Immune Checkpoint Inhibitor–related Pneumonitis Incidence, Risk Factors, and Clinical and Radiographic Features

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Recommended Reading from Harvard–Brigham and Women's Hospital Pulmonary and Critical Care Medicine Fellows; Carolyn D'Ambrosio, M.D., Director

Khunger M, 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* (1)

Reviewed by Rebecca Sternschein

Immunosurveillance is the process by which the immune system identifies and eliminates cancer cells. Failure of this system leads to malignant disease (2). One mechanism for this failure is through inhibitory checkpoints, such as CTLA-4 (cytotoxic T-lymphocyte antigen-4) and PD-1 (programmed cell death protein-1), which suppress T-cell responses against tumor cells. Monoclonal antibodies directed against these pathways are known as immune checkpoint inhibitors (ICIs). ICIs effectively block inhibition of tumor-specific T cells to improve antitumor immunity (3). The use of such immunotherapies, however, has resulted in a unique set of toxicities known as immune-related adverse events (irAEs), of which pneumonitis is particularly devastating, and even fatal (4–6).

Khunger and colleagues performed a systematic review and meta-analysis of trials identified in MEDLINE, Embase, and Scopus databases up to November 2016 to explore the incidence of pneumonitis with these novel therapies (1). Nineteen single-arm or randomized controlled trials ($N = 5,038$ patients) examining PD-1 or PD-L1 (programmed death-ligand 1) inhibitors in patients with non-small cell lung cancer (NSCLC) were included, 12 with PD-1 inhibitors and 7 with PD-L1 inhibitors.

There was a higher incidence of any-grade pneumonitis with PD-1 inhibitors than with PD-L1 inhibitors (3.6%; 95% confidence interval [CI], 2.4–4.9%; vs. 1.3%; 95% CI, 0.8–1.9%; $P = 0.001$) as well as high-grade (grade 3 or greater) pneumonitis with PD-1 inhibitors (1.1%; 95% CI, 0.6–1.7%; vs. 0.4%; 95% CI, 0–0.8%; $P = 0.02$). In addition, treatment-naïve patients had a higher incidence of any-grade pneumonitis than previously treated patients (4.3%; 95% CI, 2.4–6.3%; vs. 2.8%; 95% CI, 1.7–4%;

$P = 0.03$), but this difference did not persist for high-grade pneumonitis or when results were stratified by PD-1 versus PD-L1 inhibitors.

These data suggest that PD-1 inhibitors may be more prone to cause severe pneumonitis than PD-L1 inhibitors and that pneumonitis may be more likely to develop when an immune modulator is chosen as initial treatment approach for NSCLC. Lower pneumonitis rates with PD-L1 inhibitors may reflect sparing of PD-L2 and relative preservation of immune tolerance. There are several limitations to this review. All included trials were open-label and thus risk was high for both reporting and selection bias. Pneumonitis was also defined by purely radiographic findings and not by symptoms, which limits the assessment of pneumonitis severity to only one feature and minimizes its clinical relevance. Dose-response of immune modulator therapy with pneumonitis, as well as any assessment of association between underlying patient characteristics and development of pneumonitis, were also not reported. Further research is needed to identify patients at risk for developing pneumonitis before treatment with immune modulator therapy to improve patient safety. ■

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Khoja L, *et al.* Tumour- and Class-Specific Patterns of Immune-related Adverse Events of Immune Checkpoint Inhibitors: A Systematic Review. *Ann Oncol* (7)

Reviewed by Matthew Moll

The advent of ICIs has generated new therapeutic options for several advanced cancers (8–11). However, a wide range of irAEs are common, and sometimes even fatal. Khoja and colleagues hypothesized that irAE patterns and severity differ based on ICI class and tumor type (7).

In this systematic review, two pairs of reviewers searched MEDLINE, Embase, and Cochrane databases for prospective trials of solid tumors with single-agent treatment arms including ICIs. The primary objective was to determine how frequently irAEs from ICIs were reported; irAEs across ICI classes and tumor types were also compared.

Forty-eight trials ($N = 6,938$ patients) were identified; ICI classes included CTLA-4 (26 studies), PD-1 (17 studies), PD-L1 (2 studies), and both CTLA-4 and PD-1 inhibitors (3 studies). Comparing PD-1 and CTLA-4 inhibitors, pneumonitis was more frequent with PD-1 inhibitors (odds ratio [OR], 6.4; 95% CI, 3.2–12.7), whereas colitis (OR, 8.7; 95% CI, 5.8–12.9), hypophysitis (OR, 6.5; 95% CI, 3.0–14.3), and rash (OR, 2.0; 95% CI, 1.8–2.3) were more frequent with CTLA-4 inhibitors. Among patients receiving PD-1 inhibitors, pneumonitis occurred more in those with NSCLC (OR, 4.2; 95% CI, 1.3–14.0) or renal cell carcinoma (OR, 2.9; 95% CI, 1.7–5.1) than those with melanoma. Interestingly, multivariate analysis demonstrated that although PD1/PD-L1 inhibitor use was a risk factor for pneumonitis, tumor type was not. Death from irAEs was rare with the use of PD-1 inhibitors but, if it did occur, was usually due to pneumonitis. Alternatively, when death occurred from CTLA-4 inhibitor irAEs, it was usually related to diarrhea, colitis, or colonic perforation.

The greater incidence of pneumonitis with PD-1 inhibitors reported in this review is consistent with previous reports (12). One important limitation to this study is that comorbidities were not taken into account; for instance, patients with NSCLC are more likely to have chronic obstructive pulmonary disease or prior radiation, which may alter patients' susceptibility to pneumonitis. This study is also limited by the lack of standardized definitions for irAEs. This work highlights the broader need to understand the clinical characteristics of irAEs and patient susceptibilities, to ultimately develop better management strategies for these patients. ■

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Naidoo J, *et al.* Pneumonitis in Patients Treated with Anti-Programmed Death-1/Programmed Death Ligand-1 Therapy. *J Clin Oncol* (13)

Reviewed by Julie Ng

The use of ICIs is an important advancement in cancer therapy, but irAEs can limit their use (6, 14). Although irAEs have been reported in large clinical trials, descriptions of the clinical and radiographic features of pneumonitis from ICIs have mostly been limited to case reports and small case series (15, 16). In the largest case series to date, Naidoo and colleagues conducted a retrospective study of patients treated with PD-1/PD-L1 inhibitors to further define the clinical entity of PD-1/PD-L1 inhibitor pneumonitis (13).

Out of 915 patients, 43 were identified as having pneumonitis. The severity of pneumonitis was graded using the Common Toxicity Criteria for Adverse Events. Consistent with prior reports, the incidence was greater in patients who received combination therapy (PD-1/PD-L1 inhibitor with CTLA-4 inhibitor) than in those who received monotherapy (10% vs. 3%, $P < 0.001$). The median time to onset of pneumonitis was 2.8 months (range, 9 d to 19.2 mo). Most patients had grade 1 (17 of 43; 40%) or grade 2 (14 of 43; 33%) pneumonitis. Five radiographic subtypes seen on chest computed tomography were described: cryptogenic organizing pneumonia, ground-glass opacities, interstitial, hypersensitivity, and pneumonitis not otherwise specified. Five out of five patients with a radiographic pattern consistent with cryptogenic organizing pneumonia required treatment beyond holding therapy, compared with 11 out of 22 patients presenting with other radiographic patterns.

Clinical course varied based on pneumonitis grade. All patients with grade 1 pneumonitis had resolution/improvement, and the majority improved (15 of 17; 83%) with cessation of ICIs. Patients with grade 2 or higher pneumonitis required steroids and had improvement or resolution of their lung disease with the use of steroids alone, except for one patient who was lost to follow-up. Five patients with grade 3 or higher pneumonitis required additional immunosuppression, and one out of the five deaths that occurred was attributed solely to pneumonitis. Twelve patients (all of whom had grade 1 or 2 pneumonitis) were rechallenged with immunotherapy, and three patients had recurrent pneumonitis from the rechallenge.

Having an underlying lung condition was a risk factor for pneumonitis ($P = 0.047$), whereas current smoking compared with former smoking trended toward, but did not meet, significance ($P = 0.053$). There was no association between the occurrence of pneumonitis and a patient's FEV₁ or DL_{CO} in those who had these measurements obtained.

This study is the largest study to date describing ICI pneumonitis and treatment outcomes. One major limitation is that treatment strategies were not compared with a control group, which highlights an important area of emerging research. In addition, because of the clinical heterogeneity of ICI pneumonitis, more studies are needed to fully define the clinical spectrum of this irAE. A better understanding of the biology of pneumonitis is needed to improve our recognition and treatment of this significant adverse event. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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