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Effect of cyclooxygenase inhibitor use on immunotherapy efficacy in non-small cell lung cancer

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Abstract

Background: A synergistic effect of cyclooxygenase inhibitors (COX-I) and immune checkpoint inhibitors (ICIs) has been suggested. However, the impact of COX-I on the efficacy of ICIs is unclear. Here, we aimed to evaluate the relationship between COX-I use and the efficacy of ICI in patients with non-small cell lung cancer (NSCLC).

Methods: We retrospectively reviewed NSCLC patients who received ICI monotherapy. We defined COX-I use as regular use of COX-I other than low-dose aspirin during the initiation of ICIs to the first evaluation of efficacy. The efficacy of ICIs was evaluated with response rate (RR), disease control rate (DCR), progression free survival (PFS), and overall survival (OS). Differences in baseline characteristics by COX-I use were controlled by using an inverse probability of treatment weighting (IPW) adjusted analysis.

Results: A total of 198 patients with NSCLC received ICIs; 128, 50, and 20 patients received nivolumab, pembrolizumab, and atezolizumab, respectively; there were 65 (32.8%) COX-I users. While there was no significant difference in RR (15.4% vs. 13.5%; p = 0.828), DCR (41.5% vs. 49.6%; p = 0.294), PFS (median, 2.69 vs. 3.68 months; 95% confidence intervals [CI], 1.77–5.19 vs. 2.20–4.60 months; p = 0.630), COX-I users had significantly shorter OS than non-COX-I users (median, 6.08 vs. 16.10 months; 95% CI: 3.78–11.66 vs. 9.49–19.68 months; p = 0.003). On IPW adjusted analysis, there was no significant difference in OS (median, 7.85 vs. 15.11 months; 95% CI: 5.03–14.92 vs. 9.49–19.32 months; p = 0.081).

Conclusions: There was no additional or negative impact of COX-I use on the efficacy of ICIs in NSCLC.

KEYWORDS
cyclooxygenase inhibitor, immune checkpoint inhibitor, immunotherapy, lung cancer, oncology

INTRODUCTION

Lung cancer is the leading cause of cancer and death worldwide.[1] Immune checkpoint inhibitors (ICIs) have drastically improved the outcome of patients with non-small cell lung cancer (NSCLC), which accounts for approximately 85% of lung cancer. To date, anti-programmed cell death 1 (PD-1) antibody (nivolumab and pembrolizumab), anti-programmed cell death ligand 1 (PD-L1) antibody (atezolizumab), and anticytotoxic T-lymphocyte antigen 4 antibody (ipilimumab) are available for patients with metastatic or recurrent after resected NSCLC.[2–7]

Corticosteroids are often used for the treatment of fatigue, dyspnea, appetite loss, and metastasis to central nervous system (CNS).[8–11] However, due to the immunosuppressive properties and effect on T-cell function of corticosteroids, baseline corticosteroids use was associated

with poor outcome in patients with NSCLC who were treated with ICIs monotherapy.[12]

Non-steroidal anti-inflammatory drugs (NSAIDs) are also commonly used for the treatment of pain and fever in

TABLE 1 Baseline characteristics of the patients grouped by COX-I use

COX-I use n		Yes 65 (32.8)	No 133 (62.1)	p-value
Age[aa] (years)		68 [39–91]	73 [46–89]	0.001
Sex (woman)		19 (29.2)	40 (30.1)	>0.99
BMI (kg/m²)		19.8 [15.2–32.4]	21.5 [13.6–34.2]	0.009
Smoking history:	Never	7 (10.8)	22 (16.5)	0.392
	Ever	58 (89.2)	111 (83.5)	
ECOG-PS	0, 1	42 (64.6)	96 (72.2)	0.324
	2–4	23 (35.4)	37 (27.8)	
Histology:	Nonsquamous[bb]	46 (70.8)	89 (66.9)	0.629
	squamous	19 (29.2)	44 (33.1)	
Any driver gene alteration[cc]		4 (6.2)	23 (17.3)	0.045
PD-L1:	Negative	3 (4.6)	13 (9.8)	0.655
	Weak	13 (20.0)	23 (17.3)	
	Strong	16 (24.6)	30 (22.6)	
	Unknown	33 (50.8)	67 (50.4)	
Disease duration[dd] (months)		24.0 [0–189.7]	33.0 [0–410.4]	0.07
Resection		8 (12.3)	21 (15.8)	0.669
Number of prior chemotherapies		1 [0–10]	1 [0–7]	0.752
Fever before ICI		10 (15.4)	10 (7.5)	0.129
Metastasis to				
Adrenal grand		11 (16.9)	12 (9.0)	0.155
Bone		31 (47.7)	35 (26.3)	0.004
Central nervous system		12 (18.5)	28 (21.1)	0.711
Liver		8 (12.3)	19 (14.3)	0.827
Lung (intrapulmonary metastasis)		20 (30.8)	49 (36.8)	0.431
Distant lymph nodes		8 (12.3)	12 (9.0)	0.463
Peritoneum		1 (1.5)	2 (1.5)	>0.99
Pleura (including dissemination)		22 (33.8)	48 (36.1)	0.874
Skin		0 (0.0)	3 (2.3)	0.552
Others		6 (9.2)	3 (2.3)	0.061
Pleural effusion		19 (29.2)	43 (32.3)	0.745
Pericardial effusion		3 (4.6)	1 (0.8)	0.104
Ascites		2 (3.1)	3 (2.3)	0.664
Blood sample data				
WBC (×10³/mm³)		6.4 [1.9–22.8]	6.6 [2.8–28.5]	0.542
Neutrophil segment (%)		71.0 [32.0–91.1]	70.5 [43.3–90.3]	0.678
Lymphocyte segment (%)		14.4 [3.7–39.4]	16.1 [3.9–41.7]	0.232
Eosinophil segment (%)		2.1 [0.0–14.3]	1.4 [0.0–11.2]	0.098
CRP (mg/l)		28.2 [0.2–163.0]	9.7 [0.1–237.1]	<0.001
LDH (IU/l)		224 [85–1953]	209 [117–756]	0.257

Note: Data are shown with median and [range] or number and (percentage). *p*-values were estimated by Mann–Whitney U tests for continuous variables and Fisher's exact tests for categorical variables.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase; PD-L1, programmed cell death-ligand 1 (expression on tissue samples); WBC, white blood cell.

[a]"Age" indicates the age at the onset of ICI therapy.
[b]One patient with large-cell neuroendocrine carcinoma is included in the "nonsquamous" category in the no COX-I use group.
[c]"Any driver gene alteration" consists of *EGFR* mutation and *ALK* fusion gene.
[d]"Disease duration" indicates the time from the diagnosis of lung cancer to the initiation of ICIs.

patients with cancer. They exert an anti-inflammatory effect by inhibiting the activity of cyclooxygenase.[13] While there is a concern that NSAIDs, such as corticosteroids, may negatively affect the efficacy of ICIs by suppressing the inflammatory response, cyclooxygenase inhibitors (COX-I) have been suggested to have a synergistic antitumor effect with ICIs.[14] However, the impact of COX-I on the efficacy of ICIs among patients with NSCLC is not well-known in clinical practice.

In this study, we aimed to evaluate the relationship between COX-I use and the efficacy of treatment with ICIs in patients with NSCLC.

METHODS

We retrospectively reviewed the clinical data of patients with NSCLC who received ICI monotherapy as the initial immunotherapy. This study was reviewed and approved by the institutional review board and complied with the principles of the World Medical Association Declaration of Helsinki. We announced our intention to conduct this study and gave patients the opportunity to explain or reject it. We had no conflict of interests.

We identified patients with NSCLC who were treated with ICI monotherapy (nivolumab, pembrolizumab, and atezolizumab) at the National Hospital Organization Kyoto Medical Center between December 2015 and December 2018. All patients had been histologically diagnosed with advanced or recurrent NSCLC after surgical resection or radiotherapy. We reviewed the electronic medical records of the patients between December 2015 and December 2019. To eliminate the effect of cytotoxic agents and other premedications, we excluded patients who were treated with durvalumab or a combination of cytotoxic agents and ICIs. We also excluded patients who had undergone treatment with ICIs because we have previously reported that the efficacy of ICIs in patients with previously treated with ICIs was inferior to that with ICI naive patients.[15–17] Moreover, we excluded patients taking low-dose aspirin because they might have biased comorbidity

TABLE 2 Details of treatment regarding ICIs, COX-I and other concomitant medication

COX-I use n		Yes 65	No 133	p-value
Initial ICI:	Atezolizumab	4 (6.2)	16 (12.0)	0.353
	Nivolumab	42 (64.6)	86 (64.7)	
	Pembrolizumab	19 (29.2)	31 (23.3)	
Dose of ICI		4 [1–56]	5 [1–64]	0.26
COX-I agent:	Celecoxib	19 (29.2)		
	Loxoprofen	39 (60.0)		
	Naproxen	7 (10.8)		
Regular use of corticosteroids		15 (23.1)	20 (15.0)	0.171
Regular use of acetaminophen		5 (7.7)	23 (17.3)	0.083

Note: Data are shown with median and [range] or number and (percentage). There was no patient who used aspirin and other COX-I agents concurrently.
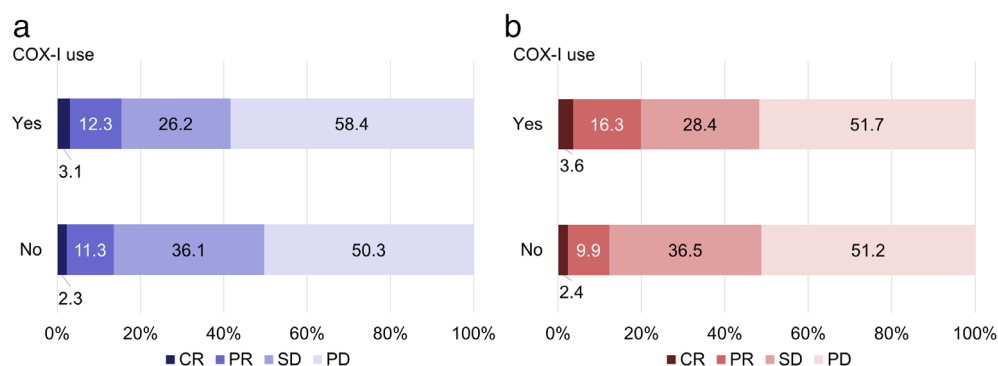

FIGURE 1 Tumor response to ICIs classified by COX-I use. Tumor response was evaluated in accordance with the response evaluation criteria in solid tumors (RECIST: version 1.1). Prevalence of each evaluation before inverse probability weighting (IPW) adjustment (a) are indicated in blue bars and after IPW adjustment (b) are indicated in red bars. COX-I, cyclooxygenase inhibitor; CR, complete remission; PR, partial response; SD, stable disease; PD, progressive disease

in cardiovascular and/or cerebrovascular diseases or the anti-inflammatory effect of low-dose aspirin might be different from that of other COX-I.

We obtained the following clinical data of participating patients: age at the onset of ICI therapy, gender, body mass index (BMI), smoking history (never vs. current or former), Eastern Cooperative Oncology Group Performance Status (ECOG-PS), histology, any existing driver gene alterations (EGFR and ALK status), status of PD-L1 expression on tissue samples, metastasis to each organ, prior therapies including chemotherapy and surgery, and disease duration. The status of PD-L1 expression on tissue samples was classified by tumor proportion score (TPS) as follows: "negative" as under 1% of TPS, "weak" as TPS between 1% to 49%, "strong" as no less than 50% of TPS, and "unknown" as not measured or failed to measure TPS.[4, 5] We also obtained the following items of blood test data measured just before the initial ICI administration: white blood cell (WBC) count, neutrophil subset, lymphocyte subset, eosinophil subset, C-reactive protein (CRP), and lactate dehydrogenase (LDH).

We defined COX-I use as regular use of COX-I from the initiation of ICI therapy to the first evaluation of treatment effect or later. Acetaminophen was excluded from COX-I use and was independently evaluated. This was because while there is uncertainty in the mechanism of action of acetaminophen and it has less anti-inflammatory activity than NSAIDs, it is more likely to be associated with the use of NSAIDs in clinical practice.[18, 19] We also defined corticosteroid use as regular use of corticosteroids at any dose from the initiation of ICI to the first evaluation of treatment effect or later. Because of the antipyretic properties of COX-I, acetaminophen, and corticosteroids, we reviewed fever within 24 h before the initial dose of ICIs. We defined fever as a condition in which the axillary temperature (0.2 to 0.5°C lower than oral temperature) was higher than 37.0°C.

All patients received either treatment with ICI monotherapy as follows: 3 mg/kg or 240 mg/dose of nivolumab every two weeks, 200 mg/dose of pembrolizumab every three weeks, or 1200 mg/dose of atezolizumab every three weeks intravenously.[2–6]

We evaluated the efficacy of ICIs by measuring the response rate (RR), disease control rate (DCR), and progression-free survival time (PFS). The RR and DCR were assessed by using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[20] Overall survival time (OS) was used as a secondary outcome. We defined PFS as the time from initiation of ICIs to the date of disease progression or death from any cause and defined OS as the time from initiation of ICIs to the date of death from any cause.

Patient characteristics were described according to the status of COX-I use. Continuous variables are presented as the median and range, and comparisons were made by using

FIGURE 2 Survival curves of progression-free survival (PFS) and overall survival (OS) classified by COX-I use. Survival curves were generated by the Kaplan–Meier method. Red and dark blue lines indicate the survival curves of the patients with and without COX-I use, respectively. Tick marks represent data censored at the last time the patient was known to be alive (PFS and OS) and without disease progression (PFS only). Median survival times and p-values were estimated by the log-rank test. (a) and (b) show survival curves of PFS and OS before inverse probability weighting (IPW) adjustment, respectively. (c) and (d) show survival curves of PFS and OS after IPW adjustment, respectively
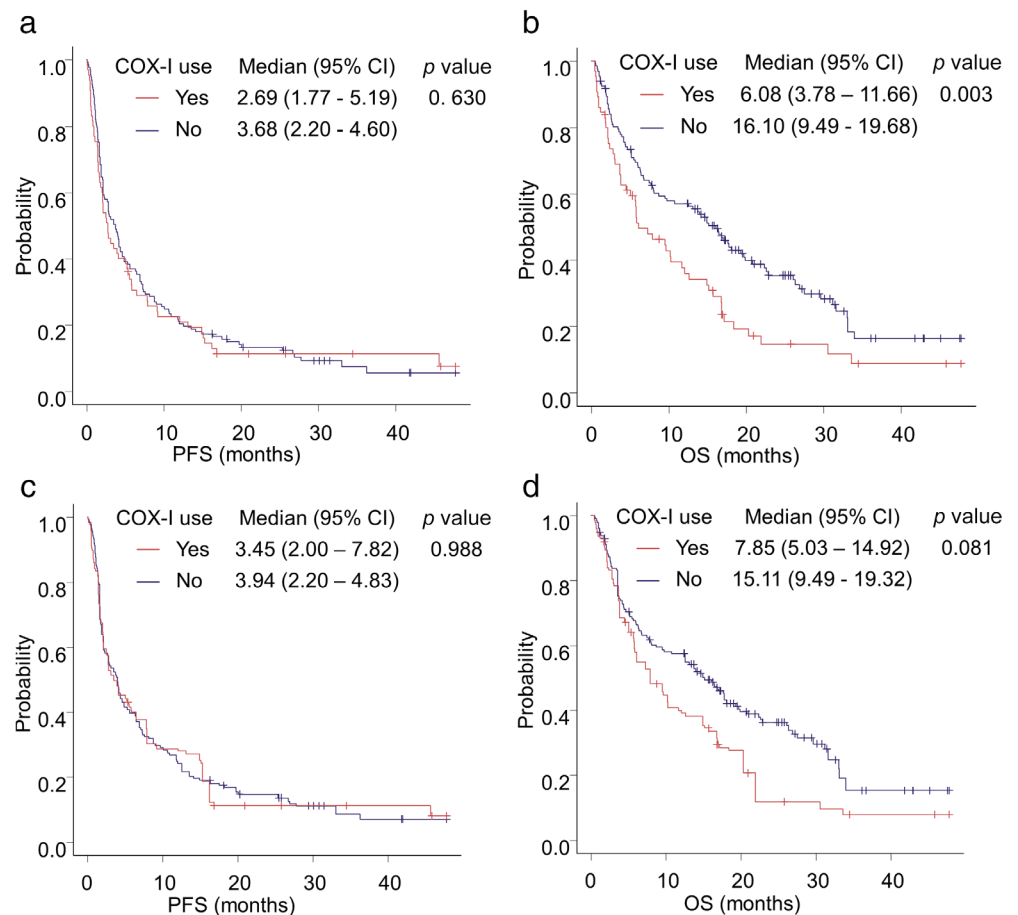
T A B L E 3 Balances between patients with and without COX-I use before and after IPW adjustment

COX-I use n		Before IPW adjustment			After IPW adjustment		
		Yes 65	No 133	SMD	Yes 54	No 132.4	SMD
Age (years)		67.4 (9.7)	71.9 (7.5)	0.516	69.6 (9.6)	70.7 (7.4)	0.128
Sex (male)		46 (70.8)	93 (69.9)	0.018	39.6 (73.4)	86 (65.0)	0.183
BMI (kg/m^2)		20.1 (3.3)	21.7 (4.4)	0.421	20.6 (3.3)	21 (4.5)	0.097
Smoking history: Current or former		58 (89.2)	111 (83.5)	0.169	47.5 (87.9)	112.9 (85.3)	0.079
ECOG-PS (score)		1.4 (1.0)	1.0 (0.9)	0.308	1.1 (1.0)	1.2 (0.9)	0.057
Histology: squamous		19 (29.2)	44 (33.1)	0.083	17.8 (32.9)	39.6 (29.9)	0.065
Any driver gene alteration		4 (6.2)	23 (17.3)	0.352	2.6 (4.8)	16.4 (12.4)	0.272
PD-L1 status:	negative	3 (4.6)	13 (9.8)	0.208	4.1 (7.6)	10.2 (7.7)	0.196
	weak	13 (20.0)	23 (17.3)		11.4 (21.0)	20.7 (15.6)	
	strong	16 (24.6)	30 (22.6)		15.3 (28.3)	32.6 (24.6)	
	unknown	33 (50.8)	67 (50.4)		23.2 (43.0)	68.9 (52.1)	
Disease duration (months)		35.6 (36.7)	58 (73.3)	0.386	40.2 (45.2)	50.5 (64.9)	0.185
Resection		8 (12.3)	21 (15.8)	0.1	7.8 (14.5)	18.4 (13.9)	0.017
Number of prior chemotherapies		1.8 (1.7)	1.6 (1.3)	0.132	1.6 (1.5)	1.6 (1.2)	0.018
Fever before ICI		10 (15.4)	10 (7.5)	0.249	7.1 (13.1)	10.2 (7.7)	0.178
Metastasis to							
Adrenal grand		11 (16.9)	12 (9.0)	0.237	4.9 (9.0)	12.2 (9.2)	0.006
Bone		31 (47.7)	35 (26.3)	0.454	19.1 (35.4)	36.6 (27.7)	0.167
Central nervous system		12 (18.5)	28 (21.1)	0.065	8.1 (15.0)	23.7 (17.9)	0.077
Liver		8 (12.3)	19 (14.3)	0.058	7 (12.9)	16.1 (12.2)	0.021
Lung		20 (30.8)	49 (36.8)	0.129	20.9 (38.6)	47.7 (36.0)	0.055
Distant lymph nodes		8 (12.3)	12 (9.0)	0.107	5.1 (9.5)	11.5 (8.7)	0.029
Peritoneum		1 (1.5)	2 (1.5)	0.003	0.3 (0.6)	1.3 (1.0)	0.045
Pleura (including dissemination)		22 (33.8)	48 (36.1)	0.047	19.1 (35.3)	44.7 (33.8)	0.033
Skin		0 (0.0)	3 (2.3)	0.215	0 (0.0)	2 (1.5)	0.176
Others		6 (9.2)	3 (2.3)	0.303	2.1 (3.9)	2.5 (1.9)	0.122
Pleural effusion		19 (29.2)	43 (32.3)	0.067	14.7 (27.2)	38.9 (29.3)	0.048
Pericardial effusion		3 (4.6)	1 (0.8)	0.241	1.3 (2.5)	3.3 (2.5)	0.001
Ascites		2 (3.1)	3 (2.3)	0.051	0.7 (1.3)	2.1 (1.6)	0.025
Blood sample data							
WBC (×10^3/mm^3)		8.1 (4.6)	7.4 (3.7)	0.161	7.9 (4.3)	7.9 (4.1)	0.005
Neutrophil segment (%)		71.1 (11.3)	70.8 (10.2)	0.032	71.8 (10.4)	71 (9.9)	0.079
Lymphocyte segment (%)		15.83 (7.9)	17.2 (8.1)	0.17	16.4 (7.6)	17 (7.9)	0.086
Eosinophil segment (%)		3 (3.1)	2.1 (2.2)	0.314	2.4 (2.5)	2.4 (2.4)	0.003
CRP (mg/l)		4.7 (4.8)	26.0 (39.7)	0.466	3.9 (4.1)	3.9 (5.4)	0.007
LDH (IU/l)		330.8 (371.4)	236.7 (103.5)	0.345	264.4 (254.9)	259.4 (127.7)	0.025
Initial ICI:	Atezolizumab	4 (6.2)	16 (12.0)	0.228	5.2 (9.6)	13.4 (10.1)	0.157
	Nivolumab	42 (64.6)	86 (64.7)		32 (59.4)	87.1 (65.8)	
	Pembrolizumab	19 (29.2)	31 (23.3)		16.8 (31.1)	31.9 (24.1)	
Dose of ICI		8.8 (10.4)	10.6 (12.7)	0.159	1.3 (2.5)	3.3 (2.5)	0.001
Regular use of corticosteroids		15 (23.1)	20 (15.0)	0.206	8.3 (15.4)	20 (15.1)	0.007
Regular use of acetaminophen		5 (7.7)	23 (17.3)	0.293	1.4 (2.6)	8.3 (6.2)	0.175
Number of items of SMD < 0.1				8(/35)			24(/35)

Note: Data are shown with mean and (standard deviation) or number and (percentage). Balances between patients with and without COX-I use are evaluated by SMD. Factors with an SMD of less than 0.1 are considered as well-balanced.

Abbreviations: BMI, body mass index; COX-I, cyclooxygenase inhibitor; CRP, C-reactive protein; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; ICI, immune checkpoint inhibitor; IPW, inverse probability weighting; LDH, lactate dehydrogenase; PD-L1, programmed cell death ligand 1; SMD, standardized mean difference; WBC, white blood cell count.

Mann–Whitney U tests. Categorical variables were presented as counts and percentages and were compared by using Fisher's exact tests. The PFS and OS curves were generated by the Kaplan–Meier method. Univariate analyses for PFS and OS were performed by using log-rank tests.

We conducted propensity score (PS) analysis to evaluate the association between COX-I use and PFS and OS to account for selection bias of COX-I use.[21] We estimated PS for each patient by using a logistic regression model with potential determinants included as independent variables and COX-I use as the dependent variable. The model included the following covariates: age, gender, BMI, smoking history, a score of ECOG-PS, histology (squamous vs. nonsquamous), any driver gene alteration, tissue PD-L1 status, prior resection, disease duration, number of prior therapeutic regimens, metastasis to each organs (adrenal glands, bone, CNS, liver, lung, distant lymph nodes, pleural dissemination, pleuritis, pericarditis, ascites, skin, and other organs), regular use of acetaminophen, fever before ICIs, agent of ICI attempt to use, and blood test data (WBC count, neutrophil subset, lymphocyte subset, eosinophil subset, CRP, and LDH).

When assessing the effect of a treatment with COX-I on outcomes, we estimated the average treatment effect (ATE). To estimate the ATE, the COX-I users' data were weighted 1/PS, while the non-COX-I users' data were weighted 1/(1 − PS). To properly address the potential selection bias, differences in baseline characteristics between COX-I users and non-COX-I users were controlled for using an inverse probability of treatment (IPW) weighting adjusted analysis. To avoid overweighting, we stabilized the ATE by multiplying the prevalence of each group. Covariate balance between the groups before and after IPW adjustment was assessed by using the standardized difference approach. After PS weighting created an acceptable balance, IPD-adjusted Kaplan–Meier curves and log-rank tests were used to compare PFS and OS between patients with and without COX-I use.[22]

Statistical tests were two sided and a p-value of less than 0.05 was considered statistically significant, with 95% confidence intervals (CIs). All statistical analyses were performed using R version 3.6.2 with RISCA package which was added for estimating p-values of IPW adjusted log-rank tests (R Foundation for Statistical Computing).

RESULTS

Of 214 patients with NSCLC who received ICIs at our institute, 198 patients were finally included in this study; 16 patients who used low-dose aspirin were excluded. At the initiation of ICIs, 65 (32.8%) patients used COX-I regularly. Patients with COX-I use were significantly younger, had a lower BMI, lower prevalence of harboring any driver gene alterations, and higher prevalence of bone metastasis (Table 1). Fever before ICI tended to be more frequently observed in patients with COX-I use, although not

significantly (15.4% vs. 7.5%; p = 0.129). In the results of blood test data measured just before the initial ICI, CRP was significantly higher in patients with COX-I use.

Among 198 patients, 128 (64.6%), 50 (25.3%), and 20 (10.1%) patients received nivolumab, pembrolizumab, and atezolizumab, respectively; there was not a significant difference in COX-I use (Table 2). Agents of COX-I used in this study were loxoprofen in 39 (60.0%) patients, celecoxib in 19 (29.2%) patients, and naproxen in seven (10.8%) patients (Table 2). Among COX-I users, there was no patient who used two or more agents. There were neither significant differences in corticosteroids nor acetaminophen use by COX-I use. Characteristics of current treatments were well-balanced between those with and without COX-I use.

Significant differences in RR and DCR were not observed between patients with and without COX-I use (RR: 15.4% vs. 13.5%; p = 0.828, DCR: 41.5% vs. 49.6%; p = 0.294) (Figure 1(a)). While there was no significant difference in PFS (median, 2.69 vs. 3.68 months; 95% confidence intervals [CI]: 1.77–5.19 vs. 2.20–4.60 months; p = 0.630) (Figure 2(a)), patients with COX-I use had significantly shorter OS than those without (median, 6.08 vs. 16.10 months; 95% CI: 3.77–11.66 vs. 9.49–19.68 months; p = 0.003) (Figure 2(b)).

We conducted PS analyses to minimize the effects of covariates in the evaluation of the association between COX-I use and the efficacy of ICIs. The logistic models used to estimate the PS yielded a c-statistic of 0.855. We evaluated the balance by calculating the SMD. An SMD of less than 0.1 suggested an appropriate variable balance, and the number of factors above 0.1 in the SMD decreased from 27 to 11 out of 35 items after IPW, which we judged to be an improvement in balance (Table 3).

Even after adjustment with IPW, there were no significant differences in RR and DCR between patients with and without COX-I use (RR: 19.9% vs. 12.3%; p = 0.171, DCR: 48.2% vs. 48.8%; p > 0.99) (Figure 1(b)). The log-rank test for PFS adjusted with IPW showed no significant differences between patients with and without COX-I use (median, 3.45 vs. 3.94 months; 95% CI: 2.00–7.82 vs. 2.20–4.83 months; p = 0.988) (Figure 2(c)). Patients using COX-I use tended to have shorter OS than those without, although this was not significant after adjustment (median, 7.85 vs. 15.11 months; 95% CI: 5.03–14.92 vs. 9.49–19.32 months; p = 0.081) (Figure 2(d)).

DISCUSSION

In this retrospective study, COX-I use was associated with shorter OS, while there were no significant differences in PFS, RR, and DCR on univariate analyses. After adjusted with IPW, there was no significant difference in RR, DCR, PFS, and OS between patients with and without COX-I use.

Cyclooxygenase inhibitors exert an anti-inflammatory effect in the acute phase by inhibiting the production of prostaglandin E2 (PGE2). PGE2 has been recognized as a

mediator of active inflammation; that is, PGE2 promotes local vasodilatation and local attraction and activates neutrophils, macrophages, and mast cells at the acute phase of inflammation.[23, 24] On the other hand, PGE2 also suppresses innate nonspecific inflammation, which is associated with chronic inflammation and cancer.[14, 25] Thus, PGE2-mediated immunomodulation is complicated, and inhibition of PGE2 production does not necessarily lead to immunosuppression.[13] In this respect, effect of COX-I is different from corticosteroids which suppress effector T cells by inhibiting the release of arachidonic acid.[26]

The synergistic effect of ICIs and COX-I has been previously suggested to be due to COX-2 driven cancer-promoting inflammation.[14] Moreover, an association between TPS and COX-2 expression has been reported in melanoma and lung cancer cell lines.[27, 28] In contrast, the existence of COX-I was not found to affect TPS of lung cancer cell lines.[28] This may explain the reason of no additional impact of COX-I use on the efficacy of ICIs in this cohort, although we were unable to assess the relationship between COX-I use and PD-L1 status because over a half of all patients lacked the data on PD-L1 status. Although there was a concern that the anti-inflammatory effect of COX-I might negatively affect the efficacy of ICIs, the results of this study suggest that there should be no hesitation in using COX-I in those patients scheduled for ICIs, unlike corticosteroids.[12]

When considering the causes of tendency of shorter OS in patients with COX-I use, the following points should be considered. First, unlike RR, DCR, and PFS, OS may not reflect the effect of pure ICI treatment because of the influence of post-treatment. In the present study, COX-I users were significantly less likely to harbor any driver gene alterations who usually had more treatment options. Second, patients with COX-I other than aspirin use tended to have cancerous pain or tumor induced fever, which were associated with disease progression. Indeed, COX-I users had higher prevalence of bone metastasis and higher values of CRP in this study. Adequate management of patients' symptoms is known to improve their outcome, even in their terminal stage.[29, 30] Taking this fact into account, it is not valid to assume that the anti-inflammatory effects of COX-I shortened only OS in patients using COX-I. Rather, poor systemic conditions requiring COX-I use might affect the shortening of OS in those patients. The fact that the difference in OS with COX-I use was no longer significant after PS adjustment for general condition and disease status of the patients may support this hypothesis. However, pain control continues to be a major problem in cancer therapy, we should use COX-I appropriately to manage the patient's symptoms regardless of the schedule of ICIs initiation.[31, 32]

Contrary to the present study, previous studies evaluating the association between COX-I and the efficacy of ICIs in NSCLC and melanoma patients showed better median PFS of COX-I users in univariate analysis.[33, 34] This discrepancy seemed to result from the difference in the baseline characteristics of each study. In the study reported by Nichetti et al. the percentage of patients with two or more in

the score of ECOG-PS was 8.8%, which was under one third compared with this study.[33] Poor performance status may strongly link to the use of COX-I other than aspirin, which was not assessed in the study. In the study reported by Wang et al. the percentage of patients who used aspirin was two-fold more than that of our study.[34] Patients who use only aspirin (and no need for other COX-I agents) may be better general condition than those who need to use other COX-I agents, which may result in the preferred trend of PFS than our study. Indeed, these studies, like the present study, failed to show significantly better PFS in COX-I users after adjusted with several baseline characteristics.

There are some limitations in this study. First, this study could not explain the causality of COX-I use on the efficacy of ICIs due to the retrospective nature of the study. However, outcomes which we evaluated were objective and quantified by the method of RECIST. Second, even if we had observed this cohort prospectively, we could not exclude the bias between COX-I use and general condition of the patients. Alike with corticosteroids, COX-I use might simply identify the patients with aggressive disease or with a need for the treatment of their symptoms.[12] Although a randomized controlled study may resolve these biases and show pure impact of COX-I use on the efficacy of ICIs, it is unethical to administer placebos to patients suffering from pain and fever. Even if a randomized controlled study were conducted by excluding patients with pain and/or fever, the result might not reflect the true effect of COX-I on ICI treatment in clinical practice. Third, the overall sample size was small and not powerful enough to adjust for factors affecting the efficacy of the ICIs. To resolve these biases as much as possible, we conducted PS analysis in this study.[21] The Cox proportional hazards model only allowed for adjustment of up to eight items at most to avoid overfitting in this study. In contrast, the PS analysis which we conducted succeeded to contain over 30 items for adjusting factors associated with COX-I use or general condition of the patients. Moreover, we chose to adjust by IPW instead of the matched-pair method to avoid loss of patient data.

This study has further limitations. The patients participated in this study had biases; this study was conducted at a single institute, and the population consisted of patients of Asian ethnicity and a higher proportion of patients with poor performance status than previous studies.[33, 34] However, we speculate that the results of this study are generalizable because of no evidence of racial differences in the effects of ICIs and of the consistency with previous studies. Furthermore, data on PD-L1 status and tumor mutation burden, which are known predictors of treatment response to ICIs, were missing in the majority of the patients.[3–6] Despite lacking the data of PD-L1 status on about a half of all patients, we included PD-L1 status in the multivariate analysis in order to add as much data relevant to the efficacy of ICIs as possible to the analysis. When adding PD-L1 status to the analysis, the missing data were grouped into a single category as "unknown". On multivariate Cox proportional hazard model, this process would take up four items for adjusting PD-L1

status, making it difficult to add other items for adjusting. We resolved the problem of overfitting as described above. Finally, the histology and the driver gene status were not fully assessed. The status of *KRAS*, *ROS-1*, and *BRAF* were not assessed because there was only one patient harboring *KRAS* mutation and there was no patient harboring *ROS-1* or *BRAF* mutation in this cohort.

In conclusion, there was no additional or negative effect of COX-I use on the efficacy of ICIs in NSCLC. To offer the benefit of adequate management against the symptoms, there is no need for hesitation in using COX-I for patients scheduled for treatment with ICIs.

CONFLICT OF INTEREST
KF received an honoraria from Boehringer Ingelheim. TM received an honoraria from Bristol Myers Squibb, Chugai Pharmaceutical, AstraZeneca, Novartis, and Boehringer Ingelheim. The other authors have no conflicts of interest to declare.

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