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Immune checkpoint inhibitor-induced pneumonitis: Incidence, clinical characteristics, and outcomes

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ORIGINAL RESEARCH REPORT

Immune Checkpoint Inhibitor-induced Pneumonitis: Incidence, Clinical Characteristics, and Outcomes

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Abstract

Background: **Immune checkpoint inhibitors (ICIs) are the newest class of anticancer drugs. Pneumonitis is increasingly being recognized as a potential complication of these agents.**

Methods: **We conducted a retrospective study of patients who received ICIs at a comprehensive cancer center. We collected data on demographics, type of malignancy, type of ICI agent, incidence of pneumonitis up to 6 weeks after receiving ICI agent, clinical characteristics, and risk factors for overall survival in patients who develop pneumonitis.**

Results: **A total of 654 patients received ICIs during the study period. The most common type of cancer for which ICI was given was adenocarcinoma of the lung (29%), followed by renal cell cancer (12%) and squamous cell lung cancer (12%). Among the study patients, 41% received nivolumab and 32% received pembrolizumab. Other patients in the study received combination of ICIs or ICI plus chemotherapeutic agent, or were part of clinical trial involving ICI. Overall 42 (6.4%) patients developed pneumonitis within 6 weeks after the last dose of treatment of any ICI agent. Of these, 81% of patients had Grade ≥ 2 pneumonitis and 45% of these required hospital admission for pneumonitis, with 10% of them requiring admission to intensive care unit. Overall, patients who received pembrolizumab-containing regimen, had prior chemotherapy, or who never had cancer-related surgery had increased risk of death.**

Conclusion: **Our large retrospective study shows real-life data of incidence of pneumonitis in patients who are treated with ICIs for cancer treatment. Our data indicate that the incidence of pneumonitis is overall lower than that reported previously with relatively good outcomes.**

Keywords: Cancer, Immune checkpoint inhibitors, Pneumonitis, Pulmonary, Toxicity

1. Introduction

The immune system has a natural cytotoxic immune response against highly immunogenic tumor cells and this requires complex interactions between various immune cells through a series of regulated steps [1,2].

However, tumor cells can sometimes evade this immune surveillance, thereby leading to progression of neoplastic process. One of the several mechanisms by which tumor cells can do this is by upregulation of immune checkpoint proteins such as cytotoxic T-lymphocyte−associated antigen 4 (CTLA4), programmed cell death-1 (PD-1), or programmed cell death ligand 1 and 2 (PD-L1/L2). The end result of increased expression of CTLA4, PD-1, and PD-L1/L2 is decreased T-cell activation, decreased tumor cell apoptosis, and increased T-cell exhaustion [3,4].

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that target CTLA4, PD-1, or PD-L1/L2 thereby reversing T-cell suppression and inducing antitumor response [5]. ICIs that inhibit PD-1 (pembrolizumab, nivolumab), PD-L1/L2(atezolizumab, avelumab, durvalumab), and CTLA-4

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(ipilimumab, tremelimumab) are currently being used to treat advanced cervical cancer [6], gastroesophageal cancer [7], metastatic melanoma [8,9], non-small cell lung cancer (NSCLC) [10–13], small cell lung cancer [14], squamous cell cancer of head and neck [15,16], renal cell carcinoma (RCC) [17], urothelial cancer [18], and lymphomas [19].

The use of ICIs is projected to increase in the coming years as studies have shown better survival, expanded indications, and better tolerance with fewer side effects compared with conventional chemotherapy [13,20–22]. More recently, ICIs are being used in combination with chemotherapy due to non-overlapping adverse effects.

Since ICIs work by hyperactivating the functions of T cells, they are associated with unique set of immune-related adverse events (IRAEs). Any organ could be affected by IRAE secondary to ICIs, but the most clinically significant IRAEs that are encountered in practice are the ones that affect the lungs, liver, kidney, gastrointestinal (GI) tract, and skin [23,24]. The severity of IRAE for each organ is defined by the National Cancer Institute – Common Terminology Criteria for Adverse Events (CTCAE) [25]. Management of IRAE depends on the grade of severity and ranges from clinical observation to high-dose systemic steroids and discontinuation of ICI being used [23,25].

The incidence of pneumonitis as an IRAE secondary to ICIs has been increasing owing to increasing use of ICIs. However, most recent meta-analysis and retrospective studies show that the incidence of pneumonitis has ranged from < 2% to 19%, and this wide range is likely attributed to patient selection for ICIs, type of primary cancer, previous known lung diseases, and possibly increasing frequency of use of ICIs recently [24,26–29]. The true incidence is still unknown and more data are needed to further characterize pneumonitis associated with ICIs. The risk factors for developing pneumonitis were use of combination ICIs and/or concurrent chemotherapy, prior thoracic radiation, and prior parenchymal lung disease [22,29,30].

Although some studies have shown that NSCLC could increase the risk of pneumonitis, the findings are not consistent and could likely be confounded by prior lung disease or worsening lung metastasis [22,24,27]. The data on outcomes of patients who developed pneumonitis are also scarce.

We conducted a retrospective analysis of patients treated with ICIs at a single comprehensive cancer center to assess the incidence of pneumonitis, risk factors for developing pneumonitis, and outcomes.

2. Methods

Study design

Our study was approved by the Wayne State University Institutional Review Board. All patients who were 18 years or older and received at least one dose of any ICI from August 3, 2011 to January 1, 2019 were included in the study. The data were obtained from our institution's pharmacy database.

Data collection

We obtained data regarding patients' demographics, type of malignancy being treated, and ICI agent used. We then reviewed the patient's electronic medical records specifically for pneumonitis up to 6 weeks following last dose of treatment with any ICI. Their data were obtained by reviewing documentation by treating oncologists, emergency department visit notes, radiology reports, and inpatient admission records. Pneumonitis was diagnosed based on new or worsening respiratory symptoms, new or worsening diffuse or multifocal infiltrates, and other causes excluded. If corticosteroids were used for any reason in these patients, we confirmed if this was possibly for pneumonitis or for other indications such as chronic obstructive pulmonary disorder exacerbation or other IRAEs. When the patient was confirmed to have pneumonitis secondary to ICI, the severity was graded based on criteria defined by CTCAE.

Statistical methods

Statistical analyses were performed mainly for 42 patients who developed pneumonitis. Patient characteristics and clinical outcomes were summarized by count and percentage for categorical variables and median and range for continuous variables. Associations between covariates of interest and hospitalization (yes vs. no, no as reference) were assessed by univariable logistic regression models, whereas univariable Cox proportional hazard regression models were used to assess associations between covariates of interest and overall survival (OS). In particular, Firth logistic and Cox proportional hazard regression models were used to reduce bias in maximum likelihood estimation caused by rare events. Due to a small sample size of 42, no multivariable analyses were performed. Proportional hazard assumption was checked and no violation was found.

3. Results

A total of 654 patients received ICIs during our study period. The use of ICIs increased over the study duration. The uses of ICIs exponentially increased during our study period; a total of 11

Table 1. Clinical characteristics of patients.

	All ($N = 42$)
Age (yr)	63 (24–85)
Race	
Caucasian	26 (62)
African-American	8 (19)
Other	8 (19)
Sex	
Male	25 (60)
Female	17 (40)
Primary cancer	
Lung cancer	22 (52)
Renal cell cancer	8 (19)
Melanoma	7 (17)
Other	5 (12)
ICI agent	
Pembrolizumab containing regimen	19 (45)
Nivolumab containing regimen	21 (50)
Durvalumab	2 (5)
Cardiovascular comorbidities	
No	31 (74)
Yes	11 (26)
Diabetes	
No	34 (81)
Yes	8 (19)
Hypertension	
No	20 (48)
Yes	22 (52)
Chronic kidney disease/ESRD	
No	36 (86)
Yes	6 (14)
Lung disease/COPD	
No	21 (50)
Yes	21 (50)
Prior chemotherapy	
No	12 (29)
Yes	30 (71)
Prior radiation	
No	24 (57)
Yes	18 (43)
Prior surgeries for cancer	
No	25 (60)
Yes	17 (40)

Data are presented as *n* (%) or median (range).
COPD = chronic obstructive pulmonary disorder; ESRD = end-stage renal disease; ICI = immune checkpoint inhibitor.

patients received ICIs in the year 2011 compared with 305 patients in 2018. Of these, 386 (59%) were males and 269 (41%) were females, with median age of 62 years. The most common type of primary cancers that were treated included adenocarcinoma of the lung (187, 29%), followed by RCC (80, 12%) and squamous cell cancer of the lung (78, 12%). Other primary cancers included melanoma (75), head and neck cancers (50), bladder (34), Hodgkin's lymphoma (26), small cell lung cancer (21), gynecologic which included ovarian, fallopian tube, cervical, and endometrial cancers (16), upper GI which included esophageal, gastroesophageal, gastric, and duodenal cancers (14), colon (13), pancreatic (11), hepatocellular carcinoma (10), poorly differentiated NSCLC (7), and mesothelioma (7). A small number of patients had rectal, cholangiocarcinoma, thyroid cancers, breast cancer, diffuse large B-cell lymphoma, multiple myeloma, testicular seminoma, yolk sac tumor, thymic, prostrate, and penile cancer. The ICI agents that were used included nivolumab (270), pembrolizumab (210), atezolizumab (32), durvalumab (23), avelumab (4), pembrolizumab plus chemotherapy (19), pembrolizumab plus ipilimumab (9), pembrolizumab plus investigational agent (12), pembrolizumab plus tyrosine kinase inhibitor (5), nivolumab plus ipilimumab (17), nivolumab plus investigational agent (19), and durvalumab plus tremelimumab (4). Overall, nivolumab-containing regimen accounted for 306 patients (47%) and pembrolizumab-containing regimen was given to 255 patients (39%). There were 30 patients who received ICI as part of clinical trial, and these were either randomized to ICI alone or ICI plus another agent.

Among 654 patients who received ICIs, 42(6.4%) patients developed pneumonitis. The baseline clinical characteristics for these patients are represented in Table 1. Of these 42 patients, 21 (50%) received nivolumab-containing regimen, 19 (45%) received pembrolizumab-containing regimen, and 2 (5%) received durvalumab. The clinical outcomes of the patients who developed pneumonitis are summarized in Table 2. All the patients who developed Grade $\geq$ 2 pneumonitis (34, 81%) received corticosteroids and ICI was discontinued subsequently. Patients with Grade 3 and Grade 4 pneumonitis (19, 45%) required hospital admission, and four of them (10%) required admission to intensive care unit. The 60-day mortality rate in patients who developed pneumonitis was 14% (6), and the cause of death in all these patients was believed to be secondary to advanced cancer rather than respiratory failure from pneumonitis. Four of the six patients (66%) had NSCLC and the other two (33%) patients had RCC.

Univariate analyses for risk factors associated with hospitalization from pneumonitis are presented in Table 3. Patients who presented with dyspnea as a symptom had a higher risk of getting hospitalized, but this was not statistically significant. Risk factors associated with OS are presented in Table 4. Patients who received pembrolizumab-containing regimen had increased risk of death compared with those who received nivolumab-containing regimen (hazard ratio [HR]: 0.208, 95% confidence interval [Cl]: 0.039–0.757, $p = .016$), who had prior chemotherapy (HR: 9.886, 95% Cl: 1.273–1271.687, $p = .02$),

Table 2. Outcomes of Patients who Developed Pneumonitis.

	All (N = 42)
Symptoms for pneumonitis	
Asymptomatic	9 (21)
Cough	17 (40)
Shortness of breath	16 (38)
Duration from receiving immune checkpoint inhibitor to pneumonitis (days)	21 (2–48)
Hospitalization for pneumonitis	
No	23 (55)
Yes	19 (45)
Use of corticosteroids	
No	8 (19)
Yes	34 (81)
Immunotherapy discontinued after pneumonitis	
No	8 (19)
Yes	34 (81)
Died within 60 days	
No	36 (86)
Yes	6 (14)

Data are presented as *n* (%) or median (range).

or who never had cancer-related surgery (HR: 0.202, 95% CI: 0.022–0.874, p = .03).

4. Discussion

Since the initial FDA approval of ipilimumab in 2011 for metastatic melanoma, the number of ICIs that are available and the indications for ICIs have been increasing exponentially [6–9,12–19]. ICIs are now indicated as first-line therapy for stage IV NSCLC without driver mutations [13] and as maintenance therapy for unresectable stage III NSCLC after chemoradiation [12].

Pneumonitis as an IRAE is a well-known side effect from ICIs; however, due to the constantly expanding indications and increasing use, the true incidence of pneumonitis remains highly variable. A large randomized controlled trial (RCT) with 834 patients with metastatic melanoma who received either pembrolizumab or ipilimumab showed that the incidence of pneumonitis was only 0.4%, although this is considered to be extremely low rate of incidence and in general most of the studies showed significantly higher rates of pneumonitis [31]. A meta-analysis involving 4,496 patients with NSCLC, melanoma, and RCC showed that the overall incidence of pneumonitis was 2.7% and that the incidence in patients with NSCLC and RCC was statistically higher than that in patients with melanoma (4.1% vs. 1.6%) [28]. Similarly, another large meta-analysis in which 3,232 patients with NSCLC who received PD-1 inhibitor showed pneumonitis incidence rate of 3.6%. This study also showed that 1,806 patients who received PD-L1/L2 inhibitors had statistically significant lower rates of pneumonitis than those who received PD-1 inhibitors (1.3% vs. 3.6%) [26].

The overall incidence of pneumonitis in our study was 6.4%, which is more in line with the real-world

Table 3. Univariable Logistic Analyses of Risk Factors Associated with Hospitalization (Yes vs. No, No as Reference).

	Event/N	HR (95% CI)	p
Age (yr)	19/42	1.023 (0.976–1.079)	0.352
Race			
Caucasian	12/26	Reference	
African-American	3/8	0.738 (0.145–3.387)	0.697
Other	4/8	1.160 (0.249–5.431)	0.847
Sex			
Male	11/25	Reference	
Female	8/17	1.128 (0.334–3.808)	0.845
Primary cancer			
Lung cancer	12/22	Reference	
Renal cell cancer	3/8	0.535 (0.102–2.524)	0.430
Melanoma	2/7	0.382 (0.058–1.974)	0.255
Other	2/5	0.600 (0.085–3.708)	0.579
ICI agent			
ICI - single agent	14/31	Reference	
ICI plus second agent	5/11	1.021 (0.261–3.903)	0.975
Cardiovascular			
No	17/31	Reference	
Yes	2/11	0.218 (0.037–0.928)	0.039
Diabetes			
No	18/34	Reference	
Yes	1/8	0.178 (0.017–0.947)	0.042
Hypertension			
No	8/20	Reference	
Yes	11/22	1.471 (0.447–4.967)	0.526
Chronic kidney disease/ESRD			
No	17/36	Reference	
Yes	2/6	0.619 (0.098–3.183)	0.570
Lung disease/COPD			
No	9/21	Reference	
Yes	10/21	1.201 (0.365–3.999)	0.762
Prior chemotherapy			
No	4/12	Reference	
Yes	15/30	1.889 (0.508–7.782)	0.346
Prior radiation			
No	10/24	Reference	
Yes	9/18	1.381 (0.415–4.662)	0.598
Prior surgeries for cancer			
No	12/25	Reference	
Yes	7/17	0.771 (0.224–2.586)	0.674
Symptoms for pneumonitis			
Asymptomatic	1/9	Reference	
Cough	8/17	3.281 (0.503–36.942)	0.224
Dyspnea	10/16	5.923 (0.894–68.168)	0.066

CI = confidence interval; COPD = chronic obstructive pulmonary disorder; ESRD = end-stage renal disease; HR = hazard ratio; ICI = immune checkpoint inhibitor.

Table 4. Univariable Cox Analyses of Risk Factors Associated with Overall Survival.

	Event/*N*	HR (95% CI)	*p*
Age (yr)	10/42	0.965 (0.929–1.009)	0.109
Duration from receiving drugs to pneumonitis (days)	10/42	0.903 (0.117–361.797)	0.561
Race			
Caucasian	7/26	Reference	
African-American	1/8	0.522 (0.055–2.393)	0.437
Other	2/8	0.988 (0.184–3.699)	0.987
Sex			
Male	5/25	Reference	
Female	5/17	1.492 (0.442–5.037)	0.509
Primary cancer			
Lung cancer	7/22	Reference	
Renal cell cancer	2/8	0.824 (0.154–3.083)	0.787
Melanoma	0/7	0.185 (0.001–1.521)	0.138
Other	1/5	0.881 (0.093–4.026)	0.886
ICI agent			
ICI - single agent	6/31	Reference	
ICI plus second agent	4/11	2.104 (0.582–6.949)	0.241
ICI agent			
Pembrolizumab-containing regimen	8/19	Reference	
Nivolumab-containing regimen	2/21	0.208 (0.039–0.757)	0.016
Durvalumab	0/2	0.410 (0.003–3.312)	0.484
Cardiovascular			
No	8/31	Reference	
Yes	2/11	0.747 (0.141–2.706)	0.678
Diabetes			
No	9/34	Reference	
Yes	1/8	0.588 (0.063–2.549)	0.520
Hypertension			
No	7/20	Reference	
Yes	3/22	0.354 (0.086–1.193)	0.095
Chronic kidney disease/ESRD			
No	10/36	Reference	
Yes	0/6	0.237 (0.002–1.844)	0.212
Lung disease/COPD			
No	3/21	Reference	
Yes	7/21	2.279 (0.678–9.384)	0.187
Prior chemotherapy			
No	0/12	Reference	
Yes	10/30	9.886 (1.273–1271.687)	0.023
Prior radiation			
No	5/24	Reference	
Yes	5/18	1.409 (0.417–4.757)	0.571
Prior surgeries for cancer			
No	9/25	Reference	
Yes	1/17	0.202 (0.022–0.874)	0.030
Symptoms for pneumonitis			
Asymptomatic	2/9	Reference	
Cough	2/17	0.371 (0.057–2.404)	0.278
Dyspnea	6/16	1.172 (0.299–6.385)	0.830
Hospitalization for pneumonitis			
No	4/23	Reference	
Yes	6/19	2.135 (0.644–7.749)	0.213
Use of steroids			
No	1/8	Reference	
Yes	9/34	1.776 (0.409–16.574)	0.485
Immunotherapy discontinued after pneumonitis			
No	2/8	Reference	
Yes	8/34	0.757 (0.209–4.003)	0.707

CI = confidence interval; COPD = chronic obstructive pulmonary disorder; ESRD = end-stage renal disease; HR = hazard ratio; ICI = immune checkpoint inhibitor.

(*continued on next page*)

experience and other retrospective studies that reported incidence of around 5% [26,28]. Although a retrospective study by Suresh et al. [27] involving 205 patients with NSCLC showed pneumonitis incidence of 19% (39/205) and patients with squamous cell subtype had higher incidence of pneumonitis (incidence rate ratio of 2.29, 95% CI: 1.08–4.83), we did not see such rates in our patients with NSCLC (272/654). This could partly be explained by patient selection for ICIs, single agent versus combination agents, underlying lung disease, and history of lung metastasis at the time of treatment. In our study group, the highest incidence rate was seen in patients with RCC (8/80,10%), metastatic melanoma (7/78, 9.3%), followed by NSCLC–adenocarcinoma (16/187, 8.5%) and NSCLC–squamous cell (4/78, 5.1%). Another important reason for such wide rates of pneumonitis in all the studies is lack of set clinical or radiological criteria, and this is not specific to ICI-induced pneumonitis. Neither clinical symptoms nor radiological findings can be specific for ICI-induced pneumonitis, and a significant number of patients can be asymptomatic [22,29] (21% in our study) and were diagnosed incidentally when computed tomography (CT) thorax was obtained for another indication. In our study, we could review CT thorax for 33 of 42 patients (79%) and the most common radiological abnormalities noted were ground glass opacities (45%), interstitial changes (42%), and pleural effusion (27%). None of these changes are specific to ICI-induced pneumonitis, and about 30% of patients had combination of radiological abnormalities. Since ICI-induced pneumonitis is a diagnosis of exclusion, we need to have high clinical suspicion and evaluate for other differential diagnosis, such as infections and tumor progression [22,27]. Our study also showed that patients who received pembrolizumab had decreased OS. Because the cause of death in all these patients is believed to be secondary to cancer progression

rather than pneumonitis, pembrolizumab was more likely an association than causal agent. Although a large meta-analysis [32] showed that PD-L1/L2 inhibitors had more incidence of pneumonitis than PD-1, there are no large studies comparing pembrolizumab and nivolumab for incidence of pneumonitis or OS after developing pneumonitis. As pembrolizumab and nivolumab belong to the same class (PD-1), significant difference in adverse effects between these two agents may be unlikely and will need large RCTs to confirm. Our study has several strengths including large patient population, most extensive type of cancers treated in a single study, several ICI agents were used both as single agents and in combination, study duration of more than 8 years during which several new agents were developed, and expanded indications for treatment. The main limitation of our study is the retrospective nature and the inherent limitations associated with it.

In conclusion, this study of large number of patients on ICIs over a long duration provides more evidence that pneumonitis is seen in around 6% of patients with relatively good outcomes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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