

Pulmonary toxicities of immune checkpoint inhibitors

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Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of many malignancies. Toxicities of immunotherapy are variable, can involve almost every organ, therefore appropriate diagnosis and management of Immune Related Adverse Events (irAEs) is important. Immune-mediated pneumonitis is an uncommon, but potentially life-threatening toxicity of ICIs. Pre-existing lung disease, a history of lung radiotherapy, age >70 years and male gender are suggested as the risk factors of pneumonitis. Dyspnoea, dry cough, fever and chest pain are typical symptoms. Diagnostic algorithms recommend radiological investigation with a chest computed tomography scan. Additional diagnostic procedures – such as pulse oximetry, spirometry, measurement of carbon monoxide diffusing capacity, bronchoscopy with BAL may be helpful. The therapeutic approach is determined by the intensity of the symptoms and CT findings. Corticosteroids and antibiotics are the drugs of choice. Hospitalisation is necessary in severe cases, and other forms of immunosuppression (infliximab, mycophenolate mofetil) may be considered. Continuation of immunotherapy can be considered with caution in patients with G1–2 toxicity, when clinical improvement was achieved and steroids were tapered.

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Introduction

In recent years, immune checkpoint inhibitors (ICIs) targeting cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1/ligand-1 (PD-1/PD-L1) have been accepted in the treatment of some malignant tumours. Ipilimumab (anti-CTLA-4 antibody), nivolumab, pembrolizumab (anti PD-1), atezolizumab and durvalumab (anti PD-L1) are widely used in clinical practice in the treatment such neoplasms as melanoma, non-small-cell lung cancer, head and neck squamous cancers, urothelial carcinoma, gastric adenocarcinoma, Hodgkin's lymphoma, hepatocellular and renal cell carcinoma [1].

The ICIs affect the immune system – restore the T cell-mediated immune response – and in consequence can lead to autoimmune complications. A broad range of immune-related

adverse events (irAEs) involve almost every organ but mostly affect the endocrine system, skin, digestive system, and lung [2].

Immune-mediated pneumonitis is an uncommon but potentially life-threatening toxicity of ICIs. 35–40% deaths of fatal irAEs are connected with pulmonary complications [3].

This paper discusses the issues concerning the pulmonary toxicity of ICIs-epidemiologic data, symptomatology and diagnostic and management recommendations.

Incidence of pneumonitis

Incidence of pneumonitis in clinical trials with anti-PD-1/PD-L1 was variable – from 0% to 10% and was less common reported in trials with anti-CTLA-4- 1% [1]. The incidence was higher when combined treatment was given – nivolumab plus

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ipilimumab or ICIs with chemotherapy [4]. A meta-analysis of 23 trials involving 12,876 patients showed significant increased risk of pneumonitis related to PD-1/PD-L1 versus chemotherapy (RR, 5.64 95% CI: 1.94–16.38, $p < 0.001$) [5].

The risk of pneumonitis is higher in patients with non-small-cell lung cancer (NSCLC) than in those with melanoma (odds ratio [OR], 1.43; 95% CI, 1.08–1.89; $p = 0.005$) and higher in patients with renal cancer than patients with melanoma (OR, 1.59; 95% CI, 1.32–1.92; $p = 0.001$) [6].

A meta-analysis of 112 trials involving 19,217 patients showed all toxicity-related death rates of 0.36% (anti-PD-1), 0.38% (anti-PD-L1), 1.08% (anti-CTLA-4), and 1.23% (PD-1/PD-L1 plus CTLA-4). Pneumonitis was the most common cause of death in anti-PD-1/PD-L1-treated patients – 35% from 333 incidents [3].

Some data from clinical practice suggests that the incidence of pneumonitis related to ICPs can be more common than those reported in clinical trials. In a retrospective analysis of 205 patients with advanced NSCLC 39 (19%) patients experienced immune-related pneumonitis during follow-up and 8 of them died (20%) [7]. Another analysis of 167 NSCLC patients showed the incidences of all-grade and grade 3–4 pneumonitis at 13.2% and 4.2%, respectively, and the mortality rate was 18.2% [8]. Combined treatment has a higher risk. In NSCLC stage III, concurrent chemoradiotherapy and adjuvant immunotherapy with durvalumab is the new standard of care. The phase III PACIFIC showed significant clinical benefit, but pneumonitis occurrence was higher in durvalumab (33.6%) vs. placebo (24.9%) patients [9].

The median onset of pneumonitis symptoms ranges from 5 to 12 weeks, but it can be observed even after 24 months of therapy [1, 7]. There are no defined risk factors for irAE of respiratory tract to date, but some data are conflicting. A history of lung radiotherapy, age >70 years, male gender, smoking and low serum albumin are suggested as the risk factors for immune-mediated pneumonitis. [7, 8, 10]. In particular, interstitial lung diseases may form a background for CIP development as autoimmune mechanisms are related. In a prospective study, Fujimoto et al. presented safety of nivolumab in patients with defined mild lung fibrosis [11]. However, in another study the lung fibrosis score was found to implicate anti-PD-1 related pneumonitis [12]. The autoimmune diseases seem not to predict development of pneumonitis [13]. There was no relation between CIP incidence and the presence of antinuclear antibodies in the study on 83 NSCLC patients treated with single ICI [14].

Many patients with lung cancer suffer from chronic obstructive lung disease (COPD) and ILD, which are *per se* a risk for the development of NSCLC. The recognition of CIP in COPD or ILD is difficult, as the symptoms are very similar and may mimic exacerbation of primary disease. The doctor should know the patient and he must know himself. The course of the complication of treatment could be worse in patients with chronic lung diseases, especially in the elderly [15]. The help

of a chest physician and a multidisciplinary team in patient management is essential.

Symptoms and diagnostics

Pulmonary toxicity is referred as checkpoint inhibitors pneumonitis (CIP) [16], ICI- pneumonitis (ICI-P) [4] or some authors prefer interstitial lung diseases (ILD) to underline similarity to the group of interstitial diseases [17]. The term CIP seems to be appropriate as it includes the relationship to ICIs and involvement of parenchymal tissue. The definition of CIP includes new symptoms from the respiratory tract and new changes in chest imaging. The clinical symptoms suggestive of CIP are not specific. Thus, it is highly important for proper diagnosis to connect new symptoms in the respiratory tract with ICI use and to state a time relationship.

The distressing respiratory symptoms of CIP are: dyspnoea and cough, fever, and chest pain. They may be accompanied by desaturation in effort. In about 30% of patients, the course of CIP is asymptomatic, with only new abnormalities visible in the chest CT [18]. In differential diagnosis of the symptoms like dyspnoea, chest pain, and fatigue, other respiratory tract diseases should be taken into account. Especially a patient history including COPD, asthma, ILD, risk factors for pulmonary embolism, previous tuberculosis, and any destructive changes need to be analysed. On the other hand, other types of irAE could be responsible for these symptoms, such as: cardiovascular, neurological or endocrinological toxicity [19]. The more – pulmonary irAE could be accompanied by these.

In clinical status, assessment and the severity of symptoms are taken into account in the appropriate classification according to the Common Terminology Criteria for Adverse Events (CTCAE) grading (tab. I.). The clinical signs like tachypnoea, tachycardia, cyanosis, a range of changes in auscultation – crackles and the time of changes developing are important. Oxygen saturation measurement (and a blood gas analysis if needed) is helpful in making a decision on medical care and hospitalisation.

Chest imaging with high-resolution computed tomography (HRCT) is of great importance in the recognition of respi-

Table I. Clinical grading of pulmonary toxicity during immune checkpoint inhibitor administration (CTCAE criteria) [19]

Grade 1, mild
Asymptomatic or mild symptoms, intervention not required
Grade 2, moderate
Symptomatic, medical noninvasive intervention needed, limiting normal activity
Grade 3, severe
Respiratory symptoms limiting self-care ADL, hospitalisation, oxygen therapy indicated
Grade 4, life threatening
Required urgent intervention, intubation, ventilatory support
Grade 5
Death of irA

ratory tract ICI toxicity. A CT scan with contrast to eliminate pulmonary embolism is suggested by some authors [7].

Generally, the parenchymal infiltrations are visible with the most frequently seen ground-glass opacities, consolidations, interlobular septal thickening and intralobular lines, micronodules, bronchiectasis and architectural distortion [4, 17, 18]. The changes are often overlapping, bilateral and separated from the primary lung tumour [16]. The classification of interstitial lung diseases (ILD) has been used to describe the CIP pattern by some authors, and the nonspecific interstitial pneumonia (NSIP), cryptogenic organising pneumonia (COP) – like pattern, acute interstitial pneumonia (AIP) are mentioned [4, 17, 18]. Pleural effusion and mediastinal adenopathy are rare. The histological reports of CIP are rather scanty. However, in some histopathological reports the NSIP, COP, AIP pattern was described in the majority of cases. The special kind of pulmonary changes after ICIs is sarcoid-like granulomatosis.

Clinical symptoms and lung changes visible in CT scan in patients treated with ICI sometimes need rapid diagnosis and an immediate decision. The main direction of differential diagnosis is progression of malignant disease or infection (fig. 1). In the first step, the analysis of CT is needed to refer to the last imaging and possible progression of the primary tumour or metastases from another body site. An analysis of possible toxicity of previous treatment: chemotherapy and radiotherapy is needed. Next, a broad spectrum of microbiological tests of sputum/material from bronchoscopy or blood should be performed. After exclusion of infection, the recognition of pneumonitis is probable. The course of pulmonary complications is

very often rapid, demanding an urgent therapeutic decision. Thus, a bronchoalveolar lavage (BAL) fluid examination might be very helpful [20]. BAL is a relatively low invasive method of respiratory tract examination, and is realised by instillation to the airways and next immediate aspiration of 100–200 mL of saline via bronchofiberscope. BAL fluid analysis allows the recognition of infection (also opportunistic), the presence of malignant cells, and confirmation of interstitial lung disorder [20]. The normal constituents of BALf are macrophages, lymphocytes and granulocytes in the following proportions: 80, <20, <5%. The predominance of lymphocytes is suggestive of active non-infectious inflammation. Delauney et al performed BAL in 55% of patients with pulmonary complications and in 80% of them lymphocytic alveolitis was observed [17]. In our experience, the BALf evaluation by microscopic examination of slides stained with haematological and histological methods could be very helpful in the differential diagnosis of new lung infiltrations in the course of ICI administration. The more frequent use of flow cytometry allows the local immune response to be characterised, which could be helpful in the choice of treatment [21, 22, 23]. Very importantly, conclusive results are obtained during some hours (unpublished data).

Treatment

The therapeutic approach is determined by the intensity of the symptoms according the CTCAE – table I [24]. Extensiveness of lung changes in the CT scans might be considered an additional risk factor [25]. Careful observation of patients and an appropriate therapy started immediately after occurrence

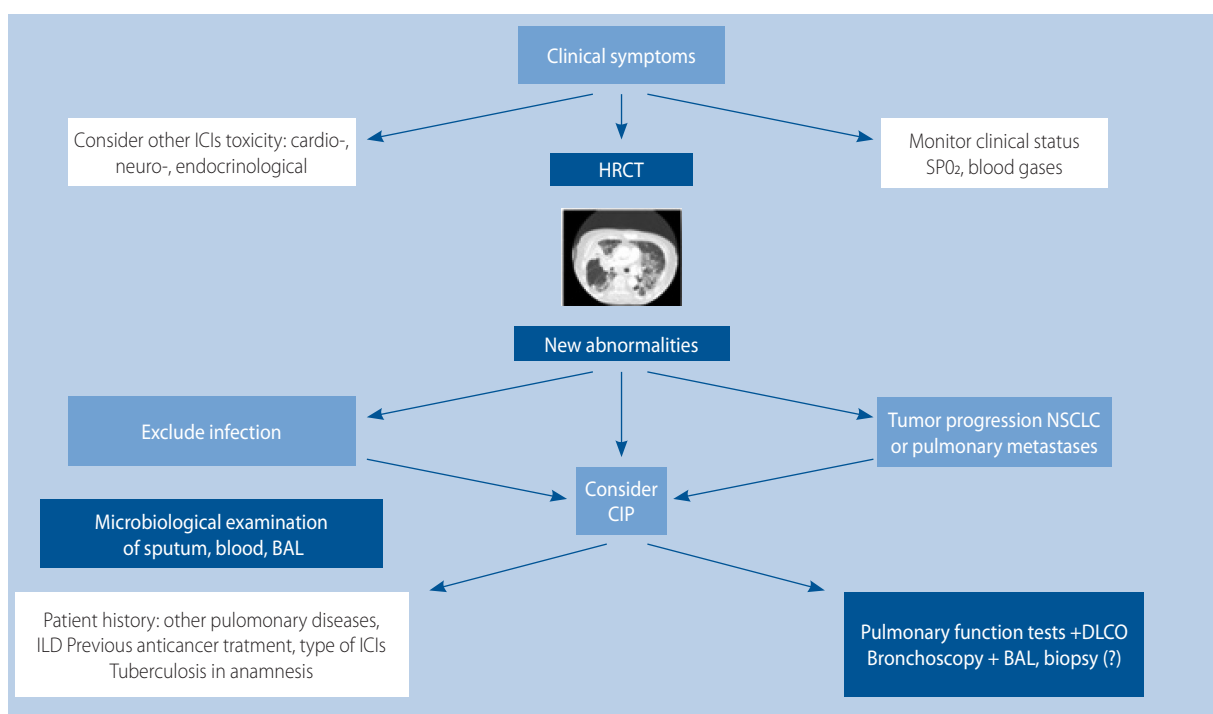


Figure 1. Diagnosis and differential diagnosis of checkpoint inhibitors pneumonitis (CIP). HRCT – high resolution computed tomography, BAL – bronchoalveolar lavage, SP02 – oxygen blood saturation, DLCO – diffusing capacity, ILD – interstitial lung disease, NSCLC – non-small-cell lung cancer

of the symptoms enable radiological regression and an improvement in the clinical status in most patients [18].

Several oncological societies have developed diagnostic and therapeutic recommendations. These are summarised in table II [1, 19, 24, 25].

Generally in asymptomatic patients with CT abnormalities (confined to one lobe of the lung or, 25% of lung parenchyma) observation and repeated CT scans are recommended. Immunotherapy can be continued or held until the resolution of radiological changes [1, 19, 24, 25].

In patients with moderate symptoms (grade 2) or abnormalities involving more than one lobe of the lung or 25–50% of lung parenchyma, temporary holding of the ICI is indicated. [1, 19, 24, 25]. Chest X-ray, blood tests and microbiological tests (for viral, opportunistic or specific bacterial – such as mycoplasma and legionella) should be considered [24]. In the case of inflammatory suspicion (fever, CRP, neutrophil counts) empirical antibiotics should be given. [24]. Empirical antibiotics can be used based on local guidelines – amoxicillin or levofloxacin might be a first option for outpatients [26]. If no evidence of infection –

steroids treatment with dose tapering by 5–10 mg/week over 4–6 weeks in case of clinical improvement. Clinical evaluation of the patient's state should be repeated after 72 hours of treatment. If no clinical improvement is achieved – hospitalisation is recommended, with intravenous corticosteroids and further diagnostic procedures. The continuation of ICI therapy is possible when complete clinical improvement was reached (and the prednisone dose reduced to 10 mg/day) [1, 19, 24, 25].

In patients with extensive CT changes involving all lung lobes or 50% of lung parenchyma and in patients with severe or life-threatening symptoms – CTCAE grades 3 and 4 – hospitalisation is mandatory (also in the Intensive Care Unit). Bronchoscopy with BAL, and microbiological testing should be performed. Empirical antibiotics and steroids intravenously are necessary. In case of clinical improvement, the dose of steroids should be slowly reduced and finally stopped after at least another 6–8 weeks. If no clinical improvement in the patient's clinical status is observed after 48 hours of therapy with steroids, the administration of immunosuppressive agents should be considered (infliximab or mycophenolate mofetil).

Table II. Management of pneumonitis in patients treated with ICs [1, 19, 24, 25]

SITC	<ul style="list-style-type: none"> Consider holding ICI Monitoring symptoms and oxygen saturation every 2–3 days; weekly clinic visits CT prior to every cycle of ICI treatment (at least every 3 weeks) Resolution of radiographic findings – consider continuation of therapy No new change or symptoms – consider continuation of therapy with close follow-up 	<ul style="list-style-type: none"> Hold ICI Pulmonary consultation for bronchoscopy with bronchoalveolar lavage methylprednisolone 1 mg/kg/day (<i>i.v.</i> or oral equivalent) Improvement – steroid taper over >4 weeks Worsening – treat as grade 3–4 Consider continuation ICI when symptoms and imaging abnormalities resolve 	<ul style="list-style-type: none"> Discontinue ICI Pulmonary consultation for bronchoscopy with bronchoalveolar lavage Methylprednisolone <i>i.v.</i> 2 mg/kg/day No clinical improvement (48–72 h) – infliximab, cyclophosphamide, mycophenolate mofetil or IVI Gy Improvement – steroid taper over >8 weeks Continuation ICI – G3, consider carefully only if symptoms and imaging abnormalities resolve G4 – Permanently discontinue ICI
ASCO	<ul style="list-style-type: none"> Hold ICI Repeat CT in 3–4 weeks; Monitor symptoms and pulseoximetry weekly Continuation of ICI after radiographic improvement No radiographic improvement – treat as G2 	<ul style="list-style-type: none"> Hold ICI Consider bronchoscopy with BAL Prednisone 1–2 mg/kg/d and taper by 5–10 mg/wk over 4–6 weeks Consider empirical antibiotics Monitor every 3 days No clinical improvement after 48–72 hours of prednisone – treat as G3 	<ul style="list-style-type: none"> Permanently discontinue ICI Bronchoscopy with BAL, consider lung biopsy Empirical antibiotics; (methyl)prednisolone <i>i.v.</i> 1–2 mg/kg/d No improvement after 48 hours – infliximab 5 mg/kg or mycophenolate mofetil <i>i.v.</i> 1 g twice a day or IVI G for 5 days or cyclophosphamide Improvement – taper corticosteroids over 4–6 weeks
NCCN	<ul style="list-style-type: none"> Consider holding ICI Reassess in 1–2 weeks Monitor symptoms and pulseoximetry Consider CT scan in 4 weeks Continuation of ICI after radiographic improvement 	<ul style="list-style-type: none"> Hold ICI Consider bronchoscopy with BAL Consider empirical antibiotics if infection has not been fully excluded Prednisone/methylprednisolone 1–2 mg/kg/d Tapering dose over 4–6 weeks 	<ul style="list-style-type: none"> Discontinue ICI (methyl) prednisolone <i>i.v.</i> 2–4 mg/kg/day, taper corticosteroids ≥6 weeks High resolution CT and respiratory review Bronchoscopy and BAL Empirical antibiotics If no improvement after 48 hours consider infliximab 5 mg/kg (second dose after 14 days) or mycophenolate mofetil <i>i.v.</i> 1–1.5 g twice a day
ESMO	<ul style="list-style-type: none"> Consider delay of treatment Monitor symptoms every 2–3 days If worsens – treat as grade 2 or 3–4 	<ul style="list-style-type: none"> Hold ICI Empirical antibiotics if suspicion of infection If no evidence of infection or no improvement with antibiotics after 48h – add in prednisolone 1 mg/kg/day orally, taper corticosteroids ≥6 weeks 	<ul style="list-style-type: none"> Discontinue ICPI (methyl) prednisolone <i>i.v.</i> 2–4 mg/kg/day, taper corticosteroids ≥8 High resolution CT and respiratory review Consider bronchoscopy and BAL Empirical antibiotics
Grade	1	2	3/4

Table III. Management of CIP – general guidelines

	Grade		ICI		Treatment
	Symptoms	CT changes extension	Management	Resumption	
G1	Asymptomatic, radiological abnormalities	Confined to 1 lobe, <25% of parenchyma	Hold therapy or continue with monitoring	Yes if resolve radiological abnormalities	Nonspecific
G2	Mild symptoms, medical intervention indicated		Hold therapy	Yes if resolution to G1	<ul style="list-style-type: none"> – Prednisone 1–2 mg/kg – Taper steroids by 5–10 mg/week, over 4–6 weeks – Empirical antibiotics if infection suspicion – If no improvement after 48 h treat as G3
G3	Severe symptoms interfering with ADL, supplementation of oxygen required	All lung lobes or >50% of parenchyma	Discontinuation	No	<ul style="list-style-type: none"> – Methylprednisolone i.v. 1–2 mg/kg – Empirical antibiotics – Prophylaxis (PCP, fungal) – Taper corticosteroids over 6–8 weeks – If no improvement after 48 h infliximab or mycophenolate mofetil
G4	Life-threatening respiratory failure, invasive support required				

In the case of CIP grade 3 or 4, a continuation of the immunotherapy is contraindicated. [1, 24, 25].

In the case of patients with toxicity G1–2 who continued treatment, the occurrence of a second episode of toxicity G \geq 2 is an indication to persistence discontinuation of ICI [4].

Prolonged use of steroids is associated with the increased risk of complications (osteoporosis, gastritis, diabetes and others) and bacterial, fungal or viral infections. [27]. Prophylaxis of pneumocystis pneumonia (PCP) with cotrimoxazol (480 mg twice daily Monday/Wednesday/Friday) is indicated for patients receiving at least 20 mg methylprednisolone or equivalent for \geq 4 weeks [24, 25, 27]. Prophylaxis of fungal infections is questionable, some recommendations suggests fluconazol for patient who receiving at least 20 mg methylprednisolone or equivalent for \geq 6 weeks [25].

Summary

Incidence of CIP in clinical trials have been reported <10%, higher rates have been reported for combinations of PD-L1 and CTLA-4 inhibitors. Some data suggest that incidence in clinical practice may be higher (about 20%). Unfortunately, this complication of immunotherapy brings with it the highest mortality. Preexisting lung disease, a history of lung radiotherapy, age >70 years, male gender, smoking and low serum albumin are suggested as the risk factors for CIP. The risk of pneumonitis is higher in patients with non-small cell lung cancer (NSCLC) than in those with melanoma or renal cell cancer. Early detection of CIP is crucial, but differential diagnosis can be problematic. Additional diagnostic procedures – such as pulse oximetry, spirometry, measurement of carbon monoxide-diffusing capacity, bronchoscopy with BAL may be helpful [28]. In the CT scans, parenchymal infiltrations with ground-glass opacities, consolidations, interlobular septal thickening and intralobular lines and micronodules are described. In most cases maintaining

ICP and systemic corticosteroid therapy are effective (general guidelines are summarised in table III).

Continuation of immunotherapy can be considered with caution in patients with G1–2 toxicity when clinical improvement was achieved and steroids were tapered (dose <10 mg prednisol/day). Pulmonary and infectious disease consultations should be considered in all symptomatic patients, especially in patients with G3–4 toxicity.

Conflict of interest: none declared

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