The Risk Factors Associated with Immune Checkpoint Inhibitor-Related Pneumonitis

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Keywords

Immune checkpoint inhibitor · Pneumonitis · Risk factors

Abstract

Background: Pneumonitis is a serious adverse event in patients treated with immune checkpoint inhibitors (ICIs), with a mortality rate of up to 20%. The risk factors for ICI-related pneumonitis remain unclear due to the scarce data and infrequent event rate of 0–10% for all grades in patients using ICIs. **Objectives:** This study evaluated the risk factors for ICI-related pneumonitis using the United States Food and Drug Administration (US FDA) Adverse Event Reporting System (FAERS) database. **Method:** To investigate the association between pneumonitis and ICIs, the FAERS database, which contains spontaneous adverse event reports submitted to the US FDA, was utilized. Data between January 2014 and December 2019 were collected. Univariate logistic regression analysis with covariates, including age, sex, and ICI use,

was performed to assess the risk of ICI-related pneumonitis. The relative risk of pneumonitis was estimated using by the odds ratio. **Results:** We identified 4,248,808 reports, including 51,166 cases of those who received eight different ICIs. Nivolumab was the most common ICI ($n = 27,273$ of 51,166 [53.3%] patients). Reporting rates of pneumonitis were significantly high in ICI users (odds ratio 29.48; 95% confidence interval [CI], 27.49–31.62). Univariate logistic regression analysis showed that pneumonitis risk was significantly associated with age. Age ≤ 60 years old was associated with an increase in the reported frequency of pneumonitis. **Conclusions:** Our data suggest that the risk of ICI-related pneumonitis may increase in certain populations, including younger age (age < 60 years) and ICIs users. These patients require careful monitoring.

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Introduction

Pneumonitis is a serious adverse event in patients treated with immune checkpoint inhibitors (ICIs), with a mortality rate of up to 20% [1]. The risk factors for ICI-related pneumonitis remain unclear due to the scarce data and infrequent event rate of 0–10% for all grades in patients using ICIs [2].

The pathogenesis of chemotherapy-related pneumonitis differs from that of ICI-related pneumonitis. ICI-related pneumonitis occurs due to an inflammatory reaction against normal tissues, suggesting different risk factors associated with the two types of pneumonitis [3]. Close clinical monitoring is warranted for early diagnosis and timely management of immune-related adverse events. In this study, we aimed to evaluate the risk factors for ICI-related pneumonitis using the US Food and Drug Administration (US FDA) Adverse Event Reporting System (FAERS) database.

Material and Methods

To investigate the association between pneumonitis and ICIs, we used the FAERS database which contains spontaneous adverse event reports submitted to the US FDA. FAERS data between January 2014 and December 2019 were collected. Pneumonitis was defined according to the eight preferred terms listed in the National Center for Biomedical Ontology Medical Dictionary for Regulatory Activities Terminology: acute interstitial pneumonitis, granulomatous pneumonitis, hypersensitivity pneumonitis, immune-mediated pneumonitis, lupus pneumonitis, pneumonitis, pneumonitis chemical, and radiation pneumonitis. Univariate logistic regression analysis with covariates, including age, sex, and

ICI use, was performed to assess the risk of ICI-related pneumonitis. The relative risk of pneumonitis was estimated using the reporting odds ratio as previously described. Informed consent and institutional review board review and approval were waived due to the anonymous nature of the data. All statistical analyses were performed using R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

We identified 4,248,808 reports, including 51,166 cases of those that received eight different ICIs (Table 1). Nivolumab was the most common ICI ($n = 27,273$ of 51,166 [53.3%] patients). Reporting rates of pneumonitis were significantly high in ICI users (odds ratio 29.48, 95% CI, 27.49–31.62) (Table 2).

As shown in Table 2, univariate logistic regression analysis showed that pneumonitis risk was significantly associated with age. Age <60 years old was associated with an increase in the reported frequency of ICI-related pneumonitis (Table 2).

Discussion/Conclusion

As ICIs have become one of the most important treatment options across various types of cancers during the last decade, understanding the risk factors for ICI-related pneumonitis is of vital importance. In this pharmacovigilance study, we demonstrated that the use of ICIs is associated with a higher risk of ICI-related pneumonitis, which was consistent with previous studies [4]. We also

Table 1. Complete analysis of patients with pneumonitis based on specific immune checkpoint inhibitors^a

Drug A	Without drug A		With drug A			
	pneumonitis/ total cases	proportion of pneumonitis (95% CI)	pneumonitis/ total cases	Proportion of pneumonitis (95% CI)	Odds ratio (95% CI)	<i>p</i> value ^b
Atezolizumab	6,860/4,243,719	0.162 (0.158–0.165)	158/5,089	3.105 (2.628–3.581)	19.79 (16.86–23.23)	<0.001
Avelumab	6,996/4,247,937	0.165 (0.161–0.169)	22/871	2.526 (1.482–3.57)	15.71 (10.28–24.00)	<0.001
Cemiplimab	7,018/4,248,802	0.165 (0.161–0.169)	0/6	0	0.020 (NA–20.53)	0.93
Durvalumab	6,747/4,247,428	0.159 (0.155–0.163)	271/1,380	19.638 (17.539–21.736)	153.59 (134.2–175.78)	<0.001
Ipilimumab	6,653/4,237,680	0.157 (0.153–0.161)	365/11,128	3.280 (2.949–3.611)	21.57 (19.38–24.00)	<0.001
Nivolumab	6,081/4,221,535	0.144 (0.140–0.148)	937/27,273	3.436 (3.219–3.652)	24.66 (23–26.45)	<0.001
Pembrolizumab	6,537/4,235,388	0.154 (0.151–0.158)	481/13,420	3.584 (3.27–3.899)	24.05 (21.89–26.42)	<0.001
Tremelimumab	7,009/4,248,578	0.165 (0.161–0.169)	9/230	3.913 (1.388–6.438)	24.64 (12.65–48.01)	<0.001

NA, not applicable. ^a All data analyzed were obtained from the US, Food and Drug Administration Adverse Event Reporting System database.

^b Hypothesis tests were 2-sided, and statistical significance was set at $p < 0.05$. *p* values were calculated by Fisher's exact test.

Table 2. Univariate logistic analysis of patients with pneumonitis^a

Characteristic	Total cases, <i>n</i>	Cases of pneumonitis	Proportion of pneumonitis (95% CI)	Odds ratio (95% CI)	<i>p</i> value ^b
Sex					
Male	1,637,147	3,497	0.214 (0.207–0.221)	1 [reference]	
Female	2,551,457	3,444	0.135 (0.130–0.139)	0.80 (0.76–0.85)	<0.001
Not reported	60,204	77	0.128 (0.099–0.156)	0.68 (0.60–0.76)	0.0039
Age, years					
<60	2,212,745	2,571	0.116 (0.112–0.121)	1 [reference]	
≥60	2,036,063	4,447	0.218 (0.212–0.225)	1.70 (1.61–1.80)	<0.001
ICIs					
Nonuser	4,208,252	5,604	0.133 (0.13–0.137)	1 [reference]	
User	40,556	1,414	3.487 (3.308–3.665)	29.48 (27.49–31.62)	<0.001
Interaction between ICIs					
Female sex	18,402	612	3.326 (3.067–3.585)	1.04 (0.93–1.17)	0.47
Age ≥60 years	34,475	1,333	3.867 (3.663–4.07)	0.68 (0.60–0.76)	<0.001

ICIs, immune checkpoint inhibitors. ^a All data analyzed were obtained from the US, Food and Drug Administration Adverse Event Reporting System database. ^b Hypothesis tests were 2-sided, and statistical significance was set at $p < 0.05$. *p* values were calculated by Fisher's exact test.

found that younger age (age <60 years) was also a risk factor for ICI-related pneumonitis. This is in contrast to a previous study that assessed the frequency of ICI-related pneumonitis in patients with non-small cell lung cancer, which showed less frequent ICI-related pneumonitis in older patients [5]. However, we found that sex was not a risk factor for ICI-related pneumonitis. Further investigation on the association between sex and other clinical variables, such as cancer type and smoking status, would be necessary.

Our study has a few limitations. The FAERS database is based on self-reporting. Therefore, various reporting biases, such as overreporting or underreporting, may be inevitable. In addition, previous treatment, start and end dates of drug use, and dose of each ICI administration may not always be sufficient [6]. Nevertheless, the FAERS database is useful for monitoring and risk assessment. Our data suggest that the risk of ICI-related pneumonitis may increase in certain populations, including younger age (age <60 years) groups and ICI users. These patients may require more careful monitoring.

Statement of Ethics

This study was conducted in accordance with the Ethical Guidelines for Epidemiological Research by the Ministry of Health, Labour, and Welfare of Japan. It also conformed to the tenets of the Declaration of Helsinki. Because this study was an observational study using global open database (FAERS) with anonymized

information, not involving treatment intervention or collection of human samples, informed consent was exempted.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

Dr. Mikami and Mr. Niimura had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. Concept and design: all authors. Acquisition, analysis, and interpretation of data: all authors. Drafting of the manuscript: Dr. Asada and Dr. Mikami. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Dr. Asada, Dr. Mikami, Dr. Zamami, and Mr. Niimura. Obtained funding: Dr. Zamami. Administrative, technical, and material support: Dr. Zamami. Supervision: Dr. Zamami.

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