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(Citation)
Thoracic Cancer,15(15):1228-1236

(Issue Date)
2024-05

(Resource Type)
journal article

(Version)
Version of Record

Received: 25 January 2024 | Accepted: 9 March 2024

DOI: 10.1111/1759-7714.15294

ORIGINAL ARTICLE

WILEY

Impact of concurrent medications on the outcome of immunotherapy in non-small cell lung carcinoma

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Abstract

Background: There have been reports on the impact of concurrent drugs on the outcome of immunotherapy for non-small cell lung carcinoma (NSCLC). However, the effect of some drugs, such as antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs), has not been clarified in patients with NSCLC. In the present study, we aimed to assess the association between concurrent drugs and the outcomes of immune checkpoint inhibitors (ICIs) alone or in combination with chemotherapy for patients with advanced NSCLC.

Methods: We retrospectively assessed patients with advanced NSCLC who underwent ICI treatment between September 2017 and December 2021 at Kobe University Hospital. We evaluated the data regarding the use of antibiotics within 30 days before ICI initiation, as well as the use of proton pump inhibitors (PPIs) and NSAIDs during ICI initiation.

Results: A total of 127 patients were assessed, among whom 28 (22.0%) patients received antibiotics, 39 (30.7%) PPIs, and 36 (28.3%) NSAIDs. No significant differences were observed between the patients with and without antibiotic use. However, patients using NSAIDs had significantly worse objective response rates (ORR) and progression-free survival (PFS) with ICI alone or in combination with chemotherapy compared to those who did not (ORR, 47.2% vs. 67.0%; $p = 0.045$. PFS, 6.3 months vs. 10.8 months; $p = 0.02$). Patients using PPIs demonstrated a worse ORR of ICI in combination with chemotherapy compared to those who did not (ORR, 45.2% vs. 72.6%; $p = 0.013$).

Conclusions: The unnecessary use of NSAIDs along with immunotherapy should be discouraged.

KEYWORDS
ICI, NSAIDs, NSCLC

INTRODUCTION

The treatment outcomes of patients with advanced non-small cell lung cancer (NSCLC) have significantly improved with the introduction of immune checkpoint inhibitors (ICI) that target programmed cell death 1 (PD-1), programmed cell death ligand 1 (PD-L1), or cytotoxic T-lymphocyte associated protein 4 (CTLA). Although ICI treatment has become a standard of care for patients with advanced NSCLC, some patients do not benefit. Several concurrent drugs have been reported to negatively affect the ICI outcomes. Corticosteroids, classified as immunosuppressant drugs, are associated with decreased progression-free survival (PFS) and overall survival (OS) in patients with NSCLC treated with ICI.[1] Proton pump inhibitors (PPIs) are associated with decreased PFS and OS in patients with

NSCLC treated with atezolizumab alone or in combination with chemotherapy.[2] Antibiotics have demonstrated conflicting associations with outcomes in cancer patients, including those with lung cancer treated with ICI. While some studies report a negative impact on OS,[3] others suggest no impairment of outcomes in patients with NSCLC treated with ICI in combination with chemotherapy.[4] Nonsteroidal anti-inflammatory drugs (NSAIDs) are reported to be associated with a longer time-to-progression in NSCLC or melanoma treated with ICI alone.[5] A further report suggested that NSAIDs are associated with better OS in NSCLC treated with ICI alone or in combination with chemotherapy.[6] In contrast, other studies reported that NSAIDs are associated with worse OS in NSCLC treated with ICI.[7,8] Others, however, found no significant differences in ICI outcomes in patients with and without NSAIDs use.[9] No consensus has been reached regarding the effect of NSAIDs on ICI outcomes in patients with advanced NSCLC.

This retrospective study aimed to assess the association between the use of concurrent drugs and the outcome of ICI alone or in combination with chemotherapy for advanced NSCLC.

METHODS

Study design

This retrospective study included patients aged 18 years or older, histologically diagnosed with advanced NSCLC, and treated with ICI alone or in combination with chemotherapy for any treatment line between September 2017 and December 2021 at Kobe University Hospital. The primary endpoint was PFS in patients with and without concurrent drug use. Secondary endpoints included objective response rate (ORR) and OS associated with concurrent drug use. Informed consent was obtained through an opt-out method, wherein patients were included unless they declined to participate after checking the study details on the hospital website. This study received approval from the Institutional Ethics Committee of Kobe University Hospital on September 5, 2023 (approval no.: B230067) and adhered to the principles of the Declaration of Helsinki.

Data collection

We retrospectively collected the following data from the medical records; sex, age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), smoking history, historical diagnosis, clinical stage according to the Union for International Cancer Control (UICC) tumor, nodes, and metastases (TNM) classification eighth edition, central nervous system (CNS) metastasis, bone metastasis, tumor response according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, PFS, OS, ICI and chemotherapy, treatment line, PD-L1 expression, and mutation status; Epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), c-ros oncogene 1 (ROS-1), and v-RAF murine sarcoma viral oncogene homolog B1 (BRAF). We analyzed data concerning the use of antibiotics and corticosteroids within 30 days before ICI initiation; as well as the use of PPIs, NSAIDs, and acetaminophen at ICI initiation; including the reasons for their use. NSAIDs included low-dose aspirin, celecoxib, and rescue doses. Rescue doses consisted of PPIs and acetaminophen.

Statistical analysis

Age is described as the median with range. Demographic variables are summarized as frequencies and percentages. PFS and OS are described with medians and 95% confidence intervals (CIs). The Mann–Whitney U test was used to examine the association between age and drug usage and Fisher's exact test to examine the association between clinical variables and drug usage and to compare ORR. Kaplan–Meier method was used to estimate PFS and OS, and the log-rank test for comparison. In the univariate and multivariate analyses, hazard ratios (HRs) for OS and PFS with 95% CI were calculated using the Cox proportional hazards model. We analyzed the following factors, including age, ECOG-PS, PD-L1, NSAIDs, and ICI in combination with chemotherapy in all patients and age, ECOG-PS, PD-L1, NSAIDs, and PPIs in patients treated with ICI in combination with chemotherapy using multivariate analysis. We used a logistic regression model to calculate the odds ratio (OR) for ORR with a 95% CI for univariate and multivariate analyses. Statistical significance was set at $p < 0.05$. These analyses were conducted using the EZR software, version 1.51 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[10]

RESULTS

Patient characteristics

After excluding two patients diagnosed with combined small cell lung carcinoma, a total of 127 patients were assessed in this study. The baseline characteristics of patients are summarized in Table 1. The median (range) age was 70 (49–85) years. Males comprised 68.5% (87/127). Smoking history was present in 106 (83.5%) patients, and 109 (85.8%) had an ECOG-PS of <2. The ratio of the patients with PD-L1 tumor proportion score (TPS) of ≥50% was 38.6%. Additionally, 20 patients (15.7%) had CNS metastases, and 40 (31.5%) had bone metastases. A total of 66 (52.8%) patients had adenocarcinoma and 35 (27.6%) had squamous cell carcinoma. Nine (7.1%) patients were EGFR positive and two (1.6%) were BRAF positive. All eight (6.3%) patients who were treated with ICI as the second- or third-line had received EGFR tyrosine kinase inhibitors (TKI) as the previous line. In this study, 93 patients (73.2%) were treated with ICI in

TABLE 1 Patient baseline characteristics.

Characteristics	$n = 127$ (%)
Age, median (range)	70 (49–85)
Elderly (≥ 75)	26 (20.5)
Sex	
Male	87 (68.5)
Female	40 (31.5)
Smoking status	
Never	20 (15.7)
Former	75 (59.1)
Current	31 (24.4)
NA	1 (0.8)
ECOG-PS	
0–1	109 (85.8)
2	12 (9.4)
3	4 (3.1)
NA	2 (1.6)
PD-L1 (TPS)	
<1%	28 (22.0)
1%–49%	36 (28.3)
≥50%	49 (38.6)
NA	14 (11.0)
Stage (IASLC 8)	
II	1 (0.8)
III	9 (7.1)
IV	90 (70.9)
Recurrent	27 (21.3)
Histology	
Adenocarcinoma	67 (52.8)
Squamous cell carcinoma	35 (27.6)
NSCLC NOS	11 (8.7)
Others	14 (11.0)
Mutation status	
Negative	116 (91.3)
EGFR	9 (7.1)
ALK	0
ROS-1	0
BRAF	2 (1.6)
CNS metastasis	20 (15.7)
Bone metastasis	40 (31.5)
Treatment line	
First-line	119 (93.7)
Second-line	4 (3.1)
Third-line	4 (3.1)
ICI alone	34 (26.8)
Pembrolizumab	30 (23.6)
Nivolumab/ipilimumab	4 (3.1)
ICI in combination with chemotherapy	93 (73.2)
Pembrolizumab in combination with chemotherapy	43 (33.9)
Atezolizumab in combination with chemotherapy	41 (32.2)
Nivolumab/ipilimumab in combination with chemotherapy	9 (7.1)
Concurrent medications	
Corticosteroids	9 (7.1)
PPIs	39 (30.7)
Antibiotics	28 (22.0)
NSAIDs	36 (28.3)
Acetaminophen	33 (26.0)

Abbreviations: ALK, anaplastic lymphoma kinase; BRAF, v-raf murine sarcoma viral oncogene homolog B1; CNS, central nervous system; ECOG-PS, Eastern Cooperative Group performance status; EGFR, epidermal growth factor receptor; IASLC, International Association for the Study of Lung Cancer; NA, not available; NOS, not otherwise specified; NSAIDs, nonsteroidal anti-inflammatory drugs; NSCLC, non-small cell lung carcinoma; PD-L1, programmed death-ligand 1; PPIs, proton pump inhibitors; ROS-1, c-ros oncogene 1S-1; TPS, tumor proportion score.

combination with chemotherapy. Among the study group, 73 (57.5%) patients received pembrolizumab, 41 (32.2%) received atezolizumab, and 13 (10.2%) received nivolumab. As concurrent drugs, nine (7.1%) patients used corticosteroids and 28 (22.0%) used antibiotics within 30 days before ICI initiation. Further, 39 patients (30.7%) used PPIs, 36 (28.3%) used NSAIDs, and 33 (26.0%) used acetaminophen at the time of ICI initiation. The use of NSAIDs was significantly more common in older patients, those with a history of smoking or with bone metastasis, compared to others. (Table 2) The use of antibiotics was significantly more common in patients with bone metastasis compared to others. No significant differences were observed in patient characteristics between those with and without PPIs, or acetaminophen (Table S1). In patients treated with ICI in combination with chemotherapy, NSAIDs use was significantly more common among older age or those with a smoking history, compared to others. No significant difference was observed in patient characteristics between those with and without antibiotics and PPIs use. In patients treated with ICI alone, no significant differences were found in patient characteristics between those with and without antibiotics, PPIs, and NSAIDs. Antibiotics were used for three (10.7%) patients with pneumonia, five (17.9%) after dental treatment, 18 (64.3%) as prophylaxis, and two (7.1%) with unclear sources of infection. Antibiotics were administered for short durations for prophylaxis or post-dental treatment. PPIs were administered for two (5.1%) patients with gastroesophageal reflux disease, one (2.6%) with gastric ulcer, one (2.6%) with radiation esophagitis, one (2.6%) with stomach cancer, and 17 (43.6%) for prophylaxis. NSAIDs were used in 18 (50%) patients with pain, four (11.1%) with cardiovascular disease, three (8.3%) with spinal canal stenosis, four (11.1%) with carotid artery stenosis, and three (8.3%) with cerebral infarction. A total of 15 (11.8%) patients used loxoprofen, 15 (11.8%) patients used aspirin, eight (6.3%)

TABLE 2 Patient characteristics associated with NSAIDs.

Characteristic	With NSAIDs, 36, *n* (%)	Without NSAIDs, 91, *n* (%)	*p*-value
Age (range)	73 (49–85)	69 (50–85)	<0.01
Sex			
Male	27 (75)	60 (65.9)	
Female	9 (25)	31 (34.1)	0.399
Smoking status			
Never	1 (2.8)	19 (20.9)	
Current or Former	35 (97.2)	71 (78)	0.013
ECOG-PS			
0–1	30 (83.3)	79 (88.8)	
2	6 (16.7)	10 (11.2)	0.394
Stage			
II–III	2 (5.6)	8 (8.8)	
IV or Recurrent	34 (94.4)	83 (91.2)	0.724
CNS metastasis			
Yes	5 (13.9)	15 (16.7)	
No	31 (86.1)	75 (83.3)	0.793
Bone metastasis			
Yes	17 (47.2)	23 (25.3)	
No	19 (52.8)	68 (74.7)	0.021
PD-L1			
<50%	21 (60)	43 (55.1)	
≥50%	14 (40)	35 (44.9)	0.685
Mutation			
Positive	1 (2.8)	10 (11.0)	
Negative	35 (97.2)	81 (89.0)	0.178
Corticosteroids use			
Yes	2 (5.6)	7 (7.7)	
No	34 (94.4)	84 (92.3)	1
ICI			
ICI	12 (33.3)	22 (24.2)	
ICI with chemotherapy	24 (66.7)	69 (75.8)	0.374

Abbreviations: CNS, central nervous system; ECOG-PS, Eastern Cooperative Group performance status; ICI, immune checkpoint inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

patients used celecoxib, and two (1.6%) patients used diclofenac.

Efficacy of immunochemotherapy

The median follow-up time was 20.4 (95% CI: 0.4–69.0) months. The median PFS of all patients was 8.4 (95% CI: 6.9–11.2) months and the median OS of all patients was 33.7 (95% CI: 24.5–NA) months. The best ORR was 61.4% (complete response [CR], 3 [2.4%]; partial response [PR], 75 [59.1%]; stable disease [SD], 21 [16.5%]; non-PR/nonprogressive disease [PD], 3 [2.4%]; PD, 12 [9.4%]; not evaluable [NE], 13 [10.2%]). As shown in Table 3, in the univariable analysis of factors associated with PFS, patients aged ≥75 years, those with bone metastasis, and those with PD-L1 TPS of <50% had significantly worse PFS.

Association between the outcome of ICI and concomitant drugs

The outcomes of ICI treatment in patients with and without concurrent drug use are shown in Table 4 and Table S2. No significant differences were observed between patients with and without PPIs (Figure 1a), antibiotics (Figure 1b), or acetaminophen use. Patients who used NSAIDs had significantly worse ORR and PFS (Figure 1c). In the multivariate analysis incorporating NSAIDs, age, PS, PD-L1, and ICI in combination with chemotherapy, only PD-L1 was an

TABLE 3 Univariate analyses of variable factors of PFS.

Characteristics	*n* (%)	PFS months (95% CI)	HR (95% CI)	*p*-value
Age (years)				
≥75	26 (20.5)	6.8 (4.4–10.7)	1.63 (1.02–2.61)	
<75	101 (79.5)	9.0 (7.5–13.6)		0.04
Sex				
Male	87 (68.5)	8.5 (6.9–12.6)	0.80 (0.51–1.23)	
Female	40 (31.5)	7.8 (5.6–14.1)		0.31
Smoking status				
Never	20 (15.7)	8.5 (6.9–12.8)	1.51 (0.91–2.51)	
Current or former	106 (83.5)	7.8 (5.6–12.6)		0.11
ECOG-PS				
0–1	109 (85.8)	9.0 (7.7–12.6)		
2	16 (12.6)	4.4 (1.2–8.5)	1.66 (0.90–3.08)	0.1
Stage				
II–III	10 (7.9)	9.0 (7.7–15.0)		
IV or recurrent	117 (92.1)	8.0 (6.9–11.2)	1.18 (0.57–2.43)	0.66
CNS metastasis				
Yes	20 (15.7)	6.8 (1.2–13.8)	1.27 (0.73–2.21)	
No	106 (83.5)	8.5 (7.5–12.1)		0.4
Bone metastasis				
Yes	40 (31.5)	6.2 (5.6–7.8)	2.28 (1.47–3.52)	
No	87 (68.5)	13.6 (8.0–15.0)		<0.01
PD-L1				
<50%	64 (50.4)	7.8 (5.7–9.0)		
≥50%	49 (38.6)	12.6 (6.9–21.8)	0.63 (0.4–0.98)	0.04
Mutation				
Positive	11 (8.7)	8.1 (0.8–11.2)	1.40 (0.70–2.81)	
Negative	116 (91.3)	8.5 (6.9–12.8)		0.33
ICI				
ICI alone	34 (26.8)	10.8 (4.8–21.8)		
ICI with chemotherapy	93 (73.2)	8.0 (6.8–11.2)	1.15 (0.72–1.84)	0.55
Corticosteroids use				
Yes	9 (7.1)	8.5 (0.2-NA)	1.00 (0.44–2.29)	
No	118 (92.9)	8.4 (6.9–11.2)		1

Abbreviations: CI, confidence interval; ECOG-PS, Eastern Cooperative Group performance status; CNS, central nervous system; HR, hazard ratio; ICI, immune checkpoint inhibitor; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TPS, tumor proportion score.

independent prognostic factor of PFS, PS was the only independent prognostic factor of OS, and PD-L1 showed a tendency toward poor ORR (Table 5 and Table S3). Excluding 40 patients who had bone metastasis, there was a tendency of shorter PFS in 19 patients who used NSAIDs than in 68 patients without NSAIDs (8.5 months; 95% CI: 3.6–15.0 vs. 13.8 months; 95% CI: 8.0–25.9, HR: 1.64; 95% CI: 0.92–2.92, $p = 0.091$) and no significant differences were shown in PFS between the patients with and without PPIs antibiotics or acetaminophen. In the multivariate analysis incorporating NSAIDs and bone metastasis, both NSAIDs and bone metastasis were independent prognostic factors of PFS (NSAIDs HR: 1.60; 95% CI: 1.03–2.49, bone metastasis HR: 2.18; 95% CI: 1.41–3.38). Among the patients treated with ICI in combination with chemotherapy, those using PPIs had a significantly worse ORR and those using NSAIDs demonstrated significantly worse ORR and PFS (Table S4 and Figure S1). Multivariate analysis of the outcomes of patients treated with ICI in combination with chemotherapy, incorporating NSAIDs, PPIs, age, PS, and PD-L1 revealed that PD-L1 was the only independent prognostic factor for ORR, age was the only independent prognostic factor for PFS, and age and PS were independent prognostic factors for OS (Table S5). A total of 15 patients treated with ICI in combination with chemotherapy, used NSAIDs and PPIs at the same time. In the multivariate

TABLE 4 Comparison of treatment outcomes of ICI alone or in combination with chemotherapy, between patients with and without concurrent drug use.

Concurrent medications	*n* (%)	ORR (%)	OR (95% CI) *p*-value	PFS month (95% CI)	HR (95% CI) *p*-value
All	127	61.4		8.4 (6.9–11.2)	
PPIs use					
Yes	39 (30.7)	48.7	0.47 (0.22–1.01)	8.0 (5.7–11.2)	1.05 (0.67–1.65)
No	88 (69.3)	67	0.075	8.5 (6.9–12.8)	0.84
Antibiotics use					
Yes	28 (21.9)	75	2.21 (0.86–5.68)	7.8 (5.9–12.8)	1.01 (0.62–1.63)
No	99 (78.0)	57.6	0.124	8.5 (6.8–12.1)	0.97
NSAIDs use					
Yes	36 (28.3)	47.2	0.44 (0.2–0.97)	6.3 (3.7–8.0)	1.72 (1.10–2.67)
No	91 (71.7)	67	0.045	10.8 (7.8–13.6)	0.02
Acetaminophen use					
Yes	33 (26.0)	60.6	0.96 (0.42–2.15)	7.8 (5.5–11.5)	1.23 (0.78–1.95)
No	94 (74.0)	61.7	1	8.5 (6.9–12.8)	0.38

Abbreviations: CI, confidence interval; HR, hazard ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; ORR, overall response rate; OR, odds ratio; PFS, progression-free survival; PPIs, proton pump inhibitors.

analysis incorporating NSAIDs and PPI, only NSAIDs were an independent prognostic factor of PFS (NSAIDs HR: 2.00; 95% CI: 1.16–3.43, $p = 0.012$. PPIs HR: 1.10; 95% CI: 0.65–1.84, $p = 0.728$). In patients treated with ICI alone, although the sample size was small, no significant differences were observed between patients with and without concurrent drug use (Table S6).

DISCUSSION

In this study, we showed the poor outcomes of ICI either alone or in combination with chemotherapy in patients using NSAIDs and the lower ORR of ICI in combination with chemotherapy in patients using PPIs in the univariate analyses. There was a tendency for the shorter PFS of the patients using NSAIDs in the multivariate analysis. To our knowledge, there have been no reports indicating worse ORR and PFS of ICI in combination with chemotherapy in patients using NSAIDs. Cyclooxygenase-2 (COX-2)-dependent prostaglandin E2 (PGE2) promotes tumor growth and regulates tumor immunosuppression.[11] However, reports indicate that adding a COX-2 inhibitor to chemotherapy did not significantly improve the PFS of NSCLC.[12,13] In mouse melanoma cells, inhibition of COX showed synergistic antitumor effects with anti-PD-1.[14] On the other hand, it has been reported that although PD-L1 expression is associated with COX-2 expression in resected NSCLC samples, COX-2 inhibitors have no effect on PD-L1 expression in lung cancer cell lines.[15] In the present study, there were no differences in PD-L1 expression between patients with and without NSAID use. No consensus has been reached regarding the effect of NSAIDs on the outcomes of ICI treatment for NSCLC.[5–9] Wang et al. reported that 20 patients using NSAIDs had longer time-to-progression than 17 patients without NSAIDs, but the sample size was small.[5] Sebastian et al. reported that patients using NSAIDs had better OS, and diclofenac had a stronger association with OS.[6] In their report, they pointed out the possibility that diclofenac had a unique and positive effect on the outcomes of ICI alone or in combination with chemotherapy, unlike other NSAIDs.[16,17] In our study, only two patients used diclofenac. This might have affected the outcomes; however, this study might be less affected by diclofenac, which is unique as NSAIDs. In addition, Sebastian et al. did not assess PFS and ORR, and determined that OS might not reflect the effect of treatment on ICI itself because of the effect of post-treatment. Kanai et al. reported no significant differences in ICI alone in patients with and without NSAIDs use, but there was a tendency for shorter OS in patients with NSAID use.[9] This study differed from our study in that the patients were treated with ICI alone, and this might have influenced the results.

The adverse effects of NSAIDs on ICI outcomes may be attributed to the gut microbiota. The gut microbiota plays an important role in maintaining homeostasis and immune system function. Disrupted gut microbiota can negatively affect ICI responses.[18] NSAIDs have been reported to be associated with alterations in microbial populations.[19–21] In this study, patients using NSAIDs had a significantly worse ORR and PFS in univariate analysis. The impact of NSAIDs on the gut microbiota may affect the outcomes. No significant difference in the outcomes of ICI alone was observed between patients treated with and without NSAIDs, likely due to the small sample size. In the previous report, bone metastasis was reported to be a prognostic factor for disease control rate, PFS, and OS in NSCLC treated with ICI,[22] and in our study, 40 patients had bone metastasis. On the other hand, there was a systematic review and meta-analysis that PFS in NSCLC treated with ICI was not influenced by bone

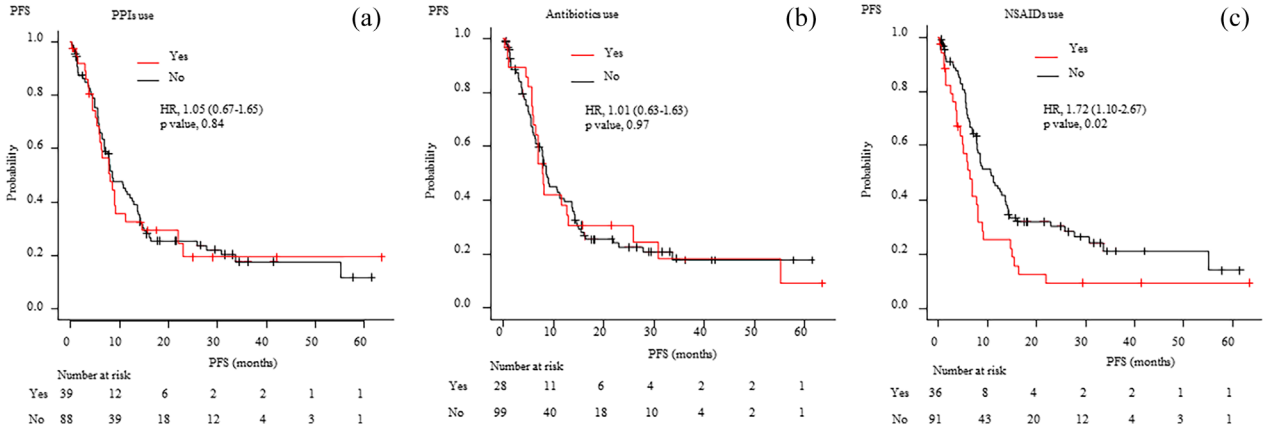

FIGURE 1 Kaplan–Meier curves of progression-free survival (PFS) in patients treated with immune checkpoint inhibitor (ICI) alone or in combination with chemotherapy, comparing those with and without proton pump inhibitors (PPIs) (a), antibiotics (b), and nonsteroidal anti-inflammatory drug (NSAID) (c) use.

TABLE 5 Multivariate analysis of factors associated with PFS and ORR in patients receiving ICI alone or in combination with chemotherapy.

Variables	ORR, OR (95% CI)	*p*-value	PFS, HR (95% CI)	*p*-value
NSAIDs	0.58 (0.24–1.42)	0.23	1.47 (0.88–2.47)	0.14
Age ≥ 75	0.68 (0.25–1.86)	0.45	1.58 (0.9–2.78)	0.11
ECOG-PS ≥2	0.42 (0.11–1.55)	0.19	1.79 (0.86–3.7)	0.12
PD-L1 TPS ≥50%	2.38 (0.85–6.64)	0.098	0.56 (0.32–0.97)	0.04
ICI with chemotherapy	1.65 (0.56–4.89)	0.37	1.14 (0.62–2.13)	0.67

Abbreviations: CI, confidence interval; ECOG-PS, Eastern Cooperative Group performance status; HR, hazard ratio; ICI, immune checkpoint inhibitor; ORR, overall response rate; OR, odds ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TPS, tumor proportion score.

metastasis.[23] In our study, NSAIDs were an independent prognostic factor of PFS in the multivariate analysis incorporating NSAIDs and bone metastasis. Bone metastases did not have a significant impact. In this study, NSAIDs were not a prognostic factor for PFS in multivariate analysis. Considering that PS, which has been reported to be a prognostic factor for PFS of ICI,[24] also showed no significant difference in multivariate analysis, the small sample size could have affected the results. However, there was a tendency for shorter PFS of patients using NSAIDs in the multivariate analysis. In contrast, no significant differences in the outcomes of ICI alone or in combination with chemotherapy were observed between patients with and without acetaminophen use. Acetaminophen may be preferable to NSAIDs for the treatment of cancer pain in patients with advanced NSCLC treated with ICI alone or in combination with chemotherapy.

In this study, the poor ORR of ICI in combination with chemotherapy in patients using PPIs was shown. PPIs disrupt the gut microbiota.[25] Although PPIs have been reported to be associated with worse outcomes in NSCLC treated with atezolizumab alone or in combination with chemotherapy,[2] in this study, which included all patients treated with atezolizumab, pembrolizumab, nivolumab, and ipilimumab alone or in combination with chemotherapy, no significant differences were observed in the outcomes of patients with and without PPIs. The impact of PPIs on the gut microbiota might affect the outcomes leading to the poor ORR of ICI in combination with chemotherapy in patients using PPIs. No significant differences in the outcomes of treatment with ICI alone were observed between patients using and not using PPIs, likely due to the small sample size.

The present study showed no significant differences in the outcomes of patients with and without antibiotic use. Antibiotics also disrupt gut microbiota.[26] However, no consensus has been reached regarding the impact of antibiotics on ICI for NSCLC.[3,4] This study also showed no differences in the outcomes of ICI for patients with and without antibiotic use.

This study had some limitations. First, this was a retrospective, single-race, single-center study. Second, there was no information on drug adherence, rescue dosage, or duration of PPIs or NSAID use. Third, we did not assess the gut microbiota of patients. The sample size was also small. Despite these limitations, assessing ORR and PFS of ICI in combination with chemotherapy in patients using NSAIDs is worthwhile.

In conclusion, the patients using NSAIDs had a tendency of poor response to ICI for advanced NSCLC, suggesting that unnecessary use of NSAIDs should be discouraged.

AUTHOR CONTRIBUTIONS

Jun Yamada: Data curation, formal analysis, investigation, methodology, and writing - original draft. Takafumi Fukui, Atsuhiko Yatani, Chihiro Mimura, Kiyoko Fukuda, Daisuke Hazama, Naoko Katsurada, Tatsuya Nagano, and Masatsugu Yamamoto: Investigation, writing - review and editing. Motoko Tachihara: Conceptualization, methodology, project administration, supervision, writing - review and editing.

ACKNOWLEDGMENTS

The authors would like to thank the patients and investigators for their respective contributions to this study.

CONFLICT OF INTEREST STATEMENT

NK received honoraria from Bristol-Myers Squibb Co., Ltd.; Chugai Pharmaceutical Co., Ltd.; and MSD K.K. TN received honoraria from AstraZeneca KK. MY received honoraria from Daiichi Sankyo Co., Ltd.; Eli Lilly Japan Co., AstraZeneca KK, Ltd., Chugai Pharmaceutical Co., Ltd, Taiho Pharmaceutical Co., Ltd. MT received honoraria from Eli Lilly Japan Co., Ltd., Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb Co., Ltd., Chugai Pharmaceutical Co., Ltd, AstraZeneca KK., MSD KK., Novartis Pharmaceuticals KK., and Takeda Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Daiichi Sankyo Co., Ltd., Pfizer Japan Inc., Janssen Pharmaceutical KK., and grants from AstraZeneca KK., Chugai Pharmaceutical Co., Ltd., Eli Lilly Japan Co., Ltd. The other authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Yamada J, Fukui T, Yatani A, Mimura C, Fukuda K, Hazama D, et al. Impact of concurrent medications on the outcome of immunotherapy in non-small cell lung carcinoma. Thorac Cancer. 2024;15(15):1228–36. https://doi.org/10.1111/1759-7714.15294