Review Article

Immune checkpoint inhibitor-related interstitial lung disease in patients with advanced non-small cell lung cancer: systematic review of characteristics, incidence, risk factors, and management

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Background: Immune checkpoint inhibitors (ICIs) are widely used in cancers with or without other treatments. Immune-related adverse events (irAEs) have been reported as side effects of ICIs and involve various organs. Pneumonitis, which is also called ICI-related interstitial lung disease (ILD), is one of the life-threatening adverse events. In this report, we reviewed the safety of ICIs and risk factors for ICI-related ILD in non-small cell lung cancer (NSCLC) patients.

Methods: Databases (The National Center for Biotechnology Information, PubMed, Cochrane Library, Google Scholar, and Embase) were searched for the literature on pulmonary adverse events and immunotherapy following PRISMA guidelines. All studies published in English between January 2016 and June 2021 were included.

Results: One-hundred twenty-five articles were included at final. Pre-existing ILD as well as asthma and chronic obstructive lung disease (COPD) were associated with high risk for the development of ICI-related ILD, however, it did not affect the prognosis. The treatment of ICI-related ILD is different according to the severity grades, which includes discontinuation of ICI, corticosteroids, and for steroid-refractory ILD, other immunosuppressants. Rechallenging of ICI should be carefully considered in selected patients.

Discussion: Patients with pre-existing lung disease and poor lung function need more attention for the development of ICI-related ILD. It is necessary to be aware of clinical manifestation of ICI-related ILD with prompt management.

Keywords: Immune checkpoint inhibitor-related interstitial lung disease (ICI-related ILD); non-small cell lung cancer (NSCLC); immune related adverse events; interstitial lung disease (ILD)

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Introduction

Immune checkpoint inhibitors (ICIs) have shown clinical benefits in various cancers, both in locally advanced and metastatic states. Furthermore, ICIs are used in combination with other treatment modalities, such as platinum-based chemotherapy. Notable trials, including ICI as neoadjuvant and adjuvant therapy, are also ongoing, extending their usage (1).

However, immune-related adverse events (irAEs) have also been reported, with a prevalence of about 20–30% (2). IrAEs show various clinical manifestations, such as pneumonitis, skin reactions, endocrinologic diseases, colitis, hepatitis, and infusion reactions (3). Among the irAEs, pneumonitis, including interstitial lung disease (ILD), is clinically significant and can be life-threatening, which frequently requires immediate clinical attention. The incidence of ICI-related ILD is approximately 4% in patients treated with PD-1 inhibitors (such as nivolumab and pembrolizumab) and 2% in those treated with PD-L1 inhibitors (such as atezolizumab and durvalumab) (4). In a meta-analysis, the incidence of ICI-related ILD was 3.6% and 1.3% in the PD-1 and PD-L1 inhibitor-treated groups, respectively.

In this study, recent evidence on possible risk factors, clinical manifestations, and safety regarding ICI-related ILD, and in-depth studies on ICI-related ILD in patients with previously diagnosed ILD were reviewed. We present the following article in accordance with the PRISMA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-93/rc).

Methods

Following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (5), an online search of the literature on pulmonary adverse events and immunotherapy was conducted. The National Center for Biotechnology Information (NCBI) PubMed, Cochrane Library, Google Scholar, and Embase databases were searched. All studies published in English between January 2016 and June 2021 were included. Various combinations of search words were tried using the following terms: ('NSCLC' OR 'non-small cell lung') AND ('interstitial lung disease' OR 'pneumonitis' OR 'organizing pneumonia') AND ('nivolumab' OR 'pembrolizumab' OR 'atezolizumab' OR 'immune checkpoint inhibitor' OR 'immunotherapy' OR 'ipilimumab') AND ('idiopathic pulmonary fibrosis' OR 'connective tissue disease'). The search strategy is illustrated in *Figure 1*.

Pathophysiology

ICIs activate and enhance antitumor activities by inhibiting intrinsic down-regulators of immunity, such as CTLA-4, PD-1, and PD-L1. However, it can also stimulate the immune system resulting in irAEs. IrAEs frequently involve the gastrointestinal tract, endocrine system, liver, and skin. They less commonly involve the central nervous system, pulmonary, cardiovascular, musculoskeletal, and hematologic systems. IrAEs in the lungs can manifest as pneumonitis (6,7).

The pathophysiology of irAEs can be explained by four mechanisms. Firstly, irAEs may have increased T-cell activity against cross-antigens shared between tumor and normal tissues. The responses of cytotoxic antigen-directed T cells may lead to ICI-induced ILD. The second mechanism involves increased baseline levels of pre-existing autoantibodies that provoke irAEs, such as anti-thyroid peroxidase, antinuclear, anti-thyroglobulin, and anti-rheumatoid factor antibodies. However, the specific antibodies that are related to ICI-related ILD remain unknown. The third mechanism is the increased levels of inflammatory cytokines. A case report showed that C-reactive protein and interleukin-6 (IL-6) levels were higher than baseline levels in a patient with NSCLC who developed ICI-related ILD after atezolizumab treatment (8). Johnson *et al.* and Lim *et al.* reported that elevated inflammatory cytokines are also related to severe ICI toxicity (9,10). The fourth mechanism is increased inflammation mediated by the complement system due to direct binding of anti-CTLA-4 antibodies with CTLA-4 on normal tissue, such as the pituitary gland. This mechanism accounts for pituitary inflammation as a specific irAE of anti-CTLA-4 therapy (7,11,12).

In short, overstimulation of the host immune system and increased levels of preexisting autoantibodies may be the underlying mechanisms behind ICI-related ILD. Further studies are needed to clarify the pathophysiological background.

Prevalence of ICI-related ILD

ICI-related ILD has a prevalence of 3–5% in NSCLC trials. In phase III Checkmate 017 and Checkmate 057, the prevalence of nivolumab-induced ILD were 4.6% (6/131)

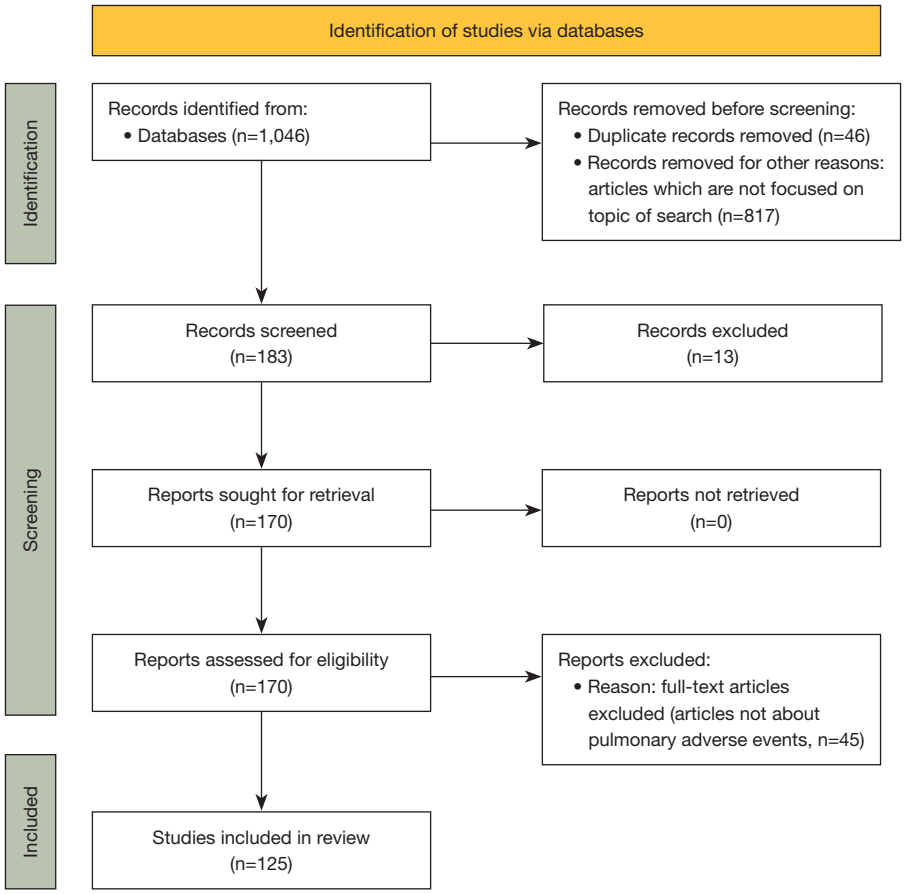

Figure 1 PRISMA flow diagram for the systemic review.

and 3.5% (10/287), respectively (13-15). A meta-analysis reported that 4.2% of patients treated with nivolumab for NSCLC developed ILD (16). However, the incidence in the real-world setting remains higher. One retrospective study using real-world data showed a much higher incidence rate of 19% (17). Another multicenter prospective study of 138 patients with NSCLC showed that the overall incidence rate of ICI-related ILD was 14.5%. This is similar to the results of other retrospective studies, ranging from 14.6% to 19.0% (18,19).

In a single-center retrospective study that included 98 patients with NSCLC, 19 patients developed immunotherapy-induced ILD. The median time to the development of ICI-related ILD was 97 days. Among the 19 patients, 10 patients had grade 1–2 and 9 patients had grade 3–4 pneumonitis (20).

The incidence of ICI-related ILD differs according to the type of ICI. According to a meta-analysis by Pillai *et al.*, the incidence of ICI-related ILD was significantly higher in patients treated with PD-1 inhibitors, such as nivolumab and pembrolizumab than in those treated with PD-L1 inhibitors, such as atezolizumab and durvalumab (4% *vs.* 2%, P=0.001) (4). In another meta-analysis by Khunger *et al.*, the incidence of ICI-related ILD was also higher in PD-1 than in PD-L1 inhibitors treated group, both for any grade (3.6% *vs.* 1.3%, P=0.001) and grade 3 or higher (1.1% *vs.* 0.4%, P=0.002). In the PD-1 inhibitor group, there was no significant difference in the incidence of ICI-related ILD between nivolumab and pembrolizumab (21).

Risk factor for ICI-related ILD

Several studies investigated the potential risk factors for ICI-related ILD. These include baseline patient characteristics, pre-existing diseases, disease features, and treatment modalities.

In a study by Cho *et al.*, patients aged >70 years old were more common in the ICI-related ILD group (54.5%

vs. 30.3%, P=0.025) (22). In another retrospective study, however, the rates of immunotherapy-related toxicities did not differ by age group (23). The prevalence of ICI-related ILD was higher in females than in males, with no statistically significant difference (17).

Pre-existing lung diseases can be risk factors for ICI-related ILD. Asthma and COPD were mentioned as possible contributing factors of ICI-related ILD. However, the association requires validation. In an FDA approval summary of pembrolizumab for metastatic NSCLC, patients with asthma or COPD more commonly developed ICI-related ILD than in those without, though there was no confirmation of statistically significant difference (5.4% *vs.* 3.1%) (24). Other studies have not reported association between prior asthma and development of ICI-related ILD. In one study, prior asthma history was associated with higher grade of ICI-related ILD if it occurs, however the size of cohort was small (25). In a retrospective study of 216 NSCLC patients who were treated with nivolumab, total and severe nivolumab-related ILD occurred more frequently in patients with pre-existing ILD than in those without (31% *vs.* 12%, P=0.014 and 19% *vs.* 5%, P=0.022, respectively) (26). Pre-existing abnormal lung image findings, such as fibrosis or inflammation, are also considered as risk factors. In a study of nivolumab-induced ILD in NSCLC patients, some patients had radiologic findings of inflammation before ICI treatment, which may have resulted from past radiation pneumonitis or bacterial pneumonia (13). In a retrospective study, pre-existing pulmonary fibrosis was associated with an increased risk of ICI-related ILD (19). Another study by Atchley *et al.* reported that a history of ILD (OR =15.7, 95% CI: 2.52–98.20), obstructive lung disease (OR =3.13, 95% CI: 1.24–7.88), including COPD (OR 2.42, 95% CI: 1.12–5.22), and pre-existing fibrosis on baseline chest CT (OR =7.06, 95% CI: 2.76–18.0) were associated with an increased risk of ICI-related ILD (27). In a multicenter prospective study, pulmonary function parameters such as FVC and FEV1, and dyspnea symptoms graded by modified Medical Research Council (mMRC) were related to the incidence of ICI-related ILD. Here, FVC showed significant association after multivariate analysis (HR =0.734, 95% CI: 0.891–0.979, P=0.0044) (18).

Prior thoracic radiotherapy has been suggested as a potential risk factor. In an FDA approval summary of pembrolizumab for metastatic NSCLC patients, the incidence of ICI-related ILD was higher in patients with prior thoracic radiation history than in patients without (6.0% *vs.* 2.6%) (24).

Tumor histologic type may also be a risk factor for ICI-related ILD. In a retrospective study of 205 NSCLC patients, squamous carcinoma showed a higher incidence rate of ICI-related ILD (IRR =2.29, 95% CI: 1.08–4.83) than other histologic types (IRR =4.32, 95% CI: 1.24–12.19) (17). However, Atchley *et al.* reported that the tumor histologic type did not show a significant association (27).

Combination ICI therapy increases the risk of ICI-related ILD. A meta-analysis of 4,496 patients with NSCLC, melanoma, and renal cell carcinoma (RCC) by Nishino *et al.* reported that the incidence of ICI-related ILD in melanoma was higher in the combination treatment than in the single ICI regimen (6.6% *vs.* 1.6%, P<0.001). Furthermore, the combination regimen showed a significantly higher association than monotherapy for ICI-related ILD (OR =2.04, 95% CI: 1.69–2.50, P<0.001) (28). Cui *et al.* showed that combination therapy was associated with an increased risk of ICI-related ILD (OR =3.42, 95% CI: 1.65–7.09, P=0.001) (29). Suresh *et al.* also suggested combination ICI therapy as a risk factor for ICI-related ILD, although it was not statistically significant (17).

There are studies that evaluated risk of ILD development in patients under combination of platinum-based chemotherapy. In the KEYNOTE-189 trial, which was phase 3 trial of 616 patients with metastatic non-squamous NSCLC who received pemetrexed, platinum-based drug and pembrolizumab or placebo, the incidence of any grade and grade 3 or higher pneumonitis was 4.4% (18/405) and 2.7% (1/405), respectively. It was higher than the placebo combination group, which was 2.5% (5/202) and 2.0% (4/202), though there was no confirmation of statistically significant difference (30). In real-world data shown in a multicenter, retrospective cohort study of advanced NSCLC patients who received platinum, pemetrexed, and pembrolizumab combination therapy, the incidence of all-grade and grade 3 or higher pneumonitis was 12.4% and 3.3%, respectively, suggesting relatively high incidence (31).

Regarding the risk factors for severe (grade 3 or higher) ICI-related ILD, Tone *et al.* reported that Eastern Cooperative Oncology Group (ECOG) performance status (PS) score 2 or higher and pre-existing ILD were significantly associated with development of severe ICI-related ILD. ECOG PS score was higher in the patients with severe ICI-related ILD than in those without (ECOG PS 2–3; 54.5% *vs.* 18.3%, P=0.01), and more patients were complicated with pre-existing ILD in severe ICI-related ILD group (27.3% *vs.* 6.7%, P=0.035) (32). In a meta-

analysis of studies about melanoma, NSCLC, and RCC, the incidence of grade 3 or higher ICI-related ILD was more frequent in NSCLC than melanoma (1.8% *vs.* 0.2%, P<0.001). Also, the combination therapy group showed higher incidence of severe ICI-related ILD than the monotherapy group (1.5% *vs.* 0.2%, P<0.001) (28).

Considering these results, patients who have poor lung function, prior lung diseases, or radiologic evidence of lung inflammation or fibrosis before administration of ICI, and who will be treated with combination ICI therapy should be closely monitored for ICI-related ILD (*Table 1*).

Radiotherapy

Radiotherapy is one of the treatment options for NSCLC and is frequently used before or after immunotherapy. Although it can improve the survival outcomes of patients, a previous history of thoracic radiotherapy can increase the risk of ICI-related ILD. In a secondary analysis of KEYNOTE-001, they assessed the association of previous radiotherapy with the clinical activity and toxicity of pembrolizumab in NSCLC. Patients with previous thoracic radiotherapy showed a higher incidence of lung toxicity than those without in all grades [13% (3/24 patients) *vs.* 1% (1/73 patients), P=0.016] (33). In a case-control study by Cui *et al.*, prior thoracic radiotherapy was significantly associated with the development of ICI-related ILD (OR =3.33, 95% CI: 1.39–7.97, P=0.007) (29). Regarding the purpose of radiotherapy, a retrospective study of 188 NSCLC patients showed that ICI-related ILD more frequently occurred in patients receiving curative radiotherapy as compared to palliative radiotherapy [89% (17/19 patients) *vs.* 11% (2/19 patients), P=0.051) (35). The treatment timing can also be important. However, a retrospective study of 79 patients with primary lung cancer or lung metastatic lesions showed no significant difference between sequential and concurrent treatment in association with ICI-related ILD occurrence (39).

Another reason for the possible increased risk of ICI-related ILD is that radiotherapy can cause radiation-induced pneumonitis. In a study on the correlation between prior radiation pneumonitis and nivolumab-related ILD, the incidence of nivolumab-induced ILD was higher in patients with a history of radiation pneumonitis than in those without (26.5% *vs.* 9.6%, P=0.018). However, the median progression-free survival (PFS) was longer in the patients with radiation pneumonitis history (3.6 *vs.* 2.3 months). Furthermore, a history of radiation pneumonitis significantly associated with a longer PFS (HR =0.59, 95% CI: 0.35–0.93, P=0.023) (34).

After the resolution of radiation-induced pneumonitis, radiation recall pneumonitis, an acute inflammatory reaction in a previously irradiated area of the lung triggered by other anticancer drugs can occur (40). In a case report by Itamura *et al.*, the patient developed radiation recall pneumonitis one month after initiating pembrolizumab, who had previously recovered from radiation pneumonitis (41).

Administering ICI with concurrent chemoradiation (CCRT) may induce higher pulmonary toxicity than monotherapy. In phase 2 KEYNOTE-799—a non-randomized trial of pembrolizumab administration with CCRT in stage III NSCLC—the incidence of grade 3 or higher ICI-related ILD was less than 10% (42). Other studies on ICI combined with CCRT have shown similar results. Grade 3–5 pneumonitis occurred in 10% of patients receiving pembrolizumab with CCRT (43), 6% in pembrolizumab consolidation after CCRT (44), 12% in nivolumab with CCRT (45), 3% in atezolizumab with CCRT (46), and 4% in durvalumab after CCRT, which is known as the PACIFIC trial (47).

In patients with previous radiation therapy or radiation-induced pneumonitis, clinicians should be more cautious regarding the risk of developing ICI-related ILD.

Radiographic manifestations of ICI related ILD

ICI-related ILD manifests in various radiological forms. They can be classified into multiple patterns according to the ATS/ERS international multidisciplinary classification of interstitial pneumonia. These include cryptogenic organizing pneumonia (COP), hypersensitivity pneumonitis (HP), acute interstitial pneumonia (AIP)/diffuse alveolar damage (DAD), and nonspecific interstitial pneumonia (NSIP)-like patterns. Among them, the COP-like pattern is the most common pattern in previous studies. In a study of NSCLC patients with nivolumab-related ILD, the main radiologic finding was COP-like (53.4%), followed by HP-like (20.2%), DAD-like (10.9%), and NSIP-like (6.3%) pattern (48). Similarly, in a study by Baba *et al.*, the most common pattern of ICI-related ILD was COP-like (47.2%), followed by HP-like (24.3%), AIP/DAD-like (13.2%), NSIP-like pattern (8.3%), and others (6.9%) (49). In patients with pre-existing ILD, Shibaki *et al.* reported that the most common radiologic finding was DAD-like (40%), followed by organizing pneumonia (OP)-like, HP-like, and other patterns (20% each, respectively) (36).

AIP-like and DAD-like manifestations are considered

Table 1 Potential risk factors for ICI-related ILD

Authors	Year	Cancer	Regimen	Design	Number	Incidence rate of ICI-related ILD	Risk factors
Sul *et al.* (24)	2016	NSCLC	Pembrolizumab	Prospective	550	3.5% (19 patients)	History of asthma/COPD; history of prior thoracic radiation
Khunger *et al.* (21)	2017	NSCLC	Nivolumab; pembrolizumab; atezolizumab; durvalumab; avelumab	Meta-analysis	5,038	2.8% (140 patients)	PD-1 inhibitors (when compared with PD-L1 inhibitors)
Kato *et al.* (13)	2017	NSCLC	Nivolumab	Case series	111	7.2% (8 patients)	Presence of inflammation in the lungs at baseline
Saverdian *et al.* (33)	2017	NSCLC	Pembrolizumab	Retrospective	97	4.1% (4 patients)	Previous treatment with radiotherapy
Tamiya *et al.* (34)	2017	NSCLC	Nivolumab	Retrospective	201	11.9% (24 patients)	History of radiation pneumonitis
Suresh *et al.* (17)	2018	NSCLC	Nivolumab; pembrolizumab; durvalumab	Retrospective	205	19% (39 patients)	Female; tumor histologic type; combination ICI therapy
Cho *et al.* (22)	2018	NSCLC	Nivolumab; pembrolizumab; durvalumab; nivolumab + ipilimumab	Retrospective	167	13.2% (22 patients)	Pre-existing interstitial lung disease
Yamaguchi *et al.* (19)	2018	NSCLC	Nivolumab; pembrolizumab	Retrospective	123	14.6% (18 patients)	Pre-existing pulmonary fibrosis
Kanai *et al.* (26)	2018	NSCLC	Nivolumab	Retrospective	216	13.9% (30 patients)	Pre-existing ILD
Voong *et al.* (35)	2019	NSCLC	Nivolumab; pembrolizumab; durvalumab	Prospective	188	19% (36 patients)	Curative-intent chest radiotherapy (when compared to palliative-intent)
Shibaki *et al.* (36)	2020	NSCLC	Nivolumab; pembrolizumab	Retrospective	331	11% (36 patients)	Pre-existing ILD
Suzuki *et al.* (18)	2020	NSCLC	Nivolumab; pembrolizumab	Prospective Cohort study	138	14.5% (20 patients)	Impaired spirometry; dyspnea defined by mMRC
Tasaka *et al.* (37)	2021	NSCLC	Nivolumab; pembrolizumab	Retrospective	461	11.7% (54 patients)	Pre-existing ILD
Isono *et al.* (38)	2021	NSCLC	Nivolumab; pembrolizumab; atezolizumab	Retrospective	119	22.7% (27 patients)	Pre-existing ILD
Atchley *et al.* (27)	2021	NSCLC SCLC	Nivolumab; pembrolizumab; nivolumab + ipilimumab	Retrospective; multicenter	315	9.5% (30 patients)	Presence of baseline fibrosis on chest CT scan; composite measure of obstructive lung disease; treatment with pembrolizumab

ICI, immune checkpoint inhibitor; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer; COPD, chronic obstructive pulmonary disease; PD-1, programmed cell death 1; PD-L1, programmed cell death-ligand 1; mMRC, Modified Medical Research Council; SCLC, small cell lung cancer.

as acute stage patterns, followed by organizing stage and fibrotic stage patterns such as NSIP (11). In a study of two nivolumab phase II trials, most of the patients (7/8) whose ILD improved previously showed radiologic patterns of OP or NSIP without traction bronchiectasis (13).

Regarding the severity of ILD, most of the patients with OP or NSIP pattern had grade 1 or 2, and all patients with a DAD pattern had grade 3 or higher. In a retrospective study, patients with long-term disease control tended to show OP patterns at the onset of ICI-related ILD (2). Saito *et al.* reported that a DAD-like pattern is associated with a worse prognosis and a higher mortality rate (48).

Radiologic patterns are also classified into typical or atypical patterns of drug-induced pneumonitis. Typical patterns include ground glass opacity (GGO) or consolidation with unilateral/bilateral nonsegmental distribution. These are relatively frequent findings during conventional chemotherapy or targeted therapy. Other atypical findings include peritumoral GGO, exacerbation of radiation fibrosis, and abnormal ipsilateral lung opacities (49). In a study of NSCLC patients with nivolumab-related ILD, most patients (87.8%) did not show peritumoral infiltration while 11.3% of patients showed peritumoral infiltration (48).

Safety in pre-existing ILD patients

Pre-existing ILD as a risk factor for development of ICI-related ILD

In several studies, pre-existing ILD was associated with an increased risk of ICI-related ILD. In a study on the prevalence of nivolumab-related ILD in NSCLC, head and neck cancer, and gastric cancer, pre-existing ILD was an independent predictor of ICI-related ILD (OR =5.92, 95% CI: 2.07–18.54, P<0.05) (50). In another retrospective study on the association between pre-existing ILD and anti-PD-L1 antibody-related ILD in NSCLC, the incidence of ICI-related ILD was higher in patients with pre-existing ILD than in those without ILD (29% *vs.* 10%, P=0.027) (36). On the other hand, a study by Yamaguchi *et al.* showed that the frequency of ICI-related ILD was not different between the pre-existing ILD group and those without it in patients receiving pembrolizumab (51).

In addition to pre-existing ILD, interstitial lung abnormalities (ILA) can be a risk factor for ICI-related ILD. ILA is defined as incidentally found increased lung density in CT without definite diagnosis of ILD. Radiologic features of ILA include ground-glass attenuation (GGA), reticular abnormalities, traction bronchiectasis, honeycombing, diffuse centrilobular nodularity, and non-emphysematous cysts (52). ILA is shown in 14% of treatment-naïve advanced NSCLC patients (53). Nakanishi *et al.* reported that the patients with pre-existing ILA showed higher incidence of ICI-related ILD than those without [6/14 (42.9%) *vs.* 7/69 (10.1%), P=0.007], and patients with GGA specifically, showed significantly higher incidence rate [6/14 (42.9%) *vs.* 1/69 (1.4%), P<0.001] (52). In another retrospective cohort study of patients with non-lung cancers (head and neck cancer, malignant melanoma, oral cavity cancer, urological cancer, and gastrointestinal cancer) who received anti-PD-1 antibody therapy, pre-existing ILA (OR =6.42, 95% CI: 1.96–21.03, P=0.002) and GGA (OR =4.05, 95% CI: 1.29–12.71, P=0.01) were independent risk factors for ICI-related ILD in each multivariate analysis model (54).

Since pre-existing ILD and ILA can be risk factors for ICI-related ILD, patients with prior ILD and abnormal lung density in baseline chest CT, especially GGA, should be carefully monitored for the development of ICI-related ILD.

Pre-existing ILD in association with prognosis

In a retrospective study by Tasaka *et al.*, clinical outcomes such as response rate (RR) and disease control rate (DCR) were not inferior in patients with pre-existing ILD compared to those without ILD (RR: 49.0% *vs.* 30.1%, P<0.01; DCR: 69.4% *vs.* 51.2%, P=0.016, respectively). Patients with pre-existing ILD also showed non-inferior median PFS and OS than those without ILD (5.9 *vs.* 3.5 months, P=0.14, and 27.8 *vs.* 25.2 months, P=0.74, respectively) (37). In another retrospective study, Isono *et al.* reported similar results (38). Though pre-existing idiopathic interstitial pneumonia was associated with an increased risk of ICI-induced ILD (HR =4.350, 95% CI: 1.225–15.440, P=0.023) among other pre-existing respiratory diseases, it was not associated with poor outcomes such as low objective response rate (ORR) or shorter OS (38). In a systemic review and meta-analysis of patients with NSCLC and pre-existing ILD by Zhang *et al.*, the incidence rates of any grade and grade 3 or higher ICI-related ILD were more frequent in patients with pre-existing ILD than in those without (OR =3.23, 95% CI: 2.06–5.06, and OR =2.91, 95% CI: 1.47–5.74, respectively). The pooled ORR in patients with pre-existing ILD was better compared to those without ILD (OR =1.99, 95% CI: 1.31–3.00). The DCR and PFS were also not inferior in patients with pre-existing ILD (pooled OR =1.46, 95% CI: 0.94–2.25 for DCR). This study suggests that ICI treatment is effective in prognosis of

NSCLC patients with pre-existing ILD, even though more frequent development of ICI-related ILD is observed (55).

Management of ICI related ILD

The primary treatment for ICI-related ILD is steroid therapy. For patients with steroid-resistant ICI-related ILD, several treatment options such as intravenous immunoglobulin (IVIG), IL-6 receptor inhibitors, TNF-inhibitors, or immunosuppressants can be considered. However, no standard treatment is currently established (56,57).

The guideline for managing irAEs in patients with ICI therapy by the American Society of Clinical Oncology recommends that the treatment should differ according to the toxicity grade. In grade 1 (mild) asymptomatic patients, close observation is needed unless there is evidence of progression or no improvement. Discontinuing ICI and corticosteroid treatment are not necessary in these patients. In grade 2 (moderate) patients, ICI treatment should be immediately stopped, and prednisolone 1–2 mg/kg/day should be administered with tapering by 5–10 mg/week over 4–6 weeks. ICI can be rechallenged after ILD improves. In grade 3 to 4 (severe) patients who need oxygen therapy, ICI treatment should be immediately withheld, and empirical antibiotics and (methyl)prednisolone IV 1–2 mg/kg/day should be administered. Other drugs such as infliximab 5 mg/kg, mycophenolate mofetil IV 1 g twice a day, IVIG for 5 days, or cyclophosphamide can be added if there is no improvement after 48 h. They recommended that ICI should be permanently discontinued in these patients (58,59). In a retrospective study of patients with NSCLC treated using nivolumab in Japan, corticosteroids were administered in more than 80% of the study patients to treat nivolumab-induced ILD. Most patients responded well to corticosteroids, even in relapse cases. Starting doses of corticosteroids varied from 0.5 to 2.0 mg/kg/day to pulse therapy. Better outcomes were observed in patients receiving more than 28 days of corticosteroid treatment (60).

Steroid-resistant cases

In some cases, steroids can show poor response, and other treatment modalities should be considered. A case report described a patient with newly-developed ILD after initiating pembrolizumab improved after five days of corticosteroid and nintedanib treatment (150 mg twice daily) (61). In another case report of steroid-refractory ICI-related ILD, a patient with nivolumab-induced ILD after receiving concurrent chemoradiotherapy and lobectomy showed improvement with initial steroid treatment (2 mg/kg intravenous methylprednisolone for 3 days, followed by 1 mg/kg/day oral prednisolone). However, ILD relapsed after conversion to oral prednisolone. Thus, the patient received one dose of 5 mg/kg intravenous infliximab and kept on 1 mg/kg/day of oral prednisolone. ILD resolved both clinically and radiologically after one month (62).

In another case of steroid-resistant ICI-related ILD, the patient was initially treated with methylprednisolone (100 mg/12 h), immunoglobulin, and antibiotics. However, the symptoms were aggravated. There was no significant improvement despite tocilizumab (8 mg/kg, iv), and tacrolimus treatment, as well as tocilizumab readministration. However, adding pirfenidone as antifibrotic treatment significantly reduced the patient's symptoms and oxygen demand (56).

One case suggested that triple combination therapy, consisting of high-dose corticosteroids, tacrolimus, and cyclophosphamide, is effective in a patient who developed ICI-related ILD after receiving pembrolizumab (63).

In a case series of 12 patients with steroid-refractory ICI-related ILD, patients were treated with IVIG (n=7), infliximab (n=2), or combination of IVIG and infliximab (n=3). The group treated with IVIG showed lower mechanical ventilation requirement rates (25%), while infliximab group and a combination therapy group showed rates of 53% and 80%, respectively. The mortality of IVIG group was lower (43%) than infliximab alone group (100%) (64).

Rechallenge

In a retrospective study of cancer patients with ICI-related ILD, ICI was rechallenged in 10 (17.2%) patients including 9 patients with NSCLC. Among them, ICI-related ILD did not recur in 7 patients. Three patients (2 patients with grade 2 and 1 with grade 1) who developed a second event of ICI-related ILD also recovered after drug discontinuation and corticosteroid treatment (65).

Shibaki *et al.* reported 2 cases (1 patient with grade 1 and 1 with grade 2) who restarted anti-PD-1 antibody, and neither patient showed relapse of ICI-related ILD (36).

In a retrospective study by Naidoo *et al.*, among 43 patients (including 9 patients with NSCLC) who developed ILD after anti-PD-1/PD-L1 treatment, 12 patients (9 patients with grade 1 and 3 with grade 2) were retreated with immunotherapy. Three patients (1 patient with grade 1 and 2 with grade 2) developed recurrent ICI-related ILD, and all patients recovered after drug discontinuation and corticosteroid therapy (66).

Sato *et al.* retrospectively analyzed the outcomes of subsequent systemic cancer therapy in NSCLC patients who developed ICI-related ILD. Among 32 (14%) patients who experienced ICI-related ILD due to anti-PD-1 therapy, 16 (50%) patients received subsequent systemic cancer treatment including chemotherapy and ICI. The median OS was longer in the patients with systemic cancer therapy than those without, but it was not statistically significant (22.2 *vs.* 4.5 months, P=0.067). The ICI-related ILD recurred in 50% of systemic cancer therapy group, and median OS was shorter in patients with recurrent ICI-related ILD, though there was no statistically significant difference (22.2 *vs.* 7.0 months, P=0.3154) (67).

As there is no definite consensus on rechallenging ICI in patients who experienced ICI-related ILD, ICI rechallenge needs careful consideration based on the severity and conditions of each patient (68). Corticosteroid treatment with immediate discontinuation of ICIs is essential for grade 2 or higher (moderate to severe) ICI-related ILD. ICI can be restarted in grade 2 after a sign of improvement, while ICI rechallenge is usually not recommended in grade 3 (severe) or higher-grade ICI-related ILD. Subsequent systemic cancer therapy after resolution of ICI-related ILD might improve survival outcomes, however, recurrence of ICI-related ILD should be monitored. In cases of steroid-refractory ICI-related ILD, administration of other immunosuppressants can be considered.

Conclusions

ICI-related ILD is relatively common in the real world and can be fatal. Patients with possible risk factors such as pre-existing pulmonary diseases, prior pneumonitis, and poor lung function should be closely monitored for the development of ICI-related ILD. If the patient manifests with ICI-related ILD, prompt management is necessary.

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Footnote

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