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Evaluation of risk factors for chemotherapy-induced nausea and vomiting in cisplatin and gemcitabine treatment for biliary tract cancer: acid suppressants do not prevent nausea

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Chemotherapy-induced nausea and vomiting (CINV) is one of the most serious adverse effects of cancer therapy. Cancer patients frequently use acid suppressants (AS) for palliation of gastrointestinal symptoms associated with malignancy and/or anticancer therapy. AS are suggested as an additional option for CINV management in several antiemetic guidelines, although their efficacy remains unknown. The aim of this study was to determine whether AS administration affects CINV incidence in cisplatin and gemcitabine treatment for biliary tract cancer. The primary endpoint was to evaluate whether AS administration was associated with the incidence of all-grade nausea in the first administration by logistic analysis. The secondary endpoints were to assess factors associated with anorexia. Prophylactic antiemetics were based on current guidelines. Nausea occurred in 34.2% of patients (grade 1, 31.7%; grade 2, 2.5%). Patients exhibiting vomiting and anorexia represented 4.2% and 39.1%, respectively, without grade 3/4 symptoms. Multivariate analysis suggested that the independent risk factors for nausea as female sex, and no- or less-alcohol drinking habit and regular narcotics administration were associated with anorexia. In contrast, AS administration was not associated with nausea and anorexia incidence (odds ratio, 95% confidence interval: 1.43, 0.64–3.23; *P*=0.38 for nausea, 1.62, 0.71–3.68; *P*=0.25 for anorexia). In conclusion, we found that AS administration is not associated with CINV incidence, and female sex is a risk factor for nausea, and non-alcohol drinking habits and regular narcotic use are factors associated with anorexia in cisplatin and gemcitabine treatment for biliary tract cancer. We should correctly administer AS depending on the patient's situation. Successful CINV management needs effective monitoring and administration of prophylactic antiemetics and counter-measure medicines for patients at risk.

1. Introduction

Chemotherapy-induced nausea and vomiting (CINV) is one of the most serious adverse effects of cancer therapy. Several antiemetic guidelines define the emetogenic risk for each chemotherapeutic agent (Aogi et al. 2021; Hesketh et al. 2017; NCCN Clinical Practice Guidelines in Oncology 2021; Roila et al. 2015), and also recommend prophylactic antiemetic regimens.

Cisplatin (CDDP) + gemcitabine (GEM) is one of the most effective treatments for biliary tract cancer (Valle et al. 2010). CDDP is categorized as high emetogenic risk (HEC) and GEM as low emetogenic risk. The Japanese guidelines categorize this regimen as moderate emetogenic risk (MEC) because the CDDP dosage is much lower than that in other malignancy treatments, although others define any dose of CDDP-including regimens as HEC (Aogi et al. 2021; Hesketh et al. 2017; NCCN Clinical Practice Guidelines in Oncology 2021; Roila et al. 2015). The incidence of all-grade nausea in this regimen is reported to be 36.8%, including 0.6%–4.0% for grade 3/4 symptoms, 12.3% for vomiting, and 40.9% for anorexia (Morizane et al. 2019; Valle et al. 2010), which is consistent with MEC classification. A combination of serotonin (5-hydroxytryptamine; $5HT_3$) receptor antagonists ($5HT_3RA$) and dexamethasone (DEX) is recommended as CINV prophylaxis in MEC regimens (Aogi et al. 2021; Hesketh et al. 2017; NCCN Clinical Practice Guidelines in Oncology 2021; Roila et al. 2015). In addition, palonosetron is superior to first-generation $5HT_3RA$ (Popovic 2014), and DEX administration on days 2 and 3 can be spared when $5HT_3RA$ is palonosetron (Aogi et al. 2021; Komatsu et al. 2015).

Gastroesophageal reflux disease (GERD) is highly prevalent among the elderly (Achem and DeVault 2014), and peptic ulcers and diffuse erosive gastritis are not uncommon among cancer patients who are under severe mental stress (Keynes 1994). Thus, cancer patients frequently use acid suppressants (AS) such as proton pump inhibitors (PPI), potassium-competitive acid blockers (P-Cab), and histamine type-2 receptor antagonists (H_2RA) for palliation of GERD, dyspepsia, or gastritis, which are associated with their malignancy and/or anticancer therapy (Budha et al. 2012). Smelick et al. (2013) suggested that approximately 40%–70% of digestive organ cancer patients use AS. AS are

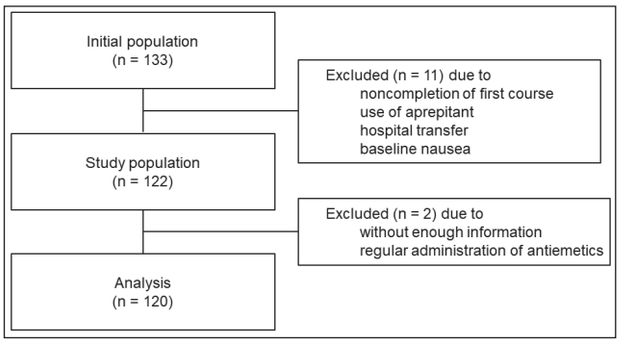

Fig. 1: Flow diagram of the cohort and exclusions in this study.

suggested as an additional option for CINV management in several antiemetic guidelines (Aogi et al. 2021; NCCN Clinical Practice Guidelines in Oncology 2021), although there are no reports evaluating their preventive efficacy in CINV cases. AS are convenient medicines as they are inexpensive and safe; if they are effective for CINV prevention, they could represent an evidence-based option in CINV management. This study first aimed to determine whether AS administration affects the incidence of CINV in CDDP + GEM treatment.

2. Investigations and results

2.1. Patient characteristics

A total of 120 patients were enrolled in this study (Fig. 1). Baseline patient characteristics are shown in Table 1. The median age was 69 years, and 61.7% were male. The proportion of patients with liver (grade 2 or higher aspartate aminotransferase, alanine aminotransferase, and total bilirubin elevation) or renal dysfunction (grade 1 or higher serum creatinine elevation) was 14.2% and 10.0%, respectively. Patients with regular administration of narcotics and AS (PPI, P-cab, and H_2RA), and regular alcohol intake (≥5 days per week) comprised 4.2%, 57.5%, and 43.3%, respectively. Patients administered with PPI, P-cab, and H_2RA accounted for 66.7%, 20.3%, and 13.0%, respectively. None of the patients reported bowel obstruction, vestibulopathy, brain metastasis, clinically significant electrolyte abnormality, uremia, gastric atony, and/or mental disorders.

Table 1: Patient characteristics

Sex (male/female)	74/46
Age (years) (median, range)	69 (31–84)
Performance status	
0 or 1	118
2	2
Body surface area (m^2) (median, range)	1.59 (1.21–2.13)
Prior treatment	26
Location of primary tumor	
Hepatic portal region	42
Gallbladder	27
Intrahepatic biliary tract	22
Distal bile duct	16
Duodenal papilla	3
Broad biliary tract	3
Others	7
Alcohol intake (≥5 days a week)	52
Smoking history (current and former)	73
Liver dysfunction	17
Renal dysfunction	12
Serum albumin (g/dL) (median, range)	3.8 (1.9–4.7)
Regular administration of narcotics	5
Regular administration of acid suppressants	69
Proton pump inhibitors	46
Potassium-competitive acid blocker	14
Histamine type 2 receptor antagonists	9
Dose reduction from initiation	20

Liver dysfunction: grade 2 or higher aspartate aminotransferase, alanine aminotransferase, and total bilirubin elevation
Renal dysfunction: grade 1 or higher serum creatinine elevation

2.2. Assessment of gastrointestinal symptoms

The incidence and severity of the gastrointestinal symptoms are shown in Table 2. Nausea occurred in 34.2% of the patients, all of whom experienced nausea only in the delayed phase (days 2–7). The severity was grade 1 (31.7%) and grade 2 (2.5%). Patients with vomiting, anorexia, and constipation accounted for 4.2%, 39.1%, and 65.0% of study patients, respectively. None of the patients experienced grade 3/4 symptoms. The incidence of nausea, vomiting, and anorexia between patients with and without AS administration was not statistically different (Table 3).

Table 2: Assessment of gastrointestinal symptoms

	Incidence (n, %)
Nausea	
Timing of appearance	
Acute phase (day 1)	0
Delayed phase (days 2–7)	41 (34.2%)
All evaluation periods	41 (34.2%)
Severity	
Grade 1	38 (31.7%)
Grade 2	3 (2.5%)
Vomiting	
Grade 1	5 (4.2%)
Anorexia	
Grade 1	43 (35.8%)
Grade 2	4 (3.3%)
Constipation	
Grade 1	75 (62.5%)
Grade 2	3 (2.5%)

Table 3: Incidence of nausea, vomiting, and anorexia in patients with and without AS administration

	Non-AS administered patients (n=51)	AS administered patients (n=69)	*P*-value
Nausea	16 (31.4%)	25 (36.2%)	0.70
Vomiting	0 (0%)	5 (7.3%)	0.07
Anorexia	18 (35.3%)	29 (42.0%)	0.57

AS; acid suppressants
AS include proton pump inhibitors (PPI), potassium-competitive acid blockers (P-Cab), and histamine type-2 receptor antagonists (H_2RA).
Number of the patients (% in the drug category) prescribed
PPI (n=46): esomeprazole 20 mg once a day; 15 (32.6%), rabeprazole 10 mg once a day; 15 (32.6%), lansoprazole 15 mg once a day; 13 (28.3%), rabeprazole 10 mg twice a day; 2 (4.3%), lansoprazole 30 mg once a day; 1 (2.2%).
P-cab (n=14): vonoprazan 10 mg once a day; 11 (78.6%), vonoprazan 20 mg once a day; 3 (21.4%).
H_2RA (n=9): famotidine 20 mg twice a day; 5 (55.6%), famotidine 20 mg once a day; 2 (22.2%), famotidine 10 mg once a day; 1 (11.1%), ranitidine 150 mg twice a day; 1 (11.1%).

2.3. Risk analysis for CINV incidence

Multivariate analysis suggested that female sex was an independent risk factor for nausea incidence (Table 4A), and non-or less-alcohol drinking habits (<5 days within a week) and regular narcotics administration were identified as factors for anorexia incidence (Table 4B). In contrast, AS administration was not associated with nausea and anorexia incidence (adjusted odds ratio, 95% confidence interval: 1.39, 0.62–3.13; *P*=0.43 for nausea, 1.57, 0.69–3.59; *P*=0.28 for anorexia).

3. Discussion

As chemotherapy in digestive organ cancers is usually conducted in outpatient settings, it is important to manage CINV to provide less onerous and safer treatment. Assessment of factors associated with CINV development can contribute to better CINV management, such as strengthening prevention and early intervention. AS have fewer adverse effects and are less expensive than aprepitant and DEX, and are recommended as a management option for gastrointestinal symptoms in cancer treatment (Aogi et al. 2021; NCCN Clinical Practice Guidelines in Oncology 2021; Talley et al. 1998). In this study, we first evaluated whether AS administration affected the incidence of CINV in the CDDP + GEM regimen using logistic analysis.

As a result, 34.2% of participating patients experienced nausea, and the incidence rates of vomiting and anorexia were 4.2% and

Table 4: Univariate and multivariate analyses for risk factors associated with frequency of (A) nausea and (B) anorexia in the first cycle

(A)	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Sex Female/Male	3.66 (1.66–8.08)	0.001**	3.34 (1.40–7.95)	0.007**
Age (years) <55/≥55	2.09 (0.63–6.93)	0.23	Excluded	-
Performance status 0 or 1/2	0.51 (0.03–8.42)	0.64	Excluded	-
Alcohol intake (≥5 days a week) Present/Absent	0.48 (0.22–1.05)	0.07	0.75 (0.31–1.83)	0.53
Smoking history Current or former/Never	0.86 (0.40–1.87)	0.71	Excluded	-
Liver dysfunction Present/Absent	1.42 (0.50–4.06)	0.51	Excluded	-
Renal dysfunction Present/Absent	0.35 (0.07–1.70)	0.19	Excluded	-
Serum albumin (g/dL) ≤3.5/>3.5	1.21 (0.49–2.95)	0.68	Excluded	-
Regular administration of narcotics Present/Absent	1.32 (0.21–8.21)	0.77	Excluded	-
Regular administration of AS Present/Absent	1.24 (0.58–2.68)	0.58	1.39 (0.62–3.13)	0.43
Dose reduction from the initiation Present/Absent	0.59 (0.20–1.76)	0.35	Excluded	-

*P<0.05, **P<0.01
CI; confidence interval, AS; acid suppressants
AS include proton pump inhibitors (PPI), potassium-competitive acid blockers (P-Cab), and histamine type-2 receptor antagonists (H_2RA).
Liver dysfunction: grade 2 or higher aspartate aminotransferase, alanine aminotransferase, and total bilirubin levels
Renal dysfunction: grade 1 or higher serum creatinine elevation

(B)	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Sex Female/Male	2.81 (1.31–6.05)	0.008**	2.18 (0.91–5.20)	0.08
Age (years) <55/≥55	1.63 (0.49–5.41)	0.42	Excluded	-
Performance status 0 or 1/2	0.64 (0.04–10.47)	0.75	Excluded	-
Alcohol intake (≥5 days a week) Present/Absent	0.28 (0.13–0.63)	0.002**	0.32 (0.13–0.79)	0.01*
Smoking history Current or former/Never	0.79 (0.37–1.67)	0.54	Excluded	-
Liver dysfunction Present/Absent	1.10 (0.39–3.13)	0.85	Excluded	-
Renal dysfunction Present/Absent	0.28 (0.06–1.34)	0.11	Excluded	-
Serum albumin (g/dL) ≤3.5/>3.5	1.97 (0.79–4.91)	0.15	Excluded	-
Regular administration of narcotics Present/Absent	6.76 (0.73–62.50)	0.09	12.38 (1.19–128.99)	0.04*
Regular administration of AS Present/Absent	1.33 (0.63–2.81)	0.46	1.57 (0.69–3.59)	0.28
Dose reduction from initiation Present/Absent	0.46 (0.16–1.37)	0.16	Excluded	-

*P<0.05, **P<0.01
CI; confidence interval, AS; acid suppressants
AS include proton pump inhibitors (PPI), potassium-competitive acid blockers (P-Cab), and histamine type-2 receptor antagonists (H_2RA).
Liver dysfunction: grade 2 or higher aspartate aminotransferase, alanine aminotransferase, and total bilirubin levels
Renal dysfunction: grade 1 or higher serum creatinine elevation

39.1%, respectively, which were similar to previous reports (Morizane et al. 2019; Valle et al. 2010). Grade 2 nausea occurred in only 2.5% of patients, and there were no cases with grade 3/4 nausea.

In logistic multivariate analysis, AS co-administration was not suggested to affect the incidence of nausea and anorexia. In addition, there were 13 patients with AS administration from treatment initiation for CINV prophylaxis; the incidence of nausea was 46.2% in these patients, 31.4% in those without AS administration, and 33.9% in those who were already prescribed AS prior to treatment initiation, which was not statistically different (P=0.58, Fig. 2). Similar results were obtained for anorexia (data not shown). Since PPI are favored because of higher potency and longer duration of action (Sontag 1990), we additionally compared the incidence of nausea in patients administered PPI, P-cab, and H_2RA, resulting in 34.8%, 42.9%, and 33.3%, respectively, without difference (P=0.88, Fig. 3). Similar results were obtained for anorexia (data not shown). In addition, AS administration did not affect the incidence of nausea in female patients, who were suggested to be at risk in this study (data not shown). In Japanese antiemetic guidelines, AS administration is recommended for acute nausea management (Aogi et al. 2021), and Tamura et al. (2015) reported that MEC regimens induce 6.7% of acute nausea. However, there were no patients experiencing it in this study, regardless of AS administration. Hence, we can speculate that AS is not suitable for CINV prevention.

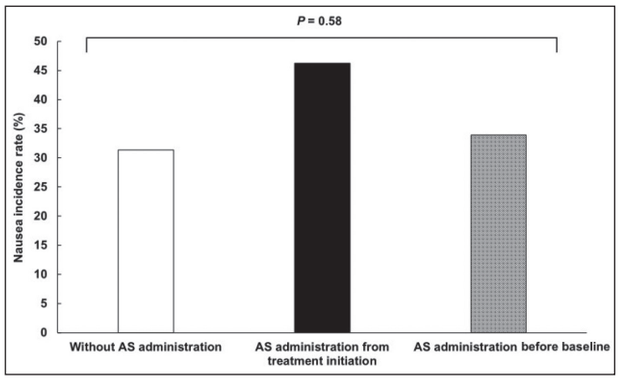

Fig. 2: Incidence of nausea in patients without acid suppressant (AS) administration, with AS administration from treatment initiation, and AS administration before baseline.

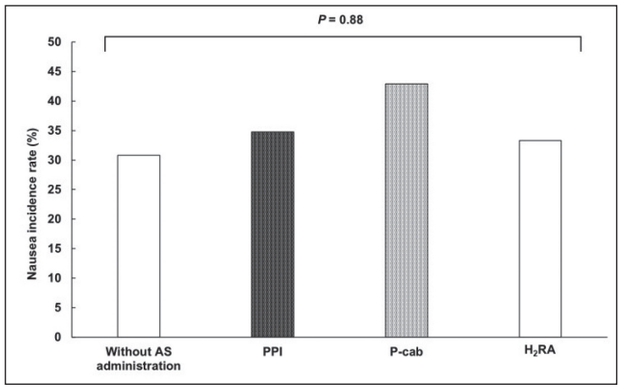

Fig. 3: Incidence of nausea in patients without acid suppressant administration, with proton pump inhibitors, potassium-competitive acid blocker, and histamine type-2 receptor antagonists. AS; acid suppressants, PPI; proton pump inhibitors, P-cab; potassium-competitive acid blocker, H2RA; histamine type-2 receptor antagonists

Number of the patients (% in the drug category) prescribed PPI (n=46): esomeprazole 20 mg once a day; 15 (32.6%), rabeprazole 10 mg once a day; 15 (32.6%), lansoprazole 15 mg once a day; 13 (28.3%), rabeprazole 10 mg twice a day; 2 (4.3%), lansoprazole 30 mg once a day; 1 (2.2%). P-cab (n=14): vonoprazan 10 mg once a day; 11 (78.6%), vonoprazan 20 mg once a day; 3 (21.4%). H2RA (n=9): famotidine 20 mg twice a day; 5 (55.6%), famotidine 20 mg once a day; 2 (22.2%), famotidine 10 mg once a day; 1 (11.1%), ranitidine 150 mg twice a day; 1 (11.1%).

In contrast, there is no definitive evidence for the differentiation between CINV and anorexia, pyrosis, and dyspepsia as multiple factors are related, and these symptoms are closely associated (Aogi et al. 2021). We consider that AS are effective for gastrointestinal symptoms due to chemotherapy-induced cumulative damage, mental stress, and non-steroidal anti-inflammatory drugs (NSAIDs) administration. The administration of AS before CDDP + GEM induction had multiple purposes—NSAID ulcer prevention (50.0%), gastrointestinal symptom prevention after cancer operation (28.6%), and symptom prevention after diagnosis (7.1%), and nausea management in prior treatment (3.6%)—suggesting that AS were frequently used for the prevention of gastrointestinal problems. Appropriate monitoring and medication depending on the patient's symptoms, especially considering AS administration for persistent gastrointestinal symptoms as well as prophylaxis for NSAIDs- or steroid-induced gastric damage, can contribute to successful gastrointestinal disorder management throughout cancer treatment.

Treatment and patient factors have been suggested to impact CINV risk (Aogi et al. 2021). Patient-related factors include age, sex, drinking habits, and experience of nausea gravidarum (Aogi et al. 2021; Tamura et al. 2015; Warr 2014). In addition, bowel obstruction, vestibulopathy, brain metastasis, electrolyte abnormality, uremia, opioid use, gastric atony, and mental disorders are also suggested as potential risk factors (NCCN Clinical Practice Guidelines in Oncology 2021). In this study, risk factors for all-grade nausea were detected in female patients. In addition, no- or less-alcohol drinking habits and regular narcotic use were identified as factors associated with all-grade anorexia although patients regularly consuming narcotics were fewer in number, and therefore, careful interpretation of its clinical significance is essential. There are a small number of reports evaluating CINV risks in MEC regimens in the real world; the results obtained in this study were consistent with previously reported factors (Aogi et al. 2021; NCCN Clinical Practice Guidelines in Oncology 2021; Tamura et al. 2015; Warr 2014). We should cautiously monitor and enhance prophylactic antiemetics and/or counter-measure medicines for breakthrough symptoms in patients with risk factors.

This study had certain limitations. First, the study was retrospectively performed at a single institution with a relatively small patient population. We calculated the number of patients to assess whether AS administration can be a preventive factor for nausea incidence by multivariate analysis as there were fewer patients for comparative study. Therefore, a comparative study considering the results of this study is needed. Second, we adopted a physician- or pharmacist-based assessment by referring to a treatment diary, which almost all patients maintained, and patient complaints. As symptoms assessment in CINV by medical personnel differs from that performed by patients (Majem et al. 2011; Tamura et al. 2015), the severity may not have been accurately assessed. Third, we evaluated CINV during the first administration. As described previously, gastrointestinal symptoms can occur due to cumulative damage due to chemotherapy, mental stress, and NSAIDs administration. Therefore, assessments involving longer evaluation periods may provide further insights although long-term evaluations include other confounders such as chemotherapeutic dose reduction, disease progression, and concomitant medication during the treatment. Fourth, we did not assess the cytochrome P450 2C19 polymorphism, which affects PPI efficacy (El Rouby et al. 2018). In addition, we were not able to assess the patients' history of motion sickness and morning sickness with pregnancy, which may have affected the results. Evaluation with sufficient information concerning patient's genetic background and risk factors will result in better outcomes. Fifth, we evaluated CINV in CDDP + GEM for biliary tract cancer as we had enough patients with AS administration. Evaluation of other emetogenic risk regimens is necessary. Finally, approximately 80% of AS patients were dosed with AS prior to treatment initiation although the major purpose for their administration was to prevent gastrointestinal symptoms. We consider that the baseline patients' digestive symptoms were well-controlled in this study owing to the exclusion criteria

adopted. In addition, we combined PPI, P-cab, and H_2RA to AS as written in the guidelines (Aogi et al. 2021; NCCN Clinical Practice Guidelines in Oncology 2021). Consequently, comparative evaluation using patients administered each drug category from treatment initiation alone will offer more precise outcomes, although there were no significant differences identified in this study.

In conclusion, we found that baseline AS administration was not associated with CINV prevention, and female sex was a risk factor for all-grade nausea, and no- or less-alcohol drinking habits and regular narcotic use were factors associated with all-grade anorexia in CDDP + GEM treatment for biliary tract cancer. We should correctly administer AS depending on the patient's situation. Successful CINV management needs effective monitoring and administration of prophylactic antiemetics and counter-measure medicines for patients at risk.

Further studies are needed to construct appropriate AS administration strategies for cancer patients.

4. Experimental

4.1. Patients

Patients with biliary tract cancer who received CDDP + GEM between November 2015 and May 2021 at Hokkaido University Hospital were retrospectively evaluated. All patients met the following baseline criteria: (1) age ≥20 years, (2) 0 to 2 Eastern Cooperative Oncology Group performance status (ECOG-PS), and (3) sufficient renal or liver function for chemotherapy induction. Patients who had baseline gastrointestinal symptoms including nausea or clinically problematic anorexia, were transferred to another hospital during the first cycle; patients who were not able to complete the first cycle, were regularly dosed with antiemetics such as metoclopramide, prochlorperazine, domperidone, and olanzapine, and corticosteroids at baseline, were administered prophylaxis other than that recommended in the guidelines (Aogi et al. 2021), and patients lacking sufficient information were excluded. The present study was approved by the Ethical Review Board for Life Science and Medical Research of the Hokkaido University Hospital (approval number: 021-0097), and was performed in accordance with the Declaration of Helsinki and STROBE statement. In view of the retrospective nature of the study, informed consent from participating subjects was not necessary.

4.2. Treatment methods

CDDP (25 mg/m^2) and GEM (1000 mg/m^2) were intravenously administered on days 1 and 8, every three weeks (Valle et al. 2010). All patients were administered 0.75 mg palonosetron and 9.9 mg DEX intravenously on day 1 as prophylaxis. Metoclopramide (5 mg), prochlorperazine (5 mg), and domperidone (10 mg) were administered as rescue doses, depending on the physician's discretion.

4.3. Evaluation of CINV

All required information was obtained from patient medical records. We strongly recommended that all patients maintain their daily diary. Adverse effects were assessed by referring to the diary and the patient complaints. Gastrointestinal toxicities were evaluated according to the Common Terminology Criteria for Adverse Events, version 5.0, by physicians or pharmacists.

The primary endpoint was to evaluate whether AS administration was associated with all-grade nausea incidence in the first administration by logistic analysis. The secondary endpoint was the assessment of correlation between AS administration and anorexia incidence. We also compared the incidence of these symptoms between specific patient groups with respect to AS administration.

4.4. Statistical analysis

We calculated the number of patients as 120, as all-grade nausea occurred in approximately 30% of cases (Valle et al. 2010); we tried to include approximately three covariates in the multivariate analysis.

In univariate and multivariate logistic analyses, potential baseline risk factors included sex, age, PS, regular alcohol intake, smoking history, liver dysfunction, renal dysfunction, serum albumin levels, regular administration of narcotics and AS, and dose reduction from the treatment initiation by referring to previous reports (Aogi et al. 2021; NCCN Clinical Practice Guidelines in Oncology 2021; Saito et al. 2021; Sekine et al. 2013). Variables that were potentially associated with the incidence of nausea and anorexia, as suggested by univariate logistic regression analysis (P<0.10) and AS co-administration, were considered when building the multivariable model. The incidence of nausea and anorexia in specific patient groups was compared using Fisher's exact probability test. All analyses were performed using JMP version 14.0 statistical software (SAS Institute Japan, Tokyo, Japan). Differences were considered statistically significant when P values <0.05.

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Ethics approval and consent to participate: All procedures performed in this study were carried out in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent was not required. The study was approved by the Ethical Review Board for Life Science and Medical Research of the Hokkaido University Hospital (approval number: 021-0097).

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

Authors' contributions: Designed the study: Y.S., performed the research: Y.S., analyzed the data: Y.S., contributed new methods or models: Y.S., wrote the paper: Y.S., Y.T. All authors have read and approved the final manuscript.

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