The Risk of Cytotoxic Chemotherapy-Related Exacerbation of Interstitial Lung Disease with Lung Cancer

Hirotsugu Kenmotsu, MD, Tateaki Naito, MD,* Madoka Kimura, MD,* Akira Ono, MD,* Takehito Shukuya, MD,* Yukiko Nakamura, MD,* Asuka Tsuya, MD,* Kyoichi Kaira, MD,* Haruyasu Murakami, MD,* Toshiaki Takahashi, MD,* Masahiro Endo, MD,† and Nobuyuki Yamamoto, MD**

Introduction: It is unknown what type of interstitial lung disease (ILD) has high risk for chemotherapy-related exacerbation of ILD. We investigated the risk of exacerbation of ILD for patients with lung cancer with ILD.

Methods: One hundred nine patients with lung cancer with ILD treated with cytotoxic chemotherapy at Shizuoka Cancer Center between August 2002 and April 2010 were retrospectively reviewed.

Results: On pretreatment computed tomography (CT) of the chest, 69 patients (63%) were identified with usual interstitial pneumonia (UIP) pattern, and 40 patients (37%) had non-UIP pattern. Patients with UIP pattern developed cytotoxic chemotherapy-related exacerbation of ILD more frequently than those with non-UIP pattern (30 versus 8%, $p = 0.005$). The incidence of grade 5 pulmonary toxicities was 9% in patients with UIP pattern, compared with 3% in those with non-UIP pattern. Multivariate analyses demonstrated that age (<70 years) and CT pattern (UIP) were significant independent risk factors for cytotoxic chemotherapy-related exacerbation of ILD. In small cell lung cancer, overall survival (OS) from the start of first-line chemotherapy was significantly shorter in UIP pattern than non-UIP pattern (median OS: 9 versus 16 months, $p = 0.0475$), whereas there was no significant difference in patients with non-small cell lung cancer (median OS: 12 versus 9 months, $p = 0.2529$).

Conclusions: Our results indicated that the incidence of exacerbation of ILD was significantly higher in patients with lung cancer with UIP pattern on CT findings than in those with non-UIP pattern. Therefore, great care is required when administering cytotoxic chemotherapy agents for patients with lung cancer with UIP pattern.

Key Words: Lung cancer, Interstitial lung disease, Usual interstitial pneumonia, Cytotoxic chemotherapy, Exacerbation.

(*J Thorac Oncol.* 2011;6: 1242–1246)

Divisions of *Thoracic Oncology, and †Diagnostic Radiology, Shizuoka Cancer Center, Nagaizumi-cho, Sunto-gun, Japan.

Disclosure: The authors declare no conflicts of interest.

Address for correspondence: Hirotsugu Kenmotsu, MD, Division of Thoracic Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan. E-mail: h.kenmotsu@scchr.jp

ISSN: 1556-0864/11/0607-1242

Interstitial lung disease (ILD) is called diffuse parenchymal lung disease and is a diverse group of pulmonary disorders classified together because of similar clinical, radiological, physiological, or pathological features.[1] Preexisting ILD or idiopathic interstitial pneumonias (IIPs) are considered to be a risk factor for drug-related ILD.[2] A prospective large cohort study for gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor, has shown that preexisting ILD is not only a strong risk factor for gefitinib-related ILD but also a strong risk factor for cytotoxic chemotherapy-related ILD.[3] Cytotoxic chemotherapy agents, such as gemcitabine, docetaxel, and amrubicin, have been reported to develop severe ILD associated with cytotoxic chemotherapy.[4–6] Chemotherapy-related ILD is not common but is a potentially fatal complication of treatment for lung cancer.

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive interstitial pneumonia of unknown cause limited to the lungs and associated with poor prognosis.[7,8] The American Thoracic Society (ATS) and European Respiratory Society (ERS) have defined IPF as clinical conditions characterized by progressive dyspnea and chronic cough, restrictive lung disease, and the histopathologic pattern of usual interstitial pneumonia (UIP).[7] In addition, in patients with IPF, the incidence of lung cancer is reported to be higher than in patients without IPF.[9–13]

In clinical practice, patients with lung cancer with ILD have been carefully treated with cytotoxic chemotherapy. Nevertheless, it is unknown what kind of chemotherapeutic agents are optimal for patients with lung cancer with ILD. In addition, it is also unknown what type of ILD has high risk for exacerbation of ILD.

To assess the risk of cytotoxic chemotherapy-related ILD, we retrospectively analyzed pretreatment computed tomography (CT) and investigated the clinical course of patients with lung cancer with ILD.

METHODS

The medical records of patients with lung cancer with ILD treated with cytotoxic chemotherapy at the Shizuoka Cancer Center between August 2002 and April 2010 were retrospectively reviewed. In this study, pretreatment CT of the chest was evaluated by one radiologist (M.E.) and two pulmonologists (H.K. and T.N.), who had no knowledge of

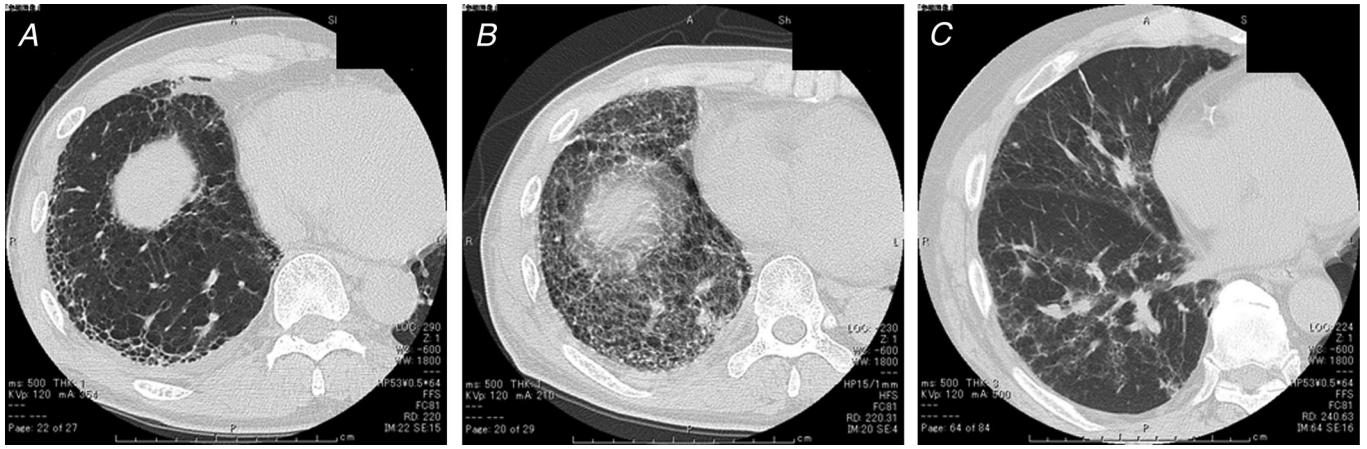

FIGURE 1. High-resolution computed tomography (HRCT) image of the chest. *A*, Pretreatment HRCT image of the chest showing subpleural distribution, honeycombing, traction bronchiectasis, and architectural distortion (UIP pattern). *B*, HRCT image of the chest showing ground-glass abnormality superimposed on pretreatment interstitial shadow (chemotherapy-related exacerbation of ILD). *C*, Pretreatment HRCT image of the chest showing patchy ground-glass opacity with reticulation, traction bronchiectasis, and architectural distortion (non-UIP pattern). UIP, usual interstitial pneumonia; ILD, interstitial lung disease.

the patient's outcome. The chest CT examinations were performed using multidetector-row CT machine at the end of suspended inspiration. CT images were reconstructed to 5-mm slice thickness, and thin section chest CT with 1 mm reconstruction thickness was also performed for evaluating primary tumor and ILD. ILD was diagnosed when the criteria of ground-glass opacity, consolidation, or reticular shadow in both lung fields were met. On the basis of CT characteristics, we classified the patients with ILD into two groups: UIP pattern and non-UIP pattern. Diagnosis of UIP pattern was based on CT features as defined by the International Consensus Statement of the ATS and ERS, showing subpleural distribution, honeycombing, traction bronchiectasis, and architectural distortion (Figure 1*A*).[7,14] All other cases, whose CT of the chest revealed ILD excluding the UIP pattern, were diagnosed as non-UIP pattern (Figure 1*C*).

Chemotherapy-related exacerbation of ILD was diagnosed on the basis of CT findings (bilateral ground-glass abnormality with or without focal consolidation, superimposed on pretreatment interstitial shadow) (Figure 1*B*).[15] Patients with apparent pulmonary infection, pulmonary embolism, or heart failure were excluded. Chemotherapy-related exacerbation of ILD was evaluated based on pneumonitis/pulmonary infiltrates by National Cancer Institute Common Terminology Criteria version 3.0—grade 3: symptomatic, interfering with activities of daily living, and oxygen indicated; grade 4: life-threatening; and grade 5: death. The patients who developed exacerbation of ILD within 1 year after thoracic radiotherapy and who received epidermal growth factor receptor tyrosine kinase inhibitor in the clinical course were excluded from chemotherapy-related exacerbation of ILD. To assess the incidence of exacerbation of ILD by treatment regimen, the duration between last administration of cytotoxic chemotherapy and the onset of exacerbation of ILD was defined as 4 weeks or less.

Univariate and multivariate analyses were performed to identify risk factors for the exacerbation of ILD associated with cytotoxic chemotherapy. All categorical variables were analyzed by the χ^2 test or Fisher's exact test, as appropriate. Multivariate analyses were performed using a logistic regression procedure to assess the relationship between various factors and exacerbation of ILD. Clinical evaluation of overall survival (OS) after the start of first-line chemotherapy was conducted by the Kaplan-Meier method to assess the time to death. The log-rank test was used to compare cumulative survival in each group. All p values were reported as two-sided, and values less than 0.05 were considered statistically significant. This study was approved by the institutional review board.

RESULTS

Patient Characteristics

One hundred nine patients were diagnosed with lung cancer with ILD and treated with cytotoxic chemotherapy. The characteristics of the patients are shown in Table 1. The median age was 69 years (range: 54–84 years), and almost all patients were smokers and men with good performance status. Histologically, adenocarcinoma, squamous cell carcinoma, and small cell lung cancer (SCLC) were observed in 33, 30, and 30%, respectively. Others included large cell carcinoma and undifferentiated non-small cell cancer. Stages III and IV were observed in 40 and 53%, respectively, and recurrence after surgical resection occurred in 7%. In SCLC, limited and extensive diseases were observed in 33 and 67%, respectively. On the basis of pretreatment CT of the chest, 69 patients (63%) were identified with UIP pattern, and 40 patients (37%) had non-UIP pattern. Although there were some imbalances between the two groups in terms of stage IV

TABLE 1. Patient Characteristics (Overall, $n = 109$)

	Total	UIP Pattern, *n* (%)	Non-UIP Pattern, *n* (%)	*p*
No. of patients	109	69	40	
Gender				0.117
Male	103	67 (97)	36 (90)	
Female	6	2 (3)	4 (10)	
Age (yr), median (range)	69 (54–84)	70 (55–84)	69 (54–80)	0.245
Smoking status				0.763
Never smoker	0	0	0	
Ex-smoker	47	29 (42)	18 (45)	
Current smoker	62	40 (58)	22 (55)	
Performance status (ECOG)				0.150
0–1	94	62 (90)	32 (80)	
2–3	15	7 (10)	8 (20)	
Histology				0.723
Adenocarcinoma	36	22 (32)	14 (35)	
Squamous cell carcinoma	33	21 (30)	11 (28)	
SCLC	33	20 (29)	13 (32)	
Others	8	6 (9)	2 (5)	
Clinical stages				0.044
IIIA and B	44	34 (49)	10 (25)	
IV	57	31 (45)	26 (65)	
Recurrence after surgical resection	8	4 (6)	4 (10)	
SCLC				0.314
Limited disease	11	8 (40)	3 (23)	
Extensive disease	22	12 (60)	10 (77)	

UIP, usual interstitial pneumonia; SCLC, small cell lung cancer; ECOG, Eastern Cooperative Oncology Group.

TABLE 2. Incidence of Cytotoxic Chemotherapy-Related Exacerbation of ILD

	No. of Patients (%)			
	Total, *n* (%)	UIP Pattern, *n* (%)	Non-UIP Pattern, *n* (%)	*p*
Overall	109	69	40	
Exacerbation of ILD	24 (22)	21 (30)	3 (8)	0.005
≥ Grade 3	22 (20)	20 (29)	2 (5)	0.003
Grade 3	5 (5)	4 (6)	1 (3)	
Grade 4	10 (9)	10 (14)	0	
Grade 5	7 (6)	6 (9)	1 (3)	

UIP, usual interstitial pneumonia; ILD, interstitial lung disease.

TABLE 3. Cytotoxic Chemotherapy Agents Considered to Cause the Exacerbation of ILD

	UIP Pattern		Non-UIP Pattern	
	No. of Patients Administered	Exacerbation of ILD (%)	No. of Patients Administered	Exacerbation of ILD (%)
Cisplatin	21	2 (10)	21	1 (5)
Carboplatin	40	5 (13)	19	0
Paclitaxel	31	1 (3)	14	0
Docetaxel	25	7 (28)	12	1 (8)
Etoposide	21	5 (24)	10	0
Vinorelbine	13	0	6	0
Gemcitabine	7	3 (43)	10	1 (10)
S-1	7	2 (29)	7	1 (14)
Irinotecan	6	2 (33)	6	0
Amrubicin	4	0	6	0
Pemetrexed	2	1 (50)	1	0

UIP, usual interstitial pneumonia; ILD, interstitial lung disease.

($p = 0.044$), there were no significant differences in patient characteristics between both groups.

Incidence of Cytotoxic Chemotherapy-Related Exacerbation of ILD

Of the 109 patients with ILD, 24 (22%) developed cytotoxic chemotherapy-related exacerbation of ILD. In particular, patients with UIP pattern developed cytotoxic chemotherapy-related exacerbation of ILD more frequently than those with non-UIP pattern (30 versus 8%, $p = 0.005$; Table 2). In addition, the incidence of grade 3 or worse pneumonitis/pulmonary infiltrates was significantly higher in patients with UIP pattern than in patients with non-UIP pattern (29 versus 5%, $p = 0.003$). Almost all of the patients who developed grade 3 or worse pulmonary toxicities received corticosteroid therapy. Nevertheless, 9% of the patients with UIP pattern died because of exacerbation of ILD, whereas 3% of those with non-UIP pattern died.

The median time from last administration of cytotoxic chemotherapy to the diagnosis of the exacerbation of ILD was 17 days (range: 0–25 days). The incidence rate of exacerbation of ILD is shown in Table 3 for each agent; docetaxel (28%) or etoposide (24%) frequently led to exacerbation of ILD for patients with UIP pattern. On the other hand, the incidence of exacerbation of ILD was relatively low for vinorelbine or paclitaxel. Cisplatin or carboplatin was mainly administered with another agent, and it was difficult to assess the risk for ILD. In patients with SCLC, 63% of exacerbation of ILD occurred during the first-line chemotherapy, whereas in patients with non-small cell lung cancer (NSCLC) the corresponding proportion was 31%. In addition, only one patient received further chemotherapy after exacerbation of ILD.

The Risk of Cytotoxic Chemotherapy-Related Exacerbation of ILD

The results of the univariate analysis of risk factors for cytotoxic chemotherapy-related exacerbation of ILD are shown in Table 4. UIP pattern on CT was significantly associated with the exacerbation of ILD ($p = 0.005$). Multivariate analyses were performed using three variables (age, performance status, and CT pattern), and the results demonstrated that age (<70 years) (odds ratio [OR]: 2.75, 95% confidence interval: 1.03–7.93) and CT pattern (UIP) (OR:

TABLE 4. Univariate Analysis of Risk Factors Associated with Cytotoxic Chemotherapy-Related Exacerbation of ILD

	No. of Patients			
	Overall	Ex of ILD	Non-Ex of ILD	*p*
No. of patients	109	24	85	
Gender				—
Male	103	24	79	
Female	6	0	6	
Age (yr)				0.0897
<70	56	16	40	
≥70	53	8	45	
ECOG-PS				0.7043
0–1	94	20	74	
2–3	15	4	11	
Histology				0.7119
NSCLC	76	16	60	
SCLC	33	8	25	
CT pattern				0.0054
UIP	69	21	48	
Non-UIP	40	3	37	
Stage				0.3186
IIIA and B	44	7	37	
IV	57	14	43	
Recurrence after surgical resection	8	3	5	

UIP, usual interstitial pneumonia; Ex, exacerbation; ILD, interstitial lung disease; PS, performance status; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group.

TABLE 5. Multivariate Analysis of Risk Factors Associated with Cytotoxic Chemotherapy-Related Exacerbation of ILD

Variable	Odds Ratio	95% CI	*p*
Age (<70 yr)	2.75	1.03–7.93	0.0495
ECOG-PS (2 and 3)	2.20	0.51–8.74	0.2653
CT pattern (UIP)	6.98	2.04–33.79	0.0053

PS, performance status; CT, computed tomography; UIP, usual interstitial pneumonia; ECOG, Eastern Cooperative Oncology Group.

6.98, 95% confidence interval: 2.04–33.79) were significant independent risk factors (Table 5).

Overall Survival

In this analysis, the median follow-up duration was 10.3 months. In SCLC, OS from the start of first-line chemotherapy was significantly shorter in patients with UIP pattern than those with non-UIP pattern (median OS: 9 versus 16 months, $p = 0.048$), whereas there was no significant difference in patients with NSCLC (median OS: 11 versus 9 months, $p = 0.334$).

DISCUSSION

In patients with IPF, the incidence of lung cancer is reported to be higher than in patients without IPF,[9–13] and IPF has been recognized to be an independent risk factor for lung carcinogenesis.[11] There are some reports that patients with lung cancer with preexisting ILD or pulmonary fibrosis have a high risk of developing exacerbation after anticancer therapy,[3,16–18] and the incidence of exacerbation of ILD was 20 to 24%.[16,17] It is very important to establish an optimal treatment, which is considered to be safe and effective, for patients with lung cancer with ILD or IPF.

To our knowledge, this is the first study to evaluate the risk of cytotoxic chemotherapy-related ILD based on pretreatment chest CT patterns. In clinical practice, patients with lung cancer with ILD have been carefully treated with cytotoxic chemotherapy. Nevertheless, it is unknown what type of ILD has a high risk for exacerbation of ILD. In this study, patients with lung cancer with UIP pattern on CT findings demonstrated a high risk of exacerbation of ILD, compared with those with non-UIP pattern. This result suggests that chest CT patterns could be a risk factor for the development of chemotherapy-related exacerbation of ILD. Although age (<70 years) was also shown to be a risk factor, these patients might tend to receive multiple drugs for longer periods than elderly patients.

As there have been few reports about chemotherapy for patients with lung cancer with ILD, the optimal agent remains controversial. From Japan, a prospective study to evaluate the safety and efficacy of weekly paclitaxel in combination with carboplatin for advanced NSCLC with IIPs was reported.[19] One of 18 patients enrolled in this prospective study developed exacerbation of IIPs. Our study also showed that carboplatin and paclitaxel were relatively safe for patients with lung cancer with ILD, for whom this regimen might be one of the optimal regimens for those patients. Our results suggested that vinorelbine might also be relatively safe for patients with ILD. Nevertheless, we could not completely rule out the influence of biopsy for lung cancer diagnosis, before chemotherapy and before radiotherapy. It is known that the long-term survival in IPF shows poor prognosis compared with non-IPF, such as nonspecific interstitial pneumonia and other subgroups of IIPs.[1] In this study, although the UIP pattern on CT was significantly associated with the exacerbation of ILD, in patients with NSCLC with UIP pattern OS was not significantly different from those with non-UIP pattern. On the other hand, OS was significantly shorter in patients with SCLC with UIP pattern than in those with non-UIP pattern, and the type of ILD might influence the prognosis of patients with SCLC with ILD. Sixty-three percent of exacerbation of ILD in patients with SCLC occurred during the first-line chemotherapy, and they could not receive subsequent chemotherapy. On the other hand, approximately 70% of exacerbation of ILD in patients with NSCLC occurred during the second or subsequent line of chemotherapy and completed first-line chemotherapy. Thus, the rate of failure in first-line chemotherapy might contribute to poor prognosis in SCLC.

A major limitation of this retrospective analysis was that the diagnosis of ILD was based on CT findings and not on histologic diagnosis. In addition, the diagnosis of exacerbation of ILD was also based on CT findings, and we could not confirm histologically the exacerbation of ILD. Although we tried to exclude infection by bacteriological examination

and heart failure by physical examination or echocardiography, we cannot completely exclude pulmonary infection, pulmonary embolism, or heart failure. Nevertheless, their clinical and radiological courses were consistent with exacerbation of ILD. It was reported that in clinical practice, surgical lung biopsies were performed in 8 to 12% of patients,[20] and the ATS/ERS consensus statement also described criteria for the clinical diagnosis of IPF.[7] Moreover, the ability of high-resolution computed tomography scanning to diagnose IPF has reported sensitivities of 43 to 78% and specificities of 90 to 97% for confident radiological diagnosis.[21–25] Thus, we consider that it is appropriate to diagnose IPF using the clinical and radiological findings in clinical practice. Further studies are needed to clarify the relationship between the radiological patterns and pathological patterns of ILD for patients with lung cancer.

In conclusion, our study indicated that in patients with lung cancer with UIP pattern on CT findings, the risk of exacerbation of ILD was significantly higher than in those with non-UIP pattern. In particular, greater care is required when administering cytotoxic chemotherapy agents for patients with lung cancer with UIP pattern on CT findings.

REFERENCES

1. King TE Jr. Clinical advances in the diagnosis and therapy of the interstitial lung diseases. *Am J Respir Crit Care Med* 2005;172:268–279.
2. Camus P, Kudoh S, Ebina M. Interstitial lung disease associated with drug therapy. *Br J Cancer* 2004;91(Suppl 2):S18–S23.
3. 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.
4. Pavlakis N, Bell DR, Millward MJ, et al. Fatal pulmonary toxicity resulting from treatment with gemcitabine. *Cancer* 1997;80:286–291.
5. Read WL, Mortimer JE, Picus J. Severe interstitial pneumonitis associated with docetaxel administration. *Cancer* 2002;94:847–853.
6. Yoh K, Kenmotsu H, Yamaguchi Y, et al. Severe interstitial lung disease associated with amrubicin treatment. *J Thorac Oncol* 2010;5:1435–1438.
7. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med* 2002;165:277–304.
8. Bjoraker JA, Ryu JH, Edwin MK, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1998;157:199–203.
9. Wiggins J, Strickland B, Turner-Warwick M. Combined cryptogenic fibrosing alveolitis and emphysema: the value of high resolution computed tomography in assessment. *Respir Med* 1990;84:365–369.
10. Matsushita H, Tanaka S, Saiki Y, et al. Lung cancer associated with usual interstitial pneumonia. *Pathol Int* 1995;45:925–932.
11. Hubbard R, Venn A, Lewis S, et al. Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study. *Am J Respir Crit Care Med* 2000;161:5–8.
12. Le Jeune I, Gribbin J, West J, et al. The incidence of cancer in patients with idiopathic pulmonary fibrosis and sarcoidosis in the UK. *Respir Med* 2007;101:2534–2540.
13. Ozawa Y, Suda T, Naito T, et al. Cumulative incidence of and predictive factors for lung cancer in IPF. *Respirology* 2009;14:723–728.
14. Lynch DA, Godwin JD, Safrin S, et al. High-resolution computed tomography in idiopathic pulmonary fibrosis: diagnosis and prognosis. *Am J Respir Crit Care Med* 2005;172:488–493.
15. Collard HR, Moore BB, Flaherty KR, et al. Acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2007;176:636–643.
16. Isobe K, Hata Y, Sakamoto S, et al. Clinical characteristics of acute respiratory deterioration in pulmonary fibrosis associated with lung cancer following anti-cancer therapy. *Respirology* 2010;15:88–92.
17. Minegishi Y, Takenaka K, Mizutani H, et al. Exacerbation of idiopathic interstitial pneumonias associated with lung cancer therapy. *Intern Med* 2009;48:665–672.
18. Niho S, Goto K, Yoh 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.
19. 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.
20. The diagnosis, assessment and treatment of diffuse parenchymal lung disease in adults. Introduction. *Thorax* 1999;54(Suppl 1):S1–S14.
21. Flaherty KR, King TE Jr, Raghu G, et al. Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? *Am J Respir Crit Care Med* 2004;170:904–910.
22. Hunninghake GW, Zimmerman MB, Schwartz DA, et al. Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2001;164:193–196.
23. Johkoh T, Müller NL, Cartier Y, et al. Idiopathic interstitial pneumonias: diagnostic accuracy of thin-section CT in 129 patients. *Radiology* 1999;211:555–560.
24. Raghu G, Mageto YN, 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. Swensen SJ, Aughenbaugh GL, Myers JL. Diffuse lung disease: diagnostic accuracy of CT in patients undergoing surgical biopsy of the lung. *Radiology* 1997;205:229–234.