Long-term outcomes in patients with immune checkpoint inhibitor induced pneumonitis

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ABSTRACT

Introduction Immune checkpoint inhibitors (ICI) have improved outcomes for patients with many malignancies. However, these treatments are associated with immune-related adverse events, including pulmonary toxicity (pneumonitis). Pneumonitis is associated with significant short-term morbidity and mortality, but long-term outcomes are not well described.

Methods We used the Vanderbilt Synthetic Derivative, a deidentified electronic health record database of >2.5 million patients seen at Vanderbilt, to identify patient charts that included treatment with pembrolizumab, nivolumab, ipilimumab, ipilimumab and nivolumab, atezolizumab or durvalumab by keyword search and ICD-10 codes for acute respiratory failure and/or bronchoalveolar lavage. We manually reviewed these charts and identified 78 subjects who met criteria for probable pneumonitis which included patients presenting with symptoms (dyspnea, hypoxia, cough) and/or CT imaging consistent with this diagnosis. We collected data on demographics, ICI regimen, hospital admissions and long-term survival.

Results Of the 78 patients (48 males; median age 64 (range 28–81)), 52 patients required at least 1 hospital admission related to pneumonitis. A total of 25 patients experienced poor short-term outcomes (including 6 referred to hospice, 11 discharged to rehabilitation and 9 deaths). There was no association with these outcomes by patient age (p=0.96), sex (p=0.60), smoking status (p=0.63) or cancer type (p=0.13). Median duration of follow-up was 8.3 months (range 0.2–110.6 months), and 29 patients (37%) were alive at last follow-up. Patients admitted to the hospital were more likely to die (p=0.002) and less likely to receive additional treatment (p<0.0001) or survive for ≥12 months with no evidence of disease (p=0.02). There were no differences in long-term outcomes for patients with underlying pulmonary comorbidities.

Discussion ICI-pneumonitis has a high likelihood of causing hospitalisation and poor outcomes, including death. While there appears to be no difference in outcomes for patients with underlying pulmonary comorbidities, those requiring admission have worse outcomes.

INTRODUCTION

Immune checkpoint inhibitors (ICI) have improved outcomes for patients with many malignancies. These therapies target inhibitory pathways on T cells allowing for increased immune system activation and T cell-mediated clearance of tumour cells. Targets include cytotoxic T-lymphocyte antigen-4 as well as programmed death protein-1 (PD-1) and its ligand, PD-L1. However, these pathways are also important in preventing autoimmunity, and their blockade is therefore associated with significant immune-related adverse events (irAEs). Pulmonary toxicity (pneumonitis) is the most commonly fatal irAE from anti-PD-1/PD-L1 monotherapy, accounting for 35% of anti-PD-1/PD-L1 related deaths. ICI-related pneumonitis has been reported in 3.5%–19% of patients with significant variability in time to onset ranging from days to years after the first cycle of ICI.

A variety of factors are thought to be associated with the development of ICI-pneumonitis. There is an increased risk with combination immunotherapy (10%) as opposed to monotherapy (3%) and an increased risk in patients with non-small cell lung cancer (NSCLC) compared with melanoma, head and neck squamous cell
cancer (SCC) or urothelial carcinoma. There is also evidence to suggest that patients with underlying interstitial lung disease (ILD) or interstitial lung abnormalities on baseline chest CT are more likely to develop ICI pneumonitis. Similarly, patient history of asthma or chronic obstructive pulmonary disease (COPD) may be associated with increased incidence of ICI-pneumonitis, although these data are limited. Prior receipt of thoracic radiotherapy has been shown to pose greater risk as well.

Patients can be asymptomatic (presenting only with findings on imaging) or present with dyspnoea, dry cough and less commonly fevers or productive cough. The diagnosis is largely based on a combination of clinical and radiographic findings. However, there are no pathognomonic radiological features and cases have presented with organising pneumonia, nonspecific interstitial pneumonia, hypersensitivity pneumonitis and diffuse alveolar damage patterns. In one case series of 144 ICI-pneumonitis patients with NSCLC treated with nivolumab, 64.2% of patients presented with ground glass opacities or consolidations bilaterally, or in the lung contralateral to tumour, suggesting this is the most common radiographic presentation. Infection and disease progression must also be considered, which can sometimes require bronchoscopic evaluation.

The guidelines on management of ICI-pneumonitis suggest holding immunotherapy temporarily or permanently as well as treating with steroids such as prednisone or IV methylprednisolone (1–2 mg/kg prednisone equivalents), depending on grade at presentation.

In terms of survival, some evidence suggests that irAEs are associated with enhanced treatment efficacy, including superior overall and progression-free survival. Conversely, studies of patients with NSCLC who develop ICI-pneumonitis have shown decreased survival compared with those who did not develop pneumonitis, consistent with the evidence that pneumonitis is the most fatal of the irAEs, and perhaps suggesting that this toxicity is associated with functional decline and decreased ability to receive additional anticancer therapy.

While pneumonitis is associated with significant short-term morbidity and mortality, long-term outcomes for these patients are not well described. More specifically, there are limited data on which patients have long-term responses to ICI and/or are able to receive additional therapy. There are also limited data on how the severity of initial presentation and baseline patient demographics may impact these outcomes. In this study, we assessed 78 patients diagnosed with probable or possible pneumonitis after treatment with ICI to better understand the association between certain patient demographics, disease characteristics or initial clinical presentations with long-term outcomes.

Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients (%)</th>
<th>n=78</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48 (62%)</td>
<td></td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>60 (28–81)</td>
<td></td>
</tr>
<tr>
<td>Cancer type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma*</td>
<td>22 (28%)</td>
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</tr>
<tr>
<td>Lung cancer*</td>
<td>40 (53%)</td>
<td></td>
</tr>
<tr>
<td>RCC</td>
<td>7 (9%)</td>
<td></td>
</tr>
<tr>
<td>Head/Neck SCC</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6 (8%)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>13 (17%)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>47 (60%)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>18 (23%)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one comorbidity</td>
<td>38 (49%)</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>34 (44%)</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>3 (4%)</td>
<td></td>
</tr>
<tr>
<td>ILD</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (4%)</td>
<td></td>
</tr>
<tr>
<td>Immunotherapy regimen†</td>
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<tr>
<td>Pembrolizumab</td>
<td>25 (32%)</td>
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<tr>
<td>Nivolumab monotherapy</td>
<td>31 (40%)</td>
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<tr>
<td>Ipilimumab monotherapy</td>
<td>9 (12%)</td>
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<tr>
<td>Ipilimumab and Nivolumab</td>
<td>12 (15%)</td>
<td></td>
</tr>
<tr>
<td>Durvalumab</td>
<td>6 (8%)</td>
<td></td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>2 (3%)</td>
<td></td>
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</tbody>
</table>

*Includes patient with melanoma and lung cancer treated with different immunotherapies.
†Six patients received separate immunotherapies prior to developing pneumonitis.

METHODS

Patients

We used the Vanderbilt Synthetic Derivative, a deidentified electronic health record database of >2.5 million patients seen at Vanderbilt, to identify patient charts that included treatment with pembrolizumab, nivolumab, ipilimumab, ipilimumab and nivolumab, atezolizumab or durvalumab by keyword search and ICD-10 codes for acute respiratory failure. We manually reviewed 351 charts and identified 78 subjects who met criteria for probable pneumonitis. Probable pneumonitis was defined as patients on active or previous ICI therapy presenting with symptoms (dyspnoea, hypoxia, cough) and/or CT imaging consistent with this diagnosis and determined, by study personnel, to be unrelated to another cause such as infection or disease progression.

We collected data on demographics, type of malignancy, ICI regimen, hospital admissions, and timing...
and dose of steroid treatment. We also collected data on which patients required admission to the intensive care unit (ICU) or general floor as a result of their pneumonitis. Pneumonitis grade was classified according to the Common Terminology Criteria for Adverse Events V.5.03.17 We defined short-term ‘poor outcomes’ as discharge to rehabilitation or hospice, or pneumonitis-related death within 30 days from initial or recurrent symptom onset or hospital admission. For patients who did not die from pneumonitis, we assessed which were able to receive additional therapy, specifically those rechallenged on ICI therapy. We also collected data on long-term outcomes until patients’ last follow-up, including death related to cancer or survival in the context of additional treatment or no evidence of disease (NED). This study was approved by the Vanderbilt University Medical Center Institutional Review Board.

Statistical analyses
Mann-Whitney U test was used to assess for association between age and poor short-term outcomes including discharge to rehabilitation, discharge to hospice or death from pneumonitis within 30 days of initial diagnosis or recurrence. To evaluate the effect of cancer type on these same outcomes, a \( \chi^2 \) test for trend was used. For categorical variables such as sex and life-time smoking, Fischer’s exact test was used to assess association. We also used Fischer’s exact test to analyse the association between admission status and long-term outcomes such as the ability to receive additional treatment, death related to cancer within 1 year, survival with treatment and survival with no evidence of disease. The association between pulmonary comorbidities and these same outcomes were assessed. All analyses were performed using GraphPad Prism V.9.0.0.

Patient and public involvement
Given the retrospective design of this study and the use of a large deidentified database, coproduction of this research with patients and the public was not feasible.

RESULTS

Patient demographics and presentation
Of the 78 patients (48 males; median age 64, (range 28–81)), there were 39 with lung cancer, 21 with melanoma, 1 with lung cancer and melanoma, 7 with renal cell carcinoma (RCC) and 10 with other malignancies. Thirty-eight patients had at least one pulmonary comorbidity, 54 of which had COPD and 60 patients were either current or former smokers (table 1). Most patients presented with shortness of breath (81%) with some also experiencing cough (49%) and fewer with fever (18%), chest pain (13%) and fatigue (12%). There were 46 patients who developed signs or symptoms of pneumonitis >60 days from ICI initiation.

Regarding treatment, there was variability in steroid dosing with 75 (96%) patients receiving steroids on initial presentation, of which 25% received IV steroids. For those who had recurrent or persistent pneumonitis, 25 (93%) patients received steroids, of which 28% received IV steroids. Intravenous methylprednisolone doses ranged from 60 mg to 200 mg total daily. Prednisone doses ranged from 40 mg to 120 mg total daily with taper plans typically lasting 4–6 weeks. Taper plans were as short as 2 weeks and as prolonged as 6 months.

Short-term outcomes
Fifty-two patients required at least one hospital admission related to pneumonitis. Specifically, 44 (56%) required hospital admission at their initial diagnosis, 22 of which received care in the ICU and 3 were intubated (table 2). Twenty-seven had recurrence of pneumonitis after initial improvement despite steroid treatment, 17 requiring admission (7 ICU and 2 requiring intubation). A total of 25 patients experienced poor short-term outcomes (including 6 referred to hospice, 11 discharged to rehabilitation and 9 deaths). On initial presentation, 6 patients were discharged to rehabilitation and 4 patients were discharged to hospice; 7 patients died in the hospital from pneumonitis. All three patients intubated on initial presentation died. On pneumonitis recurrence, five patients were discharged to rehabilitation and two patients were discharged to hospice. There were two patients who died in the hospital from recurrent pneumonitis, one of which had previously been discharged to rehabilitation. There was no association with poor outcomes (death, discharge to rehabilitation or discharge to hospice) by patient age (p=0.95), sex (p=0.62), smoking status (p=0.78), cancer type (0.13), combination ICI (p=0.75) or time to pneumonitis from ICI initiation (p=0.14). Patients with melanoma were less likely to require hospital admission related to pneumonitis (p=0.02).

Long-term outcomes
The median duration of follow-up after pneumonitis was 8.3 months (range 0.2–110.6 months), and 29 patients (37%) were alive at last follow-up, most of whom had long-term antitumour responses from ICI. For living patients, the median duration of follow-up was 41.8 months. Following treatment for pneumonitis, 43 (55%) patients were able to receive additional treatment, including 19 patients rechallenged with ICI, of which 37% subsequently progressed and 26% died (table 3). Of those rechallenged, 15 (79%) patients received the same ICI and 2 (11%) received the same ICI with the addition of an ICI in a different class. One (5%) patient received an ICI of the same class in addition to one of a different class and 1 (5%) patient received an ICI of a different class alone. Eleven (58%) of the patients rechallenged were never admitted for their pneumonitis and 8 (42%) patients had been admitted to the general floor. None of the patients admitted to the ICU were rechallenged with
an ICI. Three patients rechallenged with ICI had recurrent pneumonitis (16%).

Among the patients who did not die from pneumonitis, 29 (38%) died in less than 1 year from cancer or cancer-related complications while 18 (23%) survived greater than 1 year with additional treatment and 16 (21%) survived greater than 1 year with no evidence of disease progression. There was no difference in death from cancer in less than 1 year (p=0.06) or survival greater than 1 year with no evidence of disease (p=0.05) for those who developed pneumonitis >60 days versus <60 days from ICI initiation. However, patients who developed pneumonitis >60 days from ICI initiation were more likely to survive greater than 1 year with treatment (p=0.03).

Outcomes by hospital admission

Among patients admitted to the hospital, ICU admission was unsurprisingly associated with death or hospice compared with patients admitted to the floor (p=0.02). Patients treated as an outpatient were less likely to die or require hospice as a result of pneumonitis compared with those admitted to the hospital (p<0.01) (table 4). Patients not requiring admission more often received additional therapy compared with patients admitted to either the ICU or the floor (p<0.01) and were more likely to survive for greater than 1 year with no evidence of disease (12% vs 38%, p=0.02). Conversely, there was no association between admission status and death from cancer in less than 1 year. Most patients admitted to the ICU either died of their pneumonitis (n=9, 50%) or died within 1 year (n=5, 26%); however, four patients (24%) had long-term survival without evidence of disease.

Pulmonary comorbidities

Of 38 patients (50%) with pulmonary comorbidities, 34 (44%) had COPD, 3 had asthma and 1 had ILD. Between patients with pulmonary comorbidities and those without, there was no difference in death from pneumonitis (p=0.71), discharge to hospice (p=1.0) or admission to either the ICU (p=0.42) or the general floor (p=0.36). There was also no association with the ability to receive additional therapy (p=0.37), death from cancer in less than 1 year (0.64), survival greater than 1 year with...
treatment (p=0.79) or survival greater than 1 year with no evidence of disease (p=1.0) (table 5). The singular patient with ILD was alive at 372 days after a diagnosis of pneumonitis and able to receive additional treatment, despite requiring admission to the floor.

**DISCUSSION**

Immunotherapy-induced pneumonitis poses significant morbidity and mortality in patients being treated for a variety of malignancies. While studies have shown that there may be a survival benefit for patients who develop irAEs, there is also evidence that patients with NSCLC have decreased survival if they develop ICI-related pneumonitis.24–26 Additionally, patients with underlying ILD, asthma or COPD are thought to be more likely to develop pneumonitis.5–8 A large number of patients in this study were identified as having one or more pulmonary comorbidities, largely COPD (89%). We observed no association between underlying lung disease and death, admission, ability to receive additional therapy or long-term survival. Even though these patients may be more likely to develop pneumonitis if treated with an ICI, their short-term and long-term outcomes appear to be similar to those without underlying lung disease.

Furthermore, long-term outcomes in patients requiring hospital admission as a result of pneumonitis have not been well described. Not surprisingly, patients admitted to the ICU were more likely to die from pneumonitis than those admitted to the floor or not admitted at all (although several patients did experience long-term survival). Patients who were never admitted were less likely to die from pneumonitis and more likely to receive additional treatment, survive greater than 1 year with treatment, and survive greater than 1 year with no evidence of disease compared with patients admitted to the ICU or the floor. Whether a patient requires hospital admission for their pneumonitis can potentially indicate which patients may have less favourable long-term outcomes.

There are several limitations to this study, the first being relatively small sample size from a single institution which could limit the applicability of these findings. Data collection relied on medical records, including Oncology, Pulmonary and Emergency Department notes. Grade at presentation, using the CTCAE V.5.0, was assigned based on this documentation, which could be inconsistent across providers and specialties.17 Severity of radiographic extent were based on CT impression reads as opposed to individual review of the images. Diagnosis of COPD or other pulmonary comorbidities was obtained from notes and imaging reports as opposed to pulmonary function tests. Additionally, the deidentified medical record was limited in terms of available prescription data. The documentation of steroid dose and time course was not consistent and therefore difficult to assess in relation to outcomes. Additionally, admission criteria will vary by institution and hospitalisation may not serve as a universal predictor of poor outcomes. Last, all patients included were diagnosed with pneumonitis out of an unknown number of patients treated with immunotherapy making it impossible to quantify and comment on incidence. A
larger, longitudinal study would be helpful in confirming which patients have favourable outcomes and durable antitumour response despite developing pneumonias as a result of immunotherapy.

This study shows that for patients who develop pneumonias, admission to either the ICU or general floor portends a poor prognosis with respect to short-term and long-term survival. On the other hand, patients who do not require admission are more likely to receive additional treatment, survive greater than 1 year with treatment, and survive greater than 1 year with no evidence of disease. Further, a subset of even critically ill patients may experience long-term survival. This information can guide clinicians in predicting which patients may have more favourable outcomes at the time of diagnosis with immunotherapy-induced pneumonias.

**Contributors** Study design and concept: ADP, DBJ, JAB. Data collection and statistical analysis: ADP. Drafting of the manuscript: ADP. Critical revision of the manuscript: DBJ, JAB. ADP is responsible for the overall content as guarantor.

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**Competing interests** DBJ has served on advisory boards or as a consultant for Bristol Myers Squibb, Merck, Novartis, Iovance Biotherapeutics, Catalyst Pharmaceuticals, OncoSec, Pfizer, Mosaic ImmunoeEngineering, Targovax and Mallinkrodt and has received research funding from Incyte and Bristol Myers Squibb.

**Patient and public involvement** Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by Vanderbilt IRB #192190. As no HIPAA identifiers are available in the SD database, this study meets criteria for non-human subjects research. To ensure confidentiality and appropriate use of the SD, all study personnel entered into a data use agreement, which prohibits any use of the data not described in the project including the reidentification of the SD records. Informed consent was therefore not obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** No data are available. The database from which the data were collected is not available to the public. Participants of this study did not agree for their data to be shared publicly.

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**REFERENCES**


