Methods

Data collection

The participants of this study were patients who had serious ILD that occurred during or after treatment with irinotecan and were reported to Daiichi Sankyo Company, Limited, during the survey period (from the release of irinotecan up to May 2008).

The data used in this study were originally collected for the drug reexamination application and from spontaneous adverse reaction reports that specifically focused on cases with ILD during the postmarketing surveillance.

The original postmarketing surveillance was only conducted in Japan and covered the period from April 1994 (after approval of this product in Japan) until January 2000. All 8864 patients administered Topotecin (irinotecan) were enrolled in this postmarketing surveillance study.

ILD patient data and information were also collected from spontaneous reports submitted to Daiichi Sankyo Company, Limited, between January 2000 (after completion of the postmarketing surveillance) and May 2008. Specific case data were retrieved from these reports by using 'ILD' and 'pneumonitis' as the search terms (preferred terms).

Out of the initially identified cases, those patients having ILD for which the reporting physician could not exclude a causal relationship to irinotecan were regarded as having ILD induced by irinotecan. A total of 153 cases of serious ILD were associated with irinotecan therapy and reported as ADRs.

For each of the patients, sex, age, and type of cancer were collected. In addition, the interval (number of days) from the initiation of treatment with irinotecan to the onset of ILD was also determined, as well as the response to steroid therapy.

Evaluation of clinical information and imaging findings

Between September 2006 and 2008, respiratory physicians (A.G., N.Y.) reviewed chest imaging data collected from 31 of 153 patients at the onset of ILD. The information and images were evaluated to adjudicate whether features of ILD were associated with irinotecan. If pretreatment images were available, these were used to assess the presence or absence of preexisting ILD.

Clinical information and images were then assessed to confirm the validity of the ILD diagnosis, with patients classified into three categories: (i) patients in whom the diagnosis was judged to be valid; (ii) patients in whom the diagnosis could not be confirmed or excluded on the basis of the available images; and (iii) patients in whom the available images suggested a high likelihood of some other disease. In addition, we also evaluated patients who received steroid therapy for their ILD to assess the response to such therapy on the basis of posttreatment imaging findings.

Classification of the imaging patterns

Computed tomographic (CT) findings obtained after the onset of ILD can be categorized into the following four patterns [4,5]:

(1) Hypersensitivity pneumonia (HP) pattern: mild ground-glass changes in the bilateral lung fields, without shrinkage of the lung parenchyma or traction bronchiectasis.
(2) Organizing pneumonia (OP) pattern: infiltrative changes that are more prominent in the peripheral lung fields.
(3) Diffuse alveolar damage (DAD) pattern: bilateral patchy or diffuse infiltrative ground-glass changes, which are accompanied by structural abnormalities such as traction bronchiectasis.
(4) Nonspecific interstitial pneumonia (NSIP) pattern: patterns that do not correspond to categories 1 through 3.

Statistical analysis

The relative risk was examined by analyzing the correlation between the presence of preexisting ILD and a fatal outcome. Data were analyzed using the two-sided Fisher's exact test.

Irinotecan dosage and number of patients treated

The average dose of irinotecan administered during the postmarketing surveillance was 0.9357 g per patient. The average dose of irinotecan and the shipping volume were used to calculate the number of patients treated after the postmarketing surveillance.

Results

Clinical features of interstitial lung disease

Table 1 presents the clinical profiles of 153 patients included in this analysis. A relationship between the patient's death and ILD could not be excluded in a total of 37 cases.

With regard to the source of ADR information, to date, 66 patients [including 15 for whom a relationship between death and serious ILD could not be excluded; incidence of serious ILD: 0.74% (66 of 8864); death rate: 0.17% (15 of 8864)] have been detected as serious ILD during the postmarketing surveillance (from 1994 to 2000) and 87 patients (22 deaths) have been identified as serious ILD from spontaneous reports received after completion of the postmarketing surveillance. ILD was predominantly found in male patients (80.3%) and in patients aged 65 years or older (64.1%), with similar tendencies seen among the fatal cases.

The most common types of cancer observed were non-small cell lung cancer (26.8%), colorectal cancer (24.8%), and small cell lung cancer (24.8%). There was no association between the type of cancer and the death rate from ILD.

Table 1 Summary of patients with interstitial lung disease induced by irinotecan

	Number of patients (deaths)	Percentage (death)[a]
Sex		
Male	122 (31)	80.3 (86.1)
Female	30 (5)	19.7 (13.9)
Unknown	1 (1)	–
Age (years)	Number of patients	Percentage
<65	55 (15)	35.9 (40.5)
≥ 65	98 (22)	64.1 (59.5)
Type of cancer	Number of patients	Percentage
Non-small cell lung cancer	41 (10)	26.8 (27.0)
Colorectal cancer	38 (10)	24.8 (27.0)
Small cell lung cancer	38 (6)	24.8 (16.2)
Gastric cancer	13 (6)	8.5 (16.2)
Ovarian cancer	8 (3)	5.2 (8.1)
Lung cancer (unspecified)	7 (0)	4.6 (0)
Malignant pleural mesothelioma	2 (1)	1.3 (2.7)
Other	6 (1)	3.9 (2.7)
Time until onset (weeks)	Number of patients	Percentage[b]
≤ 2	9 (4)	10.8 (20.0)
2–4	14 (3)	16.9 (15.0)
4–8	25 (7)	30.1 (35.0)
8–16	19 (1)	22.9 (5.0)
≥16	16 (5)	19.3 (25.0)
Unknown	70 (17)	–
Anterior chemotherapy drugs	Number of patients[c]	Percentage
Platinum-containing	29	40.8
Fluoropyrimidines	23	32.4
Taxanes	6	8.5
Others or none	24	33.8
Concomitant drugs	Number of patients[d]	Percentage
Platinum-containing	40	46.5
Fluoropyrimidines	20	23.3
Taxanes	5	5.8
Others or none	13	15.1
Response to steroid therapy	Number of patients[e]	Percentage
Recovered/improved	46	61.3
Not recovered	5	6.7
Fatal	22	29.3
Unknown	2	2.7

[a]Percentage of the total number of patients analyzed ($N=153$) [percentage of the total number of deaths ($n=37$)].
[b]Percentage of the total number of patients with available data ($N=83$) [percentage of the total number of deaths with data ($n=20$)].
[c]Patients confirmed to be on anterior chemotherapy drugs ($n=71$).
[d]Patients confirmed to be on concomitant drugs ($n=86$).
[e]Patients receiving steroid therapy ($n=75$).

When the intervals between the treatment initiation and the onset of ILD were examined in the 83 patients identified from the spontaneous reports and whose clinical courses could be followed, there were 57.8% of patients who developed ILD within 8 weeks and 80.7% patients who developed ILD within 16 weeks (median: 54 days; range: 2–673 days) of starting treatments.

In 71 patients in whom the anterior chemotherapy drugs could be identified and confirmed from the spontaneous reports, 40.8, 32.4, and 8.5% were administered platinum-containing drugs, fluoropyrimidines, and taxanes, respectively. In 86 patients identified from spontaneous reports for concomitant drugs, 46.5, 23.3, and 5.8% were administered platinum-containing drugs, fluoropyrimidines, and taxanes, respectively. With regard to steroid therapy, 61.3% of 75 patients in whom the outcome of the therapy could be assessed showed a response to the steroids.

Imaging findings

Imaging information was examined in 31 patients for whom chest X-ray films or chest CT scans were available. Among these patients, 27 cases (including nine who died) had imaging evidence of ILD or pulmonary changes for which an association with irinotecan could not be excluded.

The diagnosis of ILD was judged to be unlikely in four of these 31 patients. Other possible diagnoses included infection (pneumonia), cardiogenic pulmonary edema, and lymphangitis carcinomatosis. In six other patients, ILD diagnosis was difficult to confirm based on the images provided. Of the 27 patients reported to have ADRs, five (including three deaths) had preexisting ILD at the initiation of the irinotecan treatment.

Table 2 shows the details of 18 patients in whom the images were of sufficient quality to assess the pattern of their lung disease. An HP pattern was found in seven patients, a DAD pattern in six patients, an OP pattern in three patients, an NSIP pattern in one patient, and a combination of the HP and OP patterns in one patient.

Among the 15 patients that received steroid therapy, all of the four nonresponders showed a DAD pattern of pulmonary involvement. Spontaneous improvement of the ILD without steroid therapy was noted in one patient who had an HP pattern. Serum KL-6 levels were measured at the onset of ILD in five patients, including in three patients with HP pattern (418, 449, and 597 IU/l), and in one patient with DAD pattern (3272 IU/l) and one patient with NSIP (3250 IU/l). The median interval from the initiation of irinotecan treatment to the onset of ILD was 47 days in the patients with the HP pattern and 25 days in those with the DAD pattern. Chest CT scans obtained in patient no. 5 (DAD pattern) and patient no. 6 (HP pattern) are shown in Figs 1 and 2, respectively.

In 20 of the 31 patients, it was possible to investigate each of the cases for the presence of a preexisting ILD. When the relative risk of a fatal outcome was compared between five patients with and 15 patients without preexisting ILD, the relative risk ratio was 2.25 ($P=0.29$).

Discussion

When using any anticancer drug, it is essential that we know the clinical features and incidence of relevant lung disorders [6]. As the first reports that gefitinib induced acute ILD, our understanding of how ILD is induced by molecular-targeting anticancer agents has continued to grow [7–11]. However, there have been few reports that focused on the occurrence of ILD due to cytotoxic agents such as irinotecan, and thus, the mechanism of this disease remains relatively unclear [5,6,12].

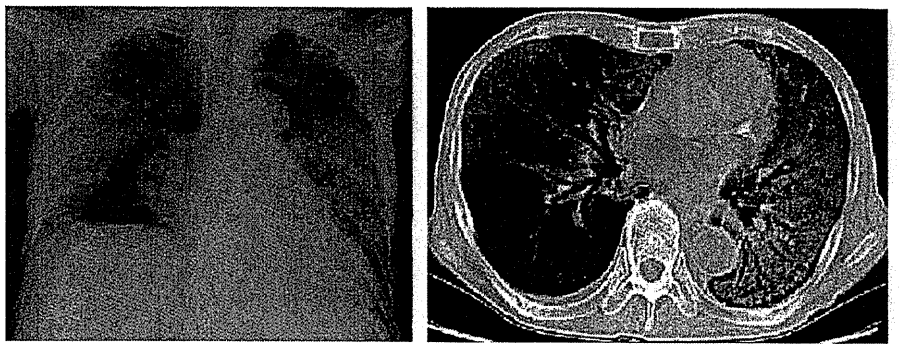
When compared with previous reports regarding other anticancer drugs, the incidence of ILD noted during this postmarketing surveillance was not particularly high

Table 2 Summary of 18 patients in whom the pattern of interstitial lung disease could be determined

Number	Age (years)	Preexisting lung disease	Clinical type	Imaging findings	Response to steroid therapy[a]	Death[b]	Serum KL-6 (IU/L)	Onset (days)	Anterior chemotherapy	Concomitant chemotherapy
1	74	Unknown	HP	Bilateral, nonsegmental ground-glass changes	○	×	NA	37	PL, FP	FP
2	73	No	HP+OP	Infiltrative changes were seen at sites of severe involvement. Shadows were darker in the right lung and nonsegmental and ground-glass changes were noted throughout almost the entire lung	○	×	NA	63	Unknown	FP
3	62	Yes	DAD	Bilateral traction bronchiectasis was prominent	×	Death	NA	24	Others	None
4	73	Unknown	DAD	Mild traction bronchiectasis	Not given	Death	NA	286	None	PL, GM
5	73	Unknown	DAD	Traction bronchiectasis was prominent. Severe bronchiectasis was noted in the peripheral areas as well	×	×	NA	22	PL, Others	FP
6	61	Yes	HP	Mainly ground-glass changes were seen	Not given	×	NA	34	PL, FP	FP
7	76	No	DAD	Ground-glass changes were mainly seen at the onset, but traction bronchiectasis subsequently occurred	○	×	NA	25	FP	FP
8	71	No	OP	Consolidation was prominent and widespread ground-glass changes were also seen. Consolidation was seen near the mantle area	○	×	NA	189	Unknown	FP
9	73	No	HP	Bilateral, nonsegmental, mild ground-glass changes	○	×	449	45	PL	PL
10	82	No	DAD	Ground-glass changes occurred throughout both lung fields. Traction bronchiectasis was seen in some areas. Interlobular septal hypertrophy was not marked	×	Death	3272	24	FP	Others
11	82	No	OP	Bilateral, nonsegmental ground-glass changes were seen with some dark infiltrative shadows. A banded lesion was also noted	○	×	NA	26	PL, TX	None
12	65	No	OP	Bilateral, nonsegmental ground-glass changes mainly in the lower lung fields. An infiltrative lesion was also noted	○	×	NA	43	None	FP
13	59	No	HP	Mild ground-glass changes	○	×	418	55	PL, FP	FP
14	65	No	DAD	Structural changes and traction bronchiectasis were found bilaterally	×	Death	NA	34	PL, FP	FP
15	73	Unknown	HP	Ground-glass changes	○	×	NA	239	PL	PL
16	68	Unknown	HP	Nonsegmental ground-glass changes. Part of the interlobular septum showed hypertrophy	Unknown	Death	597	47	None	TX
17	70	Yes	HP	Bilateral, nonsegmental ground-glass changes. In the later stage, a dark funicular infiltrative shadow was observed	○	×	NA	300	None	FP
18	71	Unknown	NSIP	Bilateral, nonsegmental ground-glass changes	○	×	3250	85	PL, FP	FP

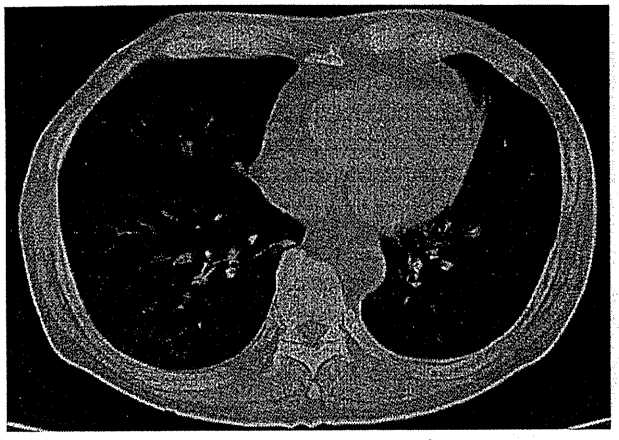
DAD, diffuse alveolar damage pattern; FP, fluoropyrimidines; GM, gemcitabine; HP, hypersensitivity pneumonia pattern; NSIP, nonspecific interstitial pneumonia pattern; OP, organizing pneumonia pattern; PL, platinum-containing drugs; TX, taxanes.
[a]○: response to steroid therapy, ×: no response to steroid therapy.
[b]Death: a causal relationship between interstitial pneumonia and death could not be excluded.

Fig. 1



Diffuse alveolar damage pattern of interstitial lung disease associated with irinotecan.

Fig. 2



Hypersensitivity pneumonia pattern of interstitial lung disease associated with irinotecan.

[6,7,13–17]. There were 103 total ILD cases (66 serious cases and 37 nonserious cases) reported during this postmarketing surveillance period. This means the percentage of ILD-related deaths in patients with ILD during the postmarketing surveillance was 14.6% (15/103). In a case–control study of gefitinib performed in Japan, the prognosis of ILD cases (ILD-related deaths in patients with ILD: 31.6%) was shown to be similar to the results found for the control (other chemotherapy) group (27.9%) [8].

Previous studies have also reported that DAD is a type of ILD characteristically caused by busulfan, carmustine, or bleomycin, whereas NSIP is associated with methotrexate [13–15]. Although a few individual cases of ILD induced by irinotecan have been reported in conjunction with imaging findings [16–17], comprehensive classifications of the patterns of the lung involvement have not been previously examined. This study was unable to determine any specific clinical or imaging features among the patients in which occurrence of ILD could potentially be related to irinotecan administration.

Outcomes and responses to steroid therapy were unfavorable when patients had diffuse alveolopathy (a DAD pattern), accompanied by traction bronchiectasis. This is in agreement with other reports that have examined the relationship between the clinical features of ILD and the response to steroid therapy [18,19].

Our steroid therapy findings raise the possibility that ILD induced by irinotecan may be either cytotoxic or noncytotoxic [20]. A previous report has suggested the possibility that mast cells could play an important role in irinotecan-induced ILD [21]. Unfortunately, owing to the small number of participants with adequate histopathological data and the scarcity of previous literature on the histopathological features of drug-induced ILD, this study was not able to further investigate the mechanism of occurrence [2,17,21–22].

However, even though this study was only able to assess 18 patients, our results do suggest that there was no specific imaging pattern related to the interval between the irinotecan treatment initiation and the onset of ILD. None of the patients in this study exhibited any progression of ILD from HP to DAD during the follow-up period.

Serum KL-6 levels were measured at the onset of ILD in five of the 18 patients. Previous studies that examined the relationship between the clinical features of drug-related ILD and KL-6 found that the serum KL-6 level was significantly elevated in patients who had DAD, whereas those with HP exhibited no increase [23–25]. KL-6 has also been reported to be one of the prognostic factors for ILD [26]. The profile of KL-6 in this study corresponded to that previously reported in the literature.

In patients being treated with irinotecan who are suspected of having ILD, the possibility exists that the condition could potentially be aggravated by continuing treatment, and thus, results in a fatal outcome. As a result of this, irinotecan has been contraindicated in patients with ILD since its original approval [27]. There have also been reports that irinotecan and other drugs are associated with an increased risk of ILD in patients who have pulmonary complications at the initiation of treatment [8,12,16,28–29].

This study showed that the prognosis of ILD related to irinotecan was poor in patients with preexisting ILD, with a relative risk for the association between preexisting ILD and death calculated to be 2.25 ($P = 0.29$). However, due to the small sample size, a statistically significant difference was not seen. When the prognostic factors for ILD associated with gefitinib were investigated, men who had a performance status of more than or equal to 2 along with an early onset of the disease were all found to be significantly associated with a poor outcome. When a multivariate analysis of risk factors for ILD associated with gefitinib was performed, it was found that being male, smoking, and having idiopathic ILD were all significant risk factors [7,8].

For ILD related to bleomycin, it has been reported that the total dose, age, and concomitant radiotherapy enhanced the risk [13–15]. As no data were available for patients without ILD in this study, attempts to assess the risk factors for ILD were considerably limited.

Due to international differences in the handling of drug-associated ILD, the degree of attention currently paid to ILD and the terminology used in case reports tend to vary from country to country [30]. In the USA, the section on adverse reactions in the irinotecan package insert states that preexisting lung disease, use of pneumotoxic drugs, radiation therapy, and treatment with colony-stimulating

factors are known risk factors for the occurrence of ILD. In addition, the insert also emphasizes that relevant patients must be closely monitored [31].

This study found a significant frequency of administration of platinum-containing drugs, fluoropyrimidines, and taxanes as both concomitant and anterior chemotherapy drugs in Japanese patients. Although it is well known that each of these drugs can cause ILD [6,9,12], this study could not assess how much irinotecan impacted the onset of ILD. Due to the limited amount of data that have been collected, clarification of the interaction of these drugs is not possible at this time. In addition, there are no apparent trends between the usage of these drugs and the imaging categorizations that can be defined based on this study data.

Conclusion

Irinotecan is contraindicated in patients with preexisting ILD, as their symptoms may be aggravated, possibly leading to death. Therefore, physicians need to confirm patients' eligibility before dosing and if treatment is possible, patients' conditions must be carefully followed after initial administration of the drug.

When patients are given irinotecan, especially within 16 weeks after treatment initiation, they need to be carefully observed for ILD-specific symptoms such as wheeze, rales, cough, and pyrexia. In addition, chest imaging studies should be conducted periodically, and if required, arterial blood gases or SpO_2 should also be measured.

In the event of any of the above abnormalities, physicians need to discontinue treatment and transfer such patients to other appropriate therapies.

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References

1 Yamada M, Kudoh S, Hirata K, Nakajima T, Yoshikawa J. Risk factors of pneumonitis following chemoradiotherapy for lung cancer. *Eur J Cancer* 1998; **34**:71–75.
2 Masuda N, Fukuoka M, Kusunoki Y, Matsui K, Takifuji N, Kudoh S, *et al.* CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. *J Clin Oncol* 1992; **10**:1225–1229.
3 Oshita F, Noda K, Nishiwaki Y, Fujita A, Kurita Y, Nakabayashi Y, *et al.* Phase 2 study of irinotecan and etoposide in patients with metastatic non-small-cell lung cancer. *J Clin Oncol* 1997; **15**:304–309.
4 Sakai F, Noma S, Kurihara Y, Yamada H, Azuma A, Kudoh S, *et al.* Leflunomide-related lung injury in patients with rheumatoid arthritis: imaging features. *Mod Rheumatol* 2005; **15**:173–179.
5 Muller NL, White DA, Jiang H, Gemma A. Diagnosis and management of drug-associated interstitial lung disease. *Br J Cancer* 2004; **91 (Suppl 2)**: S24–S30.
6 Vahid B, Marik PE. Pulmonary complications of novel antineoplastic agents for solid tumors. *Chest* 2008; **133**:528–538.
7 AstraZeneca and Iressa Expert Committee. *Final report on interstitial lung disease (ILD) related to gefetinib (Iressa Tablet 250).* Tokyo, Japan: AstraZeneca Japan; 2003.
8 Kudoh S, Kato H, Nishiwaki Y, Fukuoka M, Nakata K, Ichinose Y, *et al.* Interstitial lung disease in Japanese patients with lung cancer, a cohort and nested case-control study. *Am J Respir Crit Care Med* 2008; **177**:1348–1357.
9 Gemma A. Drug-induced interstitial lung disease associated with molecular-targeted anticancer agents. *J Nippon Med Sch* 2009; **76**:4–8.
10 Makris D, Scherppereel A, Copin MC, Colin G, Brun L, Laffite JJ, *et al.* Fatal interstitial lung disease associated with oral erlotinib therapy for lung cancer. *BMC Cancer* 2007; **7**:150.
11 Liu V, White DA, Zakowski MF, Travis W, Kris MG, Grinsberg MS, *et al.* Pulmonary toxicity associated with erlotinib. *Chest* 2007; **132**:1042–1044.
12 Camas P, Kudoh S, Ebina M. Interstitial lung disease associated with drug therapy. *Br J Cancer* 2004; **91 (Suppl 2)**:S18–S23.
13 Cooper JA Jr, White DA, Matthay RA. Drug-induced pulmonary disease. Part 1: cytotoxic drugs. *Am Rev Respir Dis* 1986; **133**:321–340.
14 Cooper JA Jr, White DA, Matthay RA. Drug-induced pulmonary disease. Part 2: cytotoxic drugs. *Am Rev Respir Dis* 1986; **133**:488–505.
15 Erasmus JJ, McAdams HP, Rossi SE. High-resolution CT of drug-induced lung disease. *Radiol Clin North Am* 2002; **40**:61–72.
16 Madarnas Y, Webster P, Shorter AM, Bjarnason GA. Irinotecan-associated pulmonary toxicity. *Anticancer Drugs* 2000; **11**:709–713.
17 Michielin O, Udry E, Périard D, Matzinger O, Lobrinus JA, Stupp R. Irinotecan-induced interstitial pneumonia. *Lancet Oncol* 2004; **5**:322–324.
18 Takatani K, Miyazaki E, Nureki S, Ando M, Ueno T, Okubo T, *et al.* High-resolution computed tomography patterns and immunopathogenetic findings in drug-induced pneumonitis. *Respir Med* 2008; **102**:892–898.
19 Cleverley JR, Screaton NJ, Hiorns MP, Flint JD, Muller NL. Drug-induced lung disease: high-resolution CT and histological findings. *Clin Radiol* 2002; **57**:292–299.
20 Fraser RS, Müller NL, Colman N, Pare PD. Pulmonary disease caused by toxins, drugs, and irradiation. In: Fraser RS, Müller NL, Colman N, Pare PD, editor. *Fraser and Pare's diagnosis of diseases of the chest.* Philaderphia: WB Saunders; 1999. pp. 2517–2592.
21 Inoue K, Hiraoka N, Kasamatsu Y, Kawahito Y, Yoshioka K, Yokoo A. A case of irinotecan-induced pneumonitis. *Jpn J Lung Cancer* 2000; **40**:219–221.
22 Maitland ML, Wilcox R, Hogarth DK, Desai AA, Caligiuri P, Abrahams C, *et al.* Diffuse alveolar damage after a single dose of topotecan in a patient with pulmonary fibrosis and small cell lung cancer. *Lung Cancer* 2006; **54**:243–245.
23 Ohnishi H, Yokoyama A, Yasuhara Y, Watanabe A, Naka T, Hamada H, *et al.* Circulating KL-6 levels in patients with drug-induced pneumonitis. *Thorax* 2003; **58**:872–875.
24 Rossi SE, Erasmus JJ, MacAdams HP, Sporn TA, Goodman PC. Pulmonary drug toxicity: radiologic and pathologic manifestations. *Radiographics* 2000; **20**:1245–1259.
25 Muller NL, Naidich DP. Disease characterized primarily by linear and reticular opacities. In: Webb WR, Muller NL, Nadich DP, editors. *High-resolution CT of the lung.* 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001. pp. 193–257.
26 Nakajima M, Kawahara Y, Yoshida K, Miyashita N, Niki Y, Matsushima T, *et al.* Serum KL-6 as a possible marker for amiodarone-induced pulmonary toxicity. *Internal Med* 2000; **39**:1097–1100.
27 Daiichi Sankyo Company Limited. *Topotecin package insert.* Tokyo: Daiichi Sankyo Company Limited; 2009.
28 Naito Y, Tsuchiya S, Ishihara S, Minato K, Shitara Y, Takise A, *et al.* Impact of preexisting pulmonary fibrosis detected on chest radiograph and CT on the development of gefitinib-related interstitial lung disease. *Am J Clin Oncol* 2008; **31**:340–344.
29 Niho S, Goto K, Yoh K, Kim YH, Ohmatsu H, Kubota K, *et al.* Interstitial shadow on chest CT is associated with the onset of interstitial lung disease caused by chemotherapeutic drugs. *Jpn J Clin Oncol* 2006; **36**:269–273.
30 Koo LC, Clark JA, Quesenberry CP, Higenbottam T, Nyberg F, Wilf MK, *et al.* National differences in reporting 'pneumonia' and 'pneumonia interstitial': an analysis of the WHO international drug monitoring database on 15 drugs in nine countries for seven pulmonary conditions. *Pharmacoepidemiol Drug Saf* 2005; **14**:775–787.
31 Pfizer. *CAMPTOSAR prescribing information.* New York: Pfizer; 2009.

The Feasibility Study of Carboplatin Plus Etoposide for Advanced Small Cell Lung Cancer with Idiopathic Interstitial Pneumonias

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Background: Idiopathic interstitial pneumonias (IIPs) are among the most common complications in patients with lung cancer. In such patients with cancer, the most serious expression of toxicity in Japan is acute exacerbation of IIPs caused by anticancer treatment. Nevertheless, there has been no consensus and no evidence presented, regarding optimal treatment for advanced lung cancer with IIP.

Patients and Methods: Chemotherapy-naive patients with advanced small cell lung cancer (SCLC) with IIP who were ineligible for curative radiotherapy were enrolled. Patients received carboplatin every 21 days at a dose of area under the curve 6.0 on day 1 and etoposide at a dose of 100 mg/m^2 on days 1 to 3.

Results: Between July 2002 and October 2008, 17 patients with SCLC with IIP, including 14 men, eight of whom were diagnosed with idiopathic pulmonary fibrosis, were enrolled and treated for a mean of 3.5 cycles of carboplatin plus etoposide. One patient (5.9%; 95% confidence interval, 0–18.4%) with clinically confirmed idiopathic pulmonary fibrosis had acute exacerbation of IIPs associated with the treatment. The overall response rate was 88.2%. The median progression-free survival, median survival time, and 1-year survival rate were 5.5 months, 8.7 months, and 29.4%, respectively.

Conclusion: This is the first report indicating that patients with advanced SCLC with IIPs may benefit from chemotherapy. Patients with advanced SCLC with IIP treated with etoposide and carboplatin combination chemotherapy gain benefits, with safety equivalent to that seen in patients without IIP. The results from this study would support, on ethical grounds, the conduct of a large-scale study to evaluate this regimen.

Key Words: Idiopathic interstitial pneumonias, Idiopathic pulmonary fibrosis, Acute exacerbation, Small-cell lung cancer, Chemotherapy.

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Small cell lung cancer (SCLC) is characterized by a rapid doubling time, a propensity for early dissemination, significant sensitivity to chemotherapy and radiotherapy, and accounts for approximately 15 to 20% of all cases of lung cancer diagnosed. The majority of these patients have extensive stage disease at the time of diagnosis. The standard treatment for patients with extensive stage SCLC is systemic chemotherapy with a combination of cisplatin and etoposide, a regimen that yields a median survival of approximately 9 months and a 2-year survival of less than 10%.[1–3] Nevertheless, elderly or poor performance status (PS) patients often have poor tolerance for a cisplatin-containing regimen. Therefore, carboplatin is widely used as an alternative.[4,5]

Idiopathic interstitial pneumonias (IIPs) seem to be associated with lung carcinogenesis. In particular, the incidence of lung cancer in patients with idiopathic pulmonary fibrosis (IPF) is higher than that in the general population, whose relative risk is reportedly 7 to 14.[6–10] Kawasaki et al.[11] reported that IPF was found in 7.5% of surgically resected lung cancer cases. Recently, it has been recognized that IPF is an independent risk factor for lung carcinogenesis.[8]

IIPs are usually characterized by slowly progressive respiratory insufficiency. Nevertheless, some patients with IIP experience acute exacerbations (AEs) generally characterized by suddenly progressive and severe respiratory failure, with new lung opacities and pathological lesions of diffuse alveolar damage. There are racial differences between Mongolians (including Japanese) and whites in the frequency of AE. Therefore, the concept of AE, which was first proposed in Japan,[12,13] has recently come to be recognized globally.[14–17] This clinical condition is lethal in many cases and significantly affects the prognosis of patients with IIP, because there is no established treatment for AE. In patients with lung cancer combined with IIP (lung cancer [LC] with IIP), idiopathic or iatrogenic AE frequently occurs after various anticancer treatments. There are some retrospective reports of exacerbation of a preexisting IIP after surgery,[18–21] but there are only a few reports of chemotherapy that are useful in designing a treatment strategy for LC with IIP. We previously indicated that combination chemotherapy with carboplatin and paclitaxel had significant antitumor efficacy and permissible safety in treatment of non-small cell lung

cancer (NSCLC) with IIP. In a limited sample size, this pilot trial showed that the response rate was as good as that of standard chemotherapy for NSCLC without IIP, and the incidence (5.6%) of AE of IIPs was lower than that in previous reports.[22]

The results of our retrospective study of LC with IIP suggested that combined chemotherapy with carboplatin and etoposide (CE) could be a candidate regimen for treatment of patients with SCLC with IIP.[23] We, therefore, conducted a prospective study of CE to assess its acceptability, in terms of safety and efficacy, in treatment of advanced SCLC with IIP.

PATIENTS AND METHODS

Study Design

Pathologically confirmed chemotherapy-naive patients with SCLC with IIPs, for whom curative radiotherapy was impossible, were eligible for enrollment. These did not include cases with unstable IIPs and acute/subacute IIPs. Patients receiving oxygen inhalation or using immunosuppressive drugs such as steroids were eligible. Histological types of lung cancer were defined according to the World Health Organization Classification of 1999. Additional eligibility criteria included Eastern Cooperative Oncology Group PS 0 to 2 and estimated life expectancy more than 3 months, measurable lesion, adequate bone marrow, hepatic, and renal functions. Written informed consent was obtained from all enrolled patients. We obtained an approval in relationship to institutional review boards in our institution.

We classified clinical IIP types into two groups: an IPF pattern and a non-IPF pattern. The IPF pattern group consisted of patients with histologically or clinically diagnosed IPF. All other cases were placed in the non-IPF pattern group. Diagnosis of IPF was made in accordance with American Thoracic Society/European Respiratory Society criteria[10] in patients previously diagnosed with usual interstitial pneumonia by either histological evaluation of open-lung biopsy or transbronchial lung biopsy specimens. In the absence of histological evidence, diagnosis of an IPF pattern was based on evidence from a high-resolution computed tomography (HRCT) scan of the chest and other clinical features. Typical chest CT findings for the IPF pattern were basal predominant, subpleural reticular abnormality with traction bronchiectasis, honeycomb cysts, and no findings of atypical features such as peribronchovascular nodules, isolated cysts, or consolidation.[24–26] In addition, the presence of other typical clinical features, including bibasilar inspiratory crackles, abnormal findings of pulmonary function tests indicative of restrictive respiratory failure, and increased serum levels of markers of damaged pneumocytes (i.e., lactate dehydrogenase [LDH], C-reactive protein [CRP], KL-6, and surfactant protein D [SP-D]) were investigated. Because we excluded subjects in the acute and subacute phase of IIPs, all patients had either clinical evidence of IPF or fibrotic nonspecific interstitial pneumonia.

Cases were defined as having AE of IIPs if they satisfied all the following criteria[12,13]: (1) exacerbation of dyspnea within 1 month; (2) newly developed diffuse pulmonary opacities on chest CT and/or chest x-ray; (3) decrease in arterial oxygen tension (Pao_2) of more than 10 mmHg under similar conditions; and (4) absence of heart failure or infectious lung diseases.

Study Treatment

Patients received carboplatin (area under the curve of 6.0) intravenously (IV) over 60 minutes on day 1, which was followed by etoposide 100 mg/m^2 IV over 60 minutes on days 1 to 3, every 3 weeks. No prophylactic granulocyte colony-stimulating factor (G-CSF) was planned. All patients received standard supportive care, as appropriate. Treatment was discontinued when one or more of the following events occurred: disease progression, unacceptable toxicity such as AE, patient refusal of further treatment, and investigator decision to terminate treatment. Patients were monitored for the development of AE for a minimum of 10 weeks after last administration of etoposide.

Statistical Considerations

Because this study has been recognized as a pilot study for a large-scale clinical trial, we considered that a large-scale clinical trial could be undertaken when less than two patients present with AE in a cohort of 17 enrolled patients (the probability that >25% of the patients would have AE is <10%).

The primary end point was the incidence of treatment-related AE. Secondary end points were toxicity, the objective response rate (ORR), the median progression-free survival (PFS), and the overall survival (OS). Evaluation was made in compliance with National Cancer Institute common toxicity criteria Version 3.0 for safety and with RECIST guidelines[27] for antitumor activity. When diagnosis of AE was uncertain, we performed the close inspection necessary for differential diagnoses such as HRCT, evaluation of cardiac function, and bacteriovirological examination. When AE was diagnosed, active treatments such as steroid therapy with IV administration of methylprednisolone and/or administration of sivelestat sodium were undertaken. Based on our previous report,[23] AE occurring within 10 weeks after final treatment was considered to be related to chemotherapy.

Examination values are reported as mean ± standard deviation. PFS was measured as the period from the start of this treatment to the identifiable time for progression. Survival time was measured as the period from the start of this treatment until death by all causes. PFS and OS were characterized using the Kaplan-Meier method. Odds ratios (ORs) and 95% confidence intervals (CIs) to assess the relative risk of AE were calculated by logistic regression analysis. Resulting p values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Patient Characteristics

Between July 2002 and October 2008, a total of 17 Japanese patients (14 men and 3 women) were enrolled in this study, and their characteristics are listed in Table 1. All patients were evaluable for toxicity and survival assessments. The median age at the time of diagnosis of lung cancer was 69 years; all patients were current or former smokers. Eight

TABLE 1. Patient Characteristics

No. of patients	17	
Gender		
Male	14	82%
Female	3	18%
Age (yr)		
Median	69	
Range	53–80	
PS (ECOG)		
0	4	23%
1	10	59%
2	3	18%
Stage		
IIIA	5	29%
IIIB	3	18%
IV	9	53%
IIPs pattern		
IPF	8	47%
Non-IPF	9	53%

PS, performance status; ECOG, Eastern Cooperative Oncology Group; IIPs, idiopathic interstitial pneumonias; IPF, idiopathic pulmonary fibrosis.

TABLE 2. Baseline Demographic Data

	Mean	±SD
CRP		
mg/dl	1.96	±3.29
LDH		
IU/L	412	±228
WBC		
mm^3	7540	±2020
Pao_2		
Torr	77.8	±11.8
KL-6		
U/ml	956	±563
Positive (>500)	86 (%)	
SP-D		
ng/ml	111.9	±75.3
Positive (>110)	33 (%)	
ANA		
Positive (>40×)	57 (%)	
%VC		
Predicted	91.4	±16.9

CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cells; Pao_2, arterial oxygen tension; ANA, antinuclear antibody; SP-D, surfactant protein D; %VC, percent vital capacity; SD, standard deviation.

TABLE 3. Incidence of Acute Exacerbation and Objective Response to Treatment

No. of patients	17
Acute exacerbation	
Treatment related	1
To death	1
Second-line treatment related	2
To death	1
Treatment unrelated	2
To death	2
Objective response	
CR + PR	15
SD	1
PD	1
Overall response rate	88.2%

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

patients were clinically confirmed cases of IPF, and nine were determined to be non-IPF pattern. There were no patients in whom histological confirmation of interstitial pneumonias was obtained. There were two patients who were diagnosed as collagen-vascular disease after the study treatment (one rheumatoid arthritis and one systemic sclerosis). One patient had received immunosuppressive agents for IIPs. This patient had a history of AE of IPF and was given 20 mg prednisolone orally. The patient received the five cycles of chemotherapy safely. Two patients routinely required oxygen inhalation for IIPs. There were nine patients with stage IV and three patients with stage IIIB. There were five patients with stage IIIA in whom chemoradiotherapy was avoided.

Table 2 presents pretreatment demographic parameters of patients. The mean serum levels of CRP and LDH were 1.96 mg/dl and 412 IU/L respectively. The mean Pao_2 was 77.8 mmHg (range, 58–99) at rest under oxygen-free status. The mean predicted vital capacity (%VC) in the respiratory function test was 91.4% (range, 69–108). Positive incidence and mean serum levels of KL-6 and SP-D were 86%, 956 U/ml and 33%, 111.9 ng/ml, respectively.

Treatment Efficacy

Table 3 summarizes the incidence of AE and the antitumor effect data. Only one patient with clinical IPF developed treatment-related AE (5.9%, 95% CI, 0–18.4%); this occurred 9 weeks after completion of the five cycles of chemotherapy where the efficacy amounted to a partial response, and the patient died of the event after 4 weeks. The survival time of this patient after registration was 38 weeks. Two patients developed AE related to second-line chemotherapy, and one patient died due to AE. Moreover, AE unrelated to treatment was observed in two patients; these patients developed AE 8 months and over 3 months after last administration of etoposide, respectively. Four of five patients with AE had clinical IPF. The incidence and mortality from AE in the total follow-up period were 29.4% and 23.5%, respectively.

The ORR was 88.2% (95% CI, 71–100%), comprising one complete response and 14 partial responses. Stable and progressive diseases were observed in one patient each. Survival analysis performed in April 2010 showed that 14 patients had died. The median follow-up period was 9 months; we could not confirm the final outcome of one patient. The median PFS was 5.5 months (Figure 1*A*), which compared well with that of 4.8 months in the Japan Clinical Oncology Group (JCOG) 9511 trial[1] with cisplatin + etoposide for SCLC without IIP. In addition, the median survival time (MST) was 8.7 months, and 1-year survival rate was

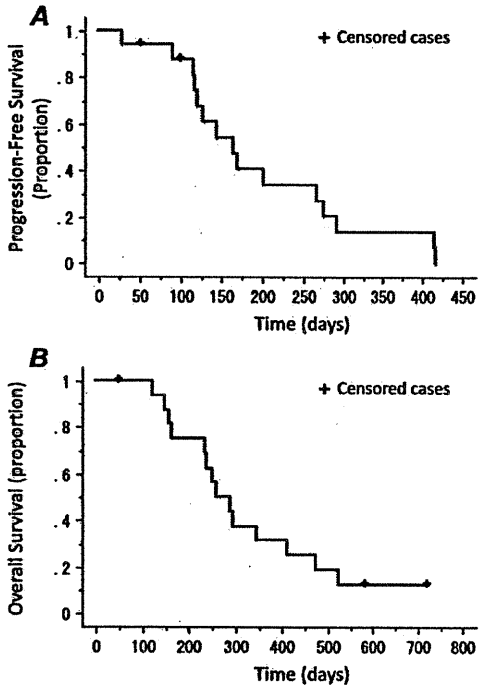

FIGURE 1. *A*, Progression-free survival (PFS) and (*B*) overall survival (OS). Vertical bars indicate censored cases at the data cutoff point. The median PFS, median survival time (MST), and 1-year survival rate were 5.3 months, 10.6 months, and 22%, respectively.

TABLE 4. Treatment-Related Adverse Events Excluding Acute Exacerbation

Toxicity	Grade 2	Grade 3	Grade 4	Grade 3–4	Percentage
Hematological					
Leukocytopenia		11	3	14	82.4
Neutropenia		3	12	15	88.2
Febrile neutropenia		2	0	2	11.8
Anemia	4	4	1	5	29.4
Thrombocytopenia	1	4	1	5	29.4
Nonhematological					
Nausea	4	1	0	1	5.9
Vomiting	1	0	0	0	0
Diarrhea	1	1	0	1	5.9
Congestive heart failure			1	1	5.9

Grade, National Cancer Institute Common Toxicity Criteria version 3.0.

29% (Figure 1*B*), compared with MST and 1-year survival rate of JCOG 9511 of 9.4 months and 37.7%, respectively.

Toxicities

Treatment-related adverse events other than AE are summarized in Table 4. The most common hematological grades 3 and 4 adverse event was neutropenia (88.2%), although febrile neutropenia was observed in two patients. Nonhematological adverse events were generally mild, the most common of which were nausea and vomiting. Only one patient with nausea was grade 3. One grade 3 congestive heart failure patient was also observed, which was considered to have been possibly due to the treatment. The improvement in condition of patients was good, and second-line treatment was performed. A mean of 3.5 cycles of treatment was given (range, 1–6 cycles), and 14 patients received three or more cycles.

TABLE 5. Patient Characteristics of SCLC and NSCLC with IIP

No. of patients	35	
Gender		
Male	28	80%
Female	7	20%
Age (yr)		
Median	69	
Range	33–81	
Performance status		
0	11	31%
1	21	60%
2	3	9%
Smoking status		
Current	25	71%
Former	7	20%
Never	3	9%
IIPs pattern		
IPF	14	40%
Non-IPF	21	60%
Acute exacerbation		
First line	2	5.7%
Second line	5	14.3%
Unrelated	3	8.6%
Total	10	28.6%

SCLC, small-cell lung cancer; NSCLC, non-small cell lung cancer; IIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis.

The Risk Factor of AE

In selecting patients, it can be recommended that those cases at high risk of AE of IIPs be excluded with a view to improvement of treatment safety. To evaluate the risk factor of AE, we conducted an analysis that integrated this study with that of NSCLC with IIP, which we reported previously.[22] Integrated patient characteristics and AE status are listed in Table 5. A total number of 35 patients were included in this integrated analysis. There were 10 patients in total with AE for the following reasons: first-line chemotherapy related, two cases; second-line chemotherapy related, five cases; and treatment unrelated, three cases. Thirty-two smokers (current and former, 91%) and three never smokers (9%) were observed. IPF and non-IPF patterns were observed in 14 (40%) and 21 (60%) patients, respectively.

Univariate analyses of various risk factors, such as clinical features and laboratory parameter, for AE in patients who had LC with IIP are presented in Table 6. Regarding clinical features, the ORs were 2.8 for men and 3.5 for elderly patients (more than median age), but neither was significant. The risk of AE in those with the IPF pattern was not

TABLE 6. Odds Ratios of Acute Exacerbation of IIPs for Various Risk Factors in the Patients Combined from Two Studies

Risk Factors	N	OR	95% CI	p
Gender				
Male	35	2.84	0.30–27.3	0.37
Age (yr)				
>69[a]	35	3.50	0.73–16.9	0.12
PS				
≥1	35	0.58	0.13–2.71	0.49
Type of IIPs				
IPF	35	3.19	0.70–14.6	0.13
LDH (IU/L)				
>254[a]	35	0.62	0.14–2.73	0.52
CRP (mg/dl)				
>1.34[a]	35	0.34	0.07–1.61	0.17
WBC (mm^3)				
>7820[a]	35	1.08	0.25–4.70	0.91
Pao_2 (Torr)				
<80[a]	27	0.18	0.03–1.14	0.07
KL-6 (U/ml)				
>762[a]	32	0.56	0.12–2.54	0.45
Positive		0.88	0.17–4.54	0.87
SP-D (ng/ml)				
>94[a]	29	2.22	0.42–11.83	0.35
Positive		0.98	0.18–5.24	0.87
%VC predicted				
<80[a]	23	0.69	0.12–3.96	0.67
ANA				
Positive	19	0.80	0.11–6.11	0.83

[a] Median.

IIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; PS, performance status; CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cells; Pao_2, arterial oxygen tension; SP-D, surfactant protein D; ANA, antinuclear antibody; %VC, percent vital capacity; OR, odds ratio; CI, confidence interval.

significantly higher than in those with a non-IPF pattern (OR: 3.19, $p = 0.13$). Neither poor PS nor smoking status increased the risk of AE. We carried out the analysis in various additional settings (data not shown), but no statistically significant risk factor was indentified in any of these cases.

DISCUSSION

Optimal chemotherapy for treatment of advanced LC with IIP still remains controversial, because there have been few reports focusing on AE of IIPs related to chemotherapy for lung cancer. In the case of chemotherapy, the incidence of treatment-related AE previously reported ranged from 8.7 to 21% in Japan.[28–31] Therefore, AE is now increasingly being recognized as a common clinical event for LC with IIP. Nevertheless, there are conflicting views as to whether chemotherapy for NSCLC with IIP can contribute to OS, because its antitumor efficacy for NSCLC is less than that for SCLC. In patients with SCLC with IIPs, we can expect that the benefit of chemotherapy outweighs the risk of AE. On the other hand, because the prognosis of SCLC without active treatment is remarkably poor, SCLC shows considerable sensitivity to chemotherapy. This is the first prospective study to analyze the safety and efficacy of a specific regimen for SCLC with IIP. In this pilot study of carboplatin combined with etoposide for advanced SCLC with IIP, we observed an incidence of treatment-related AE of 5.9%, median PFS of 5.5 months, and MST of 8.7 months.

Currently, platinum agent plus etoposide administered every 3 weeks is one of the most widely used protocols for advanced SCLC as the established standard regimen. Because of the right heart overload, the patients with hypoxemia and/or low pulmonary function often have the high risk of pulmonary congestion. We selected the chemotherapy regimen based on carboplatin not cisplatin. Moreover, CE has been reported to have good safety and efficacy in high-risk patients such as the elderly and those with poor PS.[4,5] We observed an ORR of 88% and median PFS of 5.5 months, which was comparable with the results of the randomized phase III trial (JCOG 9702) in Japanese patients without IIPs (ORR, 73%; median PFS, 5.2 months; MST, 10.6 months; 1-year survival rate, 41%).[4] Nevertheless, the MST (8.7 months) and 1-year survival rate (29%) in this study would be regarded as unsatisfactory for patients without interstitial lung disease (ILD). Because of the difference between comparatively good PFS and unsatisfactory OS, we considered that only 8 of 16 patients, excluding one patient for treatment-related death, received second-line chemotherapy. We considered that the existence of IIPs had a negative influence in performing second-line chemotherapy.

Attention is now being paid to the induction of AE of IIPs by anticancer agents, following Japanese reports of ILD developing after treatment with the epithelial growth factor receptor tyrosine kinase inhibitor gefitinib. In 3166 Japanese patients with advanced/recurrent NSCLC enrolled in a cohort and nested case-control study, gefitinib-induced ILD was manifested in 3.98%. More interestingly, that study demonstrated that a predisposing background of preexisting IIPs was an independent risk factor for developing AE, regardless of gefitinib therapy or other chemotherapies (OR: 4.8–5.6).[32]

It has recently become a well-known phenomenon that patients with IIP without lung cancer develop AE in the normal course of the disease. Kim et al.[33] reported retrospectively that the 1-year frequency was 8.5% after diagnosis. Kubo et al.[34] reported a high incidence of AE (64%) in the control group of a randomized study on the role of anticoagulants. In another prospective randomized study on the role of pirfenidone, Azuma et al.[35] found a 14% incidence in 35 untreated patients during a 9-month follow-up period.

In some cases, it can be difficult in the individual patient to differentiate AE of IIPs from lung cancer progression lymphangitic spread of the disease leading to diffuse interstitial infiltrate. The frequency of AE of IIPs seems to be higher in Japanese than in white. Serum KL-6 and SP-D levels, markers of interstitial pneumonia, are common for differential diagnosis in Japan. Another important differential diagnosis is infectious diseases, such as pneumocystis jiroveci pneumonia with typical ground-glass opacities in a multifocal or diffuse pattern in previously uninvolved area. A

serum β-D glucan is also used for the diagnosis of pneumocystis jiroveci pneumonia.

For differential diagnosis of AE, there are various infectious diseases, congestive heart failure, thromboembolism, and carcinomatous progress. We routinely performed the details of differential diagnosis of AE (i.e., HRCT, lung function test, arterial blood gas, tumor markers, KL-6, SP-D, evaluation of cardiac function by ultrasound cardiography and brain natriuretic peptide, β-D-glucan, D-dimer, and culture of sputum). HRCT is a useful modality in the diagnosis of AE. Nevertheless, the exact incidence of AE from IIPs may be overdiagnosed, because radiological changes cannot specifically identify or diagnose histpathological changes. Therefore, it would be recommended to identify histopathological/microbiological findings.

In this study, AE unrelated to anticancer treatment was observed in two patients, and a further two patients had AE related to second-line chemotherapy. The incidence of total AE, including AE related to second-line chemotherapy and AE unrelated to treatment at MST (8.7 months) and throughout the follow-up period was 18% (3/17 patients) and 29% (5/17 patients), respectively. Regardless of treatment, prolongation of the observation period may increase the numbers of AE manifested. In our previous study of NSCLC with IIP, AE related to first-line treatment with carboplatin plus paclitaxel was observed in one patient (5.6%), and AE was observed in five patients (28%) in total. Although the incidence of first-line chemotherapy-related AE was low in both studies, the incidence of total AE may be high in comparison with its incidence in IPF without lung cancer. The coexistence of lung cancer and IIPs may also be potential risk factors for AE of IIPs.

Localization of active oxygen and a growth factor, inflammatory cytokine, or vascularization factor to lung tissue plays an important role in inducing inflammation.[36] It seems that these factors induced by anticancer treatment may have been one cause of AE. Nevertheless, a useful predictive risk factor for AE or drug-induced ILD has not yet been identified. In our previous report, KL-6, SP-D, Pao_2 and %VC, which are considered to be markers of progression of IIPs, were not predictive of developing AE. There was no statistically significant difference in clinical background or values for pretreatment parameters between those who did and did not experience AE.[22]

We analyzed the predictors of development of AE for patients in this study combined with those in our previous pilot study for NSCLC.[22] Throughout the follow-up period, AE developed in 10 of 35 patients from the combined studies. We conducted univariate analysis for gender, age, PS, smoking status, IIP pattern as clinical factors and LDH, CRP, white blood cells, Pao_2, %VC, KL-6, SP-D, and antinuclear antibody from examination data before initial chemotherapy. Nevertheless, there was no statistically significant risk factor for AE even under a variety of conditions. Nonetheless, in male, elderly patients and in patients with an IPF pattern, a nonsignificant trend toward a high risk of AE was indicated. Moreover, as four of five patients with AE were clinically diagnosed with IPF in this study, IPF may be the anticipated risk factor for AE. On the other hand, using LDH, CRP, KL-6, Pao_2, and %VC as markers to reflect activity and severity of IIPs, the opposite trends to those predicted by us were indicated. It has been reported that the existence of focal usual interstitial pneumonia, which was undetectable by conventional chest CT, but confirmed in a biopsy specimen, was closely related to AE after lung resection for lung cancer.[37] These suggest that disease severity and progression of IIPs are not always correlated with the risk of AE. Large-scale studies are required for clarification.

No recommended regimen for LC with IIP has previously existed. To reduce the levels of toxicity and complications, especially various infectious diseases due to severe neutropenia, and overhydration causing lung congestion, we selected chemotherapy regimens based on carboplatin. The incidence of myelosuppression in this study was not thereby increased compared with that previously reported,[1–5] and nonhematological toxicities were mostly mild to moderate and manageable. Although a high incidence of leukocytopenia and neutropenia was evident, the acceptability of this treatment was good.

In conclusion, the combination chemotherapy of carboplatin plus etoposide used in this study during each 3-week schedule was effective and safe for patients with advanced SCLC with IIP. This is the first report indicating that chemotherapy for SCLC with IIP may be beneficial. To further confirm the feasibility of carboplatin plus etoposide for advanced SCLC with IIP, we are now carrying out a more large-scale clinical trial with detailed evaluation including proteomic analysis, to detect a risk factor for AE.

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REFERENCES

1. Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2002;346:85–91.
2. Lara PN Jr, Natale R, Crpwley J, et al. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWAG S0124. *J Clin Oncol* 2009;27:2530–2535.
3. Hanna N, Bunn PA Jr, Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. *J Clin Oncol* 2006;24:2038–2043.
4. Okamoto H, Watanabe K, Kunikane H, et al. Randomised phase III trial of carboplatin plus etoposide vs split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer: JCOG 9702. *Br J Cancer* 2007;97:162–169.
5. Skarlos DV, Samantas E, Kosmidis P, et al. Randomized comparison of etoposide-cisplatin vs. etoposide-carboplatin and irradiation in small cell lung cancer. A Hellenic Co-operative Oncology Group Study. *Ann Oncol* 1994;5:601–607.
6. Turner-Warwick M, Lebowits M, Burrows B, et al. Cryptogenic fibrosing alveolitis and lung cancer. *Thorax* 1980;35:496–499.
7. Panos RJ, Mortenson RL, Niccoli SA, et al. Clinical deterioration in patients with idiopathic pulmonary fibrosis: caused and assessment. *Am J Med* 1990;88:396–404.
8. Hubbard R, Venn A, Lewis S, et al. Lung cancer and cryptogenic fibrosing alveolitis. Population-based cohort study. *Am J Respir Crit Care Med* 2000;161:5–8.

9. Park J, Kim DS, Shim TS, et al. Lung cancer in patients with idiopathic pulmonary fibrosis. *Eur Respir J* 2001;17:1216–1219.
10. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2002;165:277–304.
11. Kawasaki H, Nagai K, Yokose T, et al. Clinicopatological characteristics of surgically resected lung cancer associated with idiopathic pulmonary fibrosis. *Surg Oncol* 2001;76:53–57.
12. Kondoh Y, Taniguchi H, Kawabata Y, et al. Acute exacerbation in idiopathic pulmonary fibrosis: analysis of clinical and pathological findings in three cases. *Chest* 1993;103:1808–1812.
13. Akira M, Hamada H, Sakatani M, et al. CT findings during phase of accelerated deterioration in patients with idiopathic pulmonary fibrosis. *Am J Roentgenol* 1997;168:79–83.
14. Ambrosini V, Cancellieri A, Chilosi M, et al. Acute exacerbation of idiopathic pulmonary fibrosis: report of a series. *Eur Respir J* 2003;22: 821–826.
15. Parambil JG, Myers JL, Ryu JH. Histopathologic features and outcome of patients with acute exacerbation of idiopathic pulmonary fibrosis undergoing surgical lung biopsy. *Chest* 2005;128:3310–3315.
16. Blivet S, Philit F, Sab JM, et al. Outcome of patients with idiopathic pulmonary fibrosis admitted to the ICU for respiratory failure. *Chest* 2001;120:209–212.
17. Stern JB, Mal H, Groussard O, et al. Prognosis of patients with advanced idiopathic pulmonary fibrosis requiring mechanical ventilation for acute respiratory failure. *Chest* 2001;120:213–219.
18. Koizumi K, Hirata T, Hirai K, et al. Surgical treatment of lung cancer combined with interstitial pneumonia: the effect of surgical approach on postoperative acute exacerbation. *Ann Thorac Cardiovasc Surg* 2004; 10:340–346.
19. Chiyo M, Sekine Y, Iwata T, et al. Impact of interstitial lung disease on surgical morbidity and mortality for lung cancer: analyses of short-term and long-term outocomes. *J Thorac Cardiovasc Surg* 2003;126:1141–1146.
20. Watanabe A, Higami T, Ohori S, et al. Is lung cancer resection indicated in patients with idiopathic pulmonary fibrosis? *J Thoracic Surg* 2008; 136:1357–1363.
21. Chida M, Ono S, Hoshikawa Y, et al. Subclinical idiopathic pulmonary fibrosis is also a risk factor of postoperative acute respiratory distress syndrome following thoracic surgery. *Eur J Cardiovasc Surg* 2008;34: 878–881.
22. Minegishi Y, Sudoh J, Kuribayasi H, et al. The safety and efficacy of weekly paclitaxel in combination with carboplatin for advanced non-small cell lung cancer with idiopathic interstitial pneumonias. *Lung Cancer* 2011;71:70–74.
23. Minegishi Y, Takenaka K, Mizutani H, et al. Exacerbation of idiopathic interstitial pneumonias associated with lung cancer therapy. *Intern Med* 2009;48:665–672.
24. Raghu G, Mageto YM, Lockhart D, et al. The accuracy of the clinical diagnosis of new-onset idiopathic pulmonary fibrosis and other interstitial lung disease: a prospective study. *Chest* 1999;116:1168–1174.
25. Nishimura K, Kitaichi M, Izumi T, et al. Usual interstitial pneumonia: histologic correlation with high-resolution CT. *Radiology* 1992;182: 337–342.
26. Johkoh T, Muller NL, Cartier Y, et al. Idiopathic interstitial pneumonias: diagnostic accuracy of thin-section CT in 129 patients. *Radiology* 1999;211:555–560.
27. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumor. *J Natl Cancer Inst* 2000;92:205–216.
28. Takenaka K, Yoshimura A, Okano T, et al. Acute exacerbation of idiopathic interstitial pneumonia complicated by lung cancer, caused by treatment for lung cancer. *Jpn J Lung Cancer* 1999;39:955–962 [Japanese].
29. Hanibuchi M, Yamaguchi T, Okada T, et al. Clinical examination of acute exacerbation of idiopathic interstitial pneumonia (IIP) combined with lung cancer after anti-cancer treatment. *Jpn J Lung Cancer* 2001; 41:281–286 [Japanese].
30. Isobe K, Hata Y, Sugino K, et al. Clinical characteristics of acute exacerbation of interstitial pneumonia associated with lung cancer after anti-cancer treatment. *Jpn J Lung Cancer* 2007;47:849–854 [Japanese].
31. Kondoh Y, Nishiyama S, Ichikawa M, et al. Issues Concerning treatment of lung cancer patients with interstitial pneumonia: acute exacerbation of interstitial pneumonia. *Jpn J Lung Cancer* 2008;48:732–736 [Japanese].
32. Kudoh S, Kato H, Nishiwaki Y, et al. Interstitial lung disease in Japanese patients with lung cancer: a cohort and nested case-control study. *Am J Respir Crit Care Med* 2008;177:1348–1357.
33. Kim DS, Park JH, Park BK, et al. Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. *Eur Respir J* 2006; 27:143–150.
34. Kubo H, Nakayama K, Yanai M, et al. Anticoagulant therapy for idiopathic pulmonary fibrosis. *Chest* 2005;128:1475–1482.
35. Azuma A, Nukiwa T, Tsuboi E, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2005;171:1040–1047.
36. Sheppard MN, Harrison NK. Lung injury, inflammatory mediators, and fibroblast activation in fibrosing alveolitis. *Thorax* 1992;47:1064–1074.
37. Fukushima K, Kawabata Y, Uchiyama T, et al. Prognosis of possible development into diffuse interstitial pneumonia for 127 patients with localized usual interstitial pneumonia. *Nihon Kokyuuki Gakkai Zassi* 1999;37:177–182 [Japanese].