VIA MEDICA

Review article

NOWOTWORY Journal of Oncology
2020, volume 70, number 3, 105–110
DOI: 10.5603/NJO.2020.0023
© Polskie Towarzystwo Onkologiczne
ISSN 0029–540X
www.nowotwory.edu.pl

Pulmonary toxicities of immune checkpoint inhibitors

Magdalena Knetki-Wróblewska[1], Joanna Domagała-Kulawik[2]

[1]*Department of Lung Cancer and Chest Tumors, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland*
[2]*Department of Internal Medicine, Pulmonary Diseases and Allergy, Medical University of Warsaw, Warsaw, Poland*

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.

NOWOTWORY J Oncol 2020; 70, 3: 105–110

Key words: pneumonitis, immune related adverse events, immune checkpoint inhibitors

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

How to cite:
Knetki-Wróblewska M, Domagała-Kulawik J. ***Pulmonary toxicities of immune checkpoint inhibitors.*** *NOWOTWORY J Oncol* 2020; 70: 105–110.

ipilumumab 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 adiuvant 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 beween 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 tachypnoe, 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 bronchofiberoscope. 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

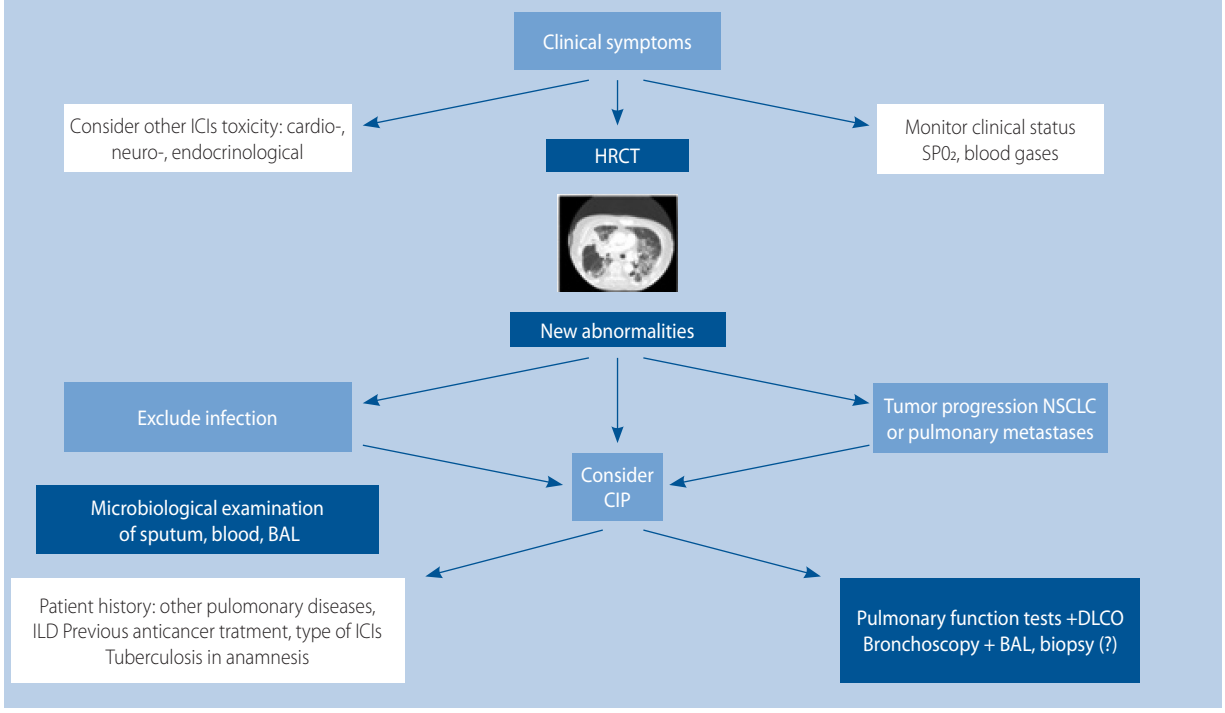

Figure 1. Diagnosis and differential diagnosis of checkpoint inhibitors pneumonitis (CIP). HRCT – high resolution computed tomography, BAL – bronchoalveolar lavage, $SP0_2$ – oxygen blood saturation, DLCO – diffusing capacity, ILD – interstitial lung disease, NSCLC – non-small-cell lung cancer

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 2550% 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 guidlines – amoxicilin or levofloxacin might be a first option for outpatients [26]. If no evidence of infection – steroids tretment 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-threating 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 ICPs [1, 19, 24, 25]

SITC	– 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 sypmtoms – consider continuation of therapy with close follow-up	– Hold ICI – Pulmonary consultation for bronchoscopy with bronchoalveolar lavage methylprednisolone 1 mg/kg/day (*i.v.* or oral equivalent) – Improvement – steroid taper over >4 weeks – Worsening – treat as grade 3–4 – Consider continuation ICI when symptoms and imaging abnormalities resolve	– Discontinue ICI – Pulmonary consultation for bronchoscopy with bronchoalveolar lavage – Methylprednisolone *i.v.* 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	– 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	– 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	– Permanently discontinue ICI – Bronchoscopy with BAL, consider lung biopsy – Empirical antibiotics; (methyl)prednisolone *i.v.* 1–2 mg/kg/d – No improvement after 48 hours – infliximab 5 mg/kg or mycophenolate mofetil *i.v.* 1 g twice a day or IVI G for 5 days or cyclophosphamide – Improvement – taper corticosteroids over 4–6 weeks
NCCN	– Consider holding ICI – Reassess in 1–2 weeks – Monitor symptoms and pulsoximetry – Consider CT scan in 4 weeks – Continuation of ICI after radiographic improvement	– Hold ICI – Consider bronchoscopy with BAL – Consider empirical antibiotics if ifnection has not been fully excluded – Prednisone/methylprednisolon 1–2 mg/kg/d – Tapering dose over 4–6 weeks	– Discontinue ICI – (methyl) prednisolone i.v. 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.v.* 1–1.5 g twice a day
ESMO	– Consider delay of treatment – Monitor symptoms every 2–3 days – If worsens – treat as grade 2 or 3–4	– 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	– Discontinue ICPi – (methyl) prednisolone *i.v.* 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	– 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	– Methylprednisolne *i.v.* 1–2 mg/kg – Empirical antibiotics – Prophyllaxis (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 ≥ 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]. Prophyllaxis 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 ≥4 weeks [24, 25, 27]. Prophyllaxis of fungal infections is questionable, some recomendations suggests fluconazol for patient who receiving at least 20 mg methylprednisolone or equivalent for ≥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 (genaral guidlines 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 prednison/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

Magdalena Knetki-Wróblewska
Maria Skłodowska-Curie National Research Institute of Oncology
Department of Lung Cancer and Chest Tumours
ul. Roentgena 5
02-781 Warszawa, Poland
e-mail: Magdalena.Knetki-Wroblewska@pib-nio.pl

Received and accepted: 27 Feb 2020

References

1. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018; 36(17): 1714–1768, doi: 10.1200/JCO.2017.77.6385, indexed in Pubmed: 29442540.
2. Liu YH, Zang XY, Wang JC, et al. Diagnosis and Management of Immune Related Adverse Events (irAEs) in Cancer Immunotherapy. Biomed Pharmacother. 2019; 120: 109437, doi: 10.1016/j.biopha.2019.109437, indexed in Pubmed: 31590992.
3. Wang DY, Salem JE, Cohen JV, et al. Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. JAMA Oncol. 2018; 4(12): 1721–1728, doi: 10.1001/jamaoncol.2018.3923, indexed in Pubmed: 30242316.
4. Cadranel J, Canellas A, Matton L, et al. Pulmonary complications of immune checkpoint inhibitors in patients with nonsmall cell lung cancer. Eur Respir Rev. 2019; 28(153), doi: 10.1183/16000617.0058-2019, indexed in Pubmed: 31597674.
5. 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.

6. 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.
7. 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.
8. 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.
9. Gray JE, Villegas A, Daniel D, et al. PACIFIC Investigators. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl J Med. 2018; 379(24): 2342–2350, doi: 10.1056/NEJMoa1809697, indexed in Pubmed: 30280658.
10. 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.
11. Fujimoto D, Morimoto T, Ito J, et al. A pilot trial of nivolumab treatment for advanced non-small cell lung cancer patients with mild idiopathic interstitial pneumonia. Lung Cancer. 2017; 111: 1–5, doi: 10.1016/j.lungcan.2017.06.008, indexed in Pubmed: 28838377.
12. Yamaguchi T, Shimizu J, Hasegawa T, et al. Pre-existing pulmonary fibrosis is a risk factor for anti-PD-1-related pneumonitis in patients with non-small cell lung cancer: A retrospective analysis. Lung Cancer. 2018; 125: 212–217, doi: 10.1016/j.lungcan.2018.10.001, indexed in Pubmed: 30429022.
13. Leonardi GC, Gainor JF, Altan M, et al. Safety of Programmed Death-1 Pathway Inhibitors Among Patients With Non-Small-Cell Lung Cancer and Preexisting Autoimmune Disorders. J Clin Oncol. 2018; 36(19): 1905–1912, doi: 10.1200/JCO.2017.77.0305, indexed in Pubmed: 29746230.
14. Yoneshima Y, Tanaka K, Shiraishi Y, et al. Safety and efficacy of PD-1 inhibitors in non-small cell lung cancer patients positive for antinuclear antibodies. Lung Cancer. 2019; 130: 5–9, doi: 10.1016/j.lungcan.2019.01.014, indexed in Pubmed: 30885351.
15. Ma Ke, Lu Y, Jiang S, et al. The Relative Risk and Incidence of Immune Checkpoint Inhibitors Related Pneumonitis in Patients With Advanced Cancer: A Meta-Analysis. Front Pharmacol. 2018; 9: 1430, doi: 10.3389/fphar.2018.01430, indexed in Pubmed: 30618738.
16. 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.
17. 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.
18. 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.
19. 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.
20. Domagala-Kulawik J. The relevance of bronchoalveolar lavage fluid analysis for lung cancer patients. Expert Rev Respir Med. 2019; 14(3): 329–337, doi: 10.1080/17476348.2020.1708720.
21. Suresh K, Naidoo J, Zhong Q, et al. The alveolar immune cell landscape is dysregulated in checkpoint inhibitor pneumonitis. J Clin Invest. 2019; 130: 4305–4315, doi: 10.1172/JCI128654, indexed in Pubmed: 31310589.
22. Tanaka K, Yanagihara T, Ikematsu Y, et al. Detection of identical T cell clones in peritumoral pleural effusion and pneumonitis lesions in a cancer patient during immune-checkpoint blockade. Oncotarget. 2018; 9(55): 30587–30593, doi: 10.18632/oncotarget.25743, indexed in Pubmed: 30093971.
23. Martins F, Sykiotis GP, Maillard M, et al. New therapeutic perspectives to manage refractory immune checkpoint-related toxicities. Lancet Oncol. 2019; 20(1): e54–e64, doi: 10.1016/S1470-2045(18)30828-3, indexed in Pubmed: 30614479.
24. Haanen J, Carbonnel F, Robert C. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017; 28: 119–142.
25. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.
26. http://antybiotyki.edu.pl/rekomendacje/rekomendacje-diagnostyki--i-terapii-zakazen/.
27. Caplan A, Fett N, Rosenbach M, et al. Prevention and management of glucocorticoid-induced side effects: A comprehensive review: Infectious complications and vaccination recommendations. J Am Acad Dermatol. 2017; 76(2): 191–198, doi: 10.1016/j.jaad.2016.02.1240, indexed in Pubmed: 28088990.
28. O'Kane GM, Labbé C, Doherty MK, et al. Monitoring and Management of Immune-Related Adverse Events Associated With Programmed Cell Death Protein-1 Axis Inhibitors in Lung Cancer. Oncologist. 2017; 22(1): 70–80, doi: 10.1634/theoncologist.2016-0164, indexed in Pubmed: 27534573.