



Management of pulmonary toxicity associated with immune checkpoint inhibitors

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Immune-related lung toxicity can be life-threatening. Early recognition and management including CT scan and bronchoscopy should be encouraged. Treatment mainly relies on steroids. In addition, re-challenge should be discussed in multidisciplinary boards. <http://bit.ly/2WNYH8I>

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ABSTRACT Immunotherapy has become a standard of care in oncology, following the recent approvals of cytotoxic T-lymphocyte-associated protein-4 and programmed cell death-1 inhibitors in lung cancer, melanoma, renal cell carcinoma, Hodgkin's lymphoma, bladder, head and neck cancers. Besides their efficacy, these agents also generate specific immune-related adverse events. Due to the increasing prescription of immune-checkpoint inhibitors, the incidence of immune toxicity will continue to rise. The awareness of immune-related adverse events is key to ensuring both diagnosis and management of the possible serious adverse events. Although severe immune-related adverse events remain rare, they can lead to discontinued treatment or to death if they are not forecasted and managed properly. Even if lung toxicity is not the most frequent adverse event, it remains critical as it can be life-threatening. Herein, the main aspects of pulmonary toxicity are reviewed and guidelines are also proposed in order to manage the possible side-effects.

Introduction

Anti-tumour immunotherapy and especially immune-checkpoint inhibitors (ICIs) now take part in the therapeutic strategy of non-small cell lung cancer (NSCLC) and other advanced solid tumours [1–3]. Therefore, due to the increasing use of ICIs, many oncologists may face side-effects.

ICIs present a favourable overall benefit-to-risk profile; however, they are linked to specific toxicities in terms of mechanisms of action, known as immune-related adverse events, greatly differing from the toxicities observed with conventional cytotoxic chemotherapies or targeted therapies. An immune-related adverse event may potentially affect any tissue but the skin, endocrine system, gastrointestinal tract or lung are the most commonly involved [4]. To date, no guidelines have been specifically provided for lung toxicity. According to the literature and considering our work and expertise as pulmonologists, radiologists and oncologists our objective is to highlight lung toxicity and share our experience on its management.

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What is the incidence of pulmonary toxicity associated with ICI treatment?

Cases of interstitial lung disease (ILD) induced by ICIs (ICI-ILD) have been reported since the first clinical trials on both anti-programmed cell death (PD)-1 and anti-programmed death-ligand (PD-L)1 antibodies. According to a meta-analysis, the overall ICI-ILD incidence was 2.7% for all grades and 0.8% for the most severe grades (grade ≥ 3). The overall incidence of ICI-ILD for all grades was between 1.4% and 5.8% in NSCLC studies, whereas in melanoma studies it was between 1% and 4.4% and in renal cell carcinoma studies it was between 2.7% and 4.8% [5]. According to our daily practice, three recent series have shown higher ILD incidences (3.5%, 5% and 11.8%, respectively) [6–8]. It is well known that the incidence increased in patients treated with combination immunotherapy as observed in melanoma trials. The incidence of pneumonitis was higher in combination regimens (including nivolumab and ipilimumab, given concurrently or sequentially, or nivolumab plus peptide vaccines) than in monotherapy (6.6%) [5]. However, a combination of immunotherapy (pembrolizumab) with chemotherapy was not linked to an increased risk of pneumonitis in lung cancer [9]. Moreover, the administration of immunotherapy (durvalumab) after chemoradiation in patients with locally advanced NSCLC was related to an acceptable rate of lung toxicity (3.4% grade 3/4 *versus* 2.6% in the placebo arm) [10, 11].

Can we forecast or predict pulmonary toxicity?

Before prescribing ICIs, it is important to identify the potential risk factors that may favour ICI-ILD.

ILD appeared to be more frequent in patients with NSCLC than in patients with melanoma (4.1% *versus* 1.6%, $p=0.002$), with an earlier time to onset [8]. Tobacco smoke exposure or chronic lung diseases in patients with lung cancer could explain this difference. Lung tumour burden may also limit pulmonary endurance to external stress factors and promote pulmonary toxicity [11].

The following study assessed nivolumab safety in patients with NSCLC and idiopathic interstitial pneumonia. It included six patients and none of them developed any grade of pneumonitis; however, this result should be confirmed in a larger cohort [12]. Other parameters, such as COPD or a radiotherapy history, which are often associated with a higher risk of pneumonitis in patients receiving epidermal growth factor receptor tyrosine-kinase inhibitors, have not been identified to date for ICIs. Thoracic radiotherapy may increase local inflammation and release tumour antigens into pulmonary tissues and thus potentiate pulmonary toxicity [13]. It is important to monitor respiratory functions before starting immunotherapy in patients with COPD. Another meta-analysis suggests a higher incidence of any grade of toxicity and greater severity of ILD with anti-PD-1 treatment compared with anti-PD-L1 [14]. The sparing of PD-1/PD-L2 interactions with PD-L1 inhibitors may explain this finding [15]. The previous meta-analysis also highlights a significantly higher rate of all-grade pneumonitis in treatment-naïve patients [14]. This area needs further investigation in the light of recent US Food and Drug Administration (FDA) approval of first-line chemotherapy (either as single agent or in combination with chemotherapy). As the incidence is also higher with combined treatments rather than monotherapy, patients treated with bi-therapy (anti-PD-1 and anti-cytotoxic T-lymphocyte-associated protein (CTLA)-4) need close clinical and radiological follow-up [5].

Dysimmune diseases are usually contraindications for immunotherapy, except for type 1 diabetes, for hypothyroidism requiring treatment only with hormonal substitution and skin diseases requiring only topical treatment (*e.g.* vitiligo and psoriasis). JOHNSON *et al.* [16] evaluated immune-related adverse event frequency in a retrospective review of patients treated for advanced melanoma with ipilimumab and with pre-existing autoimmune disorders. They included 30 patients with autoimmune disorders such as systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, psoriasis and autoimmune thyroiditis. A total of 50% of patients presented with neither autoimmune disease flares nor immune-related adverse events. Overall, 27% of patients needed steroid treatment due to autoimmune disease exacerbations. 33% of patients presented with grade 3 to 5 immune-related adverse events (especially colitis, hypophysitis and thyroiditis) being reversible with corticotherapy and, in two cases, with infliximab [16]. MENZIES *et al.* [17] included 52 patients with advanced melanoma treated with anti-PD-1 and pre-existing autoimmune disorders (such as rheumatoid arthritis, Sjogren's syndrome, immune thrombocytopenic purpura and psoriasis). Furthermore, 38% showed other flare autoimmune disorders and 29% had other immune-related adverse events. Only six patients needed to discontinue the treatment (two due to flares and four due to new immune-related adverse events) and there were no treatment-related deaths [17]. More recently, LEONARDI *et al.* [18] identified 56 patients with NSCLC treated with anti-PD-L1 with an autoimmune disease. An autoimmune disease exacerbation occurred in 13 (23%) patients and four of them needed systemic steroids. A total of 21 (38%) patients developed a mild immune-related adverse event (74% grade 1–2) and eight patients required steroids [18]. Therefore, immunotherapy may be considered in patients with immune disorders with a very close follow-up; however, the results need to be confirmed in prospective studies.

Other potential risk factors for dysimmunity should be identified, such as opportunistic pathogenic agents, drugs or occupational exposures. Before initiating ICIs, thorough research of family or personal medical history is required to screen potential autoimmune disorders.

Finally, no biomarker predicting the occurrence of lung toxicity has been identified to date.

How to diagnose ILD associated with ICI treatment?

Time to onset and symptomatology

ICI-ILD symptoms remain unspecific, therefore differential diagnoses are possible. Clinicians should beware of lately appearing respiratory symptoms while treating patients with ICIs. Alerting clinical signs are usually a dry cough, progressive dyspnoea and fine inspiratory crackles. As most cases of ICI-ILD occur during the first 2 months of treatment, clinicians should pay particular attention to the start of treatment.

NISHINO *et al.* [8] described ICI-ILD in 20 patients (10 cases of melanoma, six of lymphoma and four of NSCLC) with a median time to onset of 2.6 months. In a study performed by NAIDOO *et al.* [19], 43 cases of ICI-ILD were assessed, most of them with presenting melanoma (n=26) or NSCLC (n=9), the median time to onset was 2.8 months. We carried out a study in 24 centres including stage IV NSCLC (n=48), metastatic melanoma (n=13) and three other types of cancer, showing that ICI-ILD occurred in 3.5% (64 out of 1826 cases). The median time to onset was 2.3 months and was significantly earlier in patients with NSCLC (2.1 months) than in patients with melanoma (5.2 months) ($p=0.02$) (table 1) [6].

Radiological patterns

The main differential diagnoses are tumour progression, pulmonary infections and, in cases of dyspnoea, pulmonary embolism. Thus, we highly recommend performing a high-resolution computed tomography (CT) scan with a contrast agent to rule out differential diagnoses and provide evidence for ICI-ILD. In these cases, CT scan changes mainly include ground-glass opacities and condensations [8]. In the series by NISHINO *et al.* [8], radiological analysis found an organising pneumonitis pattern in 65.5%, nonspecific interstitial pneumonitis pattern in 15%, and hypersensitivity pneumonitis pattern in 10%. According to NAIDOO *et al.* [7], the most frequent patterns were ground-glass opacities in 37%, organising pneumonitis in 19%, and hypersensitivity pneumonitis pattern in 22% .

In our study, we found organising pneumonitis pattern in 23%, hypersensitivity pneumonitis in 16% and no suggestive pattern in 36% [6]. Most of the representative radiological patterns are presented in figure 1. Comparisons between these three studies are detailed in both table 1 and figure 2. The imaging findings follow the classification of interstitial pneumonia according to the American Thoracic Society/European Respiratory Society classification [20]. The organising pneumonitis pattern was defined by peripheral consolidations and air bronchograms as the main CT features. The nonspecific interstitial pneumonitis pattern was defined by several CT scan features, such as ground-glass opacities with marked traction bronchiectasis. Peribronchovascular predominance with subpleural sparing is also described. Furthermore, the hypersensitivity pattern is shown by centrilobular nodules or a bronchiolitis-like appearance [8, 20].

TABLE 1 Comparison between the three studies

Study	NAIDOO <i>et al.</i> [7]	NISHINO <i>et al.</i> [8]	DELAUNAY <i>et al.</i> [6]
Cases n	43	20	64
Histology	26 Melanoma 9 NSCLC 4 Haematological malignancies 1 Bladder carcinoma 1 Breast carcinoma 1 Pancreatic carcinoma 1 Head and neck carcinoma	10 Melanoma 4 NSCLC 6 Lymphoma	13 Melanoma 48 NSCLC 1 Lymphoma 2 Head and neck carcinoma
Incidence	5%	11.8%	3.5%
Time to pneumonitis onset	2.8 months (9 days to 19.2 months)	2.6 months (0.5–11.5)	2.3 months (0.2–27.4)

Data presented as median (range), unless otherwise stated. NSCLC: nonsmall cell lung cancer.

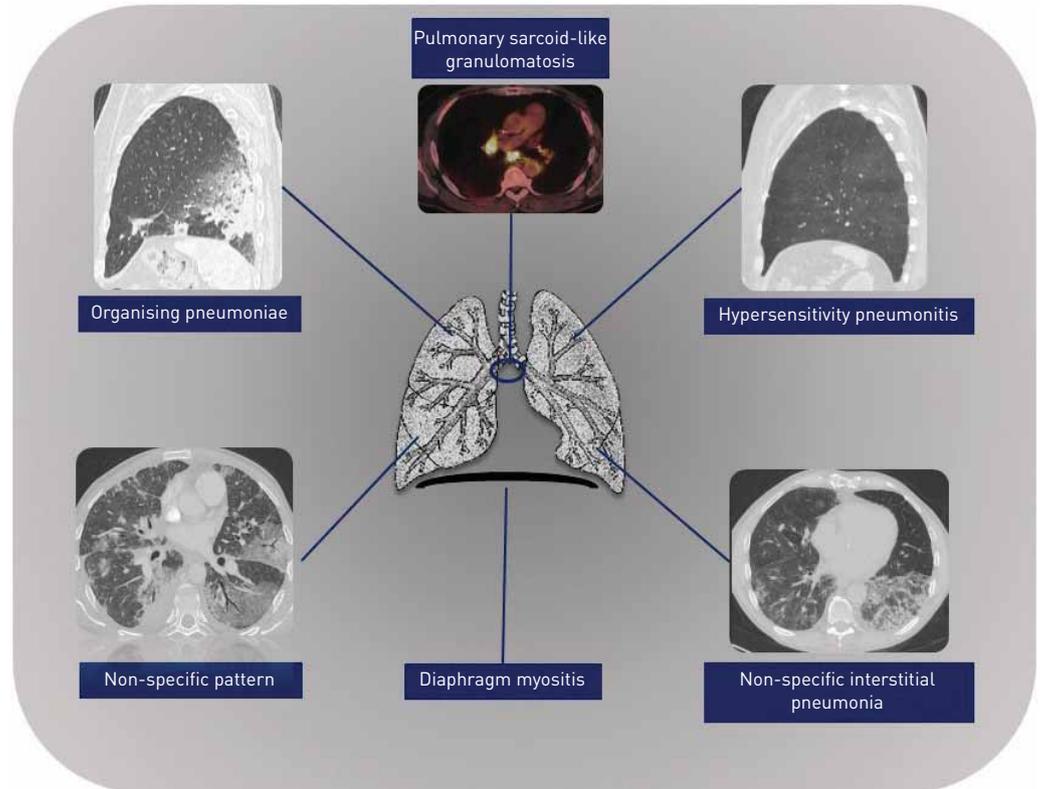


FIGURE 1 Main respiratory toxicities linked to immunotherapy.

Cytopathological criteria

We recommend the early use of bronchoscopy to obtain a bronchoalveolar lavage. Distal biopsies may also help to rule out differential diagnosis, such as infection or tumour progression, as well as provide evidence regarding ICI-ILD, such as a high percentage of lymphocytes and a T-cell infiltrate (figure 3). In our series, we found a predominance of lymphocytes in bronchoalveolar lavages, and biopsies showed lymphocytic infiltration [6]. Some case reports have shown an increase in activated T-cells in the bronchoalveolar lavage of patients with organising pneumonia. This cell population may be involved in this complication pathogenesis [21]. Histopathological findings, when possibly reached, were numerous: cellular interstitial pneumonitis, organising pneumonia, diffuse alveolar damages, and sometimes no specific abnormalities were identified [7, 8, 22].

The high number of lymphocytes contained in bronchoalveolar lavage fluid and the rapid clinical improvement after administration of systemic steroids or treatment withdrawal suggests an immune-mediated mechanism for ILD [23]. The European Society for Medical Oncology (ESMO) recommendations state that a surgical lung biopsy using video-assisted thoracoscopic surgery may be used to secure specific diagnosis [24]. We suggest that transbronchial per-endoscopy biopsies should instead be recommended according to the 2018 American Society of Clinical Oncology (ASCO) clinical practice guidelines [25]. In typical cases, early steroid treatment without invasive procedures may be proposed. Anyway, both biopsy indications and the selection of the most accurate procedures should be discussed within a multidisciplinary board that includes pulmonologists.

How to treat ILD-ICI

There are no validated recommendations for ICI-ILD treatment, and patient management is currently guided by both clinical experience and trial guidelines. Both the Society of Immunotherapy of Cancer (SITC) and the ASCO have provided a definition on how to establish the severity grades [26]. Recently, the ASCO developed clinical practice guidelines based on expert consensus. The grading of pneumonitis was based on Common Terminology Criteria for Adverse Events definitions. Grade 1 was defined by an asymptomatic aspect, grade 2 by a symptomatic aspect as a limiting instrumental activities of daily living (ADL) and indicated medical intervention, grade 3 by severe symptoms limiting self-care ADL and indicated oxygen, and grade 4 by life-threatening respiratory compromise and indicated urgent intervention [25]. Moreover, according to the ESMO, the severity grade of pneumonitis was defined as

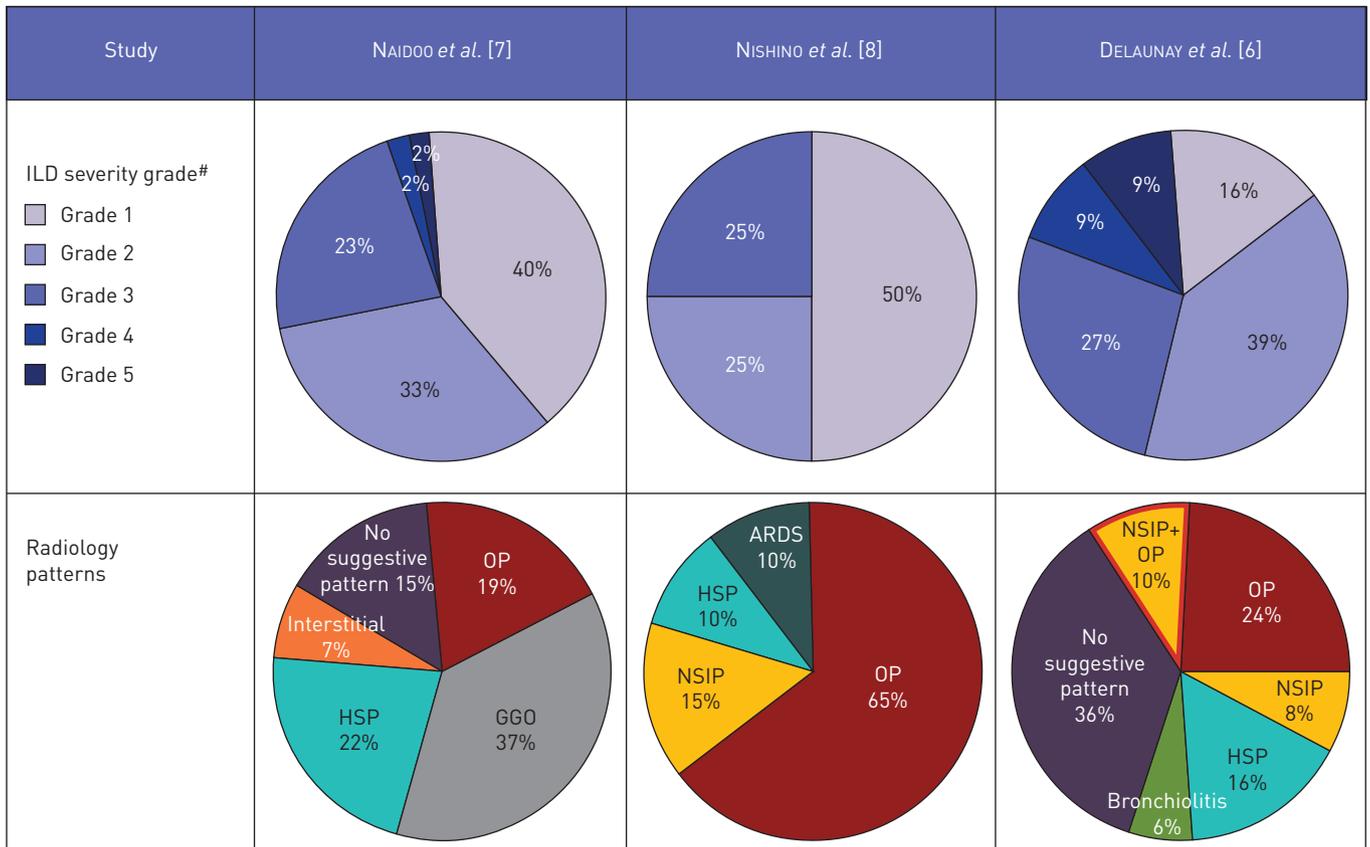


FIGURE 2 Comparison between three studies: severity grade and radiological patterns. OP: organising pneumoniae; HSP: hypersensitivity pneumonitis; NSIP: non-specific interstitial pneumoniae; GGO: ground-glass opacities; ARDS: acute respiratory distress syndrome. #: Common Terminology Criteria for Adverse Events 4.0.

follows: grade 1 radiographic changes only; grade 2 mid/moderate new symptom occurrence (dyspnoea, cough and chest pain); and grade 3 and 4 severe new symptoms (new or worsening hypoxia, threat to life and breathing difficulties) [24].

Nowadays, ICI-ILD treatment is based on systemic steroids, as suggested in clinical trials, and is based on drug-related interstitial pneumonitis treatment [27]. For asymptomatic grade 1 we suggest either a close follow-up or low-dose steroids (0.5–1 mg·kg⁻¹). For grade 2, steroids may systematically be proposed at 1–2 mg·kg⁻¹ per day as recommended by the 2018 ASCO Guidelines [25]. Immunotherapy may be reconsidered if the toxic event recovers without complications. For grade ≥3, a higher dose of steroids (2–4 mg·kg⁻¹) is recommended with drug holding. An intravenous steroid bolus may be considered for the most severe cases. Regarding any grade, CT monitoring should be proposed (figure 4). Steroid tapering should be conducted very slowly and carefully over ≥6 weeks, as relapses of pneumonitis were reported during this period. It seems necessary to consider a longer period of corticosteroid taper (>6 weeks) in order to avoid relapse. Moreover, according to the literature, it seems that if the pneumonitis episode is more severe (higher than grade 3) relapse occurs prematurely and mostly in cases where the treatment length is shorter (<5 weeks) [28, 29].

In cases of organised pneumonia, the treatment could be similar to the cryptogenic form of the disease [30]. Some examples of improvement after treatment are shown in figure 5.

Immunosuppressive drugs, such as infliximab or cyclophosphamide, have been proposed in clinical trials and initially approved by the US FDA for patients receiving ipilimumab, and especially for digestive toxicities such as colitis. A recent case report suggests that an interleukin-17 blockade may provide relief from immune-mediated skin and gastrointestinal toxic effects [31]. However, no data are currently available for either immunosuppressive drugs (especially infliximab or cyclophosphamide) or specific inhibition of interleukin-17 for ICI-ILD treatment.

In the series by NAIDOO *et al.* [19], immunosuppressive drugs were administered to five patients when high-dose steroids were insufficient; however, the use of an immunosuppressive drug may trigger a risk of

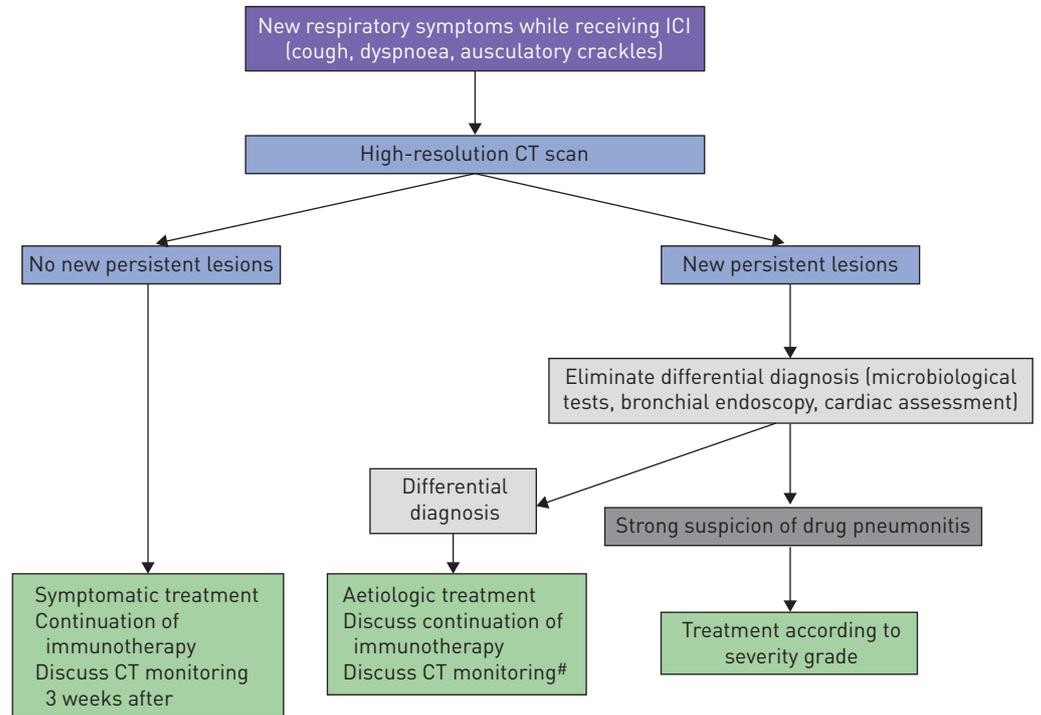


FIGURE 3 Suggested “decision tree” for interstitial lung disease induced by immune-checkpoint inhibitors (ICI) treatment. CT: computed tomography. #: progressive cancer lesions, infection, pulmonary embolism or heart failure.

infection. In their series, three out of five patients treated with anti-tumour necrosis factor (TNF), died as a consequence of sepsis: one from *Pseudomonas aeruginosa*, one from herpes simplex virus infection, and another one from mucormycosis [19]. SITC, ASCO and ESMO also suggest considering infliximab (5 mg·kg⁻¹), mycophenolate mofetil intravenously (1 g twice a day) or cyclophosphamide if there is no clinical improvement after steroids and supportive care [24–26]; however, the risk of infection and lung

Severity grade (CTCAE 4.0)#	Grade 1	Grade 2	Grade 3	Grade 4
Immunotherapy treatment				
Corticosteroids		 (0.5–1 mg·kg ⁻¹)	 (2–4 mg·kg ⁻¹)	 (4 mg·kg ⁻¹ bolus i.v.)
Rechallenge				
TDM monitoring				

FIGURE 4 Suggested management according to severity grade. Grade 1: asymptomatic, clinical or diagnostic observation only; intervention not indicated; Grade 2: symptomatic, medical intervention indicated; limiting instrumental activities of daily living; Grade 3: severe symptoms; limiting self-care activities of daily living, oxygen indicated; Grade 4: life-threatening respiratory compromise; urgent intervention indicated (e.g. tracheotomy or intubation). #: a disorder characterised by inflammation focally or diffusely affecting the lung parenchyma.

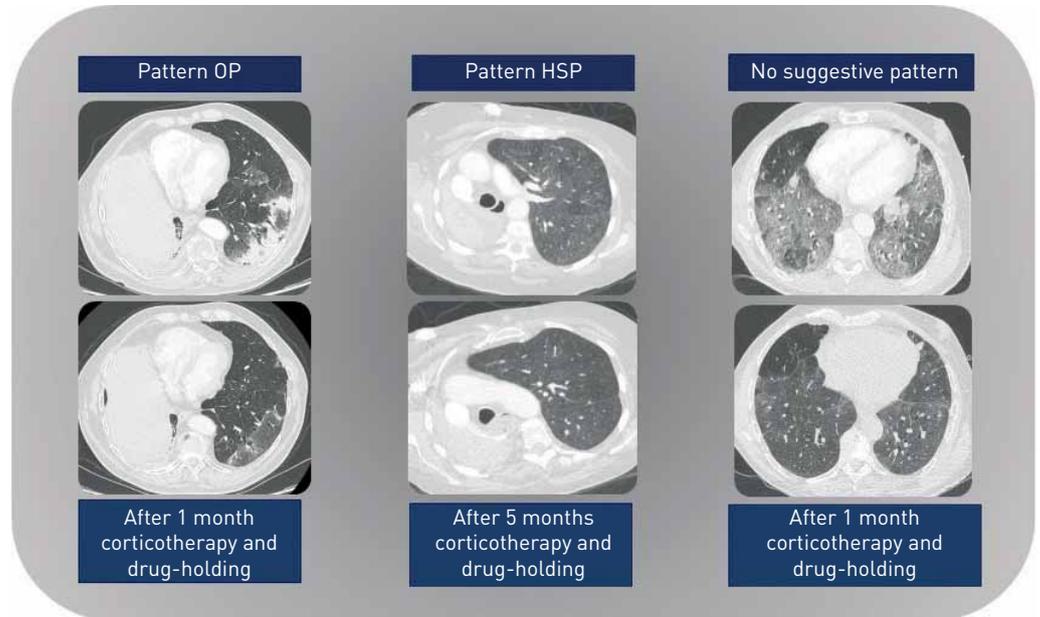


FIGURE 5 Interstitial lung disease induced by immune-checkpoint inhibitors improvement after treatment. OP: organising pneumoniae; HSP: hypersensitivity pneumonitis.

toxicity caused by anti-TNF drugs and the lack of knowledge on pathophysiological mechanisms of ICI-ILD make the use of this biotherapy particularly complex. This use should be discussed within a multidisciplinary board. Moreover, prophylactic antibiotherapy may be considered after microbiological assessments. If immunosuppression is prolonged, *Pneumocystis* prophylaxis also needs to be considered.

Can we re-challenge patients with immunotherapy following lung toxicity?

NAIDOO *et al.* [19] reported on 12 patients who were re-challenged. Overall, nine patients experienced no second event of pneumonitis while being re-challenged (eight were initially grade 1 and one was grade 2), and three experienced recurrent pneumonitis (one grade 1 and two grade 2).

We also reported on 10 patients who restarted immunotherapy. All re-challenged cases occurred after clinical resolution of pneumonitis. Among our 10 patients, recurrent ILD was observed in three cases. The second episode was successfully assessed by suspended ICI treatment plus steroids [6]. A recent retrospective study aimed to show the safety and benefit of retreatment following immune-related adverse events. When 68 out of 482 patients with NSCLC treated with anti-PD-L1 developed an immune-related adverse events they required treatment discontinuation; among these patients, 38 were retreated. Recurrent immune-related adverse events were more frequent when the initial immune-related adverse events required hospitalisation [32]. There is no established recommendation for a re-challenge, and options should be discussed by a multidisciplinary board, taking into account the expected benefits and risks for each patient.

Other pulmonary toxicities

Sarcoid-like granulomas induced by ipilimumab, nivolumab and pembrolizumab have been reported and are probably underestimated [33, 34]. The radiological patterns are variable: from multiple pulmonary micronodular opacities or ground-glass infiltrates in subpleural and perihilar parenchyma to lymph node enlargement. Histologic examination could demonstrate non-necrotising granulomas [35]. This immune reaction may induce granulomas with epithelioid and giant cells surrounded by a ring of CD4⁺ and CD8⁺ T-lymphocytes. The bronchoalveolar lavage typically demonstrates lymphocytic alveolitis with increased CD4:CD8 ratios. Organising pneumonia is characterised by lymphocytic interstitial inflammation [33]. Both of these entities occur from a T-helper-1 uncontrolled immune response but usually do not coexist. These results suggest, once again, an immune-mediated mechanism of toxicity.

Two cases of diaphragm myositis were reported with anti-PD-1 monotherapy and with a combination of anti-CTLA-4 and anti-PD-1 therapy. In the first case, anti-PD-1 treatment induced fatal respiratory failure with necrotising myositis of the diaphragm [36]. In the second case, this combination treatment induced fatal progressive hypoventilation [37].

Notably, two cases of tuberculosis have been reported in patients who were treated with anti-PD-1 agent for lymphoma and NSCLC [38]. A very recent study reported tuberculosis reactivation in patients treated with anti-PD-1 and suggested an immune reactivation syndrome [39].

Finally, one case of recurrent allergic bronchopulmonary aspergillosis has been reported [40]. The authors described that elevated serum immunoglobulin (Ig)E (up to $2514 \text{ kU}\cdot\text{L}^{-1}$), and positive *Aspergillus fumigatus* IgE antibodies were consistent with a diagnosis of allergic bronchopulmonary aspergillosis. The patient was treated with both itraconazole and steroids that rapidly improved his condition.

What is the impact of immune-related adverse events on patient outcomes?

Whether immune-related adverse events are associated with clinical outcome remains unclear. Retrospective studies have found higher rates of disease control in patients who experienced immune-related adverse events [41]. A study assessed the benefit of atezolizumab (an anti-PD-L1 treatment) in patients with and without immune-related adverse events in the primary efficacy population (n=850). Overall survival favoured patients who received atezolizumab and presented immune-related adverse events *versus* those who did not (HR 0.79, 95% CI 0.60–1.05) [42]. A recent prospective study included 38 patients with advanced NSCLC treated with anti-PD-1. In this study, patients with immune-related adverse events presented a higher objective response rate (63.6% *versus* 7.4% $p < 0.01$) and longer progression free-survival (HR 0.10, 95% CI 0.04–1.46; $p = 0.13$) [43].

These results should be confirmed because the correlation between toxicity and longer survival may be due to a lead-time bias. In other words, patients whose tumours progress show a higher mortality rate, whereas those who respond to immunotherapies have a longer treatment duration and are more likely to develop immune-related adverse events [44].

Organisation

Patients should be informed that most immune-related adverse events are reversible if they are detected early and specifically addressed. However, patients need to beware of the warning signs for the major organ toxicities linked to ICIs. Educational therapeutic programmes can optimise toxicity management. We also propose that each centre sets up a specialists' network that can manage the most frequent side-effects. Such a collaborative initiative could standardise and facilitate immune-related adverse event management, and this has already been reported in some centres, such as the Gustave Roussy Cancer Center (Villejuif, France) [45]. Moreover, local, regional or national dedicated boards specialised in immune-related adverse events are also very useful at collecting data and may guide patients towards the best strategies. Large registries and international efforts are also essential to avoid less frequent side-effects.

Conclusion

Lung toxicities associated with ICI treatment are not exceptional. They usually occur during the first few months and are linked to nonspecific clinical symptoms but have suggestive radiological signs. Awareness of radiological patterns and clinical manifestations of ICI-ILD are necessary to rapidly diagnose and treat these possible serious events. Endoscopy, including bronchoalveolar lavage and transbronchial lung biopsies can refine a diagnosis by excluding pulmonary infection and showing lymphocytic alveolitis.

Additional studies are required to further understand the clinical characteristics and chronology of these adverse effects and to clarify the mechanism(s) leading immunotherapy to cause these immune-related events.

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