Title 論文題目	Risk factors for acute exacerbation of idiopathic interstitial pneumonias in patients undergoing lung cancer treatment （肺癌治療を受けている患者における特発性間質間質性肺炎の急性増悪のリスク因子）
Author(s) 著　者	多屋, 哲也
Degree number 学位記番号	乙第 3080 号
Degree name 学位の種別	博士（医学）
Issue Date 学位取得年月日	2020-02-07
Original Article 原著論文	Japanese Journal of Clinical Oncology. 2019 Aug 14.
Doc URL	
DOI	
Resource Version	Publisher Version

JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2019, 00(00)1–9
doi: 10.1093/jjco/hyz115
Original Article

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Risk factors for acute exacerbation of idiopathic interstitial pneumonia in patients undergoing lung cancer treatment

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Received 20 February 2019; Accepted 03 July 2019

Abstract

Objective: Identifying risk factors for cancer treatment-related acute exacerbations (AEs) of idiopathic interstitial pneumonia (IIP) in patients with lung cancer.
Methods: We retrospectively reviewed clinical records of 98 patients with concurrent lung cancer and IIPs diagnosed and treated at the Sapporo Medical University Hospital from January 2010 to December 2014.
Results: Of the 98 patients with concurrent lung cancer and IIPs, 14 patients (14.3%) had AEs. A total of 10 patients died. The univariate analysis revealed that the patients with idiopathic pulmonary fibrosis (IPF) or usual interstitial pneumonia (UIP) patterns on chest computed tomography (CT) had significantly higher rates of AE than those with non-IPF or non-UIP patterns, respectively. Further, those with a reduced percentage of forced vital capacity (%FVC) predictive values or elevated Krebs von den Lungen-6 (KL-6) presented significantly higher rates of AE. Our multivariate analysis identified that UIP pattern on chest CT and each 10% decrease in %FVC were significant independent risk factors for AEs. Of the 14 patients who experienced AEs, 10 cases were associated with cancer treatment. The treatment-specific incidences were 3/40 (7.5%) for surgery, 5/50 (10.0%) for chemotherapy, and 2/26 (7.7%) for radiation therapy. After comparing the AE incidences in 55 cases receiving one treatment (monotherapy group) and in 29 cases receiving two types of treatment or more (multitherapy group), we found no significant differences.
Conclusions: Chest CT UIP patterns and reduced %FVC are independent risk factors for AE. Moreover, AE incidence did not increase in the multitherapy group compared with the monotherapy group.

Key words: lung cancer, idiopathic interstitial pneumonia, acute exacerbation

Introduction

Idiopathic interstitial pneumonia (IIP) are a serious health complication associated with high mortality covering nine different clinical types of unknown cause, including idiopathic pulmonary fibrosis (IPF), which has the poorest prognosis and accounts for over 50% of all IIPs (1). Mortality and morbidity are high in patients with IIPs because of respiratory failure that leads to chronic deterioration, or acute exacerbations (AEs), and frequent onset of concurrent lung cancer. Particularly, 10–30% of patients with IPF have concurrent lung cancer (2–7). Patients with IPF have a 7–14-fold higher risk of lung cancer than people without IPF, indicating that IPF is an independent risk factor for lung cancer (7–8). Conversely, AEs are

associated with an extremely poor prognosis with a mortality rate for the first onset at 50–80% (9–10). A study of patients with IPF in Japan and Korea reported that the most common cause of death was AE (40–46%) (3,11).

In patients with concurrent lung cancer and IIPs, cancer treatment may cause AEs, and the reported incidences of AE associated with surgery, chemotherapy, or radiotherapy range from 9.3% to 42.9% (12–19). Therefore, the choice between the life-prolonging benefit of cancer treatment and the risk of AE onset is a challenging problem in clinical practice. Generally, pulmonologists, at a tertiary care hospital, specialize in diagnosing the interstitial lung diseases (ILDs) and IIPs; however, medical oncologists, radiotherapists or respiratory surgeons oversee lung cancer treatment. Therefore, it is possible that many lung cancer patients with concurrent IIPs are not regarded as candidates for lung cancer treatment due to the risk of treatment-related AEs, and safe treatment for this group has not been established. The current American guidelines for lung cancer treatment National Comprehensive Cancer Network/American Society of Clinical Oncology (NCCN/ASCO) do not provide information regarding patients treated with concurrent ILDs (20–22). In Japan, there is an accumulation of experience regarding patients with concurrent lung cancer and IIPs because pulmonologists themselves diagnose and treat such patients. The Japanese Respiratory Society published 'Statement on Interstitial Pneumonia Combined Lung Cancer' and providing guidance and calling for the construction of evidence (23). Although multitherapies that combine surgery, chemotherapy, and radiotherapy for lung cancer treatment are recommended, there has not been a detailed study on whether AE risk differs between patients undergoing monotherapy and those undergoing multitherapy.

It is hoped that lung cancer patients with IIPs should be treated effectively with low risk. AE caused by lung cancer treatment is the most serious adverse event compared to patients without IIP. To identify AE risk factors related to cancer treatment, we retrospectively analyzed IIP patients who underwent lung cancer treatment at a tertiary care hospital.

Patients and methods

We retrospectively selected patients who had complicated ILDs with lung cancer and were treated at Sapporo Medical University Hospital in Japan from January 2010 to December 2014. We excluded patients with identifiable ILD complications, such as those with collagen disease, pneumoconiosis and hypersensitivity pneumonitis. We classified IIPs following the international multidisciplinary classification of 2013 (1).

Three pulmonologists used chest high-resolution computed tomographies (HRCTs) from the time of lung cancer diagnosis to the time of retrospective study review. Then, they independently classified the cases into two groups based on the image patterns: one for patients with UIP patterns (UIP pattern group) and one for patients with image patterns, which were either possible UIP or inconsistent with UIP (non-UIP pattern group). The pulmonologists based their diagnoses on the American Thoracic. Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Society (ATS/ERS/JRS/ALAT) diagnostic criteria (24). The three pulmonologists interpreted the CT images using both 5-mm and 1-mm thicknesses and concerted the cases with divergent diagnoses after a further discussion on the diagnoses. For this study, we used the definition of AE advocated by Collard et al. (25) to conform to the diagnostic criteria of AEs. The diagnostic criteria involve examining the development of dyspnea or its unexplained worsening within the last 30 days. Moreover, HRCT is used to verify new bilateral ground-glass abnormalities and/or consolidation superimposed on existing interstitial shadows. The final requirement is the exclusion of other etiologies including infection, left-sided heart failure, pulmonary embolism, and identifiable causes of acute lung injury.

We defined cancer treatment-related AEs as those occurring within 4 weeks from the time of surgical operation, or within 8 weeks from the end of chemotherapy, or within 6 months from the start of radiation therapy (15,16,26). We grouped into patients who experienced AEs (AE-IIP group) and those who did not (Stable IIP group) during the observation period. We collected data based on age, sex, smoking history, performance status (PS), chest CT findings, histological type and clinical stage of lung cancer, surfactant protein (SP)-A, SP-D, KL-6, forced vital capacity (FVC), diffusing capacity of the lung for carbon monoxide (DLCO) and treatment contents. In addition, we grouped the patients into a monotherapy group (patients underwent a single cancer treatment of surgery, chemotherapy, or radiation therapy), or a multitherapy group (patients underwent two or more treatments simultaneously or sequentially), and we analyzed the risk of AE in both groups.

For statistical analysis, we performed the univariate analysis using the chi-square test or Fisher's exact test, and the multivariate analysis using logistic regression. We considered $P < 0.05$ as statistically significant. We performed all the statistical analyses using the JMP version 13 software (SAS Institute, Cary, NC, USA). The institutional review board of the Sapporo Medical University Hospital approved this study (approval number 272–91; ref. 2015/12/11).

Results

Patient background

The clinical characteristics of all subject patients, the AE-IIP group and the Stable IIP group are shown in Table 1. The study included 98 lung cancer patients with IIPs as the underlying disease. Their mean age was 70 years (IQR, 65–76), 90.8% were men, 96.9% were current or previous smokers and 80.6% were PS $\leq$ 1. The histological types of lung cancer were adenocarcinoma in 41 patients (41.8%), squamous cell carcinoma in 34 patients (34.7%) and small-cell carcinoma in 11 patients (11.2%). More than half ($n = 57$) of the patients had stages IA-IIIB (UICC-TNM classification, 7th edn).

The IIP disease types were IPF in 52 patients (53.1%), nonspecific interstitial pneumonia (NSIP) in three patients (3.0%), and unclassifiable IIPs in 43 patients (43.9%). CT imaging patterns were UIP in 46 patients (46.9%) and non-UIP patterns in 52 patients (53.1%). Concurrent pulmonary emphysema was found in 52 patients (53.1%). Of the IPF patients, Pirfenidone has been administered to the three patients. All 98 patients received either surgical therapy, chemotherapy, radiotherapy or a combination of these, or received best supportive care.

Risk of AE in patients with IIPs

Among the 98 patients with concurrent lung cancer and IIP, AEs occurred in 14 patients (14.3%) and 10 patients died. There were nine cases (one autopsy case) of imaging findings following the diffuse alveolar damage (DAD) pattern, with the outcome of all cases being death. There were four cases of imaging findings following the organizing pneumonia (OP) pattern, for all of which the outcome was survival. In addition, there was one case of a DAD + OP pattern (one autopsy case), where the outcome was death.

Table 1. Patient characteristics

	n (%) or Median (IQR; Range)			
	Total	AE-IIP	Stable IIP	*P*
n	98	14	84	
Age	70 (65–76; 48–87)	69 (65.8–74.3; 62–80)	70.5 (65–76; 48–87)	0.8668
Gender				0.3502
Male	89 (90.8)	14 (100)	75 (89.3)	
Female	9 (9.2)	0 (0)	9 (10.7)	
Ever smoker	95 (96.9)	14 (100)	81 (96.4)	1
Pack-years	54.5 (42–80; 0–188)	60.5 (44.3–80; 35–117)	53 (41.3–80.8; 0–145)	0.4835
ECOG · PS				1
0–1	79 (80.6)	11 (78.6)	68 (80.9)	
2–4	19 (19.4)	3 (21.4)	16 (19.1)	
Histology				0.4996
Adenocarcinoma	41 (41.8)	4 (28.6)	37 (44.1)	
Squamous cell carcinoma	34 (34.7)	6 (42.9)	28 (33.3)	
Small-cell carcinoma	11 (11.2)	1 (7.1)	10 (11.9)	
Others	12 (12.3)	3 (21.4)	9 (10.7)	
Clinical stages				0.3835
≦IIIB	57 (58.2)	4 (28.6)	53 (63.1)	
IV	41 (41.8)	10 (71.4)	31 (36.9)	
IIP type				0.0464*
IPF	52 (53.1)	11 (78.6)	41 (48.8)	
NSIP	3 (3.0)	0 (0)	3 (3.6)	
Unclassifiable	43 (43.9)	3 (21.4)	40 (47.6)	
HRCT				
UIP pattern	46 (46.9)	11 (78.6)	35 (58.3)	0.0183
Non-UIP pattern	52 (53.1)	3 (21.4)	49 (41.7)	
Emphysema	52 (53.1)	5 (35.7)	47 (56.0)	0.2471
Non-emphysema	46 (46.9)	9 (64.3)	37 (44.0)	
SP-A (ng/ml)	48.5 (39.5–68.8; 10.7–145)	46 (41.8–67.8; 23.3–83.1)	49.5 (38.9–68.8; 10.7–145)	0.8927
SP-D (ng/ml)	99.6 (71.7–172; 10–735)	150 (72.6–288.5; 28–452)	96 (71–150; 10–735)	0.1969
KL-6 (U/ml)	516 (326–818; 113–3600)	881.5 (451–1246; 129–3600)	482 (312–792; 113–1790)	0.0436
%FVC (%)	98.3 (82.6–116.7; 50.3–153.4)	79.7 (74.2–94.5; 58–112.5)	103.2 (90.2–117.9; 50.3–153.4)	0.005
%DLco (%)	54.1 (42.5–66.7; 15.9–81.9)	53.3 (46.6–68.6; 23.3–74.5)	54.1 (41.8–66.2; 15.9–81.9)	0.963

IQR, interquartile range; AE-IIP, acute exacerbation of idiopathic interstitial pneumonia; stable IIP, non-exacerbation of idiopathic interstitial pneumonia; ECOG, Eastern Cooperative Oncology Group; PS, performance status; IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia; HRCT, high-resolution computed tomography; UIP, usual interstitial pneumonia; SP-A, surfactant protein A; SP-D, surfactant protein D; KL-6, sialylated carbohydrate antigen Krebs von den Lungen-6; %FVC, focal vital capacity % predicted; %DLco, diffusing capacity of the lung carbon monoxide % predicted.

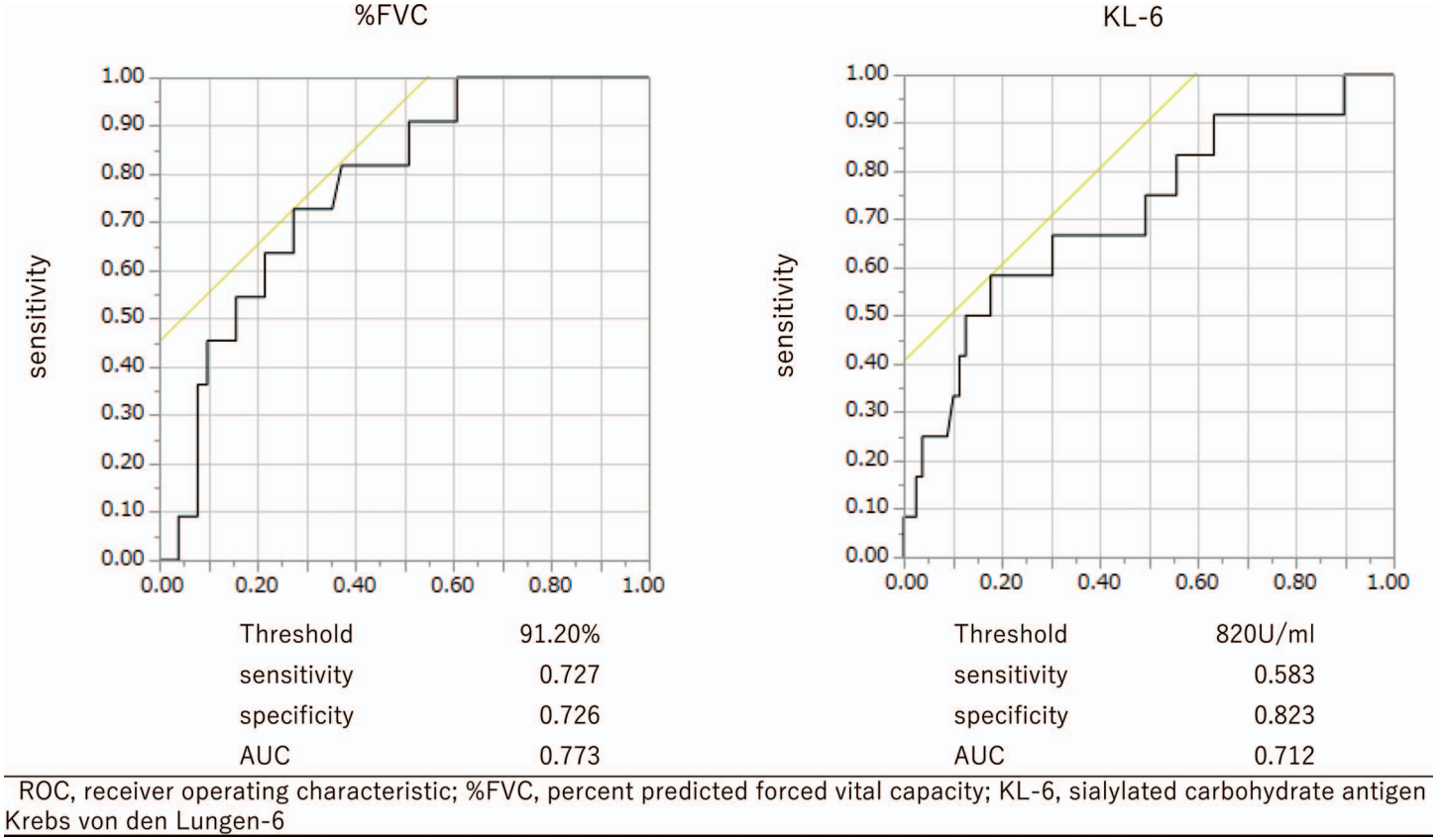
*Fisher's exact test (IPF vs NSIP and Unclassifiable).

The univariate analysis revealed that the patients with IPF ($P = 0.0464$) or UIP patterns ($P = 0.0183$) had significantly higher rates of AE than those with non-IPF or non-UIP patterns, respectively. We found AEs in five patients out of 52 patients with pulmonary emphysema (9.6%) and nine patients experienced AEs out of 46 patients with non-pulmonary emphysema (19.6%). However, no significant difference was found in the frequency between the two groups ($P = 0.2471$). Further, those with reduced FVC% predictive values ($P = 0.005$) or elevated KL-6 ($P = 0.0436$) presented significantly higher rates of AE (Table 1). Moreover, our receiver operating characteristic (ROC) curve analysis revealed that the %FVC cutoff values were 91.2% (sensitivity, 0.727; specificity, 0.726; and AUC, 0.773), and KL-6 cutoff values were 820 U/ml (sensitivity, 0.583; specificity, 0.823; and AUC, 0.712) (Fig. 1).

In the multivariable analysis in this research, due to there being a low number of AE occurrences, we statistically limited the independent variables used. By changing the independent variables that were significant in univariable analysis or independent variables that were considered to be important, three models were constructed. On univariate analysis of IIP type, IPF was significant but was excluded from multivariate analysis due to the strong correlation to UIP patterns on CT. Consistently in all models, UIP patterns on CT and each 10% decrease in %FVC were independent risk factors for AE (Table 2).

Treatment details for AE patients

The treatment for lung cancer is presented in Table 3. Aggressive or palliative treatment was administered to 84 patients, and best supportive care was administered to 14 patients. We observed treatment-related AEs in 10 patients (10.2%), with 30 day/90 day mortality rates of 60%/60%, respectively. The median time from the end of treatment to the onset of AE is 23 days (range: 5–69 days). Further, we found AEs to be unrelated to cancer treatment in four



ROC, receiver operating characteristic; %FVC, percent predicted forced vital capacity; KL-6, sialylated carbohydrate antigen Krebs von den Lungen-6

Figure 1. ROC curve analysis of %FVC and KL-6.

Table 2. Multivariate analysis of risk factors associated with AE in patients with concurrent lung cancer and IIPs

Variable	Odds ratio	95% CI	*P* (Wald test)	*P* (likelihood ratio test)
Model 1				
UIP pattern on HRCT	15.01	1.37–164.16	0.0265	0.0068
%FVC (per 10% decreased)	1.7	1.06–2.71	0.0277	0.0119
%DLco (per 10% decreased)	0.88	0.43–1.80	0.1118	0.0917
Model 2				
UIP pattern on HRCT	15.56	1.25–193.09	0.0326	0.0068
%FVC (per 10% decreased)	1.67	1.03–2.69	0.0365	0.0119
%DLco (per 10% decreased)	0.63	0.36–1.12	0.1179	0.0955
KL-6 (per 100 U/ml increased)	0.9	0.76–1.06	0.2226	0.1396
Model 3				
UIP pattern on HRCT	15.67	1.43–171.79	0.0243	0.0061
%FVC (per 10% decreased)	1.7	1.06–2.73	0.029	0.0127
%DLco (per 10% decreased)	0.62	0.35–1.09	0.0994	0.0776
ECOG-PS (2–4)	0.45	0.03–7.73	0.5847	0.5925

IIP, idiopathic interstitial pneumonia.

Table 3. Selection of treatment

Treatment	*n* (%)
Total	98 (100)
Surgery alone	26 (26.5)
Chemotherapy alone	22 (22.5)
Radiotherapy alone	7 (7.1)
Surgery + chemotherapy	9 (9.2)
Surgery + radiotherapy	1 (1.0)
Surgery + chemotherapy+radiotherapy	4 (4.1)
Chemotherapy + radiotherapy	15 (15.3)
Best supportive care	14 (14.3)

Table 4. Causes of AE

Causes of AE		AE *n* (%)
Treatment-related		10 (10.2)
Surgery		3 (3.1)
	(Surgery alone)	3
Chemotherapy		5 (5.1)
	(Chemotherapy alone)	4
	(Chemotherapy + radiotherapy→Chemotherapy)	1
Radiotherapy		2 (2.0)
	(Chemotherapy→radiotherapy)	2
Non-treatment-related		4 (4.1)
Infection		3
TBB		1

TBB; transbronchial biopsy.

patients (4.1%), with 30-day/90-day mortality rates of 50%/50%. Antecedent infections may have triggered the exacerbations in three of the patients and a complication of a procedure involving transbronchial biopsy triggered the exacerbation in the other patient (Table 4).

Surgery. A total of 40 patients underwent surgery, including surgery alone and surgery combined with other therapies (lobectomy in 34 patients, segmentectomy in four patients and partial resection in two patients). Among these patients, three (7.5%) experienced AEs after surgery (Table 4) and all had lobectomies. In one patient, surgical stress was thought to be the AE trigger. In the remaining two patients, AEs occurred after postoperative complications (an infection caused by postoperative bronchial stump fistula in one patient, and postoperative pneumonia and pyothorax in the other).

Chemotherapy. A total of 50 patients received chemotherapy, either alone or in combination with other therapies. AEs occurred during chemotherapy in five patients (10.0%) (Table 4). AEs occurred in four patients given chemotherapy alone, and one patient experienced an AE during chemotherapy, after receiving combined radiotherapy.

We calculated the frequencies of AE onsets according to chemotherapy regimen (Table 5). Thirteen chemotherapy regimens were administered a total of 67 times. Thirty-three patients were treated with the first regimen alone and 17 patients were treated with the second regimen after the first regimen. In nine patients given VP-16-based chemotherapy, we found no AEs. We found AEs in one out of 19 patients (5.3%) given pemetrexed (PEM)-based chemotherapy, and in one out of 18 patients (5.6%) given paclitaxel (PTX)-based chemotherapy. However, AEs occurred in two out of 12 patients (16.7%) given vinorelbine (VNR)-based chemotherapy, indicating a relatively higher AE incidence. We attributed the AE to the presence of an underlying severe infection with febrile neutropenia in one of these two patients. Additionally, we found AE onset in one out of nine patients (11.1%), given docetaxel (DOC)-based chemotherapy. In comparison between combination chemotherapy and single-agent chemotherapy, AEs occurred in two out of 54 patients (3.7%) given platinum-based doublet chemotherapy and three of 13 patients (23.1%) given single-agent chemotherapy.

Radiotherapy. Radiotherapy, including radiotherapy alone and radiotherapy combined with other therapies, was administered to 27 patients. A total of six patients received irradiation of the primary pulmonary lesion, two patients with stage IA disease received stereotactic irradiation therapy aiming for a radical cure and two patients with stage IIIA disease received a combined chemoradiation therapy using fractionated irradiation. In addition, two patients received palliative irradiation for pain control with the

Table 5. Main chemotherapy agents associated with the onset of AE

	n (%)	
	Total	AE
PEM-based	19	1 (5.3)
CDDP + PEM	3	1
CBDCA + PEM + BEV	1	0
CBDCA + PEM	14	0
PEM alone	1	0
PTX-based	18	1 (5.6)
CBDCA + PTX	13	1
CBDCA + nabPTX	5	0
VNR-based	12	2 (16.7)
CDDP + VNR	7	0
CBDCA + VNR	1	0
VNR alone	4	2
DOC-based	9	1 (11.1)
CDDP + DOC	1	0
DOC alone	8	1
VP-16-based	9	0
CDDP + VP-16	1	0
CBDCA + VP-16	8	0

PEM, pemetrexed; CDDP, cisplatin; CBDCA, carboplatin; BEV, bevacizumab; PTX, paclitaxel; nabPTX, nanoparticle albumin-bound paclitaxel; VNR, vinorelbine; DOC, docetaxel; VP-16, etoposide.

fractionated irradiation method only. None of these six patients who received irradiation of the primary lesion experienced AE. Palliative irradiation, not including the primary lesion in the irradiation field, was administered to 21 patients (14 patients with the lung included in the irradiation field and seven patients without). During radiotherapy, two patients experienced AEs (7.4%) (Table 4). These two patients received palliative irradiation for metastatic lesions in the thoracic vertebrae and their lungs were included in the irradiation field.

Comparison between the monotherapy and multitherapy groups (Table 6)

The monotherapy and multitherapy groups consisted of 55 patients and 29 patients, respectively. In the monotherapy group, six patients experienced AEs associated with lung cancer treatment (10.9%), and among them, five died (9.1%). In the multitherapy group, we found AEs in four patients (13.8%); and among them, two died (6.9%). However, we found no significant difference between the two groups in terms of the incidence of AE ($P = 0.7314$, Fisher's exact test).

Discussion

Lung cancer patients with IIPs are exposed to the risk of AE associated with cancer treatment. This seems to be a major factor in hesitation among doctors to provide cancer treatment for such patients and tends to lead to missed opportunities for improvement. This hesitancy appears to stem from the fact that patients with IIPs are excluded from clinical trials for the development of anticancer drugs and thus there is little evidence of safety. Lung cancer treatment including surgery, chemotherapy and radiotherapy is provided by monotherapy or a combination of therapies, and treatment decisions are based on disease stage, recurrence and metastasis status. When planning treatment for lung cancer in patients with IIPs, it is very important to accurately estimate the risk of developing AE for each treatment, and it is possible to provide the best treatment options in each case. In this study, we clarified risk factors of AE onset in the treatment of lung cancer in IIP patients and found no significant difference in the incidence of AE between monotherapy and multitherapy.

A comparison between the AE-IIP and Stable IIP groups highlighted statistically significant differences in the patterns of HRCT images and %FVC values. Further, these variables were identified as independent risk factors for AE. Kenmotsu et al. (15) reported that when assessing the risk of chemotherapy-related AE of interstitial pneumonia (IP), a UIP pattern displayed on CT images was a risk factor for AE with an odds ratio of 6.98. Our results confirm these findings with an even higher odds ratio of 15.01 (Model 1; 95% CI, 1.37–164.16). Therefore, the presence of a UIP pattern on a CT image is an extremely important risk factor signaling the likely presence of AE. In a retrospective study by Enomoto et al. (27) among patients who received chemotherapy, a low baseline %FVC value was identified as a risk factor for AE, and the odds ratio for IP exacerbation for each 1% increase in FVC was 0.97 (95% CI, 0.94–0.99). We also examined the odds ratio for each 10% decrease in FVC by creating a dummy variable and reported an odds ratio of 1.7 (Model 1; 95% CI, 1.03–2.69). Accordingly, the risk of AE-IP appears to increase with a decrease in FVC. We calculated an FVC cutoff value of 91.2% for AE based on a ROC curve. The value of 91.2% was within the normal range, but this may be because 52 (53.1%) of 98 patients included also had concurrent pulmonary emphysema, which may mask the decrease in FVC. A higher incidence of lung cancer has been reported among patients with concurrent emphysema than among those with fibrosis alone (28). Moreover, the incidence of lung cancer in combined with pulmonary fibrosis and emphysema is high at 46.8% (29). Our univariate analysis results indicate that among several candidate biomarkers, KL-6 might be useful to predict the risk of AE. Ohshimo et al. (30) conducted a prospective study on patients with IPF and reported that elevated KL-6 level was a risk factor for AE with a cutoff value of 1300 U/ml (30). However, compared with that study, our study reported a lower cutoff value of 820 U/ml. Our study subjects also had lung cancer and received treatment for this disease, which may have further lowered the cutoff value. However, in our multivariate analysis result, KL-6 was not an independent risk factor. The significant correlation between %FVC and KL-6 levels in this study ($\rho = -0.319$; $P = 0.014$) may be one reason for the dropout of KL-6 in multivariate analysis. All these findings together suggest that patients showing a non-UIP pattern, a %FVC $\geq$ 91.2% and a KL-6 level $<$ 820 U/ml, can receive treatment for lung cancer with a significant level of safety than other patients.

In a large-scale retrospective study, Sato et al. (16) reported that the incidence of AE caused by surgery was 9.3%, and in our study, AEs were observed in three out of the 40 patients who underwent surgery (7.5%), which was a roughly comparable incidence. All of the patients who developed AE had undergone lobectomy. No studies have focused on reductive surgery in concurrent lung cancer and IIPs, but it is possible that the extent of pneumonectomy correlates with the AE onset. There is only sparse evidence for recommending a regimen of lung cancer chemotherapy for patients with IP including IIPs. A small population, prospective study of carboplatin [cyclobutane-1,2-dicarboxylic acid (CBDCA)] + PTX for patients with concurrent non–small-cell lung cancer and IP showed that AE occurred in one of 18 patients (5.6%) (17). Another prospective study of CBDCA + VP-

Table 6. AE caused by cancer treatment in the monotherapy group and multitherapy group

	n (%) or Median (IQR; Range)		
	Monotherapy	Multitherapy	*P*
n	55	29	
Treatment-related AE	6 (10.9)	4 (13.8)	0.7314
Stable	49 (89.1)	25 (86.2)	
UIP pattern	26 (47.2)	15 (51.7)	0.8191
KL-6 (U/ml)	566.5 (353–818; 207–3600)	440 (319–840.5; 113–1670)	0.4397
%FVC (%)	98.3 (80.2–116.9; 50.3–153.4)	103.7 (88.6–121.9; 69.9–142)	0.5378

16 for patients with small-cell lung cancer and IP showed evidence of AE in one out of 17 patients (5.9%) (18). In our study, consistent with previous studies, the frequency of AE onsets was relatively low on PTX-based regimens and VP-16 based regimens. In addition, it was shown that the frequency of AE onsets was also low on PEM-based regimens. Thus, PTX, VP-16 and PEM-based chemotherapies can be administered to IPF patients with relative safety. Furthermore, in the comparison between combination chemotherapy and single-agent chemotherapy, the frequency of AE onset was high in single-agent chemotherapy. This result indicates that the risk of AE onset is elevated in patients judged to require single-agent chemotherapy rather than combination chemotherapy due to deterioration of the general condition. Taking into consideration the therapeutic effect of single-agent chemotherapy and the risk of AE onset, it might be recommended not to perform chemotherapy for patients who could not undergo combination chemotherapy. In general, most patients with concurrent lung cancer and IIPs do not receive irradiation. Therefore, few studies have focused on treatment. Our results showed that six patients who received irradiation of the primary lesion suffered no AEs; however, we observed AEs in two out of seven patients (28.6%) who received palliative irradiation in the lung area. All of the six patients who received irradiation of the primary lesions had combined pulmonary fibrosis, emphysema and mild fibrotic lesions on chest CT, and thus stereotactic radiation therapy was selected for all six patients. Based on our results, particular care is required for irradiation of the lung fields, even in cases of palliative irradiation.

We found no significant differences in AE incidences between the monotherapy and the multitherapy groups. This shows that both groups are comparable in terms of AE risk. For patients for whom monotherapy is not the cause of AE, the risk of AE may not increase even if treatment is successively changed. For patients with concurrent lung cancer and IIPs, studies on monotherapies and on multitherapies are warranted.

We found that most patients diagnosed with non-UIP patterns of HRCT did not undergo histopathological diagnosis by surgical lung biopsy, which accounted for 44 of 55 patients (84.6%) diagnosed with unclassifiable IIPs. It may be that in many cases of concurrent lung cancer, diagnostic examinations such as surgical lung biopsy cannot be sufficiently performed, which leads to an increase in the rate of unclassifiable IIPs according to the international classification. Further, it is possible that non-IIP patients, such as those with chronic hypersensitivity pneumonitis or ILD preceding connective tissue disease, could have been categorized as having unclassifiable IIPs due to insufficient pathological evidence. However, this study is likely an accurate representation of current clinical realities.

One of the limitations of this study is that ours was a single-center study, with few regimens for each respective chemotherapy, and insufficient radiotherapy sessions. A second limitation has to do with the diagnosis of AE based on CT findings alone, given that histopathological diagnoses are not obtained in most cases. Although we excluded infections based on a bacteriological examination, as well as heart failure based on physical findings and echocardiography, we were unable to entirely exclude respiratory infections, pulmonary embolisms or left heart failures. From the evaluation of the clinical course and progress on imaging, the diagnoses of AE were reliable.

Conclusion

In patients with lung cancer and IIPs, we found that UIP patterns on chest CT and reduced %FVC on respiratory function tests were risk factors for AE onset. The odds ratio for the association between AE and UIP pattern was particularly strong. Moreover, our results suggest that patients who received monotherapy with no AEs are unlikely to experience AEs when combined with multitherapy.

Conflict of interest statement

None declared.

Ethical approval

The protocol was approved by the Institutional Review Board of the Sapporo Medical University Hospital (approval number 272–91; ref. 2015/12/11).

Acknowledgements

The authors would like to thank Enago and Mr. Allen Paul Heffel for the English language review. The authors would also like to thank Professor Hirofumi Onishi, Department of Public Health, Sapporo Medical University for statistical supervision.

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Mini-abstract

In patients with concurrent lung cancer and IIPs, Chest CT UIP patterns and reduced %FVC, are independent risk factors for AE.