

Severe Immune-related Adverse Events and Their Effect on Survival in Patients With Advanced Non-small Cell Lung Cancer Receiving Immune Checkpoint Inhibitors

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Abstract

Background/Aim: Immune checkpoint inhibitors (ICIs) have become central in the treatment of non-small cell lung cancer (NSCLC). The occurrence of immune-related adverse events (irAEs) is a critical issue in the management of patients with NSCLC receiving ICIs. Recent studies have suggested that patients who develop irAEs may have a better prognosis than those who do not. However, the most problematic cases involved the development of severe irAEs. This study aimed to investigate the clinical impact of severe irAEs (grade ≥ 3) in patients with NSCLC treated with ICIs.

Patients and Methods: We analyzed 122 patients from a prospective database of consecutive patients with NSCLC who received first-line ICI-containing treatment between November 2018 and October 2024. Patients were classified into two groups: 48 treated with anti-programmed death-ligand 1 (anti-PD-L1) therapy and 74 treated with anti-programmed death-1 (anti-PD-1) therapy. We retrospectively compared the incidence of severe irAEs between the two groups and evaluated the clinical outcomes of severe irAEs on the survival.

Results: Among 122 patients, 24 (19.7%) experienced severe irAEs. The incidence of severe irAEs was significantly higher among patients treated with anti-PD-1 than among those treated with anti-PD-L1. The incidence of irAE-related death was also higher in the anti-PD-1 group than in the anti-PD-L1 group, with pneumonitis accounting for most of these fatalities (87.5%). There were no significant differences in the progression-free or overall survival between patients with and without severe irAEs. A multivariable analysis showed that the use of anti-PD-1 therapy was associated with a worse overall survival.

Conclusion: Treatment with anti-PD-1 was associated with an increased risk of severe irAEs. The incidence of severe irAEs was not associated with an improved survival rate.

Keywords: Lung cancer, immune checkpoint inhibitor, toxicity.



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Introduction

Immune checkpoint inhibitors (ICIs) have become a central component of the treatment for non-small-cell lung cancer (NSCLC). Programmed cell death protein 1 (PD-1) inhibitors, their ligand PD-L1 inhibitors, and combinations with chemotherapy are now established as standard first-line therapies for NSCLC (1-5). Although ICIs provide remarkable clinical benefits, immune-related adverse events (irAEs) remain a major concern for both clinicians and patients. Reliable methods for predicting and managing irAEs have not been established.

When irAEs occur, lung cancer treatment must often be interrupted, potentially limiting therapeutic efficacy. To assess the safety and broader implications of ICIs, it is essential to understand clinical outcomes following the onset of irAEs. Previous studies have reported that the development of irAEs may be associated with a favorable prognosis in patients with advanced cancers, including NSCLC (6-9). Consequently, physicians sometimes explain that patients experiencing irAEs may have better outcomes. However, most irAEs described in prior studies have been mild (grade 1-2), typically manageable with hormone replacement therapy or low-dose corticosteroids, and therefore not considered clinically problematic. By contrast, severe irAEs (Grade ≥ 3) are of particular concern (10-12). These events can cause significant organ toxicity and often require aggressive management with high-dose corticosteroids or immunosuppressive agents. Furthermore, severe irAEs carry the risk of treatment-related mortality, and their prognostic implications remain unclear.

We hypothesized that patients with NSCLC who develop severe irAEs during ICI therapy do not achieve favorable outcomes. This study aimed to clarify the clinical impact of severe irAEs in patients with NSCLC treated with ICIs.

Patients and Methods

Study population. This single-center retrospective cohort study was conducted using a prospective database of consecutive patients with NSCLC without actionable

genomic alterations treated between November 2018 and October 2024. During this period, 126 patients received first-line treatment including ICI therapy. Four patients who received anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) therapy were excluded because the sample size was small. Finally, 122 patients who were treated with either anti-PD-1 or anti-PD-L1 agents were included in the analysis.

Baseline clinical data collected from medical records at treatment initiation included age, sex, comorbidities, smoking history, Eastern Cooperative Oncology Group performance status (PS), tumor histology, disease stage, programmed death-ligand 1 (PD-L1) tumor proportion score (TPS), primary treatment, and ICI regimen administered. Following primary treatment, we obtained outcome data, including the dates of disease progression, death, and last confirmed survival, as well as information regarding irAEs (severity, type, and dates of irAE-related death).

The primary endpoint was the incidence of severe irAEs (grade ≥ 3), classified according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Grade 3-5 toxicities were recorded from initiation of first-line therapy to initiation of second-line therapy. In cases in which multiple severe irAEs occurred in a single patient, only the first event was recorded. Secondary endpoints included the progression-free survival (PFS) and overall survival (OS). PFS was defined as the time from the date of the clinical diagnosis of lung cancer to documented disease progression or death from any cause. OS was defined as the time from the clinical diagnosis to death due to any cause. The tumor response was assessed by attending physicians using the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) (13).

Complete follow-up data, including the disease progression, PFS, and OS, were available for all patients, and no data were missing. Chest radiography was performed at baseline, monthly, and whenever the symptoms developed. Chest-abdominal computed tomography (CT) and contrast-enhanced brain magnetic resonance imaging (MRI) were performed at baseline,

every 16 weeks, and as indicated. We retrospectively analyzed the incidence of irAEs and clinical outcomes.

First-line treatments. In this study, all patients received at least one dose of ICI, including pembrolizumab, atezolizumab, or durvalumab. Treatment regimens included ICI monotherapy, ICI in combination with chemotherapy, or ICI administered following chemoradiation. We previously reported that upfront dose reduction in the first cycle of first-line chemotherapy is safe and effective for elderly patients with NSCLC (14). Chemotherapy plus ICI was administered following our protocol.

Assessment of PD-L1 TPS. Tumor PD-L1 expression was assessed using 22C3 pharmDx assay (Agilent Technologies, Santa Clara, CA, USA). The tumor proportion score (TPS) was calculated as previously described.

Statistical analyses. Baseline characteristics are summarized as frequency (%) for categorical variables and as median values with ranges or interquartile ranges (IQRs) for continuous variables. Comparisons between the groups were performed using the *t*-test for continuous variables and Fisher's exact test for categorical variables. All *p*-values were two-tailed. The PFS and OS were analyzed using the Kaplan-Meier method, and survival curves were compared using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox proportional hazards model. Statistical significance was set at $p < 0.05$.

All analyses were performed using the EZR software program (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a modified version of R commander (version 1.62; The R Foundation for Statistical Computing, Vienna, Austria).

Ethics statement. This study was conducted at the Higashiosaka City Medical Center. The study protocol was reviewed and approved by the Institutional Review Board of Higashiosaka City Medical Center (approval no. 02-0973). The requirement for informed consent was waived because

this study was based on a retrospective review of the patients' medical records.

Results

Subjects. The baseline characteristics of the patients are summarized in Table I. Among the 122 patients included in this study, 24 (19.7%) experienced severe irAEs. The proportions of squamous cell carcinoma and anti-PD-1 treatment use were significantly higher in patients with severe irAEs than in those without irAEs. The results of the Cox regression analysis are presented in Table II. The multivariable model included the age, PS, histological subtype, PD-L1 TPS, use of anti-PD-1 therapy, and presence of interstitial pneumonia (IP). A stepwise regression analysis identified the use of anti-PD-1 therapy as significantly associated with the incidence of severe irAEs.

Incidence of severe irAEs. The incidence of severe irAEs is summarized in Table III. Severe irAEs occurred significantly more frequently in patients treated with anti-PD-1 therapy than in those treated with anti-PD-L1 therapy ($p = 0.011$). Among the 24 patients who experienced severe irAEs, pneumonitis was the most common, occurring in 15 (62.5%) patients. The incidence of pneumonitis was higher in the anti-PD-1 group than in the anti-PD-L1 group.

The incidence of irAE-related death is shown in Table IV. Of the 24 patients with severe irAEs, 8 (33.3%) died. The rate of irAE-related death was higher in the anti-PD-1 group than in the anti-PD-L1 group, although the difference was not statistically significant ($p = 0.108$). Of the eight fatal cases, seven (87.5%) were attributable to pneumonitis.

Survival analyses. The PFS and OS rates of each group are shown in Figure 1. Among the patients with severe irAEs, the median PFS was 1.48 [95%CI=1.08-not available (NA)] years. Among patients without severe irAEs, the median PFS was 1.29 (95%CI=1.05-2.19) years. There was no significant difference between the two groups ($p = 0.399$).

Table I. Baseline characteristics of patients with advanced non-small cell lung cancer stratified by severe immune-related adverse events (irAEs).

Variables	Control group (N=98)	Severe irAE group (N=24)	p-Value
Sex, n (%)			0.375
Male	82 (83.7)	18 (75.0)	
Female	16 (16.3)	6 (25.0)	
Age, years			
Median (range)	74 (34-92)	74.5 (55-87)	0.317
Comorbidities, n (%)			
Hypertension	51 (52.0)	16 (66.7)	0.254
Dyslipidemia	25 (25.5)	3 (12.5)	0.278
Diabetes	25 (25.5)	3 (12.5)	0.278
COPD	41 (41.8)	7 (29.2)	0.352
IP	7 (7.1)	2 (8.3)	1.000
Smoking history, n (%)			
Yes	94 (95.9)	22 (91.7)	0.336
PS, n (%)			0.380
0	19 (19.4)	6 (25.0)	
1	44 (44.9)	13 (54.2)	
2 or more	35 (35.7)	5 (20.8)	
Histology, n (%)			0.029
Adenocarcinoma	55 (56.1)	14 (58.3)	
Squamous	25 (25.5)	10 (41.7)	
Others	18 (18.4)	0 (0.0)	
Clinical stage, n (%)			0.243
Recurrence after surgery	14 (13.5%)	5 (20.0%)	
Unresectable ≤III	29 (27.9%)	10 (40.0%)	
Unresectable IV	61 (58.7%)	10 (40.0%)	
PD-L1 TPS, n (%)			0.501
High (>50%)	45 (45.9)	13 (54.2)	
Others	53 (54.1)	11 (45.8)	
Primary treatments, n (%)			0.210
ICI alone	24 (24.5)	6 (25.0)	
ICI plus chemotherapy	56 (57.1)	17 (70.8)	
Anti-PD-L1 treatment following chemoradiotherapy	18 (18.4)	1 (4.2)	
Immunotherapy regimen, n (%)			0.011
Anti-PD-1 treatment	54 (55.1)	20 (83.3)	
Anti-PD-L1 treatments	44 (44.9)	4 (16.7)	

Values are shown as the number (%), mean±SD, or median and range (minimum and maximum). COPD: Chronic obstructive pulmonary disease; ICI: immune checkpoint inhibitor; IP: interstitial pneumonia; PS: performance status; PD-1: programmed cell death protein 1; PD-L1: programmed death-ligand 1; TPS: tumor proportion score.

In patients with severe irAEs, the median OS was 1.90 (95%CI=1.29-3.36) years. In patients without severe irAEs, the median OS was 1.95 (95%CI=1.20-NA) years. There was no significant difference between the two groups ($p=0.771$).

Multivariable analyses related to the OS. Finally, we performed multivariable Cox regression analyses (Table V). The model included the age, PS, PD-L1 TPS, use of anti-PD-1 therapy, and presence of IP. A stepwise regression

analysis indicated that a poor PS and use of anti-PD-1 therapy were associated with a worse OS in patients with advanced NSCLC.

Discussion

The clinical impact of severe irAEs has not been fully clarified. In this study, treatment with anti-PD-1 agents was significantly associated with severe irAEs, most of which were fatal pneumonitis. A survival analysis

Table II. Logistic regression analyses of the incidence of severe immune-related adverse events.

Variable	Odds ratio	95%CI	p-Value
Age ≥ 75 vs. < 75 years	0.931	0.347-2.500	0.887
PS 2-4 vs. 0-1	0.451	0.143-1.430	0.175
Squamous	1.500	0.539-4.190	0.436
PD-L1 high TPS	1.250	0.484-3.210	0.649
PD-1 vs. PD-L1	4.990	1.360-18.30	0.015*
The presence of IP	2.250	0.348-14.60	0.394

*Variables selected using the stepwise method in regression analysis. CI: Confidence interval; IP: interstitial pneumonia; PS: performance status; PD-1: programmed cell death protein 1; PD-L1: programmed death-ligand 1; TPS: tumor proportion score.

Table III. Incidence of severe immune-related adverse events stratified by PD-L1 or PD-1.

Variable	PD-L1 group (N=48)	PD-1 group (N=74)	p-Value
irAEs	4 (8.3%)	20 (27.0%)	0.011
Pneumonitis	3 (6.3%)	12 (16.2%)	0.102
Hypopituitarism	0 (0.0%)	4 (5.4%)	0.109
Hypoadrenalism	0 (0.0%)	1 (1.4%)	0.419
Colitis	0 (0.0%)	1 (1.4%)	0.419
Hepatitis	1 (2.1%)	0 (0.0%)	0.213
Hypothyroidism	0 (0.0%)	1 (1.4%)	0.419
Cholangitis	0 (0.0%)	1 (1.4%)	0.419

Values are shown as number (%). PD-1: Programmed cell death protein 1; PD-L1: programmed death-ligand 1.

demonstrated no significant differences between patients with and without severe irAEs.

Previous studies have shown that the development of irAEs is linked to a favorable prognosis (6-9), likely because most irAEs are mild (grade ≤ 2), rarely life-threatening, and typically manageable with short-term treatment interruptions and corticosteroids. However, in our study, the patients who developed severe irAEs did not experience favorable outcomes. Consistent with our findings, Sugai *et al.* reported that while mild irAEs were associated with an improved prognosis, severe irAEs were not (10). Miyamoto *et al.* reported that severe irAEs were significantly associated with a shorter OS in elderly patients (age ≥ 70 years old) than in non-elderly patients and with a favorable OS in non-elderly patients (15). As

Table IV. The causes of immune-related adverse event-related death.

Variable	PD-L1 group (N=48)	PD-1 group (N=74)	p-Value
irAE-related death	1 (2.1%)	7 (9.5%)	0.108
Pneumonitis	1 (2.1%)	6 (8.1%)	0.162
Hypopituitarism	0 (0.0%)	0 (0.0%)	1.000
Hypoadrenalism	0 (0.0%)	0 (0.0%)	1.000
Colitis	0 (0.0%)	0 (0.0%)	1.000
Hepatitis	0 (0.0%)	0 (0.0%)	1.000
Hypothyroidism	0 (0.0%)	0 (0.0%)	1.000
Cholangitis	0 (0.0%)	1 (1.4%)	0.419

Values are shown as number (%). PD-1: Programmed cell death protein 1; PD-L1: programmed death-ligand 1.

this study included both elderly and younger patients, the potential negative prognostic impact of advanced age may have been mitigated.

Among patients with NSCLC receiving ICI therapy, pneumonitis is a particular concern (16). In this analysis, pneumonitis accounted for the majority of the irAE-related deaths. Similarly, Sugai *et al.* reported that all fatal cases of severe irAEs were attributable to pneumonitis (10). Several studies have also shown that the occurrence of irAEs is generally associated with an improved prognosis; however, pneumonitis remains an exception and is linked to unfavorable outcomes (17-19). Although many irAEs can be controlled with oral corticosteroids or hormone replacement therapy, pneumonitis may progress to poor outcomes, including death, even when treated with high-dose intravenous steroid pulse therapy. In this study, the majority of patients who developed pneumonitis but did not progress to Grade 5 sought medical attention promptly after the onset of symptoms (data not shown). Early detection and prompt management of pneumonitis may help prevent mortality and improve outcomes even when severe irAEs develop.

We found that the incidence of severe irAEs was significantly higher in patients receiving anti-PD-1 therapy than in those receiving anti-PD-L1 therapy, which is consistent with previous studies (20, 21). Previous studies have suggested that anti-PD-L1 therapy may induce fewer irAEs than anti-PD-1 therapy, likely because of differences

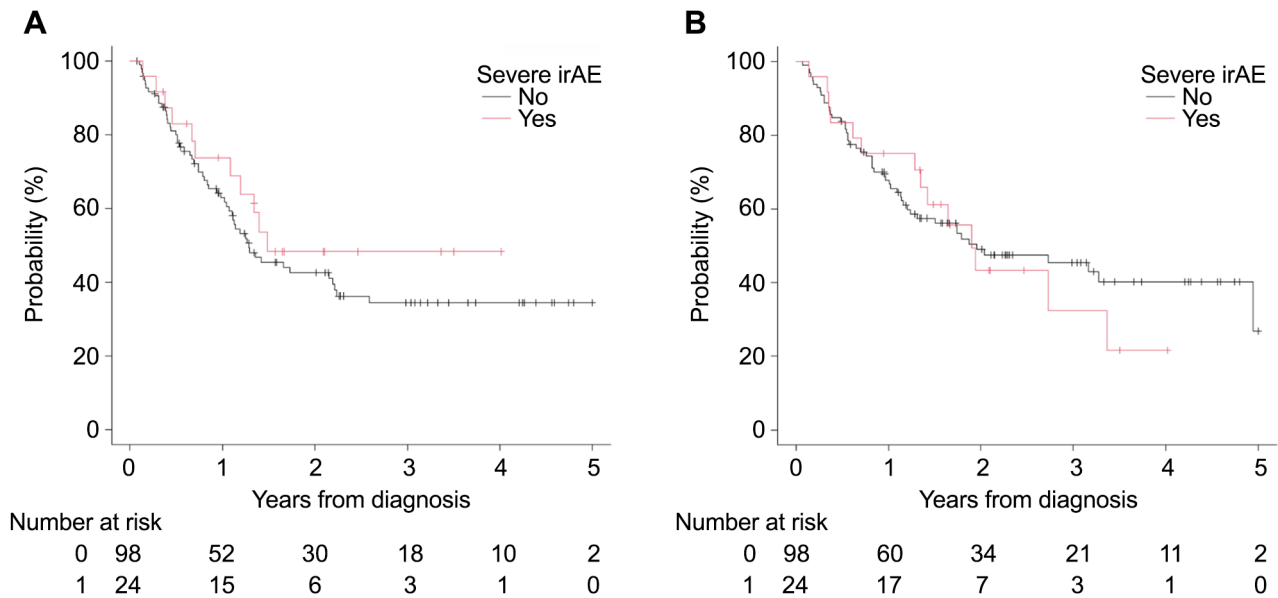


Figure 1. Kaplan-Meier survival curves for the progression-free survival (A) and overall survival (B) in each group. irAEs: Immune-related adverse events.

in their binding activity. Anti-PD-1 therapy inhibits both PD-L1 and PD-L2 interactions, whereas anti-PD-L1 therapy selectively blocks PD-L1 and PD-L2 is thought to contribute to immune homeostasis (22, 23). As previously reported, the patient population at our institution predominantly consists of elderly individuals (14). We found that irAE-related mortality was more frequent among patients receiving anti-PD-1 therapy than anti-PD-L1 therapy, and anti-PD-1 therapy was associated with a worse OS. These results suggest that the preferential use of anti-PD-L1 therapy should be considered in high-risk groups, such as elderly patients, to reduce the risk of fatal irAEs.

Study limitations. First, this study was conducted at a single institution, which limits the generalizability of the findings. Second, the relatively small sample size may have reduced the statistical power of the analysis. Third, the evaluation of severe irAEs was performed by attending physicians, potentially leading to variability in assessments. Finally, when multiple severe irAEs occurred in the same patient, only the first event was included. Therefore, the cumulative clinical impact of multiple severe irAEs was not evaluated in this study.

Table V. Cox regression analyses of the overall survival.

Variable	Hazard ratio	95%CI	p-Value
Age ≥ 75 vs. < 75	0.860	0.508-1.455	0.573
PS 2-4 vs. 0-1	1.736	1.041-2.896	0.035*
PD-L1 high TPS vs. others	0.491	0.289-0.835	0.009*
PD-1 vs. PD-L1	2.190	1.209-3.967	0.010*
The presence of IP	1.873	0.707-4.959	0.207

*Variables selected using the stepwise method in the regression analysis. CI: Confidence interval; IP: interstitial pneumonia; PS: performance status; PD-1: programmed cell death protein 1; PD-L1: programmed death-ligand 1; TPS: tumor proportion score.

Conclusion

In conclusion, the incidence of severe irAEs was not associated with improved survival rates. Pneumonitis accounted for the majority of severe fatal irAEs. Treatment with anti-PD-1 therapy has been linked to an increased risk of severe irAEs in patients with advanced NSCLC receiving ICI monotherapy or ICI combined with chemotherapy. These findings suggest that anti-PD-L1 therapy may be preferable for high-risk or elderly patients.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Takashi Nojiri, Akiisa Omura, Hiroshi Nishimura, Kiyotsugu Iede, Yuki Takeyasu, Utae Katsushima, and Masahiko Higashiyama made substantial contributions to the study concept or data analysis or interpretation, drafted the manuscript critically for important intellectual content, approved the final version of the manuscript to be published, and agreed to be accountable for all aspects of the work.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI)- or language learning model (LLM)-based technology was used to generate text or figures for this manuscript.

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