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Autoantibody Positivity Is a Risk Factor for Chemotherapy-induced Exacerbation of Interstitial Pneumonia in Lung Cancer

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Abstract. *Background: No study has yet investigated the incidence of chemotherapy-induced acute exacerbation of interstitial pneumonia (AE-IP) in patients with autoantibody-positive IP and lung cancer. Herein, we retrospectively compared the incidence of chemotherapy-induced AE-IP in patients with lung cancer between those with autoantibody-positive and -negative IP. Patients and Methods: Between October 2003 and December 2018, patients with lung cancer who received chemotherapy, underwent serological test of antinuclear antibody or rheumatoid factor, and were diagnosed with IP were enrolled. Results: A total of 81 patients were enrolled; autoantibody-positive cases were observed in 23.5%. Autoantibody positivity was an independent risk factor for chemotherapy-induced AE-IP at 6 months after initiation of chemotherapy for lung cancer. The time to onset of AE-IP was significantly shorter in autoantibody-positive patients than in the seronegative patients. Conclusion: Chemotherapy-induced AE-IP developed earlier in patients with autoantibody than in those without. Therefore, the potential development of AE-IP in autoantibody-positive patients warrants monitoring.*

Lung cancer is the most lethal type of cancer (1), with 2.4-10.9% of all cases being complicated with interstitial pneumonia (IP) upon lung cancer diagnosis (2). Although the clinical course of IP is usually chronic, certain patients experience acute respiratory deterioration, termed acute exacerbation (AE). The incidence of AE of IP in patients with lung cancer who undergo chemotherapy has been reported to range between 10% and 30% (3, 4). Furthermore, it has been reported that 25-70% of patients with AE-IP do not survive from the onset of AE-IP (5-8). In most of these previous studies, patients with idiopathic IP, which accounts for the majority of cases, were enrolled.

Previous reports have shown that some patients diagnosed with idiopathic IP had autoantibodies, with positive rates for antinuclear antibody (ANA), rheumatoid factor (RF), and anti-cyclic-citrullinated peptide (CCP) at 16.8-56.3%, 6-17.6%, and 1.0-7.3%, respectively (9). To date, patients with IP with autoantibodies but who do not meet the criteria for collagen vascular disease (CVD) are referred to as having IP with autoimmune features (IPAF) (10). The IPAF criteria described a large number of autoantibodies, including ANA, RF, anti-CCP, anti-double-stranded deoxyribonucleic acid (dsDNA), anti-Sjögren's-syndrome-related antigen A, anti-Sjögren's-syndrome-related antigen B, anti-ribonucleoprotein, anti-Smith, anti-topoisomerase 1, anti-transfer ribonucleic acid (tRNA), anti-polymyositis-systemic sclerosis, and anti-melanoma differentiation-associated protein 5 antibodies (10). Among these antibodies, ANA (≥1/320) and RF (≥2 ×the upper limit of normal) have been detected in 49.9% and 14.6% of patients with IPAF (11-21). Conversely, the rates of positivity for anti-CCP, anti-dsDNA, anti-Sjögren's-syndrome-related antigen A and -B for patients with IPAF were reported to be 7.6%, 4.1%, 23.7%, and 3.1%, respectively (11-21). These results indicate that positivity for ANA or RF is higher than that of other antibodies in patients with IPAF. Two previous studies compared the incidence of AE-IP between patients with IPAF and idiopathic IP, showing that the incidence of AE-IP was significantly lower in patients with IPAF than in those with idiopathic IP (16, 17). However, as

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Key Words: Interstitial pneumonia, acute exacerbation, autoantibody, autoimmune antibody, lung cancer.

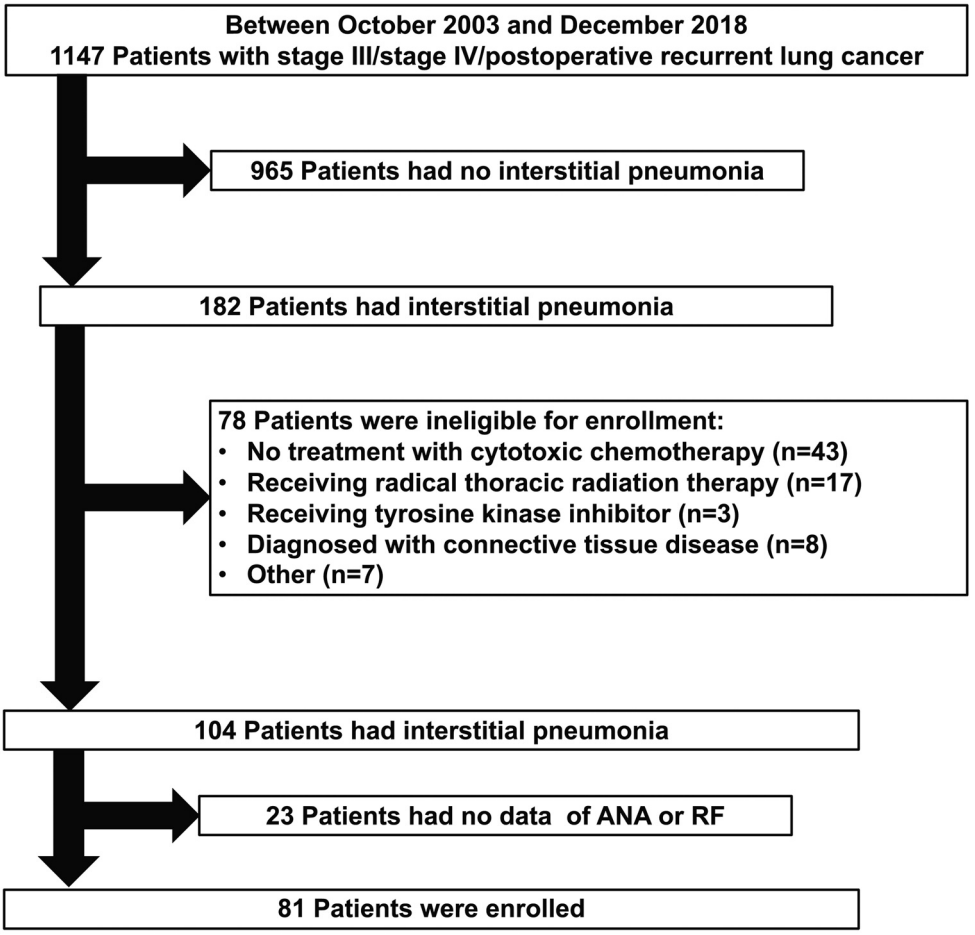

Figure 1. *Flowchart of patient enrollment. ANA: Antinuclear antibody; RF: rheumatoid factor.*

far as we are aware, there has been no study comparing the incidence of chemotherapy-induced AE-IP between autoantibody-positive and -negative patients with lung cancer.

For patients with advanced lung cancer, immune checkpoint inhibitors (ICI) alone and with platinum doublet chemotherapy is used as standard treatment (22-25). However, pre-existing IP has been reported as a risk factor for the development of ICI-induced AE-IP in patients with non-small-cell lung carcinoma. In addition, the incidence of ICI-induced AE-IP has been reported to be 20-30%, which is higher than that of chemotherapy-induced AE-IP (26-28). Therefore, the frequency of chemotherapy administration to patients with lung cancer with lP as an early line of treatment is higher than that of ICI or ICI with chemotherapy.

Hence, in this study, we retrospectively investigated the incidence of chemotherapy-induced AE-IP in patients with ANA- or RF-positive IP and lung cancer and determined whether autoantibody positivity is a risk factor for the development of AE-IP.

Patients and Methods

Study design and participants. Among patients with advanced lung cancer diagnosed at Hiroshima University Hospital between October 2003 and December 2018, those who had IP and underwent serological tests for ANA or RF, and received chemotherapy using cytotoxic drugs were retrospectively enrolled. Patients who had received definitive radiotherapy or tyrosine kinase inhibitors and were diagnosed with CVD were excluded. We collected patient background and clinical data before the start of chemotherapy, and information on the presence or absence of AE-IP following treatment. This study was approved by the Ethical Committee for Epidemiology of Hiroshima University (no. E-2226). All procedures associated with studies involving human participants were performed in accordance with the ethical standards of the Institutional Research Committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Regarding patient consent, the opt-out method was applied in this retrospective study.

Serological evaluation. ANA and RF were investigated before administration of chemotherapy. Positivity for ANA and RF was

Table I. *Comparison of clinical characteristics between autoantibody-positive and -negative patients.*

Characteristic	Autoantibody		*p*-Value
	Negative (n=62)	Positive (n=19)	
Age, years			
Median (range)	72 (56-87)	76 (60-85)	0.421
Gender, n (%)			<0.010
Male	58 (93.5)	13 (68.4)	
Female	4 (6.5)	6 (31.6)	
Pack-years			
Median (range)	53 (15-250)	45 (0-120)	0.342
ECOG PS, n (%)			0.411
0-1	51 (82.3)	14 (73.7)	
≥2	11 (17.7)	5 (26.3)	
Histology, n (%)			0.049
NSCLC	37 (59.7)	16 (84.2)	
SCLC	25 (40.3)	3 (15.8)	
Stage, n (%)			0.225
III	15 (24.2)	3 (15.8)	
IV	41 (66.1)	16 (84.2)	
Recurrence	6 (9.7)	0 (0)	
KL-6, U/ml			
Median (range)	592 (249-2122)	759 (223-2478)	0.251
Lung function test			
Number	55	16	
FEV1%, %			
Median (range)	77.3 (44.5-100.0)	70.25 (46.2-83.0)	0.046
%FVC, %			
Median (range)	88.4 (43.7-122.2)	92.7 (47.6-120.9)	0.967
CT pattern, n (%)			0.289
UIP	21 (33.9)	4 (21.1)	
Non-UIP	41 (66.1)	15 (78.9)	
Observation period, days			
Median (range)	288 (22-1288)	257 (18-2137)	0.489
Immunosuppressive therapy, n (%)			0.549
Yes	6 (9.7)	1 (5.3)	
No	56 (90.3)	18 (94.7)	

CT: Computed tomography; ECOG PS: Eastern Cooperative Oncology Group performance status; FEV: forced expiratory volume; FVC: forced vital capacity; KL-6: Krebs von den Lungen-6; NSCLC; non-small cell lung cancer; SCLC: small cell lung cancer; UIP: usual interstitial pneumonia.

based on IPAF criteria. For ANA positivity, a titer of at least 1:320 was required (10). RF positivity was defined as a level twice the upper limit of normal or greater (10).

Computed tomographic (CT) evaluation. IP was defined by the existence of bilateral reticulation and consolidation or ground-glass attenuation on CT prior to the initial chemotherapy intervention. The IP patterns were classified into three categories, namely usual IP (UIP), possible UIP, and inconsistent with UIP, based on the statement of American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Society (29). CT was evaluated by two pulmonologists who were blinded to the patient's clinical findings, and the final diagnosis was determined in consultation with these pulmonologists.

Definition of AE-IP. Chemotherapy-induced AE-IP was diagnosed when all of the following criteria were met (30): i) Acute exacerbation of dyspnoea within 1 month; ii) new appearance of ground-glass attenuation and infiltration shadows on both sides on CT; iii) no evidence of pulmonary infection (no improvement by antibiotic administration), or overt heart failure; iv) AE-IP developed within 1 month after the latest chemotherapy. AE-IP was evaluated as pneumonitis based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. (31).

Statistical analysis. A *t*-test or Wilcoxon rank-sum test was performed to compare the mean values of the two groups. For binary variables, we used the chi-square test. Unless otherwise stated, all results are presented as the median (range). The time to onset of AE-IP was analysed using the Kaplan–Meier method and compared using the log-rank test to examine the significance of differences between groups. Univariate and multivariate analyses using Cox regression model identified risk factors for the development of AE-IP. Previous studies reported that UIP pattern, a low percentage of forced vital capacity, smoking habit, and non-small cell lung cancer are risk factors for AE-IP (32-35). Therefore, we performed multivariate analysis using these factors as covariates. A value of $p<0.05$ was considered statistically significant. All statistical analyses were performed using JMP® Pro 14.2.0 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics. Data on a total of 1,147 patients with advanced lung cancer were extracted and 182 had IP. Of the 182 patients, no data on either ANA and RF were available for 23. In addition, 78 patients were ineligible for enrolment; finally, 81 patients were enrolled (Figure 1). The comparison of patient characteristics between patients with and without autoantibody is shown in Table I. The proportion of female patients was significantly higher in the autoantibody-positive group than in the -negative group (31.6% *vs.* 6.5%, $p<0.01$). The proportion of patients with small-cell lung cancer was significantly lower in the positive group than in the negative group (15.8% *vs.* 40.3%, $p=0.049$). Pulmonary function tests showed that the autoantibody-positive group had a significantly lower 1% forced expiratory volume (70.25% *vs.* 77.3%, $p=0.046$). No patients had collagenous physical findings.

Chemotherapy regimen. First-line and second-line treatment regimens are presented in Table II. Chemotherapy regimens were classified into three categories according to their risk of chemotherapy-induced AE-IP: High (AE-IP frequency ≥30%), moderate (AE-IP frequency 11-29%), and low (AE-IP frequency ≤10%) (34). There was no significant difference in the proportion of patients in the respective risk groups between the autoantibody-positive and negative groups.

Table II. *Comparison of chemotherapy regimens between autoantibody-positive and -negative patients.*

Risk group	Regimen	Autoantibody		*p*-Value
		Negative (n=62)	Positive (n=19)	
	First line			
High	CDDP+GEM	2	0	
	GEM	1	0	
	Total	3/62	0/19	0.328
Moderate	Platinum+PEM	4	1*	
	PEM	3	2	
	DTX	2	2	
	VNR	5	3	
	Total	14/62	8/19	0.094
Low	Platinum+ETP	25	4	
	CBDCA+PTX	13	4	
	CBDCA+nab-PTX	4	0	
	S-1	3	3	
	Total	45/62	11/19	0.225
	Second line	n=37	n=9	
High	AMR	10	3	
	GEM	0	1	
	Total	10/37	4/9	0.308
Moderate	Platinum+PEM	1*	1	
	PEM	1	2	
	DTX	6*	0	
	NGT	2	0	
	VNR	1	0	
	Total	11/37	3/9	0.833
Low	Platinum+ETP	6	0	
	CBDCA+PTX	1	1	
	CDDP+VNR	1	0	
	Nab-PTX	1	1	
	S-1	7	0	
	Total	16/37	2/9	0.246

AMR: Amrubicin; CBDCA: carboplatin; CDDP: cisplatin; DTX: docetaxel; ETP: etoposide; GEM: gemcitabine; NGT: nogitecan; PEM: pemetrexed; Platinum: cisplatin or carboplatin; PTX: paclitaxel; S-1: tegafur/gimeracil/oteracil; VNR: vinorelbine. *Including one case used in combination with bevacizumab.

Table III. *Incidence and characteristics of acute exacerbation of interstitial pneumonia (AE-IP) between autoantibody-positive and -negative patients.*

	Autoantibody		*p*-Value
	Negative (n=62)	Positive (n=19)	
At 6 months, n (%)			
Incidence of AE-IP	9 (14.5)	7 (36.8)	0.032
Line of treatment, n (%)			
1	8 (88.9)	6 (85.7)	0.848
2	1 (11.1)	1 (14.3)	
3	0 (0)	0 (0)	
Event grade, n (%)*			
1	0 (0)	0 (0)	0.576
2	2 (22.2)	3 (42.9)	
3	3 (33.3)	1 (14.3)	
4	1 (11.1)	0 (0)	
5	3 (33.3)	3 (42.9)	
At 1 year, n (%)			
Incidence of AE-IP	16 (25.8)	8 (42.1)	0.173
Line of treatment, n (%)			
1	8 (50.0)	6 (75.0)	0.424
2	6 (37.5)	1 (12.5)	
3	2 (12.5)	1 (12.5)	
>4	0 (0)	0 (0)	
Event grade, n (%)*			
1	1 (6.3)	0 (0)	0.533
2	2 (12.5)	3 (37.5)	
3	4 (25.0)	2 (25.0)	
4	2 (12.5)	0 (0)	
5	7 (43.8)	3 (37.5)	

*Common Terminology Criteria for Adverse Events version 4.0 was used (31).

Incidence and characteristics of chemotherapy-induced AE-IP. The incidence of AE-IP at 6 months after initiation of chemotherapy was significantly higher in the autoantibody-positive group than in the seronegative group (36.8% *vs.* 14.5%, $p=0.032$) (Table III). Conversely, the severity or treatment line of AE-IP was not significantly different between the two groups. Kaplan–Meier analysis showed that the time to onset of AE-IP in the autoantibody-positive group was significantly shorter than in the seronegative group at 6 months ($p=0.030$). Conversely, this difference was not observed at 1 year ($p=0.115$) (Figure 2).

Cox proportional hazard analysis for the risk factor of AE-IP. We performed Cox regression analysis to investigate whether patient background factors, including autoantibody positivity, were risk factors for the development of AE-IP at 6 months after chemotherapy initiation (Table IV). Univariate and multivariate analyses showed that autoantibody positivity was a significant factor [hazard ratio=2.845, 95% confidence interval (CI)=1.059-7.647, $p=0.038$; and 3.624 (1.161-11.309), $p=0.026$, respectively].

Kaplan–Meier analysis of time to onset of AE-IP between autoantibody-positive and-negative groups in patients who developed AE-IP. We compared the time to onset of AE-IP between autoantibody-positive and negative groups only in patients who developed AE-IP. Table V lists the characteristics of patients who developed AE-IP in the autoantibody-positive and -negative groups; there were no significant differences in patient characteristics. In addition, chemotherapy regimens at the onset of AE-IP were not

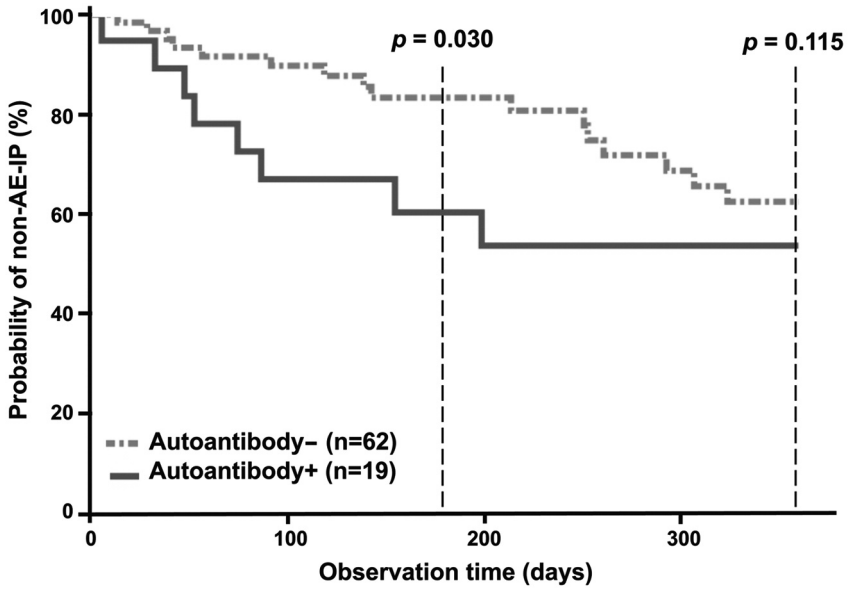

Figure 2. *Kaplan–Meier analysis of time to onset of acute exacerbation of interstitial pneumonia (AE-IP) according to autoantibody serology. The time to onset in the autoantibody-positive group was significantly shorter than in the seronegative group at 6 months (p=0.030). Conversely, this difference was not observed at 1 year (p=0.115).*

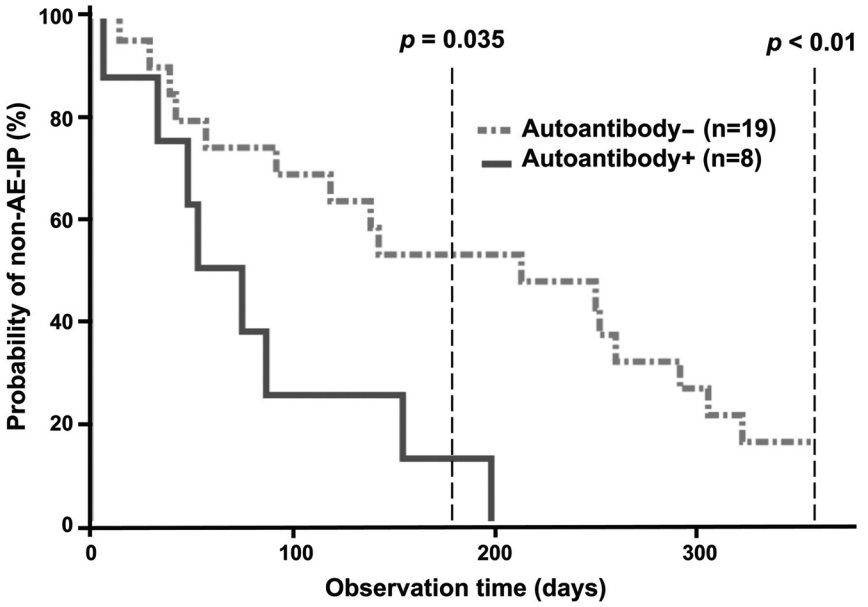

Figure 3. *Kaplan–Meier analysis of time to onset of acute exacerbation of interstitial pneumonia (AE-IP) between autoantibody-positive and -negative patients who developed AE-IP. The time to onset was significantly shorter in the autoantibody-positive group compared to the autoantibody-negative group at 6 months (p=0.035) and 1 year (p<0.01).*

significantly different between the groups (Table VI). Kaplan–Meier analysis showed that the time to onset of AE-IP was significantly shorter in the autoantibody-positive group compared to the autoantibody-negative group [median (95% confidence intervaI): at 6 months: 64 (6-155) days *vs*. not reached (57 days – not reached), log-rank test p=0.035; at 1 year: 64 (6-155) *vs*. 214 (57-293) days, log-rank test p<0.01] (Figure 3).

Table IV. *Cox analysis of the risk factors of acute exacerbation of interstitial pneumonia.*

Analysis	Univariate analysis	Hazard ratio	95% CI	*p*-Value
Univariate				
Age	≥75 Years	1.353	0.507-3.609	0.545
Gender	Male	2.538	0.335-19.227	0.367
ECOG PS	≥2	1.631	0.458-5.805	0.450
Pack-years	≥40	0.734	0.236-2.281	0.593
Histology	NSCLC	0.907	0.329-2.498	0.850
CT pattern	UIP	2.032	0.755-5.466	0.159
KL-6	≥1,000 U/ml	1.157	0.373-3.589	0.800
FEV1%	<70%	1.200	0.402-3.585	0.743
%FVC	<80%	1.589	0.557-4.532	0.386
Autoantibody	Positive	2.845	1.059-7.647	0.038
Multivariate				
Pack-year	≥40	0.633	0.187-2.138	0.462
Histology	NSCLC	0.803	0.245-2.630	0.717
CT pattern	UIP	1.935	0.587-6.370	0.277
%FVC	<80%	1.472	0.486-4.460	0.493
Autoantibody	Positive	3.624	1.161-11.309	0.026

CI: Confidence interval; CT: computed tomography; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FEV: forced expiratory volume; FVC: forced vital capacity; KL-6: Krebs von den Lungen-6; NSCLC: non-small cell lung cancer; UIP: usual interstitial pneumonia.

Discussion

To the best of our knowledge, this is the first study to investigate the incidence of chemotherapy-induced AE-IP in autoantibody-positive patients with lung cancer. In this study, the incidence of AE-IP at 6 months after initiation of chemotherapy was significantly higher in the autoantibody-positive group than in the seronegative group. Multiple Cox regression analysis showed that autoantibody positivity was an independent risk factor for AE-IP. Furthermore, Kaplan–Meier analysis showed that AE-IP developed earlier in patients with autoantibody than in those without. We showed that the incidence of chemotherapy-induced AE-IP was higher and the onset was earlier in autoantibody-positive patients compared to seronegative patients in this study. Several previous studies have shown that autoantibodies positivity is associated with IP complications in patients with CVD (36-38). Indeed, the RF-positive rate in patients with rheumatoid arthritis was reported to be significantly higher in patients with rheumatoid arthritis-associated interstitial lung disease than in those without (39). In addition, the titers of RF and anti-CCP antibodies were significantly higher in patients with IP and RA than in those without IP (40), and RF positivity has been shown to be a risk factor for IP progression (41). Furthermore, another study showed that patients with dermatomyositis complicated with IP had a higher proportion of antibodies than those without IP (42). These findings support a higher frequency and earlier development of chemotherapy-induced AE-IP in autoantibody-positive patients than in autoantibody-negative patients.

Furthermore, the histopathological features of IP with and without autoantibodies are considered to affect the onset of AE-IP due to chemotherapy. It has been reported that surgical lung biopsy sample in patients with IPAF showed lymphocyte aggregation and lymphocyte infiltration with germinal centres in the lung interstitium (14). Similarly, in autoimmune antibody-positive IP, lymphocyte infiltration would be expected to be higher than in antibody-negative IP. Chemotherapeutic agents directly damage epithelial and endothelial cells in the lungs. After such damage, inflammatory cells migrate from the vasculature into the interstitium, where they release cytokines that induce further inflammation (43). Therefore, chemotherapy-induced AE-IP is likely to occur in patients with lymphocyte-infiltrated IP. This may explain why the autoantibody-positive IP group developed AE-IP more frequently and earlier than the autoantibody-negative group.

In this study, the incidence of the AE-IP at 6 months after initiation of chemotherapy was higher in autoantibody-positive than -negative patients. This is inconsistent with the results of previous studies showing that the IPAF group had a lower frequency of AE-IP compared to those with idiopathic pulmonary fibrosis (16, 17). This discrepancy may be attributable to the fact that immunosuppressive therapy was not administered to most of the autoantibody-positive patients in this study. Steroids and immunosuppressants were administered to several patients with IPAF in a study that showed that the IPAF group had a lower incidence of AE-IP (16). If immunosuppressive therapy had been performed in

Table V. *Comparison of patient characteristics between autoantibody-positive and-negative patients who developed acute exacerbation of interstitial pneumonia.*

Characteristic	Autoantibody		*p*-Value
	Negative (n=19)	Positive (n=8)	
Age, years			
Median (range)	70 (56-85)	74 (60-79)	0.814
Gender, n (%)			
Male	18 (94.7)	6 (75.0)	0.136
Female	1 (5.3)	2 (25.0)	
Pack-years			
Median (range)	48 (20-120)	47 (0-100)	0.769
ECOG PS, n (%)			
0-1	18 (94.7)	6 (75.0)	0.136
≥2	1 (5.3)	2 (25.0)	
Histology, n (%)			
NSCLC	11 (57.9)	7 (87.5)	
SCLC	8 (42.1)	1 (12.5)	0.136
Stage, n (%)			
III	3 (15.8)	1 (12.5)	0.600
IV	14 (73.7)	7 (87.5)	
Recurrence	2 (10.5)	0 (0)	
KL-6, U/ml			
Median (range)	600 (249-2122)	716 (282-2431)	0.613
Lung function test			
Number	17	6	
FEV1%, %			
Median (range)	73.8 (54.1-85.5)	72.6 (56.6-83.0)	0.585
%FVC, %			
Median (range)	75.4 (51.7-105.0)	69.3 (47.6-99.5)	0.220
CT pattern, n (%)			
UIP	7 (36.8)	3 (37.5)	0.974
Non-UIP	12 (63.2)	5 (62.5)	
Immunosuppressive therapy, n (%)			
Yes	1 (5.3)	0 (0)	0.508
No	18 (94.7)	8 (100)	

CT: Computed tomography; ECOG PS: Eastern Cooperative Oncology Group ; FEV: forced expiratory volume; FVC: forced vital capacity; KL-6: Krebs von den Lungen-6; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; UIP: usual interstitial pneumonia.

antibody-positive patients in our study, chemotherapy-induced AE-IP may have been less frequent than in the antibody-negative group.

This study has limitations. Firstly, it was a retrospective study and was conducted at a single facility. Therefore, it is necessary to verify the results through prospective multicentre joint research using a high number of cases. Secondly, AE-IP was not pathologically diagnosed in this study, therefore, the AE-IP findings on CT might reflect non-AE-IP *i.e.* capillary-leak syndrome arising due to chemotherapy, especially in patients with pre-existing cardiac dysfunction.

Table VI. *Chemotherapy regimens at onset of acute exacerbation of interstitial pneumonia.*

Risk group	Regimen	Autoantibody		*p*-Value
		Negative (n=19)	Positive (n=8)	
High	AMR	2	1	
	Total	2/19	1/8	0.881
Moderate	CBDCA+PEM+BEV	0	1	
	CDDP+PEM	1	0	
	DTX+RAM	1	0	
	DTX+BEV	1	0	
	DTX	1	1	
	VNR	2	1	
	NGT	2	0	
	PEM	0	1	
	Total	8/19	4/8	0.706
Low	CBDCA+ETP	3	0	
	CBDCA+PTX	3	1	
	Nab-PTX	2	0	
	S-1	1	2	
	Total	9/19	3/8	0.637

AMR: Amrubicin; BEV: bevacizumab; CBDCA: carboplatin; CDDP: cisplatin; DTX: docetaxel; ETP: etoposide; NGT: nogitecan; PEM: pemetrexed; PTX: paclitaxel; RAM: ramucirumab; S-1: tegafur/gimeracil/oteracil; VNR: vinorelbine.

In conclusion, we showed that autoantibody positivity was an independent risk factor for developing chemotherapy-induced AE-IP at 6 months after the initiation of chemotherapy for lung cancer. Furthermore, AE-IP developed earlier in patients with autoantibodies than in those without. Therefore, the potential development of chemotherapy-induced AE-IP in autoantibody-positive patients warrants monitoring.

Conflicts of Interest

N. Hattori has received funds from Pfizer, Taiho Pharmaceutical, ONO Pharmaceutical, Chugai Pharmaceutical, Eli Lilly Japan and lecture fees, honoraria from Pfizer, Taiho Pharmaceutical, Chugai Pharmaceutical, and Eli Lilly Japan. K. Fujitaka has received lecture fees, honoraria from Pfizer, Taiho Pharmaceutical, Chugai Pharmaceutical, and Eli Lilly Japan. H. Iwamoto has received lecture fees, honoraria from Taiho Pharmaceutical. S. Miyamoto has received lecture fees, honoraria from Taiho Pharmaceutical. T. Masuda has received lecture fees, honoraria from Taiho Pharmaceutical, Chugai Pharmaceutical, and Eli Lilly Japan. K. Yamaguchi has received lecture fees, honoraria from Pfizer and Chugai Pharmaceutical. The other Authors have no conflicts of interest to declare.

Authors' Contributions

Noriaki Ito: Conceptualisation, validation, formal analysis, investigation, data curation, writing - original draft, and visualisation. Takeshi Masuda: Conceptualisation, methodology,

formal analysis, resources, writing - review and editing. Taku Nakashima: Resources, writing – review and editing, and supervision. Satoshi Nakao: Investigation, resources, writing – review and editing. Kakuhiro Yamaguchi: Resources, writing – review and editing. Shinjiro Sakamoto: resources, writing – review and editing. Yasushi Horimasu: Resources, writing – review and editing. Shintaro Miyamoto: Resources, writing – review and editing. Hiroshi Iwamoto: Resources, writing – review and editing. Kazunori Fujitaka: Resources, writing – review and editing. Hironobu Hamada: Resources, writing – review and editing. Noboru Hattori: Resources, writing – review and editing, supervision, and project administration.

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