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Case Report

Acute-Onset Pneumonitis while Administering the First Dose of Durvalumab

Erwin H.J. Tonk[a] Anne S.R. van Lindert[b] Joost J.C. Verhoeff[c] Karijn P.M. Suijkerbuijk[a]

[a]Department of Medical Oncology, University Medical Center Utrecht Cancer Center, Utrecht, The Netherlands; [b]Department of Pulmonology University Medical Center Utrecht Cancer Center, Utrecht, The Netherlands; [c]Department of Radiotherapy, University Medical Center Utrecht, Utrecht, The Netherlands

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Abstract
In locally advanced non-small cell lung cancer (NSCLC) patients, consolidation therapy with durvalumab (an anti-PD-L1 monoclonal antibody) has proven to significantly increase both progression free and overall survival after chemoradiotherapy. Here, we describe a case of acute pneumonitis during durvalumab administration for locally advanced NSCLC, causing persistent symptomatology and steroid treatment to date. To our knowledge, acute-onset pneumonitis during infusion of a PD-L1 inhibitor has not been described previously. This case illustrates that ICI-induced pneumonitis can occur anytime during treatment, especially after chemoradiation.

Introduction

In the treatment of non-small cell lung cancer (NSCLC), immune checkpoint inhibitors have proven to increase long-term survival by activating T cells via inhibition of programmed cell death 1 ligand (PD-L1) on the T cell surface. Recently, PD-L1 inhibition with durvalumab

Karijn P.M. Suijkerbuijk
Department of Medical Oncology
University Medical Center Utrecht Cancer Center
Heidelberglaan 100, NL–3584 CX Utrecht (The Netherlands)
E-Mail K.Suijkerbuijk@umcutrecht.nl

has been increasingly used in the adjuvant setting to treat locally advanced NSCLC [1]. These new treatment strategies come with a wide spectrum of immune-related adverse events, which can severely impact quality of life or even be fatal. In a recent meta-analysis of 20 128 patients treated with PD-1- or PD-L1 inhibitors, pneumonitis was the most common cause of death, accounting for 28% of fatal events [2].

Although severe pneumonitis was described as rare and well manageable in the PACIFIC-1 trial, experience outside clinical trials for stage III NSCLC patients is yet to be revealed. Here we describe the first case of acute-onset pneumonitis while administering the first dose of durvalumab.

Case Report

A 72-year old male patient was treated with concurrent chemoradiation (33 × 2 Gy with carboplatin / pemetrexed) for stage IIIB NSCLC, resulting in a partial response. Eight weeks after completing chemoradiotherapy, the patient received durvalumab (10 mg/kg) as consolidation therapy. During infusion of the first cycle, he developed fever and severe dyspnea. An allergic reaction was suspected and treated with clemastin, dexamethasone and acetaminophen intravenously. After one hour, hypoxemia remained necessitating 4 L of oxygen suppletion. A high-resolution (HR)-CT scan of the thorax showed bilateral abnormalities of the lungs with diffuse ground-glass opacities, extending way beyond previously irradiated areas (Fig. 1). A bronchoscopy 1 day later showed mild inflammation. Bacterial cultures and viral PCR remained negative. Treatment for severe immune checkpoint inhibitor (ICI)-induced pneumonitis with prednisolone 2 mg/kg/day was initiated upon diagnosis and resulted in clinical recovery after 3 days. A steroid taper was given for three months and durvalumab was not reintroduced thereafter.

Six months after onset and 3 months after discontinuing steroids, the patient suddenly relapsed, with HR-CT showing new consolidations bilaterally in an organizing pneumonia (OP) pattern. Clinical symptoms improved after 7 days on oral prednisolone 1 mg/kg/day. Mycophenolic acid was initiated and steroids were again tapered for three months. A year after starting durvalumab, the patient was still experiencing dyspnea on exertion, with the HR-CT scan revealing restrictive marks with fibrosis in both lungs. No evidence of clinical progression or relapse of NSCLC has been observed 12 months post treatment.

Discussion/Conclusion

Early pneumonitis within days after initiation of PD-1 inhibition has been reported previously [3, 4]. Nevertheless, acute-onset pneumonitis upon administration of the first dose of PD-L1 inhibition has not previously been described. In a retrospective review of 915 patients developing pneumonitis after receiving PD-1/PD-L1 inhibitors, median time of onset of pneumonitis was 2.8 months (range 9 days – 19.2 months) [5].

In recent literature, PD-L1 inhibitors have been associated with a significant lower incidence of pneumonitis than PD-1 inhibitors. In a systematic review covering 3232 advanced NSCLC patients, pneumonitis was diagnosed in 3.6% of patients on PD-1 inhibition, compared to 1.3% of anti-PD-L1 treated patients [6]. This difference could be explained by the interaction between PD-1 and PD-L2, which is not affected by PD-L1 inhibitors [7].

While grade 3–4 pneumonitis was relatively common occurring in 3.4% of the patients treated with durvalumab in stage III NSCLC, it was reported in only 1% of the advanced NSCLC patients treated with durvalumab in the ATLANTIC study [1, 8]. These data suggest that the incidence of pneumonitis is higher for stage III patients receiving anti-PD-L1 as consolidation treatment after chemoradiation. Potential explanations for this difference include sequential administration of radiotherapy and ICI [9] and the lower tumor load in stage III disease [10].

This case of acute-onset severe pneumonitis during durvalumab infusion illustrates that clinicians should remain cautious of ICI-induced pneumonitis occurring at any time during and after treatment, especially following chemoradiation.

Statement of Ethics

The patient has declared no objection to anonymous use and publication of clinical data. This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Disclosure Statement

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Author Contributions

ET, JV, AvL and KS collected and interpreted the clinical data acquisited and have prepared and revised the manuscript. All authors read and approved the final manuscript.

References

1 Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al.; PACIFIC Investigators. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl J Med. 2018 Dec;379(24):2342–50.
2 Wang Y, Zhou S, Yang F, Qi X, Wang X, Guan X, et al. Treatment-Related Adverse Events of PD-1 and PD-L1 Inhibitors in Clinical Trials: A Systematic Review and Meta-analysis. JAMA Oncol. 2019 Apr;5(7):1008.
3 Nakahama K, Tamiya A, Taniguchi Y, Sasaki Y, Akira M, Atagi S. Severe acute interstitial lung disease after nivolumab in three non-small cell lung cancer patients with imaging findings of airway obstruction adjacent to lung tumors. J Infect Chemother. 2017 Dec;23(12):826–9.
4 Costa RB, Benson A, Yaghmai V, Costa RL, Zhou H, Behdad A, et al. An Extremely Rapid Case of Pneumonitis with the Use of Nivolumab for Pancreatic Adenocarcinoma. Case Rep Oncol Med. 2018 Apr;2018:6314392.

5 Naidoo J, Wang X, Woo KM, Iyriboz T, Halpenny D, Cunningham J, et al. Pneumonitis in Patients Treated With Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy. J Clin Oncol. 2017 Mar;35(7):709–17.
6 Khunger M, Rakshit S, Pasupuleti V, Hernandez AV, Mazzone P, Stevenson J, 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 Aug;152(2):271–81.
7 Xiao Y, Yu S, Zhu B, Bedoret D, Bu X, Francisco LM, et al. RGMb is a novel binding partner for PD-L2 and its engagement with PD-L2 promotes respiratory tolerance. J Exp Med. 2014 May;211(5):943–59.
8 Garassino MC, Cho BC, Kim JH, Mazières J, Vansteenkiste J, Lena H, et al.; ATLANTIC Investigators. Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label, single-arm, phase 2 study. Lancet Oncol. 2018 Apr;19(4):521–36.
9 von Reibnitz D, Chaft JE, Wu AJ, Samstein R, Hellmann MD, Plodkowski AJ, et al. Safety of combining thoracic radiation therapy with concurrent versus sequential immune checkpoint inhibition. Adv Radiat Oncol. 2018 May;3(3):391–8.
10 Sondak VK, McArthur GA. Adjuvant immunotherapy for cancer: the next step. Lancet Oncol. 2015 May;16(5):478–80.

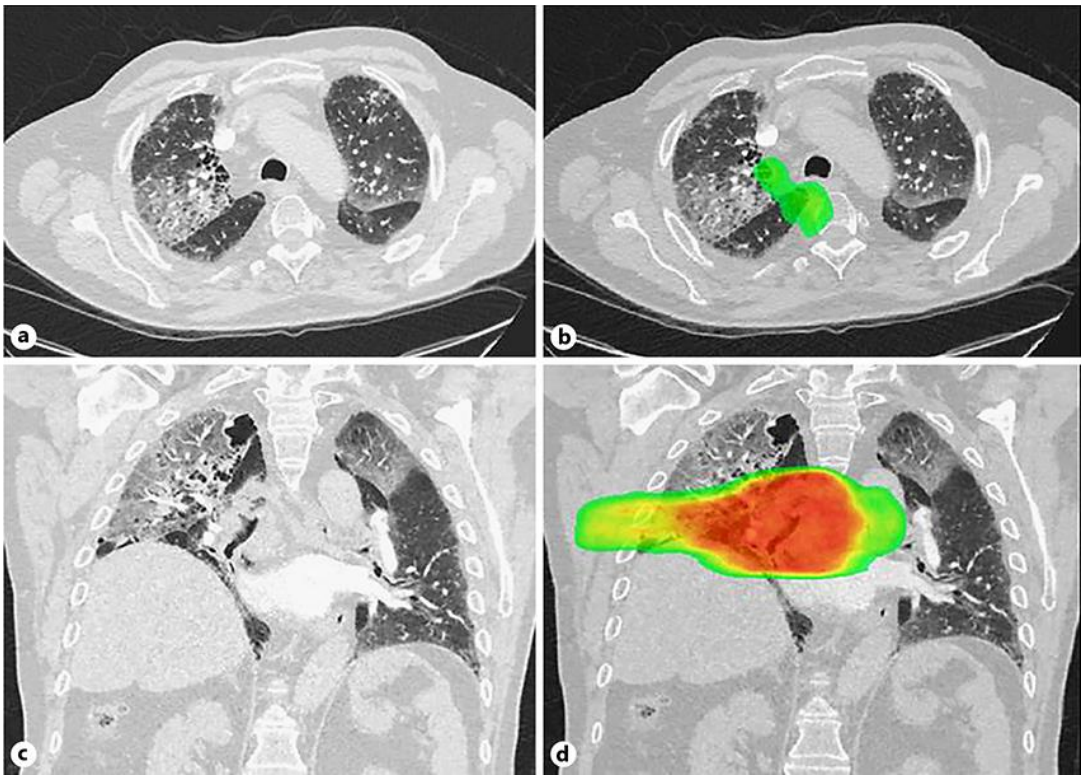

Fig. 1. **a** Axial Computed Tomography scan showing bilateral infiltration, with diffuse ground-glass opacities. **b** Axial Computed Tomography scan with irradiated overlay, showing bilateral infiltration extending beyond the previously irradiated field (colored area in green). **c** Coronal Computed Tomography scan, showing bilateral infiltration, with diffuse ground-glass opacities. **d** Coronal Computed Tomography scan with irradiated overlay, showing bilateral infiltration extending beyond the previously irradiated field (colored area, red highest dosage, green lower dosage).