Review Article

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Immune Checkpoint Inhibitor-Related Pulmonary Toxicity: A Comprehensive Review, Part II

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Abstract: The development of immune checkpoint inhibitors (ICIs) has changed the treatment paradigm for cancer. The ICIs nivolumab, pembrolizumab, and cemiplimab target programmed cell death protein 1, and durvalumab, avelumab, and atezolizumab target programmed death ligand 1. Ipilimumab targets cytotoxic T lymphocyte–associated antigen-4. Used as monotherapy or in combination, they have shown remarkable efficacy in melanoma, lung cancer, and many other solid tumors, and indications continue to evolve. These checkpoint inhibitors are typically well tolerated; however, they may cause immune-mediated adverse effects, resulting in inflammation of any organ system. Pulmonary toxicity is vital to recognize, and it can be more challenging to diagnose in patients with lung cancer, given the nature of the disease course and treatment.

Key Words: immune checkpoint inhibitors, pembrolizumab, pneumonitis, pulmonary sarcoidosis, pulmonary toxicities

In part I of this review, we discussed the pulmonary adverse events (AEs) of programmed cell death protein 1 (PD-1) inhibitor (nivolumab).[1] Here, in part II, we focus on the pulmonary AEs of PD-1 inhibitor (pembrolizumab), PD-ligand 1 (PD-L1) inhibitors (durvalumab, avelumab, and atezolizumab), and the combination of a PD-1 inhibitor (nivolumab) with a cytotoxic T lymphocyte–associated antigen 4 inhibitor (ipilimumab). These AEs include dyspnea, pneumonitis, pleural effusion, pulmonary sarcoidosis, pulmonary tuberculosis (TB), acute fibrinous organizing pneumonia (OP), OP, eosinophilic pneumonia, adult respiratory distress syndrome, and lung cavitation.

We conducted an electronic literature search for studies in the English language published in MEDLINE/PubMed from January 1, 2010 to June 30, 2019. The search terms included "pembrolizumab," "nivolumab," "atezolizumab," "durvalumab," "avelumab," "ipilimumab," interstitial lung disease," "pneumonitis," "organizing pneumonia," "eosinophilic pneumonia,", "tuberculosis," "invasive aspergillosis," "pleural effusion," "lung cavitation," and "asthma."

Pembrolizumab

Pembrolizumab-Induced Pneumonitis

Pneumonitis is a noninfectious lung inflammation characterized by alveolar and interstitial infiltration.[2] Patients usually present with dry, nonproductive cough, shortness of breath, fatigue, and occasionally chills and fever. Examination findings include tachypnea, tachycardia, cyanosis, and bilateral basal crackles.[2,3]

A meta-analysis conducted by Cui et al[2] examined the relationship between the risks of pneumonitis, pneumonitis-related death, and PD-1 inhibitor treatment in patients with cancer. A total of 12 clinical trials were included, and 4 of these trials evaluated pembrolizumab. The pembrolizumab dose in those studies varied (2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, or 200 mg every

Key Points

- There is a focus on pulmonary adverse effects of PD-1 inhibitor (pembrolizumab), PD-L1 inhibitors (durvalumab, avelumab, and atezolizumab), and the combination of a PD-1 inhibitor (nivolumab) with a cytotoxic T lymphocyte–associated antigen 4 inhibitor (ipilimumab).
- This is a concise review of the following reported adverse effects: dyspnea, pneumonitis, pleural effusion, pulmonary sarcoidosis, pulmonary tuberculosis, acute fibrinous organizing pneumonia, organizing pneumonia, eosinophilic pneumonia, adult respiratory distress syndrome, and lung cavitation.
- A brief review of management is included.

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3 weeks). Subgrouped by dose, a subanalysis of studies reporting the incidences of all grades of pneumonitis associated with pembrolizumab monotherapy was reported. When compared with nivolumab, pembrolizumab was associated with an increased risk of high-grade pneumonitis. The risk of all grades of pneumonitis was higher with pembrolizumab irrespective of the dose compared with the conventional treatment used in the control groups. The risk of high-grade pneumonitis was higher only with pembrolizumab 200 mg every 3 weeks compared with a control regimen.[2]

Pembrolizumab-Induced De Novo Development or Reactivation of Pulmonary Granulomatosis/Sarcoidosis

Few case reports have described de novo pulmonary sarcoid-like reaction or pulmonary sarcoidosis reactivation after starting pembrolizumab. Patients with sarcoidosis can be asymptomatic with incidental findings on imaging or they may present with shortness of breath, cough, or sputum production.[4–8]

Sarcoidosis and sarcoid-like reactions can occur as a consequence of several malignancies and/or their therapies. The diagnosis can be especially challenging because it may mimic the progression of malignancy with the development of new lung lesions (parenchymal infiltrates) and mediastinal and hilar lymphadenopathy. To make it more complicated, sarcoidosis, like most malignancies, has increased fludeoxyglucose avidity on positron emission tomography/computed tomography (CT) scan.[4,5] As such, a tissue biopsy usually is required to differentiate between neoplastic disease progression and immunotherapy-related sarcoidosis. The biopsy can be done by bronchoscopy with transbronchial or endobronchial ultrasound-guided biopsy, video-assisted thoracoscopy, or surgical excision and lymph node sampling.[4,6,7] The biopsy usually shows evidence of noncaseating granulomas with an elevated CD4:CD8 ratio. Diagnosis also can be made by the coexistence of cutaneous and eye involvement. An underlying infectious process must be ruled out because it could mimic sarcoidosis. In patients who cannot undergo tissue biopsy, pembrolizumab should be stopped, and if the patient is symptomatic, then suppressive treatment with glucocorticoid should be considered. Improvement in clinical symptoms and radiological findings usually occurs within a median interval of 3.1 months. In cases of tumor progression, no improvement will be seen.[4,5,7,8]

Pembrolizumab-Related OP

OP usually affects the distal bronchioles, respiratory bronchioles, alveolar ducts, and alveolar walls. The primary area of injury is within the alveolar wall. The optimal method to establish the diagnosis is a histopathologic study through lung biopsy via video-assisted thoracoscopic surgery or open thoracotomy. Bronchoscopy with bronchoalveolar lavage (BAL) shows a decreased CD4:CD8 T cell ratio, an increase in activated T lymphocytes, and a lymphocyte increase of 20% to 40%.[9]

Multiple case reports have been published describing pembrolizumab-related organizing pneumonia. Leroy et al[3] reported two cases of pembrolizumab-related pneumonitis. Both cases involved two men in their 80s with metastatic melanoma. In the first case, the patient was previously treated with temozolomide and was started on pembrolizumab 10 mg/kg every 3 weeks. In the second case, the patient previously had surgery and radiotherapy and was then started on pembrolizumab 2 mg/kg every 2 weeks. Both presented with dyspnea and cough after 11 cycles and 4 cycles, respectively. Both cases had a CT scan consistent with OP, and bronchoscopy with BAL showed negative bacterial, acid-fast bacilli, fungal cultures, and low CD4:CD8 T cell ratios at 22% and 35%, respectively. In both cases, a surgical lung biopsy was not done on a risk–benefit basis. Pembrolizumab was stopped, and oral prednisolone at a dose of 0.5 mg/kg/day was started in both cases with a slow taper, with resultant symptomatic and radiological improvement in both cases.[3]

A third case was reported by Fragkou et al.[9] A 64-year-old woman with stage IV mucosal melanoma was treated with pembrolizumab as a third-line therapy; prior treatments were dacarbazine followed by ipilimumab. After four pembrolizumab cycles, the patient presented with dyspnea, tachypnea, and bilateral coarse crackles and areas of bronchial breathing. A chest radiograph showed a patchy alveolar infiltrate. She was diagnosed as having pneumonia and was started on antibiotics; however, because of the lack of improvement after 3 days, she underwent a high-resolution CT scan of the chest, which showed patchy consolidations predominantly in subpleural and peribronchial distribution. Bronchoscopy with BAL showed a decreased CD4:CD8 T cell ratio of 40%, and cultures were negative. The findings were consistent with OP, so pembrolizumab was stopped, and the patient was started on prednisolone with a long taper. The patient had rapid clinical and radiological improvement.[9]

Pembrolizumab-Related Pulmonary Infection Reactivation (TB)

Lee et al[10] reported a case of an 87-year-old Chinese man who was started on pembrolizumab 2 mg/kg every 21 days for relapsed nodular sclerosis Hodgkin lymphoma. The patient developed a fever and unintentional weight loss shortly after completing his fifth cycle of pembrolizumab. Mycobacterium TB grew on a sputum culture 3 weeks after the initial investigations. The patient was treated with a three-drug combination (rifampicin, isoniazid, and ethambutol), and pembrolizumab was stopped in view of the clinical remission of the Hodgkin lymphoma and the diagnosis of active TB. The patient was not on any immunosuppressive medications and did not develop any immune-related AEs (irAE).[10]

Because of the limited use of immune checkpoint inhibitors (ICIs) in developing countries where there is a high prevalence of latent TB infection combined with the lack of long-term

follow-up data in these nations, reactivation of TB may be underreported. Before the use of ICIs, screening for latent TB may be necessary for areas with a high prevalence of latent TB.[11]

Fatal Steroid-Resistant Airway Inflammation (Severe Fatal Asthma Exacerbation)

Ogawa et al[12] reported a case of a 71-year-old man with a history of asthma, well-controlled with daily inhaled corticosteroids and long-acting β2-agonists, and stage IIIB squamous cell carcinoma of the lung. Pembrolizumab 200 mg every 3 weeks was started as a first-line therapy. On day 20, after beginning treatment, the patient presented with dyspnea and wheezing. A CT scan of the chest showed no significant findings in the lung fields, although the tumor size decreased. The patient was started on β2-agonist inhalational therapy with symptomatic improvement suggesting a reversible airway obstruction. He was started on budesonide, salbutamol, and an oral leukotriene modifier, and because the patient was still symptomatic, systemic prednisolone and inhaled tiotropium were added. His condition continued to deteriorate with the development of acute hypercapnic respiratory failure leading to intubation and mechanical ventilation on day 36, and he died on day 58. An autopsy was performed, and histologic analysis revealed narrowing of the airway lumen and epithelial basement membrane thickening, goblet cell hyperplasia, and increased volume of airway smooth muscle that suggested the possibility of typical asthma exacerbation. The airway inflammation, however, was characterized by $CD8^+$ lymphocytes infiltrating into bilateral airways with no detection of eosinophils, which is consistent with previously reported findings in cases of irAEs. The authors recommended that steroid-resistant asthma-like symptoms should be recognized when a PD-1 inhibitor is administered for cancer treatment.[12]

Alveolar Hemorrhage Related to Pembrolizumab

Sugano et al[13] reported a case of alveolar hemorrhage in a 67-year-old woman with metastatic adenocarcinoma. She was started on pembrolizumab treatment (200 mg/day). After four cycles, a chest radiograph revealed bilateral consolidations. CT scan of the chest showed bilateral peribronchovascular ground-glass opacities and a crazy-paving pattern. Laboratory data revealed anemia. The workup was negative for vascular connective tissue disease and vasculitis. BAL fluid from the right lower lobe gradually became bloody, cultures were negative, and no evidence of malignancy was apparent. Transbronchial lung biopsy from the right lower lobe showed thickening of the alveolar walls with myxofibrous and lymphocytic infiltrations. Agglutination of red blood cells was observed in the air spaces of the alveoli, but no hemosiderin-laden macrophages were seen. The patient was diagnosed as having interstitial lung disease (ILD) with alveolar hemorrhage related to pembrolizumab. Oral prednisolone at 1 mg/kg/day was started for 2 weeks, with the rapid resolution of abnormal radiographic findings. Oral prednisolone was tapered off during the course of 3 months without recurrence of pneumonitis.[13]

Combination Therapy with Nivolumab/Ipilimumab

Nivolumab/Ipilimumab-Related Pneumonitis

The incidence of pneumonitis during PD-1 inhibitor monotherapy versus nivolumab plus ipilimumab combination therapy (given concurrently or sequentially) was compared in three studies of patients with melanoma.[14–17] The incidence of pneumonitis, all grades, and grade 3 or higher, was significantly higher in the nivolumab and ipilimumab combination therapy group compared with PD-1 inhibitor monotherapy. There was only one pneumonitis-related death reported in the nivolumab plus ipilimumab combination therapy group. This may indicate the additive toxic effects of the two agents on the lung.[17]

In another study comparing nivolumab with nivolumab plus ipilimumab in recurrent small-cell lung cancer patients, treatment-related pneumonitis was reported in 8 patients across all of the treatment cohorts, and 1 reported death in the nivolumab plus ipilimumab combination therapy group.[18]

In a meta-analysis conducted by Cui et al,[2] 2 of the 12 trials evaluated nivolumab plus ipilimumab combination therapy. When compared with nivolumab monotherapy, nivolumab/ipilimumab combination therapy had a higher risk of all-grade pneumonitis. The odds ratio for all-grade pneumonitis with nivolumab/ipilimumab combination therapy compared with nivolumab monotherapy in these two studies was 3.54, and the odds ratio for high-grade pneumonitis with nivolumab/ipilimumab combination therapy compared with nivolumab monotherapy was 2.35. Pneumonitis can occur from 7.4 to 24.3 months after the initiation of treatment.[19]

A CT scan of the chest showed a spectrum of findings that are seen typically in interstitial cases of pneumonia (eg, adult respiratory distress syndrome, nonspecific interstitial pneumonia), diffuse ground-glass opacities, reticular opacities, consolidation, traction bronchiectasis, decreased lung volumes and effusions. Physicians should be aware of the significantly higher incidence of pneumonitis during combination therapy and carefully evaluate patients for possible symptoms and signs of pneumonitis.[17]

Nivolumab/Ipilimumab-Related Sarcoidosis

Reuss et al[20] reported a case of pulmonary and cutaneous sarcoidosis in a patient with recurrent stage IIB melanoma after being treated with nivolumab plus ipilimumab combination therapy. Physicians need to be aware of this condition as accurate identification of this process is essential because sarcoidosis can mimic disease progression and granuloma formation can mimic metastatic disease on imaging and examination. Also, the clinical findings can vary greatly and can occur a long time after treatment with ICIs. Positron emission tomography-CT can show fludeoxyglucose-avid lesions, and the angiotensin-converting

enzyme level can be high, but tissue remains the gold standard for diagnosis.[20]

PD-L1 Inhibitors

In general, PD-L1 inhibitors have a lower incidence of pneumonitis of any grade when compared with PD-1 inhibitors, with an overall incidence of all-grade pneumonitis in the PD-L1 inhibitor group of 1.3%. When PD-L1 inhibitors are used in a frontline setting, they are associated with a significantly higher incidence of all-grade pneumonitis compared with previously treated patients, however.[21]

Atezolizumab

Atezolizumab-Related Pneumonitis

Several phase I studies examining the efficacy of PD-L1 inhibitors in advanced urothelial carcinoma and various other malignancies did not report any cases of pneumonitis.[22–25] Other studies, however, evaluated anti-PD-L1 inhibitor in patients with advanced non–small-cell lung carcinoma (NSCLC) reported the occurrence of pneumonitis grade 1 to 2 in 1% of the participants. The BIRCH (Study of Atezolizumab in Participants With PD-L1 Positive Locally Advanced or Metastatic Non–Small-Cell Lung Cancer) study and the POPLAR (Study of Atezolizumab versus docetaxel for patients with previously treated NSCLC) study reported the development of grade 3 pneumonitis in 0.6% and 2%, respectively, of the patients with advanced NSCLC.[23,26,27] There was one treatment-related death because of pneumonia reported in the BIRCH study.[26]

In the OAK (Atezolizumab Versus Docetaxel in Patients with Previously Treated Non–Small-Cell Lung Cancer) study, a Phase III open-label multicenter randomized controlled trial comparing atezolizumab and docetaxel in patients with previously treated NSCLC, the incidence of pneumonitis was low, with 1% overall occurrence and < 1% being grade 3, with no grade 4 events.[28]

Durvalumab

Durvalumab-Related Pneumonia/Pneumonitis

The PACIFIC study was a Phase III study comparing durvalumab as consolidation therapy with placebo in patients with stage III NSCLC who did not have disease progression after two or more cycles of platinum-based chemoradiotherapy. In this study of patients who received durvalumab, pneumonitis or radiation pneumonitis of any grade occurred in 33.9% compared with 24.8% in the placebo group. Pneumonitis or radiation pneumonitis of grades 3 to 4 occurred in 3.4% of the durvalumab group and in 2.6% of the placebo group. Pneumonia of any grade occurred in 13.1% of the durvalumab group and in 7.7% of the placebo group, and pneumonia of grades 3 to 4 occurred in 4.4% of the durvalumab group and in 3.8% of the placebo group. The study authors concluded that durvalumab has manageable AEs after chemoradiotherapy and has lower AEs than in other studies in the same disease context. Pneumonitis or radiation pneumonitis in patients receiving durvalumab was mostly low grade, and the incidence of grades 3 to 4 was well balanced between the two groups. Although the incidence of pneumonitis and radiation pneumonitis was increased in both groups, this was expected after definitive chemoradiotherapy.[29]

In the updated analysis of the PACIFIC study, the most frequent AEs leading to discontinuation of the trial regimen were pneumonitis 4.8% in the durvalumab group compared with 2.6% in the placebo group, radiation pneumonitis 1.3% in the durvalumab group compared with 1.3% in the placebo group, and pneumonia 1.1% in the durvalumab group compared with 1.3% in the placebo group.[30]

The ATLANTIC (Durvalumab as Third-Line or Later Treatment for Advanced Non-Small-Cell Lung Cancer) study is an open-label, single-arm, Phase II study that assessed the effect of durvalumab treatment in three cohorts of patients with NSCLC defined by epidermal growth factor receptor/anaplastic large-cell lymphoma kinase status and tumor expression of PD-L1. Grade 3 to 4 pneumonitis occurred in 4 patients (1% of the patients). Pneumonitis was the most common serious AE that occurred in 5 patients (1%).[31]

Avelumab

Avelumab-Related Pneumonia/Pneumonitis

A multicenter, single-group, open-label Phase II trial assessed treatment with avelumab in patients with stage IV Merkel cell carcinoma that had progressed after cytotoxic chemotherapy. The number of potential irAEs related to avelumab was low, and most adverse events were low grade and manageable, with only one patient developing pneumonia. There were no grade 4 events or treatment-related deaths.[32]

Brie et al[33] reported a case of avelumab-related pneumonitis in a 66-year-old woman who was treated with avelumab and axitinib for renal cell cancer. CT scan of the chest 3 months after starting avelumab and axitinib showed an incidental finding of ground-glass opacities, interlobular thickening, and mediastinal lymphadenopathy. An exhaustive workup did not reveal any infectious or immunological causes. The patient was diagnosed as having drug-related pneumonitis, and avelumab and axitinib were stopped, with a resolution of the radiological abnormalities. No glucocorticoids were used.[33]

Sarcoidosis-like Granulomatous Lung Reaction Related to Avelumab

Balestra et al[34] reported a 76-year-old man with ocular melanoma treated initially with cobalt radiation implant, with recurrence 30 years later that was treated with 8 cycles of protein-bound paclitaxel with good response. One year later, the patient was found to have metastatic disease to the liver and was started on avelumab. The patient had a good response

with symptomatic improvement and a decrease in the size of the liver metastases. One month after beginning avelumab, the patient developed extensive mediastinal and hilar lymphadenopathy. Endobronchial ultrasound-guided biopsy with fine needle aspiration revealed noncaseating granulomatous inflammation. BAL cultures, acid-fast bacilli culture, and fungal culture were negative. CT scan of the chest 4 months after starting avelumab showed an increase in the size of mediastinal lymph nodes and new diffuse bilateral miliary lung nodules. The patient underwent bronchoscopy with transbronchial cryobiopsy of the left upper lobe, which showed noncaseating granulomatous inflammation. Repeat BAL cultures, acid-fast bacilli, and fungal cultures were negative.[33,34] The patient was diagnosed as having a sarcoidosis-like reaction (drug-related granulomatous inflammation) secondary to avelumab. Avelumab was discontinued, and the patient was started on paclitaxel. A repeat CT scan of the chest 3 months after the discontinuation of avelumab showed resolution of mediastinal lymphadenopathy and pulmonary miliary nodules. No glucocorticoids were used.[34]

Management

The National Comprehensive Cancer Network provides guidelines on how to manage toxicity caused by immunotherapy, including pneumonitis. Pneumonitis, defined as inflammation of the lung parenchyma (focal or diffuse), is noted on the CT scan as ground-glass opacities. There are definitions to grade the severity of the toxicity and treatments specific to each grade. Mild or grade 1 toxicity is defined as <25% of lung parenchyma involved and confined to one lobe, and the patient is asymptomatic. Treatment for mild pneumonitis is to hold immunotherapy and reassess in 1 to 2 weeks, check resting and ambulating pulse oximetry, and consider a CT of the chest with contrast. Moderate or grade 2 toxicity is defined as <25% of lung parenchyma involved and confined to one lobe; however, the patient has symptoms, including cough, shortness of breath, chest pain, and hypoxia requiring increased oxygen. Immunotherapy should be held, and pulmonary consultation should be obtained. Infectious workup, including viral panel, sputum culture, blood culture, and urine culture should be obtained.

Bronchoscopy with BAL can be considered to rule out both infection and malignancy. A repeat CT scan of the chest in 3 to 4 weeks is recommended. Systemic glucocorticoids (prednisolone/methylprednisolone) at 1 to 2 mg/kg/day also are recommended, with a taper over 4 to 6 weeks, and if there is no improvement in 48 to 72 hours, then the patient should be treated as grade 3 toxicity. For grade 2 toxicity, immunotherapy rechallenge may be attempted once pneumonitis improves to less than or equal to grade 1 toxicity, and the patient is off glucocorticoids. Severe toxicity is grades 3 and 4 toxicity. Grade 3 toxicity involves >50% of lung parenchyma or multiple lobes, and the patient has severe symptoms that limit the activities of daily living, and grade 4 toxicity is a life-threatening respiratory compromise. With severe toxicity, it is recommended to discontinue immunotherapy permanently and admit the patient for further workup, including bronchoscopy with BAL. Pulmonary and infectious disease consultations are recommended. The patient should be started on empiric antibiotics until the infection is ruled out, as well as methylprednisolone 1 to 2 mg/kg/day with a long taper of ≥6 weeks. After 48 hours, if there is no improvement, then infliximab 5 mg/kg intravenously or mycophenolate mofetil 1 to 1.5 mg twice daily or intravenous immunoglobulin 2 g/kg in divided doses can be added to the high-dose glucocorticoid. If the patient experiences grade 3 or 4 toxicity, then it is not recommended to rechallenge with immunotherapy.[35]

In cases of less frequently encountered pulmonary toxicity, case reports have guided treatment. Immunotherapy-related ILD, ILD with alveolar hemorrhage, immunotherapy-related OP, and immunotherapy-related pulmonary sarcoidosis were treated with high doses of systemic glucocorticoids. Reactivation of TB or aspergillus was treated for the disease processes with anti-TB therapy and voriconazole, respectively. For patients with immunotherapy-related asthma, oral glucocorticoids and inhaled long-acting β-agonists in combination with an inhaled corticosteroid were used.

Conclusions

Recognition and management of pulmonary toxicity caused by immunotherapy are critical because cancer treatment paradigms have shifted and immunotherapies are more frequently used. Continued reports of pulmonary toxicity caused by immunotherapy are essential to provide a comprehensive understanding of possible complications that providers need to be able to recognize and treat. Identifying toxicity quickly and treating promptly may prevent morbidity and mortality in cancer patients treated with checkpoint inhibitors.

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