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Pulmonary toxicities of immune check point inhibitors in the management of cancer: mini review

Abstract

Immune-checkpoint inhibitors (ICIs) have revolutionized treatment of solid malignancies, leading in some cases to durable responses. However, an unchecked immune response might lead to mild to severe immune-related adverse events (irAEs). Pulmonary toxicity, though often referred to as Immune checkpoint inhibitor–related pneumonitis (ICI-pneumonitis), covers a broad and overlapping spectrum of pulmonary manifestations and has been described in < 10% of patients receiving ICI either alone or in combination. However, the actual numbers in real-world populations are high, and are likely to increase as the therapeutic indications for ICIs continue to expand to include other malignancies. Drug withdrawal is the mainstay of treatment for ICI-pneumonitis. However, a good number of patients with higher grades of toxicity may need corticosteroids. Patients with refractory disease need additional immunosuppressive agents. In this brief review, we succinctly discuss the incidence, risk factors, mechanisms, clinical and radiologic manifestations, diagnosis and summarize the current management strategies of ICI-pneumonitis

Key words: cancer, immune check point inhibitors, immunotherapy, pulmonary toxicity

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Introduction

Cancer immunotherapy, particularly immune-checkpoint inhibitors (ICIs), has transformed the treatment of solid malignancies and has brought in a major paradigm shift in cancer treatment [1–6]. It has considerably improved the prognosis in non-small cell lung cancer (NSCLC) and now is used in the treatment of other cancers as well [7, 8]. Checkpoint inhibitors induce long term remission, the effects persisting even after discontinuation of treatment. In addition, they significantly improve the overall survival of metastatic cancers [5, 9].

Mechanism

Immune check point inhibitors act by boosting the body's natural tumor killing response, a totally different approach from the conventional chemotherapy. Immunotherapy in a way hyper-activates the immune system whereas chemotherapy can weaken it [9]. The primary cells of the immune response, T helper and cytotoxic T lymphocytes (CTL), are primed and activated once antigen-presenting cells (APC) reveal the tumor antigens on major histocompatibility complexes (MHC) to the T cell receptors [10]. The activated T-cell then triggers the production of effector T-cells which secrete cytokines that mediate the immune response against tumor cells and a variety of bacterial, viral, fungal, and parasitic organisms [11]. The immune system thus recognizes antigen as malignant cells and target them for destruction [10]. These responses must be balanced, appropriate and timely. An overactive response at times can trigger an autoimmune process causing damage to normal tissues, whereas an underresponsiveness leads to immune tolerance to the multiplying tumor cells

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[11]. This is controlled by a complex network of regulatory signals derived from T-regulatory cells (Treg), macrophages, cytokines, and immune checkpoints. Many immune checkpoint molecules exist controlling the immune response, either augmenting or inhibiting the process [8, 10, 11]. These checkpoints curb the host directed responses, and prevent the development of an autoimmune disease [12].

Two distinct checkpoints have received maximum attention. Immediately on presentation of a tumor antigen to a T-cell, a checkpoint protein cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) can inhibit T-cell activation by competitively binding APC costimulatory ligands [7]. A second checkpoint by the programmed cell death protein 1 (PD-1) receptor exists on activated T cells, Treg cells, B cells, and natural killer cells [7]. The ligands of this receptor, PD-L1 and PD-L2 once bound also lead to T-cell apoptosis and exhaustion. So, when these check points are inhibited, newly activated, unexhausted T-cells become available for tumor destruction. The recently developed monoclonal antibodies directed against immune checkpoints can thus control the intrinsic immune response against tumor antigens by releasing the brake on T-cell activation by antigen presenting cells [7, 13]. However, for an effective functioning the tumor must express sufficient quantity and quality of tumor antigens, which should then be recognized by the appropriate T-cells whose response should not get prematurely halted by any counter regulatory mechanisms [7].

Cancer cells often evade immune destruction in a number of distinct ways, intrinsic or extrinsic, leading to tumor development and survival [14]. These include induction and recruitment of other immunosuppressive cells into the tumor microenvironment, overexpression of immune checkpoint molecules CTLA-4, PD-1 and its ligand PD-L1, disruption of T-cell function and signaling, defective antigen presentation and production of anti-inflammatory cytokines [10, 11, 15]. Moreover, a less immunogenic population of neoplastic cells are created by a slow process of selective adaptation to immune surveillance, a process called "immune sculpting" [14, 16]. At times, the dense fibrotic stroma around tumor acts as a barrier to these T-cells. All these facilitate the proliferation of malignant cells, leading to the manifestations of cancer [17].

Ipilimumab was introduced for the treatment of advanced melanoma in 2011.[5] Since then nine ICIs: ipilimumab (anti-cytotoxic T-lymphocyte antigen-4), nivolumab, pembrolizumab, cemiplimab, dostarlimab, toripalimab (anti- PD-1), atezolizumab, avelumab, and durvalumab (anti-PD-L1) are now FDA-approved or fast tracked [18, 19]. More than 50 immunotherapy agents including other immune checkpoints such as LAG3, TIGIT, TIM3, B7H3, CD39, CD73, adenosine A2A receptor, and CD47 are in different phases of clinical development [20, 21]. Drugs like tislelizumab, camrelizumab and sintilimab are available for prescription in other world markets [22, 23]. Studies like CheckMate 227 and CheckMate 9LA have confirmed that a chemo-free or chemo-reform doublet immunotherapy, the latter being more effective, improves patients' overall survival with a favorable safety profile regardless of their PD-L1 expression status [24]. However, immunotherapy is effective only in a select group of patients. Strategies for expanding its scope include combination of PD-1 and CTLA-4 blockade, concomitant conventional treatments such as chemotherapy or radiotherapy, priming the immune system prior to checkpoint inhibitor therapy with neoantigen-based vaccines, addition of vascular endothelial growth factor (VEGF) inhibitors and targeting the mechanism of resistance [10].

Adverse effects

Autoimmune-like/inflammatory side-effects develop in almost every organ, including skin, brain, pituitary, eye, thyroid, liver, adrenal, kidney, pancreas, colon, and lung if the unchecked immune response ensuing checkpoint blockade turns against self-antigens [25]. Such adverse events, termed 'immune-related adverse events' (irAEs) range from mild to severe and even life-threatening at times. Reversible irAEs include fatigue, pruritus, rash, myalgia, arthralgia, loss of appetite and hypo or hyperthyroidism [9]. Irreversible adverse events consist of diabetes mellitus, uveitis, arthritis and, in some cases of hypothyroidism. Endocrine irAEs like hypophysitis, thyroid dysfunction, insulinitis, adrenalitis, hypoparathyroidism, pituitary ACTH-dependent Cushing's syndrome are not uncommon [26]. Rare events like acral necrosis, diaphragmatic involvement leading to respiratory insufficiency, and vasculitis mainly large vessel vasculitis have been reported [27–29]. A threefold higher incidence of cardiovascular events including myocardial infarction, need for revascularization, and stroke, and progress of atherosclerosis have been noted in some studies [30]. A meta-analysis showed an increased risk of pneumonia in cancer patients treated with anti-CTLA-4 alone and anti-PD-1, or

anti-PDL-1, either alone or in combination with anti-CTLA-4 or chemotherapy [31, 32]. The infection rate over a 4-year period in three hospitals in New York (NY, USA) was 7.3% in melanoma patients treated with ICIs, highest being with ipilimumab (73%) [33]. Infections occurred within a median of 19.2 (< 1–70) weeks after immunotherapy initiation and were responsible for death in 17% of cases. Most infections were of bacterial origin (79.3%), primarily pneumonia (28.2%) and bloodstream infections (28.2%). Severe irAEs that can be potentially life-threatening are hepatitis, colitis, hypophysitis, pneumonitis, myocarditis, Guillain-Barre syndrome, myasthenia gravis and encephalitis [9]. Luckily, incidence of connective tissue diseases was found to be low with the use of PD-1/PD-L1 inhibitors. The incidence of irAEs also varies by ICI regimen, tumor type, disease setting and, possibly, ethnicity [34]. It may also differ with the drugs used, colitis and hypophysitis more common with CTL4 blockade and pneumonitis and thyroiditis with PD-1. The host genetic background is also likely to play a role in irAE susceptibility. In a pilot exploratory study on 89 melanoma patients who received ICIs, 30 variants or single-nucleotide polymorphisms were identified of which 12 were associated with an increased risk with a decreased risk in the remaining [35]. When compared to adverse events resulting from chemotherapy, irAEs can have a delayed onset and may persist longer. Moreover, irAEs including pulmonary toxicities might occur at any point during or after treatment. However, we still do not know who will develop these toxicities or how long they will last [36].

Pulmonary toxicities

Immune checkpoint inhibitor-related pneumonitis (ICI-pneumonitis)

Pulmonary toxicity of ICIs can be severe and require early identification and management. Although often referred to as pneumonitis, pulmonary toxicity associated with ICIs covers a broad and overlapping spectrum of pulmonary manifestations. Pneumonitis, a severe, potentially life-threatening irAE, has been described in < 10% of patients receiving anti-PD-1/PD-L1 therapy either alone or in combination, and appears to occur more commonly in patients with lung cancer. Though several guidelines have helped to unify the classification, pneumonitis severity, and standardize treatment approaches, significant gaps still remain [37]. Even the terminology is not uniform. People use pneumonitis, checkpoint induced pneumonitis (CIP) or ICI-related interstitial lung disease (ICI-I LD) synonymously. American Thoracic Society (ATS) multidisciplinary panel in 2019 suggested "Immune checkpoint inhibitor–related pneumonitis" (ICI-pneumonitis) as a common terminology to define this type of manifestations [38]. It is a potentially fatal irAE that is often difficult to treat and manifests as a spectrum of lung involvement; acute (acute interstitial pneumonia), organizing (organizing pneumonia), fibrotic (nonspecific interstitial pneumonia) and hypersensitivity (hypersensitivity pneumonitis). Based on the National Cancer Institute (NCI) and National Institutes of Health (NIH) definitions, Common Terminology Criteria for Adverse Events (CTCAE), low grade pneumonitis is defined as Grade 1 with asymptomatic radiographic changes or Grade 2 if chest image findings are accompanied by only mild symptoms. High-grade pneumonitis is diagnosed when significant symptoms limit self-care; Grade 4 when it is life threatening and Grade 3 when it is not. Grade 5 denotes all respiratory-related deaths. Grade 3 or higher toxicity needs hospitalization, as it involves > 50% of lung parenchyma, limit daily activities and will require supplemental oxygen [39, 40]. However, the use of CTCAE may under or overestimate the incidence and severity of toxicities. The irAEs associated with other organ systems may occur concomitantly, precede or follow the development of pneumonitis.

Incidence

A meta-analysis by Nishino and colleagues evaluating 20 studies on PD-1 inhibitor specifically on NSCLC, melanoma, and renal cell carcinoma trials found that the overall incidence for pneumonitis ranged from 0% to 10.6% [41]. The overall incidence during PD-1 inhibitor monotherapy was 2.7% for all-grade and 0.8% for grade 3 or higher pneumonitis. Severe pneumonitis was higher (1.5%) with combination immunotherapy. The overall incidence of pneumonitis for all grades was between 1.4% and 8.5 % in NSCLC studies. A meta-analysis evaluating 6360 patients showed a higher incidence of high-grade pneumonitis, 1.53%, than the previous reports, though the overall incidence was lower at 2.92% [42]. In a study of 64 ICI-pneumonitis cases, Delaunay and colleagues reported that 45.3% (29/64) were classified as severe, including six fatalities [43]. Naidoo and colleagues found 12 patients (27%) who developed grade 3 or higher pneumonitis out of the 43 patients with pneumonitis [44]. Grade 1 pneumonitis was seen in 40% and grade

2 in 33% in the same study. A systematic review and meta-analysis of nineteen clinical trials with 5,038 NSCLC patients found that 35% of all pneumonitis cases associated with PD-1 or PD-L1 inhibitors were severe [45].

More recent reports including studies incorporating real-world populations report a much higher rate of pneumonitis (13–19%) [41, 46, 47]. In a retrospective study from Japan on 170 NSCLC patients treated with PD-1 blockade, the incidence of pneumonitis was reported to be 16% [46]. Suresh et al noted an incidence of 19% in patients with NSCLC treated with PD-1 or PD-L1 inhibitors; of which 48% were grade 3 or 4 and 5%, grade 5 [47]. The reasons for the higher reported incidence may be due to better awareness of the toxicity, increased pharmacovigilance, or increased co-morbidities in patients treated outside of clinical trials [37]. While the incidence of all grade pneumonitis appears to be higher in real-world populations, the percentage of grade 3 and above toxicities remains consistent at around 40% of those who develop pneumonitis in both real life and clinical trials [37].

Type of drug

The incidence of pulmonary toxicity varies with different drugs [19]. Due to the different toxicity profiles, PD-1 inhibitors were found to induce more pulmonary toxicity than the CTLA-4 inhibitors (OR 6.4, 95% CI 3.2–12.7) [48]. On the contrary, IrAEs as a whole occur more frequently with CTLA-4 inhibitors (60–90%) compared with PD-1/L-1inhibitors (39–70%). The toxicity profiles of the PD-1 and PD-L1 inhibitors may also be different, the incidence of all grade pneumonitis being higher with PD-1 than with PD-L1 inhibitors [45]. Khunger and colleagues noted a higher incidence of pneumonitis of any grade (3.6% vs. 1.3%) and severe pneumonitis (1.1% *vs*. 0.4%) with PD-1 inhibitors when compared to PD-L1 inhibitors [45]. Hence, pneumonitis is more frequent with PD-1 monoclonal antibodies when compared to anti-CTL-4 or anti-PD-L1, though the latter is not uniformly reported from all studies. However, the incidence of pneumonitis varies among the different PD-1 inhibitors as well. Combination therapy with anti-PD1 and anti-CTLA4 also appears to be associated with increased risk of pneumonitis [19, 31, 49]. In the CheckMate 227 study, the incidence of all-grade (3.8% *vs*. 2.3%), or grade 3–4 pneumonitis (2.3% *vs*. 1.5%) was more with nivolumab plus ipilimumab than with nivolumab monotherapy in patients with NSCLC [50]. The incidence of irAEs with ipilimumab and pembrolizumab is dose-dependent, with greater toxicity observed at higher dose levels. However, Wu et al. observed that PD-1 inhibitor-related pneumonitis was not associated with its dosage [42].

Risk factors

Several retrospective studies and case series have reported risk factors for pneumonitis. Higher incidence is reported in patients with a history of smoking, pre-existing lung disease, or the type of NSCLC and in treatment-naïve patients. Interestingly, adenocarcinoma was associated with lower odds of development of pneumonitis at 12 months than with the squamous type [11]. Male gender, smoking history, early multiline treatment, baseline lung disease, active lung infection, and history of chest radiotherapy were potential risk factors for the development of lung toxicity. However, not all studies found gender or smoking as a risk factor for pneumonitis [11]. Though heavy smokers are at a higher risk for developing pneumonitis, they surprisingly benefit from the treatment with ICIs [36]. A performance status (PS) score ≥ 2 was a risk factor for grade ≥ 3 pneumonitis, and a combination of PS ≥ 2 and ≥ 50 pack-years of smoking were independent risk factors of pneumonitis of any grade [36]. A high-risk for ICI-pneumonitis was noted in patients with NSCLC when treated with epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR-TKI) in combination with ICIs [51]. Studies show that ICI plus radiotherapy (RT) led to a higher risk of fatigue, cough, pruritus and pneumonitis than RT with placebo or ICI alone [52]. Pulmonary irAEs while on ICI were more if they received more intensive curative intent chest radiation, as opposed to palliative radiotherapy [53]. Combining ICI with stereotactic body radiation therapy (SBRT) have noted increased rates of pneumonitis [54]. Radiation recall pneumonitis, occurring > 1 year or more after radiation is more frequent with ICI therapy than conventional chemotherapy [55]. Interestingly, extra thoracic metastasis were associated with a significantly lower incidence of pneumonitis [56].

Onset and symptoms

Patient with irAEs usually present within weeks to months after initiation of treatment; however, some irAEs can develop even after cessation of therapy [57]. Pneumonitis can develop within days after initiation of therapy, with an earlier onset for those receiving combination therapy compared to those receiving monotherapy. The median time to onset of pulmonary

toxicity after initiation of immunotherapy was found to be 2·3 months, occurring earlier in lung cancer (2·1 months), compared to melanoma (5·2 months). Presenting symptoms may be subtle, including unresolving cough, dyspnea, fever, and hypoxia [11]. Hence, a need for increasing oxygen support or a declining oxygen saturation should be evaluated in a timely fashion [57].

Pattern

Imaging findings are non-specific and can mimic an infectious pneumonia or worsening metastatic disease [58]. Organizing pneumonia (OP) and non-specific interstitial pneumonitis are the most prominent forms of ICI-pneumonitis. The usual radiographic findings include ground glass opacities (GGO), consolidation, bronchiectasis, inter-lobular septal thickening, diffuse alveolar hemorrhage and pleural effusions [11]. Nodules, mediastinal adenopathy and reverse halo sign also have been reported [59]. The inflammatory response typically localizes to the interstitium and alveoli and results in several distinct histopathological patterns of interstitial lung disease. Patterns seen on CT scan are variable and include organizing pneumonia, non-specific interstitial pneumonia, hypersensitivity pneumonitis (HP), and bronchiolitis. More severe forms of pulmonary toxicity, such as acute interstitial pneumonia leading to acute respiratory distress syndrome are also a common scenario. Nishino et al., reporting on patients in 10 different trials of nivolumab noted an OP pattern in 65.5%, non-specific interstitial pneumonitis pattern in 15%, HP pattern in 10% and acute interstitial pneumonia/ARDS in 10% of cases [60]. Naidoo et al noted a lower percentage of OP, 19% and a higher percentage of HP 22%. They also recorded GGO in 37% and pneumonitis not otherwise specified in 15% [44]. In another study, OP pattern was seen in 23.4%, HP in 15.6% and no suggestive pattern in in 36% [43]. Radiologic severity at the time of pneumonitis was classified as mild, moderate and severe in approximately 56%, 22% and 22% patients respectively in the above study by Naidoo et al. [44] Extensive pneumonitis was seen more in the lower lobes compared to the middle and upper lobes and was more common in lung cancer patients [60].

Pulmonary function

Pulmonary function tests in irAEs most commonly show a restrictive pattern with a reduced diffusion capacity [13]. Eight-out-of-16 patients and nine-out-of-12 patients in a series had a lower forced expiratory volume in 1 s (FEV_1) and carbon monoxide diffusing capacity (DLCO), respectively [44]. As for any other interstitial lung disease, monitoring of pulmonary function with spirometry, DLCO, pulse oximetry and a 6-minute walk test can be used to detect the insult early, or to assess the response to therapy. However, Frazen et al. reported a significant decrease in forced vital capacity (FVC) or DLCO after 9 weeks of ipilimumab in 23.6%, with only one patient showing features of pneumonitis [61]. Hence, the value of FVC or DLCO for screening or early diagnosis of pneumonitis remains unclear in patients regularly assessed by chest CT [62].

Pathology

Bronchoalveolar lavage (BAL) fluid might reveal inflammatory and lymphocytic infiltration. In one series, 80% of cases had T-lymphocytic alveolitis. Histopathological findings included cellular interstitial pneumonitis (36%), organizing pneumonia (27%), and diffuse alveolar damage (9%). In more than one-quarter of cases, no pathological abnormalities are identified [44]. In addition , acute lung injury pattern and fibrosis can also be seen [63].

Biomarkers

The identification of biomarkers for irAEs has great relevance in clinical practice but is really challenging. Significantly higher levels of Interleukin (IL)-17A and IL-35 in the plasma and BAL were found to be associated with the severity of pneumonitis [64]. Similarly, increase in CXC chemokine receptor 2 (CXCR2), IL-1RA and IL-2RA were well correlated with the development of ICI-pneumonitis [65]. Interestingly, ICI-pneumonitis patients can have a higher level of baseline peripheral-blood absolute eosinophil count [66]. Xu et al. has concisely reviewed the role of quite a large number of potential biomarkers taken from circulating blood, affected organs, tumor microenvironment or clinical parameters in predicting irAEs [67]. These markers can be grouped as those accompanying the immune-related pulmonary toxicity and those predicting the toxicity development.

Management

Multiple organizations including the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), Society for Immunotherapy of Cancer (SITC), National Comprehensive Cancer Network (NCCN), and European Respiratory Society (ERS) have published guidelines on the diagnosis and management of

ICI induced pneumonitis [39, 40, 62, 68]. The key factor is early recognition and intervention, and requires multidisciplinary effort by pulmonologists, medical oncologists, and radiologists with an increased awareness of treatment-induced pulmonary toxicity among the emergency and primary care physicians [57]. Champiat et al. defined five pillars for the management of patients on ICI therapy: prevention, anticipation, detection, treatment, and monitoring [69]. Recent guidelines by ASCO for the management of irAEs in patients treated with ICI advice clinicians to hold immunotherapy until the patient's pneumonitis is grade 1 or less, and permanently discontinue ICI therapy for any patient experiencing grade 3 to 4 toxicity [3, 68]. Interestingly, development of pneumonitis has been found to be associated with a shorter patient survival.

Drug withdrawal is the mainstay of treatment for pneumonitis of all grades. In a large retrospective analysis, 86% of cases with pulmonary toxicity due to ICI improved with corticosteroids. No specific treatment is needed for asymptomatic grade 1 toxicity. But a close follow up is advised. Steroids at doses of 1–2 mg/kg per day for grade 2 (prednisone orally or methylprednisolone IV) and a higher doses of 2–4 mg/kg (IV methylprednisolone) for ≥ grade 3 are recommended (Figure 1) [11, 40, 68].

If improvement is noticed, doses of corticosteroids can be reduced and slowly tapered over 4–8 weeks. Pulse steroid doses may be needed for most severe cases with acute respiratory failure [62]. Patients with grade 2 toxicity and above may need evaluation for infections and a bronchoscopy should be considered. Patients with grades 1–2 pneumonitis can often be managed as outpatients, while those with grade 3 pneumonitis or higher require hospitalization. For patients with grade 1 pneumonitis, re-challenge following resolution of infiltrates with close follow-up is a reasonable option.

Additional immunosuppressive therapy may be required for irAEs refractory to corticosteroid treatment. Steroid-refractory pneumonitis, exhibiting mostly a diffuse alveolar damage radiographic pattern, constitute about 20% of referrals for multidisciplinary irAE care [70]. Immunosuppressive drugs, such as infliximab or cyclophosphamide, have been approved for refractory irAEs. Interleukin-17 blockade was tried for immune-mediated skin and gastrointestinal toxic effects. There are no clear recommendations for infliximab, cyclophosphamide or specific inhibition of IL-17 for treatment of pneumonitis [19]. A patient who developed fatal diffuse alveolar hemorrhage while receiving nivolumab did not respond to infliximab and high-dose corticosteroids [71]. Other, immunosuppressive agents such as tumor necrosis factor (TNF)--alpha antagonists, azathioprine, methotrexate, mycophenolate mofetil (MMF) anti-thymocyte globulin (ATG), calcineurin inhibitors, may also be effective. Triple therapy with high-dose corticosteroids, tacrolimus, and cyclophosphamide for steroid-refractory ICI-pneumonitis has been reported [72]. Plasmapheresis may be required in some cases. Addition of Intravenous immunoglobulins (IVIG) to high-dose corticosteroid therapy as a treatment for steroid-refractory ICI-pneumonitis has shown a favorable toxicity/benefit profile [73]. Martins et al. recommend anti-TNFa drugs (etanercept, adalimumab, certolizumab, and golimumab) in refractory cases and anti-IL-1 therapy (anakinra or canakinumab) if pneumonitis do not respond to anti-TNFa [74]. Anti-IL- 6 (tocilizumab) was also reported to be an effective treatment for steroid-refractory cases [75]. However, clinical practice guidelines for management of steroid-refractory ICI pneumonitis are yet to be developed.

Other pulmonary manifestations

In addition to pneumonitis, ICI therapy has been associated with few other pulmonary complications most notable being pulmonary sarcoidosis and sarcoid-like granulomatous reaction [76, 77]. Usually sarcoidosis-like reaction appears around 14 weeks after initiation of an ICI [78]. This may often be misinterpreted on imaging studies as treatment failure and tumor progression. Clinicians should be aware of this and biopsies should be considered for evaluation of new lesions developing while on immunotherapy [78–80]. Though these reactions usually resolve if the ICI is stopped, it still can be continued under close observation [78, 79, 81]. Corticosteroids are indicated only in cases of significant symptoms or organ dysfunction. Pleural effusions were reported in 6% of patients receiving nivolumab in the phase III, Checkmate 057 trail [82].

Cases of new infection with tuberculosis, as well as tuberculosis reactivation have been reported in patients treated with anti-PD-1 agents [83, 84]. An increased risk of pneumonia and bacterial blood stream infections as well as opportunistic infections like invasive aspergillosis, pneumocystis jiroveci pneumonia, cytomegalovirus-enterocolitis and strongyloides hyperinfection have been reported [33, 85]. Serious infections developed in 7.3% of melanoma patients at around 135 days from the initiation of

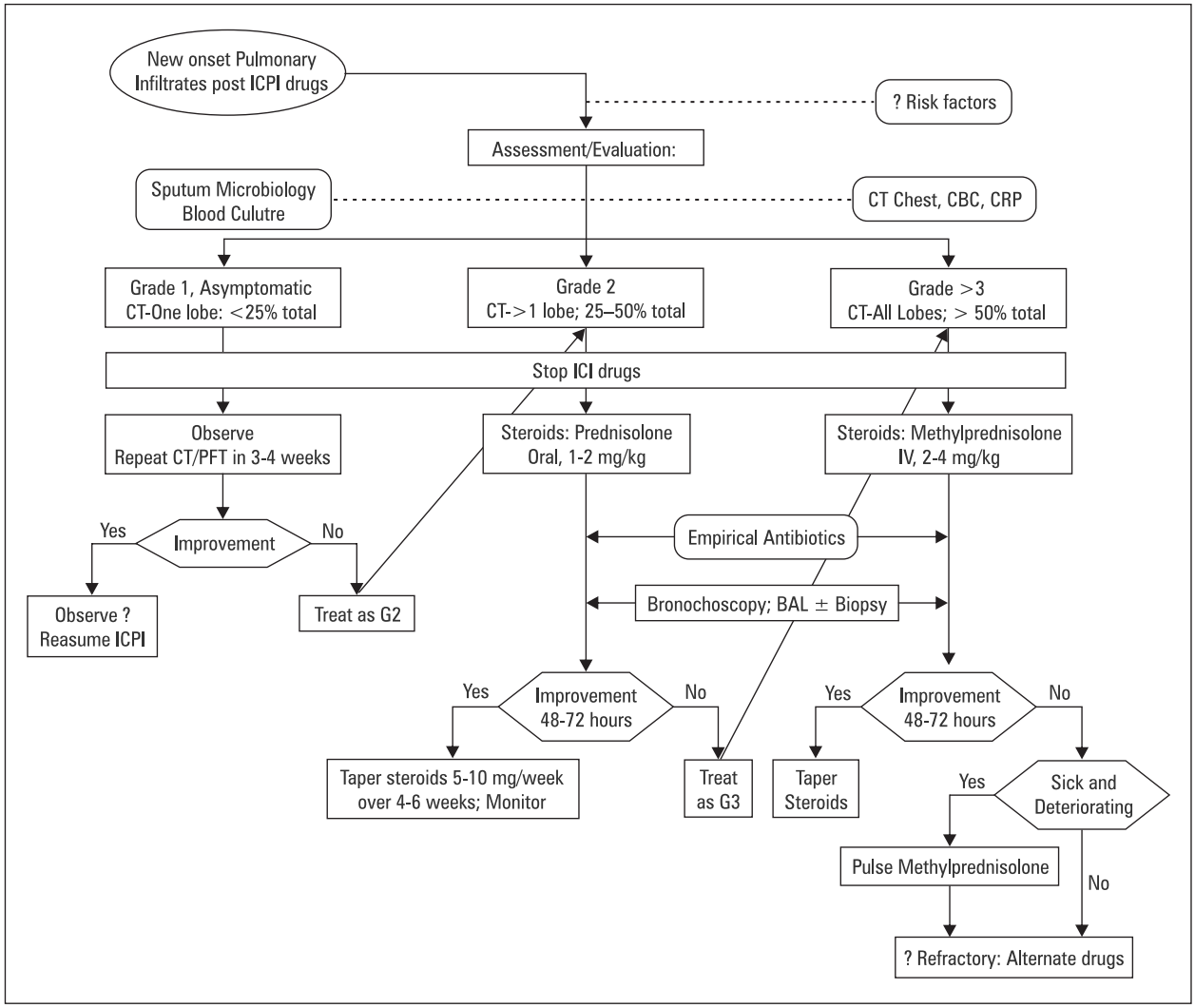

Figure 1. Management of pulmonary toxicity related to immune checkpoint inhibitors

ICI blockade. New onset asthma was reported in a patient with lung adenocarcinoma, 9 months after starting nivolumab which responded well to the standard treatment [86]. Though eosinophilic granulomatosis with polyangiitis (EGPA) following treatment with ICI for a stage IV melanoma was reported, the authors concluded that it could also be considered as hypereosinophilic asthma with systemic manifestations as there was no evidence of genuine vasculitis [87]. One case of recurrent allergic bronchopulmonary aspergillosis has also been reported [88].

Concerns

Pseudo-progression is an unconventional clinical response to ICI therapy, in which an increase in the size of tumor lesions is followed by a reduction in tumor burden [11]. The incidence differ for different tumor and is seen in 2.8–15.8% of all ICI-treated patients. This is categorized as early and delayed based on a ≥ 25% increase in tumor burden in imaging within 12 weeks or after 12 weeks respectively from the start of immunotherapy [89]. Distinguishing pseudo-progression from true tumor progression is often challenging and the possibility has to be kept in mind before discontinuation of the drug. Histopathologic examination remains the gold standard. Radiographic follow-up, Superparamagnetic iron oxide nanoparticle (SPION) T2-weighted MRI, Ultrasound, PET-CT, levels of circulating tumor DNA (ctDNA) and IL-8 are the other modalities to distinguish pseudoprogression from true progression [89]. In contrast, hyper-progression, represents a true tumor growth in which there is a very rapid and sustained progression of tumor following the initiation of immunotherapy [11]. This ICI-related rapid surge in tumor burden has primarily been reported following PD-1/PD-L1 therapies for lung cancer.

Some patients do not respond initially and some develop resistance later. The occurrence of primary resistance depends on the absent or low expression of PD-L1, low tumor mutational burden, and disruption of critical signaling pathways in the tumor or it's epigenetic properties [20, 90]. Patient's overall micro flora make-up also contributes to this characteristic [91]. On the other hand, the mechanisms for secondary resistance are not well understood. The two types of resistance may share pathways in common and may utilize different immune evasion strategies [20].

Coronavirus (COVID-19) disease poses a threat for patients with cancer nowadays and may persist to be a problem for some time to come. Treatment with ICI's may ameliorate the early phase by contributing to viral clearance and also through the reactivation of PD-1þ viral epitope–specific T-cells. The opposite also can happen; promotion of different immune-activating mechanisms may favor progression of COVID-19 disease toward its more aggressive inflammatory late stage [92]. A study on 423 symptomatic COVID cases from the epicenter of the US outbreak noted substantial rates of hospitalization, severe respiratory outcomes (20%) and death (12%) in patients with cancer. Age older than 65 years and treatment with ICIs were the predictors for hospitalization and severe disease [93]. However, a study with a small number of patients found that PD-1 blockade did not appear to affect the severity of COVID-19 in patients with lung cancer [94].

Conclusions

Immune checkpoint immunotherapy is a major breakthrough in cancer treatment. The prognosis for many patients with NSCLC and other advanced solid tumors has improved. However, immune related adverse events do occur, and range from mild to severe and possibly life-threatening reactions. Though the reported numbers may seem clinically trivial at this point, the actual number in real-world populations may be high and definitely will increase as the therapeutic indications for ICIs continue to expand to include other malignancies. However, a risk assessment method for ICI induced pneumonitis has not been established and the prediction of pneumonitis occurrence is difficult. Presently, clinical vigilance, prompt detection, close monitoring and early intervention are key factors in management. Future developments could include discovery of new molecules, identification of biomarkers for predicting ICI efficacy or toxicity, and the introduction of less complex and less toxic combinations of chemotherapy and immunotherapy.

Conflict of interest

None declared.

References

1. Burney IA. Immunotherapy in cancer: incremental gain or a quantum leap? Oman Med J. 2017; 32(1): 1–2, doi: 10.5001/omj.2017.01, indexed in Pubmed: 28042395.
2. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med. 2015; 372(4): 311–319, doi: 10.1056/NEJMoa1411087, indexed in Pubmed: 25482239.
3. Bala-Hampton JE, Bazzell AF, Dains JE. Clinical management of pneumonitis in patients receiving snti-PD-1/PD-L1 therapy. J Adv Pract Oncol. 2018; 9(4): 422–428, indexed in Pubmed: 30719394.
4. Madden K, Kasler MK. Immune checkpoint inhibitors in lung cancer and melanoma. Semin Oncol Nurs. 2019; 35(5): 150932, doi: 10.1016/j.soncn.2019.08.011, indexed in Pubmed: 31561846.
5. Robert C. A decade of immune-checkpoint inhibitors in cancer therapy. Nat Commun. 2020; 11(1): 3801, doi: 10.1038/s41467-020-17670-y, indexed in Pubmed: 32732879.
6. Rosenberg J, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. The Lancet. 2016; 387(10031): 1909–1920, doi: 10.1016/s0140-6736(16)00561-4.
7. Suresh K, Naidoo J, Lin CT, et al. Immune checkpoint immunotherapy for non-small cell lung cancer: benefits and pulmonary toxicities. Chest. 2018; 154(6): 1416–1423, doi: 10.1016/j.chest.2018.08.1048, indexed in Pubmed: 30189190.
8. Vaddepally RK, Kharel P, Pandey R, et al. Review of indications of FDA-approved immune checkpoint inhibitors per NCCN guidelines with the level of evidence. Cancers (Basel). 2020; 12(3), doi: 10.3390/cancers12030738, indexed in Pubmed: 32245016.
9. Miranda Poma J, Ostios Garcia L, Villamayor Sanchez J, et al. What do we know about cancer immunotherapy? Long-term survival and immune-related adverse events. Allergol Immunopathol (Madr). 2019; 47(3): 303–308, doi: 10.1016/j.aller.2018.04.005, indexed in Pubmed: 29983240.
10. Sanghera C, Sanghera R. Immunotherapy - strategies for expanding its role in the treatment of all major tumor sites. Cureus. 2019; 11(10): e5938, doi: 10.7759/cureus.5938, indexed in Pubmed: 31788395.
11. Shannon VR. Pneumonitis associated with immune checkpoint inhibitors among patients with non-small cell lung cancer. Curr Opin Pulm Med. 2020; 26(4): 326–340, doi: 10.1097/MCP.0000000000000689, indexed in Pubmed: 32452900.
12. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity. 2013; 39(1): 1–10, doi: 10.1016/j.immuni.2013.07.012, indexed in Pubmed: 23890059.
13. Rashdan S, Minna J, Gerber D. Diagnosis and management of pulmonary toxicity associated with cancer immunotherapy. The Lancet Respiratory Medicine. 2018; 6(6): 472–478, doi: 10.1016/s2213-2600(18)30172-3.
14. Aldarouish M, Wang C. Trends and advances in tumor immunology and lung cancer immunotherapy. J Exp Clin Cancer Res. 2016; 35(1): 157, doi: 10.1186/s13046-016-0439-3, indexed in Pubmed: 27686848.
15. Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer. 2016; 54: 139–148, doi: 10.1016/j.ejca.2015.11.016, indexed in Pubmed: 26765102.
16. Matsushita H, Vesely MD, Koboldt DC, et al. Cancer exome analysis reveals a T-cell-dependent mechanism of cancer im-

munoediting. Nature. 2012; 482(7385): 400–404, doi: 10.1038/nature10755, indexed in Pubmed: 22318521.
17. Vinay DS, Ryan EP, Pawelec G, et al. Immune evasion in cancer: Mechanistic basis and therapeutic strategies. Semin Cancer Biol. 2015; 35 Suppl: S185–S198, doi: 10.1016/j.semcancer.2015.03.004, indexed in Pubmed: 25818339.
18. Gomatou G, Tzilas V, Kotteas E, et al. Immune checkpoint inhibitor-related pneumonitis. Respiration. 2020; 99(11): 932–942, doi: 10.1159/000509941, indexed in Pubmed: 33260191.
19. Zhu S, Fu Y, Zhu Bo, et al. Pneumonitis induced by immune checkpoint inhibitors: from clinical data to translational investigation. Front Oncol. 2020; 10: 1785, doi: 10.3389/fonc.2020.01785, indexed in Pubmed: 33042827.
20. Bagchi S, Yuan R, Engleman EG. Immune checkpoint inhibitors for the treatment of cancer: clinical impact and mechanisms of response and resistance. Annu Rev Pathol. 2021; 16: 223–249, doi: 10.1146/annurev-pathol-042020-042741, indexed in Pubmed: 33197221.
21. Calling time on the immunotherapy gold rush. The Lancet Oncology. 2017; 18(8): 981, doi: 10.1016/s1470-2045(17)30521-1.
22. Li L, Lou A, Yu J. Immune checkpoint inhibitor-related pneumonitis induced by camrelizumab: a case report and review of literature. Ann Palliat Med. 2021; 10(7): 8460–8466, doi: 10.21037/apm-21-23, indexed in Pubmed: 34044548.
23. Liu SY, Wu YL. Tislelizumab: an investigational anti-PD-1 antibody for the treatment of advanced non-small cell lung cancer (NSCLC). Expert Opin Investig Drugs. 2020; 29(12): 1355–1364, doi: 10.1080/13543784.2020.1833857, indexed in Pubmed: 33044117.
24. Deng H, Zhou C. From CheckMate 227 to CheckMate 9LA: rethinking the status of chemotherapy in the immunotherapy era-chemo-free or chemo-reform? Transl Lung Cancer Res. 2021; 10(4): 1924–1927, doi: 10.21037/tlcr-21-179, indexed in Pubmed: 34012802.
25. Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol. 2016; 27(7): 1362, doi: 10.1093/annonc/mdw141, indexed in Pubmed: 27072927.
26. Agrawal L, Bacal A, Jain S, et al. Immune checkpoint inhibitors and endocrine side effects, a narrative review. Postgrad Med. 2020; 132(2): 206–214, doi: 10.1080/00325481.2019.1709344, indexed in Pubmed: 31876444.
27. Khaddour K, Singh V, Shayuk M. Acral vascular necrosis associated with immune-check point inhibitors: case report with literature review. BMC Cancer. 2019; 19(1): 449, doi: 10.1186/s12885-019-5661-x, indexed in Pubmed: 31088420.
28. Haddox CL, Shenoy N, Shah KK, et al. Pembrolizumab induced bulbar myopathy and respiratory failure with necrotizing myositis of the diaphragm. Ann Oncol. 2017; 28(3): 673–675, doi: 10.1093/annonc/mdw655, indexed in Pubmed: 27993808.
29. Daxini A, Cronin K, Sreih AG. Vasculitis associated with immune checkpoint inhibitors-a systematic review. Clin Rheumatol. 2018; 37(9): 2579–2584, doi: 10.1007/s10067-018-4177-0, indexed in Pubmed: 29923081.
30. Drobni ZD, Alvi RM, Taron J, et al. Association between immune checkpoint inhibitors with cardiovascular events and atherosclerotic plaque. Circulation. 2020; 142(24): 2299–2311, doi: 10.1161/CIRCULATIONAHA.120.049981, indexed in Pubmed: 33003973.
31. Abdel-Rahman O, Fouad M. Risk of pneumonitis in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. Ther Adv Respir Dis. 2016; 10(3): 183–193, doi: 10.1177/1753465816636557, indexed in Pubmed: 26944362.
32. Su Q, Zhu EC, Wu JB, et al. Risk of pneumonitis and pneumonia associated with immune checkpoint inhibitors for solid tumors: a systematic review and meta-analysis. Front Immunol. 2019; 10: 108, doi: 10.3389/fimmu.2019.00108, indexed in Pubmed: 30778352.
33. Del Castillo M, Romero FA, Argüello E, et al. The spectrum of serious infections among patients receiving immune checkpoint blockade for the treatment of melanoma. Clin Infect Dis. 2016; 63(11): 1490–1493, doi: 10.1093/cid/ciw539, indexed in Pubmed: 27501841.
34. Senan S, Bahce I. Pulmonary toxicity in patients treated with immune checkpoint inhibitors and radiation. Ann Oncol. 2020; 31(12): 1597–1598, doi: 10.1016/j.annonc.2020.10.476, indexed in Pubmed: 33091560.
35. Abdel-Wahab N, Diab A, Yu RK, et al. Genetic determinants of immune-related adverse events in patients with melanoma receiving immune checkpoint inhibitors. Cancer Immunol Immunother. 2021; 70(7): 1939–1949, doi: 10.1007/s00262-020-02797-0, indexed in Pubmed: 33409738.
36. Okada N, Matsuoka R, Sakurada T, et al. Risk factors of immune checkpoint inhibitor-related interstitial lung disease in patients with lung cancer: a single-institution retrospective study. Sci Rep. 2020; 10(1): 13773, doi: 10.1038/s41598-020-70743-2, indexed in Pubmed: 32792640.
37. Reuss JE, Suresh K, Naidoo J. Checkpoint inhibitor pneumonitis: mechanisms, characteristics, management strategies, and beyond. Curr Oncol Rep. 2020; 22(6): 56, doi: 10.1007/s11912-020-00920-z, indexed in Pubmed: 32415399.
38. Sears CR, Peikert T, Possick JD, et al. Knowledge gaps and research priorities in immune checkpoint inhibitor-related pneumonitis. An official American Thoracic Society research statement. Am J Respir Crit Care Med. 2019; 200(6): e31–e43, doi: 10.1164/rccm.201906-1202ST, indexed in Pubmed: 31518182.
39. Haanen JB, Carbonnel F, Robert C, et al. ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017; 28(suppl_4): iv119–iv142, doi: 10.1093/annonc/mdx225, indexed in Pubmed: 28881921.
40. Puzanov I, Diab A, Abdallah K, et al. Society for Immunotherapy of Cancer Toxicity Management Working Group. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer. 2017; 5(1): 95, doi: 10.1186/s40425-017-0300-z, indexed in Pubmed: 29162153.
41. Nishino M, Giobbie-Hurder A, Hatabu H, et al. Incidence of programmed cell death 1 inhibitor-related pneumonitis in patients with advanced cancer: A systematic review and meta-analysis. JAMA Oncol. 2016; 2(12): 1607–1616, doi: 10.1001/jamaoncol.2016.2453, indexed in Pubmed: 27540850.
42. Wu J, Hong D, Zhang X, et al. PD-1 inhibitors increase the incidence and risk of pneumonitis in cancer patients in a dose-independent manner: a meta-analysis. Sci Rep. 2017; 7: 44173, doi: 10.1038/srep44173, indexed in Pubmed: 28272463.
43. Delaunay M, Cadranel J, Lusque A, et al. Immune-checkpoint inhibitors associated with interstitial lung disease in cancer patients. Eur Respir J. 2017; 50(2), doi: 10.1183/13993003.00050-2017, indexed in Pubmed: 28798088.
44. Naidoo J, Wang X, Woo KM, et al. Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. J Clin Oncol. 2017; 35(7): 709–717, doi: 10.1200/JCO.2016.68.2005, indexed in Pubmed: 27646942.
45. Khunger M, Rakshit S, Pasupuleti V, et al. Incidence of pneumonitis with use of programmed death 1 and programmed death-ligand 1 inhibitors in non-small cell lung cancer: A systematic review and meta-analysis of trials. Chest. 2017; 152(2): 271–281, doi: 10.1016/j.chest.2017.04.177, indexed in Pubmed: 28499515.
46. Fukihara J, Sakamoto K, Koyama J, et al. Prognostic impact and risk factors of immune-related pneumonitis in patients with non-small-cell lung cancer who received programmed death 1 inhibitors. Clin Lung Cancer. 2019; 20(6): 442–450.e4, doi: 10.1016/j.cllc.2019.07.006, indexed in Pubmed: 31446020.
47. Suresh K, Voong KR, Shankar B, et al. Pneumonitis in non-small cell lung cancer patients receiving immune checkpoint immunotherapy: incidence and risk factors. J Thorac Oncol. 2018; 13(12): 1930–1939, doi: 10.1016/j.jtho.2018.08.2035, indexed in Pubmed: 30267842.
48. Khoja L, Day D, Wei-Wu Chen T, et al. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. Ann Oncol. 2017; 28(10): 2377–2385, doi: 10.1093/annonc/mdx286, indexed in Pubmed: 28945858.
49. Cui P, Liu Z, Wang G, et al. Risk factors for pneumonitis in patients treated with anti-programmed death-1 therapy: A case-control study. Cancer Med. 2018; 7(8): 4115–4120, doi: 10.1002/cam4.1579, indexed in Pubmed: 29797416.

50. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med. 2018; 378(22): 2093–2104, doi: 10.1056/NEJMoa1801946, indexed in Pubmed: 29658845.
51. Oshima Y, Tanimoto T, Yuji K, et al. EGFR-TKI-associated interstitial pneumonitis in nivolumab-treated patients with non-small cell lung cancer. JAMA Oncol. 2018; 4(8): 1112–1115, doi: 10.1001/jamaoncol.2017.4526, indexed in Pubmed: 29327061.
52. Xu Z, Feng J, Weng Y, et al. Combination of immune checkpoint inhibitors and radiotherapy for advanced non-small-cell lung cancer and prostate cancer: A meta-analysis. J Oncol. 2021; 2021: 6631643, doi: 10.1155/2021/6631643, indexed in Pubmed: 33488711.
53. Voong KR, Hazell SZ, Fu W, et al. Relationship between prior radiotherapy and checkpoint-inhibitor pneumonitis in patients with advanced non-small-cell lung cancer. Clin Lung Cancer. 2019; 20(4): e470–e479, doi: 10.1016/j.cllc.2019.02.018, indexed in Pubmed: 31031204.
54. Tian S, Switchenko JM, Buchwald ZS, et al. Lung stereotactic body radiation therapy and concurrent immunotherapy: a multicenter safety and toxicity analysis. Int J Radiat Oncol Biol Phys. 2020; 108(1): 304–313, doi: 10.1016/j.ijrobp.2019.12.030, indexed in Pubmed: 31982496.
55. Sul J, Blumenthal GM, Jiang X, et al. FDA approval summary: pembrolizumab for the treatment of patients with metastatic non-small cell lung cancer whose tumors express programmed death-ligand 1. Oncologist. 2016; 21(5): 643–650, doi: 10.1634/theoncologist.2015-0498, indexed in Pubmed: 27026676.
56. Cho JY, Kim J, Lee JS, et al. Characteristics, incidence, and risk factors of immune checkpoint inhibitor-related pneumonitis in patients with non-small cell lung cancer. Lung Cancer. 2018; 125: 150–156, doi: 10.1016/j.lungcan.2018.09.015, indexed in Pubmed: 30429014.
57. Davies M. Acute and long-term adverse events associated with checkpoint blockade. Semin Oncol Nurs. 2019; 35(5): 150926, doi: 10.1016/j.soncn.2019.08.005, indexed in Pubmed: 31514992.
58. Thomas R, Sebastian B, George T, et al. A review of the imaging manifestations of immune check point inhibitor toxicities. Clin Imaging. 2020; 64: 70–79, doi: 10.1016/j.clinimag.2020.04.007, indexed in Pubmed: 32334270.
59. Murphy KP, Kennedy MP, Barry JE, et al. New-onset mediastinal and central nervous system sarcoidosis in a patient with metastatic melanoma undergoing CTLA4 monoclonal antibody treatment. Oncol Res Treat. 2014; 37(6): 351–353, doi: 10.1159/000362614, indexed in Pubmed: 24903767.
60. Nishino M, Ramaiya NH, Awad MM, et al. PD-1 inhibitor-related pneumonitis in advanced cancer patients: radiographic patterns and clinical course. Clin Cancer Res. 2016; 22(24): 6051–6060, doi: 10.1158/1078-0432.CCR-16-1320, indexed in Pubmed: 27535979.
61. Franzen D, Schad K, Kowalski B, et al. Ipilimumab and early signs of pulmonary toxicity in patients with metastastic melanoma: a prospective observational study. Cancer Immunol Immunother. 2018; 67(1): 127–134, doi: 10.1007/s00262-017-2071-2, indexed in Pubmed: 28983773.
62. Cadranel J, Canellas A, Matton L, et al. Pulmonary complications of immune checkpoint inhibitors in patients with non-small cell lung cancer. Eur Respir Rev. 2019; 28(153), doi: 10.1183/16000617.0058-2019, indexed in Pubmed: 31597674.
63. Nishiyama O, Shimizu S, Haratani K, et al. Clinical implications of bronchoscopy for immune checkpoint inhibitor-related pneumonitis in patients with non-small cell lung cancer. BMC Pulm Med. 2021; 21(1): 155, doi: 10.1186/s12890-021-01523-5, indexed in Pubmed: 33964920.
64. Wang YiNa, Lou DF, Li DY, et al. Elevated levels of IL-17A and IL-35 in plasma and bronchoalveolar lavage fluid are associated with checkpoint inhibitor pneumonitis in patients with non-small cell lung cancer. Oncol Lett. 2020; 20(1): 611–622, doi: 10.3892/ol.2020.11618, indexed in Pubmed: 32565986.
65. Schoenfeld JD, Nishino M, Severgnini M, et al. Pneumonitis resulting from radiation and immune checkpoint blockade illustrates characteristic clinical, radiologic and circulating biomarker features. J Immunother Cancer. 2019; 7(1): 112, doi: 10.1186/s40425-019-0583-3, indexed in Pubmed: 31014385.
66. Chu X, Zhao J, Zhou J, et al. Association of baseline peripheral-blood eosinophil count with immune checkpoint inhibitor-related pneumonitis and clinical outcomes in patients with non-small cell lung cancer receiving immune checkpoint inhibitors. Lung Cancer. 2020; 150: 76–82, doi: 10.1016/j.lungcan.2020.08.015, indexed in Pubmed: 33080551.
67. Xu Ya, Fu Y, Zhu Bo, et al. Predictive biomarkers of immune checkpoint inhibitors-related toxicities. Front Immunol. 2020; 11: 2023, doi: 10.3389/fimmu.2020.02023, indexed in Pubmed: 33123120.
68. Brahmer JR, Lacchetti C, Thompson JA. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline summary. J Oncol Pract. 2018; 14(4): 247–249, doi: 10.1200/JOP.18.00005, indexed in Pubmed: 29517954.
69. Champiat S, Lambotte O, Barreau E, et al. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. Ann Oncol. 2016; 27(4): 559–574, doi: 10.1093/annonc/mdv623, indexed in Pubmed: 26715621.
70. Balaji A, Hsu M, Lin CT, et al. Steroid-refractory PD-(L)1 pneumonitis: incidence, clinical features, treatment, and outcomes. J Immunother Cancer. 2021; 9(1), doi: 10.1136/jitc-2020-001731, indexed in Pubmed: 33414264.
71. Shannon VR, Subudhi SK, Huo L, et al. Diffuse alveolar hemorrhage with nivolumab monotherapy. Respir Med Case Rep. 2020; 30: 101131, doi: 10.1016/j.rmcr.2020.101131, indexed in Pubmed: 32577370.
72. Utsumi H, Araya J, Okuda K, et al. Successful treatment of steroid-refractory immune checkpoint inhibitor-related pneumonitis with triple combination therapy: a case report. Cancer Immunol Immunother. 2020; 69(10): 2033–2039, doi: 10.1007/s00262-020-02600-0, indexed in Pubmed: 32415507.
73. Petri CR, Patell R, Batalini F, et al. Severe pulmonary toxicity from immune checkpoint inhibitor treated successfully with intravenous immunoglobulin: Case report and review of the literature. Respir Med Case Rep. 2019; 27: 100834, doi: 10.1016/j.rmcr.2019.100834, indexed in Pubmed: 31008047.
74. Martins F, Sykiotis G, Maillard M, et al. New therapeutic perspectives to manage refractory immune checkpoint-related toxicities. The Lancet Oncology. 2019; 20(1): e54–e64, doi: 10.1016/s1470-2045(18)30828-3.
75. Stroud CRg, Hegde A, Cherry C, et al. Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade. J Oncol Pharm Pract. 2019; 25(3): 551–557, doi: 10.1177/1078155217745144, indexed in Pubmed: 29207939.
76. Berthod G, Lazor R, Letovanec I, et al. Pulmonary sarcoid-like granulomatosis induced by ipilimumab. J Clin Oncol. 2012; 30(17): e156–e159, doi: 10.1200/JCO.2011.39.3298, indexed in Pubmed: 22547608.
77. Faviez G, Bousquet E, Rabeau A, et al. [Sarcoid-like granulomatosis in cancer patients treated with immune checkpoints inhibitors]. Rev Mal Respir. 2018; 35(9): 963–967, doi: 10.1016/j.rmr.2018.08.003, indexed in Pubmed: 30220489.
78. Gkiozos I, Kopitopoulou A, Kalkanis A, et al. Sarcoidosis-like reactions induced by checkpoint inhibitors. J Thorac Oncol. 2018; 13(8): 1076–1082, doi: 10.1016/j.jtho.2018.04.031, indexed in Pubmed: 29763666.
79. Mitchell MA, Hogan K, Amjadi K. Atezolizumab-induced sarcoid-like granulomatous reaction in a patient with urothelial cell carcinoma. Immunotherapy. 2018; 10(14): 1189–1192, doi: 10.2217/imt-2018-0035, indexed in Pubmed: 30326785.
80. Reuss JE, Kunk PR, Stowman AM, et al. Sarcoidosis in the setting of combination ipilimumab and nivolumab immunotherapy: a case report & review of the literature. J Immunother Cancer. 2016; 4: 94, doi: 10.1186/s40425-016-0199-9, indexed in Pubmed: 28031822.
81. Montaudié H, Pradelli J, Passeron T, et al. Pulmonary sarcoid-like granulomatosis induced by nivolumab. Br J Dermatol. 2017; 176(4): 1060–1063, doi: 10.1111/bjd.14808, indexed in Pubmed: 27291635.
82. Bukamur H, Katz H, Alsharedi M, et al. Immune checkpoint inhibitor-related pulmonary toxicity: focus on nivolum-

ab. South Med J. 2020; 113(11): 600–605, doi: 10.14423/SMJ.0000000000001166, indexed in Pubmed: 33140115.
83. Picchi H, Mateus C, Chouaid C, et al. Infectious complications associated with the use of immune checkpoint inhibitors in oncology: reactivation of tuberculosis after anti PD-1 treatment. Clin Microbiol Infect. 2018; 24(3): 216–218, doi: 10.1016/j.cmi.2017.12.003, indexed in Pubmed: 29269089.
84. Reungwetwattana T, Adjei AA. Anti-PD-1 antibody treatment and the development of acute pulmonary tuberculosis. J Thorac Oncol. 2016; 11(12): 2048–2050, doi: 10.1016/j.jtho.2016.10.008, indexed in Pubmed: 27866633.
85. Inthasot V, Bruyneel M, Muylle I, et al. Severe pulmonary infections complicating nivolumab treatment for lung cancer: a report of two cases. Acta Clin Belg. 2020; 75(4): 308–310, doi: 10.1080/17843286.2019.1629078, indexed in Pubmed: 31179880.
86. Maeno K, Fukuda S, Oguri T, et al. Nivolumab-induced asthma in a patient with non-small-cell lung cancer. Ann Oncol. 2017; 28(11): 2891, doi: 10.1093/annonc/mdx455, indexed in Pubmed: 28945837.
87. Roger A, Groh M, Lorillon G, et al. PATIO group. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) induced by immune checkpoint inhibitors. Ann Rheum Dis. 2019; 78(8): e82, doi: 10.1136/annrheumdis-2018-213857, indexed in Pubmed: 29936437.
88. Pradere P, Michot JM, Champiat S, et al. Allergic broncho-pulmonary aspergillosis following treatment with an anti-programmed cell death protein 1 monoclonal antibody therapy. Eur J Cancer. 2017; 75: 308–309, doi: 10.1016/j.ejca.2016.12.027, indexed in Pubmed: 28259013.
89. Jia W, Gao Q, Han A, et al. The potential mechanism, recognition and clinical significance of tumor pseudoprogression after immunotherapy. Cancer Biol Med. 2019; 16(4): 655–670, doi: 10.20892/j.issn.2095-3941.2019.0144, indexed in Pubmed: 31908886.
90. Marwitz S, Scheufele S, Perner S, et al. Epigenetic modifications of the immune-checkpoint genes and in non-small cell lung cancer results in increased expression. Clin Epigenetics. 2017; 9: 51, doi: 10.1186/s13148-017-0354-2, indexed in Pubmed: 28503213.
91. Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science. 2018; 359(6371): 91–97, doi: 10.1126/science.aan3706, indexed in Pubmed: 29097494.
92. Maio M, Hamid O, Larkin J, et al. Immune checkpoint inhibitors for cancer therapy in the COVID-19 era. Clin Cancer Res. 2020; 26(16): 4201–4205, doi: 10.1158/1078-0432.CCR-20-1657, indexed in Pubmed: 32540850.
93. Robilotti EV, Babady NE, Mead PA, et al. Determinants of COVID-19 disease severity in patients with cancer. Nat Med. 2020; 26(8): 1218–1223, doi: 10.1038/s41591-020-0979-0, indexed in Pubmed: 32581323.
94. Luo J, Rizvi H, Egger JV, et al. Impact of PD-1 blockade on severity of COVID-19 in patients with lung cancers. Cancer Discov. 2020; 10(8): 1121–1128, doi: 10.1158/2159-8290.CD-20-0596, indexed in Pubmed: 32398243.