ANTICANCER RESEARCH *37*: 5791-5795 (2017)
doi:10.21873/anticanres.12021

The Prognosis of Small Cell Lung Cancer in Patients with Pulmonary Fibrosis

YOKO MATSUMOTO, SAYAKA OHARA, RYUTARO FURUKAWA and KAZUHIRO USUI

Division of Respirology, NTT Medical Center Tokyo, Tokyo, Japan

Abstract. *Background/Aim: The purpose of this study was to assess the prognosis of small cell lung cancer (SCLC) based on the underlying pulmonary disease. Patients and Methods: A total of 204 patients with SCLC were reviewed and categorized into three groups: normal, emphysema and fibrosis. Results: The median overall survival duration (OS) in patients with normal lungs (n=57), with emphysema (n=105) and fibrosis (n=42) was 21.3, 16.4 and 10.8 months (p=0.063). In limited-stage disease (LD), the median OS in patients with fibrosis (7.4 months) was shorter than normal (52.7 months) or emphysema patients (26.4 months) (p=0.034). In extensive-stage disease (ED), the median OS in patients with fibrosis (12.7 months) was not significantly different from normal (11.4 months) or emphysema patients (13.5 months) (p=0.600). Conclusion: Patients with fibrosis had a poorer prognosis than normal or emphysema patients in LD-SCLC, but the coexistence of pulmonary fibrosis did not affect the prognostic outcomes in ED-SCLC.*

Lung cancer is the leading cause of cancer death in many countries, and small cell lung cancer (SCLC) accounts for 12-15% of all lung cancer cases (1). SCLC is related to smoking and strongly associated with emphysema and pulmonary fibrosis (1-3). Although SCLC is sensitive to chemotherapy and radiotherapy, these treatment modalities are limited in patients with pulmonary fibrosis, as acute lung injury frequently occurs during chemotherapy and thoracic irradiation (4, 5). We conducted a retrospective study to examine the prognosis of SCLC patients according to the underlying pulmonary diseases to evaluate the prognostic significance of pulmonary fibrosis.

Correspondence to: Yoko Matsumoto, Division of Respirology, NTT Medical Center Tokyo, 5-9-22 Higashigotanda Shinagawa, Tokyo, Japan. Tel: +81 34486111, Fax: +81 34486135, e-mail: yokomatsumoto45@gmail.com

Key Words: Acute lung injury, emphysema, interstitial pneumonitis, pulmonary fibrosis, small cell lung cancer.

Patients and Methods

Patients. The medical records for a series of consecutive patients with SCLC treated in the Division of Respirology, NTT Medical Center Tokyo, between August 2001 and May 2016 were retrospectively reviewed. Patients with emphysema and fibrosis on chest computed tomography (CT) at the diagnosis of SCLC were prospectively identified to assess the risk of interstitial lung disease (ILD). The study protocol was reviewed and approved by the Ethics Committee of NTT Medical Center Tokyo. Patients were categorized into three groups based on the chest CT findings: those with normal lungs (except for the tumor), emphysema, or pulmonary fibrosis, as described previously (6-8). We collected the clinical and demographic data, including the gender, age, Eastern Cooperative Oncology Group Performance Status (PS), smoking history, clinical stage of SCLC, treatment, treatment-related toxicity and survival. Patients were diagnosed with acute lung injury if the following criteria were met: (i) new radiographic alveolar infiltrates; (ii) evidence of hypoxemia as defined by worsened gas exchange and (iii) exclusion of other possible causes for (i) and (ii), especially left cardiac failure and progression of cancer.

Statistical analyses. To compare the differences in the CT findings between the subgroups, the Kruskal–Wallis test was performed for continuous variables, and the chi-square test or Fisher's exact test was used for categorical variables. The survival time was estimated by the Kaplan-Meier method, and differences in the survival time between the subgroups were analyzed by the log-rank test. The length of the survival was defined as the duration (in months) from the initial therapy until death or last follow-up. The data were analyzed using the SPSS Statistics software program (Version 24 for Windows; SPSS Inc., Chicago, IL, USA) and p-values of <0.05 were considered to indicate statistical significance.

Results

Characteristics of SCLC patients with pulmonary fibrosis. A total of 204 patients with histologically-proven SCLC were reviewed. Emphysema and fibrosis were identified in 105 (51.5%) and 42 (20.6%) patients with SCLC, respectively. Forty (95.2%) of 42 patients with fibrosis had fibrosis combined with emphysema. The clinical characteristics of patients according to underlying pulmonary disease are summarized in Table I. All patients with fibrosis had a history of heavy smoking (median of 50 pack-years), and 36

of the 42 patients with fibrosis (85.7%) were male. There were no significant differences between the three groups in the PS or clinical stage (limited or extensive).

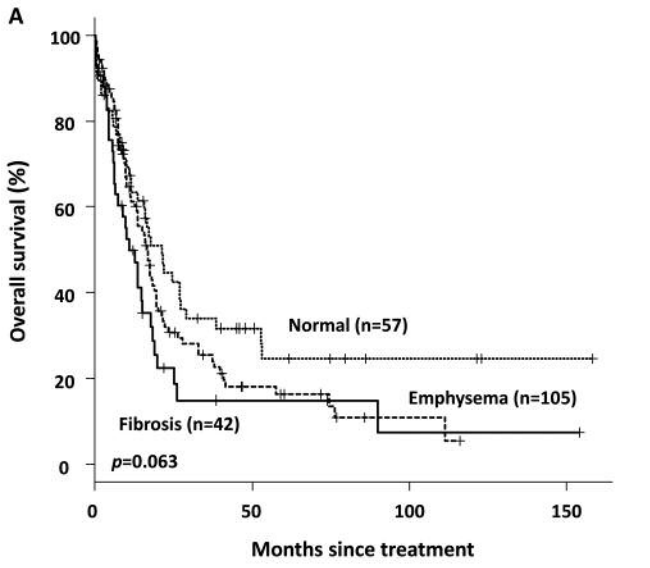
Treatment of SCLC patients with pulmonary fibrosis. The treatment modalities and chemotherapy regimens used as first-line and throughout the entire treatment period are summarized in Table I. Eleven patients received both surgery and chemotherapy, and four received both surgery and chemoradiotherapy. One patient with fibrosis experienced acute lung injury after five days of surgery and received no further treatment for SCLC. Patients with fibrosis were treated with chemoradiotherapy (3/42, 7.1%) significantly less often than those with normal lungs (19/57, 33.3%) or emphysematous lungs (36/105, 34.3%). Irinotecan was used in 2 patients (4.8%) with fibrosis as first-line chemotherapy, and in 5 patients (11.9%) throughout the treatment period, which was less frequent than in those with normal lungs or emphysematous lungs (p=0.014 and p<0.001, respectively). Amrubicin was used in 17 (40.5%) patients with fibrosis, 23 (40.4%) patients with normal lungs and 59 (56.2%) patients with emphysema, that was not significantly different (p=0.079). The proportion of patients with fibrosis who received second-line chemotherapy was similar to that of normal patients and patients with emphysema (fibrosis: 26/42, 61.9%; normal: 31/57, 54.4%; emphysema: 67/105, 63.8%; p=0.496).

Survival duration of SCLC patients with pulmonary fibrosis. The median overall survival duration (OS) in patients with fibrosis was 10.8 months from the start of treatment (Figure 1A). The median OS in patients with fibrosis was shorter than that in normal patients (21.3 months) and patients with emphysema (16.4 months), but the difference was not statistically significant (p=0.063). In limited-stage disease (LD), the median OS in patients with fibrosis (7.4 months) was significantly shorter than that in normal patients (52.7 months) or that in patients with emphysema (26.4 months) (p=0.034) (Figure 1B). In contrast, in extensive-stage disease (ED), the median OS in patients with fibrosis (12.7 months) was not significantly different from that in normal patients (11.4 months) or that in patients with emphysema (13.5 months) (p=0.600) (Figure 1C).

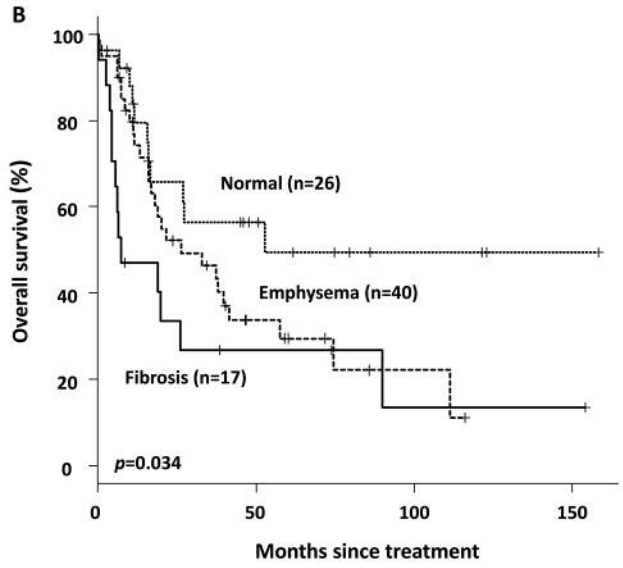
Acute lung injury in SCLC patients with pulmonary fibrosis. Acute lung injury was diagnosed in 10 of the 204 patients (4.9%). The incidence of acute lung injury according to characteristics and type of treatment is summarized in Table II. Acute lung injury occurred in 5 (11.9%) patients with fibrosis, which was significantly more frequent than in normal patients (0/57, 0%) and emphysema patients (5/105, 4.8%) (p=0.025). Among those with fibrosis who experienced acute lung injury, one patient received best supportive care only, one received surgery only and one received surgery and chemotherapy. All patients with acute lung injury who received chemoradiotherapy were in the emphysema group. There were no statistically significant differences in the incidence rate for acute lung injury between treatment modalities and clinical stages. There was a tendency for the incidence of acute lung injury to increase as the number of chemotherapeutic agents increased (p=0.019, Table II and Figure 2). After receiving amrubicin, one patient experienced acute lung injury. As 99 patients received amrubicin throughout the treatment period, the incidence rate was estimated to be 1.0%. This is rather rare compared

Table I. *Characteristics of normal patients and those with emphysema and fibrosis*.

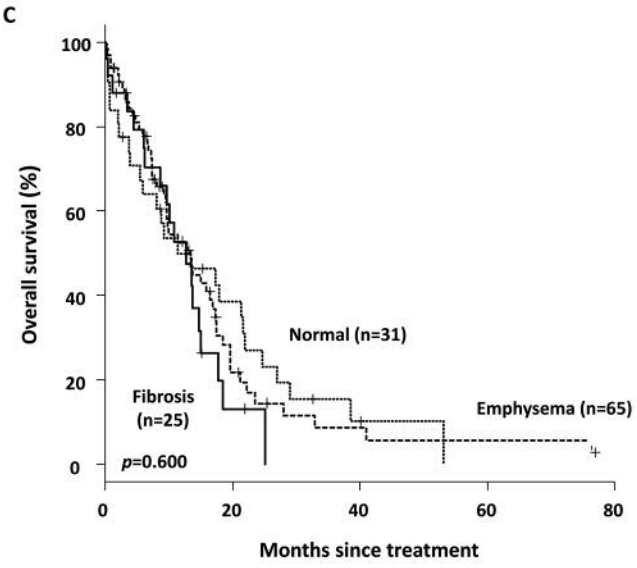
N=204	Normal (n=57)	Emphysema (n=105)	Fibrosis (n=42)	*p*-Value
Age, years				
Median	68	72	74	0.055
Range	50-83	50-90	45-89	
Gender, n (%)				
Male	35 (61.4)	91 (86.7)	36 (85.7)	<0.001
PS, n (%)				
0-1	42 (73.7)	85 (81.0)	33 (78.6)	0.561
>2	15 (26.3)	20 (19.0)	9 (21.4)	
Smoking status, n (%)				
Ex/current	54 (94.7)	103 (98.1)	42 (100)	0.215
Smoking history (pack-years)				
Median	45	55	50	0.122
Range	0-141	0-280	7.5-200	
Clinical stage, n (%)				
Limited disease	26 (45.6)	40 (38.1)	17 (40.5)	0.648
Extensive disease	31 (54.4)	65 (61.9)	25 (59.5)	
Treatment, n (%)				
Surgery	1 (1.8)	8 (7.6)	7 (16.7)	0.024
Chemotherapy	34 (59.6)	62 (59.0)	33 (78.6)	0.069
Chemoradiotherapy	19 (33.3)	36 (34.3)	3 (7.1)	0.003
Best supportive care only	4 (7.0)	7 (6.7)	5 (11.9)	0.545
First-line chemotherapy, n (%)				
Platinum+irinotecan	15 (26.3)	26 (24.8)	2 (4.8)	0.014
Platinum+etoposide	35 (61.4)	66 (62.9)	34 (81.0)	0.075
Platinum+amrubicin	2 (3.5)	3 (2.9)	0 (0)	0.498
Platinum+paclitaxel	1 (1.8)	0 (0)	0 (0)	0.274
Amrubicin	0 (0)	3 (2.9)	0 (0)	0.238
Chemotherapy, n (%)				
Irinotecan	25 (43.9)	49 (46.7)	5 (11.9)	<0.001
Amrubicin	23 (40.4)	59 (56.2)	17 (40.5)	0.079
Etoposide	39 (68.4)	77 (73.3)	35 (83.3)	0.241
Number of regimens, n (%)				
One	53 (93.0)	98 (93.3)	36 (85.7)	0.292
Two	31 (54.4)	67 (63.8)	26 (61.9)	0.496
Three or more	13 (22.8)	33 (31.4)	9 (21.4)	0.330



	Normal	Emphysema	Fibrosis
Median OS (95% CI)	21.3 (14.5-28.1)	16.4 (13.2-20.0)	10.8 (5.5-16.2)



	Normal	Emphysema	Fibrosis
Median OS (95% CI)	52.7 (15.8-NA)	26.4 (16.1-41.6)	7.4 (4.3-26.1)



	Normal	Emphysema	Fibrosis
Median OS (95% CI)	11.4 (5.4-21.7)	13.5 (9.5-16.8)	12.7 (6.2-15.0)

Figure 1. *The overall survival duration (OS) in patients with small-cell lung cancer (SCLC), according to the underlying pulmonary disease (normal: dotted line; emphysema: dashed line; fibrosis: solid line), (A) for the overall population, (B) in patients with limited-disease SCLC and (C) in patients with extensive-disease SCLC. 95% CI: 95% confidence interval; NA: not assessed.*

to irinotecan- or etoposide-induced acute lung injury (irinotecan: 3/79, 3.8%; etoposide: 3/151, 2.0%; p=0.435). The prognosis of patients with acute lung injury was poor; the mortality rate and median survival duration from the onset of acute lung injury were 100% and 34.5 days (range=2-107 days), respectively.

Discussion

The prognosis of patients with fibrosis was relatively poor in LD-SCLC, but that in ED-SCLC was similar to that of normal and emphysema patients in the present study. Severe acute lung injury occurred more frequently in those with fibrosis, irrespective of the treatment modality and clinical stage.

Small cell lung cancer is characterized by rapid growth and early metastasis and known as one of the most fatal malignancies (9). Cigarette smoking is a risk factor for the development of both SCLC and ILD, such as idiopathic pulmonary fibrosis (1, 3). Combination chemotherapy, generally platinum-based plus etoposide or irinotecan, is the standard first-line treatment for ED-SCLC (9, 10). For LD-SCLC, early chemoradiotherapy of accelerated hyperfractionated radiation therapy concurrent with platinum-based chemotherapy is recommended (11). However, the treatment options are limited in patients with pulmonary fibrosis because of acute exacerbation caused by chemotherapy and thoracic irradiation (4). Ohe *et al*. reported that pulmonary fibrosis was associated with treatment-related death from thoracic radiotherapy (5). Irinotecan is a key drug

Table II. *Incidence of acute lung injury.*

	Total, n	Acute lung injury, n (%)	*p*-Value
Underlying pulmonary disease			
Normal	57	0 (0)	0.025
Emphysema	105	5 (4.8)	
Fibrosis	42	5 (11.9)	
Stage			
Limited disease	83	5 (6.0)	0.539
Extended disease	121	5 (4.1)	
Treatment			
Surgery	14	2 (14.3)	0.442
Chemotherapy	123	6 (4.9)	
Chemoradiotherapy	56	2 (3.6)	
Best supportive care only	15	1 (6.7)	
Chemotherapy, n (%)			
Irinotecan	79	3 (3.8)	0.435
Amrubicin	99	1 (1.0)	
Etoposide	151	3 (2.0)	
Number of regimens, n (%)			
One	187	2 (1.1)	0.019
Two	124	2 (1.6)	
Three or more	55	4 (7.3)	

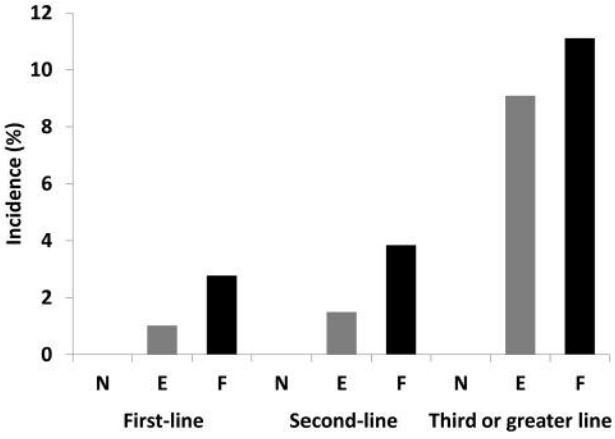


Figure 2. *The incidence of acute lung injury according to the underlying pulmonary disease (N: Normal; E: emphysema; F: fibrosis).*

of SCLC but is now considered contraindicated for patients with ILD. Regardless this situation, the prognostic significance of pulmonary fibrosis in patients with SCLC has not been well evaluated.

Whether or not pulmonary fibrosis is a prognostic factor in patients with SCLC is unknown. Miyazaki *et al*. reported that 15 (4.5%) out of 332 SCLC patients were diagnosed with ILD, and the presence of ILD was an unfavorable prognostic factor (12). Togashi *et al*. reported that 28 (23.0%) out of 122 SCLC patients receiving platinum-based combination chemotherapy had ILD, and preexisting ILD was associated with a shorter overall survival (13). Kashiwabara *et al*. reported that the OS in SCLC patients with ILD (N=7, 12.7 months) was not inferior to that in patients without ILD (N=21, 14.8 months) (14). In our study, the median OS in patients with fibrosis was shorter than that in normal patients or patients with emphysema, but the difference was not statistically significant. In LD-SCLC, the median OS in patients with fibrosis was significantly shorter than that in normal patients or those with emphysema. The fact that few patients with fibrosis underwent chemoradiotherapy might have affected this result. The median OS in patients with fibrosis was similar to that in normal patients or those with emphysema in ED-SCLC. Patients with fibrosis who received second-line chemotherapy accounted for 61.9% of our population (26/42), which was more frequent than in the previous studies (12, 13), and the proportion receiving second-line chemotherapy might have affected the prognostic outcomes. The present findings suggest that chemotherapy may be effective even for relapsed SCLC patients with pulmonary fibrosis after sufficient consideration of the risks and benefits.

Patients with fibrosis had a high incidence of acute lung injury. The incidence of acute lung injury tended to increase with the number of chemotherapeutic agents, both in patients with emphysema and with fibrosis. A standard chemotherapy regimen for patients with SCLC and ILD has not been established. The incidence of acute lung injury related to platinum-based plus etoposide was 2.0% (3/151) in this study, which was similar to that reported previously in patients with SCLC and ILD (15, 16). The incidence of acute lung injury related to amrubicin ranged from 3.3%-12.5% in previous studies (17-19). In our study, only 1 (1.0%) of 99 patients who received amrubicin experienced acute lung injury. Seventeen patients (40.5%) with fibrosis received amrubicin, and the incidence of acute lung injury related to amrubicin in patients with fibrosis was estimated to be 5.9%. Amrubicin might be tolerable for patients with SCLC and ILD.

The present study had several limitations. First, this was an observational and retrospective study that was performed at a single institution. The indications for therapy and the selection of treatment were not uniform for all patients, which limits the evaluation of the treatment effects. A multivariate analysis was not performed because it was not possible to evaluate all of the potential confounding variables related to the survival time.

In conclusion, the prognosis of patients with fibrosis was relatively poor in LD-SCLC, but that in ED-SCLC was similar to that of normal and emphysema patients. Severe acute lung injury occurred more frequently in those with fibrosis,

irrespective of the treatment modality and clinical stage. Further studies are necessary to evaluate the association between SCLC and pulmonary fibrosis and to determine the standard therapeutic options for patients with SCLC and pulmonary fibrosis.

Acknowledgements

The Authors would like to thank all of the participants in the study.

References

1 Govindan R, Page N, Morgensztern D, Read W, Tierney R, Vlahiotis A, Spitznagel EL and Piccirillo J: Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: Analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol *24(28)*: 4539-4544, 2006.

2 Huang R, Wei Y, Hung RJ, Liu G, Su L, Zhang R, Zong X, Zhang ZF, Morgenstern H, Brüske I, Heinrich J, Hong YC, Kim JH, Cote M, Wenzlaff A, Schwartz AG, Stucker I, Mclaughlin J, Marcus MW, Davies MP, Liloglou T, Field JK, Matsuo K, Barnett M, Thornquist M, Goodman G, Wang Y, Chen S, Yang P, Duell EJ, Andrew AS, Lazarus P, Muscat J, Woll P, Horsman J, Teare MD, Flugelman A, Rennert G, Zhang Y, Brenner H, Stegmaier C, van der Heijden EH, Aben K, Kiemeney L, Barros-Dios J, Pérez-Ríos M, Ruano-Ravina A, Caporaso NE, Bertazzi PA, Landi MT, Dai J, Hongbing Shen H, Fernandez-Tardon G, Rodriguez-Suarez M, Tardon A and Christiani DC: Associated links among smoking, chronic obstructive pulmonary disease, and small cell lung cancer: a pooled analysis in the International Lung Cancer Consortium. EBioMedicine *2(11)*: 1677-1685, 2015.

3 Baumgartner KB, Samet JM, Stidley CA, Colby TV and Waldron JA: Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. Am J Respir Crit Care Med *155(1)*: 242-248, 1997.

4 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(7)*: 1242-1246, 2011.

5 Ohe Y, Yamamoto S, Suzuki K, Hojo F, Kakinuma R, Matsumoto T, Ohmatsu H and Nishiwaki Y: Risk factors of treatment-related death in chemotherapy and thoracic radiotherapy for lung cancer. Eur J Cancer *37(1)*: 54-63, 2001.

6 Usui K, Ushijima T, Tanaka Y, Tanai C, Noda H, Abe N, Horiuchi H and Ishihara T: The frequency of epidermal growth factor receptor mutation of nonsmall cell lung cancer according to the underlying pulmonary diseases. Pulm Med *2011*: 290132, 2011.

7 Usui K, Tanai C, Tanaka Y, Noda H and Ishihara T: The prevalence of pulmonary fibrosis combined with emphysema in patients with lung cancer. Respirology 16(2): 326-331, 2011.

8 Cottin V, Nunes H, Brillet PY, Delaval P, Devouassaoux G, Tillie-Leblond I, Israel-Biet D, Court-Fortune I, Valeyre D, Cordier JF and the Groupe d'Etude et de Recherche sur les Maladies "Orphelines'' Pulmonaires (GERM''O''P): Combined pulmonary fibrosis and emphysema: A distinct underrecognised entity. Eur Respir J *26(4)*: 586-593, 2005.

9 Rudin CM, Ismaila N, Hann CL, Malhotra N, Movsas B, Norris K, Pietanza MC, Ramalingam SS, Turrisi AT and Giaccone G: Treatment of small-cell lung cancer: American society of clinical oncology endorsement of the American college of chest physicians guideline. J Clin Oncol *33(34)*: 4106-4111, 2015.

10 Noda K, Nishiwaki Y, Kawahara M, Negoro S, Sugiura T, Yokoyama A, Fukuoka M, Mori K, Watanabe K, Tamura T, Yamamoto S and Saijo N: Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med *346(2)*: 85-91, 2002.

11 Turrisi AT, Kim K, Blum R, Sause WT, Livingston RB, Komaki R, Wagner H, Aisner S and Johnson DH: Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med *340(4)*: 265-271, 1999.

12 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(3)*: 763-767, 2010.

13 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(4)*: 304-311, 2012.

14 Kashiwabara K, Semba H, Fujii S, Tsumura S and Aoki R: Difference in benefit of chemotherapy between small cell lung cancer patients with interstitial pneumonia and patients with non-small cell lung cancer. Anticancer Res *35(2)*: 1065-1071, 2015.

15 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(3)*: 1175-1180, 2013.

16 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(4)*: 801-807, 2011.

17 Miura Y, Saito Y, Atsumi K, Takeuchi S, Miyanaga A, Mizutani H, Minegishi Y, Noro R, Seike M, Shinobu K, Kubota K and Gemma A: Interstitial lung disease associated with amrubicin chemotherapy in patients with lung cancer: a single institutional study. Japanese J Clin Oncol *46(7)*: 674-680, 2016.

18 Sekine I, Okamoto H, Horai T, Nakagawa K, Ohmatsu H, Yokoyama A, Katakami N, Shibuya M, Saijo N and Fukuoka M: A randomized phase III study of single-agent amrubicin *vs*. carboplatin/etoposide in elderly patients with extensive-disease small-cell lung cancer. Clin Lung Cancer *15(2)*: 96-102, 2016.

19 Yoh K, Kenmotsu H, Yamaguchi Y, Kubota K, Ohmatsu H, Goto K, Niho S, Ohe Y, Saijo N and Nishiwaki Y: Severe interstitial lung disease associated with amrubicin treatment. J Thorac Oncol *5(9)*: 1435-1438, 2010.

Received September 4, 2017
Revised September 21, 2017
Accepted September 22, 2017