Real-world Evaluation of Second Line Chemotherapy for Patients With Advanced Non-small Cell Lung Cancer Harboring Preexisting Interstitial Lung Disease

Satoshi Igawa (✉ igawa@kitasato-u.ac.jp)

Department of Respiratory Medicine, Kitasato University School of Medicine <https://orcid.org/0000-0002-7527-8766>

Masanori Yokoba

Kitasato University School of Allied Health Sciences: Kitasato Daigaku Iryo Eisei Gakubu

Akira Takakura

Kitasato University School of Medicine: Kitasato Daigaku Igakubu

Shinji Hosotani

Kitasato University School of Medicine: Kitasato Daigaku Igakubu

Yoshiro Nakahara

Kitasato University School of Medicine: Kitasato Daigaku Igakubu

Takashi Sato

Kitasato University School of Medicine: Kitasato Daigaku Igakubu

Hisashi Mitsufuji

Kitasato University School of Nursing: Kitasato Daigaku Kango Gakka

Jiichiro Sasaki

Kitasato University School of Medicine: Kitasato Daigaku Igakubu

Katsuhiko Naoki

Kitasato University School of Medicine: Kitasato Daigaku Igakubu

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Abstract

Background: The optimal second and subsequent lines of chemotherapy for patients with non-small cell lung cancer (NSCLC) who have preexisting interstitial lung disease (ILD) are unclear. Hence, we examined the clinical efficacy and safety of second-line chemotherapy in such patients, including any exacerbation of preexisting ILD.

Methods: The medical records of patients with NSCLC and preexisting ILD who received both first- and second-line chemotherapy were retrospectively reviewed.

Results: Twenty-four patients with a median age of 71 years who were treated between April 2013 and March 2021 were included. The response rate after second-line chemotherapy with S-1 (n=13), docetaxel (n=8), pemetrexed (n=2), or docetaxel plus ramucirumab (n=1) was 12.5%, with a median progression-free survival (2nd line PFS) of 3.8 months. The overall survival from a start of first-line chemotherapy (1st line OS) and post-progression survival (PPS) post-first-line chemotherapy were 18.7 and 9.7 months, respectively. Spearman rank correlation and linear regression analyses showed that PPS was strongly correlated with 1st line OS ($R = 0.85$, $P < 0.00001$). Importantly, the 2nd line PFS was also significantly correlated with 1st line OS ($R = 0.71$, $P = 0.0001$). While second-line chemotherapy-related acute exacerbation of ILD was observed in 7 patients (29.2%), there were no treatment-related fatalities.

Conclusions: Second-line chemotherapy has a strong positive impact on the OS of patients with NSCLC who have preexisting ILD. Given the findings of this study, second-line chemotherapy may be valuable in terms of prolonging long-term OS.

Introduction

Preexisting interstitial lung disease (ILD) is a risk factor for drug-induced ILD [1]. It has been reported that the rate of preexisting ILD in patients with lung cancer is 2–8% [2], and that their prognosis is poor. Moreover, 5–20% of such patients can experience acute exacerbation of ILD (AE-ILD) induced by chemotherapy [3–5]. Previous studies that evaluated the safety and efficacy of platinum doublet chemotherapy in patients with NSCLC who have concurrent ILD found that their median survival times ranged from 7 to 16 months [5-116-12].

A large phase III study showed that a combination of carboplatin (CBDCA) plus nanoparticle albumin-bound paclitaxel (nab-PTX) significantly improved the objective response rate of patients with advanced NSCLC compared to that elicited by CBDCA plus solvent-based PTX [12]. Retrospective studies have indicated that CBDCA plus nab-PTX is effective and feasible in patients with NSCLC who have ILD [13, 14]. Moreover, a prospective study also demonstrated the effectiveness and safety of CBDCA plus nab-PTX in such patients [15]. Therefore, this combination is administered to patients with NSCLC and ILD in clinical practice in Japan.

Meanwhile, as patients with NSCLC have been excluded from most clinical trials of second-line agents, a standard second-line chemotherapy regimen has not been established for patients with NSCLC who have ILD; to our knowledge, there have been no studies evaluating the safety and efficacy of post-first-line chemotherapy in this patient population. Hence, the objective of this retrospective real-world study was to determine whether second-line chemotherapy is effective and feasible for patients with advanced NSCLC who have preexisting ILD.

Patients And Methods

Patient selection

The eligibility criteria for this retrospective cohort study were NSCLC confirmed via histological or cytological examination, a clinical diagnosis of ILD, and having received both of CBDCA plus nab-PTX as first-line chemotherapy and second-line chemotherapy at Kitasato University Hospital between April 2013 and December 2020. Additionally, measurable target lesions as observed on chest radiography, high-resolution computed tomography (CT) of the chest and abdomen, magnetic resonance imaging (MRI) of the head, positron emission tomography (PET), or combined PET/CT imaging were also required. The clinical disease stage was defined according to the Union for International Cancer Control TNM classification, 8th edition. The classification of ILD was determined by 2 experienced observers (A.T. and S.H.), while the subtype of ILD was estimated using the guidelines for the management of incidental pulmonary nodules from the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society Official Clinical Practice Guideline [16], as detected on CT images. This study was approved by the Institutional Ethics Review Board of Kitasato University Hospital. Informed consent was waived because of the retrospective nature of the study.

Treatment

All patients received second-line chemotherapy after failure of first-line treatment with CBDCA plus nab-PTX. Pegfilgrastim was administered prophylactically in a 6 mg fixed dose to patients after they received the first dose of chemotherapy at the physician's discretion to reduce the incidence of febrile neutropenia associated with second-line chemotherapy. After starting second-line chemotherapy, 50 $\mu\text{g}/\text{m}^2/\text{day}$ or 2 $\mu\text{g}/\text{kg}/\text{day}$ recombinant human granulocyte colony-stimulating factor was used in accordance with the national health insurance coverage of Japan; the indications for this treatment were as follows: (a) fever (defined in principle as a body temperature $> 37.5^\circ\text{C}$) with a neutrophil count of $\leq 1000/\text{mm}^3$, (b) a neutrophil count of $500/\text{mm}^3$, or (c) a neutrophil count of $500/\text{mm}^3$ before completing the same chemotherapy that resulted in a neutrophil count of $\leq 1000/\text{mm}^3$. Second-line chemotherapy was discontinued owing to disease progression, unacceptable toxicity such as AEILD, patient refusal of further treatment, or a decision by the head doctor to terminate treatment.

Response evaluation

Before the initiation of second-line chemotherapy, lesions were evaluated using plain chest radiography, CT of the chest and abdomen, PET or bone scintigraphy, and CT or MRI of the cranium. PET or bone scintigraphy, as well as CT or MRI of the cranium, were performed at 6-month intervals (or earlier if patients had significant tumor-associated symptoms). Tumor control was assessed using the Response Evaluation Criteria in Solid Tumors (version 1.1). The best overall response and maximum tumor control were recorded as tumor responses.

Toxicity assessment and dose modification

Toxicity was graded according to the Common Terminology Criteria for Adverse Events, version 4.0. The dose of each treatment regimen was reduced in subsequent cycles upon the development of grade 4 neutropenia that lasts ≥ 4 days, febrile neutropenia, grade 4 thrombocytopenia, grade 3 or higher peripheral neuropathy, and/or grade 4 non-hematologic adverse events. Patients received supportive care as required. AE-ILD was confirmed if the following criteria were met: i) exacerbation of dyspnea within 1 month, ii) newly developed diffuse pulmonary opacity, and iii) absence of heart failure and infectious lung disease, as previously described [17, 18].

Statistical analysis

Progression-free survival (PFS) following second-line chemotherapy (2nd line PFS) was defined as the interval between the date of second-line chemotherapy initiation and that of disease progression or the patient's death. Survival time attributable to second-line chemotherapy (2nd line OS) was defined as the interval between the date of commencing second-line chemotherapy and that of the patient's death or last follow-up. The interval between the start of first-line chemotherapy and the date of the patient's death or last follow-up was defined as first-line overall survival (1st line OS). Post-progression survival (PPS) of patients who received second-line chemotherapy was defined as the interval between the date of disease progression post-first-line chemotherapy treatment and that of the patient's death or last follow-up. Survival curves were plotted using the Kaplan-Meier method. Spearman's rank correlation and linear regression analyses were used to examine whether PPS and 2nd line PFS were correlated with 1st line OS. Statistical significance was set at $P < 0.05$. Statistical analysis was performed using the SPSS software for Windows (version 28.0; IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

Twenty-four patients who satisfied the criteria for this retrospective cohort study were included in the efficacy and safety analyses. The patients' demographic data, including the treatment regimens used as second-line therapy, are shown in Table 1. Their median age was 71 years; 23 (96%) were current smokers and an equal number had a favorable Eastern Cooperative Oncology Group performance status score. Of the 24 patients, none had collagen vascular disease or a history of exposure to dust or asbestos;

moreover, ILD was diagnosed in all patients with idiopathic interstitial pneumonia before first-line treatment.

Table 1
Patient characteristics (*n* = 24)

	Total <i>n</i> (%)
Age in years, median (range)	71 (59–77)
Sex	21 (87)
Male	3 (13)
Female	
ECOG performance status score	23 (96)
1	1 (4)
2	
Smoking status	23 (96)
Current smoker	1 (4)
Never or former light smoker	
Histology	10 (41)
Squamous carcinoma	11 (46)
Adenocarcinoma	3 (13)
Not otherwise specified	
Stage	3 (13)
IIIA	4 (16)
IIIB	17 (71)
IV	
Type of interstitial pneumonia	9 (38)
UIP	5 (21)
Probable UIP	8 (33)
Alternate	2 (8)
Indeterminate for UIP	

ECOG, Eastern Cooperative Oncology Group; UIP, usual interstitial pneumonia

	Total <i>n</i> (%)
Second-line regimen	13 (55)
S-1	8 (33)
Docetaxel	1 (4)
Docetaxel + ramucirumab	2 (8)
Pemetrexed	
ECOG, Eastern Cooperative Oncology Group; UIP, usual interstitial pneumonia	

Response and survival data

The response rate was 12.5% (Table 2). The median follow-up time from the start of second-line therapy was 9.4 months, and the median 2nd line PFS and OS were 3.8 (95% confidence interval [CI], 1.7–5.7) months and 8.8 (95% CI, 6.4–11.2) months, respectively (Fig. 1). Meanwhile, the median 1st line OS and PPS were 18.7 (95% CI, 11.2–26.4) months and 9.7 (95% CI, 7.4–12.0) months, indicating that the PPS was strongly associated with OS ($R = 0.85$, $R^2 = 0.723$, $P < 0.00001$, Fig. 2a). The PFS following second-line chemotherapy was also significantly associated with OS ($R = 0.71$, $R^2 = 0.504$, $P = 0.0001$, Fig. 2b). Of the 19 patients who had disease progression following second-line chemotherapy, 8 received subsequent-line treatment.

Table 2
Tumor response to second-line chemotherapy

	Total (<i>n</i> = 24)
Complete response	0
Partial response	3
Stable disease	9
Progressive disease	11
Not evaluable	1
Response rate (95% confidence interval), %	12.5 (2.0–23.0)
Disease control rate (95% confidence interval), %	50.0 (34.1–65.9)

Toxicity

The chemotherapy-related adverse events are summarized in Table 3; the most common were hematological toxicities such as neutropenia and leukopenia. Second-line chemotherapy-related AE-ILD was observed in 7 patients (29.2%) who received docetaxel (n = 4), pemetrexed (n = 2), and S-1 (n = 1). Other non-hematological toxicities were relatively mild, and no treatment-related deaths were observed. Subsequent chemotherapy was not administered to 7 patients with AE-ILD. We evaluated the risk factors for AE-ILD (Table 4) by comparing the 7 patients who experienced this adverse event to the 17 who did not. The incidence of AE-ILD was significantly higher in patients with squamous cell histology than in those with other types, and was significantly lower in patients who received S-1 than in those who received other agents.

Table 3
Treatment-related adverse events

	Grade			
	≤ 2	3	4	Percent ≥ 3
Leukopenia	3	2	1	12.5
Neutropenia	3	3	2	20.8
Thrombocytopenia	3	0	0	0
Anemia	0	0	0	0
Febrile neutropenia	0	1	0	4.1
Nausea	3	0	0	0
Anorexia	3	0	0	0
Constipation	4	0	0	0
Fatigue	2	0	0	0
Peripheral neuropathy	1	0	0	0
Mucositis	0	0	0	0
AST/ALT	3	0	0	0
Creatinine	0	0	0	0
Hyperglycemia	0	0	0	0
Hyponatremia	2	0	0	0
AE-ILD	7	0	0	0
AST/ALT, aspartate aminotransferase/alanine aminotransferase; AE-ILD, acute exacerbation of interstitial lung disease.				

Table 4
Risk factors for acute exacerbation of interstitial lung disease.

	AE-ILD (+)	AE-ILD (-)	P-value
Sex	5	16	0.19
Male	2	1	
Female			
Age (years)	7	11	0.09
<75	0	6	
≥75			
Smoking status	0	1	0.71
Never smoker	7	16	
Ever smoker			
ECOG performance status score	5	14	0.87
0–1	2	3	
2–3			
Histology	6	4	0.009
Squamous	1	13	
Adenocarcinoma or NOS			
Interstitial pneumonia pattern	5	9	0.36
UIP or probable UIP	2	8	
Other type			
Chemotherapy regimen	6	5	0.01
DOC or PEM	1	12	
S-1			
ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified; UIP, usual interstitial pneumonia; DOC, docetaxel; PEM, pemetrexed.			

Discussion

Second-line chemotherapy regimens following front-line CBDCA plus nab-PTX for patients with NSCLC who have preexisting ILD has not been evaluated in clinical trials; therefore, the effectiveness of such

treatments in this patient population has remained unknown to date. To our knowledge, ours is the first study to evaluate the safety and efficacy of second-line chemotherapy in this population.

A randomized phase III trial of pemetrexed versus docetaxel in patients with NSCLC previously treated with chemotherapy revealed overall response rates of 9.1% and 8.8%, respectively, with a median PFS of 2.9 months in each arm [19]. Another phase III trial of S-1 versus docetaxel in East Asian patients with NSCLC previously treated with platinum-based chemotherapy demonstrated a response rate and PFS of 8.3% and 2.89 months in the S-1 arm, respectively, and of 9.9% and 2.86 months in the docetaxel arm, respectively [20]. Accordingly, our study showed that second-line chemotherapy with docetaxel, pemetrexed, and S-1 in patients with NSCLC and preexisting ILD who had undergone front-line CBDCA plus nab-PTX was as effective as it was in patients previously treated for advanced NSCLC who did not have ILD.

AE-ILD occurred in 29.2% of our patients, indicating a high frequency of this adverse event caused by second-line chemotherapy; this was consistent with findings in previous studies [4, 5, 21] (Table 5). Data from previous studies and ours suggest that AE-ILD should be monitored in patients with NSCLC undergoing second-line chemotherapy if they have preexisting ILD. Previous studies indicated that the incidence of AE-ILD was significantly higher in patients with the usual interstitial pneumonia (UIP) pattern than in those without during first-line chemotherapy [22, 23]. While our study showed that the frequency of AE-ILD was higher in patients with a UIP or probable UIP pattern than it was in those with other patterns, there was no significant difference ($P = 0.36$). Meanwhile, we showed that the incidence of AE-ILD was significantly higher in patients with squamous cell histology than in those with other histological types, and was significantly lower in patients who received S-1 than in those treated with other regimens. To our knowledge, this is the first study to identify risk factors for second-line chemotherapy-related AE-ILD.

Table 5
Summary of existing reports on the incidence of acute exacerbation of interstitial lung disease (including a present study).

	<i>n</i>	Acute exacerbation of interstitial lung disease
Kenmotsu et al. [5]	57	17 (29.9%)
Kenmotsu et al. [7]	49	19 (38.8%)
Fujita et al. [22]	4	2 (50%)
Present study	24	7 (29.2%)

Although S-1 and 5-fluorouracil (5-FU) have been widely used for the treatment of various cancers in Japan and other Asian countries (including gastrointestinal, breast, and pancreatic cancers) [24–27], there are only a few reported cases of S-1- and 5-FU-induced ILD [28–31]. This suggests that S-1, a prodrug of 5-FU, rarely causes ILD. With respect to lung cancer, a Japanese prospective study found that S-1 plus CBDCA treatment is safe and effective for patients with NSCLC who have ILD [32]. Thus, S-1

monotherapy may be a reasonable choice as a second-line chemotherapy regimen for this patient population based on the low incidence of AE-ILD.

Although immune checkpoint-blocking agents such as the programmed cell death 1 (PD-1) inhibitors nivolumab and pembrolizumab were shown to be beneficial for patients with NSCLC in 2 phase III trials, the incidence of drug-induced ILD is higher in patients treated with these agents than in those treated with cytotoxic drugs (5% in the nivolumab group vs. 0% in the docetaxel group and 5.8% in the pembrolizumab group vs. 0.7% in the platinum-based chemotherapy group) [22, 23]. A previous study found that the incidences of severe nivolumab-related pneumonitis were 19% and 5% in patients with and without ILD, respectively [24]. The incidence of pneumonitis when using atezolizumab, an established antibody targeting the PD-1 ligand in patients with recurrent NSCLC [33], was reported to be lower than that when using other PD-1 antibodies or cytotoxic agents [34]. Therefore, atezolizumab may be a safer second-line therapy option from among the various immune checkpoint inhibitors that are available. However, a Japanese phase II study evaluating atezolizumab for previously treated patients with NSCLC and ILD showed that the incidences of pneumonitis were 29.4% for all grades, 23.5% for grades ≥ 3 , and 5.9% for grade 5 [35]; this indicated that patients with NSCLC and ILD have an increased risk of immune checkpoint inhibitor-induced pneumonitis. Hence, the safety of these agents in such patients is unclear, and additional safety data are warranted from a clinical trial comprising a larger and more carefully selected cohort of patients.

In our study, PPS and 2nd line PFS were significantly associated with 1st line OS. Previously, Imai *et al.* reported that the PPS after failure of first-line chemotherapy has a greater effect on OS as calculated from the start of first-line chemotherapy in patients with lung cancer [36, 37]. Given that our findings suggest that second or further-line treatment improves the OS of patients with NSCLC whether or not they have coexisting ILD, such treatment ought to be considered for those with ILD despite the apparent risk of AE-ILD.

Our study had several limitations. The results obtained cannot be considered definitive owing to the study's retrospective, single-center design and relatively small sample size. Moreover, the diagnosis of ILD was based on CT findings and not histological analysis, as was the diagnosis of ILD exacerbation. However, the American Thoracic Society/European Respiratory Society Consensus Statement offers criteria for the clinical diagnosis of idiopathic pulmonary fibrosis via CT [38], and high-resolution CT scanning reportedly has sensitivities of 43–78% and specificities of 90–97% for the diagnosis of ILD [39–43]. Therefore, we consider it appropriate to diagnose the subtype of ILD and any exacerbation of this condition using clinical and radiological findings in clinical practice.

In conclusion, second-line chemotherapy significantly improves the OS of patients with NSCLC who have coexisting ILD. Given these findings, second-line chemotherapy ought to be considered for this patient population.

Declarations

Ethics approval and consent to participate: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Institutional Ethics Review Board of Kitasato University Hospital. The requirement for informed consent was waived owing to the retrospective nature of the study.

Consent for publication: All authors the study gave consent to publication of this study.

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Availability of data and material: The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author contributions: All authors contributed to the study conception and design. Data collection was performed by SH and AT, and analysis was performed by SI. The first draft of the manuscript was written by SI and KN. All authors commented on versions of the manuscript. All authors read and approved the final version of the manuscript.

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Compliance with Ethical Standards

Disclosure of potential conflicts of interest: All authors declare no conflicts of interest.

Research involving human participants and/or animals: This study does not include human participants and animals.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Figures

Figure 1

Kaplan-Meier plots of (a) progression-free survival (2nd line PFS) and (b) overall survival (2nd line OS) following second-line chemotherapy. CI, confidence interval

Figure 2

Spearman correlation graphs comparing (a) overall survival (1st line OS) and post-progression survival (PPS), and (b) 1st line OS and progression-free survival (2nd line PFS). There were 2 outliers in these data. The R values represent Spearman's rank correlation coefficient, while the R² values represent linear regression