BRIEF REPORT

Pretreatment Lung Function and Checkpoint Inhibitor Pneumonitis in NSCLC

Joshua E. Reuss, MD,[a,b,*] Emily Brigham, MD, MHS,[c] Kevin J. Psoter, PhD,[d] Khinh Ranh Voong, MD,[e] Bairavi Shankar, BS,[a] David S. Ettinger, MD,[a] Kristen A. Marrone, MD,[a,b] Christine L. Hann, MD,[a,b] Benjamin Levy, MD,[a,b] Josephine L. Feliciano, MD,[a,b] Julie R. Brahmer, MD,[a,b] David Feller-Kopman, MD,[c] Andrew D. Lerner, MD,[c] Hans Lee, MD,[c] Lonny Yarmus, DO,[c] Russell K. Hales, MD,[e] Franco D'Alessio, MD,[c] Sonye K. Danoff, MD, PhD,[c] Patrick M. Forde, MBBCH,[a,b] Karthik Suresh, MD,[c] Jarushka Naidoo, MBBCH, MHS[a,b]

[a]*Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland*
[b]*Bloomberg-Kimmel Institute for Cancer Immunotherapy at Johns Hopkins University, Baltimore, Maryland*
[c]*Division of Pulmonary Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland*
[d]*Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland*
[e]*Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland*

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ABSTRACT

Introduction: Checkpoint inhibitor pneumonitis (CIP) is a serious toxicity of anti–programmed death-(ligand) 1 immunotherapy. Whether pretreatment differences in pulmonary function exist in patients who develop CIP is unknown. We analyzed the pulmonary function tests (PFTs) of patients with NSCLC treated with immune checkpoint inhibitors (ICIs) to evaluate whether pretreatment lung function was associated with CIP development.

Methods: Patients were included if they completed greater than or equal to 1 PFT within 2 years preceding ICI initiation. CIP status (CIP+: developed CIP, CIP−: did not develop

*Corresponding author.

Drs. Suresh and Naidoo contributed equally to this work.

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Address for correspondence: Joshua E. Reuss, MD, Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD. E-mail: jreuss1@jhmi.edu

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CIP) was determined clinically. Generalized estimating equation–based linear regression was used to evaluate the effects of time and CIP on lung function. Primary outcomes included the following: percent-predicted forced expiratory volume in 1 second (FEV1pp), percent-predicted forced vital capacity (FVCpp), and FEV1/FVC.

Results: A total of 43 patients (34 CIP−, 9 CIP+) with 79 PFTs (59 CIP−, 20 CIP+) were included. CIP+ patients had a 21.7% lower pretreatment FEV1pp compared with the CIP− group (95% confidence interval: −38.6 to −4.7). No statistically significant differences in FVCpp or FEV1/FVC were observed. The prevalence of obstructive lung disease was similar in both groups at 67% and 62% for the CIP+ and CIP− cohorts, as was the prevalence of current/former smoking at 100% and 93%, respectively.

Conclusions: Pretherapy differences in lung function were evident between patients who did and did not develop CIP, though the prevalence of obstructive lung disease was similar. Prospective studies are needed to validate these findings, inform potential risk factors for CIP, and investigate the effects of ICI treatment and CIP on pulmonary function in patients with NSCLC.

Keywords: Non–small cell lung cancer; Pneumonitis; Pulmonary function tests; Immune checkpoint inhibitor; Immunotherapy

Introduction

In the past decade, the advent of immune checkpoint inhibitors (ICIs) targeting programmed death-(ligand) 1 (PD-(L)1) has revolutionized the treatment of advanced NSCLC. With increased use, there has been heightened appreciation of a potentially fatal class of ICI-related toxicities collectively labeled immune-related adverse events (irAEs).[1]

Checkpoint inhibitor pneumonitis (CIP) is an irAE defined by inflammation of the lungs that is typically accompanied by cough and dyspnea, though it may be asymptomatic.[2] Although early trials of ICIs in NSCLC estimated a CIP incidence of 3% to 5%,[3] retrospective analyses of real-world populations suggest that this may be substantially higher. We previously conducted a single-center retrospective analysis of 205 patients with ICI-treated NSCLC, finding a CIP incidence of 19%.[4] Furthermore, we found that CIP was independently associated with increased mortality.[5] Similar retrospective studies have corroborated these findings.[6–8] There is thus a critical need to improve our understanding of CIP risk factors, and to develop methods for early detection and effective monitoring in patients with NSCLC on ICI therapy.

Pulmonary function tests (PFTs) are a noninvasive method of assessing lung function and have been used in oncology to monitor for drug toxicities, including bleomycin-induced pulmonary fibrosis.[9] Key monitored parameters include the following: percent-predicted forced expiratory volume in 1 second (FEV1pp), percent-predicted forced vital capacity (FVCpp), and FEV1/FVC. Emerging evidence suggests that PFTs may be helpful for detecting early pulmonary toxicity in patients receiving ipilimumab (anti-CTLA4).[10] Whether differences in pulmonary function are associated with anti–PD(L)1 initiation or CIP is unknown. Furthermore, it is unknown whether patients who manifest clinically important CIP have pretreatment differences in lung function that may predispose to CIP development. Given these gaps in our understanding, and to further build on our previous analyses in patients with NSCLC who developed CIP, we retrospectively analyzed PFTs in patients with NSCLC treated with anti–PD-(L)1 ICIs at Johns Hopkins University to evaluate whether pretreatment lung function was associated with CIP development.

Materials and Methods

Study Population

Patients from a previously described cohort of patients with NSCLC[4,5] treated with PD-(L)1 ICI as standard of care or on trial at Johns Hopkins University from January 1, 2007, to July 31, 2017, were included if they obtained greater than or equal to 1 PFT within 2 years preceding ICI initiation. We initially planned to analyze PFT data preceding and after ICI initiation, but owing to a paucity of PFT data in the post-ICI initiation interval, our analyses were limited to the pre-ICI initiation period (Supplementary Figs. 1 and 2).

Patient demographics, oncologic characteristics, and clinical pulmonary diagnoses were abstracted from electronic medical records. CIP status (CIP+: developed CIP, CIP−: did not develop CIP) was evaluated clinically as previously described[4,5] by the treating oncologist in consultation with a multidisciplinary irAE team consisting of multiple subspecialties, including medical oncology, pulmonology, and infectious disease among others. Therapies included PD-(L)1 ICI with or without additional agents.

Statistical Analysis

Descriptive statistics were used to summarize demographic and clinical data. Linear regression on the

basis of generalized estimating equations with an unstructured covariance was used to evaluate the change in lung function in the pre-ICI initiation period and to evaluate differences in pretreatment lung function between the CIP− and CIP+ patient groups. The primary outcomes of interest were FEV1pp, FVCpp, and FEV1/FVC. p value less than 0.05 was considered statistically significant for all comparisons. Analyses were performed using R.[11]

Results

A total of 43 patients (34 CIP−, 9 CIP+) with 79 PFTs (59 CIP−, 20 CIP+) met the criteria for inclusion (Supplementary Fig. 1 and Table 1). There were 23 patients who had 1 PFT recorded in the pre-ICI interval, 9 who had 2 PFTs, and 11 who had greater than or equal to 3 PFTs (Supplementary Fig. 2 and Table 1). The median time from closest preceding PFT to ICI

Table 1. Baseline Demographics

Demographics	CIP− (n = 34)	CIP+ (n = 9)	All (N = 43)
Patient demographics			
Median age, y	69	69	69
Female sex, n (%)	17 (50)	2 (22)	19 (44)
Race, n (%)			
Non-hispanic White	26 (76)	6 (66)	32 (74)
African American	8 (24)	3 (33)	11 (26)
Smoking, n (%)			
Current	5 (14)	0 (0)	5 (11)
Former	27 (79)	9 (100)	36 (84)
Never	2 (5)	0 (0)	2 (5)
Clinical pulmonary diagnoses	14 (41)	5 (55)	20 (44)
COPD	13 (38)	2 (22)	15 (34)
ILD	1 (3)	1 (11)	2 (5)
Pulmonary HTN	1 (3)	0 (0)	1 (2)
Asthma	2 (6)	0 (0)	2 (5)
OSA	2 (6)	2 (22)	4 (9)
Pulmonary medication use[a]	15 (44)	4 (44)	19 (44)
Prn only	5 (15)	1 (11)	6 (14)
Scheduled	10 (29)	3 (33)	13 (30)
Pretreatment PFTs/patient, n (%)			
1	19 (56)	4 (44)	23 (53)
2	8 (24)	1 (11)	9 (21)
3+	7 (21)	4 (44)	11 (26)
Oncologic characteristics			
Tumor histology, n (%)			
Squamous	12 (35)	7 (77)	19 (44)
Adenocarcinoma	21 (61)	2 (23)	23 (53)
Other[b]	1 (2)	0 (0)	1 (2)
Initial cancer stage, n (%)			
I	5 (14)	0 (0.0)	5 (11)
II	5 (14)	1 (11)	6 (14)
III	17 (50)	6 (66)	23 (53)
IV	7 (20)	2 (22)	9 (20)
Enrolled in ICI trial	19 (55)	5 (55)	24 (55)
Previous chemotherapy, n (%)	23 (67)	8 (89)	31 (72)
Previous surgery, n (%)	14 (41)	3 (33)	17 (39)
Previous thoracic radiation, n (%)	12 (35)	7 (77)	19 (44)
ICI agent, n (%)			
Nivolumab monotherapy	20 (58)	5 (55)	25 (58)
Pembrolizumab monotherapy	9 (26)	0 (0.0)	9 (20)
Durvalumab monotherapy	1 (3)	0 (0.0)	1 (2)
Nivolumab + ipilimumab	4 (12)	4 (45)	8 (19)

[a]Inhaled and nebulized medications.
[b]Other: NSCLC NOS, poorly differentiated carcinoma.
CIP−, patients who did not develop checkpoint inhibitor pneumonitis; CIP+, patients who developed checkpoint inhibitor pneumonitis; COPD, chronic obstructive pulmonary disease; HTN, hypertension; ICI, immune checkpoint inhibitor; ILD, interstitial lung disease; NOS, not otherwise specified; OSA, obstructive sleep apnea; PFT, pulmonary function test; prn, as needed.

Table 2. Association Between Pre-ICI Lung Function and CIP Status[a]

Variable	FEV1pp, % [95% CI]	FVCpp, % [95% CI]	FEV_1/FVC, [95% CI]
Time	−1.7 [−9.9 to 6.4]	11.6 [−0.7 to 24.0]	−0.2 [−4.7 to 4.4]
CIP	−21.7 [−38.6 to −4.7][b]	−7.1 [−26.9 to 12.7]	−1.4 [−13.1 to 10.4]
Time:CIP	−7.6 [−27.8 to 12.5]	−2.2 [−20.8 to 16.4]	1.2 [−6.0 to 8.4]

[a]Linear regression on the basis of the general estimating equation Y(t) ~ time + CIP + time:CIP was used to evaluate the association between pre-ICI lung function and CIP development. An unstructured covariance specification was used.
[b]$p < 0.05$.
CI, confidence interval; CIP, checkpoint inhibitor pneumonitis; FEV_1pp, percent-predicted forced expiratory volume in 1 second; FVCpp, percent-predicted forced vital capacity; ICI, immune checkpoint inhibitor.

administration was 112 days for the entire cohort. The median time from closest PFT to ICI administration was 106 days for the CIP− cohort and 158 days for the CIP+ cohort. Pretreatment characteristics of this population, overall and by CIP status, are presented in Table 1. Characteristics were similar between groups although a greater percentage of CIP+ patients underwent previous thoracic radiation (77% versus 35% in the CIP− group). In addition, squamous tumor pathology was more prevalent in the CIP+ group (77% versus 35% in the CIP− group). The prevalence of clinically diagnosed pulmonary conditions at ICI treatment initiation was similar between groups, though a greater percentage of patients in the CIP− group had clinically diagnosed chronic obstructive pulmonary disease at the start of ICI therapy (38% versus 22% in the CIP+ group). The prevalence of inhaled respiratory medication use at ICI treatment initiation was similar between groups.

Results of generalized estimating equation–based linear regression models analyzing PFT data in the pre-ICI period are presented in Table 2. The CIP+ patient group had a significantly lower pretreatment FEV1pp (−21.7%; 95% confidence interval [CI]: −38.6 to −4.7) compared with the CIP− group. This relationship was not observed for FVCpp (−7.1%; 95% CI: −26.9 to 12.7) or FEV1/FVC (−1.4%; 95% CI: −13.1 to 10.4). Given the association between CIP and lower pretreatment FEV1pp, but not FVCpp, we hypothesized that obstructive lung function, defined by FEV1/FVC less than 70 according to the Global Obstructive Lung Disease criteria,[12] may be more prevalent in the CIP+ group. Nevertheless, the prevalence of obstructive lung physiology was similar in both groups at 67% and 62% for CIP+ and CIP− groups, respectively (data not illustrated). In addition, the percentage of current/former smokers was similar in both groups at 100% and 93%, respectively (Table 1).

Discussion

In this retrospective study, we found that patients with ICI-treated NSCLC with PFT data who developed CIP had a lower pretreatment FEV1pp compared with the CIP− group, with no observed differences in FVCpp or FEV1/FVC. The prevalence of PFT-determined obstructive lung disease, inhaled respiratory medication use, and current/former smoking was similar in both groups.

Identification of CIP risk factors is an ongoing area of research. In our study, previous thoracic radiotherapy seemed to be more prevalent in patients who developed CIP. Others have observed similar findings.[13] Furthermore, there is evidence that the real-world incidence of CIP after definitive chemoradiation for locally advanced NSCLC may be higher than that observed in clinical trials,[14] with real-world analyses reporting an incidence of approximately 24%.[15] In addition, multiple studies propose both preexisting interstitial lung disease and pulmonary fibrosis as risk factors for CIP.[6,16] A plausible unifying theme among these variables is that decreased lung function, or preexisting pulmonary disease resulting in decreased function, may be a CIP risk factor. In our analysis, before ICI initiation, we did not find statistically significant differences in FVCpp, an indicator of restriction seen in fibrotic/interstitial lung diseases. However, the CIP+ group had a 21.7% lower FEV1pp compared with the CIP− group, suggesting a potential role for preexisting lung function, specifically function of the airways reflected by FEV1pp, in determining CIP risk. Several meta-analyses suggest that CIP incidence may be higher in NSCLC, in which patients are frequently current/former smokers and more likely to have compromised lung function, at times manifested by diseases of the airways, such as chronic obstructive pulmonary disease.[3] Nevertheless, further work is needed to validate this finding, as the observed prevalence of PFT-determined obstructive lung physiology, inhaled respiratory medication use, and current/former smoking between the CIP+ and CIP− groups in our study was similar.

Our results are consistent with those of a recently reported prospective cohort study in Japan.[17] In this study, patients who developed CIP had significantly lower pretreatment FEV1pp (68.0% versus 79.5%, $p = 0.0275$) and FVCpp (69.4% versus 84.8%, $p = 0.0016$) compared with patients who did not develop CIP. Although we did not observe a statistically significant

difference in FVCpp in our analysis, this difference may represent variability owing to the small number of CIP cases in both studies versus true treatment variation or fundamental differences in risk factors across populations. Though additional evidence is needed, both studies lend consistency to the potential of pretreatment lung function as a measurable CIP risk factor. Taken together, this highlights a need for additional prospective investigation of on-treatment pulmonary function in patients with ICI-treated NSCLC to substantiate the predictive value of lung function for CIP development.

Our study has several limitations. First, this is a retrospective analysis of a population that did not undergo uniform standardized PFT testing. Therefore, only a limited number of patients with ICI-treated NSCLC obtained PFTs during the study period (43 of 205 patients),[4,5] and among those who did, there was variability in the timing and frequency of testing. Thus, selection bias may have been introduced; however, the demographics of this subgroup are similar to those of the entire population of patients with NSCLC treated with ICIs at our center in this period.[4,5] There were also insufficient data in our cohort to evaluate pulmonary diffusion capacity, a critical PFT variable for assessing overall pulmonary health. In addition, only 21 patients had post-ICI PFT data and less than half of these had corresponding pretreatment PFTs (Supplementary Fig. 2), precluding an examination of lung function dynamics after ICI initiation and immediately preceding/following CIP development. These are all important parameters to address in furthering our understanding of CIP pathophysiology and in clarifying the potential use of on-treatment PFTs in assessing CIP risk. To investigate these questions, prospective studies with PFT measurements obtained at standardized intervals before/after ICI initiation, in addition to preceding/following CIP development, are needed. This could prove logistically challenging, as PFTs are often difficult to obtain in the setting of newly diagnosed metastatic NSCLC and in patients with clinically important CIP requiring hospitalization (grade $\geq$3) that mandates expedited treatment. Nevertheless, multiple societal guidelines for irAE management including the National Comprehensive Cancer Network now recommend baseline PFTs before ICI initiation and as a component of the diagnostic workup for CIP,[18] suggesting prioritization of PFTs will improve.

Conclusions

In this retrospective study, we observed differences in pretreatment lung function between patients who did and did not develop CIP, adding to a small but growing body of literature suggesting pretreatment lung function may represent a CIP risk factor. Additional prospective studies are needed to confirm these results, and to further investigate the effects of ICI initiation and CIP development on pulmonary health. These endeavors will be vital to evaluating the applicability of surveillance PFTs in CIP risk assessment.

CRediT Authorship Contribution Statement

Joshua E. Reuss: Conceptualization, Investigation, Writing—original draft, Writing—review and editing, Visualization.

Emily Brigham: Conceptualization, Formal analysis, Writing—review and editing, Supervision.

Kevin J. Psoter: Methodology, Formal analysis, Writing—review and editing, Supervision.

Khinh Ranh Voong, David S. Ettinger, Kristen A. Marrone, Christine L. Hann, Benjamin Levy, Josephine L. Feliciano: Resources, Writing—review and editing.

Bairavi Shankar, David Feller-Kopman, Andrew D. Lerner, Hans Lee, Lonny Yarmus, Russell K. Hales, Franco D'Alessio: Writing—review and editing.

Julie R. Brahmer: Resources, Writing—review and editing, Supervision.

Sonye K. Danoff: Writing—review and editing, Visualization, Supervision.

Patrick M. Forde: Resources, Writing—review and editing, Visualization, Supervision.

Karthik Suresh: Conceptualization, Methodology, Formal analysis, Resources, Data curation, Writing—review and editing, Visualization, Supervision.

Jarushka Naidoo: Conceptualization, Resources, Writing—review and editing, Visualization, Supervision.

Ethics Approval and Informed Consent

The study was approved by the Johns Hopkins University institutional review board. Informed Consent: Given this was a retrospective study of a de-identified patient database, informed consent was not required.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2021.100220.

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