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# Effect of renin-angiotensin system inhibitors on pemetrexed plus platinum-induced hematological toxicities: a multicenter retrospective study using three propensity score analyses

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Hematological toxicities induced by pemetrexed plus platinum therapy remain a critical issue in clinical practice. We hypothesized that inhibition of the renin-angiotensin system (RAS) can ameliorate pemetrexed-induced hematological toxicities through drug-drug interactions involving organic anion transporters. Thus, this study aimed to clarify whether RAS inhibitors (RASIs) could prevent pemetrexed plus platinum-induced hematological toxicities. We retrospectively analyzed data from 305 consecutive patients with non-small cell lung cancer or malignant pleural mesothelioma who received their first cycle of a pemetrexed plus platinum regimen and were treated with or without RASIs. The primary endpoint was the incidence of severe myelosuppression after the first cycle. Propensity score (PS)-matched, PS-adjusted, and inverse probability of treatment weighting (IPTW) analyses were used. The number of patients with grade ≥3 hematological toxicities was 27 (8.9%). PS-matched analyses revealed that the concomitant use of RASIs was slightly associated with a lower risk of grade ≥3 hematological toxicities (odds ratio [OR], 0.68; 95% confidence interval [CI], 0.20–2.32; $p = 0.536$). Additionally, sensitivity analyses using PS-adjusted and IPTW methods demonstrated similar results (OR, 0.63; 95% CI, 0.19–2.15; $p = 0.463$ and OR, 0.37; 95% CI, 0.11–1.29; $p = 0.117$, respectively). These findings suggest that RASIs might prevent pemetrexed plus platinum-induced hematological toxicities.

## 1. Introduction

Lung cancer is the most frequently diagnosed cancer globally and is the leading cause of cancer-related death (Bray et al. 2018). Several pivotal phase III trials have shown that pemetrexed, a multi-targeted antifolate, is a key drug for patients with non-squamous, non-small cell lung cancer (NSCLC) and malignant pleural mesothelioma (MPM) (Scagliotti et al. 2008; Grønberg et al. 2009; Paz-Ares et al. 2012; Barlesi et al. 2013; Patel et al. 2013; Zalcman et al. 2016). According to the current national and international clinical practice guidelines, a combination therapy comprising pemetrexed and platinum is the first-line chemotherapy for patients with NSCLC and MPM (The Japan Lung Cancer Society 2019; National Comprehensive Cancer Network 2020a; National Comprehensive Cancer Network 2020b). However, pemetrexed plus platinum therapy induces severe hematological toxicities in 25.8–40.0% of patients (Grønberg et al. 2009; Patel et al. 2013). To date, knowledge about the predictive risk factors for hematological toxicities in patients receiving this combination therapy in clinical practice is limited. In addition, no preventive treatment is available to avoid these toxicities, except for vitamin $B_{12}$ and folic acid supplements.

Approximately 70–90% of pemetrexed is excreted unmetabolized in the urine, primarily via tubular secretion (Rinaldi et al. 1999; Nakagawa et al. 2006). In the proximal tubules, membrane transport proteins, which are expressed specifically at the basolateral membrane, are responsible for pemetrexed urinary secretion. Pemetrexed is a hydrophilic anionic compound that is eliminated by organic anion transporters (OATs), which are transmembrane proteins (Kurata et al. 2014). A previous study investigating the characteristics of pemetrexed transport *via* various solute carrier transporters revealed that the drug is primarily transported by OAT3, and its plasma clearance is mediated by OAT3 uptake (Kurata et al. 2014). As pemetrexed-induced hematological toxicities have been correlated with drug exposure, decreased clearance of the drug might result in greater systemic exposure, which in turn could lead to severe myelosuppression. Several investigators have demonstrated that the co-administration of OAT3 inhibitors, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and lansoprazole, a proton pump inhibitor (PPI), can exacerbate pemetrexed-induced hematological toxicities (Posada et al. 2015; Ikemura et al. 2016; Kawazoe et al. 2017; Araki et al. 2019). However, data regarding these drug-drug interactions are not consistent among studies.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are commonly used to treat various cardiovascular diseases. ACEIs prevent the generation of angiotensin II by inhibiting ACE, whereas ARBs specifically

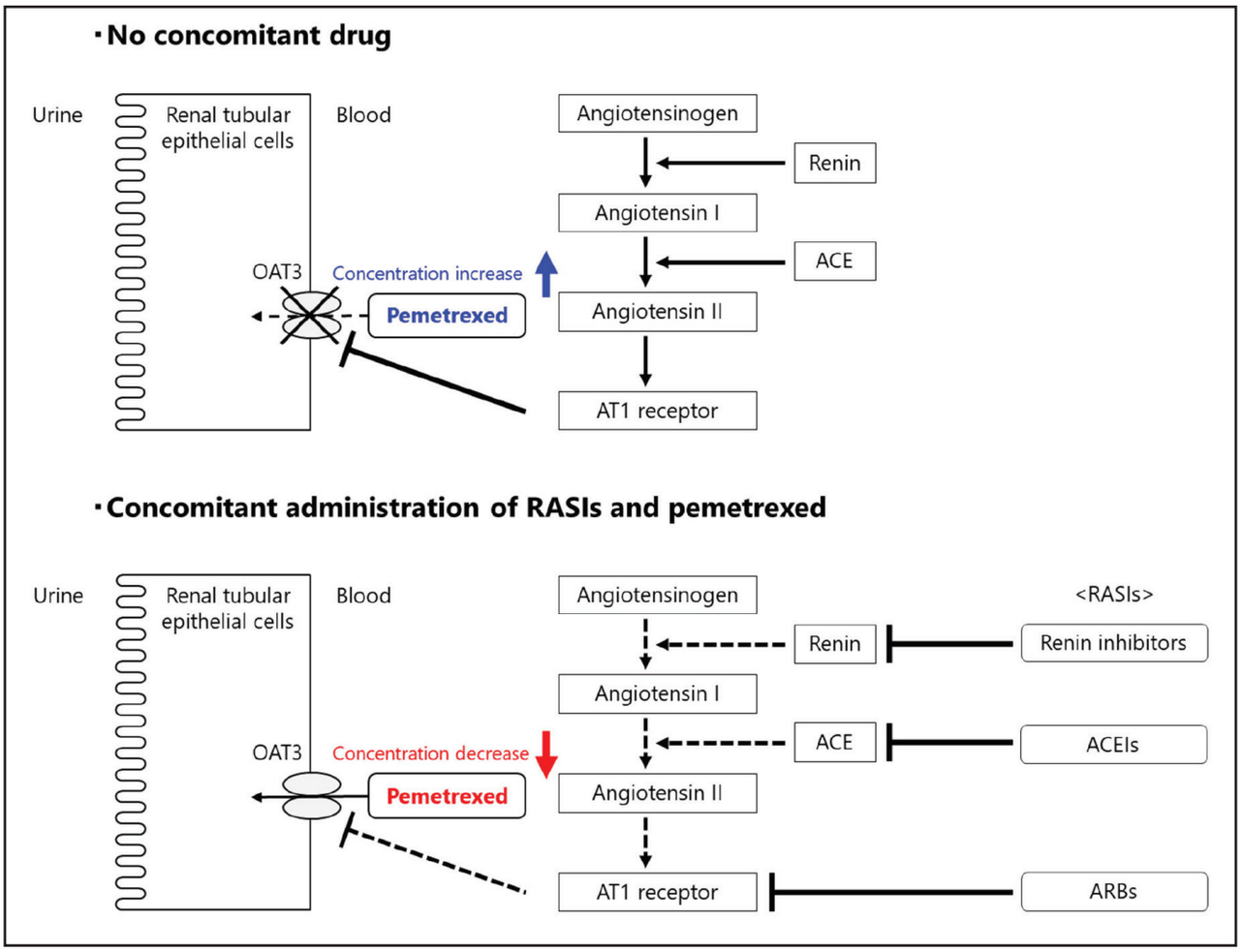


Fig. 1: Hypothesis of drug-drug interactions between pemetrexed and renin-angiotensin system (RAS) inhibitors, involving organic anion transporter 3. The upper panel shows the normal flow of pemetrexed excretion without RAS inhibitors. The lower panel shows the suppressive flow of pemetrexed excreted with RAS inhibitors. Black arrows and T-type arrows show the mechanism of action of the pharmacological and inhibitory effects, respectively. OAT3, organic anion transporter 3; RASIs, renin-angiotensin system inhibitors; ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; AT1, angiotensin II type 1; ARB, angiotensin II receptor blocker

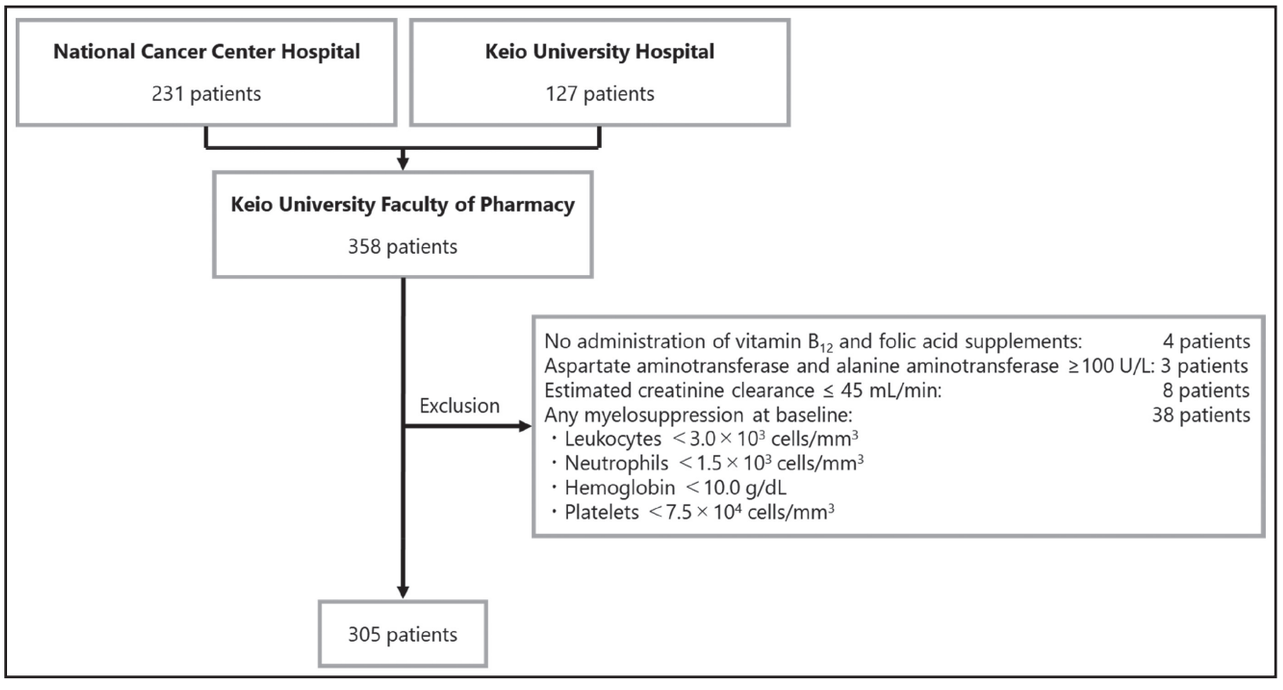


Fig. 2: Patient enrollment flowchart

block the interaction between angiotensin II and the angiotensin II type 1 (AT1) receptor. AT1 receptor signal transduction inhibits OAT3 activity via the activation of protein kinase Cα (Duan et al. 2010; Li and Zhuo 2011). Taken together, we hypothesized that these renin-angiotensin system inhibitors (RASIs) could have a preventive effect on pemetrexed-induced hematological toxicities through drug-drug interactions involving OAT3 (Fig. 1). However, the therapeutic benefits of RASIs have not yet been investigated with respect to pemetrexed plus platinum-induced hematological toxicities based on a large-scale multicenter study. Therefore, in this study, we aimed to determine whether RASIs can prevent pemetrexed plus platinum-induced hematological toxicities using real-world data.

## 2. Investigations and results

### *2.1. Patient characteristics*

A flowchart illustrating the patient enrollment process is presented in Fig. 2. No patient was lost to follow-up. Based on the exclusion criteria, 53 patients were excluded from the analysis due to a bias related to hematological toxicities. Data from 305 patients were analyzed in this study. The baseline patient characteristics are listed in Table 1. Of these patients, 48 (15.7%) concomitantly received RASIs. The median age of the patients was 64 years (interquartile range [IQR]: 57–70 years). The median dose of pemetrexed was 500 mg/m$^2$ (IQR: 497–500 mg/m$^2$). The number of patients who received cisplatin and carboplatin-based regimens

**Table 1: Baseline patient characteristics**

| Patient characteristics | Overall (*N* = 305) | RASI group (*N* = 48) | Non-RASI group (*N* = 257) | *p*-value |
|---|---|---|---|---|
| Sex, *n* (%) | | | | |
| Male | 179 (58.7) | 32 (66.7) | 147 (57.2) | 0.265[a)] |
| Female | 126 (41.3) | 16 (33.3) | 110 (42.8) | |
| Age (years), median [IQR] | 64 [57–70] | 69 [65–74] | 62 [56–68] | <0.001[b)] |
| BMI (kg/m$^2$), median [IQR] | 22 [20–24] | 24 [22–26] | 22 [20–24] | <0.001[b)] |
| Cancer type, *n* (%) | | | | |
| NSCLC | 284 (93.1) | 45 (93.7) | 239 (93.0) | 1.000[a)] |
| MPM | 21 (6.9) | 3 (6.3) | 18 (7.0) | |
| Regimen | | | | |
| PEM + CDDP ± BEV, *n* (%) | 181 (59.3) | 22 (45.8) | 159 (61.9) | 0.054[a)] |
| PEM + CBDCA ± BEV, *n* (%) | 124 (40.7) | 26 (54.2) | 98 (38.1) | |
| PEM dose (mg/m$^2$), median [IQR] | 500 [497–500] | 500 [498–500] | 500 [497–500] | 0.656[b)] |
| CDDP dose (mg/m$^2$), median [IQR] | 75 [73–75] | 75 [74–75] | 75 [73–75] | 0.794[b)] |
| CBDCA dose (AUC), median [IQR] | 6 [5–6] | 5 [5–6] | 6 [5–6] | 0.057[b)] |
| Combination of BEV, *n* (%) | 52 (17.1) | 6 (12.5) | 46 (17.9) | 0.412[a)] |
| Baseline laboratory data, median [IQR] | | | | |
| Leukocytes (×10$^3$ cells/mm$^3$) | 6.7 [5.3–8.2] | 6.9 [5.9–7.7] | 6.6 [5.3–8.4] | 0.516[b)] |
| Neutrophils (×10$^3$ cells/mm$^3$) | 4.4 [3.4–5.8] | 4.4 [3.7–5.4] | 4.4 [3.3–5.9] | 0.347[b)] |
| Hemoglobin (g/dL) | 12.9 [12.0–13.7] | 12.8 [12.1–13.7] | 12.9 [12.0–13.7] | 0.922[b)] |
| Platelets (×10$^4$ cells/mm$^3$) | 26.0 [21.9–33.2] | 26.8 [21.8–31.6] | 26.0 [21.9–33.2] | 0.770[b)] |
| Aspartate aminotransferase (U/L) | 21 [18–27] | 20 [17–28] | 21 [18–27] | 0.853[b)] |
| Alanine aminotransferase (U/L) | 17 [12–25] | 16 [12–25] | 17 [13–25] | 0.924[b)] |
| Estimated creatinine clearance (mL/min) | 79.4 [67.9–98.8] | 74.3 [62.6–87.7] | 80.4 [68.5–101.9] | 0.009[b)] |
| Coadministration drugs, *n* (%) | | | | |
| ARBs | 42 (13.8) | 42 (13.8) | None | |
| ACEIs | 6 (2.0) | 6 (2.0) | None | |
| NSAIDs | 68 (22.3) | 4 (8.3) | 64 (24.9) | 0.013[a)] |
| Lansoprazole | 41 (13.4) | 5 (10.4) | 36 (14.0) | 0.647[a)] |
| Other PPIs | 46 (15.1) | 9 (18.8) | 37 (14.4) | 0.509[a)] |

RASIs, renin-angiotensin system inhibitors; IQR, interquartile range; BMI, body mass index; NSCLC, non-small cell lung cancer; MPM, malignant pleural mesothelioma; PEM, pemetrexed; CDDP, cisplatin; CBDCA, carboplatin; BEV, bevacizumab; AUC, area under the curve; ARBs, angiotensin II receptor blockers; ACEIs, angiotensin-converting enzyme inhibitors; NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor.
a) Fisher's exact test, b) Student's *t*-test

was 181 (59.3%) and 124 (40.7%), respectively. The total number of patients who were concomitantly administered ARBs, ACEIs, NSAIDs, lansoprazole, and other PPIs was 42 (13.8%), six (2.0%), 68 (22.3%), 41 (13.4%), and 46 (15.1%), respectively. The age, body mass index (BMI), regimen, dose of carboplatin, estimated creatinine clearance, and co-administration of NSAIDs were different between groups, whereas other baseline patient characteristics were well balanced between the groups.

### *2.2. Endpoint*

The proportions of patients with grade ≥3 and grade ≥2 hematological toxicities were 8.9% ($n = 27$) and 29.2% ($n = 89$), respectively. The primary endpoints are listed in Table 2. A propensity score (PS)-matched analysis revealed that the concomitant use of RASIs was slightly associated with a lower risk of grade ≥3 hematological toxicities (odds ratio [OR], 0.68; 95% confidence interval [CI], 0.20–2.32; $p = 0.536$). Additionally, sensitivity analyses using PS-adjusted and inverse probability of treatment weighting (IPTW) methods, which included 305 patients in both groups, demonstrated similar results (OR 0.63; 95% CI, 0.19–2.15; $p = 0.463$ and OR 0.37; 95% CI, 0.11–1.29; $p = 0.117$, respectively). The secondary endpoints are listed in Table 3. A PS-matched analysis revealed that the concomitant use of RASIs was slightly associated with a lower risk of grade ≥2 hematological toxicities (OR, 0.73; 95% CI, 0.29–1.80; $p = 0.489$). Additionally, sensitivity analyses using PS-adjusted and IPTW methods demonstrated similar results (OR, 0.77; 95% CI, 0.35–1.69; $p = 0.510$ and OR 0.66; 95% CI, 0.19–2.31; $p = 0.512$, respectively).

## 3. Discussion

To date, there is limited knowledge about the predictive risk factors associated with hematological toxicities in patients receiving pemetrexed plus platinum regimens. We hypothesized that the inhibition of RAS prevents pemetrexed plus platinum-induced hematological toxicity through drug-drug interactions involving OAT3. Based on the results from PS-matched, PS-adjusted, and IPTW analyses, the present study showed that RASIs might prevent pemetrexed plus platinum-induced hematological toxicities in a relatively large number of patients in a clinical setting.

To our knowledge, this is the first study to investigate whether the use of RASIs can ameliorate pemetrexed-induced hematological toxicities through drug-drug interactions involving OAT3. According to a review of previous studies (Burckhardt 2012), some ARBs inhibit OAT3. In the present study, olmesartan and valsartan were classified as ARBs with strong inhibitory effects on OAT3, whereas candesartan, losartan, and telmisartan were classified as weak inhibitors of OAT3, based on the *in vitro* results of previous studies (Burckhardt 2012). According to recent U.S. Food and Drug Administration guidelines on drug-drug interactions, an unbound $C_{max}/IC_{50}$ ratio ≥ 0.1 is considered a positive indicator of drug-drug interactions. The unbound $C_{max}/IC_{50}$ ratios of olmesartan (1.6) and valsartan (0.9) were determined to be greater than 0.1, whereas those for candesartan, losartan, and telmisartan were much less than 0.1 (all values were < 0.01). Therefore, olmesartan and valsartan could inhibit OAT3 and interact with pemetrexed. In the present study, however, the number of patients co-administered olmesartan and valsartan was seven and five, respectively, and we could not conduct an ad hoc analysis among ARBs owing to the small number of patients.

According to a previous study (Mita et al. 2006), although tubular secretion is the predominant mechanism of pemetrexed excretion in patients with normal renal function, glomerular filtration becomes dominant when renal function decreases. In patients with impaired renal function, RASI administration might decrease the glomerular filtration rate (GFR) temporally by decreasing the intra-glomerular pressure, thereby reducing the excretion of pemetrexed. This suggests that the RASIs exert both a preventive effect against the hematological toxicity of pemetrexed through OAT3-mediated drug-drug interactions and an inductive effect through temporary reductions in the GFR.

In the present study, carboplatin users had a significantly higher incidence of grade ≥ 3 or higher blood toxicity than cisplatin users ($p = 0.002$), which is consistent with the results of a previous study (Rossi et al. 2012). In addition, another study (Gutierrez et al. 2016) reported that grade ≥ 3 hematological toxicity with carboplatin, especially thrombocytopenia, occurs more frequently in obese patients (BMI ≥ 27) than in non-obese patients (BMI < 27). Among the carboplatin users in this study, the RASI-co-administered group tended to have a higher incidence of thrombocytopenia and a higher proportion of obese patients than the RASI-non-co-administered group (incidence of thrombocytopenia, $p = 0.127$; obese patients, $p = 0.215$). This suggests that the preventive effect of RASIs on the hematological toxicity of pemetrexed might have been masked by the hematological toxicity of carboplatin in obese patients. In this study, PS matching was used as the primary analysis. Additionally, sensitivity analyses using PS-adjusted and IPTW methods were used.

The present study has several limitations. First, this was a retrospective observational study. Thus, we could not ascertain the exact time of administration of concomitant drugs in patients who received RASIs, NSAIDs, and/or lansoprazole. Therefore,

**Table 2: Odds ratios and confidence intervals for the primary endpoint of grade ≥3 hematological toxicities**

| | | 1:1 PS matching | | PS-adjusted analysis | | IPTW | |
|---|---|---|---|---|---|---|---|
| Variables | | OR (95% CI) | *p*-value | OR (95% CI) | *p*-value | OR (95% CI) | *p*-value |
| RASIs | Yes | 0.68 (0.20–2.32) | 0.536 | 0.63 (0.19–2.15) | 0.463 | 0.37 (0.11–1.29) | 0.117 |
| | No | 1 | | 1 | | 1 | |

PS, propensity score; IPTW, inverse probability of treatment weighting; OR, odds ratio; CI, confidence interval; RASIs, renin-angiotensin system inhibitors.

**Table 3: Odds ratios and confidence intervals for the secondary endpoint of grade ≥2 hematological toxicities**

| | | 1:1 PS matching | | PS-adjusted analysis | | IPTW | |
|---|---|---|---|---|---|---|---|
| Variables | | OR (95% CI) | *p* value | OR (95% CI) | *p* value | OR (95% CI) | *p* value |
| RASIs | Yes | 0.73 (0.29–1.80) | 0.489 | 0.77 (0.35–1.69) | 0.510 | 0.66 (0.19–2.31) | 0.512 |
| | No | 1 | | 1 | | 1 | |

PS, propensity score; IPTW, inverse probability of treatment weighting; OR, odds ratio; CI, confidence interval; RASIs, renin-angiotensin system inhibitors.

the blood concentration of the concomitant drug might not have been sufficient at the time of pemetrexed administration, and potential drug-drug interactions involving OAT3 might not have occurred. Second, the timing of blood tests was inconsistent; thus, the frequency of hematological toxicities might have been underestimated. Therefore, we could not fully adjust for the causative variables owing to the small number of events ($n$ = 27) of grade ≥3 hematological toxicities. In addition, we performed PS-matched, PS-adjusted, and IPTW analyses to reduce the potential confounding bias of an observational study with clinical differences in patient characteristics. The fact that PS-matched, PS-adjusted, and IPTW analyses cannot control for unmeasured confounders might have affected the results and was a major limitation. Thus, the findings of this study should be confirmed with larger studies based on a larger patient population. Furthermore, a prospective cohort study is warranted to ensure that the timing of blood tests is consistent among all patients.

This is the first large-scale, multicenter study to demonstrate that among patients with NSCLC or MPM who had received their first cycle of pemetrexed plus platinum, RASIs might prevent pemetrexed plus platinum-induced hematological toxicities. These findings provide preliminary information about the association between RASIs and pemetrexed plus platinum-induced hematological toxicities in Japanese patients with NSCLC or MPM. Our results can likely be translated to other Asian populations, highlighting the need for additional research in this area.

## 4. Experimental

### *4.1. Study design*

This multicenter retrospective observational study was carried out at the National Cancer Center Hospital, a high-volume cancer center in Tokyo, Keio University Hospital, a tertiary hospital in Tokyo, and Keio University Faculty of Pharmacy, a private pharmacy school in Tokyo. Research members from the Keio University Faculty of Pharmacy acquired data from electronic medical records at the National Cancer Center Hospital and Keio University Hospital. Data integration and analyses were performed at the Keio University Faculty of Pharmacy. The methodology used in this study has been described previously (Toda et al. 2017; Kawazoe et al. 2018; Uchida et al. 2018). Consecutive patients, aged ≥20 years with NSCLC or MPM, who had received at least one course of a pemetrexed plus platinum regimen between December 2014 and November 2018, were included. The other eligibility criteria were as follows: 1) pemetrexed-naïve before the investigation period, 2) no history of the use of investigational or unapproved drugs before and during the investigation period, and 3) availability of laboratory data from days 8 to 21. Patient records were de-identified and analyzed anonymously. We extracted the necessary baseline clinical and demographic information, including age, sex, body surface area, BMI, cancer type, chemotherapy regimen and dose, concomitant drugs (including RASIs, NSAIDs, and/or PPIs), laboratory data before chemotherapy, and chemotherapy-related hematological toxicities. Patients who met any of the following criteria were excluded from the study: 1) no administration of vitamin $B_{12}$ and folic acid supplements, 2) inadequate functionality of the bone marrow, liver, or kidney before chemotherapy (leukocytes $<3.0 \times 10^3$ cells/mm$^3$, neutrophils $<1.5 \times 10^3$ cells/mm$^3$, hemoglobin <10.0 g/dL, platelets $<7.5 \times 10^4$ cells/mm$^3$, aspartate aminotransferase and alanine aminotransferase ≥100 U/L, and estimated creatinine clearance (calculated by the Cockcroft-Gault formula [Cockcroft and Gault 1976]) ≤45 mL/min).

The study protocol was approved by the ethics committees of the National Cancer Center Hospital (approval number: 2019-200), Keio University Hospital (approval number: 20180310), and Keio University Faculty of Pharmacy (approval number: 200918-1), and the study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research involving Human Subjects by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare of Japan. Japanese law does not require individual informed consent from participants in non-invasive observational trials, such as in the present study. Therefore, we used the official website of the National Cancer Center Hospital and Keio University Hospital as an opt-out method rather than acquiring written or oral informed consent.

### *4.2. Chemotherapy regimen*

All patients received pemetrexed (500 mg/m$^2$) for 10 min along with cisplatin (75 mg/m$^2$) or carboplatin (target area under the curve: 6) with or without bevacizumab (15 mg/kg). The chemotherapy dose was modified according to the clinician's discretion.

### *4.3. Endpoint*

The primary endpoint was the incidence of grade ≥3 hematological toxicities, including leukopenia, neutropenia, anemia, and thrombocytopenia, in accordance with the Common Terminology Criteria for Adverse Events, version 4.0 (National Cancer Institute, Common Terminology Criteria for Adverse Events). The secondary endpoint was the incidence of grade ≥2 hematological toxicities, including leukopenia, neutropenia, anemia, and thrombocytopenia. The nadir of these hematological toxicities in each patient was determined to be the lowest value recorded on days 8 to 21 after chemotherapy. In the present study, the frequency of laboratory testing was determined at the clinician's discretion.

### *4.4. Statistical analysis*

Fisher's exact test was used to compare categorical data, and a Student's $t$-test was used to compare continuous data between the RASI and non-RASI groups. To investigate the differences between the groups accounting for potential independent variables reported in several previous studies, including a report by one of our co-authors (Ikesue et al. 2015; Posada et al. 2015; Ikemura et al. 2016; Kawazoe et al. 2017; Araki et al. 2019), we used three PS methods to reduce the effects of confounders in a logistic regression model. The PS of the co-administration of RASIs was estimated for each patient using multivariable logistic regression (Rosenbaum and Rubin 1983), with the following baseline characteristics as covariates: patient's age (years), BMI (kg/m$^2$), platinum chemotherapy type (cisplatin or carboplatin), baseline neutrophils ($\times 10^3$ cells/mm$^3$), baseline hemoglobin (g/dL), baseline estimated creatinine clearance (mL/min), NSAIDs (yes or no), and lansoprazole (yes or no). The primary analysis used PS matching. In the PS-matching analysis, 1:1 matching without replacement (greedy nearest neighbor matching algorithm) with a caliper width equal to 0.2 of the standard deviation of the logit of the PS was applied to create a matched sample (Austin 2011). We also performed sensitivity analyses using PS-adjusted (including the PS as an additional covariate) and IPTW (D'Agostino 1998) methods. The results are shown as ORs and 95% CIs. According to the recommendation of the American Statistical Association (Wasserstein and Lazar 2016; Wasserstein et al. 2019), $p < 0.05$ should be avoided when interpreting $p$-values. Hence, a statistical significance of $p < 0.05$ was avoided. Instead, we interpreted the results based on point estimates with their CIs. We did not impute missing data. All analyses were performed using SAS version 9.4 and JMP version 15.0.0 (SAS Institute, Inc., Cary, NC, USA).

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