. Progression-free survival (PFS) (A) and overall survival (OS) (B) of patients with SCLC with Interstitial Lung Disease who received platinum agents plus etoposide as first-line chemotherapy. The vertical bars indicate the censored cases at the cut-off date. The median PFS, median OS, and 1-year survival times were 4.5 months [5.4 months, limited disease (LD) stage; 3.7 months, extensive disease (ED) stage], 9.4 months (10.6 months, LD stage; 8.2 months, ED stage), and 32%, respectively.

tumor response evaluation. The median PFS after first-line chemotherapy and the median OS were 4.5 months (5.4 months, LD stage; 3.7 months, ED stage) (Figure 1A) and 9.4 months (10.6 months, LD stage; 8.2 months, ED stage), respectively (Figure 1B). Regarding the PFS and OS, the differences between the LD and ED stages were not statistically significant.

Incidence of acute exacerbation of ILD. Only one patient (2%) developed an acute exacerbation of ILD during first-line chemotherapy (carboplatin plus etoposide). During second- or third-line chemotherapy, five patients developed acute exacerbation of ILD. The regimens immediately before the development of the acute exacerbation of ILD were amrubicin in three patients, a combination of irinotecan,

cisplatin, plus etoposide in one, and topotecan in one patient. The characteristics of all six patients with acute exacerbations of ILD, are listed in Table III. All the patients were smokers and men with a good PS before chemotherapy. The median time from the last administration of chemotherapy to the development of the acute exacerbation of ILD was 37 days. Although all the patients with acute exacerbation of ILD were treated using steroids, three out of the six patients did not improve and died. The results of univariate analyses of risk factors (age, sex, Brinkman index, LDH levels, and PS) for the acute exacerbation of ILD are listed in Table IV. No significant risk factors for acute exacerbation of ILD were identified. The results of the multivariate analysis for the acute exacerbation also showed that none of the variables were significant.

Discussion

In our study, the results for the 52 patients with SCLC with pre-existing ILD indicated that the combination of platinum agents plus etoposide as first-line chemotherapy yielded an ORR of 69%, a median PFS of 4.5 months, and a median OS of 9.4 months. Although directly comparable historical control data were not available, the observed efficacy in our study was the same as the results of two previous randomized phase III trials with platinum agents plus etoposide for ED stage patients with SCLC [Japan Clinical Oncology Group (JCOG) 9511: ORR=67.5%; PFS=4.8 months; median OS=9.4 months; and JCOG 9702: ORR=73%; PFS=5.2 months; median OS=10.6 months] (3, 4). Furthermore, the incidence of acute exacerbation of ILD during first-line chemotherapy observed in our study, was 2% (1/52). The combination of platinum agents plus etoposide seems to be effective and tolerable as a first-line chemotherapy for patients with SCLC with preexisting ILD.

The incidence of lung cancer is reported to be higher in patients with ILD than in patients without (8). In patients with lung cancer, pre-existing ILD has been reported to be a risk factor for the development of anticancer agent-associated acute exacerbation of ILD, which is a fatal complication of treatment. There are some reports regarding the safety and efficacy of chemotherapy for advanced or recurrent NSCLC with pre-existing ILD (6, 12, 13), and the incidence of acute exacerbation of ILD in NSCLC is reported to range from 20% to 24% in Japan, although the chemotherapeutic regimens that were administered were not the same (14, 15). Minegishi *et al*. reported the results of feasibility study for carboplatin plus etoposide in 17 SCLC patients with idiopathic interstitial pneumonias (IIPs) (16). The results indicated that the acute exacerbation of IIP occurred in one (5.9%) out of the 17 patients, with a median PFS of 5.5 months and a median OS of 8.7 months. However, that study was limited in that it included a small number of patients. It

Table III. Summary of data for six patients who developed acute exacerbation of Interstitial Lung Disease.

No.	Age (years)	Gender	PS	BI index	Prior chemotherapy	Time to AE after prior chemotherapy	Initial manifestations	AE status	Time to death after last chemotherapy (days)
1	71	Male	1	940	Carboplatin, Etoposide (1st line)	5 (day 5 in cycle 1)	Dyspnea	Died	19
2	53	Male	2	1490	Amrubicin (3rd line)	17 (day 17 in cycle 1)	Dyspnea, fever	Died	30
3	70	Male	1	1150	Cisplatin, Etoposide, Irinotecan (2nd line)	140 (day 93 in cycle 3)	Dyspnea	Died	123
4	50	Male	1	330	Topotecan (2nd line)	52 (day 24 in cycle 2)	Dyspnea	Improved	–
5	63	Male	1	960	Amrubicin (2nd line)	23 (day 23 in cycle 1)	Dyspnea, fever	Improved	–
6	62	Male	1	620	Amrubicin (3rd line)	73 (day 17 in cycle 3)	Dyspnea	Improved	–

PS, Performance status; BI, Brinkman index; AE, acute exacerbation.

was also unclear whether chemotherapy regimens such as platinum agents plus etoposide, which is the most frequently used regimen worldwide (4, 17), were feasible in patients with SCLC, with pre-existing ILD at the time of the start of our study.

In our study, acute exacerbation of ILD during second- or third-line chemotherapy occurred in five (16%) out of the 33 patients who received subsequent chemotherapy, compared with 2% (1/52) of the patients who received platinum agents plus etoposide as first-line chemotherapy. Previous reports have also shown that second-line chemotherapy has a high frequency and risk of the acute exacerbation of ILD, consistent with the results of the present study (15, 16). We speculated that the difference in the incidence of acute exacerbation of ILD between the first-line and subsequent chemotherapy regimens can be accounted for by some of the effective agents used for refractory SCLC, such as amrubicin and irinotecan, which are reportedly associated with a high incidence of acute exacerbation in patients with pre-existing ILD (18, 19).

Our study has a major limitation in that the diagnosis of acute exacerbation of ILD was not based on pathological findings but only on results of chest CT findings and the clinical course. We cannot completely exclude the possibility that the patients had developed lymphangitic carcinomatosis or some other disease, rather than acute exacerbation of ILD. However, pathological findings for the diagnosis of acute exacerbation of ILD are difficult to obtain. Therefore, we diagnosed acute exacerbation of ILD based on clinical and radiographic findings that were consistent with drug-induced ILD. Moreover, the pathological diagnosis of ILD using an open lung biopsy before treatment is extremely difficult and impractical, since chemotherapy should be started as soon as possible after the diagnosis of SCLC, which is characterized

Table IV. Relationship between clinical variables and acute exacerbation of Interstitial Lung Disease.

	No. of patients	Incidence of AE (%)	p-Value
Total	52	12	
Age			
<70 years	18	22	0.17
≥70 years	34	6	
Gender			
Male	50	12	>0.99
Female	2	0	
PS			
0/1	46	0	
2/3	6	13	
Smoking index			
<1000	21	14	0.68
≥1000	31	10	
LDH			
Normal	30	7	0.38
High (more than upper limit of normal)	22	18	

PS, Performance status; LDH, lactate dehydrogenase.

by rapid growth and widespread metastatic disease. We consider that the diagnosis of pre-existing ILD and the acute exacerbation of ILD based on clinical and radiological findings is appropriate in clinical practice.

Our findings indicated that the combination of platinum agents plus etoposide is feasible and effective for the treatment of patients with SCLC with pre-existing ILD. A further large study is warranted to enable definitive conclusions to be drawn.

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