Risk factors for pneumonitis in advanced extrapulmonary cancer patients treated with immune checkpoint inhibitors

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Abstract

Background

Immune-mediated pneumonitis has a high mortality rate; however, little is known about the related risk factors. We analyzed the risk factors for pneumonitis, such as smoking and lung metastasis (LM), among extrapulmonary primary tumors.

Methods

We retrospectively collected data of 110 patients treated with immune checkpoint inhibitors (ICIs) (nivolumab/pembrolizumab) for extrapulmonary primary tumors at the Shiga University of Medical Science Hospital, between January 2015 and December 2019. The frequency of pneumonitis was evaluated based on the time between the start of ICI treatment and the onset of symptomatic or all pneumonitis. The severity of pneumonitis was graded according to the Common Terminology Criteria for Adverse Events, version 5.0. We analyzed the risk factors, such as the absence or presence of interstitial lung disease (ILD) and lung metastases (LMs), or other clinical factors, including smoking status before ICI administration.

Results

The Cox proportional hazards regression analysis revealed that the smoking index and presence of ILD were significant factors for an increased rate of all pneumonitis (hazard ratio [HR] = 20.3, 95% confidence interval [CI] = 20.0–20.4; $p = 0.02$ and HR = 4.3, 95% CI = 1.2–12.1; $p = 0.03$, respectively). LM was significantly related to an increased rate of symptomatic pneumonitis (HR = 6.8, 95% CI = 1.3–124.2; $p = 0.02$).

Conclusions

Smoking index and ILD were the significant risk factors for ICI-induced pneumonitis. LM was a significant risk factor for ICI-induced symptomatic pneumonitis. Therefore, pre-screening for ILD and LM and the recognition of patients' smoking histories are important for determining the risk of ICI-induced pneumonitis and allowing safe ICI administration.

Introduction

Immune checkpoint inhibitors (ICIs) are currently the first choice of treatment for several advanced carcinomas.¹ However, with the increasing number of patients receiving ICIs, the incidence of immune-related adverse events (ir-AEs) has also risen. There are various ir-AEs, and their profiles vary depending on the cancer type rather than on the ICI drugs used. AEs in areas located close to the primary lesions tend to occur as ir-AEs. For example, the incidence rate of skin rash during nivolumab (NIVO) therapy is 15% in malignant melanoma, which is higher than that associated with other malignancies, such as non-squamous non-small cell lung cancer (9%), gastric or gastro-esophageal junction cancer (7%), and esophageal squamous cell carcinoma (11%).^{2–5} Skin rash incidence during pembrolizumab (PEM) treatment is also higher in melanoma than in other malignancies.^{6–9} Diarrhea frequency in association with NIVO is 21% in DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer, while it is 8% in non-squamous non-small cell lung cancer, 16% in melanoma, and 7% in gastric or gastro-esophageal junction cancer.^{2–4, 10} Pneumonitis is a potentially serious complication associated with checkpoint inhibitors. It is defined as focal or diffuse inflammation of the lung parenchyma. Asymptomatic patients can be treated by only stopping the drug, but symptomatic patients need glucocorticoids, including prednisone with close follow-up. Additional immunosuppression, including infliximab or cyclophosphamide or intravenous immunoglobulin and mycophenolate mofetil, may be needed if the patient's condition worsens, though the benefit from these treatments is not clear. Even after recovery, it is recommended that patients with moderate or severe disease should not resume treatment. Hypoxia may occur and progress rapidly, leading to death.^{11–13} As reported based on the univariate generalized estimating equation model for programmed cell death 1 inhibitor-related pneumonitis, non-small cell lung cancer is related to a significantly higher incidence of pneumonitis than melanoma for all-grade pneumonitis (4.1% vs. 1.6%; $p = 0.002$). Comparing the incidence of pneumonitis, non-small cell lung cancer does not show incidence rates significantly different from those of renal cell carcinoma.¹⁴ Both carcinomas have been previously implicated in smoking and carcinogenesis; thus,

smoking-related cancers, such as lung cancer and renal cell carcinoma, may be linked to pneumonitis. Other than the presence of interstitial lung disease (ILD)^{15–18} and differences in carcinoma, the risk factors for pneumonia are unclear. Therefore, we analyzed the risk factors, including smoking and lung metastasis (LM), for pneumonitis in extrapulmonary primary tumors.

Materials And Methods

Study design and participants

We retrospectively collected data of 110 patients with advanced head and neck cancer, gastric cancer, renal cell cancer, urothelial cancer, peritoneal mesothelioma, and melanoma, who were treated with programmed cell death 1 inhibitor (NIVO or PEM) at the Shiga University of Medical Science Hospital, between January 2015 and December 2019. To analyze the effect of LM, cancers originating in the lung fields, such as lung cancer, pleural mesothelioma, and primary pulmonary melanoma, were excluded. Patients simultaneously treated with other cancer therapies involving cytotoxic agents, except ICIs, were also excluded. All patients who received the first ICI regimen and patients who received the second ICI regimen were excluded. The rates of pneumonitis were measured based on the time between the start of ICI treatment and the onset of symptomatic ($\geq$ grade 2 [G2]) or all ($\geq$ grade 1 [G1]) pneumonitis. This retrospective study was approved by the Institutional Review Board of Shiga University of Medical Science (R2020-037), which waived the need for written informed consent because of the retrospective design.

Medical record review

The severity of pneumonitis was graded according to the Common Terminology Criteria for Adverse Events, version 5.0. The diagnosis of pneumonitis was established and the evaluation of its severity was performed based on patients' clinical symptoms, physical examination findings, and radiographic images through a medical record review. The diagnostic criteria for pneumonitis were as follows: 1) temporal eligibility; 2) correct identification of ICI; 3) new consolidation or ground-glass abnormality on both sides on chest computed tomography (CT); and 4) exclusion of other causes, including pulmonary embolism, pulmonary infection, and heart failure. In each case of pneumonitis, the pattern of pneumonitis was classified according to the American Thoracic Society/European Respiratory Society guidelines¹⁹ into ☐) organizing pneumonia (OP) pattern, ☐) nonspecific interstitial pneumonia (NSIP) pattern, ☐) usual interstitial pneumonia pattern, ☐) hypersensitivity pneumonitis pattern, ☐) acute interstitial pneumonia/acute respiratory distress syndrome pattern, and ☐) unclassifiable pattern, with reference to preceding studies.^{20,21} All chest CT findings were reviewed by the consensus of a pulmonologist (Yasuki Uchida) and a radiologist (Yukihiro Nagatani). Other clinical data were collected through a medical record review. Ever smokers were defined as current and former smokers. Never smokers were defined as those who have never smoked. We evaluated the amount of smoking as pack-years.

Statistical analysis

The characteristics and treatment-related factors of patients with and without LM were compared using the Mann–Whitney *U* test or Fisher's exact test, as appropriate. The rate of pneumonitis was estimated using Kaplan–Meier curves and compared using two-sided log-rank tests. Hazard ratios (HRs) were estimated using Cox proportional hazards regression analysis. All *p*-values were two-sided, and those ≤ 0.05 were considered statistically significant. Predictors with *p*-values < 0.05 in the univariate analysis were included in a multivariate model. LM, ILD, and the amount of smoking (pack-years) were included in a multivariate model. Two-sided Cohen's *k*-coefficients were used to calculate the level of agreement in terms of the pneumonitis pattern in the radiologic assessment between the pulmonologist and the radiologist. All statistical analyses were performed using JMP version 11 (SAS Institute Inc., Cary, NC, USA), R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria),²² and EZR version 1.50 on R commander (Saitama Medical Center, Jichi Medical University, Saitama, Japan).²³

Results

Patient characteristics

The results of the comparison of the clinical characteristics between the LM+ (*n* = 69) and LM- (*n* = 41) groups are shown in Table 1. Significant differences were observed in the sex ratio (male/female, 56/13 vs. 26/15, *p* = 0.045) and smoking history (current/former/never, 21/27/21 vs. 4/18/19, *p* = 0.036) between the LM + and LM – groups. There was no significant difference in patients' age, amount of smoking, types of cancer, body mass index, line of ICI therapy, ICI cycle number, immunotherapy regimen,

and ILD. Two patients (one with head and neck cancer and the other with urothelial cancer) had received radiotherapy prior to ICI administration, but they did not develop pneumonitis.

Table 1
Patient and treatment characteristics of those with LM (LM+) and without LM (LM-)

Patient characteristics	All n = 110	LM+ n = 69	LM- n = 41	p-value LM + vs. -
Age				0.37
Median (range)	68 (34–84)	68 (34–84)	67 (38–83)	
Sex				0.045
Male	82	56	26	
Female	28	13	15	
Smoking history				0.036
Current	25	21	4	
Former	45	27	18	
Never	40	21	19	
Amount of smoking (pack-years)				0.089
Median (range)	21.75 (0–190)	25.00 (0–190)	3.50 (0–80)	
Types of cancer				0.219
Head and neck cancer	23	14	9	
Gastric cancer	17	8	9	
Renal cell cancer	29	22	7	
Urothelial cancer	15	11	4	
Malignant melanoma	25	14	11	
Peritoneal mesothelioma	1	0	1	
BMI (kg/m ²)				0.99
Median (range)	20.37 (14.61–36.49)	20.45 (14.61–36.49)	20.30 (14.63–31.87)	
Immunotherapy				0.41
NIVO	95	58	37	
PEM	15	11	4	
ILD				0.49
Yes	10	5	5	
No	100	64	36	
BMI, body mass index; NIVO, nivolumab; PEM, pembrolizumab; ILD, interstitial lung disease; LM, lung metastasis.				

Among 110 patients who received ICIs, 18 (16.3%) developed pneumonitis. Table 2 presents clinical details of the 18 patients who developed pneumonitis. Sixteen of the 18 patients were male, and their median age was 69 (range 54–81) years; 15 patients received NIVO and 3 received PEM. Six patients had head and neck cancer, five had renal cell carcinoma, three each had gastric cancer and

urothelial cancer, and one had malignant melanoma. Four patients had coexisting ILD. Fourteen patients had LM. Six patients were current smokers, 10 were former smokers, and two were never smokers. The median amount of smoking was 38.37 (range, 0–190) pack-years. The OP pattern was most commonly observed (9 of 18; 50.0%), followed by the NSIP pattern (5 of 18; 27.8%). Three patients (16.7%) had concomitant NSIP and OP patterns. Hypersensitivity pneumonia patterns were found in one patient (5.6%). Cohen's κ -coefficient was 0.648.

Table 2
Clinical characteristics of 11 patients with pneumonitis

Pt	Tumor	sex	Age, year	Agents	ILD	LM	Smoking history	Smoking amount, pack-years	Time to the onset of pneumonitis, day	Grade	Radiographic pattern
1	HNC (Sq)	M	73	NIVO	–	+	F	67.5	112	1	OP + NSIP
2	HNC (Sq)	M	79	NIVO	+	–	F	57	42	1	OP + NSIP
3	HNC (Undifferentiated)	M	68	NIVO	+	+	F	48	87	2	NSIP
4	HNC (Sq)	M	66	NIVO	–	+	C	22.5	59	1	OP + NSIP
5	HNC (Sq)	M	71	NIVO	–	–	F	40	6	1	OP
6	HNC (Sq)	M	69	NIVO	–	+	C	50	111	5	NSIP
7	MM	F	78	NIVO	–	–	N	0	105	1	OP
8	GC (AdSq)	M	72	NIVO	–	+	C	26.5		2	NSIP
9	GC (Ad)	M	58	NIVO	–	+	C	36	20	1	OP
10	GC (Ad)	M	81	NIVO	–	+	F	15	287	1	HP
11	RCC (clear cell)	M	74	NIVO	–	+	F	36.75	771	2	NSIP
12	RCC (clear cell)	M	54	NIVO	–	+	C	16	371	2	OP
13	RCC (clear cell)	M	63	NIVO	–	–	F	64.5	105	2	OP
14	RCC (clear cell)	F	64	NIVO	–	+	N	0	25	2	OP
15	RCC (clear cell)	M	73	NIVO	+	+	F	22.5	129	2	OP
16	UC	M	69	PEM	+	+	C	12	2	5	NSIP
17	UC	M	64	PEM	–	+	F	102	343	3	OP
18	UC	M	69	PEM	–	+	F	190	229	2	OP
Ad, adenocarcinoma; C, current; F, female; F, former; GC, gastric cancer; HNC, head and neck cancer; HP, hypersensitivity pneumonia; ILD, interstitial lung disease; LM, lung metastasis; M, male; MM, malignant melanoma; N, never; NIVO, nivolumab; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; PEM, pembrolizumab; RCC, renal cell carcinoma; Sq, squamous carcinoma; UC, urothelial carcinoma.											

The median duration between treatment initiation and the occurrence of asymptomatic (G1) and symptomatic ($\geq$ G2) pneumonitis was 3.8 months (range, 0.1–27.5) and 4.0 months (range, 0.1–27.5), respectively. The worst pneumonitis grade and numbers in total in the LM + and LM – groups are summarized in Table 3.

Table 3
Numbers and rates of worst pneumonitis grade

Pneumonitis grade	All	LM+	LM-
no. of patients (%)	n = 110	n = 69	n = 41
None	92	56	36
Grade 1	7	3	4
Grade 2	8	7	1
Grade 3	1	1	0
Grade 4	0	0	0
Grade 5	2	2	0
LM, lung metastasis.			

Incidence of pneumonitis

The cumulative incidence of all pneumonitis was 29.0% (95% confidence interval [CI] = 11.0–43.3) for all patients, 6.8% (95% CI = 0–15.7) for never smokers, and 36.3% (95% CI = 14.7–52.5) for ever smokers. The cumulative incidence of symptomatic pneumonitis was 22.1% (95% CI = 3.6–37.1) for all patients, 2.6% (95% CI = 0–7.4) for never smokers, and 28.3% (95% CI = 5.7–45.6) for ever smokers. The incidence of all pneumonitis was significantly higher ($p = 0.04$) and that symptomatic pneumonitis was not significantly higher ($p = 0.09$) in the ever smoker group, though the ever smoker group tended to show a higher frequency of all pneumonitis (Figs. 1A and 1B). The cumulative incidence of all pneumonitis was 35.2% (95% CI = 10.7–53.0) in the LM + group and 15.7% (95% CI = 1.5–27.9) in the LM – group, while the cumulative incidence of symptomatic pneumonitis was 31.3% (95% CI = 6.0–49.8) in the LM + group and 3.3% (95% CI = 0–9.5) in the LM – group. The incidence of symptomatic pneumonitis was significantly higher ($p = 0.03$) and that of all pneumonitis was not significantly higher ($p = 0.27$) in the LM + group; however, the incidence in the LM + group tended to be higher (Figs. 1C and 1D).

Table 4 shows the results of the Cox proportional hazards regression analysis for the incidence of all and symptomatic pneumonitis. The amount of smoking (HR = 20.26 per 20-pack year increase, 95% CI = 20.04–20.44; $p = 0.022$), smoking history (ever smoker vs. never smoker [HR = 4.05, 95% CI = 1.15–25.63; $p = 0.027$]), and ILD (HR = 4.25, 95% CI = 1.19–12.06; $p = 0.028$) were associated with all pneumonitis and LM (HR = 6.76, 95% CI = 1.29–124.16; $p = 0.020$), the amount of smoking (HR = 20.33 per 20-pack-year increase, 95% CI = 20.08–20.54; $p = 0.015$), and ILD (HR = 6.06, 95% CI = 1.30–21.56; $p = 0.025$) were significantly associated with an increase in the rate of symptomatic pneumonitis.

Table 4
Univariate analyses of the incidence of pneumonitis using a Cox proportional hazards model

Factor	Symptomatic pneumonitis		All pneumonitis	
	HR (95% CI)	p-values	HR (95% CI)	p-values
LM		0.020		0.26
+ vs. –	6.76 (1.29–124.16)		1.77 (0.66–5.52)	
Age		0.70		0.20
per 1-year increase	1.01 (0.96–1.08)		1.03 (0.98–1.09)	
Sex		0.19		0.15
Male vs. Female	3.26 (0.62–59.88)		2.62 (0.75–16.58)	
Smoking history				
Ever vs. Never	4.92 (0.94–90.36)	0.061	4.05 (1.15–25.63)	0.027
Amount of Smoking (pack-years)		0.015		0.022
per 20-pack year increase	20.33 (20.08–20.54)		20.26 (20.04–20.44)	
BMI (kg/m ²)		0.82		0.63
per 1 kg/m ²	0.98 (0.84–1.13)		0.97 (0.86–1.08)	
ILD		0.025		0.028
Yes vs. No	6.06 (1.30–21.56)		4.25 (1.19–12.06)	
CI, confidence interval; BMI, body mass index; HR, hazard ratio; ILD, interstitial lung disease; LM, lung metastasis.				

Discussion

This study had two major findings. First, the amount of smoking was identified as a significant risk factor for the onset of both symptomatic and all pneumonitis. Second, LM was a significant risk factor for the development of symptomatic pneumonitis.

For every 20-pack-year increase in the amount of smoking, the risk of symptomatic or all pneumonitis increased by 20.3 times. Current and former smokers had a significantly higher risk of pneumonitis than never smokers. In contrast, there was no difference in the pneumonitis risk between current and past smokers. To the best of our knowledge, this study is the first to show that the smoking index is an independent risk factor for immune checkpoint inhibitor-related pneumonitis in extrapulmonary cancer patients. Naidoo et al. demonstrated that the incidence of pneumonitis, including in lung cancer, was not significantly different between never smokers (19 of 43 [44%]) and both former/current smokers (24 of 43 [56%]); however, current smokers showed a tendency for higher incidence rates than former smokers (5 of 23 vs. 0 of 19, $p = 0.053$).²⁴ Though they differ in details, they tend to be consistent with the results of our study. Delaunay et al. reported that a majority of patients who developed pneumonitis were either current (26.7%) or former (53.3%) smokers, with a median consumption of 40 (5–80) pack-years.²¹ The smoking index is an independent risk factor for acute exacerbation in patients with cancer complicated by interstitial pneumonia, who are receiving cytotoxic anticancer drugs.²⁵ In terms of other pulmonary diseases, smoking is a risk factor in idiopathic pulmonary fibrosis,^{26,27} but there is currently a lack of clarity on the involvement of smoking and coexisting emphysema in acute exacerbation events.^{28–31} Concerning radiation pneumonitis, the existing data on smoking and comorbid emphysema as risk factors are not consistent.^{32–35} Conversely, interstitial pneumonia was correlated with symptomatic or all pneumonitis in this study. Similarly, in some studies, ILD was identified as a risk factor for immune-mediated pneumonitis.^{15–18} ILD is also a risk factor in radiation pneumonitis^{36,37} and other anticancer drug-related pneumonia cases,^{38,39} which should be noted in pneumonitis. LM is a significant risk factor for the development of symptomatic pneumonitis. Nishino et al. compared the incidence of pneumonitis in association with PD-1 inhibitor use across different tumor types and reported that the incidence in non-small cell lung cancer was significantly higher in both all-grade (4.1% vs. 1.6%; $p = 0.002$)

and $\geq$ grade 3 (1.8% vs. 0.2%; $p < 0.001$) diseases than in melanoma.¹⁴ If the lesion is located in the chest, such as in lung cancer, the risk of symptomatic pneumonitis may increase. Therefore, symptomatic pneumonitis requires attention regarding the administration of ICIs for cancers that originate outside the chest with pulmonary metastases. To the best of our knowledge, this is the first study to demonstrate a relationship between symptomatic immune-mediated pneumonitis and LM. As the population was limited in this study and the analysis of the relationship between smoking and LM was not the primary endpoint, it is necessary to validate our findings in a larger number of patients independent of anticancer drug use. Recently, ICI use has been suggested to be associated with the severity of coronavirus disease (COVID-19) and the related rate of hospitalization.⁴⁰ Therefore, the presence of viral infection may also need to be examined as a risk factor for pneumonitis. None of the patients in this study had COVID-19, and the disease was still not endemic in Japan at the end of this study.

The diagnosis of drug-induced pneumonitis types, such as immune-mediated pneumonitis, is difficult to establish based on imaging alone and must be considered in conjunction with other examinations such as clinical history, pulmonary function tests, cardiac evaluation, histopathology, and bronchoscopy. Therefore, the quality of this type of study and patient care would be better if radiologists and respiratory physicians who provide care to the patient in clinical practice work together. In fact, a majority of the patients with pneumonitis in this study consulted respiratory physicians and were diagnosed through bronchoscopy or other means.

The frequency of pneumonitis varies from 2.7–16.9% across reports.^{14, 16–18, 20, 21, 24, 41} At 13.2–16.9%, the incidence of pneumonitis is higher in the Japanese population^{16–18, 41} than in the non-Japanese population (3.5–11.8%).^{20, 21, 24} It has been reported that the Japanese population also tends to have a high incidence of pneumonitis that is induced by the use of epidermal growth factor receptor tyrosine kinase inhibitors.^{38, 42} It is unclear whether this can be attributed to race or the presence of confounding factors unique to Japan, such as the prevalence of interstitial pneumonia or the amount of smoking. Alternately, the fact that there is a tendency to repeat imaging studies in Japan may have facilitated the detection of grade 1 asymptomatic pneumonitis. If the prevalence of pneumonitis is high in the Japanese population and low in the non-Japanese population, it may be easier to investigate risk factors for pneumonitis in Japanese people who are more likely to experience a higher rate of events. It should also be considered that the incidence varies with the follow-up duration.

This study had some limitations. First, it had a retrospective design and included a relatively small number of patients with immune-mediated pneumonitis treated in a single institution. This could be a possible reason for the wide 95% CIs for several factors. Second, data on asymptomatic (G1) pneumonia during the follow-up of patients with cancers with extrapulmonary origins may be missed owing to a lack of routine chest imaging evaluations, such as chest radiography. Finally, several performance statuses and pulmonary function parameter values were missing and could not be analyzed. Therefore, validation in a multicenter, prospective study that considers these points is necessary.

Conclusions

In this study, which aimed to examine the predictors of pneumonitis development risk in association with the administration of ICIs for extrapulmonary tumors, the smoking index was found to increase the risk of pneumonitis regardless of the past or current smoking status. Similarly, interstitial pneumonia and LM also increased the risk of pneumonitis development. Pre-screening for ILD and LM and recording patients' smoking history can aid in the determination of the risk of pneumonitis and ensure safe ICI administration. It is our sincere hope that our findings can be used for the successful management of immune-mediated pneumonitis to increase the life expectancy of cancer patients.

Abbreviations

ICI: immune checkpoint inhibitor, ir-AE: immune-related adverse event, NIVO: nivolumab, PEM: pembrolizumab, ILD: interstitial lung disease, LM: lung metastasis, OP: organizing pneumonia, NSIP: nonspecific interstitial pneumonia

Declarations

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Author contributions

Conception/design: YU; Provision of study material or patients: YU, DK, HN, KF, MY, and YN; Collection and/or assembly of data: YU, DK, HN, KF, MY, and YN; Data analysis and interpretation: YU, DK, STM, YN; Manuscript writing: YU; All authors have read and approved the final manuscript.

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Figures

Figure 1

Cumulative incidence of pneumonitis. Kaplan–Meier curves showing the cumulative incidence of pneumonitis of all pneumonitis (A, C) and symptomatic pneumonitis (B, D). A and B pertain to ever smokers and never smokers. C and D represent those with lung metastases (LM+) and those without it (LM-).