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REVIEW ARTICLE

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# Management of nivolumab-induced pulmonary toxicity — pneumonitis

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## ABSTRACT

Immune-mediated pneumonitis is an uncommon but potentially life-threatening toxicity of nivolumab. The incidence of pneumonitis is < 10%, but may be higher when nivolumab is combined with other agents. In most cases pneumonitis is recognised in the first weeks of treatment. Dry cough and dyspnoea are the most common signs of this adverse event. Diagnostic algorithms recommend radiological investigation with a chest computed tomography scan. In cases of grade 2 or higher pneumonitis, bronchoscopy with BAL is recommended. Management should be conducted according to the clinical symptoms; corticosteroids and antibiotics are the drugs of choice. In severe cases, hospitalisation is necessary and other forms of immunosuppression (infliximab, mycophenolate mofetil) may be considered.

**Key words**: nivolumab, pulmonary toxicity

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## Introduction

In recent years, immunocompetent drugs have become more and more important in oncological therapy. Nivolumab, a human monoclonal antibody belonging to the immunoglobulins class G4 (IgG4) is one of these agents. Nivolumab binds to the programmed death type 1 receptor (PD-1) and blocks its interaction with PD-L1 and PD-L2 ligands. An important clinical benefit of nivolumab administration has been demonstrated in patients with melanoma, non-small cell lung cancer, clear cell renal cancer, Hodgkin lymphoma, squamous cell head and neck carcinoma, and urinary bladder cancer [1].

The use of nivolumab and other immunocompetent drugs is associated with the risk of the occurrence of immune-related adverse events (irAE). The most frequent are endocrinopathies (impaired function of the thyroid gland) and skin changes [2]. In a small percentage of patients, parenchymal complications are diagnosed including the involvement of the respiratory system.

This paper discusses the issues concerning the pulmonary toxicity of nivolumab-epidemiologic data, and the symptomatology and diagnostic and management recommendations of this rare but potentially fatal complication.

## Symptomatology

In patients with immune-mediated pneumonitis cough and dyspnoea are usually present, and sometimes we may also observe elevated body temperature and chest pain. In the majority of cases, the immune-induced pneumonitis is diagnosed in the first weeks of therapy; however, it may occur even after several or a dozen months from the start of the therapy with the immunocompetent drug [3, 4]. The median time from the beginning of the immunocompetent therapy to the occurrence of symptoms of immune-induced pneumonitis is 10 weeks [3].

In differential diagnosis, other causes of the observed symptoms should be included. First the progression of the neoplastic disease (in the case of the lung cancer patients or patients with another neoplasm but with the presence of lung metastases), and then infectious complications and other immune dependent adverse events.

**Table 1. The most common causes of occurrence of lung and chest symptoms in patients with diagnosed lung cancer [5]**

| General and oncologic symptoms | Immunologic reasons |
|---|---|
| Pneumonitis | Immunologic pneumonitis |
| Progression of the neoplastic changes in the lungs | Endocarditis |
| Pulmonary thromboembolism | Pericarditis |
| Chest infiltration | Polyradiculopathy |
| Progression of the bone changes | |
| Oedema | |
| Anaemia | |
| Overdose of opioids | |

**Table 2. Grades of pulmonary toxicity according to CTCAE criteria [6]**

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|
| **Symptoms** | Diagnostic observation only<br>Clinically asymptomatic | Clinical symptoms<br>Restriction of patient's activity<br>Intervention indicated | Intensive clinical symptoms,<br>Oxygen therapy | Life-threatening symptoms | Death |

The most common respiratory symptoms of autoimmune pneumonitis:
— dyspnoea;
— cough;
— haemoptysis;
— chest pain.

The Table 1 presents the most frequent lung and chest symptoms in patients with diagnosed lung cancer.

The intensity of the respiratory tract syndromes may vary. Sometimes only a few abnormalities are detected on routinely performed imaging tests evaluating the efficacy of the immunocompetent therapy. In other cases the patient's condition deteriorates rapidly and admission to an Intensive Care Unit becomes necessary.

The Common Toxicity Criteria of Adverse Events (CTCAE) grades of toxicity are presented in Table 2.

## Prevalence

A meta-analysis involving 11 phase II and phase III clinical trials and a group of 6004 patients (including 3595 patients receiving immunocompetent drugs: nivolumab, pembrolizumab, atezolizumab, ipilimumab) showed a modest increase of the relative risk of the occurrence of pulmonary complications in patients receiving immunocompetent drugs compared to patients on chemotherapy (RR 2.65, p = 0.06). A separate analysis of patients treated with nivolumab (the patient treated in the Check Matc-025 study had been excluded from this analysis) has proven an increased relative risk of pulmonary toxicity grade 1 or 2 (RR 2.99, p = 0.02) [7]. In the studies that were included in the presented meta-analysis, the pulmonary complications related to the administration of nivolumab occurred rarely, in about 3–5% of patients, and grade 3 or higher in only 1% of treated persons [7]. More frequently (in about 10% of patients) this complication was diagnosed in patients receiving concurrently nivolumab and ipilimumab [3].

The Table 3 presents the data concerning the prevalence of pulmonary toxicities treated with nivolumab in the randomised, phase III clinical trials.

## Risk factors of immune pneumonitis occurrence

The factors potentially increasing the risk of immunocompetent drug-induced pulmonary toxicity include: diagnosis of lung cancer, advanced age, presence of chronic obstructive pulmonary disease (COPD), cigarette smoking, and previous chest radiotherapy [3, 4]. Special attention should be drawn to patients with sarcopaenia, patients on beta-blockers, antibiotics (quinolones, beta-lactams), or on antiarrhythmic agents or on anticonvulsants and with familial history of autoimmune disorders (presented clinical factors increase the risk of all type of complications related to the immune system) [5, 14].

**Table 3. The prevalence of pulmonary complications in patients treated with nivolumab within the phase III clinical trials**

| Study/Author | Indication | Number of patients receiving nivolumab | Pulmonary complications | | | |
|---|---|---|---|---|---|---|
| | | | Any grade (%) | | Grade ≥ 3 (%) | |
| Borghaei 2015 [8] | Non-squamous lung cancer | 292 | 2 | | 1 | |
| Brahmer 2015 [9] | Squamous lung cancer | 131 | 2 | | - | |
| Motzer 2015 [10] | Clear cell renal cancer | 410 | 4 | | 1 | |
| Ferris 2016 [11] | Head and neck Cancers | 240 | 2.1 | | 1 patient | |
| Weber 2015 [12] | Melanoma | 272 | 2 | | - | |
| Larkin 2015 [13] | Melanoma* | 630 (314 in combination with ipilimumab) | N | N+I | N | N+I |
| | | | 4.5 | 10.2 | 0.3 | 0.6 |

*The authors quote the percentage of patients in whom dyspnoea was observed. N — nivolumab; I — ipilimumab

## Diagnostics

Diagnosis of immune-modulated pneumonitis is based on exclusion of other causes of the abnormalities observed in the imaging exams and of the concomitant clinical syndromes. Computed tomography (CT) imaging is essential in the diagnostics of patients on immunocompetent therapy, who experience exacerbation of dyspnoea, cough, or chest pain [15, 16]. It permits exclusion of progression of neoplastic disease as a reason for the deterioration of a patient's clinical state and other aetiological factors of dyspnoea (pericardial effusion, pleural effusion, pulmonary thromboembolism). A radiological image of the immune-mediated pneumonitis may be variable. Several types of radiological changes related to immunocompetent-drugs have been described (Fig. 1) [16]:

— cryptogenic organising pneumonia (COP),
— ground glass opacities (GGO);
— interstitial changes;
— hypersensitivity;
— pneumonitis not otherwise specified.

In patients admitted to the ward it is recommended that bronchoscopy with bronchoalveolar lavage (BAL) be performed as well as microbiological tests. The microbiological screening should include, despite the typical pathogens of the lower respiratory tract infections, testing for the presence of *Pneumocystis jirovecii, Pneumocystis carinii, Legionella pneumophilia, Chlamydia pneumoniae, Mycoplasma pneumoniae*, and of the flu virus [17]. Moreover, the microbiological diagnostics should be based on the sputum culture and the peripheral blood culture.

A lung biopsy done during the bronchoscopy may also be helpful. In some cases the pathomorphological image indicates the diffuse alveolar damage (DAD), organising pneumonia (OP), or an interstitial pneumonia [16].

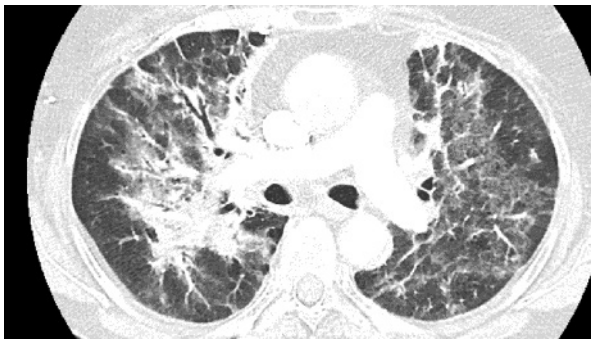

**Figure 1.** Radiological image of immune-mediated pneumonitis during nivolumab therapy (CT scan from the archives of Oncology Centre Institute)

## Treatment

The therapeutic approach is determined by the intensity of the respiratory tract syndromes. Careful observation of patients and an appropriate therapy started immediately after occurrence of the symptoms enables radiological regression and improvement of the clinical state in about 90% of patients [16].

If the radiological test detects some abnormalities, but they are not associated with any clinical symptoms (CTCAE grade I), watchful observation of the patient is recommended (control every 72 hours) as well as continuation of the immunocompetent therapy [4].

In patients with moderate symptoms (most frequently cough and dyspnoea, CTCAE grade 2) a temporary withdrawn of the nivolumab therapy and performing a chest CT is recommended. In the case of detection of interstitial inflammatory changes it is recommended to start oral corticosteroids (methyltrienolone 1 mg/kg/day). It is also recommended that clinical evaluation of the patient's state is repeated after 72 hours of treatment. If no clinical improvement is achieved,

**Table 4. Management schedule of patients with immunocompetent agents induced pneumonitis [3]**

| Grade 1 | Grade 2 | Grade 3–4 |
|---|---|---|
| Continuation of the immunotherapy | STOPPING OF THE IMMUNOTHERAPY | HOSPITALIZATION |
| Control of patient's clinical state every 72 hours | CT | END OF IMMUNOTHERAPY |
| | Methylprednizolone orally 1 mg/kg/day | CT, bronchoscopy with BAL |
| | If the symptoms regress(to grade 1), readministration of immunotherapy is feasible | Methylprednizolone 2–4 mg/kg/day IV |
| | | Antibiotic therapy |
| | Reduction of the dose of steroids after achievement of the clinical improvement (for ≥ 4 weeks) | If the syndrome resolves (G1), reduction of the dose of steroids (during ≥ 6 weeks) |
| | | No clinical improvement after 48 hours — infliximab or mycophenolate mofetil |

CT — computed tomography; BAL — bronchoalveolar lavage

it is recommended to admit patient to hospital and to administer corticosteroids intravenously as well as to finally end the immunocompetent therapy. If clinical improvement is achieved, the dose of corticosteroids should be gradually reduced and stopped after 4–5 weeks of therapy. The continuation of nivolumab therapy is possible if complete clinical improvement is reached (and the prednisone dose reduced to 10 mg/day) [4].

In patients with pronounced symptoms and life-threatening symptoms (CTCAE grade 3 and 4) hospitalisation is mandatory (also to the Intensive Care Unit). The therapy involves methylprednisolone 2–4 mg per day IV (or an equivalent dose of any other steroid) and empiric antibiotic therapy. The antibiotics by first choice in community-acquired pneumonia are amoxicillin with clavulanic acid [18]. If no clinical improvement of the patient's clinical state is observed after 48 hours of therapy with steroids, the administration of immunosuppressive agents should be considered (infliximab or mycophenolate mofetil). On the other hand, when clinical improvement is achieved the dose of steroids should be slowly reduced and finally stopped after at least another six weeks. If the diagnosis of immune-modulated grade 3 or 4 pneumonitis is made, a continuation of the immunocompetent therapy is clearly contraindicated.

The Table 4 shows the summary of presented recommendations.

## Summary

Immune-modulated pneumonitis is a rare complication of immunocompetent drugs therapy also including nivolumab. The risk of this complication is especially high in patients with diagnosis of lung cancer, in advanced age, with chronic obstructive pulmonary disease, cigarette smokers, or patients who have had previous chest radiotherapy. The immune-modulated pneumonitis usually develops in the first few weeks of treatment (the median time to occurrence of this complication is 10 weeks). However, some case reports of patients with late diagnosis of immune-modulated pneumonitis (even after 20 months of therapy) have been published. Each patient with new symptoms involving the respiratory system (especially a dry cough or dyspnoea) should be carefully observed and have a chest CT in order to determine the reasons for the symptoms. In patients with moderate syndromes, a temporary withdrawal of the nivolumab therapy and administration of oral steroids are recommended. Improvement of the clinical state and radiological regression of the changes enables the continuation of the immunocompetent therapy. Lack of clinical improvement requires hospitalisation and intensification of the therapy, and is a contraindication to continue nivolumab therapy.

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