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Brief Report: Inhaled corticosteroid use and the risk of checkpoint inhibitor pneumonitis in patients with advanced cancer

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Abstract

Background: Checkpoint inhibitor pneumonitis (CIP) is an immune related adverse event that may complicate treatment with immune checkpoint inhibitors (ICI) and can cause significant morbidity. We sought to identify predictors for the development of CIP, and whether the use of inhaled corticosteroids (ICS) at time of ICI may be protective.

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Code availability: All analyses were conducted using the SAS system, version 9.4 (SAS Institute Inc., Cary, NC). No custom codes were used.

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Ethics approval: This retrospective study was approved by Institutional Review Board at the Ohio State University (IRB Study ID #2016C0070, PI: Dwight H. Owen, MD, MS). All procedures performed in studies involving human participants or their data were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate: A waiver of consent was granted by the Institutional Review Board at the Ohio State University for this retrospective study.

Methods: Patients with advanced cancer treated with ICI from 2011 and 2018 were included in this study. CIP attribution to ICI was determined by treating physician at time of diagnosis. Predictors were assessed by univariate and multivariable Cox proportional hazard models.

Results: We identified 837 pts treated with ICI, of whom 30 (3.6%) developed grade 2 or higher CIP. 82 patients (9.8%) were receiving ICS at time of ICI and had increased risk of developing CIP with hazard ratio (HR) of 4.22 (95% CI: 1.93-9.21, $p < 0.001$) compared to those patients not receiving ICS. Patients with age ≥ 65 years had increased risk of developing CIP (HR 2.12, 95% CI: 1.02-4.40, $p = 0.044$), as did 209 patients with lung cancer (198 NSCLC and 11 SCLC) compared to other types of cancers (HR 3.15, 95% CI: 1.54-6.46, $p = 0.002$). In multivariable analysis, age ≥ 65 years, lung cancer diagnosis, and ICS use remained statistically associated with development of CIP, with adjusted HR for ICS 3.09 (95% CI: 1.32-7.24, $p = 0.009$).

Conclusions: Patients treated with ICS at time of ICI initiation had an increased risk of developing CIP. We further identified older adults with age ≥ 65 years and lung cancers as independent risk factors for CIP.

Keywords

immune-related adverse event (irAE); immune checkpoint inhibitor (ICI); pneumonitis; steroids; inhaled corticosteroid (ICS); immunotherapy

Introduction

Immune checkpoint inhibitors (ICI) are an integral part of the cancer treatment landscape [1]. Antibodies targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death (PD-1) / programmed cell death ligand 1 (PD-L1) pathways have led to remarkable improvements in overall survival in many cancers [1–3]. Despite the success for many patients, ICIs are associated with unique toxicities termed immune-related adverse events (irAEs) that may lead to morbidity, treatment discontinuation and rarely death [4].

irAEs can affect any organ system, and checkpoint inhibitor pneumonitis (CIP) has one of the highest morbidity and mortality of all irAEs [5–8]. The underlying mechanism for CIP is poorly understood. Evidence suggests CIP is an inflammatory infiltrative lung process brought on by the heightened immunity within the body by ICI [4,9]. We hypothesized that inhaled corticosteroid (ICS) use may offer protection in patients receiving ICI. In this study, we studied the association between CIP and ICS, as well as other potential variables that might be predictive for CIP.

Materials and Methods

We conducted a retrospective study of patients with advanced cancers treated with ICI between 2011 and 2018 at the Ohio State University. Approval was obtained from the institutional review board. Data were extracted primarily through chart review via the electronic medical record system. Research Electronic Data Capture (REDCap) was used for data collection [10]. Medication lists at the time of ICI initiation were reviewed for the presence of ICS at time of ICI initiation by pharmacy database query and confirmed by manual chart review. The following ICS were included: fluticasone, budesonide,

mometasone, beclomethasone, ciclesonide, and flunisolide. Intranasal steroids were excluded. Common Terminology Criteria for Adverse Events (CTCAE) Version 5 was used to define the severity of CIP [11]. Grade 2 or higher CIP were determined by treating physician at time of CIP diagnosis based on the clinical picture, imaging findings, exclusion of other plausible diagnoses, and response to treatment consistent with prior studies [12]. Time to CIP was defined as weeks from the start of ICI to diagnosis. Patients who never developed CIP were censored at the time of last follow up or death.

Cox proportional hazards models were used to assess univariate associations between potential predictors for CIP. Cumulative hazard functions were plotted for significant predictors ($p < 0.05$) in univariate analysis. These predictors were entered into a multivariable Cox proportional hazards model. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) were reported. Kaplan-Meier method was used to estimate median overall survival (OS) and log rank test was used to compare OS between patients with and without CIP. A p -value of < 0.05 was considered statistically significant. All analyses were conducted using the SAS system, version 9.4 (SAS Institute Inc., Cary, NC).

Results

Out of 837 patients with advanced cancer treated with ICI in our study, 30 (3.6%) patients developed CIP. Overall, 477 (57.0%) were male and median age was 62.5 years. The median time to the diagnosis of CIP was 11.4 (interquartile range 4.2-23.5) weeks. Out of 30 patients with CIP, 12 (40.0%) had grade 2, 14 (46.7%) had grade 3, 1 (3.3%) had grade 4, and 3 (10%) had grade 5 CIP. (Table 1)

Univariate analysis (Figure 1 and Table 2)

The 354 (42.3%) patients with age ≥ 65 years had a statistically significant increased risk of developing CIP with hazard ratio (HR) of 2.12 (95% CI: 1.02-4.40, $p = 0.044$) when compared to 483 (57.7%) patients who were < 65 years. In this cohort, 209 (25.0%) patients with lung cancer (198 NSCLC and 11 SCLC) had significant increased risk of developing CIP compared to other types of cancers with HR 3.15 (95% CI: 1.54-6.46, $p = 0.002$).

The 82 (9.8%) patients who were on ICS had significant increased risk of developing CIP with HR 4.22 (95% CI: 1.93-9.21) and $p < 0.001$. Among the 82 patients who were on ICS, 60 (73.2%) had COPD, 6 (7.3%) had asthma, 3 (3.7%) had COPD and asthma, and 13 (15.9%) had unknown or undocumented indication for ICS. COPD by itself was not a statistically significant predictor of CIP in our cohort with HR 1.67 (95% CI: 0.72-3.90, $p = 0.234$).

A total of 489 (58.4%) patients in our cohort were previous or current smokers at time of treatment with ICI. Smoking status was not significantly associated with the development of CIP (HR 1.53, 95% CI: 0.72-3.26, $p = 0.274$). Of the 489 former and current smokers, 336 (68.7%) had known smoking pack year history, which was not associated with CIP ($p = 0.906$).

Other variables including gender, immunotherapy type, line of therapy, prior chemotherapy, and prior radiotherapy were not significantly associated with CIP in univariate analysis (Table 2).

Multivariable analysis (Table 2)

In multivariable analysis, age ≥ 65 years, lung cancer, and ICS all remained statistically significant predictors of CIP: HR 2.02 (95% CI: 1.06-4.58, $p=0.035$) for age ≥ 65 years, HR 2.29 (95% CI: 1.05-5.00) for lung cancer with $p=0.038$, and HR 3.09 (95% CI: 1.32-7.24, $p=0.009$) for being on ICS.

We did not detect any statistically significant difference in median OS among patients who developed CIP. Median OS was 16.36 months (95% CI: 7.33-not reached) for patients who developed CIP versus 13.57 months (95% CI: 11.30-15.54) in those patients who did not ($p=0.585$). There was no statistically significant difference in median OS between those who received or did not receive ICS ($p=0.345$).

Discussion

We identified a strong association between ICS use at the time of ICI treatment initiation and the development of CIP. To our knowledge, this is the first report of the association between ICS and ICI. Interestingly, we found no association between COPD and CIP, although patients older than 65 years and those with a diagnosis of lung cancer did have higher rates of CIP as previously reported [6,13,14].

ICI use has led to a significant improvement in long term survival for patients with advanced cancer [15,16,17]. Despite the progress made in recent years, irAEs still pose significant challenge in cancer treatment [8]. Although mild to moderate irAEs have been associated with improved outcome, severe forms of irAE may lead to treatment discontinuation and even mortality [18,19]. CIP is one of the more common serious irAE and carries one of the highest mortality. [20]

The mechanism of CIP is not well defined. Current evidence suggests CIP is an inflammatory infiltrative lung disease contributed by upregulated T-cell activities, increased level of cytokines productions, and amplified complement and auto-antibody mediated immunological processes [4,9]. Patients with lung cancer have increased pulmonary inflammation from underlying malignancies at baseline [21,4,9], which may predispose to the development of inflammatory response and risk of CIP. Our finding of elevated risk of developing CIP in lung cancer compared to other cancers is consistent with previous studies [13,6,14].

COPD is another condition that can result in chronic inflammation of the pulmonary system [22,23]. Unlike lung cancer, no increased risk of developing CIP was observed in patients with COPD. Although the severity for COPD defined by pulmonary function tests and its subtypes were not available for analysis, we did not find smoking history to be a significant predictor of CIP [24].

We hypothesized that the anti-inflammatory effect exerted by ICS would result in lower risk for CIP, however we observed a higher risk of developing CIP in patients prescribed ICS at time of ICI treatment initiation. The use of ICS is usually reserved for patients with advanced or symptomatic COPD and therefore may be a surrogate marker of the degree of inflammation caused by COPD. These patients may warrant closer monitoring during ICI treatment. Encouragingly, no survival difference was identified in patients who developed CIP. In this cohort, we did not find a statistically significant association between COPD and CIP, though patients on ICS had increased risk of developing pneumonitis in our study. We also identified patients with age ≥ 65 years as an independent risk factor for developing CIP.

We acknowledge there are multiple limitations in our study. First, we were unable to establish any causal relationship through a retrospective cohort study. Second, we were not able to effectively address medication adherence through chart view. Third, the diagnosis of irAE is fraught with challenges and irAE are known to occur even after treatment discontinuation [25,20]. Our study included patients treated over a significant time frame and our institutional approach to irAE and pneumonitis specifically has evolved with the changing guidelines for diagnosis and management of irAE. Finally, there are limitations to drawing conclusions regarding different grades of CIP given small numbers of cases. Future prospective studies are needed delineate the relationship between ICS and CIP, as well as other risks factors to aid in patient selection and monitoring while on ICI.

Conclusion

In this study, we found no protective effect of ICS for the development of pneumonitis, and instead found a higher risk of pneumonitis among patients treated with ICS at the time of immune checkpoint inhibitor therapy. We also identified older adults with age ≥ 65 years and lung cancers as independent risk factors for the development of checkpoint inhibitor pneumonitis.

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Abbreviations:

CIP	Checkpoint inhibitor pneumonitis
ICS	Inhaled corticosteroid
ICI	Immune checkpoint inhibitor
irAEs	Immune-related adverse events
OS	Overall survival

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Figure 1:

Univariate cumulative hazard plots of developing checkpoint inhibitor pneumonitis for a) inhaled corticosteroid, b) lung cancer, c) age in univariate analysis. Inhaled corticosteroid, lung cancer, and age remained statistically significant in multivariate analysis.

Table 1.

Patient demographics

Patient			Percent		
Patient			Percent		
Age			Gender		
<65 Years	483	57.7%	Male	477	57.0%
65 Years	354	42.3%	Female	360	43.0%
CIP Grade			ICI		
2	12	1.4%	Nivolumab	376	44.9%
3	14	1.7%	Ipiliumab	180	21.5%
4	1	0.1%	Pembrolizumab	141	16.8%
5	3	0.4%	Nivo + Ipi	61	7.3%
			Other	79	9.4%
Line of therapy			Cancer types		
1st	287	34.3%	Melanoma	310	37%
2nd	259	30.9%	NSCLC	198	23.7%
3rd	272	32.5%	RCC	73	8.7%
Unknown	19	2.3%	Other	256	30.6%
ICS			COPD		
No	755	90.2%	No	703	84.0%
Yes	82	9.8%	Yes	134	16.0%
Ever Smoked			Prior Chemo		
No	348	41.6%	No	325	38.8%
Yes	488	58.3%	Yes	386	46.1%
Unknown	1	0.1%	Unknown	126	15.1%

Table 2.

Univariate and multivariate analysis of each variable in Cox proportional hazard models with hazard ratio and p value. Age, inhaled corticosteroid use, and lung cancer diagnosis were all significantly associated with the development of checkpoint inhibitor pneumonitis in both univariate and multivariate analysis.

Univariate Analysis					
		HR		95% CI	P
Age	<65 Years				
	65 Years	2.12	1.02	4.40	0.044
Gender	Female				
	Male	1.51	0.71	3.22	0.291
ICI	Ipilimumab				
	Nivolumab	2.63	0.76	9.17	
	Pembrolizumab	3.63	0.96	13.70	
	Ipi + Nivo	2.79	0.56	13.81	
	Other	1.62	0.27	9.69	0.395
Cancer type	Other				
	Lung cancer	3.15	1.54	6.46	0.002
COPD	No				
	Yes	1.67	0.72	3.90	0.234
ICS	No				
	Yes	4.22	1.93	9.21	<0.001
Ever Smoked	No				
	Yes	1.54	0.72	3.29	0.267
Line of Therapy	1st				
	2nd	0.48	0.19	1.23	
	3rd or beyond	0.62	0.26	1.45	0.244
Prior Chemo	No				
	Yes	1.21	0.56	2.62	0.636
Multivariable Analysis*					
Age	<65 Years				
	65 Years	2.20	1.06	4.58	0.035
Cancer type	Other				
	Lung cancer	2.29	1.05	5.00	0.038
ICS	No				

Univariate Analysis				
	HR	95% CI		P
Yes	3.09	1.32	7.24	0.009

* Multivariable analysis includes the variables with a p-value <0.05 in the univariate analysis.

ICI, immune checkpoint inhibitor; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids;