REVIEW

Current pharmacotherapies for advanced lung cancer with pre-existing interstitial lung disease : A literature review and future perspectives

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Abstract : Patients with interstitial lung disease (ILD), especially those with idiopathic pulmonary fibrosis, are at increased risk of developing lung cancer (LC). Pharmacotherapy for advanced LC has dramatically progressed in recent years ; however, management of LC with pre-existing ILD (LC-ILD) is challenging due to serious concerns about the risk of acute exacerbation of ILD (AE-ILD). As patients with LC-ILD have been excluded from most prospective clinical trials of advanced LC, optimal pharmacotherapy remains to be elucidated. Although the antitumor activity of first-line platinum-based cytotoxic chemotherapy appears to be similar in advanced LC patients with or without ILD, its impact on the survival of patients with LC-ILD is limited. Immune checkpoint inhibitors may hold promise for long-term survival, but many challenges remain, including safety and appropriate patient selection. Further understanding the predictive factors for AE-ILD after receiving pharmacotherapy in LC-ILD may lead to appropriate patient selection and lower treatment risk. The aim of this review was to summarize the current evidence related to pharmacotherapy for advanced LC-ILD and discuss emerging areas of research. J. Med. Invest. 71 : 9-22, February, 2024

Keywords **:** *interstitial lung disease, lung cancer, comorbidity, acute exacerbation, pharmacotherapy*

INTRODUCTION

Interstitial lung disease (ILD) is a risk factor for lung cancer (LC) development. LC with pre-existing ILD (LC-ILD) has a worse prognosis than that without (1). Idiopathic pulmonary fibrosis (IPF) is one of the most common ILDs. The incidence of LC comorbidity with IPF is generally considered to be approximately 10-20% (2). The greatest concern in LC-ILD is acute exacerbation (AE) of ILD (AE-ILD) during the treatment course. AE-ILD is frequently catastrophic and makes cancer management difficult. The Japanese population is more prone to drug-induced pneumonitis than other countries (2). Since patients with LC-ILD have been excluded from most prospective clinical trials of advanced LC, the optimal pharmacotherapy for such patients remains to be elucidated.

In this review article, we summarize the current evidence related to the treatments for advanced LC-ILD and discuss future perspectives.

EPIDEMIOLOGY AND RISK FACTORS OF AE-ILD

ILD comprises a diverse group of diffuse parenchymal lung diseases characterized by cellular proliferation, interstitial inflammation, fibrosis, or a combination of such findings within the alveolar wall (3). ILD usually manifests with slowly progressive respiratory insufficiency. However, some patients experience AE-ILD characterized by suddenly progressive and severe respiratory failure not due to infection, and new lung opacities that are considered pathological lesions of diffuse alveolar damage.

A Japanese epidemiologic survey reported that the median survival time (MST) of IPF patients was 35 months, the most

Abbreviations :
ILD, interstitial lung disease ; LC, lung cancer ; LC-ILD, lung cancer with pre-existing interstitial lung disease ; IPF, idiopathic pulmonary fibrosis ; AE, acute exacerbation ; AE-ILD, acute exacerbation of interstitial lung disease ; MST, median survival time ; NSIP, non-specific interstitial pneumonia ; CVD, collagen vascular disease ; CVD-ILD, collagen vascular disease-related interstitial lung disease ; FVC, forced vital capacity ; DLco, diffusing lung capacity for carbon monoxide ; KL-6, Krebs von den Lungen-6 ; CI, confidence interval ; IIPs, idiopathic interstitial pneumonias ; COP, cryptogenic organizing pneumonia ; CPFE, combined pulmonary fibrosis and emphysema ; OR, odds ratio ; LC-IPF, lung cancer with pre-existing idiopathic pulmonary fibrosis ; LC-IIPs, lung cancer with pre-existing idiopathic interstitial pneumonias ; NSCLC, non-small cell lung cancer ; NSCLC-ILD, non-small cell lung cancer with pre-existing interstitial lung disease ; AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis ; NSCLC-IPF, non-small cell lung cancer with pre-existing idiopathic pulmonary fibrosis ; mGAP, modified gender, age and physiology ; UIP, usual interstitial pneumonia ; ICI, immune checkpoint inhibitor ; PFS, progression-free survival ; OS, overall survival ; GEM, gemcitabine ; CBDCA, carboplatin ; nab-PTX, nanoparticle albumin-bound paclitaxel ; ORR, overall response rate ; PTX, paclitaxel ; S-1, tegafur-gimeracil-oteracil potassium ; BSC, best supportive care ; HR, hazard ratio ; DTX, docetaxel ; PEM, pemetrexed ; VNR, vinorelbine ; SCLC, small cell lung cancer ; SCLC-ILD, small cell lung cancer with pre-existing interstitial lung disease ; VP-16, etoposide ; TKI, tyrosine kinase inhibitor ; EGFR, epidermal growth factor receptor ; ALK, anaplastic lymphoma kinase ; BRAF, v-raf murine sarcoma viral oncogene homolog B ; KRAS, Kirsten rat sarcoma viral oncogene homolog ; BEV, bevacizumab ; irAE, immune-related adverse event ; CIP, checkpoint inhibitor pneumonitis

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common cause of death was AE (40%) (4), and the annual AE frequency in the natural course is 5-15% (5, 6). AE typically occurs in patients with IPF ; however, other fibrotic forms of ILD have also been shown to possess the potential to develop AE (7, 8). Park *et al*. reported that patients with idiopathic non-specific interstitial pneumonia (NSIP) and collagen vascular disease (CVD)-related ILD (CVD-ILD) experienced AE-ILD with a 1-year incidence of 4.2% and 3.3%, respectively (7). Associated predictive factors for AE-ILD include worse dyspnea score (modified Medical Research Council, shortness of breath questionnaire), worse pulmonary physiology (forced vital capacity [FVC], diffusing lung capacity for carbon monoxide [DLco]), worse 6-minute walking distance, worse oxygenation, and elevated serum Krebs von den Lungen-6 (KL-6) level at baseline. At least 10% decline in FVC at 6 months, past history of AE-ILD, comorbidities (pulmonary hypertension, coronary artery disease), baseline prednisone use, and air pollution exposure are also reported to increase risk for AE (9-13). AE-ILD is well established to be a serious and frequently lethal condition, and the mortality rate is about 30-50% (14). The manifestation of AE is an issue of major concern for the management of ILD due to a lack of established treatment strategies (15).

THE PREVALENCE OF LC COMORBIDITY IN ILD

Patients with ILD, especially those with IPF, are at increased risk for comorbidities, such as pulmonary hypertension, obstructive sleep apnea syndrome, gastroesophageal reflux, coronary heart disease, and LC (16). A possible association between ILD and LC was suggested as early as 1965 (17). Several subsequent studies demonstrated that the incidence of LC in IPF patients is higher than that in the general population, whose relative risk reportedly ranges between 5.0 and 14.1 (18-20). The frequency significantly differed between the reported cohorts ; however, IPF had a high rate of LC comorbidity, reaching a cumulative rate of 2.7-31.3% (18, 21-27) (Table 1). Recently, a meta-analysis of 35 studies reported that the total rate of LC prevalence in IPF patients was 13.5% (95% confidence interval [CI] : 10.4-17.4) (16).

Although there have only been a few reports, the risk of LC comorbidity is also considered to be increased in patients with idiopathic interstitial pneumonia (IIP) other than IPF (16, 20, 28). Kreuter *et al*. reported that the frequencies of LC complication are 15.8%, 4.2%, and 5.6% for IPF, idiopathic NSIP, and cryptogenic organizing pneumonia (COP), respectively (29). There is also limited evidence available regarding LC-ILD ; however, the rates of LC comorbidity were reported to be high in the following diseases with secondary ILD : hypersensitivity pneumonitis (10.6%) (30), pneumoconiosis (52.7%) (31), asbestosis (6-23%) (32), and CVDs (12.3-19.4%) such as rheumatoid arthritis, systemic sclerosis, and polymyositis/dermatomyositis (33, 34). In patients aged ≤ 60, the incidence of LC was higher in those with CVD-ILD than in non-CVD-ILD except for IPF (35). Combined pulmonary fibrosis and emphysema (CPFE) is a disease entity characterized by the coexistence of pulmonary fibrosis and emphysema (36). CPFE has a high rate of comorbidity with LC (37-39). Koo *et al*. reported that patients with CPFE have an estimated odds ratio (OR) of 9.06 for developing squamous cell lung cancer compared to those without underlying lung disease (37). Moreover, recent retrospective studies reported extremely high incidences of LC comorbidity in CPFE patients (25.0-46.8%) (38, 39).

RISK FACTORS FOR THE DEVELOPMENT OF BOTH ILD AND LC

The common risk factors for the development of both ILD and LC include smoking, environmental and occupational exposure to harmful substances, bacterial or viral infections, and chronic tissue damage (40, 41). In a recent retrospective cohort study of 938 IPF patients, the strongest predictors for the development of LC were male sex, current smoking, and decline in FVC of ≥ 10%/year (42). In addition, genetic alterations in the pathogenesis of both LC and ILD, especially IPF, have been reported, including microsatellite instability, loss of heterozygosity, cell cycle regulating gene (*MYCL1*, *p16^{INK4}*, *TP53*, *FHIT*) mutations (43), pulmonary surfactant system genes (*NKX2-1*/*TTF1*, *SFTPA1*, *SFTPA2*, *SFTPB*, *SFTPC*) mutations (44), and telomerase gene (*TERT*) mutations (45). In pathological analyses of LC-ILD, LC has been shown to develop on the basis of antecedent ILD that exhibits persistent inflammation, fibrosis, and dysregulated cytokine signaling in the lung (46), indicating the involvement of fibrotic lesions relating to the carcinogenesis process. In patients with CVD-ILD, CVD and its treatment have been suggested as a possible underlying factor for LC (2).

THE PROGNOSIS OF LC-ILD

The survival outcomes of LC with pre-existing IPF (LC-IPF) are worse than in patients with either disease alone. Tomassetti *et al*. investigated the influence of comorbid LC on IPF prognosis and reported that the MST of patients with LC-IPF was 38.7 months, which was significantly shorter than 63.9 months for patients those with IPF alone (24). An OR in the LC-IPF group

Table 1. Prevalence of lung cancer in idiopathic pulmonary fibrosis patients

First author	Year	Number of IPF patients	Prevalence of LC (%)	Patients with lung cancer				Reference
				Male (%)	Mean age (years)	Smoker (%)	MST (months)	
Le Jeune I	2007	1064	2.7	62.4	71.5	56.8	NA	18
Yoon JH	2018	1108	2.8	61.3	65.0	77.4	5.0	21
Lee KJ	2012	1685	6.8	94.7	68.5	92.3	26.9	22
Kato E	2018	632	11.1	94.3	66.8	100.0	11.2	23
Tomassetti S	2015	181	12.7	82.6	66.9	91.3	38.7	24
Ozawa Y	2009	103	20.4	95.2	65.5	66.7	13.1	25
Park J	2001	281	22.4	96.8	66.8	88.9	NA	26
Nagai A	1992	99	31.3	87.1	70.9	87.1	NA	27

IPF, idiopathic pulmonary fibrosis ; LC, lung cancer ; MST, median survival time ; NA, not applicable

was 7.0 times that of the IPF group. MSTs of patients with LC-IPF revealed wide-ranged variation from 5.0 to 38.7 months (Table 1), because the evidence regarding the survival of LC-IPF patients was limited by small sample sizes compared with either disease alone, and patient population and adopted methods for survival analysis were different among each study.

Conversely, to investigate the impact of comorbid IPF on LC prognosis, two retrospective studies to compare post-surgical survival of stage I LC patients with or without comorbid IPF were performed and found that 5-year survivals of LC-IPF patients were significantly lower than those without IPF (47, 48). Moreover, IPF-comorbidity was identified as a poor prognostic factor of LC patients in a multivariate analysis (47).

ILD subtype affects treatment-related toxicities and mortality with increased adverse events and worse survival in LC patients with IPF compared to those with NSIP or COP (29). Omori *et al*. retrospectively examined 103 post-surgical LC patients with pre-existing IIPs (LC-IIPs), 46 with IPF, and 57 with non-IPF, and reported that the 5-year survival rate was significantly higher in LC patients with non-IPF (53.2%) than those with IPF (22.1%) (49).

THE INCIDENCE AND RISK FACTORS OF AE-ILD IN LC-ILD INDUCED BY CYTOTOXIC CHEMOTHERAPY

Comorbid ILD is an obstacle to the treatment of LC, because idiopathic or iatrogenic AE-ILD frequently occurs after anticancer treatment, including surgery, irradiation, targeted therapy, and chemotherapy (50-53). The incidence of chemotherapy-related AE-ILD in LC-ILD patients markedly varied among studies due to factors such as genetic predisposition, patient characteristics, chemotherapy regimen, and the definition of chemotherapy-related AE-ILD, with reported rates ranging from 1.6% to 41.7% (15, 54-67) (Table 2). However, the accurate incidence and mortality rate of AE-ILD remain to be fully elucidated, as these studies had a small number of patients with AE. Recently, two meta-analyses of first-line chemotherapy for non-small cell lung cancer (NSCLC) with pre-existing ILD (NSCLC-ILD) demonstrated that the pooled rates of AE-ILD were 8.47% (95% CI : 5.04-12.6) (68) and 8.07% (95% CI : 6.12-10.26) (69) compared to an incidence of 10-30% for chemotherapy-related AE-ILD in patients with LC-ILD (70). Given the annual AE risk in the natural course of ILD (5-15%) (5, 6) and the general risk of drug-induced pneumonitis in patients without ILD (≤ 5%) (2), we predict the risk of AE in LC-ILD treated with cytotoxic chemotherapy to be high.

Recently, Kobayashi *et al*. demonstrated that the incidence of acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) increased and that the 1-year survival rate and MST in patients with NSCLC with pre-existing IPF (NSCLC-IPF) decreased with increasing the modified gender, age and physiology (mGAP) index score (71). These findings indicated that mGAP index score might predict AE-IPF and its prognosis in patients with LC-ILD. There have been several studies to evaluate risk factors except mGAP index score for the development of AE-ILD caused by cytotoxic chemotherapy in patients with LC-ILD. Putative predictive factors for chemotherapy-related AE-ILD were reported to be : performance status ≥ 2 (72), usual interstitial pneumonia (UIP) patterns in high-resolution computed tomography (73, 74), a pathologic NSCLC type (75), impaired pulmonary function (73, 75), and elevated serum KL-6 and surfactant proteins D level (72), although these factors remain inconclusive due to insufficient evidence. A subgroup analysis of a recent meta-analysis showed the difference in 1-year survival rate between studies with better lung function and those with poorer lung function was significant (56.0% vs. 29.0%), suggesting the usefulness of evaluating lung function in chemotherapy for patients with

Table 2. Incidence of chemotherapy-related AE-ILD in principal studies assessing the efficacy and safety of first-line chemotherapy in advanced NSCLC-ILD

First author	Year	Study design	Treatment	N	Age, median (years)	Male (%)	UIP/non-UIP (%)	FVC/DLco, median (%)	AE-ILD (%)	Reference
Otsubo K	2022	Phase III	CBDCA+nab-PTX+Nintedanib	121	71	89.3	100.0/0.0	82.9/58.5	4.1	67
Otsubo K	2022	Phase III	CBDCA+nab-PTX	122	71	91.0	100.0/0.0	85.1/60.0	1.6	67
Kenmotsu H	2019	Phase II	CBDCA+nab-PTX	94	70	89.4	53.2/46.8	90.1/63.7	4.3	54
Asahina H	2019	Phase II	CBDCA+nab-PTX	36	68.5	72.2	33.3/66.7	96.4/73.1	5.6	55
Minegishi Y	2011	Pilot	CBDCA+wPTX	18	71	77.8	33.3/66.7	82/NA	5.6	56
Fukuizumi A	2019	Phase II	CBDCA+wPTX	35	68	88.6	51.4/48.6	89/70	12.1	57
Sekine A	2016	Phase II	CBDCA+S-1	21	67	90.5	57.1/42.9	91/63.4	9.5	58
Hanibuchi M	2018	Phase II	CBDCA+S-1	33	70	90.9	66.7/33.3	NA	6.1	59
Igawa S	2018	Retrospective	CBDCA+nab-PTX	34	71	85.3	47.1/52.9	NA	6.3	60
Yasuda Y	2018	Retrospective	CBDCA+nab-PTX	12	73	91.7	25.0/75.0	81.7/90.7	8.3	61
Fujita T	2018	Retrospective	CBDCA+nab-PTX	8	77	87.5	50.0/50.0	81.5/NA	25	62
Araya T	2019	Retrospective	CBDCA+nab-PTX	9	69	88.9	55.6/44.4	112.4/55.8	22.2	63
Choi MK	2014	Retrospective	CBDCA+GEM, CBDCA+PEM	52	67	86.5	NA	NA	13.5	64
Kenmotsu H	2015	Retrospective	Platinum-based chemotherapy	104	67	91.3	67.3/32.7	NA	25	65
Kakiuchi S	2017	Retrospective	Platinum-based chemotherapy	47	72	93.2	NA	NA	5.7	15
Fujita T	2019	Retrospective	Platinum+PEM	24	70	91.7	8.3/91.7	91.2/NA	41.7	66

Cited from reference number 69 and revised.
AE-ILD, acute exacerbation of interstitial lung disease ; NSCLC-ILD, non-small cell lung cancer with pre-existing interstitial lung disease ; UIP, usual interstitial pneumonia ; FVC, forced vital capacity ; DLco, diffusing lung capacity for carbon monoxide ; CBDCA, carboplatin ; nab-PTX, nanoparticle albumin-bound paclitaxel ; wPTX, weekly paclitaxel ; S-1, tegafur-gimeracil-oteracil potassium ; PEM, pemetrexed ; GEM, gemcitabine ; NA, not applicable

LC-ILD (69). In addition, most previous prospective studies of cytotoxic chemotherapy enrolled patients with %FVC ≥ 50% and %DLco ≥ 30% who do not require oxygen administration. In clinical practice, the indication of cytotoxic chemotherapy should be considered for patients with LC-ILD when they meet the abovementioned conditions.

THE EFFECT OF FIRST-LINE CHEMOTHERAPY FOR NSCLC-ILD

Recently, new treatment strategies for advanced LC have been used, such as molecular-targeted drugs and immune checkpoint inhibitors (ICIs), which can significantly prolong progression-free survival (PFS) and overall survival (OS) of patients. However, further studies to establish treatments for LC-ILD are needed, as almost all clinical trials of LC uniformly excluded patients with pre-existing ILD due to serious concerns about the risk of triggering AE-ILD by anticancer treatments (70). As a result, there is currently insufficient evidence to assess the risks and benefits of chemotherapy in this patient population.

The Japanese package inserts of anti-cancer agents for LC contain descriptions relating to ILD. Irinotecan is contraindicated in patients with ILD including IPF. Gemcitabine (GEM) and amrubicin are also contraindicated in patients with ILD, which is clearly identifiable by plain chest X-ray and accompanied by clinical symptoms. Careful administration is recommended for many anti-cancer agents, and a warning relating to ILD is included (Table 3).

Recently, several prospective clinical trials focusing on conventional carboplatin (CBDCA)-containing regimens for patients with NSCLC-ILD have been conducted in Japan, which may improve the quality of evidence (Table 4). In two single-arm phase II studies that included relatively large number of patients (94 and 36 patients, respectively) (54, 55), a combination of CBDCA plus nanoparticle albumin-bound paclitaxel (nab-PTX) was evaluated as first-line chemotherapy for NSCLC-ILD. The incidence of AE-ILD was relatively low (4.3-5.6%) ; however, one patient in each group suffered a fatal AE-ILD in both studies. The efficacy outcome was favorable, with an overall response rate (ORR) of 51.1-55.6%, a median PFS of 5.3-6.2 months, and an MST of 15.4 months in each study. Two Japanese phase II trials of first-line CBDCA plus weekly paclitaxel (PTX) for NSCLC-ILD have also been reported in 18 and 35 patients (56, 57). They reported an incidence of AE-ILD of 5.6-12.1% with no fatal event, a high ORR of 61.1-69.7%, median PFS of 5.3-6.3 months, and an MST of 10.6-19.8 months. Sekine *et al*. and our group conducted single-arm prospective phase II trials of CBDCA plus tegafur-gimeracil-oteracil potassium (S-1) for chemotherapy-naïve patients with NSCLC-ILD in 21 and 33 patients, respectively (58, 59). The incidence of AE-ILD was 6.1-9.5% with no patients experiencing fatal AE-ILD, ORR was 33.3% in both studies, median PFS was 4.2-4.8 months, and MST was 9.7-12.8 months. A recent meta-analysis of first-line chemotherapy for 684 patients with NSCLC-ILD reported that the risk of AE-ILD in the nab-PTX group was significantly lower compared to other treatment regimens (4.98 vs. 11.92%), and the risk of AE-ILD in the nab-PTX group also tended to be lower than the PTX and S-1 groups (69). These observations suggest that CBDCA plus nab-PTX is a safer chemotherapeutic regimen for this patient population. Taken together with these findings, some conventional CBDCA-containing regimens may be feasible, valid, and associated with a relatively good ORR and PFS. However, these studies were likely underpowered to demonstrate an effect on OS, given their relatively small sample sizes. Moreover, no randomized phase III studies have been conducted in this patient population. Therefore, it remains to be determined whether chemotherapy prolongs the survival of advanced LC-ILD compared to best supportive care (BSC) as initial treatment, given that chemotherapy-related AE-ILD may become a direct cause of mortality in these patients.

More recently, Miyamoto *et al*. performed a retrospective multi-center cohort study to investigate whether chemotherapy improves OS and influences the risk of AE in LC-IIPs compared to BSC. Their findings suggest that chemotherapy as initial treatment for LC-IIPs improves OS (hazard ratio [HR] : 0.629, 95% CI : 0.506-0.783) irrespective of LC histology ; however, it was significantly associated with AE-ILD (OR : 1.787, 95% CI : 1.026-3.113) compared to BSC (72). Although there is no drug with adequately established safety for the treatment of LC-ILD at present, the aforementioned findings suggest that traditional chemotherapy still plays a critical role in the treatment of this patient population. However, optimal treatment strategies for patients with LC-ILD must balance efficacy and unique safety considerations.

THE EFFECT OF SECOND-LINE OR LATER CHEMOTHERAPIES FOR NSCLC-ILD

Second-line or later chemotherapy for NSCLC-ILD has a higher risk of AE-ILD than first-line chemotherapy. Our group demonstrated that the incidence of AE-ILD in patients with LC-ILD increased from 6.3% during first-line treatment to 9.5-20.0% during second-line or later chemotherapy (15). Single-agent chemotherapy of docetaxel (DTX), pemetrexed (PEM), vinorelbine (VNR), and GEM, which are standard second-line or later treatments for NSCLC, were reported to have relatively high AE-ILD incidences of 14.3-44.4%, 12.0-50.0%, 0.0-28.6%, and 42.9%, respectively (15, 65, 74, 76, 77). A nationwide surveillance in Japan was conducted to investigate the details of second-line treatment for LC-ILD and found that the incidences of AE-ILD for DTX, VNR, and PEM monotherapy were 15.3%, 25.0%, and 28.6%, respectively (78). These findings suggest that implementation of standard-of-care systemic therapy has a high risk of AE-ILD in patients with NSCLC-ILD. These drugs are not actively recommended due to toxicity considerations. Second-line or later chemotherapy for this patient population has very limited efficacy and survival benefit (65, 76, 78). In a previous study of second-line treatment among 127 patients with NSCLC-ILD, ORR was 7.4% and MST from the first day of treatment to second-line chemotherapy was 8.0 months, which were worse than first-line chemotherapy (78). Thus, patients with NSCLC-ILD have few standard-of-care treatment options for second-line or later cytotoxic chemotherapy.

THE EFFECT OF CHEMOTHERAPIES FOR SMALL CELL LUNG CANCER WITH PRE-EXISTING ILD

The options for first-line chemotherapy in small cell lung cancer (SCLC) are limited compared to NSCLC, but cytotoxic chemotherapy generally has remarkable benefits (79, 80). Thus, patients with SCLD with pre-existing ILD (SCLC-ILD) are more likely to receive chemotherapy in clinical practice despite the risk of AE-ILD (15, 81, 82). Further studies are needed to evaluate the efficacy and safety of chemotherapy for patients with SCLC-ILD. Only one prospective study of chemotherapy for this patient population has been reported. Minegishi *et al*. investigated the feasibility of a combination of CBDCA plus etoposide (VP-16) as first-line chemotherapy in 17 patients with SCLC-ILD (83). Although the incidence of AE-ILD was relatively low

Table 3. Descriptions regarding interstitial lung diseases in the Japanese package inserts of anticancer agents for lung cancer

Class	Drug	Precautionary statement	Frequency of associated ILD
Cytotoxic chemotherapeutic agent	Cisplatin	Precautions	less than 0 1%
	Carboplatin	Precautions	0.1%
	Nedaplatin	Precautions	less than 0 1%
	Paclitaxel	Careful administration	0.5%
	Nanoparticle albumin-bound paclitaxel	Careful administration	0.8%
	Docetaxel	Careful administration	0.6%
	Vinorelbine	Careful administration	1.4%
	Irinotecan	Contraindication	0.9%
	Etoposide	Precautions	less than 0 1%
	Gemcitabine	Contraindication*	1.0%
	Pemetrexed	Careful administration	3.6%
	Tegafur/uracil	Precautions	less than 0 1%
	Tegafur/gimeracil/oteracil potessium	Careful administration	0.3%
	Amrubicin	Contraindication*	0.1 to less than 5%
	Nogitecan	Careful administration	unknown
Molecular-targeted drug	Gefitinib	Careful administration	1 to less than 10%
	Erlotinib	Careful administration	4.4%
	Afatinib	Careful administration	3.1%
	Osimertinib	Careful administration	2.7%
	Dacomitinib	Careful administration	2.2%
	Crizotinib	Careful administration	1.7%
	Alectinib	Careful administration	1.7%
	Ceritinib	Careful administration	1.4%
	Brigatinib	Careful administration	6.3%
	Lorlatinib	Careful administration	0.9%
	Dabrafenib	Precautions	unknown
	Trametinib	Precautions	unknown
	Tepotinib	Careful administration	3.8%
	Capmatinib	Careful administration	6.2%
	Selpercatinib	Careful administration	0.8%
	Entrectinib	Precautions	1.2%
	Sotorasib	Careful administration	1.1%
	Bevacizumab	Precautions	0.4%
	Ramucirumab	Precautions	0.4-1.7%
	Trastuzumab deruxtecan	Careful administration	10.1%
Immune checkpoint inhibitor	Nivolumab	Careful administration	5.1%
	Pembrolizumab	Careful administration	3.1%
	Atezolizumab	Careful administration	2.8%
	Durvalumab	Careful administration	4.9%
	Ipilimumab	Precautions	unknown
	Tremelimumab	Careful administration	3.2%

Cited from reference number 2 and revised.
*Contraindication in patients with interstitial lung diseases that are clearly identifiable by plain chest X-ray and is accompanied by clinical symptoms
ILD, interstitial lung disease

(5.9%), one patient died as a result of the event. The efficacy outcomes, ORR, median PFS, and MST, were 88.2%, 5.5 months, and 8.7 months, respectively. Retrospective studies of first-line chemotherapy for SCLC-ILD have also been reported (15, 81, 82) (Table 5). In these studies, a combination of platinum-containing drugs plus VP-16 demonstrated a relatively tolerable incidence of AE-ILD (1.9-17.9%) and showed favorable efficacy outcomes that were equivalent to those in SCLC without ILD, with a high ORR of 69.2-79.3%, median PFS of 4.3-4.5 months, and MST of 9.4-9.9 months. Another retrospective study also found that the OS in SCLC with IIPs was not inferior to that without IIPs (12.7 vs. 14.8 months) (84). Taken together with these findings, a combination of platinum-containing drugs plus VP-16 is a suitable standard treatment regimen for chemotherapy-naïve SCLC-ILD.

In general, second-line chemotherapy is considered to exert worse efficacy than first-line chemotherapy. However, second-line chemotherapy for refractory or recurrent SCLC-ILD is anticipated to improve survival (85, 86). Several retrospective analyses reported ORR of 16.7-29.4% and MST of 3.6-8.7 months (78, 85-87) (Table 5), which were almost the same as those in SCLC without ILD. However, second-line chemotherapy had a higher risk of AE-ILD compared to first-line chemotherapy in SCLC-ILD, and the incidence of AE-ILD was reported to be 8.3-29.4% (85-88). The establishment of evidence-based consensus treatment strategies for this patient population is a challenging and urgent issue.

THE EFFECT OF MOLECULAR-TARGETED DRUGS FOR DRIVER ONCOGENE-POSITIVE NSCLC-ILD

The identification of actionable gene alterations in NSCLC is being promoted. A subset of NSCLC patients with driver gene mutations/translocations is preferentially recommended to receive therapies with tyrosine kinase inhibitors (TKIs) targeting the respective gene alterations as initial treatment (89). However, molecular-targeted drugs, such as epidermal growth factor receptor (EGFR)-TKIs and anaplastic lymphoma kinase (ALK)-TKIs, are associated with developing drug-induced ILD (90, 91). Some studies reported that pre-existing ILD was a significant risk factor for the development of drug-induced ILD (70, 92, 93). In a prospective epidemiologic cohort study that included 3,166 Japanese patients with advanced or recurrent

Table 4. Summary of prospective studies to evaluate the efficacy and safety of chemotherapy in advanced NSCLC-ILD

First author	Year	Study design	N	Regimen	ORR (%)	mPFS (months)	MST (months)	AE-ILD (%)	Reference
Otsubo K	2022	Phase III	121	CBDCA+nab-PTX+Nintedanib	69.0	6.2	15.3	4.1	67
Otsubo K	2022	Phase III	122	CBDCA+nab-PTX	56.0	5.5	13.0	1.6	67
Kenmotsu H	2019	Phase II	94	CBDCA+nab-PTX	51.1	6.2	15.4	4.3	54
Asahina H	2019	Phase II	36	CBDCA+nab-PTX	55.6	5.3	15.4	5.6	55
Minegishi Y	2011	Pilot	18	CBDCA+wPTX	61.1	5.3	10.6	5.6	56
Fukuizumi A	2019	Phase II	35	CBDCA+wPTX	69.7	6.3	19.8	12.1	57
Sekine A	2016	Phase II	21	CBDCA+S-1	33.3	4.2	9.7	9.5	58
Hanibuchi M	2018	Phase II	33	CBDCA+S-1	33.3	4.8	12.8	6.1	59

NSCLC-ILD, non-small cell lung cancer with pre-existing interstitial lung disease ; ORR, overall response rate ; mPFS, median progression-free survival ; MST, median survival time ; AE-ILD, acute exacerbation of interstitial lung disease ; CBDCA, carboplatin ; nab-PTX, nanoparticle albumin-bound paclitaxel ; wPTX, weekly paclitaxel ; S-1, tegafur-gimeracil-oteracil potassium

Table 5. Summary of studies to evaluate the efficacy and safety of chemotherapy in advanced SCLC-ILD

First author	Year	Study design	Regimen	Treatment line	N	ORR (%)	mPFS (months)	MST (months)	AE-ILD (%)	Reference
Minegishi Y	2011	Prospective	CBDCA+VP-16	First-line	17	88.2	5.5	8.7	5.9	83
Togashi Y	2012	Retrospective	Platinum+VP-16, Platinum+CPT-11	First-line	28	78.6	4.4	9.9	17.9	81
Yoshida T	2013	Retrospective	Platinum+VP-16	First-line	52	69.2	4.5	9.4	1.9	82
Kakiuchi S	2017	Retrospective	Platinum+VP-16	First-line	27	79.3	4.3	NA	7.4	15
Fujimoto D	2015	Retrospective	CBDCA+PTX, PTX, NGT	Second-line	23	21.7	2.1	7.1	13.0	85
Saijo A	2019	Retrospective	PTX, nab-PTX, CBCDA+PTX	Second-line	17	29.4	2.7	3.6	29.4	87
Suzuki H	2011	Retrospective	NGT	Second-line	12	16.7	NA	5.9	8.3	86
Enomoto Y	2015	Retrospective	NGT	Second-line or later	23	NA	NA	NA	21.7	88
Kakiuchi S	2017	Retrospective	Various regimens	Second-line	16	NA	NA	NA	6.3	15
Minegishi Y	2020	Retrospective	Various regimens	Second-line	74	25.7	NA	8.7	NA	78

SCLC-ILD, small cell lung cancer with pre-existing interstitial lung disease ; ORR, overall response rate ; mPFS, median progression-free survival ; MST, median survival time ; AE-ILD, acute exacerbation of interstitial lung disease ; CBDCA, carboplatin ; VP-16, etoposide ; CPT-11, irinotecan ; PTX, paclitaxel ; NGT, nogitecan ; nab-PTX, nanoparticle albumin-bound paclitaxel ; NA, not applicable

NSCLC, the cumulative incidence of drug-induced ILD was 4.0% (95% CI : 3.0-5.1) at 12 weeks of gefitinib treatment (52). Overall OR for gefitinib vs. chemotherapy was 3.2 (95% CI : 1.9-5.4), and pre-existing ILD was associated with an increased risk of developing AE-ILD. In a meta-analysis that included 20 eligible studies with 2261 patients treated with ALK-TKIs for advanced NSCLC, the overall pooled incidence of pneumonitis was 2.14% (95% CI : 1.37-3.34). In addition, the incidence of pneumonitis was significantly higher in studies from Japan compared to those of non-Japan origin (6.25% vs. 1.14%) (91).

Actionable gene alteration-positive cases in NSCLC-ILD are rare, and a study found that only 0.4% of lung adenocarcinoma patients with *EGFR* mutations had pre-existing ILD (94). Masai *et al*. investigated genetic features of primary lung adenocarcinoma occurring in the setting of UIP pattern and reported that the frequencies of gene mutation/translocation of *EGFR*, *v-raf murine sarcoma viral oncogene homolog B*^{V600E} (*BRAF*^{V600E}), and *ALK* were 2.3%, 2.7%, and 0.0%, respectively (95). Activating mutations in *Kirsten rat sarcoma viral oncogene homolog* (*KRAS*) are reported to be present in 25-39% of non-squamous NSCLCs, and a higher rate of *KRAS* mutation (30.2%) was observed in lung adenocarcinoma with comorbid UIP (95) in contrast to lower rates of the abovementioned actionable gene mutations and translocations. Recently, some KRAS^{G12C} inhibitors (sotorasib, adagrasib) have been developed ; however, the pulmonary toxicities of these drugs remain to be elucidated. In a phase III trial, comparing sotorasib versus DTX for previously treated NSCLC with *KRAS*^{G12C} mutation, fatal treatment-related ILD was reported in one patient (0.6%) in the sotorasib group (96). In driver oncogene-positive NSCLC-ILD, molecular-targeted drugs must be administered with special precautions.

THE EFFECT OF MONOCLONAL ANTIBODIES (ANGIOGENESIS INHIBITORS) FOR NSCLC-ILD

Vascular endothelial growth factor is considered to play an important role in the pathogenesis of AE of IPF (97) ; however, the relationship between angiogenesis inhibitors and ILD remains to be elucidated. Previous small-scale studies reported that standard chemotherapy plus bevacizumab (BEV) in treatment-naïve NSCLC-ILD had a relatively low AE-ILD incidence of 0.0-12.0% (98-102) (Table 6). The efficacy outcomes for chemotherapy plus BEV had an ORR of 25.0-72.0%, with a median PFS of 5.3-8.0 months and MST of 8.5-16.1 months, which are comparable to the results of a phase III trial of patients with advanced NSCLC without ILD (103). In addition, a retrospective study reported that first-line chemotherapy combined with BEV had a significantly lower risk of AE-ILD than chemotherapy alone in patients with NSCLC-ILD (0.0% vs. 22.6%) (101). Although the safety of the administration of angiogenesis inhibitors in NSCLC-ILD remains to be elucidated, the concomitant use of angiogenesis inhibitors is unlikely to increase the risk of AE-ILD associated with cytotoxic chemotherapy in this patient population.

THE EFFECT OF ICIS FOR LC-ILD

ICIs hold a prominent position in the frontline management of patients with advanced LC. While immune system activation has critical implications for cancer treatment, ICIs pose challenges due to immune-related adverse events (irAEs) due to non-specific immune activation (104). Checkpoint inhibitor pneumonitis (CIP) is a potentially serious and fatal irAE that occurs with a relatively high frequency (105). However, clinical outcomes of ICIs in LC-ILD are largely unknown, since this patient population is often excluded from clinical trials (106, 107). The incidence of CIP in NSCLC patients with ILD has been analyzed in predominately retrospective studies and reported to be 11.1-42.9%, which is higher than in those without ILD (5.8-11.6%) (108-116) (Table 7). Recent meta-analyses of ICI therapy also found a significantly higher incidence of any grade and grade ≥ 3 pneumonitis in NSCLC patients with ILD, especially IPF, than in those without ILD (107, 117). Accumulating evidence suggests risk factors other than pre-existing IPF for CIP include patients aged > 70 years old (118) ; those with Eastern Cooperative Oncology Group performance status score 2 or higher (119) ; comorbid lung diseases, such as asthma and chronic obstructive pulmonary disease (120) ; pre-existing interstitial lung abnormalities on baseline chest computed tomography (112) ; decreased FVC (121) ; prior thoracic radiotherapy (120) ; squamous cell lung carcinoma (122) ; and combination ICI therapy (123). However, the associations among these potential risk factors and CIP requires further confirmation and validation. Although significant safety concerns remain, the therapeutic efficacies of ICIs in NSCLC patients with ILD were reported to be comparable to those without ILD. In a retrospective study to evaluate efficacy outcomes of ICIs in NSCLC patients with or without ILD, ORR, median PFS, and MST of NSCLC patients with ILD were not significantly different from those without ILD (49.0 % vs. 30.1 %, 5.9 months vs. 3.5 months, and 27.8 months vs. 25.2 months, respectively) (114). These findings suggest that ICIs should not be evenly withheld in LC-ILD despite their increased risk of CIP. However, clinicians should be extremely cautious when using ICIs especially in patients with the possible risk factors described above, given that CIP is relatively common and can be fatal in some cases.

Table 6. Summary of studies to evaluate the efficacy and safety of bevacizumab combined with chemotherapy in advanced NSCLC-ILD

First author	Year	Study design	Regimen	N	ORR (%)	mPFS (months)	MST (months)	AE-ILD (%)	Reference
Omori M	2023	Phase II	CBDCA+wPTX+BEV	17	52.9	5.7	12.9	5.9	102
Suzuki H	2013	Retrospective	CBDCA+PTX+BEV	4	25	NA	NA	0	98
Shimizu R	2014	Retrospective	CBDCA+PTX+BEV	10	40	5.3	16.1	10	99
Enomoto Y	2015	Retrospective	CBDCA+PTX+BEV	25	72	7.2	8.5	12	100
Hamada S	2019	Retrospective	Platinum+PEM+BEV, PEM+BEV, CBDCA+PTX+BEV	48	NA	8.0	NA	0	101

NSCLC-ILD, non-small cell lung cancer with pre-existing interstitial lung disease ; ORR, overall response rate ; mPFS, median progression-free survival ; MST, median survival time ; AE-ILD, acute exacerbation of interstitial lung disease ; CBDCA, carboplatin ; wPTX, weekly paclitaxel ; BEV, bevacizumab ; wPTX, weekly paclitaxel ; PEM, pemetrexed ; NA, not aplicable

Table 7. Summary of studies to evaluate the efficacy and safety of immune checkpoint inhibitors in advanced NSCLC-ILD

First author	Year	Study design	Regimen	Number of ILD patients	ORR (%)	mPFS (months)	MST (months)	Incidence of CIP (%)		Reference
								ILD group	non-ILD group	
Fujimoto D	2019	Phase II	Nivolumab	18	38.9	7.4	15.6	11.1	NA	108
Ikeda S	2022	Phase II	Atezolizumab	17	6.3	3.2	15.3	29.4	NA	109
Kanai O	2018	Retrospective	Nivolumab	26	26.9	2.9	NA	30.8	11.6	110
Yamaguchi T	2018	Retrospective	Nivolumab, Pembrolizumab	37	NA	NA	NA	35.1	5.8	111
Nakanishi Y	2019	Retrospective	Nivolumab, Pembrolizumab	14	42.9	NA	NA	42.9	11.6	112
Shibaki R	2020	Retrospective	Nivolumab, Pembrolizumab	17	NA	NA	NA	29.4	9.9	113
Tasaka Y	2021	Retrospective	Nivolumab, Pembrolizumab	49	49.0	5.9	27.8	30.6	9.5	114
Isono T	2021	Retrospective	Nivolumab, Pembrolizumab	20	26.7	NA	14.6	35.0	6.6	115
Nishiyama N	2020	Retrospective	Pembrolizumab, Nivolumab, Atezolizumab	48	45.8	4.7	NA	14.5	NA	116

NSCLC-ILD, non-small cell lung cancer with pre-existing interstitial lung disease ; ORR, overall response rate ; mPFS, median progression-free survival ; MST, median survival time ; CIP, checkpoint inhibitor pneumonitis ; ILD, interstitial lung disease ; NA, not applicable

PREVENTIVE EFFECT OF PHARMACOTHERAPY-RELATED AE-ILD IN LC-ILD BY ANTI-FIBROTIC AGENTS

Recently, anti-fibrotic agents, such as pirfenidone and nintedanib, have become available for IPF treatment. Furthermore, nintedanib has been demonstrated to prevent AE. In a randomized phase III trial of IPF (the INPULSIS study), there were significantly fewer AE-IPF in the nintedanib group than in the placebo group (1.9% vs. 4.7%) (124). Although there is no definite evidence regarding whether antifibrotic drugs prevent AE-ILD during LC treatment, some recent studies reported that a combination of chemotherapy with antifibrotic agents may protect against the development of AE-ILD. In a retrospective cohort study that included 14 NSCLC with pre-existing IPF, no patients who received pirfenidone in combination with first-line chemotherapy (CBDCA plus either nab-PTX or S-1) or late-line ICIs developed AE-IPF (125). Moreover, in a retrospective single-center study to evaluate the prophylactic effect of perioperative pirfenidone treatment in LC-IPF, the incidence of AE-IPF within 90 postoperative days was significantly lower in patients treated with perioperative pirfenidone than in those that did not receive it (3.2% vs. 21.1%) (126). These findings were supported by the findings of the J-SONIC study, a randomized phase III trial to assess the efficacy and safety of CBDCA and nab-PTX with or without nintedanib for advanced NSCLC-IPF. Although nintedanib with chemotherapy improved OS in patients with non-squamous NSCLC (HR : 0.61, 95% CI : 0.40-0.93), there was no significant difference in exacerbation-free survival between the two groups (HR : 0.89, 90% CI : 0.67-1.17) (67). Further studies are required to elucidate the prophylactic effect of anti-fibrotic agents on preventing AE-ILD during treatment of LC.

CONCLUSIONS AND FUTURE PERSPECTIVES

The establishment of evidence-based consensus treatment strategies for LC-ILD is an urgent issue. However, no randomized controlled trials of pharmacotherapy for LC-ILD have shown an improvement of OS compared to BSC at present. Moreover, there is no drug with adequately established efficacy and safety profiles in this patient population. However, accumulating evidence suggests that pharmacotherapy can prolong survival of LC-ILD, and it is widely applied in actual medical practice for applicable cases. Kakiuchi *et al*. reported that 86.5% of patients with advanced LC-ILD chose chemotherapy, not BSC, as initial therapy, indicating that patients want to receive an anti-cancer treatment with an acceptable risk-to-benefit balance (15). Whether anti-fibrotic agents prevent the risk of pneumonitis or AE-ILD during LC treatment remains uncertain, but further understanding of the predictive factors for AE-ILD after receiving pharmacotherapy in LC-ILD may assist reasonable treatment choice. Several prospective studies to explore new treatment strategies for patients with LC-ILD are now in progress (Table 8). The results of these trials may provide new treatment options for this patient population.

CONFLICT OF INTEREST DISCLOSURE

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Table 8. Representative on-going prospective studies to examine the efficacy and safety of pharmacotherapies for patients with LC-ILD

Study ID	Phase	Sample size	Title	Primary outcome	Date of disclosure
UMIN000038594	NA	10	A prospective observational study of pembrolizumab and chemotherapy for lung cancer patients with interstitial abnormalities	Incidence of pneumonitis	2019/11/21
CRB5180004	NA	22	A multicenter, open-label, prospective study of durvalumab, etoposide, and carboplatin for unresectable small cell lung cancer with mild idiopathic interstitial pneumonia (DREAM study)	Severe pneumonitis-free rate	2021/1/15
UMIN000034849	I/II	15	A prospective study of efficacy and safety of atezolizumab for patients with non-small cell lung cancer and interstitial pneumonia	Incidence of drug-induced pneumonitis	2018/11/12
CRB3180025	II	33	A phase II study of carboplatin, etoposide and nintedanib for unresectable limited/extensive disease small cell lung cancer with idiopathic pulmonary fibrosis (TORG1835/NEXT-SHIP study)	Incidence of AE-IPF	2019/10/18
UMIN000050630	II	24	Rechallenge chemotherapy with carboplatin plus paclitaxel or nab-paclitaxel for patients with non-small-cell lung cancer and interstitial lung disease	Overall response rate	2023/3/20
UMIN000029411	III	230	Phase III study of perioperative pirfenidone therapy in patients with non-small-cell lung cancer combined with idiopathic pulmonary fibrosis for confirming the effect for prevention of postoperative acute exacerbation (PIII-PEOPLE study)	Incidence of AE-IPF	2017/10/15

LC-ILD, lung cancer with pre-existing interstitial lung disease ; ID, identification ; NA, not applicable ; AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis

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