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Impact of Corticosteroids for IrAEs on the Clinical Outcome of Immunotherapy in Patients With NSCLC

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Abstract. *Background/Aim: The impact of corticosteroids for the treatment of immune-related adverse events (irAEs) on the antitumor effect of programmed cell death-1 (PD-1) inhibitor is unclear. Patients and Methods: A total of 172 patients with non-small cell lung cancer (NSCLC) treated with PD-1 inhibitors were retrospectively reviewed. Patients were divided into four groups: those who did not develop irAEs [1] and those who developed irAE and were either not treated with corticosteroids [2] or treated with low [3] or high doses [4], and overall survival (OS) was analyzed by the time of corticosteroid treatment. Landmark analysis was performed using Cox proportional hazard model with time-dependent covariates. Results: A high-dose steroid treatment within 60 days correlated with a significantly worse OS than that of the group with irAEs without steroids (p=0.004). Moreover, there was no significant difference in OS between the irAE without steroid and low-dose steroid groups. Conclusion: Early severe irAEs and high-dose corticosteroid treatment were poor prognostic factors in patients with NSCLC treated with PD-1 inhibitors.*

Immune checkpoint inhibitors (ICIs) have been a standard treatment option for different types of cancer, including non-small cell lung cancer (NSCLC). Nivolumab and pembrolizumab are anti-programmed cell death-1 (PD-1) inhibitors, which have promising efficacy compared with conventional systemic chemotherapy for advanced stage NSCLC (1-5). The whole body's immune system can be overactivated by ICIs causing immune-related adverse events (irAEs), which are caused by the immune system attacking itself (6). Most irAEs are mild or moderate and well tolerated, whereas serious irAEs occur less frequently. Immunosuppressive therapy, including systemic corticosteroids, is the most common standard irAE treatment, although the irAE management strategies vary based on their types and grades (7).

IrAEs and corticosteroid treatment have been demonstrated by several studies to be ICI treatment predictive factors. Early irAE development is a favorable predictive factor in patients with different cancer types (8-13). By contrast, using systemic corticosteroid therapy as the initial ICI treatment is a poor prognostic factor (14, 15). Therefore, there is a dilemma regarding systemic corticosteroid use against irAEs because they might reduce the ICI efficacy. Several factors associated with irAE effects and corticosteroid efficacy for ICI treatment must be considered. These include the onset time of irAEs or management with systemic corticosteroids and their doses. Several studies have investigated early irAE development and systemic corticosteroid use. However, few studies have examined late-onset irAE development and systemic corticosteroid use. Therefore, this study examined whether the timing and dose of corticosteroids used had an effect on clinical efficacy.

Patients and Methods

Patient eligibility. This study included patients with advanced-stage ICI-naïve NSCLC patients treated with PD-1 inhibitor (nivolumab or pembrolizumab) monotherapy at Aichi Cancer Center Hospital between January 2015 and November 2019. Nivolumab was administered at a fixed dose of 3 mg/kg or 240 mg/body every 2 weeks and pembrolizumab at a fixed dose of 200 mg/body every 3 weeks. Patients treated with systemic corticosteroids or other immunosuppressive agents at treatment initiation or during PD-1 inhibitor therapy for any causes other than irAEs and those with a

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poor Eastern Cooperative Oncology Group (ECOG) performance status (PS) score (≥2) were excluded. All data were retrospectively obtained from the medical records. The end of the follow-up period was 31 December 2020. All procedures performed in this study involving human participants were in accordance with the provisions of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This study was approved by the Institutional Review Board of Aichi Cancer Center Hospital (No. 2022-0-081). The ethics committees waived the need for formal consent from the participants.

Outcomes. Overall survival (OS) and time-to-treatment failure (TTF) were assessed to evaluate clinical outcomes. OS was defined as the duration between the PD-1 treatment initiation and death from any cause. TTF was defined as the duration between the start and discontinuation of PD-1 treatment or death from any cause. IrAEs were defined as adverse events with a potential immunological basis, according to a previous study (16). Moreover, the National Cancer Institute Common Toxicity Criteria for Adverse Events was used to grade irAEs (version 4.0) (17).

Statistical analysis. Patients were divided into four groups: the [1] without irAE, [2] irAE without steroid, [3] irAE and low-dose steroid, [4] irAE and high-dose steroid groups. A high dose of the steroid was defined as a dose equivalent to ≥0.5 mg/kg of prednisolone, and a low dose was defined as a prednisolone dose equivalent to <0.5 mg/kg. To examine differences in treatment efficacy depending on the timing of corticosteroid administration, we examined whether steroids were administered within 60 days of the initiation of treatment or after 60 days.

To investigate the appropriate causal relationship between the effects of irAEs, corticosteroids, and clinical outcomes, we performed a landmark analysis and used a Cox proportional hazard model with time-dependent covariates. The landmark analysis aimed to evaluate patients who did not develop disease progression, those who died, and those who were not censored within a specific time period from the start of PD-1 inhibitor treatment (18). The current study used a 60-day landmark point in the landmark analysis. The Cox proportional hazard model with time-dependent covariates was used to investigate the effects of irAEs and systemic corticosteroid treatment during PD-1 treatment (not at the start). Then, the hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated (19).

Specifically, we assumed the following model:

$$\lambda_i(t) = \lambda_0(t) \times exp\{\beta_0 x_{0i}(t) + \beta_1 x_{1i}(t) + \beta_2 x_{2i}(t) + \boldsymbol{\gamma}^T \boldsymbol{z}_i\},$$

i (subject)=1, …, N, x_0 (t)=0, 1 (developed irAE after time t), x_1 (t)=0, 1 (use of low-dose corticosteroids after time t), x_2 (t)=0, 1 (use of high-dose corticosteroids after time t), where λ_i(t) stands for the hazard value at time t and λ_0(t) is the baseline hazard value at time t. If a patient developed irAEs at time t, covariate x_0 was changed from 0 to 1. Similarly, if low-dose corticosteroids were used at time t, x_1 was changed from 0 to 1. If high-dose corticosteroids were used at time t, x_2 was changed from 0 to 1. The bald parameter γ represents fixed covariates for adjusting hazard λ(t). Furthermore, considering the effect of period, time t was separated at 60 days and analyzed. The following time-fixed covariates were used for adjustment: sex (male *vs*. female), age (≥75 *vs*. <75 years), ECOG PS score (0 *vs*. 1), treatment line (≤second *vs*. ≥third), histopathology (squamous cell carcinoma *vs*. non-squamous cell carcinoma), EGFR mutation or ALK fusion (positive *vs*. negative), and PD-L1 expression (0% *vs*. ≥1%). The survival curve was assessed using the extended Kaplan–Meier method adjusted for time-dependent covariates to explain changes in covariates (20). All comparisons were two-tailed, and a p-value <0.05 indicated statistically significant differences. This was exploratory research; thus, we did not use multiplicity adjustment methods. Statistical analyses were performed using the SAS software (version 9.4: SAS Institute) and R software (version 4.0.5: R Development Core Team, Vienna, Austria).

Results

Characteristics of patients. This study included 375 patients treated with PD-1 inhibitors for advanced-stage NSCLC. Patients who previously received immunotherapy (n=10), those treated with corticosteroids for conditions other than irAEs (n=55), those with a poor PS score (≥2) (n=32), and those with an unknown PD-1 status (n=45) were excluded. In the landmark analysis, 61 patients with a progression-free survival of <60 days were not included. Finally, 172 patients were included in the analysis. The median follow-up period was 742 days (range=83-2,057 days). There was no patient background bias among the four groups (Table I).

irAEs. Table II presents the summary of irAEs. In total, 144 (84%) of 172 patients developed irAEs. Moreover, 78 (45%) were not treated with corticosteroids, regardless of the development of irAEs (irAE without steroid group), 37 (22%) were treated with the high dose (high-dose-steroid group), and 29 (17%) were treated with the low dose (low-dose steroid group). In the irAE without steroid group, most irAEs were mild or moderate. In the high-dose steroid group, all irAEs were grade 2 or 3, and the most common irAE was pneumonitis (n=13). In the low-dose steroid group, patients frequently presented with grade 2 irAEs, and the most common irAEs were pneumonitis (n=9), rash/pruritus (n=10), and adrenal insufficiency (n=6). None of the patients presented with grade 4 or higher irAE. The median onset of irAEs was 63 days (range=1-882 days). The median onset of high-dose corticosteroids was 84 days (range=9-882 days), and that of low-dose corticosteroids was 91 days (range=2-680 days). The median treatment duration of high-dose corticosteroids was 14 days (range=4-42 days), and that of low-dose corticosteroids was 90 days (range=8-850 days).

Clinical outcomes. A landmark analysis was performed using the Cox proportional hazards model with time-dependent covariates to examine differences in clinical outcomes by corticosteroid dose and timing of steroid administration. In

Table I. *Characteristics of patients according to the development of immune-related adverse events (irAEs) and corticosteroid use*.

Characteristics	Number of patients			
	irAE without steroid group (%)	High-dose steroid group (%)	Low-dose steroid group (%)	Without irAE group (%)
Number	78 (45.4)	37 (21.5)	29 (16.9)	28 (16.3)
Age (years)				
<75	61 (78.2)	27 (73)	27 (93.1)	25 (89.3)
≥75	17 (21.8)	10 (27)	2 (6.9)	3 (10.7)
Sex				
Male	59 (75.6)	28 (75.7)	24 (82.8)	18 (64.3)
Female	19 (24.4)	9 (24.3)	5 (17.2)	10 (35.7)
PS score				
0	35 (44.9)	15 (40.5)	12 (41.4)	14 (50)
1	43 (55.1)	22 (59.5)	17 (58.6)	14 (50)
Smoking history				
Current or former	64 (82.1)	30 (81.1)	26 (89.7)	22 (78.6)
Never	14 (18)	7 (18.9)	3 (10.3)	6 (21.4)
Treatment line				
First or second	54 (69.2)	24 (64.9)	20 (69)	19 (67.9)
≥Third	24 (30.8)	13 (35.1)	9 (31)	9 (32.1)
Histopathology				
Sq	16 (20.5)	11 (29.7)	8 (27.6)	6 (21.4)
Non-Sq	62 (79.5)	26 (70.3)	21 (72.4)	22 (78.6)
EGFR mutation or ALK infusion				
Positive	12 (15.4)	3 (8.1)	1 (3.5)	6 (21.4)
Negative	66 (84.6)	34 (91.9)	28 (96.6)	22 (78.6)
PD-L1				
0%	15 (19.2)	7 (18.9)	2 (6.9)	4 (14.3)
≥1%	63 (80.8)	30 (81.1)	27 (93.1)	24 (85.7)

PS: Performance status; Adeno: adenocarcinoma; Sq: squamous; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; PD-L1: programmed cell death ligand-1.

Table II. *Summary of immune-related adverse events (irAEs) according to grade*.

Number	irAE without steroid group[a] N=78	High-dose-steroid group[b] N=37	Low-dose steroid group[b] N=29
		Grade 1/2/3	
Rash/pruritis	36/22/0	0/2/5	0/8/2
Diarrhea/colitis	14/0/0	0/4/2	0/0/0
Hepatotoxicity	18/8/1	0/2/4	0/0/1
Pneumonitis	8/1/0	0/13/5	2/7/0
Thyroid dysfunction	18/6/0	0/0/0	0/2/0
Adrenal insufficiency	1/0/0	0/0/0	0/6/0
Hypophysitis	0/0/0	0/0/0	0/1/0

[a]Some patients developed more than one irAE. Therefore, the total number of irAEs exceeded the number of patients. [b]Types of irAE that lead to the use of steroids. Patients that used both high-dose and lose-dose steroids were classified into the high-dose steroid group.

the analysis within 60 days, the median OS in the irAE without steroid, high-dose steroid, and without irAE groups was 38.7, 12.2, and 19.8 months, respectively (Figure 1A). However, that of the low-dose steroid group was not reached.

The median TTF was also longest in the low-dose steroid group as well as OS (irAEs without steroid group: 10.2, high-dose steroid group: 5.8, low-dose steroid group: 15.4 and without irAE group: 6.2 months) (Figure 2A). In the adjusted hazard ratios of the OS analysis, the high-dose

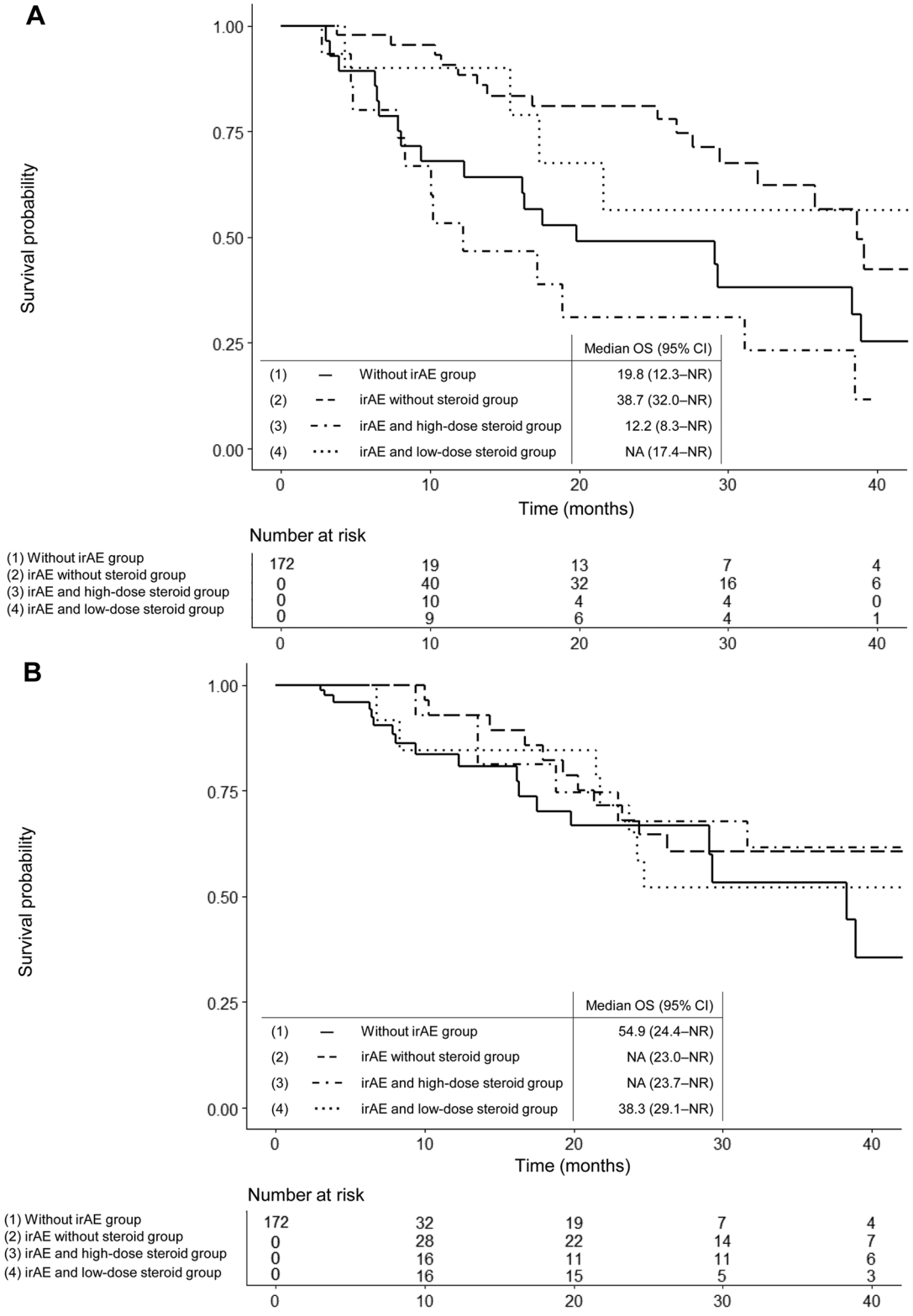

Figure 1. *Extended Kaplan–Meier curves with consideration of time-dependent covariates for overall survival (OS) in 172 patients with non-small cell lung cancer treated with programmed death-1 (PD-1) inhibitors. (A) The OS of patients treated with corticosteroids, those who developed immune-related adverse events (irAEs), and those who did not within 60 days from PD-1 inhibitor treatment initiation. (B) The OS of patients treated with corticosteroids, those who developed irAEs, and those who did not after 60 days from PD-1 inhibitor treatment initiation.*

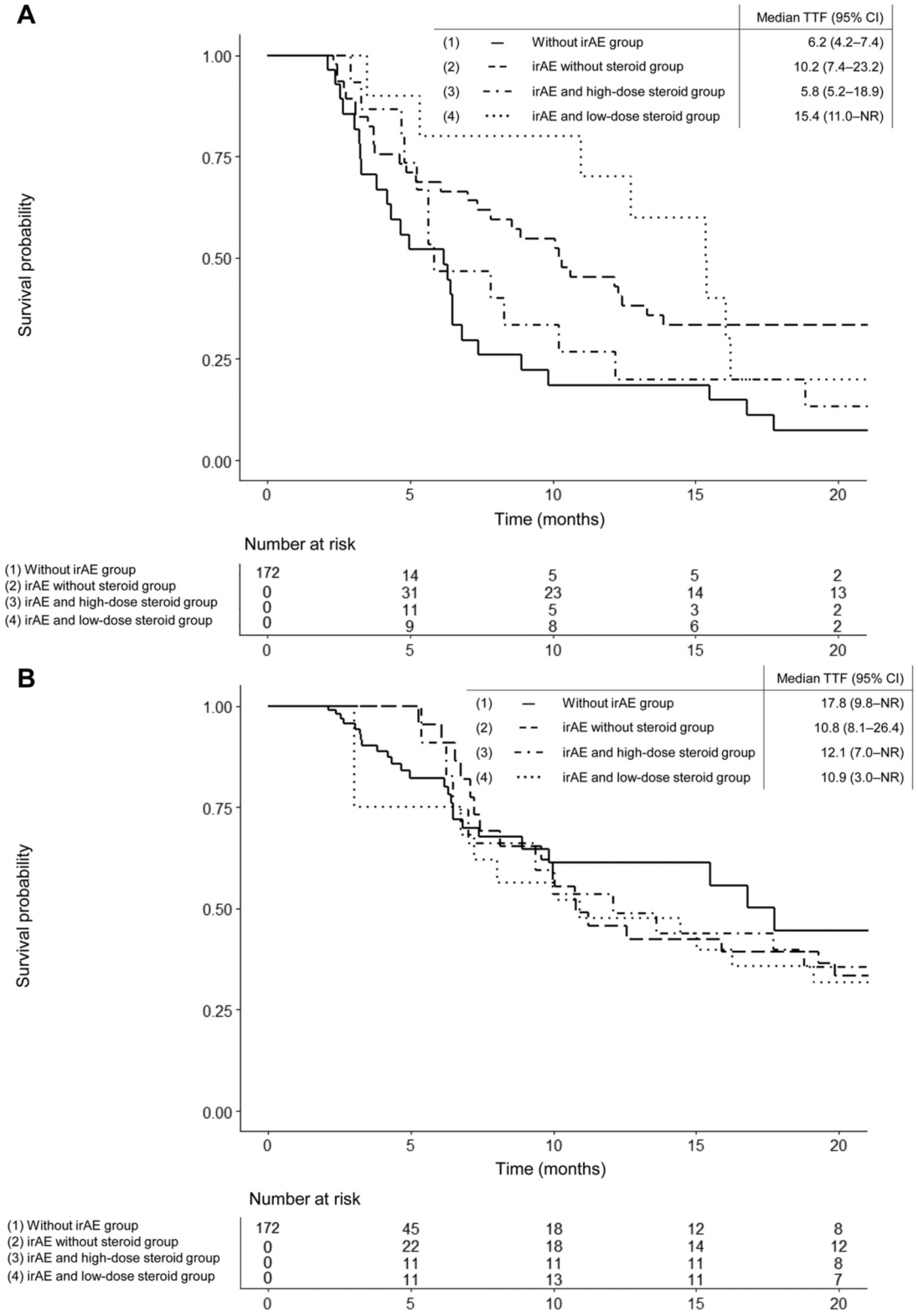

Figure 2. *Extended Kaplan–Meier curves with consideration of time-dependent covariates for time-to-treatment failure (TTF) in 172 patients with non-small cell lung cancer treated with programmed death-1 (PD-1) inhibitors. (A) The TTF of patients treated with corticosteroids, those who developed immune-related adverse events (irAEs), and those who did not within 60 days from PD-1 inhibitor treatment initiation. (B) The TTF of patients treated with corticosteroids, those who developed irAEs, and those who did not after 60 days from PD-1 inhibitor treatment initiation.*

Table III. *Overall survival of patients who developed immune-related adverse events (irAEs) and those treated with corticosteroids within or after 60 days after programmed cell death-1 (PD-1) inhibitor treatment initiation.*

Onset of irAEs and administration of corticosteroids	Reference=irAE without steroid	HR (95%CI)	*p*-Value
Within 60 days from the start of PD-1 inhibitor treatment	High-dose steroid	3.213 (1.454-7.100)	0.004
	Low-dose steroid	1.034 (0.338-3.166)	0.953
	Without irAE	2.600 (1.301-5.198)	0.007
After 60 days from the start of PD-1 inhibitor treatment	High-dose steroid	0.781 (0.289-2.106)	0.625
	Low-dose steroid	1.164 (0.443-3.062)	0.758
	Without irAE	1.546 (0.720-3.319)	0.264

CI: Confidence interval.

Table IV. *Time-to-treatment failure in patients who developed immune-related adverse events (irAEs) and those treated with corticosteroids within or after 60 days from programmed cell death-1 (PD-1) inhibitor treatment initiation.*

Onset of irAEs and administration of corticosteroids	Reference=irAE without steroid	HR (95%CI)	*p*-Value
Within 60 days from the start of PD-1 inhibitor treatment	High-dose steroid	1.708 (0.883-3.305)	0.112
	Low-dose steroid	1.208 (0.561-2.603)	0.629
	Without irAE	2.300 (1.301-4.066)	0.004
After 60 days from the start of PD-1 inhibitor treatment	High-dose steroid	0.971 (0.472-1.997)	0.936
	Low-dose steroid	1.222 (0.566-2.639)	0.610
	Without irAE	1.026 (0.531-1.982)	0.939

CI: Confidence interval.

steroid group (HR=3.21, 95%CI=1.45-7.10, p=0.004) and the without irAE group (HR=2.60, 95%CI=1.30-5.20, p=0.007) had a significantly lower OS than that of the irAE without steroid group (Table III). There was no significant difference in terms of OS between the irAE without steroid and low-dose steroid groups (HR=1.034, 95%CI=0.338-3.166, p=0.953). The HR of TTF and OS had a similar tendency (Table III and Table IV).

In contrast, in the analysis after 60 days, the median OS in the irAE without steroid and without irAE groups was 54.9 and 38.3 months (Figure 1B), respectively. Furthermore, the median TTFs were 10.8, 12.1, 10.9, and 17.8 months in group 1, 2, 3, and 4, respectively (Figure 2B). There were no significant differences in terms of OS and TTF after 60 days among the four groups (Table III and Table IV).

Discussion

The association between corticosteroid treatment and ICI efficacy has been reported in several studies (14, 15, 21-23). However, almost all studies focused on baseline corticosteroid treatment and clinical outcome effects. A few studies have investigated the association between corticosteroid treatment for early-onset irAEs and clinical outcomes (21, 24). Starting corticosteroid use at irAE onset and its influence on the therapeutic effect was one of the clinical issues that should be elucidated. Therefore, the effects of early- and late-onset irAEs and corticosteroid use on clinical outcomes became the focus of our study. Patients were excluded if they were treated with corticosteroid for factors other than irAEs at the start of ICIs treatment or during the ICIs treatment to eliminate selection bias in our study.

The high-dose steroid and without irAEs group had a significantly shorter OS than that of the irAE without steroid group within 60 days. However, the outcomes were not significantly different from the low-dose steroid group. There was no significant difference in OS and TTF among the no irAE, irAE without steroid, irAE with low dose steroid, and irAE with high-dose steroid groups after 60 days. The irAE group had a significantly better prognosis than the no irAE group based on previous reports. However, the group requiring high-dose corticosteroid was not distinguished from the others (8-13). In particular, the steroid-treated, irAE without steroid, and without irAE groups did not differ, even though the corticosteroid use is a poor prognostic factor, and irAEs are a favorable prognostic factor. Interestingly, the without irAE and irAE treated with high-dose steroid group had a significantly worse prognosis within 60 days after treatment initiation. These are important data for decision making regarding corticosteroid indication and dose for irAEs.

Tokunaga *et al*. assessed the corticosteroids effects to improve the irAE management, which can cause immunosuppression on tumor immunity (25). They hypothesized that the effect of immunosuppressive medication on tumor immunity can vary

based on the dose and treatment onset in mice. CD8+ memory T cells were involved in long-term immunity promoted by ICIs, and fatty acid oxidation is important for memory T cell development (26, 27). Tokunaga *et al*. also demonstrated that the fatty acid oxidation regulated gene expression was significantly reduced with high-dose corticosteroid treatment, which, consequently, decreased antitumor efficacy. However, in their study, tumor size reduction was not affected even with late high-dose corticosteroid treatment. Hence, high-dose corticosteroid treatment can inhibit the memory T cell differentiation, which occurs in the early stages of treatment. Furthermore, the effect of corticosteroids is limited after memory T cells are differentiated in the late stages of treatment. Therefore, their findings were consistent with our results showing that early and high-dose corticosteroids are associated with poor clinical outcomes.

In the present study, a landmark analysis was conducted using the Cox proportional hazard model with time-dependent covariates. Landmark analysis is widely used for analyzing the association between adverse events and clinical efficacy (18). However, landmark analysis would exclude patient number, and does not consider late-onset adverse events. irAEs could occur at different times and are different from conventional chemotherapy adverse events. Hence, the Cox proportional hazard model with time dependent covariates was used to analyze the association between various onset times of irAEs and steroid treatment (19, 28-31). The advantage of this is that it avoids the time-dependent bias caused by the standard Cox proportional hazard model (32-34).

The current study had several limitations. First, this was a retrospective and exploratory research, and a relatively small sample size was included. Therefore, the association between clinical outcome and uncommon irAEs (*e.g.*, type 1 diabetes and myasthenia gravis) could not be analyzed. Second, the statistical model used in this study assumed that the effect of steroid treatment could have resulted from the steroid therapy until events (death, censoring, and tumor progression). Therefore, further studies must be conducted to validate the association between duration of steroid treatment (*e.g.*, tapering of steroids) and efficacy of PD-1 inhibitor treatment. Finally, corticosteroid treatment indicates the severity of irAEs generally. Therefore, prognosis might have been affected by the development of irAEs, rather than the steroid treatment. It is challenging to identify which factor had more impact on prognosis.

In conclusion, early and severe irAEs and high-dose systemic corticosteroid treatment were associated with a poor clinical outcome in patients with NSCLC treated with PD-1 inhibitor monotherapy. However, low-dose corticosteroid for irAEs was not correlated with clinical outcomes. Nevertheless, further studies must be conducted to validate the association between clinical outcomes and PD-1 inhibitor therapy, types and severities of irAEs, and duration of steroid treatment.

Conflicts of Interest

Dr. Yamaguchi received personal fees from Ono Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, Taiho Pharmaceutical, AstraZeneca, MSD, and Bristol Meyers Squibb outside the submitted work. Dr. Oya received personal fees from AstraZeneca, Daiichi Sankyo, Ono Pharmaceutical, Chugai Pharmaceutical, Taiho Pharmaceutical, Eli Lilly, Bristol Myers Squibb, and Amgen outside the submitted work. The other Authors have no conflicts of interest to disclose in relation to this study.

Authors' Contributions

Study concepts and study design: KS; Data acquisition: KS, TY, YO; Statistical analysis: KS, KM; Manuscript preparation: KS; Manuscript editing: all Authors.

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