Second-line Chemotherapy for Patients with Small Cell Lung Cancer and Interstitial Lung Disease

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Abstract. *Background: The safety and efficacy of second-line chemotherapy for treating patients with small cell lung cancer (SCLC) and interstitial lung disease (ILD) have not been elucidated to date. Patients and Methods: Between January 2005 and September 2013, we analyzed 23 patients with SCLC and ILD who received second-line chemotherapy. Pre-existing ILD was diagnosed according to clinical features and pretreatment chest high-resolution computed tomography results. Results: The overall objective response rates and disease control rates were 22% and 52%, respectively. The median respective durations of progression-free survival and overall survival were 2.1 months (95% confidence interval (CI)=2.0-3.0 months) and 7.1 months (95% CI=3.6-11.3 months), respectively. Three patients with unusual interstitial pneumonia pattern (13%) developed chemotherapy-related pneumonitis. Conclusion: Second-line treatment may be an effective and safe option for SCLC patients with ILD after sufficient evaluation of risks and benefits.*

Lung cancer is the leading cause of cancer death worldwide. Small cell lung cancer (SCLC) accounts for 15% to 20% of all lung cancer patients, and prognosis remains poor (1).

Interstitial lung disease (ILD) is characterized by damage to the lung parenchyma by varying patterns of inflammation and fibrosis, and has been shown to be associated with lung carcinogenesis (2-4). Recent studies reported that smokers with ILD in unselected populations are relatively common and their prevalence appears to be increasing (5-7).

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Evidence indicates that pre-existing ILD is a risk factor for chemotherapy-related exacerbation of ILD (8, 9). Patients with advanced SCLC and ILD treated with etoposide and carboplatin combination chemotherapy gain benefits, with safety equivalent to what is seen in patients without ILD, according to a previous study (10). However, the safety and efficacy of second-line chemotherapy for treating patients with SCLC with ILD has not been elucidated, though it may provide significant palliation of symptoms and result in survival prolongation in patients without ILD (11-15).

Therefore, we conducted a retrospective study to evaluate the safety and efficacy of second-line chemotherapy for treatment of patients with SCLC with ILD.

Patients and Methods

Patients. We analyzed 23 patients with SCLC and ILD who received second-line chemotherapy at the Kobe City Medical Center General Hospital between January 2005 and September 2013. Results were analyzed retrospectively using case and radiographic records. Patients who reported never smoking were designated never smokers, those who smoked within 1 year of diagnosis were categorized as current smokers, and all others were designated former smokers. Enrolled patients were stratified by type of relapse (chemotherapy sensitive relapse, defined as relapse at an interval of >90 days after completion of first-line chemotherapy, and chemotherapy-refractory relapse, defined as no response to first-line chemotherapy or relapse within 90 days after completion of first-line chemotherapy) (16). The Ethics Committee of the Kobe City Medical Center General Hospital approved of this study.

Treatment. Treatment regimens were as follows: i. Paclitaxel-carboplatin group: every 4 weeks, carboplatin at a dose determined by the area under the curve (AUC) 5-6 was administered on day 1, and paclitaxel at a dose of 60-80 mg/m^2 was administered on days 1, 8, and 15. Each 4-week treatment schedule was designated as one cycle; ii. Paclitaxel group: Every 4 weeks, paclitaxel at a dose of 70-100 mg/m^2 was administered on days 1, 8, and 15. Each 4-week treatment schedule was designated as one cycle; iii. Topotecan group: Every 3 weeks, topotecan at a dose of 1.0 mg/m^2 was administered on days 1-5. Each 3-week treatment schedule was designated as one cycle. The approved dosage of topotecan in Japan

Table I. *Patients' characteristics*

Characteristics	All patients (%) (*n*=23)
Age (years)	
Range	62-80
Median	71
Sex	
Men	18 (78)
Women	5 (22)
Smoking status	
Never	0 (0)
Current or former	23 (100)
ECOG PS*	
0 or 1	17 (74)
2	5 (22)
3 or 4	1 (4)
Stage at diagnosis	
Limited stage	5 (22)
Extensive stage	18 (78)
Radiologic features of interstitial lung disease	
UIP	18 (78)
Non-UIP	5 (22)
Relapse type	
Refractory relapse	14 (61)
Sensitive relapse	9 (39)
Second line chemotherapy	
Carboplatin/Paclitaxel	8 (35)
Paclitaxel	10 (43)
Topotecan	5 (22)

ILD, Interstitial lung disease; UIP, usual interstitial pneumonia; ECOG PS, Eastern Cooperative Oncology Group Performance Status. *PS prior to opting for second-line chemotherapy.

Table II. *Response to second-line chemotherapy*

Regimen	N	ORR (%)	DCR (%)
Carboplatin+paclitaxel	8	3/8 (38)	6/8 (75)
Paclitaxel	10	2/10 (20)	4/10 (40)
Topotecan	5	0/5 (0)	2/5 (40)
Total	23	5/23 (22)	12/23 (52)

ORR, Objective response rate; DCR, disease control rate.

Table III. *Treatment-related adverse events*

Toxicity	Grade					
	1	2	3	4	5	≥3 (%)
Pneumonitis	0	0	1	0	2	3 (13)
Leukopenia	2	4	10	0	-	10 (43)
Neutropenia	2	5	5	5	-	10 (43)
Anemia	1	6	6	0	0	6 (26)
Thrombocytopenia	1	1	3	1	-	4 (17)
Febrile Neutropenia	-	-	1	1	0	2 (9)
Neuropathy	0	2	0	0	0	0 (0)

was determined by the Japanese Ministry of Labour, Health, and Welfare from the results of previous phase I and phase II studies in Japanese chemotherapy-naive patients (17).

Interstitial lung disease (ILD). Preexisting ILD was diagnosed according to clinical features, and pretreatment chest high-resolution computed tomography (HRCT) results. All patients received HRCT according to standard clinical practice, and the presence of ILD was evaluated by at least two pulmonologists. We divided ILD into usual interstitial pneumonia (UIP) and non-UIP patterns. Diagnosis of UIP pattern was determined using computed tomography (CT) features defined by the International Consensus Statement of the American Thoracic Society and European Respiratory Society (18). UIP and possible UIP were considered UIP pattern in this study. Chemotherapy-related exacerbation of ILD was diagnosed according to HRCT findings (bilateral ground-glass abnormality with or without focal consolidation superimposed on pretreatment interstitial shadow) (19). We excluded patients with apparent pulmonary infection, pulmonary embolism, or heart failure. Chemotherapy-related exacerbation of ILD was evaluated according to the presence of pneumonitis/pulmonary infiltrates by the United States National Cancer Institute Common Terminology Criteria version 3.0 as follows: Grade 3, symptomatic, interfering with activities of daily living, and oxygen indicated; Grade 4, life-threatening; and Grade 5, death. To assess the incidence of chemotherapy-related exacerbation of ILD, the duration between the last administration of cytotoxic chemotherapy and the onset of exacerbation of ILD was defined as 4 weeks or fewer.

Patient evaluation and statistical analysis. A CT scan was performed within 28 days before initiating treatment to assess the primary tumor and was repeated every 2 to 3 months. All responses were defined according to the RECIST criteria. A response was confirmed at least 4 weeks (for a complete or partial response) or 6 weeks (for stable disease) after the first documentation. Progression-free survival (PFS) was measured from the start of treatment to the time of progression. Overall survival (OS) was measured from the start of second-line treatment until death by all causes. PFS and OS were determined using the Kaplan–Meier method. The log-rank test was used to compare the cumulative survival of each group. Continuous variables were analyzed using the Student *t*-test, and the results are expressed as means±standard deviation (SD). Dichotomous variables were analyzed using the Chi-square test or the Fisher exact test, as appropriate. The relationship between numerical and categorical variables was compared using the Wilcoxon signed-rank test. All tests were two-tailed, and $p< 0.05$ was considered statistically significant. All statistical analyses were performed using JMP 11 software (SAS Institute, Cary, NC, USA).

Results

Patients' characteristics. Patiens' clinical characteristics are summarized in Table I. All patients were Japanese, including 18 men (78%) and 5 women (22%) with a median age of 71

Table IV. *Summary of the results of the studies that evaluated the efficacy of second-line chemotherapy (topotecan or paclitaxel) in SCLC patients without ILD.*

Study	Regimen and patients	N	PFS* (months)	OS* (months)
O'Brien, *et al*. (11)	Topotecan 42% sensitive relapse	71	3.8	6.0
Von Pawel, *et al*. (12)	Topotecan 100% sensitive relapse	107	3.1	5.8
Yamamoto, *et al*. (13)	Paclitaxel (76% 2nd-line and 24% further) 52% sensitive relapse	21	Not reported	5.8
Groen, *et al*. (14)	Carboplatin plus paclitaxel 0 % sensitive relapse	35	4.8	7.1
Inoue, *et al*. (16)	Topotecan 63 % sensitive relapse	30	2.2	8.4
Mori, *et al*. (29)	Carboplatin plus paclitaxel 62% sensitive relapse	29	3.8	6.8
Our study	ILD patients 39% sensitive relapse	23	2.1	7.1

SCLC, Small cell lung cancer; ILD, interstitial lung disease. *Median

years (range=62-80 years). Of the 23 analyzed patients, 17 patients (78%) were identified with a UIP pattern, and 5 (22%) had a non-UIP pattern. Eight patients received paclitaxel and carboplatin, ten received paclitaxel monotherapy, and five received topotecan monotherapy.

Efficacy and toxicity. Tables II and III summarize treatment responses and adverse events. The overall objective response rates (ORR) and disease control rates (DCR) were 22% and 52%, respectively. The median respective durations of PFS and OS were 2.1 months (95% confidence interval [CI] = 2.0-3.0 months) and 7.1 months (95%CI= 3.6-11.3 months), as shown in Figure 1. The ORRs and PFS were 40%, 20%, and 0%, and 3.0 months (95%CI= 2.0-3.7 months), 2.1 months (95%CI= 0.5-3.7 months), and 2.0 months (95%CI= 0.9-5.6 months) in the carboplatin-paclitaxel, paclitaxel-monotherapy, and topotecan-monotherapy groups, respectively. There was no significant difference in median PFS between groups with respect to sensitive and refractory relapse (2.1 months [95%CI= 1.6-3.7 months] *vs*. 2.1 months [95%CI= 1.6-3.0 months], p=0.260).

Three patients with UIP pattern developed chemotherapy-related pneumonitis. One patient received topotecan and two received paclitaxel monotherapy. All of these cases occurred after completion of the first chemotherapy cycle. Two patients died of pneumonitis and the other of cancer progression approximately 14 weeks after the event.

Discussion

The present study proved the efficacy and safety of second-line chemotherapy for patients with SCLC and ILD.

As seen, the median respective durations of PFS and OS were 2.1 months and 7.1 months. PFS was slightly shorter than the results of second-line chemotherapy trials in patients with SCLC without ILD, and OS was comparable to these results (Table IV). A previous report also demonstrated that the median PFS of first-line chemotherapy had a shorter trend in patients with SCLC and ILD (20). However, since it has been reported that OS is still the best criterion for predicting treatment efficacy and the historical OS of patients who received best supportive care alone as second-line therapy was much shorter than our results, our findings demonstrate the efficacy of second-line chemotherapy for treating patients with SCLC and ILD (11, 21).

We also showed that treatment containing paclitaxel might be a safe option for patients with SCLC and pre-existing ILD as second-line therapy. In the study, the frequency of chemotherapy-related exacerbation of ILD was 13%, which was as safe as regimens previously reported for patients with lung cancer and ILD (22-25). Furthermore, paclitaxel and carboplatin combination chemotherapy has been reported effective and relatively safe for patients with advanced NSCLC with ILD (26). In our study, all three patients who developed chemotherapy-related exacerbation had a UIP pattern, which has been reported to induce a higher incidence of ILD exacerbation than non-UIP pattern (27). Taken together, our findings indicate that second-line treatment may be a suitable option for SCLC patients with ILD, especially after sufficient evaluation of the risks and the benefits.

SCLC is the most aggressive type of lung cancer and survival following relapse from first-line treatment is generally poor (1, 11). Previous studies have demonstrated that second-line chemotherapy for treating patients with relapsing SCLC is effective (11, 12, 28). In addition, it has been demonstrated that patients with lung cancer and ILD benefit from chemotherapy, though previous studies have shown that the prognosis of lung cancer patients with ILD is poor (10, 20, 24-26, 29). Furthermore, since recent studies have reported that smokers with ILD in unselected populations are relatively common and their prevalence appears to be increasing, there exists a need to establish effective and safe chemotherapy regimens in patients with lung cancer and ILD (5-7). Based on our results, a prospective, larger study is warranted to determine the efficacy and safety of second-line therapy for SCLC patients with ILD in order to improve the prognosis of these patients.

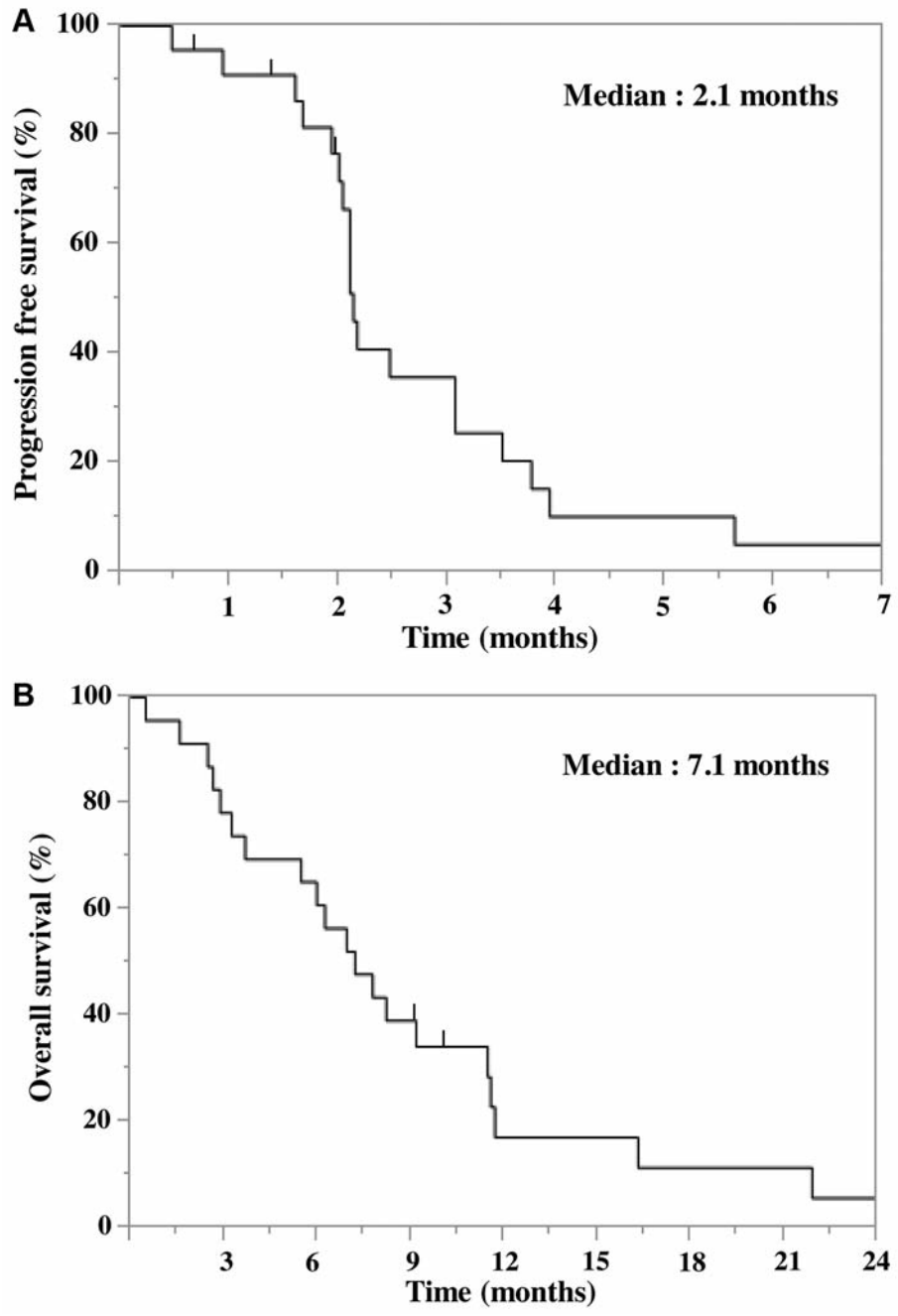

Figure 1. *Kaplan–Meier analyses. A. Progression-free survival. B. Overall survival.*

In the present study, most patients received paclitaxel-containing chemotherapy. The major therapeutic options of second-line chemotherapy for SCLC include topotecan, amrubicin monotherapy, and the combination of cyclophosphamide, doxoroubicin, and vincristine (11, 12, 16, 28). However, clinical activity with the use of paclitaxel in a second-line setting either as a monotherapy (13) or in combination with carboplatin has been demonstrated (14, 30). In addition, paclitaxel- containing chemotherapy regimens have been reported as relatively safe for patients with advanced NSCLC with ILD (24, 26). Therefore, we often administer paclitaxel-containing chemotherapy for SCLC patients with ILD.

Although our findings are of particular interest, there exist certain limitations. Firstly, the interpretation of the results is

limited by the small number of patients involved and by the retrospective nature of the study. Consequently, prospective, larger studies are urgently needed. Secondly, the diagnosis of ILD was based only on HRCT findings in all patients. Third, patient selection was confined to Japanese patients. Therefore, the results of this study may not apply to other populations.

In conclusion, this is the first report to indicate that SCLC patients with ILD may benefit from second-line chemotherapy. Further assessment in a large-scale prospective study is required to confirm these findings.

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Conflicts of Interest

The Authors have no conflicts of interest to disclose.

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