






Immune checkpoint inhibitor-associated interstitial lung diseases: some progress but still many issues

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Immune checkpoint inhibitor use is increasing so clinicians must be aware of autoimmune complications especially ILD <http://ow.ly/UCQU30dkg2M>

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Immunotherapy for cancer management is an old concept in which therapeutic agents are used to modulate immune cells rather than directly target cancer cells. However, it is the recent discovery of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), and programmed cell death protein (PD-1) and its ligand PD-L1 that represents the latest major advance in cancer therapy. Immune checkpoint inhibitors (ICIs) are monoclonal antibodies blocking CTLA-4 (ipilimumab and tremelimumab), PD-1 (nivolumab and pembrolizumab) and PD-L1 (atezolizumab, durvalumab and avelumab). By unbalancing the immune system, immune checkpoint blockade also has a specific set of toxicities by favouring the development of dysimmune manifestations, also termed immune-related adverse events [1].

Multiple organ systems can be affected by immune-related adverse events including the skin, gastrointestinal tract, liver, kidney, endocrine glands, nervous system, musculoarticular system, eyes, heart and haematologic cells [2]. Consistently, pulmonary toxicity was not rare, sometimes serious and potentially life-threatening. In a recent meta-analysis including >4000 patients from 20 PD-1 inhibitor trials (nivolumab or pembrolizumab), NISHINO *et al.* [2] estimated an overall incidence of pneumonitis during PD-1 inhibitor monotherapy to be 2.7% (95% CI 1.9–3.6%) for all grades and 0.8% for grade ≥ 3 [2]. This study importantly highlighted the incidence of pulmonary immune-related adverse events but was not designed to characterise the presentations of these pulmonary complications. Indeed, the term “pneumonitis”, usually used for lung immune-related adverse events, covers a wide and overlapping spectrum of pulmonary manifestations. In this context, the study by DELAUNAY *et al.* [3] brings major additional information to this field regarding the presentation, management and evolution of what are referred to as ICI-associated interstitial lung diseases (ILDs).

Indeed, this series represent the largest series of well-defined ICI-ILDs with a systematic assessment of clinical and radiological findings [3]. The estimate of overall incidence was 3.5%, which is consistent with

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recent meta-analyses [2, 4]. ICI-ILD is characterised by an early onset, usually in the 2 months following initiation of immunotherapy. Disturbingly, ICI-ILD is also characterised by a very wide range of clinical and radiological presentations. The most common pattern was organising pneumonia but this represented only a quarter of cases, followed by hypersensitivity pneumonitis, nonspecific interstitial pneumonia and bronchiolitis [3]. Notably, it was not possible to describe a suggestive pattern in a third of the patients. This variability in presentation, in conjunction with previous reports of sarcoidosis-like manifestations [5], suggests an individual-specific pulmonary response to a common initial trigger (*i.e.* an ICI). In this study, a significant proportion of patients underwent bronchoalveolar lavage (>50%), allowing the authors to confirm its potential role in the diagnosis of ICI-ILD since T-lymphocytic alveolitis was found in 80% of cases [3]. Even if the mechanisms of ICI-ILD are not clearly demonstrated, these results infer a deregulation of T-cells as supported by pathological assessments showing evidence of inflammation and lymphocytic infiltration [3].

Identification of risk factors for ICI-ILD is essential to screen patients at higher risk and to increase awareness of this potential life-threatening complication. The risk of immune-related adverse events in patients with pre-existing autoimmune diseases is largely unknown since these diseases usually represent a contraindication to ICI use. A complete personal and family medical history is thus required to screen potential autoimmune disorders before ICI initiation. In the meta-analysis published by NISHINO *et al.* [2], multivariable analysis demonstrated significant higher odds of pneumonitis in non-small cell lung cancer (OR 1.43, 95% CI 1.08–1.95) and renal cell carcinoma (OR 1.59, 95% CI 1.32–1.92), as compared to melanoma. Pneumonitis-related deaths were mainly observed in patients with non-small cell lung cancer [2]. The higher incidence and severity of pneumonitis in non-small cell lung cancer may be explained by an increased susceptibility due to frequent tobacco exposure and/or underlying chronic respiratory diseases (chronic obstructive pulmonary disease, pulmonary fibrosis and tumoural involvement). DELAUNAY *et al.* [3] reported a high proportion of current or ex-smokers (80%) with a median smoking history of 40 pack-years in ICI-ILD.

There are very few data comparing the risk of immune-related adverse events according to different ICIs. The CTLA-4 inhibitor ipilimumab has been associated with pneumonitis [6]. In the meta-analysis published by NISHINO *et al.* [2], combination therapy with nivolumab and ipilimumab for melanoma was associated with higher odds of all-grade (OR 2.04, 95% CI 1.69–2.50) and grade ≥ 3 pneumonitis (OR 2.86, 95% CI 1.79–4.35) than monotherapy, suggesting a synergic toxic effect. KHUNGER *et al.* [4] recently published a meta-analysis (19 trials in 5038 patients) comparing the incidence of pneumonitis in trials with PD-1 or PD-L1 inhibitors in non-small cell lung cancer. Pneumonitis was more frequently reported in patients receiving PD-1 inhibitors than in those receiving PD-L1 inhibitors (3.6% *versus* 1.3% for all grades and 1.1% *versus* 0.4% for grade ≥ 3). These observations emphasise the need to improve awareness of immune-related adverse events in patients treated with ICI for non-small cell lung cancer, especially in those receiving combination therapies.

Most of these immune-related adverse events can be managed by drug withdrawal and counteracting lymphocyte activation with corticosteroids. In cases of severe toxicity or in the absence of a response to corticosteroids, the option of additional immunosuppressive treatments should be discussed [7]. Management of ICI-ILD is probably similar and DELAUNAY *et al.* [3] reported recovery or improvement in two thirds of patients. However, ICI-ILD may be associated with high morbidity and nearly 10% of these patients died as a direct result of this complication. No patients in this series received other immunosuppressive therapy and data to support their use are lacking, although it has been suggested that infliximab may have been effective in a patient with pneumonitis related to anti-PD-1 [8]. However, lymphocyte activation by ICIs and treatment of immune-related adverse events by corticosteroids are diametrically opposed objectives, raising the issue of the potential effects of immunosuppression on cancer control.

In the vast majority of cases, severe or life-threatening immune-related adverse events necessitate the definitive discontinuation of immunotherapy. Nevertheless, the risk of recurrence with another ICI remains largely unknown. For less severe adverse events or after complete resolution, the question of ICI reintroduction could be raised. To date, there is no recommendation for dose reduction as phase I studies did not demonstrate a clear correlation between dose and immune-related adverse events [4]. In nonsevere ICI-ILD (grade ≤ 2), reintroduction of an ICI may be discussed based on individual benefit/risk ratio but data from large cohorts are lacking. In the series of DELAUNAY *et al.* [3], 10 (17.2%) patients, all with grade 1 or 2 ICI-ILD, were re-challenged for immunotherapy and only one had recurrent ILD.

The efficacy of ICI in the treatment of cancer is expected to lead to broad diffusion of these treatments in the near future and clinicians should be aware of their autoimmune complications, with an emphasis on potentially fatal ICI-ILD. Better identification of patients at risk of immune-related adverse events should

be a priority in order to limit the risk of severe complications. Diagnosis of ICI-ILD is clearly challenging because of the broad spectrum of radiological presentations and the differential diagnoses, including cancer progression, infections, co-medication-induced lung disease and unrelated complications. In the absence of evidence-based recommendations, clinicians should investigate patients for possible underlying chronic respiratory diseases and may consider performing a baseline high-resolution computed tomography of the chest before initiation of ICI. In addition, bronchoalveolar lavage and bronchial biopsies are useful to eliminate a respiratory infection or tumour progression, and document pulmonary inflammation, at the time of suspected ILD diagnosis. A better understanding of the mechanisms of ICI-ILD would be worthwhile as it may be of interest to understand the largely unknown pathophysiology of ILD in general and could lead to innovative strategies for these diseases.

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