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Effect of Systemic Corticosteroid Therapy on the Efficacy and Safety of Nivolumab in the Treatment of Non-Small-Cell Lung Cancer

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Abstract

Introduction: Corticosteroids are used to treat immune-related adverse events (irAEs) associated with nivolumab. However, patients with non-small-cell lung cancer who are administered corticosteroids before the initiation of nivolumab treatment are commonly excluded from clinical trials. The appropriate timing for corticosteroid administration in relation to nivolumab treatment, effects of corticosteroids on the efficacy of nivolumab, and resulting adverse events are not clearly understood. In this study, the effects of differences in the timing of corticosteroid administration on nivolumab efficacy and the resulting adverse events were examined.

Methods: A retrospective study was conducted with 109 patients who were treated with nivolumab at Sapporo Minami-Sanjo Hospital between December 2015 and March 2018.

Results: Of the 109 patients treated with nivolumab, 12 patients were administered corticosteroids before the first cycle of nivolumab (pre-CS), and 33 patients were administered corticosteroids after the first cycle of nivolumab (post-CS). These 2 groups were compared with the control group comprising 64 patients who were not administered corticosteroids (non-CS). The objective response rate in the post-CS group was significantly higher than that in the non-CS group, and the disease control rate in the pre-CS group was significantly lower than that in the non-CS group. The overall survival time and progression-free survival time in the pre-CS group were significantly shorter than those observed in the non-CS group; however, these did not differ from those in the post-CS group.

Conclusions: These results suggest that corticosteroids administered to patients with non-small-cell lung cancer after initiation of nivolumab treatment did not affect the disease prognosis. Thus, corticosteroids can be administered immediately for rapid treatment of irAEs.

Keywords

nivolumab, corticosteroid, non-small-cell lung cancer

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Introduction

Nivolumab is a human programmed cell death ligand 1 (PD-1)-blocking antibody that functions as an immune checkpoint inhibitor. Nivolumab inhibits tumor growth by inhibiting the binding of PD-1 to its ligands PD-L1 and PD-L2, thereby increasing the proliferation, activation, and cytotoxic activity of tumor antigen-specific T cells.[1,2] However, newly formed autoantibodies due to increased anti-tumor activity of T cells produce an autoimmune response to normal tissues, resulting in various types of immune-related adverse events (irAEs).[3-5] Although immunosuppressive therapy with corticosteroids is used against irAEs,[6] it decreases the T cell count and cellular immunity, leading to an immunocompromised state.[7]

Corticosteroids are widely administered as antiemetic agents to patients with lung cancer. Moreover, these are used to treat fever, pneumonia, allergies, and central nervous system (CNS) metastases.[8-12] Corticosteroids can be administered to patients with lung cancer either before or after the initiation of nivolumab treatment. However, patients administered corticosteroids before the initiation of nivolumab treatment are commonly excluded from clinical trials. Furthermore, studies on the effects of corticosteroids administered to nivolumab-treated patients in clinical practice are limited. Some reports suggest that corticosteroids administered during nivolumab treatment do not affect the efficacy of nivolumab,[13-15] whereas others suggest that corticosteroid administration together with nivolumab treatment initiation reduces nivolumab efficacy.[16-18] There exist no studies in which patients administered corticosteroids before or after nivolumab treatment initiation are compared with those not concomitantly administered corticosteroids over the same time at a single medical institution. Therefore, the appropriate timing of corticosteroid administration in relation to nivolumab administration and its effects on nivolumab efficacy and adverse events are unknown.

In this study, patients with non-small-cell lung cancer who were administered corticosteroids before and after the initiation of nivolumab treatment were compared with those not administered corticosteroids. The time of corticosteroid administration, the effects of differences in the timing of concomitant corticosteroid treatment on nivolumab efficacy, and the resulting adverse events were investigated.

Patients and Methods

Patients

A total of 113 patients were treated with nivolumab (3 mg/kg at 2-week intervals) at Sapporo Minami-Sanjo Hospital between December 2015 and March 2018, of which 4 patients did not meet the inclusion criteria. Thus, a total of 109 patients were included in this study. Patients who withdrew from the study without further treatment at Sapporo Minami-Sanjo Hospital after the initial administration of nivolumab were excluded. The patients were divided into the following 3 groups: (i) non-CS group (control group) that was not systemically administered corticosteroids; (ii) pre-CS group that was systemically administered corticosteroids before the first cycle of nivolumab administration; and (iii) post-CS group that was systemically administered corticosteroids initiated during nivolumab treatment (after the first cycle of nivolumab administration).

Data Collection

The survey items were (i) sex, (ii) age at initial nivolumab administration, (iii) smoking history, (iv) disease stage at initial nivolumab administration according to the UICC TMN "Classification of Malignant Tumors" (version 7); (v) histotype according to the Japan Lung Cancer Society's "Classification of Lung Cancer" (version 8), (vi) presence or absence of epidermal growth factor receptor (EGFR) mutations, (vii) performance status at initial nivolumab administration according to the Eastern Cooperative Oncology Group criteria, (viii) nivolumab treatment line (i.e., first-line, second-line, etc.) at its initial administration, (ix) number of nivolumab doses administered, (x) presence or absence of CNS metastases, (xi) in the case of corticosteroids administration before initial nivolumab administration, cumulative dose equivalent to that of prednisolone was given; administration duration; and reasons for administration; and (xii) in the case of administration after nivolumab administration: initial dose equivalent to that of prednisolone; and reasons for administration. These items were determined retrospectively from the physicians' records, nurses' records, patients' compliance records, and the MiRaIs ordering system.

Endpoints

In accordance with the Response Evaluation Criteria in Solid Tumors (version 1.1), the best overall response was judged to be complete response (CR). Other responses studied were partial response (PR), stable disease (SD), and progressive disease (PD). The objective response rate (ORR) was defined as the proportion of patients showing CR or PR, and the disease control rate (DCR) was calculated as ORR plus the proportion of patients with SD. The overall survival time (OS) was described as the time from the date of nivolumab initiation to the date of a patient's death or the study cut-off date (March 31, 2018). The progression-free survival (PFS) referred to the time from the date of initial nivolumab administration until either the diagnosis of PD or the study cut-off date. Adverse events were diagnosed in accordance with the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.0). The primary endpoints were OS and PFS, and the secondary endpoints were ORR, DCR, and incidence of adverse events.

Statistical Analyses

The study was continued until a patient's death or the study cut-off date. The χ^2 test and Dunnett's test for the ordinal and nominal scales, respectively, were used to compare patients'

Table 1. Characteristics of the Patients.

		All patients n = 109	Non-CS group n = 64	Pre-CS group n = 12	Post-CS group n = 33	p-value
Gender, n (%)	Male	80 (73)	44 (69)	11 (92)	25 (76)	0.24[a)]
	Female	29 (27)	20 (31)	1 (8)	8 (24)	
Age, years, median (quartile)		67 (60, 73)	67 (60, 73)	63 (57, 67)	67 (61, 72)	0.31[b)]
Smoking history, n (%)	Never smokers	14 (13)	12 (19)	0 (0)	2 (6)	0.08[a)]
	Former smokers	95 (87)	52 (81)	12 (100)	31 (94)	
Histological subtypes, n (%)	Non-squamous	67 (62)	40 (63)	8 (67)	19 (58)	0.86[a)]
	Squamous	42 (38)	24 (37)	4 (33)	14 (42)	
EGFR mutation status, n (%)	EX19del / L858R	3 (3) / 2 (2)	3 (5) / 1 (2)	0 (0) / 0 (0)	0 (0) / 1 (3)	0.89[a)]
	Wild type	61 (56)	34 (53)	8 (67)	19 (58)	
	Not inspected	43 (39)	26 (40)	4 (33)	13 (39)	
Stage, n (%)	III A / III B	23 (21) / 13 (12)	10 (16) / 6 (9)	1 (8) / 3 (25)	12 (36) / 4 (12)	0.05[a)]
	IV / Recurrent	54 (50) / 19 (17)	38 (59) / 10 (16)	6 (50) / 2 (17)	10 (30) / 7 (22)	
ECOG-PS at first cycle of nivolumab, n (%)	0, 1	96 (88)	56 (88)	10 (83)	30 (91)	0.77[a)]
	≧2	13 (12)	8 (12)	2 (17)	3 (9)	
Number of lines of nivolumab, n (%)	2	30 (28)	20 (31)	1 (8)	9 (27)	0.58[a)]
	≧3	79 (72)	44 (69)	11 (92)	24 (73)	
CNS metastasis at diagnosis, n (%)	YES	13 (12)	9 (14)	3 (25)	1 (3)	0.10[a)]
	NO	96 (88)	55 (86)	9 (75)	32 (97)	
Number of nivolumab cycle, median (quartile)		6 (4, 11)	7 (4, 12)	4 (2, 4)	8 (6, 11)	<0.01[b)]*

a) Dunnett test, b) Kruskal-Wallis test, *$p < 0.05$, non-CS vs pre-CS. EGFR, epidermal growth factor receptor; ECOG PS, Eastern Cooperative Oncology Group performance status; CNS, central nervous system; non-CS, not systemically administered corticosteroids; post-CS, systemic corticosteroid administration initiated during nivolumab treatment; pre-CS, systemic corticosteroid administration before the first cycle of nivolumab administration.

backgrounds and the best OS. OS and PFS were estimated using the Kaplan–Meier method, and inter-group comparisons were conducted using the log-rank test. In addition, the nivolumab treatment duration and the period from nivolumab discontinuation to a patient's death or the study cut-off date were displayed using a Swimmer plot for each group. The timing of systemic corticosteroid administration after nivolumab treatment was evaluated. Differences were considered significant at levels below 5% ($p < 0.05$). The statistical software used was the Bell Curve for Excel (Social Survey Research Information Co., Ltd.)

Ethical Statement

This study was performed in compliance with the Ethical Guidelines for Medical Research on Human Subjects. Our study was approved by the Sapporo Minami-Sanjo Hospital's Ethics Committee (approval no. 28-8). All patients provided written informed consent before enrollment into the study. We ensured that the confidential information of patients was protected. The data were anonymized before handling.

Results

The study included a total of 113 patients who were administered nivolumab at Sapporo Minami-Sanjo Hospital between December 2015 and March 2018. The evaluation was performed with 109 patients. Within 14 days of the initial nivolumab administration, 4 patients were excluded due to death resulting from the progression of the primary disease or when continued treatment was deemed inappropriate. Patients' demographics and medical history were as follows: (i) sex: 80 males (73%), 29 females (27%); (ii) median age: 67 years (quartiles: 60 and 73 years); (iii) performance status at nivolumab treatment initiation: 0 to 1, 96 patients (88%); 2 or higher, 13 patients (12%); (iv) nivolumab treatment line at initiation: first-line: 30 patients (28%); second-line or later: 79 patients (72%); and (v) median number of nivolumab doses administered: 6 (quartiles: 4 and 11; Table 1). In 109 patients, the best OS reported were CR in 0 patient (0%), PR in 22 patients (20%), SD in 55 patients (51%), and PD in 32 patients (29%), with an ORR of 20% and a DCR of 71% (Figure 1). The median OS was 11.2 months and the median PFS was 3.2 months (Figure 2A, B).

The selected patients were divided into a non-CS group (64 patients, 59%), pre-CS group (12 patients, 11%), and post-CS group (33 patients, 30%). The pre-CS and post-CS groups were compared with the non-CS control group.

Patients' Background Factors

No significant inter-group differences were found in sex, age, smoking history, histotype, presence or absence of EGFR mutations, disease stage, performance status, treatment line, or presence or absence of previous or current CNS metastases. However, the number of nivolumab cycles was significantly lower in the pre-CS group than in the non-CS group (Table 1). Patients in the pre-CS group required systemic corticosteroid

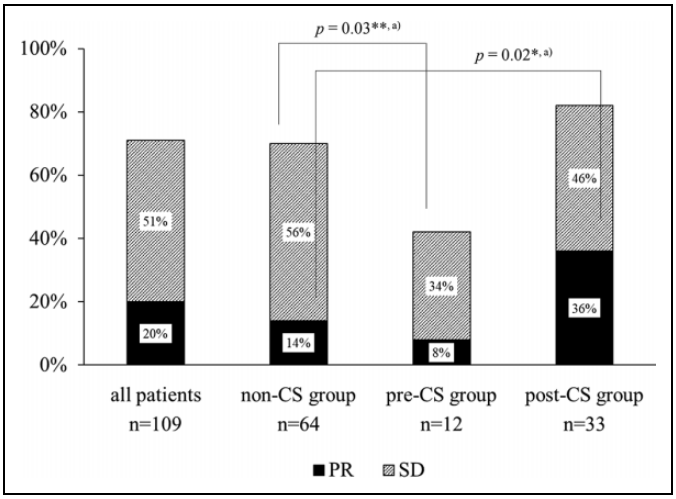

Figure 1. Best response to nivolumab. a) chi-square test, *ORR, $p < 0.05$, non-CS vs post-CS, **DCR, $p < 0.05$, non-CS vs pre-CS. non-CS, not systemically administered corticosteroids; post-CS, systemic corticosteroid administration initiated during nivolumab treatment; pre-CS, systemic corticosteroid administration before the first cycle of nivolumab administration; PR, partial response; SD, stable disease; ORR, objective response rate; DCR, disease control rate.

treatment for drug-related pneumonia caused by previously prescribed cytotoxic anti-cancer agents (4 patients [33%]), cerebral edematous symptoms after radiotherapy for CNS metastases (2 patients [17%]), asthma (2 patients [17%]), neoplastic fever (2 patients [17%]), and appetite loss (2 patients [17%]) (Table 2A). The median cumulative dose equivalent to that of prednisolone was 1,140 mg (quartiles: 485 and 3,515 mg), the median administration duration was 94 days (quartiles: 31 and 175 days), and the median starting dose of prednisolone was 0.3 mg/kg (quartiles: 0.3 and 0.4 mg/kg). In contrast, patients were administered systemic corticosteroid treatment for irAEs including pneumonia in 6 patients (18%), diarrhea in 5 patients (15%), hepatic dysfunction in 3 patients (9%), myocarditis in 2 patients (6%), pruritus in 2 patients (6%), encephalitis in 1 patient (3%), Trousseau's syndrome for which the causal relationship with nivolumab was uncertain in 1 patient (3%), obstructive pneumonia in 2 patients (6%), cerebral edematous symptoms after radiotherapy for CNS metastases in 2 patients (6%), neoplastic fever in 1 patient (3%), pneumonia of unknown cause other than infection in 2 patients (6%), carcinomatous lymphangiosis in 1 patient (3%), appetite loss in 2 patients (6%), meningeal dissemination in 1 patient (3%), nausea by ileus in 1 patient (3%), and pleural effusion in 1 patient (3%) (Table 2B). The median cumulative dose equivalent to that of prednisolone was 2,605 mg (quartiles: 997 and 4,315 mg), the median administration duration was 97 days (quartiles: 28 and 220 days), and the median starting dose of prednisolone was 0.5 mg/kg (quartiles: 0.3 and 0.7 mg/kg). Thus, the reason for the systemic administration of corticosteroids was different between the pre-CS and post-CS groups. In addition, the median duration of systemic administration of corticosteroids was similar in both these groups. However, the median cumulative dose of corticosteroids, equivalent to that of prednisolone, was higher in the post-CS group than in the pre-CS group.

Efficacy

To investigate the effects of corticosteroids on efficacy, the best OS in the pre-CS and post-CS groups was compared with that in the non-CS group. The ORR in the post-CS group was significantly higher than that in the non-CS group (36% vs. 14%; $p = 0.02$), and the DCR in the pre-CS group was significantly lower than that in the non-CS group (42% vs. 70%; $p = 0.03$; Figure 1). The median OS (interquartile range) was 11.9 months (7.9, 20.9) in the non-CS group, 2.2 months (1.8, 4.5) in the pre-CS group, and 12.5 months (4.7, 16.0) in the post-CS group. The median OS in the pre-CS group was significantly shorter than that in the non-CS group; however, no significant differences were observed in the post-CS and non-CS groups ($p < 0.01$; $p = 0.72$; Figure 3A). The median PFS was 3.3 months (1.6, 6.4) in the non-CS group, 0.9 months (0.7, 1.8) in the pre-CS group, and 3.6 months (2.2, 12.2) in the post-CS group. The PFS in the pre-CS group was significantly shorter than that in the non-CS group; however, no significant differences in PFS were observed in the post-CS group relative to that in the non-CS group ($p < 0.01$; $p = 0.23$; Figure 3B).

The development of irAEs potentially affected the relationship between the administration of corticosteroids and the therapeutic effects of nivolumab. Therefore, the post-CS group was further classified according to the presence or absence of irAEs, and the therapeutic effects were compared between the groups. The irAEs group comprised 19 patients from the post-CS group, whereas the non-irAEs group comprised 14 patients. The irAEs group showed a significant difference in DCR (95% vs. 64%), with no significant difference in ORR (47% vs. 21%) compared with the non-irAEs group ($p = 0.03$ and $p = 0.13$). The median OS (interquartile range) was 13.5 months (5.1, 14.1) and 12.5 months (3.6, 11.9) in the irAEs group and non-irAEs group, respectively ($p = 0.30$; Figure 4A). The median PFS was 5.1 months (3.0, 9.6) and 2.2 months (0.9, 5.5) in the irAEs and non-irAEs groups, respectively ($p = 0.17$; Figure 4B).

The nivolumab treatment duration and the period from nivolumab discontinuation to a patient's death or the study cut-off date for the 3 groups were displayed using a Swimmer plot. The relationship between the timing of systemic corticosteroid administration after nivolumab treatment initiation was investigated. At the cut-off date, the number of surviving patients was 31 (48%) in the non-CS group, 0 (0%) in the pre-CS group, and 14 (42%) in the post-CS group. The number of patients who were still administered nivolumab was 12 (19%) in the non-CS group, 0 (0%) in the pre-CS group, and 7 (21%) in the post-CS group. In the non-CS group, certain patients showed long-term survival even after early discontinuation of nivolumab administration; nivolumab administration was re-initiated in 6 patients (9%). In the pre-CS group, the survival time after discontinuation of nivolumab administration was usually short, and no patients were re-administered nivolumab. In the

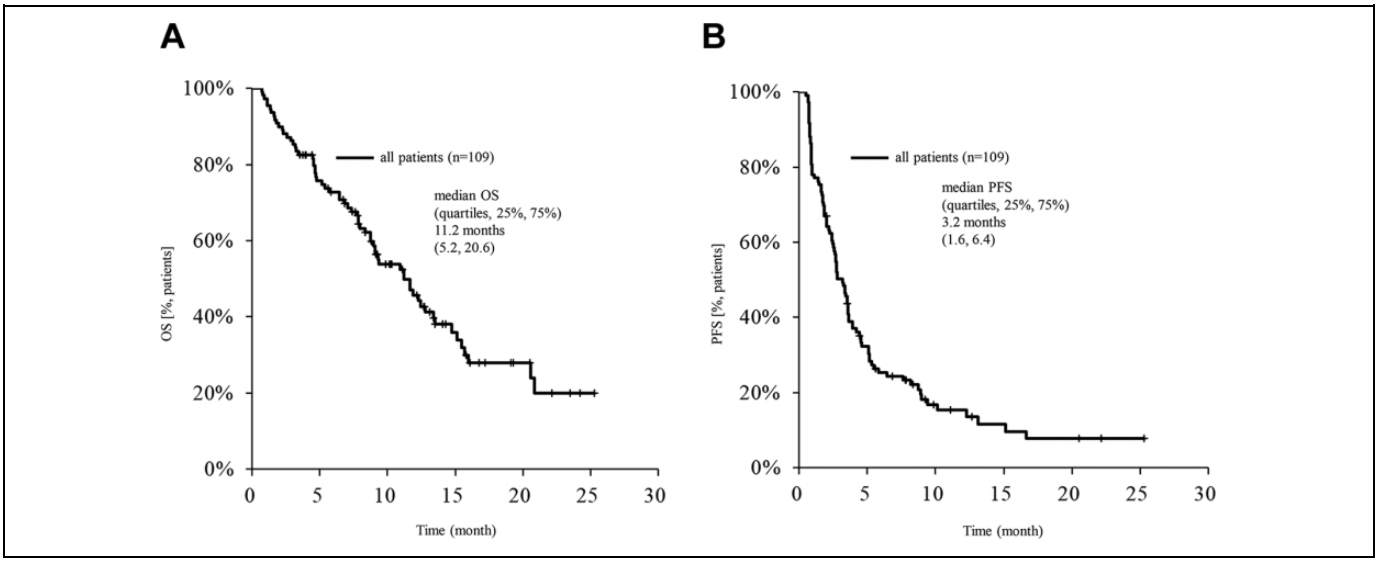

Figure 2. Kaplan-Meier curve of (A) OS and (B) PFS in patients with non small lung cancer.

Table 2. The Reasons For Using Steroids in the Pre-CS Group (A) and Post-CS Group (B).

(A)

	Pre-CS group, n = 12
Drug-related pneumonia caused by cytotoxic anti-cancer agents previously prescribed, n (%)	4 (32)
Cerebral edematous symptoms after radiotherapy for CNS metastases, n (%)	2 (17)
Asthma, n (%)	2 (17)
Neoplastic fever, n (%)	2 (17)
Appetite loss, n (%)	2 (17)

(B)

		Post-CS group, n = 33
Using steroids with irAE, n = 19	Pneumonitis, n (%)	6 (18)
	Diarrhea, n (%)	5 (15)
	Hepatic dysfunction, n (%)	3 (9)
	Myocarditis, n (%)	2 (6)
	Pruritus, n (%)	2 (6)
	Encephalitis, n (%)	1 (3)
Using steroids with non-irAE, n = 14	Obstructive pneumonia, n (%)	2 (6)
	Cerebral edematous symptoms after radiotherapy for CNS metastases, n (%)	2 (6)
	Pneumonia of unknown cause other than infection, n (%)	2 (6)
	Appetite loss, n (%)	2 (6)
	Carcinomatous lymphangiosis, n (%)	1 (3)
	Neoplastic fever, n (%)	1 (3)
	Meningeal dissemination, n (%)	1 (3)
	Torsoow's syndrome, n (%)	1 (3)
	Nausea by ileus, n (%)	1 (3)
	Pleural effusion, n (%)	1 (3)

CNS, central nervous system; post-CS, systemic corticosteroid administration initiated during nivolumab treatment; pre-CS, systemic corticosteroid administration before the first cycle of nivolumab administration.

post-CS group, nivolumab administration was re-initiated in 3 patients (9%). The duration of systemic corticosteroid administration was less than 200 days after the initiation of nivolumab administration in most patients because of irAEs; it was more than 400 days in only 2 patients (Figure 5).

irAEs

To investigate the effects of corticosteroids on irAEs, the incidence of irAEs in the pre-CS and post-CS groups was compared with that in the non-CS group. No significant differences in the incidence of the following irAEs were found between the pre-CS

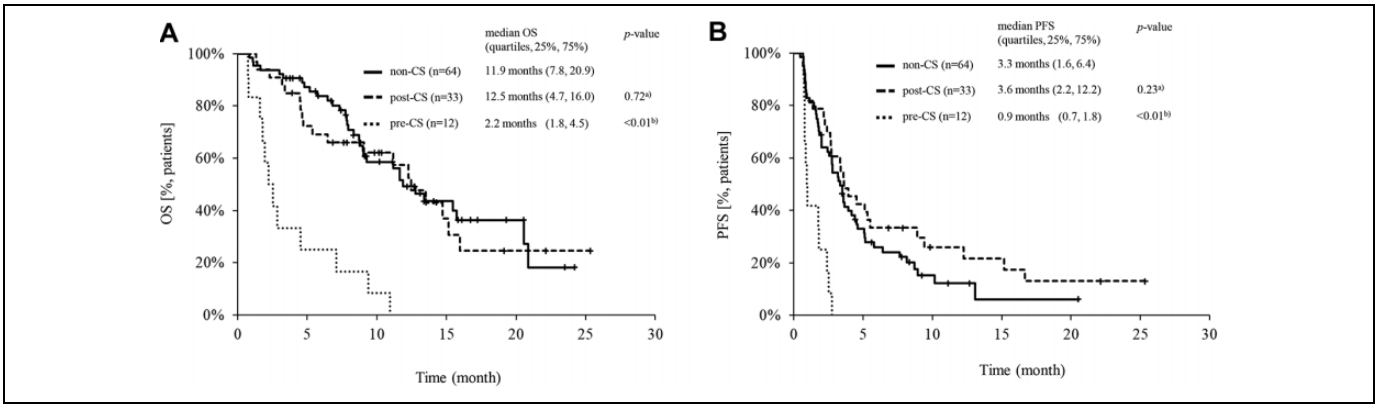

Figure 3. Kaplan-Meier curve of (A) OS and (B) PFS of post-CS group and pre-CS group to non-CS group. a) Log-rank test, non-CS vs post-CS, b) Log-rank test, non-CS vs pre-CS; non-CS, not systemically administered corticosteroids; post-CS, systemic corticosteroid administration initiated during nivolumab treatment; pre-CS, systemic corticosteroid administration before the first cycle of nivolumab administration.

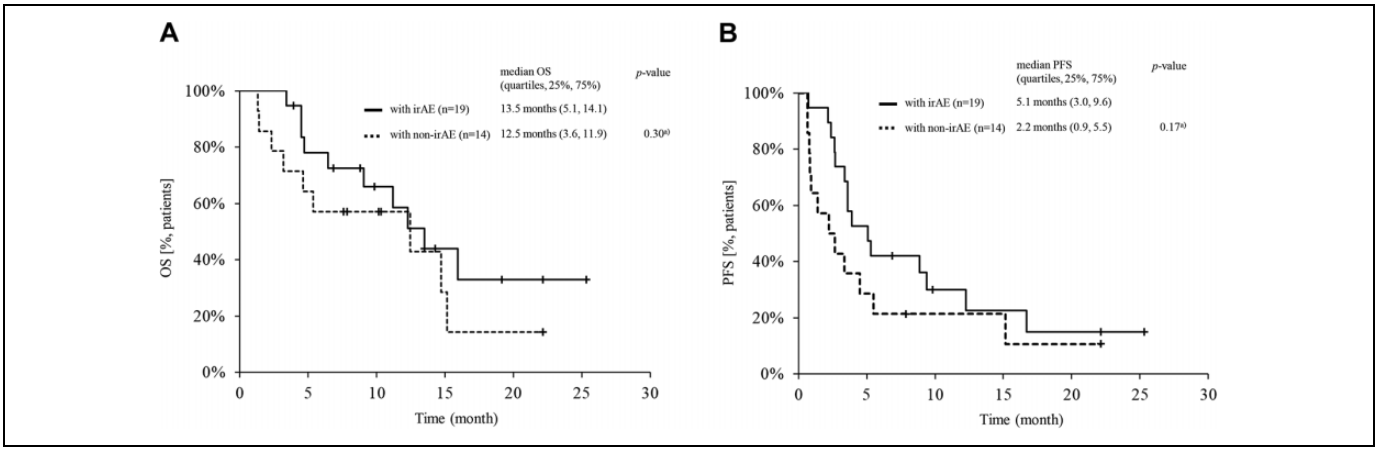

Figure 4. Kaplan-Meier curve of (A) OS and (B) PFS of using steroids with irAE group and non-irAE group within the post-CS. a) Log-rank test, with irAE vs with non-irAE, b) Log-rank test, with irAE vs with non-irAE; with irAE, using steroids with irAE group within post-CS; with non-irAE, using steroids with non-irAE group within post-CS.

or post-CS groups and the non-CS groups: diarrhea, pneumonia, infusion reaction, fatigue, nausea, red rash, pruritus, dry skin, stomatitis, hyperthyroidism, hypothyroidism, myocarditis, increased serum creatinine, increased serum aspartate aminotransferase (AST), increased serum alanine aminotransferase (ALT), and hyperglycemia. The incidence of the following irAEs was significantly higher in the post-CS group than in the non-CS group: pneumonitis (3% and 18%, respectively, $p = 0.04$) and AST increase (20% and 39%; $p = 0.04$). Serious irAEs of grade 3 or higher were as follows (Table 3): (i) non-CS group: hyperglycemia in 1 patient (2%), (ii) pre-CS group in 0 patient, and (iii) post-CS group: pneumonitis in 2 patients (6%); encephalitis in 1 patient (3%); pruritus in 2 patients (6%); myocarditis in 2 patients (6%); AST increase in 3 patients (9%); ALT increase in 2 patients (6%); and hyperglycemia in 4 patients (12%).

Discussion

Corticosteroids may be administered to patients with lung cancer either before or after the initiation of nivolumab treatment. However, patients administered corticosteroids before nivolumab treatment initiation are generally excluded from clinical trials. In addition, the appropriate timing of corticosteroid administration in relation to nivolumab treatment, the effects of corticosteroids on nivolumab efficacy, and potential adverse events are unknown. In this study, patients administered corticosteroids before and after the initiation of nivolumab were compared with patients not administered corticosteroids. The time of administration, the effects of differences in the timing of concomitant corticosteroid treatment on nivolumab efficacy, and the resulting adverse events were investigated.

The incidence of ORR, DCR, and irAE incidence in 109 patients treated with nivolumab in this study were approximately the same as that in the Checkmate 017 study, conducted in patients previously treated for squamous cell lung cancer,[19] and the Checkmate 057 study conducted in patients with non-squamous non-small-cell lung cancer,[20] demonstrating that the efficacy and tolerability can be ensured even in clinical practice (Figure 1, Table 3). In this study, the incidence of irAEs in the pre-CS group did not differ from that in the non-CS group;

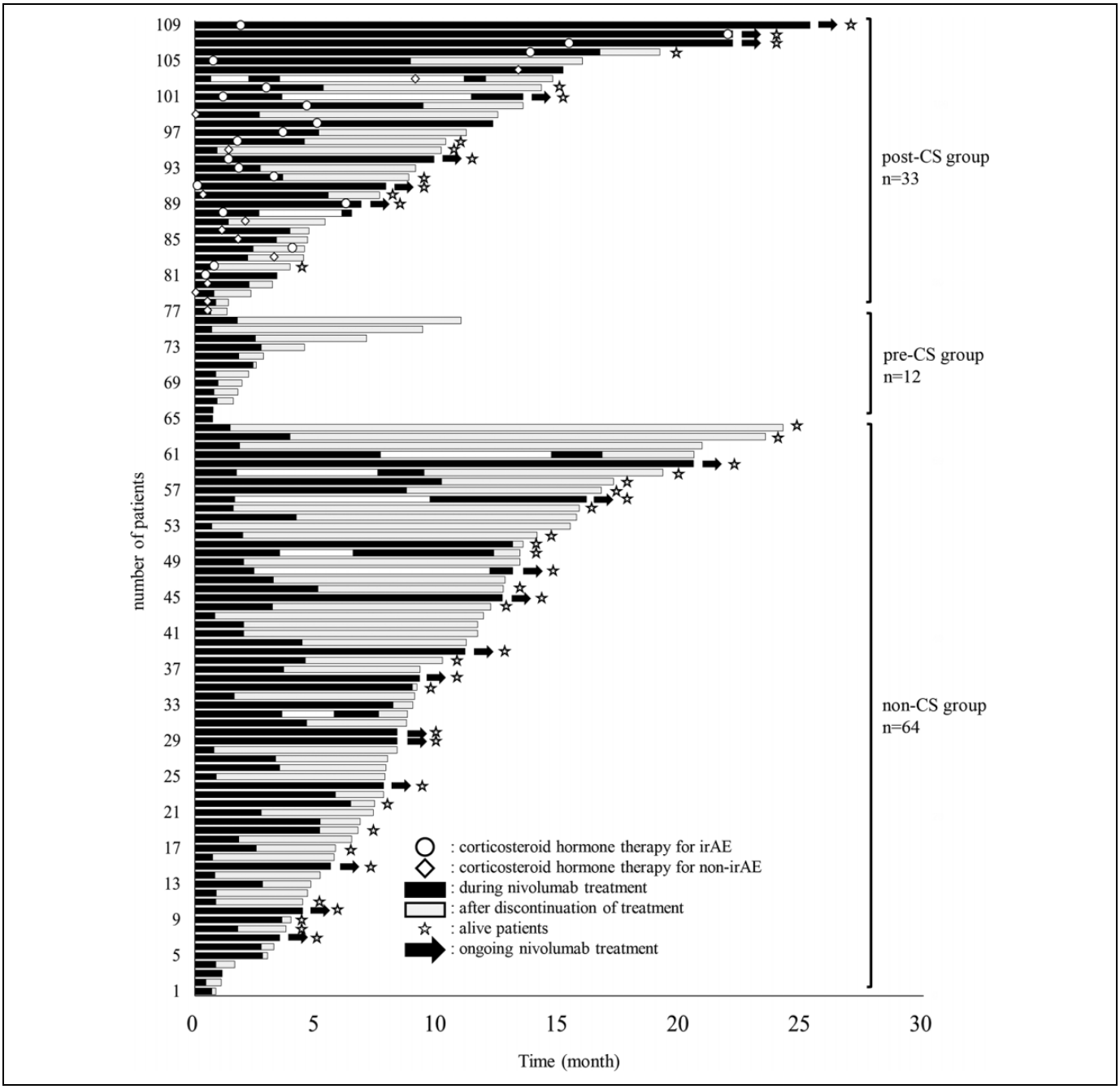

Figure 5. Swimmer plots that duration of treatment. irAE, immune-related adverse events; non-CS, not systemically administered corticosteroids; post-CS, systemic corticosteroid administration initiated during nivolumab treatment; pre-CS, systemic corticosteroid administration before the first cycle of nivolumab administration.

however, the ORR, DCR, OS, and PFS significantly decreased in the pre-CS group than in the non-CS group (Figure 1). Corticosteroid administration before the first administration of nivolumab causes poor efficacy of nivolumab.[16-18] Moreover, corticosteroid administration causes a decrease in T cell count and induces an immunosuppressive state.[7] In this study, although there were no significant differences in PS or treatment lines between each group, the number of nivolumab cycles administered in the pre-CS group was significantly lower and OS was also inferior. In addition, the reasons for corticosteroid administration in pre-CS included the treatment of previous cytotoxic anti-cancer drug-induced pneumonia, tumor fever, anorexia, and central nervous system metastases after radiation therapy for cerebral edema. The pre-CS group comprised patients who were administered corticosteroids before the first administration of nivolumab, suggesting that the patient's general condition had already deteriorated (or was likely to deteriorate). Thus, the therapeutic effect of nivolumab

Table 3. Adverse Events.

	All patients		Non-CS group		Pre-CS group			Post-CS group		
	n = 109		n = 64		n = 12		*p*-value [a)]	n = 33		*p*-value [a)]
All grade										
Pneumonitis	8	(7)	2	(3)	0	(0)	0.71	6	(18)	0.04
Diarrhea	9	(8)	3	(5)	1	(8)	0.88	5	(15)	0.09
Encephalitis	1	(1)	0	(0)	0	(0)	N.A.	1	(3)	0.34
Infusion reaction	12	(11)	7	(11)	2	(17)	0.85	3	(9)	0.54
Fatigue	19	(17)	11	(17)	1	(8)	0.39	7	(12)	0.63
Nausea	8	(7)	5	(8)	1	(8)	0.76	2	(6)	0.55
Erythema	17	(16)	9	(14)	0	(0)	0.19	8	(24)	0.21
Pruritus	20	(18)	13	(20)	0	(0)	0.09	7	(21)	0.92
Skin dryness	7	(6)	4	(6)	0	(0)	0.49	3	(9)	0.82
Mucositis oral	5	(5)	4	(6)	0	(0)	0.49	1	(3)	0.44
Hyperthyroidism	15	(14)	8	(13)	0	(0)	0.23	7	(21)	0.26
Hypothyroidism	12	(11)	6	(9)	0	(0)	0.34	6	(18)	0.18
Myocarditis	2	(2)	0	(0)	0	(0)	N.A.	2	(6)	0.11
Creatinine increased	16	(15)	8	(13)	1	(8)	0.57	7	(21)	0.26
AST increased	30	(28)	13	(20)	4	(33)	0.91	13	(39)	0.04
ALT increased	22	(20)	8	(13)	5	(42)	0.99	9	(27)	0.07
Hyperglycemia	18	(17)	8	(13)	1	(8)	0.57	9	(27)	0.07
Grade3≦										
Pneumonitis	2	(2)	0	(0)	0	(0)	N.A.	2	(6)	0.11
Encephalitis	1	(1)	0	(0)	0	(0)	N.A.	1	(3)	0.34
Pruritus	2	(2)	0	(0)	0	(0)	N.A.	2	(6)	0.11
Myocarditis	2	(2)	0	(0)	0	(0)	N.A.	2	(6)	0.11
AST increased	3	(3)	0	(0)	0	(0)	N.A.	3	(9)	0.04
ALT increased	2	(2)	0	(0)	0	(0)	N.A.	2	(6)	0.11
Hyperglycemia	5	(5)	1	(2)	0	(0)	0.84	4	(12)	0.04

a) Chi-squared test. AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; N.A., not available; non-CS, not systemically administered corticosteroids; post-CS, systemic corticosteroid administration initiated during nivolumab treatment; pre-CS, systemic corticosteroid administration before the first cycle of nivolumab administration.

may be obstructed due to poor immunoreactivity suggesting that corticosteroid administration before the first dose of nivolumab could be a poor prognostic factor for treatment with immune checkpoint inhibitors. Hence, it is essential to determine whether systemic corticosteroids have been administered at nivolumab treatment initiation and if so, sufficient precautions should be taken.

The concomitant corticosteroid administration after nivolumab treatment initiation did not affect OS and PFS (Figure 3A, B). Nivolumab increases the anti-tumor activity of T cells that control the autoimmune response. As a result, newly formed autoantibodies produce an autoimmune response to normal tissues, causing various types of irAEs.[3-5] Therefore, corticosteroid administration for treating irAEs may interfere with the therapeutic effect of nivolumab. Certain reports suggested that corticosteroid administration during the nivolumab treatment period did not affect the efficacy of nivolumab,[13-15] whereas others stated that corticosteroid administration together with nivolumab treatment initiation reduced nivolumab efficacy.[16-18] Tokunaga et al. reported the function of steroids after the initiation of immunotherapy. Steroids selectively inhibited $CD8^+$ T cells with low affinity for self-antigens, such as those associated with irAEs. In contrast, steroids did not inhibit memory T cells in tumor antigen-specific T cells that killed tumor cells, thus maintaining a long-term anti-tumor effect.[21] This report indicates that mechanisms of the therapeutic effect of corticosteroids vary depending on the timing of their administration. The relationship between developed irAEs and the therapeutic effect of nivolumab in patients with non-small-cell lung cancer has been explored in previous studies.[22-24] In the present study, no differences were observed in the therapeutic effect of nivolumab between the post-CS group and the non-CS group, or between the irAEs sub-group and the non-irAEs sub-group (from the post-CS group). Thus, the therapeutic effects of nivolumab were not inferior in these groups. These results suggested that administering corticosteroids to patients who had developed irAEs did not affect the therapeutic efficacy of nivolumab in the post-CS group. The incidence of irAEs was approximately the same in both groups; however, the incidence of grade 3 or higher irAEs was more in the post-CS group. However, this difference could be attributed to the fact that corticosteroids were administered to treat grade 3 or higher irAEs, and not because they increased irAE incidence or severity. The study of effects of the timing of corticosteroid administration on nivolumab efficacy in the post-CS group using a Swimmer plot revealed that corticosteroid administration, irrespective of whether soon after nivolumab treatment initiation or at a later time point, did not affect the efficacy.

Therefore, we did not consider the timing of corticosteroid administration after nivolumab treatment initiation, and corticosteroids could be administered immediately when irAEs occurred.

No effect was observed in response to irAEs on the efficacy and adverse events of concomitant corticosteroid administration during nivolumab treatment, or corticosteroid administration before nivolumab treatment initiation. Our results, which were similar to those stated in previous reports,[15-18] suggested that corticosteroid administration before nivolumab treatment initiation led to poor prognosis and efficacy. Conversely, corticosteroid administration after nivolumab administration did not affect prognosis, suggesting that corticosteroids could be administered immediately to achieve a rapid response if irAEs occurred. This is the first reported study where patients administered corticosteroids before and after nivolumab treatment initiation were compared with those not administered corticosteroids at the same time.

The limitations of this study include the small sample size. Moreover, the study was conducted at a single medical institution, and the patients administered corticosteroids before nivolumab treatment initiation could have been in a state of weakness and frailty. However, investigating the effects of corticosteroids on irAEs and nivolumab efficacy is necessary for pharmacists to provide fact-based advice to physicians and explanations to patients. In addition, as immunotherapy continues to progress, further studies are warranted to investigate other groups of patients not included in the current clinical trials.

Authors' Note

This study was carried out in compliance with the Ethical Guidelines for Medical Research on Human Subjects. Our study was approved by Sapporo Minami-Sanjo Hospital's Ethics Committee (approval no. 28-8). All patients provided written informed consent prior to enrollment in the study.

Declaration of Conflicting Interests

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