Original Article

Subsequent systemic therapy for non-small cell lung cancer patients with immune checkpoint inhibitor-related interstitial lung disease

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Background: Although immune checkpoint inhibitors (ICIs) are effective for advanced non-small cell lung cancer (NSCLC), ICIs may cause interstitial lung disease (ILD), which results in treatment discontinuation and is sometimes fatal. Despite the high incidence of ICI-related ILD, there are few cancer treatment options for patients. This study aimed to evaluate the safety and efficacy of subsequent systemic cancer therapy in NSCLC patients with ICI-related ILD.

Methods: We retrospectively assessed NSCLC patients who received programmed cell death-1 (PD-1) inhibitors as first- to third-line therapy at participating institutions of the Niigata Lung Cancer Treatment Group from January 2016 to October 2017.

Results: This analysis included 231 patients, 32 (14%) of whom developed ICI-related ILD. Of these patients, 16 (7%) received subsequent systemic cancer treatments. The median overall survival (OS) tended to be longer in the systemic cancer therapy group than in the no systemic cancer therapy group [22.2 months (95% CI: 1–NE) *vs.* 4.5 months (95% CI: 1–NE); P=0.067]. ICI-related ILD recurred in half of the patients who received systemic cancer therapy, and the median OS tended to be shorter in patients with recurrent ICI-related ILD [22.0 months (95% CI: 1–NE) *vs.* 7.0 months (95% CI: 1–NE); P=0.3154].

Conclusions: According to the current study, systemic cancer treatment is effective in patients with ICI-related ILD; however, its safety is uncertain because of the high risk of ICI-related ILD recurrence and poor survival outcome following ILD recurrence.

Keywords: Non-small cell lung cancer (NSCLC); PD-1; PD-L1; interstitial lung disease (ILD); immune-related adverse event (irAE)

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Introduction

Immune checkpoint inhibitors (ICIs) have emerged as a promising treatment for advanced-stage lung cancer. In particular, programmed cell death-1 (PD-1) and PD-ligand 1 (PD-L1) antibodies show excellent therapeutic effects in terms of improving overall survival (OS) and progression-free survival (PFS) in patients with advanced-stage lung cancer (1-5). However, ICIs cause immune-related adverse events (irAEs) because these drugs act on the immune system (6). IrAEs occur in various organs, and skin rash, endocrine toxicities and liver dysfunction are particularly frequent (7). Since irAEs could be severe and even fatal, some patients are required to discontinue ICIs. On the other hand, previous studies have indicated that patients who discontinue ICIs due to irAEs have a worse prognosis than those who continue ICIs (8).

Previous studies have also reported that the antitumor effects of ICIs are augmented in patients with irAEs (9,10). Furthermore, the therapeutic effects of cytotoxic chemotherapies are enhanced after ICI treatment (11,12). Readministration of ICIs and cytotoxic chemotherapies seems to be beneficial for patients who discontinue ICIs due to irAEs. By contrast, both ICIs and chemotherapies in patients with irAEs increase the risk of irAE recurrence. Simonaggio and colleagues reported that 55% of patients who received rechallenge with ICIs experienced recurrence with the same or different irAEs (13). The second irAE was not worse than the first, and they concluded that readministration of ICIs was acceptable in patients who discontinued ICIs due to irAEs.

ICI-related interstitial lung disease (ILD) often leads to treatment discontinuation and is sometimes fatal (1,8). We previously demonstrated that the prognosis of patients with ICI-related ILD was worse than that of patients with other irAEs, and there is a correlation between prognosis and the radiological findings of ILD (14). Previous studies have also demonstrated that cytotoxic chemotherapies and tyrosine kinase inhibitors (TKIs) are risk factors for ILD recurrence (15-17). However, data on the risk of ICI-related ILD recurrence and the prognosis of patients with ICI-related ILD after subsequent systemic cancer therapy are lacking.

In the present study, we performed a retrospective analysis to determine the safety and efficacy of systemic cancer therapy in non-small cell lung cancer (NSCLC) patients with ICI-related ILD.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/tlcr-21-198).

Methods

Study design and patients

We retrospectively analyzed consecutive patients who received PD-1 inhibitor treatment as first- to third-line therapy at participating institutions of the Niigata Lung Cancer Treatment Group from January 2016 to October 2017. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board of Niigata University (the registration number: 2017-0295) and each participating institution. Individual consent for this retrospective analysis was waived.

Study assessment

All patient data were collected retrospectively, and ICI-related ILD patients were considered. In this study, we investigated the safety and efficacy of chemotherapy and ICI treatment as posttreatment based on OS, the treatment duration, the tumor response, and radiological features. ICI-related ILD was diagnosed by the attending physician at each institution, and chest CT scans were reviewed by two independent respiratory physicians and one radiologist. Regardless of whether patients had interstitial lung abnormality at baseline, we diagnosed ICI-related ILD if patients had pneumonitis after the initiation of anti-PD-1 therapy. ICI-related ILD was graded according to the Common Terminology Criteria for Adverse Events version 4.0. OS was defined as the time between the start date of anti-PD-1 therapy and death from any cause.

Statistical analysis

We created Kaplan-Meier OS curves for both groups and tested for significant differences with the log-rank test. To minimize lead-time bias associated with time-dependent factors, we performed landmark analysis including only patients who were alive or whose ICI-related ILD was under control at 6 weeks after the onset of initial ICI-related ILD (n=30). Continuous variables are presented as the median (range) and were compared by 2-sided *t*-tests. Categorical variables were compared by Fisher's exact test or the chi-square test. All the reported P values are 2-sided, and $P<0.05$ was considered significant. Statistical analysis

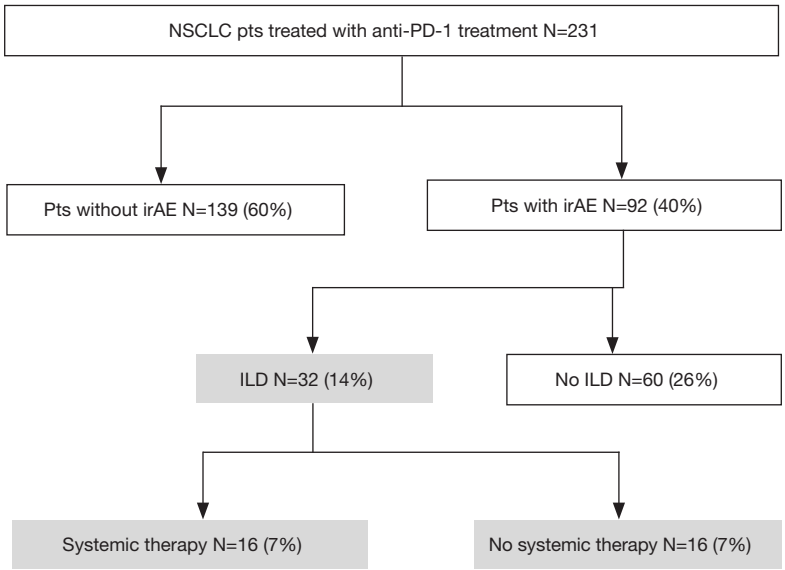

Figure 1 Patient flow diagram. NSCLC, non-small cell lung cancer; PD-1, programmed cell death-1; Pts, patients; irAE, immune-related adverse event; ILD, interstitial lung disease.

was performed using JMP 9.0.2 statistical software (SAS Institute, Cary, NC, USA).

Results

Characteristics of the study population

The current study included 231 patients and the observation period for this study was from January 2016 to November 2019, 32 (14%) of whom developed ICI-related ILD during anti-PD-1 therapy. Of these patients, 16 (50%) received subsequent systemic cancer treatment, and 16 (50%) did not receive systemic cancer treatment after anti-PD-1 therapy (*Figure 1*). *Table 1* shows the baseline characteristics of patients with or without subsequent systemic cancer therapy at the start of anti-PD-1 therapy. No significant differences were observed in terms of age, sex, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, disease stage, histology, line of anti-PD-1 therapy, PD-L1 expression, type of anti-PD-1 therapy, initial response to anti-PD-1 therapy, baseline interstitial lung abnormality, grade of the initial episode of ICI-related ILD, or radiological features.

OS with subsequent systemic cancer treatment

Kaplan-Meier OS curves of the groups with and without subsequent systemic cancer treatment are shown in *Figure 2*. The median OS tended to be longer in the systemic cancer therapy group than in the no systemic cancer therapy group [22.2 months (95% CI: 1–NE) *vs.* 4.5 months (95% CI: 1–NE); P=0.067]. To minimize immortal time bias, we performed 6-week landmark analysis (n=30, Figure S1). Median OS in patients receiving subsequent cancer therapy was tended to be longer than that in patients who did not receive subsequent cancer therapy [22.0 months (95% CI: 7.3–NE) *vs.* 5.5 months (95% CI: 2.2–NE); P=0.165].

Subsequent systemic cancer treatment regimens

Of the 16 patients who received subsequent systemic cancer therapy, 8 (9 regimens) developed recurrent ICI-related ILD (*Table 2*). There were no significant differences in patient characteristics between patients with and without the recurrence of ICI-related ILD (Table S1). The grade of recurrent ICI-related ILD was 2 or less in 7 of 9 regimens (78%). The grade of the first episode of ILD was 2 or less in 11 of 16 patients (69%), and the recurrent episode of ICI-related ILD was not more severe than the first (P=0.629). All patients were treated with methylprednisolone (mPSL) pulse therapy and/or prednisolone (PSL). No patient died of ICI-related ILD, but one patient died of the progression of NSCLC. Other 7 patients responded to steroid therapies and recovered from the recurrence of ICI-related ILD. Regimens in the ILD recurrence group were S-1, docetaxel

Table 1 Baseline characteristics

Characteristic	Subsequent systemic therapy (N=16)	No systemic therapy (N=16)	P value
Median age (range), years	65 [45–74]	67 [59–82]	0.091[a]
Sex, n (%)			0.37[b]
Male	12 [75]	14 [87]	
Female	4 [25]	2 [13]	
Smoking status, n (%)			0.29[b]
Current or former	13 [81]	15 [94]	
Never	3 [19]	1 [6]	
ECOG-PS, n (%)			0.19[b]
0	4 [25]	5 [31]	
1	10 [63]	6 [38]	
≥2	1 [6]	5 [31]	
Unknown	1 [6]	0	
Disease stage, n (%)			0.25[b]
IIIB	0	1 [6]	
IV	8 [50]	11 [69]	
Relapse after local therapy	8 [50]	4 [24]	
Histology, n (%)			0.31[b]
Adenocarcinoma	4 [25]	8 [50]	
Squamous carcinoma	10 [63]	6 [38]	
Others	2 [13]	2 [13]	
Line of anti-PD-1 therapy, n (%)			0.63[b]
1	2 [13]	4 [24]	
2	9 [56]	7 [44]	
3	5 [31]	5 [31]	
PD-L1 expression, n (%)			0.19[b]
<1	1 [6]	0	
1–49%	0	1 [6]	
≥50%	2 [13]	6 [38]	
Unknown	13 [81]	9 [56]	
Anti-PD-1 therapy, n (%)			0.10[b]
Nivolumab	14 [88]	10 [63]	
Pembrolizumab	2 [13]	6 [38]	
Response to anti-PD-1 therapy			0.63[b]

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	Subsequent systemic therapy (N=16)	No systemic therapy (N=16)	P value
CR	2 [13]	1 [6]	
PR	4 [25]	5 [31]	
SD	6 [38]	3 [19]	
PD	3 [19]	4 [25]	
NE	1 [6]	3 [19]	
Baseline interstitial lung abnormality, n (%)	3 [19]	0	0.07[b]
Grade of initial ILD			0.69[b]
1–2	11 [69]	12 [75]	
3–4	5 [31]	4 [24]	
Radiologic features, n (%)			0.52[b]
COP-like	9 [56]	7 [44]	
GGO	7 [44]	8 [50]	
Not otherwise specified	0	1 [6]	
Systemic steroid use, n (%)	13 [81]	11 [69]	0.43[b]
Time to the ILD, days (range)	42 (1-523)	38 (5-340)	0.97[a]

Differences between groups were identified using [a]student's *t*-test or [b]Chi-Square test. ECOG, Eastern Cooperative Oncology Group; PS, performance status; PD-1, programmed cell death-1; PD-L1, PD-ligand 1; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; ILD, interstitial lung disease; COP, cryptogenic organizing pneumonia; GGO, ground glass opacity.

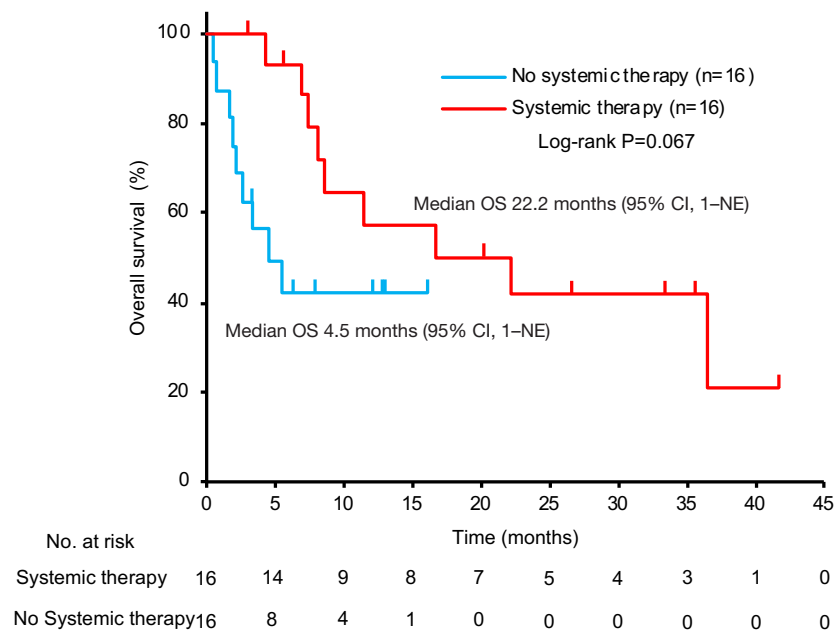

Figure 2 Overall survival curves of patients with or without systemic cancer therapy after the 1st episode of ICI-related ILD. OS, overall survival; CI, confidence interval; NE, not evaluable; ICI, immune checkpoint inhibitor; ILD, interstitial lung disease.

Table 2 Demographics of patients with recurrent ICI-related ILD (n=8)

Clinical features	ILD recurrence (N=8)
Duration of systemic cancer therapy, days [range]	5 [1–183]
Treatment cycles, median [range]	1 [1–14]
Grade of ILD, n [%]	
1	1 [11]
2	6 [67]
3	1 [11]
4	1 [11]
5	0
Systemic steroid therapy, n [%]	
mPSL pulse	4 [44]
PSL ≥30 mg/day	3 [33]
PSL <30 mg/day	2 [22]

ICI, immune checkpoint inhibitor; ILD, interstitial lung disease; PSL, prednisolone; mPSL, methylprednisolone.

Table 3 Regimens of systemic therapy

Regimen	ILD recurrence (N=8)	No ILD recurrence (N=8)
S-1, n [%]	2 [22]	3 [13]
DTX+RAM, n [%]	2 [22]	2 [8]
Nivolumab, n [%]	2 [22]	2 [8]
DTX, n [%]	1 [10]	3 [13]
Atezolizumab, n [%]	1 [10]	2 [8]
CBDCA+VNR, n [%]	1 [10]	0
CBDCA+S-1, n [%]	0	3 [13]
VNR, n [%]	0	2 [8]
nab-PTX, n [%]	0	2 [8]
Amrubicin, n [%]	0	1 [4]
CDDP+PEM, n [%]	0	1 [4]
Nedaplatin, n [%]	0	1 [4]
Irinotecan, n [%]	0	1 [4]
Gemcitabine, n [%]	0	1 [4]
Total number of regimens	9	24

DTX, docetaxel; RAM, ramucirumab; CBDCA, carboplatin; VNR, vinorelbine; nab-PTX, nab-paclitaxel; CDDP, cisplatin; PEM, pemetrexed; ILD, interstitial lung disease.

plus ramucirumab, and nivolumab [in 2 patients each (22%)] and docetaxel, atezolizumab, and carboplatin plus vinorelbine [in one patient each (11%)] (*Table 3*).

Tumor responses to systemic cancer therapy

Kaplan-Meier OS curves of the groups with and without ICI-related ILD recurrence are shown in *Figure 3*. The median OS was longer in the ILD nonrecurrence group than in the ILD recurrence group [22.0 months (95% CI: 1–NE) *vs.* 7.0 months (95% CI: 1–NE); P=0.3154]. *Table 4* demonstrates tumor responses to systemic cancer therapy in patients with and without ICI-related ILD recurrence. There were no significant differences in overall response rate (10% *vs.* 8%, P=0.88) and disease control rate (30% *vs.* 54%, P=0.47) between two groups.

Figure 4 shows the comparison of radiological features between the first episode of ICI-related ILD and the second and subsequent episodes of ILD. Eight of nine patients with ILD recurrence had the same radiologic features between the first and second episodes of ILD. Only one patient with cryptogenic organizing pneumonia (COP) had a ground-glass opacity (GGO) at recurrence.

The ILD nonrecurrence group did better than the ILD recurrence group in terms of the disease control rate (54% *vs.* 22%, P=0.029). The overall response rate was similar between groups (8% *vs.* 11%).

Duration of treatment

The Swimmer's plot shows the duration of treatment after the start of subsequent systemic cancer treatment (*Figure 5*). All patients stopped subsequent therapies when ICI-related ILD relapsed. Two patients in the ILD recurrence group who were rechallenged with ICIs had sustained therapeutic effects at the data cutoff even after ICI discontinuation.

Discussion

NSCLC patients with ILD including ILD induced by systemic cancer therapy had poor survival outcomes (18). Although the development of tyrosine-kinase inhibitors and ICIs dramatically improved the survival of NSCLC patients, poor outcomes have been reported in patients with ILD related to TKIs and ICIs (19,20). It remains unclear how to treat NSCLC patients with drug-induced ILD. The current study demonstrated that patients who received subsequent

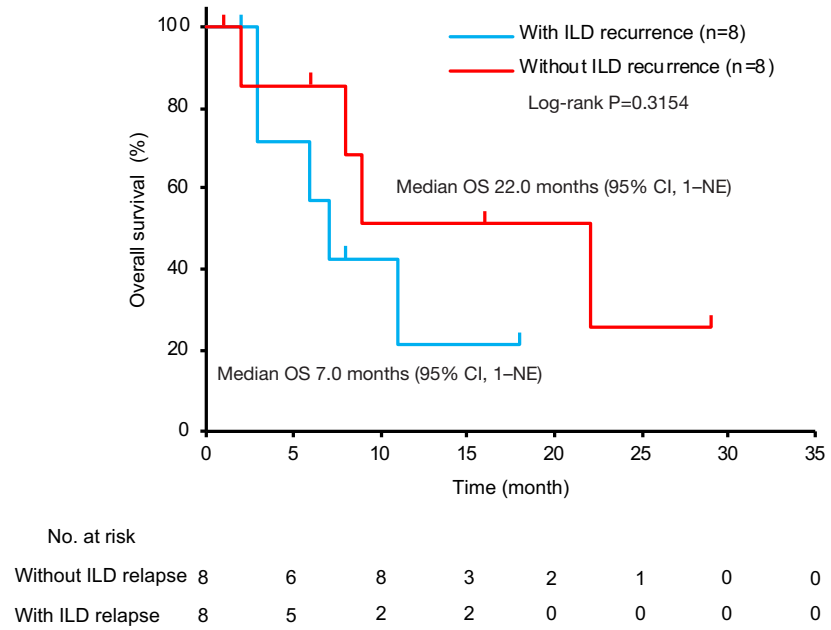

Figure 3 Overall survival curves of patients with or without ILD recurrence after systemic cancer therapy. ILD, interstitial lung disease; OS, overall survival; CI, confidence interval; NE, not evaluable.

Table 4 Tumor responses to systemic therapy

Tumor response	ALL systemic therapy	ILD recurrence	No ILD recurrence	P value
PR	3	1	2	
SD	13	2	11	
PD	13	6	7	
NE	5	1	4	
ORR	9%	10%	8%	0.88[a]
DCR	47%	30%	54%	0.47[a]

Differences between groups were identified using [a]Chi-Square test. ILD, interstitial lung disease; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; ORR, overall response rate; DCR, disease control rate.

systemic cancer therapy had a better prognosis than those who did not receive systemic cancer therapy after the onset of ICI-related ILD. Recent meta-analyses revealed that patients treated with PD-1 inhibitors had a significantly higher incidence of drug-induced ILD than those treated with chemotherapy. Su *et al.* showed that PD-1 inhibitors significantly increased grade 1-5 and grade 3-5 pneumonitis (risk ratio: 5.17, 95% CI: 2.82–9.47, P<0.001; risk ratio, 4.14, 95% CI: 1.82–9.42, P<0.001) (17). Huang *et al.* also demonstrated that the odds ratios (ORs) of immune-related all-grade and high-grade pneumonitis were significant for nivolumab (all-grade: OR =6.29, 95% CI: 2.67–16.75; high-grade: OR =5.95, 95% CI: 2.35–17.29) and pembrolizumab (all-grade: OR =5.78, 95% CI: 2.79–13.24; high-grade: OR =5.33, 95% CI: 2.49–12.97) compared with chemotherapy (21). Indeed, the current study showed that ICI-related ILD developed in 32 of 231 NSCLC patients (14%, *Figure 1*). Despite the high risk of ILD development, there are few cancer treatment options for NSCLC patients with ICI-related ILD. The efficacy and safety of posttreatment for drug-induced ILD that developed following epidermal growth factor receptor (EGFR)

Radiologic features of ILD recurrence		1st ILD	
		GGO (N=4)	COP-like (N=4)
2nd or 3rd ILD	GGO	5	1
	COP-like	0	3

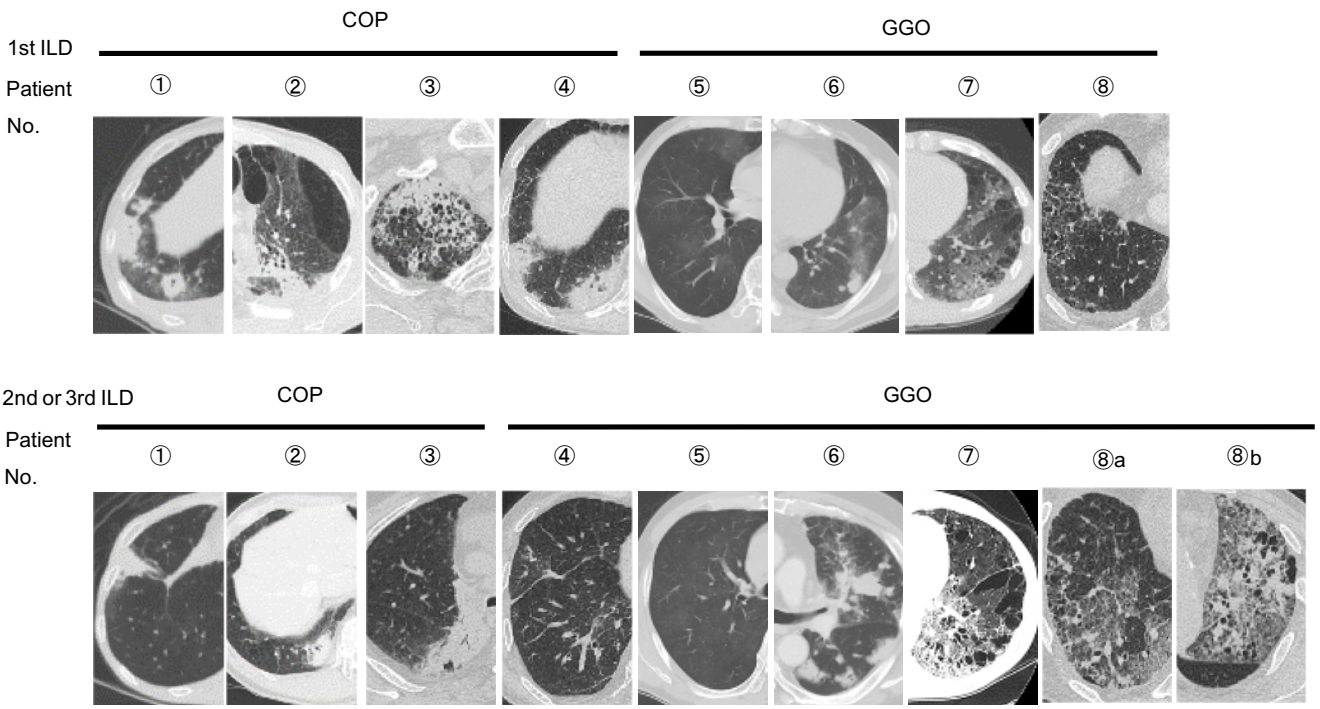

Figure 4 Comparison of radiologic features between the 1st and 2nd episodes of drug-induced ILD. Patient number 8 had 2 recurrences post-ILD treatment. ILD, interstitial lung disease; GGO, ground glass opacity; COP, cryptogenic organizing pneumonia.

TKIs and chemotherapy have been shown in existing reports (22,23). The median OS from the occurrence of chemotherapy-induced ILD tended to be longer in patients who received subsequent chemotherapy than in patients who did not (7.3 *vs.* 1.9 months, P=0.233) (22). Similarly, the median OS from the occurrence of EGFR-TKI-induced ILD was longer in patients who were rechallenged with EGFR-TKIs than in those who were not (15.5 *vs.* 3.5 months, P=0.029) (23). Furthermore, rechallenge with EGFR-TKIs was well tolerated even in patients with EGFR-TKI-induced ILD. In the current study, we showed that OS in patients who received subsequent systemic cancer therapies, including ICIs and cytotoxic chemotherapies, tended to be longer than that in patients who did not receive subsequent therapies (*Figure 2*).

Systemic cancer therapy in patients with ICI-related ILD is associated with a high risk of ILD recurrence. Simonaggio *et al.* demonstrated that ICI retreatment after the initial irAE resulted in a second irAE in 55% of patients (13). They also showed that the severity of the second irAE was not worse than that of the first irAE (13). The current study demonstrated that 8 of 16 patients (50%) with ICI-related ILD experienced ILD recurrence after sequential systemic cancer therapy (*Table 2*). There is a possibility that the recurrence of ILD was due to the natural history of ICI-related ILD; however, all but one

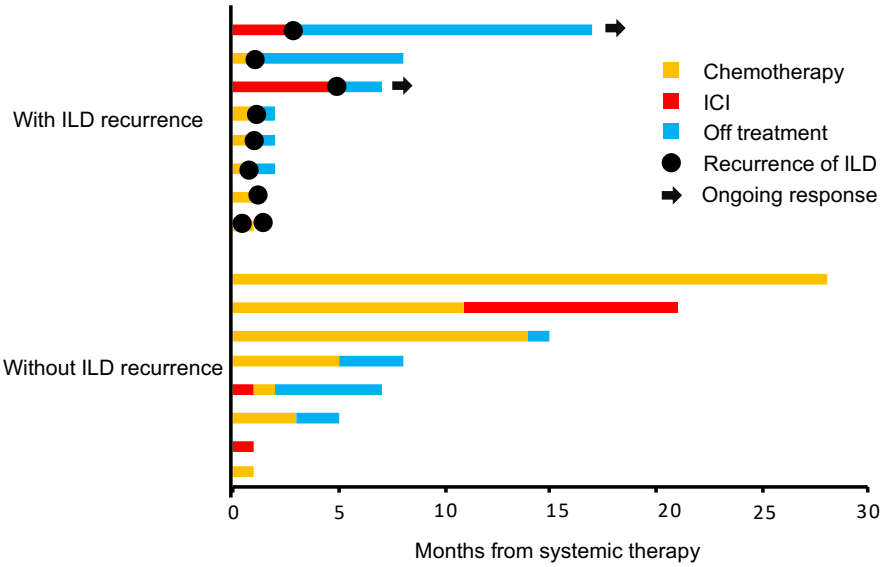

Figure 5 Duration of treatment with or without ILD recurrence after systemic cancer therapy. ILD, interstitial lung disease; ICI, immune checkpoint inhibitor.

patient recovered from ICI-related ILD and no patients experienced the recurrence of ILD in the no subsequent systemic cancer therapy group. Therefore, we considered that systemic cancer therapy following ICI-related ILD caused the recurrence of ILD. Patients did not receive subsequent systemic cancer therapy for a variety of reasons. Thirteen patients did not receive subsequent systemic cancer therapy at a physician's discretion, one patient for deterioration of PS, one patient did not recover from ILD and one patient had complete remission of NSCLC. These reasons for not treating patients with ICI-related ILD might affect their prognosis. Although a high frequency of ILD recurrence was observed, grade 2 or less ILD occurred in 78% of regimens (*Table 2*). Similar to the report by Simonaggio and colleagues on the severity of second irAEs, the results from our study also indicated that the severity of the second episode of ILD was not worse than that of the first (*Tables 1,2*). On the other hand, the current study showed that ILD recurrence was associated with a poor prognosis. Both chemotherapy and ICI rechallenge caused a second episode of ILD; however, a long response duration was observed only in patients who received ICI retreatment (*Figure 5*).

The current study demonstrated that patients who received subsequent systemic cancer therapies had a better prognosis than those who did not; however, patients who developed ILD recurrence had a poor prognosis (*Figures 2,3*). The results from this study suggest that predictive factors for ILD recurrence are required to administer systemic cancer therapy to patients with ICI-related ILD. We previously reported that patients with a GGO had shorter survival times than those with COP (14). However, there was no difference in the risk of ILD recurrence according to radiological features, and recurrent ICI-related ILD often showed similar imaging findings (*Figure 4*). Three out of 16 patients in systemic cancer therapy group had interstitial lung abnormalities before initial ICI treatment (*Table 1*). In these 3 patients, 2 had the recurrence of ICI-related ILD after the subsequent cancer therapy. Interstitial lung abnormalities might be the risk of the recurrence of ICI-related ILD after subsequent cancer therapy.

To our knowledge, this is the first report to evaluate subsequent systemic cancer treatment after the onset of ICI-related ILD, and we believe that the results from this study will aid in future clinical practice. The limitations of the present study include the relatively small number of patients with ILD and its retrospective nature. Further study is warranted to establish an appropriate systemic cancer treatment for patients with ICI-related ILD.

Conclusions

According to the current study, systemic cancer treatment

is effective in patients with ICI-related ILD; however, its safety is uncertain because of the high risk of ILD recurrence and poor survival outcome following ILD recurrence.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board of Niigata University (the registration number: 2017-0295) and each participating institution. Individual consent for this retrospective analysis was waived.

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