Title: Intergenerational comparison of 5-HT_3RA in the prevention of chemotherapy-induced nausea and vomiting in gastric cancer patients receiving cisplatin-based chemotherapy: an observational study using a Japanese administrative claims database

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Abstract

Purpose

In chemotherapy-induced nausea and vomiting (CINV), the superiority of the second-generation 5-hydroxytryptamine-3 receptor antagonist (5-HT_3RA) over the first-generation 5-HT_3RA is shown in the delayed emesis in cycle 1. We evaluate the antiemetic efficacy in real-world clinical practice that has not been sufficiently investigated in clinical trials.

Methods

We included patients who were diagnosed with gastric cancer between April 2012 and June 2017 from the medical claims databases and were treated with cisplatin (≥50 mg/m^2) and standard antiemetic therapy (5-HT3 + neurokinin-1 receptor antagonist [NK1RA] + dexamethasone). We compared the second-generation 5-HT_3RA (2^{nd} group) and the first-generation 5-HT_3RA (1^{st} group) groups to evaluate the additional antiemetic drug as the CINV event.

Results

In total, 3,798 patients were extracted; 1,440 and 2,358 patients were included in the 1^{st} and 2^{nd} groups, respectively. The clinical and demographic characteristics did not differ between the groups. In the overall (Days 1-6) in cycle 1, 51.7% and 44.3% of patients in the 1^{st} and 2^{nd} groups, respectively, had a CINV event. In the acute phase (Days 1-2), 38.7% and 30.2% and in the delayed phase (Days 3-6), 35.8% and 32.1% of patients in the 1^{st} and 2^{nd} groups, respectively, had a CINV event. Furthermore, the CINV event trend was the same as in cycles 1 to 5.

Conclusion

The proportion of CINV events in the 2^{nd} group was smaller than that in the 1^{st} group at any cycle. These findings may suggest consistent antiemetic efficacy of second-generation 5-HT_3RA throughout the cycle.

Keywords: Supportive care, Chemotherapy-Induced Nausea and Vomiting, 5-hydroxytryptamine-3 receptor antagonist, Database, gastric cancer, cisplatin

Introduction

Chemotherapy-induced nausea and vomiting (CINV) induces poor chemotherapy compliance and poor patient quality of life [1-2]. New antiemetics have significantly improved CINV, but CINV remains a critical adverse event associated with chemotherapy [3].

Patients receiving highly emetogenic chemotherapy (HEC) will have more than 90% of the risk of vomiting without antiemetics [4]. HEC includes anticancer drugs such as cisplatin, dacarbazine, and anthracycline, as well as cyclophosphamide regimens. CINV is classified into three types according to the time of CINV expression. Acute emesis is observed within 24 hours after the initiation of chemotherapy, delayed emesis is observed after 24 hours following chemotherapy, and anticipatory emesis is observed before chemotherapy in patients who have experienced significant CINV during previous chemotherapy. Delayed emesis often occurs after the patient is discharged from the hospital, which causes underestimation of CINV for the healthcare providers and inadequate control of CINV for the patient [5].

The purpose of antiemetic therapy is complete prevention of CINV. For HEC, the triplet combination of 5-hydroxytryptamine-3 receptor antagonist (5-HT_3RA) + neurokinin-1 receptor antagonist (NK1RA) + dexamethasone (DEX) is the standard antiemetic therapy specified in the guidelines [6-8]. If CINV occurs even after administration of these antiemetics, additional antiemetic with different mechanisms, dopamine receptor antagonists, benzodiazepine anxiolytics, and multi-receptor antipsychotics will be administered.

Among the antiemetic agents, 5-HT_3RAs consist of first-generation 5-HT_3RA (azasetron, granisetron, indisetron, ondansetron, dolasetron, ramosetron, and tropisetron) and second-generation 5-HT_3RA (palonosetron). In the phase III trial that investigated the differences between 5-HT_3RA generations, the second-generation 5-HT_3RA showed a better antiemetic effect in the delayed emesis for patients receiving HEC for the first time [9]. However, in almost all clinical trials, the antiemetic effect was evaluated only during the first cycle, but the continuity of HEC was not evaluated. In real-world clinical practice, HEC is repeatedly administered to the patient until the therapeutic goal is obtained. Additionally, for the second and subsequent HECs, the suppression of CINV would become more difficult due to anticipatory emesis [10]. Therefore, the effect of the second-generation 5-HT_3RA on the first-generation 5-HT_3RA for HEC repeatedly administered under clinical practice has not been sufficiently investigated.

In Japan, patients with advanced or recurrent gastric cancer are treated with cisplatin-based regimens as first-line chemotherapy [11]. The most common regimen is the fluoropyrimidine anticancer drug (tegafur, gimeracil, oteracil potassium (S-1), or capecitabine) + cisplatin; if the human EGFR-related 2 (HER2) is positive, trastuzumab is also used. Although cisplatin is effective for the treatment of gastric cancer, control of CINV caused by cisplatin is important for maintaining compliance.

The aim of this study was to evaluate the real world effectiveness of second-generation 5-HT_3RA compared with first-generation 5-HT_3RA for CINV caused by the repeatedly administered cisplatin-based regimen in clinical practice in patients with gastric cancer. Efficacy was assessed using the medical claims database with additional antiemetics as the frequency of CINV events. In order to evaluate the continuity

of HEC, we also evaluated the cisplatin administration status by cycle.

Method

Data source

This was a retrospective nationwide cohort study in Japan in which the medical claims database provided by the Medical Data Vision Co.,Ltd. (MDV; Tokyo, Japan) was used. This database was derived from acute care hospitals under the Japanese Diagnosis and Procedure Combination (DPC) system. As of June 2017, it contained approximately 20 million patients, which included 162 designated cancer care hospitals (approximately 40% of all such hospitals in Japan) and included 307 acute care hospitals (approximately 18%). This database contained information on sex, age, diagnosis (International Classification of Diseases [ICD]-10 code), prescription information (date, dose, frequency), height, weight, and smoking status. Several studies using this database in oncology have been reported [12, 13].

Study cohort

The study cohort was identified based on the diagnosis and prescription of drugs. The initial administration of cisplatin defined the index date (Day1). Eligibility criteria included patients with gastric cancer (ICD-10 code C16) from April 2012 to June 2017, who received anticancer drugs (fluoropyrimidine (S-1 or capecitabine)(Day-59 - Day60) and cisplatin ($\geq$50 mg/m^2)(Day1)), in addition to the triplet combination antiemetics (5-HT$_3$RA (1st first-generation 5-HT3RA or 2nd generation 5-HT3RA), NK1RA, and DEX)(Day1).

The exclusion criteria were as follows: less than 20 years of age; the combined use of radiation therapy; a medical history of nausea, vomiting, dehydration , or mental illness from Day -29 - Day0; the use of antiemetic drugs; cases with death from Day 1-5; and cisplatin over use.

Based on the generation of 5-HT$_3$RA used at the first cisplatin administration (cycle 1), the groups were divided into first-generation (1st group) and second-generation (2nd group) 5-HT$_3$RA groups.

Cisplatin administration was excluded from the analysis if it was administered more than 1 year after the first dose or if the interval between doses of cisplatin exceeded 90 days in order to evaluate a series of treatments. Moreover, the cisplatin was administered up to five times in order to evaluate the CINV events.

With the exception of dolasetron, all first-generation 5-HT$_3$RA s were approved in Japan before 2004. The approvals for aprepitant (NK1RA), fosaprepitant (NK1RA), and palonosetron (second-generation 5-HT$_3$RA) were in 2009, 2011, and 2010, respectively. Olanzapine's insurance coverage for CINV was after June 2017.

Outcome measures

The outcome of CINV events was defined as the additional antiemetic drug administered from Day 1 to Day 6 in each cycle. The proportion of CINV events was evaluated by cycle (cisplatin administered every

time) for up to five cycles and it was also evaluated daily. Patients who discontinued cisplatin were excluded from the analysis of the cycle. The use of additional antiemetic drugs was evaluated according to the antiemetic guidelines [7]. The acute, delayed, and overall phase events were defined as Days 1-2, Days 3-6, and Days 1-6, respectively.

Statistical analysis

Mean and standard deviation (SD) were calculated for continuous variables, and numbers and proportions were calculated for categorical data. Fisher's exact test was used for comparisons between proportions, and the Wilcoxon rank-sum test was used for comparisons between continuous variables.

Primary analysis was performed by calculating the risk difference in the CINV events. The proportion of CINV events was determined for each cycle based on grouping. An unadjusted risk difference and a Cochran-Mantel-Haenszel (CMH) adjusted risk difference by patient risk factors (sex, smoking history, and age [≥60 years or <60 years]) with 95% confidence intervals (CI) were calculated for the acute, delayed, and overall phases. Subgroup analyses (patient risk factors, cisplatin dose [≥70 mg/m^2 or <70 mg/m^2], and NK1RA [aprepitant or fosaprepitant]) were conducted to investigate the consistency of the effect by calculating the unadjusted risk difference. The period until the first CINV event in cycle 1 was described using the Kaplan-Meier method and estimate the median and 95% CI. The log-rank test was used to compare the groups. The time course of the CINV events by the day period in cycle 1 was analyzed.

Three sensitivity analyses were conducted to evaluate the robustness of the proportion of CINV events by cycle. First, a comparison was conducted for the generation of 5-HT$_3$RA actually used for each cycle as that may have changed between cycles in this study. Therefore, we evaluated the efficacy of 5-HT$_3$RA in each cycle as a sensitivity analysis. Second, we also analyzed the group using propensity score (PS) matching based on patient risk factors and cisplatin dose per body surface area (BSA) using 1:1 matching and a caliper width of 0.2 SD with the greedy nearest neighbor matching method. Third, we conducted inverse probability of treatment weighting(IPTW) with average treatment effect(ATE) weighting using PS.

Two sided p-values less than 0.05 were considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics

This study was approved by the Ethics Committee of the Graduate School and Faculty of Medicine, Kyoto University (approval number: R1893, February 20, 2019). The study was performed according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects by the Ministry of Health, Labor and Welfare. The need for informed consent was exempted since anonymized data were used.

Results

Overall, 5,417 patients were extracted from the database according to the eligibility criteria; 1,619 patients were excluded according to the exclusion criteria, thus, 3,798 patients were included in the analysis (Fig.1). The primary reasons for exclusion were prior antiemetic drug use (n=1,075) and the patient's medical history (n=899). Among the eligible patients, 1,440 and 2,358 patients were included the 1st and 2nd groups, respectively. Patient demographics are shown in Table 1. The patient risk factors (sex, smoking history, age) and the dose of cisplatin per BSA in cycle one did not significantly differ between the groups.

The use of antiemetic drugs, concomitant anticancer agents, and opioids are shown in Supplementary Table 1. In the 1st group, 1,311 (91.0%) patients received granisetron, followed by 96 (6.7%) and 58 (4.0%) of patients who received ramosetron and azasetron, respectively. In the 2nd group, all patients received palonosetron. In the 1st group, 1,242 (86.3%) and 199 (13.8%) patients received aprepitant and fosaprepitant, respectively. In the 2nd group, 1,760 (74.6%) and 602 (25.5%) patients received aprepitant and fosaprepitant, respectively. In the 1st group, 100%, 79.3%, 72.6%, 35.0%, and 9.3% patients received DEX on Day 1, 2, 3, 4, and 5, respectively. In the 2nd group, 100%, 77.7%, 70.4%, 35.2%, and 6.1% patients received DEX on Day 1, 2, 3, 4, and 5, respectively. Among other concomitant anticancer drugs, 238 (16.5%) and 35 (2.4%) patients received trastuzumab and docetaxel in the 1st group, respectively. Additionally, 375 (15.9%) and 101 (4.3%) patients received trastuzumab and docetaxel in the 2nd group, respectively.

Outcome

Table 2 shows a summary of the CINV events. The risk difference in cycle 1 was -7.39% (95% CI -10.66 to -4.12), -8.49% (-11.61 to -5.36), and -3.66% (-6.77 to -0.55) for the overall, acute, and delayed phases. There were significantly fewer events in the 2nd group for cycle 1. There was a similar trend for the overall phase and acute phase events from cycles 2- 5. However, the delayed phase events did not significantly differ between the groups, with the exception of cycle 1. The CMH-adjusted risk difference showed the same tendency. In the sensitivity analyses, the same tendency was observed in the PS-matched group (Supplementary Tables 2 and 3) and the IPTW analyses (Table 2). The analysis of the actually administered 5-HT_3RA taking into consideration the switch of generation was shown in Supplementary Table 4. In the subgroup analysis in cycle 1, the 2nd group showed consistently good trends in the most baseline characteristics (~~Supplementary~~ Table ~~5~~3). The additional antiemetic drugs used in cycle 1 are shown in Supplementary Table ~~6~~5.

The time-to-first-CINV event was significantly longer in the 2nd group than in the 1st group ($p<0.0001$) (Fig.2). The median time was 6 days (95% CI 5 to not to be estimated) in the 1st group and more than 6 days (95% CI could not be estimated) in the 2nd group. The proportion of patients with CINV events was higher in the 1st group than in the 2nd group at Day 1 and slightly higher at Day3-4 (Fig.3).

The treatment status of cisplatin and the proportion of patients who had their 5-HT_3RA switched for each cycle are shown in Supplementary Table 6~~Table 3~~. The median number of cycles in each group was three; 514 (35.7%) and 857 (36.3%) patients in the 1st and 2nd groups were able to receive cisplatin for 5 cycles.

There was no significant difference in the treatment status of cisplatin between the groups. After cycle 2, more than 5% of the patients in the 1st group were switched to the 2nd generation 5-HT_3RA.

Discussion

In this study, we investigated the intergenerational comparison of 5-HT_3RA with NK1RA and DEX using an administrative database. We found that cisplatin-induced CINV events in the acute and overall phases were significantly lower in the 2nd group than in the 1st group from cycles 1-5 in real-world clinical practice. The consistent efficacy in the sensitivity analyses indicated the robustness of the efficacy in the 2nd group over the 1st group. Furthermore, 2nd group also showed effectiveness in the time-to-first-CINV event. Conversely, the administration status of cisplatin did not differ between the groups, and the treatment intensity in the next cycle did not change even if the frequency of CINV events decreased.

We observed more substantial differences in the acute phase, with an 8.49% improvement compared to the delayed phase, with a 3.66% improvement in cycle 1. These findings differed from those used in clinical trials, one of which evaluated the three-drug combination (5-HT_3RA + NK1RA + DEX) in HEC. That study found a complete response (CR) proportion for the acute and delayed phase improvement between the second-generation 5-HT_3RA and first-generation 5-HT_3RA were reported to be approximately 0% and 8%, respectively [9]. The following differences may have caused this discrepancy. First, we could not obtain an accurate prescription time from the database. The definitions for the acute (0-24 hours) and delayed (24-120 hours) phases in clinical trials could not be accurately distinguished in this study; we used days 1-2 and 3-6 for the acute and delayed phases. Second, a CINV event in this study was defined as the use of only an additional antiemetic drug, which differs from that used in clinical trials. In clinical trials, the CR criteria have been defined as no use of rescue therapy (additional antiemetic drugs) and no vomiting. The validity of the CINV definition in this study has not been examined.

Additionally, unlike clinical trials, the actual administration of an additional antiemetic drug was not clear in real-world clinical practice. The use of rescue medication on Days 1 and 5 have been reported to be approximately 8% and 20%, respectively, in clinical trials; however, they were approximately 20% and 10% in this study [14]. This difference was probably due to prophylactic administration, which might reduce the difference in the delayed phase and increase the difference in the acute phase in this study. ~~But~~However the effectiveness of the 2nd group was observed at Day3-4 in the time course of CINV events. This may be due to the suppressing the peak of delayed emesis by the 2nd group.

The proportion of CINV events up to 5 cycles tended to decrease in both groups, but the differences between groups were consistent. This trend was also consistent with the results previously reported in clinical trials [15]. Patients who received cisplatin multiple times are considered to be in a relatively good condition in which cancer has not progressed, and no serious adverse events have occurred. Therefore, the CINV events decreased with each cycle.

The 5-HT_3RA switch was often observed in the 1st group. In cycle 5, 8.2% of patients in the 1st group

were using the second-generation 5-HT_3RA, and 2.0% of patients in the 2nd group were using the first-generation 5-HT_3RA, respectively. Insufficient antiemetic effect would cause this switching of the generation of 5-HT_3RA in the 1st group more frequently. The frequency of CINV events that evaluated the switching of patients increased slightly in the 2nd group, but the overall trend did not change. HEC after cycle 2, would be more difficult to suppress CINV due to anticipatory emesis. Not causing the first CINV is important to avoid anticipatory emesis. It might have been better to use second-generation 5-HT_3RA from the beginning instead of switching after CINV occurred.

Olanzapine has recently been reported to affect CINV positively [14, 16]. Therefore, the four-drug combination is a new option for the prevention of CINV in HEC. However, the use of olanzapine was only 0.1% in this study. In almost all the study periods, olanzapine was not covered by insurance for nausea and vomiting in Japan [7]. Moreover, the guidelines in Japan ~~did~~has not been recommend the use of olanzapine yet. Therefore, we could adequately compare the CINV effect in the three-drug combination during this study period.

In this study, there was little variation in subgroups of patient risk factors between the groups. Based on the subgroup analysis, the 2nd group showed consistently good trends in most subgroups. Although the number of patients was small, the difference between groups might be small for the cisplatin dose (≥70 mg/m^2) subgroup at all phases. For this subgroup, more powerful antiemetic therapy, like adding olanzapine, may be useful.

Additionally, the percentage of NK1RA(aprepitant or fosaprepitant) usage was slightly different between the groups. But the efficacy of aprepitant and fosaprepitant for prevention of CINV have been reported to be the same [17]. And the subgroup analysis of NK1RA and other subgroups tended to be about the same trend. Therefore this difference may have little impact on the comparison of CINV efficacy.

Gastric cancer –patients were extracted from the database using the ICD-10 code and prescribed drugs in this study. The validity of the diagnosis of solid metastatic tumors in the DPC was previously reported as having a sensitivity and specificity of 58.5% and 98.5%, respectively [18]. Although the diagnosis of gastric cancer with the ICD-10 code has not been validated. The proportion of HER2-positive advanced or recurrent gastric cancer in Japan was reported to be approximately 10–20%, and the proportion of concomitant use of trastuzumab was approximately 16.1% in this study [19-21]. Other concomitant drugs (docetaxel and irinotecan) are also commonly used drugs for gastric cancer. Therefore, we believe that the patients included in this study were appropriately extracted as advanced gastric cancer—.

Comparability between groups is often a problem in non-randomized studies. However, there were no significant differences in the clinical and demographic characteristics including sex, age, smoking history, and initial dose of cisplatin, which were patient risk factors for CINV without any adjustment in this study. We cannot eliminate the impact of unmeasured– confounding factors, but we expected the comparability between the groups to be high in this study.

The two sensitivity analyses conducted using PS reduced the effect of observed confounding factors—.

Almost all the results were the same for the PS-adjusted and unadjusted analyses. This might also support the robustness of the findings regarding CINV in this study.

The administration status of cisplatin did not change between the groups. Nausea and vomiting are unpleasant adverse events for patients and are known to reduce quality of life. However, in clinical practice, the cisplatin dose reduction or modification, which is solely due to nausea and vomiting, may not have been actively conducted. The median number of treatment cycles in clinical trials was reported to be three to six; however, in this study, the median number of treatment cycles was three in both groups [22, 23]. The early discontinuation of treatment before dose adjustment may be one reason for the lack of difference between the groups. The cycle of cisplatin in this study may have been too short to evaluate the continuity of HEC.

Limitations

We were not able to obtain the patient-reported outcomes of nausea and vomiting that are acquired in clinical trials from this database. Therefore, the sensitivity of the CINV event in this study was expected to be low. In clinical trials, the most commonly reported patient-reported outcomes was nausea, followed by the administration of rescue medication, and finally vomiting [14]. Perhaps nausea first occurred, and rescue medication was administered before vomiting. Therefore, we could evaluate severe nausea, which required additional antiemetics and vomiting in this study. Due to this property, the definition of CINV event in this study was considered to have a certain level of sensitivity.

It was also difficult to distinguish the additional antiemetics needed for prophylactic administration or the treatment of nausea and vomiting. Therefore, the CINV event in this study may overestimate nausea and vomiting events. Similarly, because the prescription time could not be obtained, it was difficult to clearly distinguish the CINV events which occurred between the acute and delayed phases. However, in cycle 1, there were significant differences in the proportion of CINV events both in the acute and delayed phases, and even after cycle 2, the 2nd group had fewer CINV events than the 1st group. Therefore, second-generation 5-HT$_3$RA antiemetics would not be inferior to the first-generation 5-HT$_3$RA.

Finally, this study only evaluates the CINV event in gastric cancer patients receiving cisplatin-based chemotherapy. Therefore, different results may be obtained with other cancers and other HEC. Especially, the median number of treatment cycles of cisplatin was short in this study, so other HEC may have been suitable for assessing the continuity of HEC.

Conclusions

We investigated the effect of the second-generation 5-HT$_3$RA on the first-generation 5-HT$_3$RA for HEC in the triplet combination antiemetics repeatedly administered under clinical practice for the first time. Although we could not observe the improvement in the continuity of cisplatin administration. The observed consistent reduction of additional antiemetics would mean the prevention of CINV in the second-generation 5-HT$_3$RA and this benefit was not observed in the clinical trials. The antiemetic effect against cisplatin-

based chemotherapy in gastric cancer patients would be more effective in the second-generation 5-HT_3RA than in the first-generation 5-HT_3RA throughout the entire cycle.

Declarations

Conflict of interest /Competing interests

Y. K is an company employee of Taiho Pharmaceutical Co.,Ltd Japan. K. K received advisory fees from Shin Nippon Biomedical Laboratories, Ltd., Japan, JMDC Inc., Japan, LEBER, Inc., Japan; holds stocks of Real World Data, Co., Ltd., Japan; and research funds from Sumitomo Dainippon Pharma Co., Ltd., Japan, Pfizer Inc., Japan, Stella Pharma Corporation., Japan, Cmic Co., Ltd., Japan, Suntory Beverage & Food Limited, Japan, Medical Platform Co., Ltd, Japan, Eisai Co., Ltd., Japan, Kyowa Hakko Kirin Co., Ltd., Japan, Mitsubishi Corporation, Japan, and Real World Data, Co, Ltd, Japan. The other authors have no direct or indirect conflicts of interest.

Ethics approval:

This study was approved by the Ethics Committee of the Graduate School and Faculty of Medicine, Kyoto University (approval number: R1893, February 20, 2019) The study was performed according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects by the Ministry of Health, Labor, and Welfare.

Consent to participate:

The need for informed consent was exempted because anonymized data were used.

Consent to publish: All authors provided consent to publish this work.

Availability of data and materials: Not applicable

Code availability: Not applicable

Authors' contributions

Y. K contributed to the study conception and all authors contributed to the development and improvement of the protocol and study design. The first draft of the manuscript was written by Y. K., and all authors read and approved the final manuscript. Taiho Pharmaceutical Co., Ltd. took no part in this study,

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Table 1. The patient demographics and characteristics of gastric cancer patients receiving cisplatin-based chemotherapy (n=3,798)

	1st group (n=1,440)	2nd group (n=2,358)	*p*-value
Sex (n (%))			0.35*1
Male	1,078 (74.9)	1,798 (76.3)	
Female	362 (25.1)	560 (23.8)	
Smoking history (n (%))			0.53*1
Yes	686 (47.6)	1,151 (48.8)	
No	599 (41.6)	978 (41.5)	
Unknown	155 (10.8)	229 (9.7)	
Cancer status (n (%))			0.47*1
New-onset	1,145 (79.5)	1,909 (81.0)	
Relapse	283 (19.7)	434 (18.4)	
Unknown	12 (0.8)	15 (0.6)	
Age (mean (SD))	65.1 (9.5)	65.7 (9.3)	0.13*2
Charlson comorbidity index (mean (SD))	6.2 (3.1)	6.2 (3.2)	0.91*2
Height (cm) (mean (SD))	162.5 (8.4)	162.6 (8.4)	0.56*2
Weight (kg) (mean (SD))	56.2 (10.7)	56.4 (10.1)	0.44*2
Body surface area (m^2) (mean (SD))	1.59 (0.17)	1.59 (0.16)	0.47*2
Cisplatin dose (1cycle) (mg/m^2) (mean (SD))	61.8 (11.0)	62.0 (12.7)	0.60*2
Concomitant fluoropyrimidine anticancer drug (n (%))			0.97*1
Tegafur, Gimeracil, Oteracil Potassium	1,151 (79.9)	1,886 (80.0)	
Capecitabine	289 (20.1)	472 (20.2)	

*1: Fisher's exact test, *2: Wilcoxon rank sum test

n: number, %: percent, SD: standard deviation

Table 2. CINV event summary (acute (Days 1-2), delayed (Days 3-6), overall (Days 1-6)) with event proportion and risk difference (unadjusted, CMH, IPTW) with 95% CI up to 5 cycles (n=3,798)

	n	1st group event n (%)	n	2nd group event n (%)	Risk difference (% (95%CI))	CMH Adjusted Risk difference (% (95%CI))	IPTW Risk difference (% (95%CI))
CINV event overall (Days1-6)							
Cycle 1	1440	744 (51.7)	2358	1044 (44.3)	-7.39 (-10.66 to -4.12)	-7.40 (-10.67 to -4.14)	-7.14 (-10.41 to -3.87)
Cycle 2	1149	512 (44.6)	1922	722 (37.6)	-7.00 (-10.59 to -3.40)	-6.87 (-10.47 to -3.27)	-6.81 (-10.41 to -3.21)
Cycle 3	901	378 (42.0)	1428	494 (34.6)	-7.36 (-11.42 to -3.30)	-7.24 (-11.30 to -3.19)	-7.13 (-11.19 to -3.07)
Cycle 4	707	289 (40.9)	1139	384 (33.9)	-7.16 (-11.71 to -2.62)	-7.05 (-11.60 to -2.51)	-6.99 (-11.54 to -2.44)
Cycle 5	514	198 (38.8)	857	280 (32.7)	-5.85 (-11.10 to -0.60)	-5.66 (-10.93 to -0.40)	-5.59 (-10.84 - -0.34)
CINV event acute (Days 1-2)							
Cycle 1	1440	557 (38.7)	2358	712 (30.2)	-8.49 (-11.61 to -5.36)	-8.52 (-11.65 to -5.40)	-8.36 (-11.49 to -5.24)
Cycle 2	1149	431 (37.5)	1922	542 (28.2)	-9.31 (-12.76 to -5.86)	-9.24 (-12.69 to -5.79)	-9.17 (-12.62 to -5.73)
Cycle 3	901	317 (35.2)	1428	410 (28.7)	-6.47 (-10.37 to -2.57)	-6.43 (-10.34 to -2.53)	-6.33 (-10.23 to -2.42)
Cycle 4	707	250 (35.4)	1139	312 (27.4)	-7.97 (-12.34 to -3.59)	-7.83 (-12.22 to -3.45)	-7.91 (-12.28 to -3.53)
Cycle 5	514	167 (32.5)	857	234 (27.3)	-5.19 (-10.21 to -0.16)	-5.07 (-10.12 to -0.01)	-4.98 (-10.01 to 0.04)
CINV event delayed (Days 3-6)							
Cycle 1	1440	515 (35.8)	2358	757 (32.1)	-3.66 (-6.77 to -0.55)	-3.65 (-6.76 to -0.54)	-3.47 (-6.58 to -0.35)
Cycle 2	1149	311 (27.1)	1922	486 (25.3)	-1.78 (-5.00 to 1.44)	-1.66 (-4.88 to 1.57)	-1.69 (-4.92 to 1.53)
Cycle 3	901	214 (23.8)	1428	310 (21.7)	-2.04 (-5.55 to 1.46)	-1.82 (-5.33 to 1.69)	-1.93 (-5.44 to 1.57)
Cycle 4	707	158 (22.3)	1139	245 (21.5)	-0.84 (-4.73 to 3.05)	-0.74 (-4.63 to 3.15)	-0.77 (-4.66 to 3.13)
Cycle 5	514	112 (21.8)	857	179 (20.9)	-0.90 (-5.39 to 3.59)	-0.70 (-5.20 to 3.80)	-0.86 (-5.35 to 3.64)

n: number, %: percent, CI: confidence interval CMH: Cochran-Mantel-Haenszel, IPTW: inverse probability of treatment weighting,

CINV: chemotherapy-induced nausea and vomiting

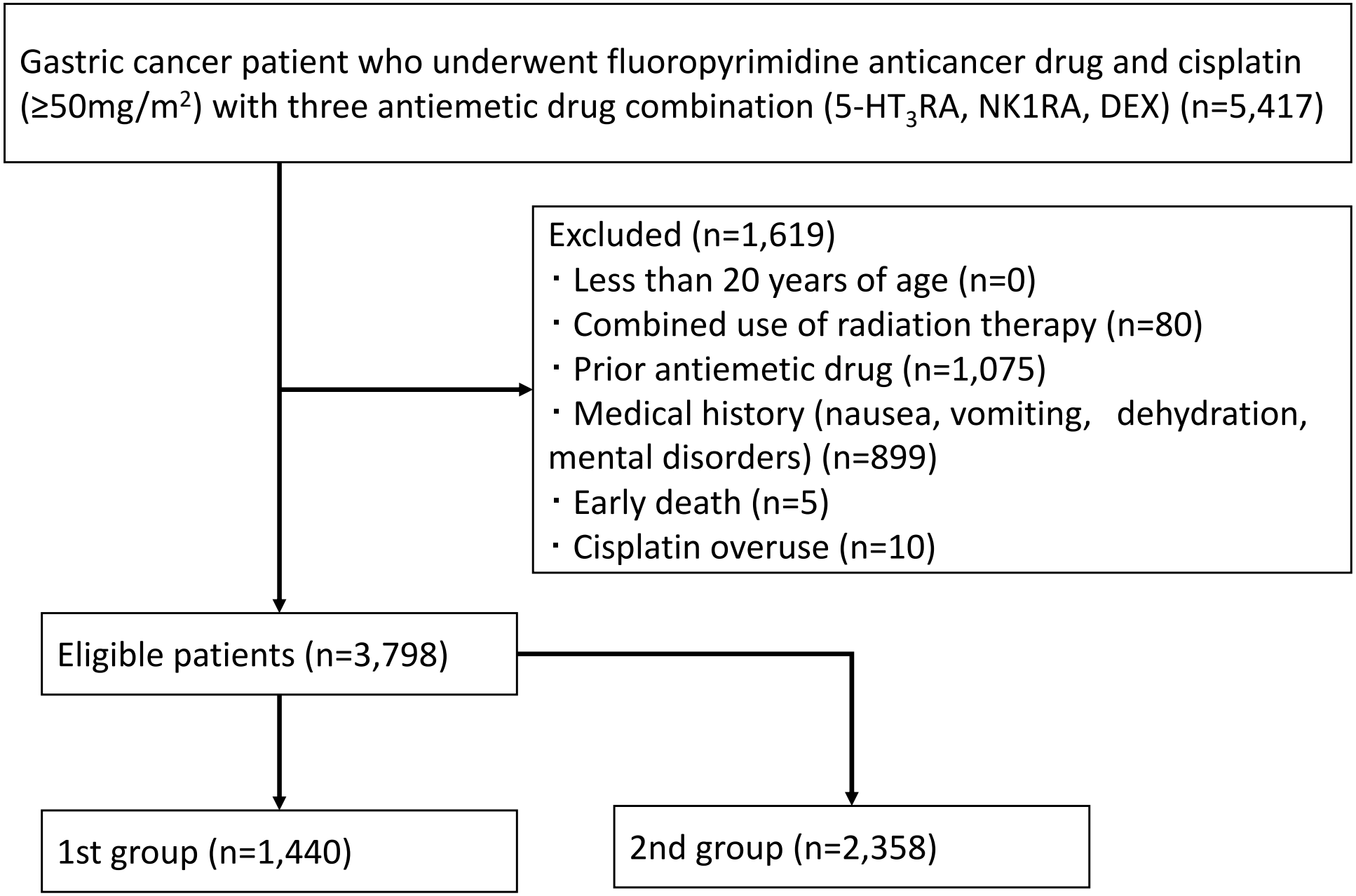
Table 3. CINV event summary with event proportion and unadjusted risk difference with 95% CI in cycle 1 in the subgroups (n=3,798)

	n	1st group event n (%)	n	2nd group event n (%)	Risk difference (95%CI)
CINV event overall (Day1-6)					
Male	1,078	536 (49.7)	1,798	786 (43.7)	-6.01 (-9.77 to -2.24)
Female	362	208 (57.5)	560	258 (46.1)	-11.39 (-17.94 to -4.83)
Age (<60)	299	166 (55.5)	472	236 (50.0)	-5.52 (-12.73 to 1.70)
Age (≥60)	1,141	578 (50.7)	1,886	808 (42.8)	-7.82 (-11.48 to -4.15)
Smoking history (No)	599	312 (52.1)	978	454 (46.4)	-5.67 (-10.74 to -0.59)
Smoking history (Yes or unknown)	841	432 (51.4)	1,380	590 (42.8)	-8.61 (-12.88 to -4.34)
Cisplatin dose (mg/m^2) (<70)	1,231	645 (52.4)	2015	866 (43.0)	-9.42 (-12.95 to 5.89)
Cisplatin dose (mg/m^2) (≥70)	209	99 (47.4)	343	178 (51.9)	4.53 (-4.06 to 13.12)
Aprepitant	1,242	650 (52.3)	1,760	782 (44.4)	-7.90 (-11.52 to -4.28)
Fosaprepitant	199	95 (47.7)	602	263 (43.7)	-4.05 (-12.04 to 3.94)
CINV event acute (Day1-2)					
Male	1078	417 (38.7)	1798	554 (30.8)	-7.87 (-11.48 to -4.26)
Female	362	140 (38.7)	560	158 (28.2)	-10.46 (-16.71 to -4.21)
Age (<60)	299	123 (41.1)	472	170 (36.0)	-5.12 (-12.18 to 1.94)
Age (≥60)	1141	434 (38.0)	1886	542 (28.7)	-9.30 (-12.78 to -5.82)
Smoking history (No)	599	223 (37.2)	978	304 (31.1)	-6.14 (-10.98 to -1.31)
Smoking history (Yes or unknown)	841	334 (39.7)	1380	408 (29.6)	-10.15 (-14.24 to -6.06)
Cisplatin dose (mg/m^2) (<70)	1231	494 (40.1)	2015	599 (29.7)	-10.40 (-13.79 to -7.01)
Cisplatin dose (mg/m^2) (≥70)	209	63 (30.1)	343	113 (32.9)	2.80 (-5.16 to 10.77)
Aprepitant	1,242	484 (39.0)	1,760	541 (30.7)	-8.23 (-11.70 to -4.77)
Fosaprepitant	199	74 (37.2)	602	172 (28.6)	-8.61 (-16.24 to -0.99)
CINV event delayed (Day3-6)					
Male	1078	363 (33.7)	1798	556 (30.9)	-2.75 (-6.29 to -0.79)
Female	362	152 (42.0)	560	201 (35.9)	-6.10 (-12.55 to 0.36)
Age (<60)	299	110 (36.8)	472	172 (36.4)	-0.35 (-7.33 to 6.63)

Age (≥60)	1141	405 (35.5)	1886	585 (31.0)	-4.48 (-7.95 to -1.00)
Smoking history (No)	599	214 (35.7)	978	330 (33.7)	-1.98 (-6.83 to 2.86)
Smoking history (Yes or unknown)	841	301 (35.8)	1380	427 (30.9)	-4.85 (-8.90 to -0.79)
Cisplatin dose (mg/m^2) (<70)	1231	435 (35.3)	2015	612 (30.4)	-4.96 (-8.31 to -1.62)
Cisplatin dose (mg/m^2) (≥70)	209	80 (38.3)	343	145 (42.3)	4.00 (-4.42 to 12.41)
Aprepitant	1,242	440 (35.4)	1,760	565 (32.1)	-3.32 (-6.76 to 0.12)
Fosaprepitant	199	75 (37.7)	602	192 (31.9)	-5.79 (-13.49 to 1.90)

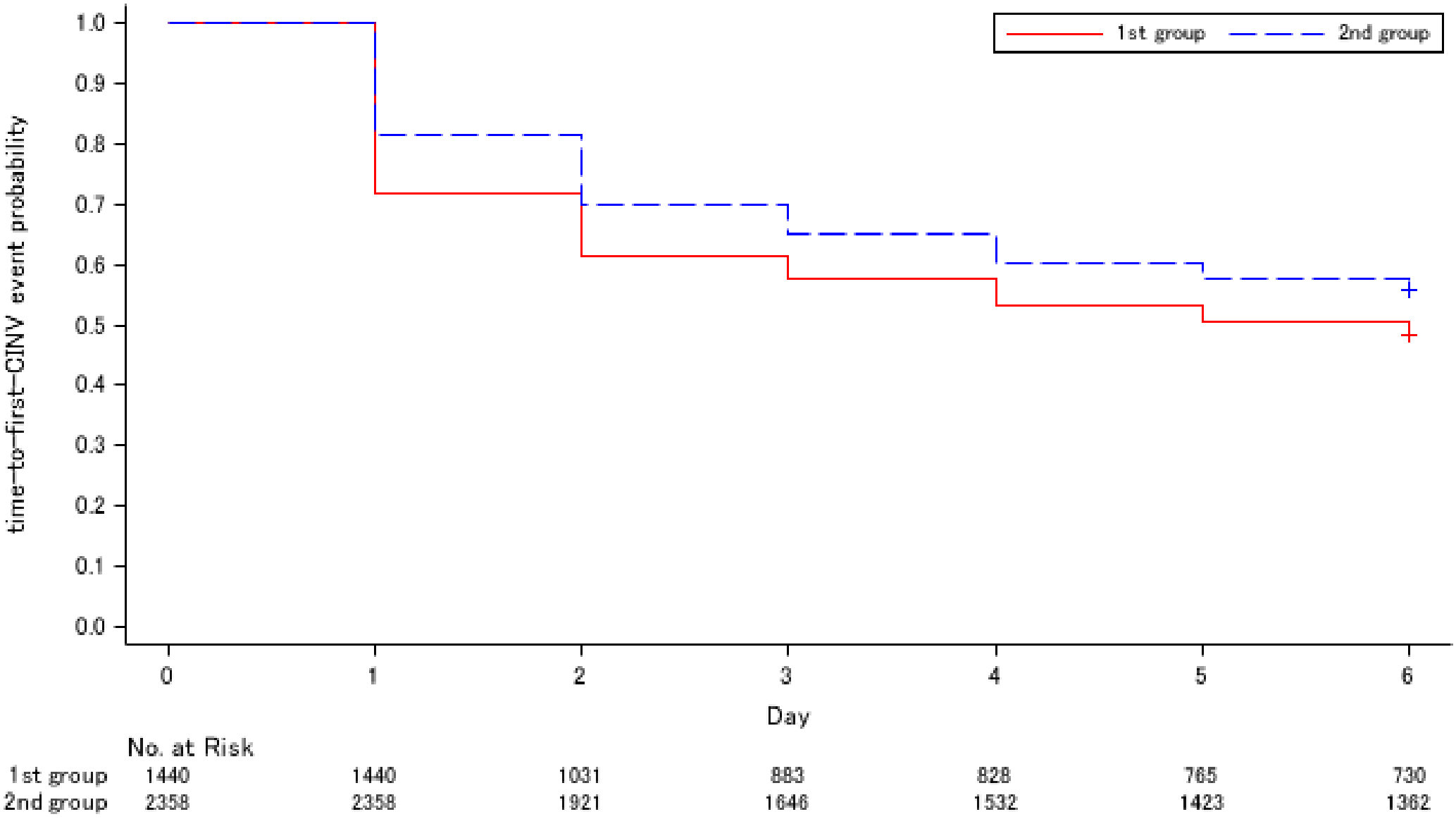
CINV: chemotherapy-induced nausea and vomiting, %: percent, CI: confidence interval,

NK1RA: neurokinin-1 receptor antagonist, n: number



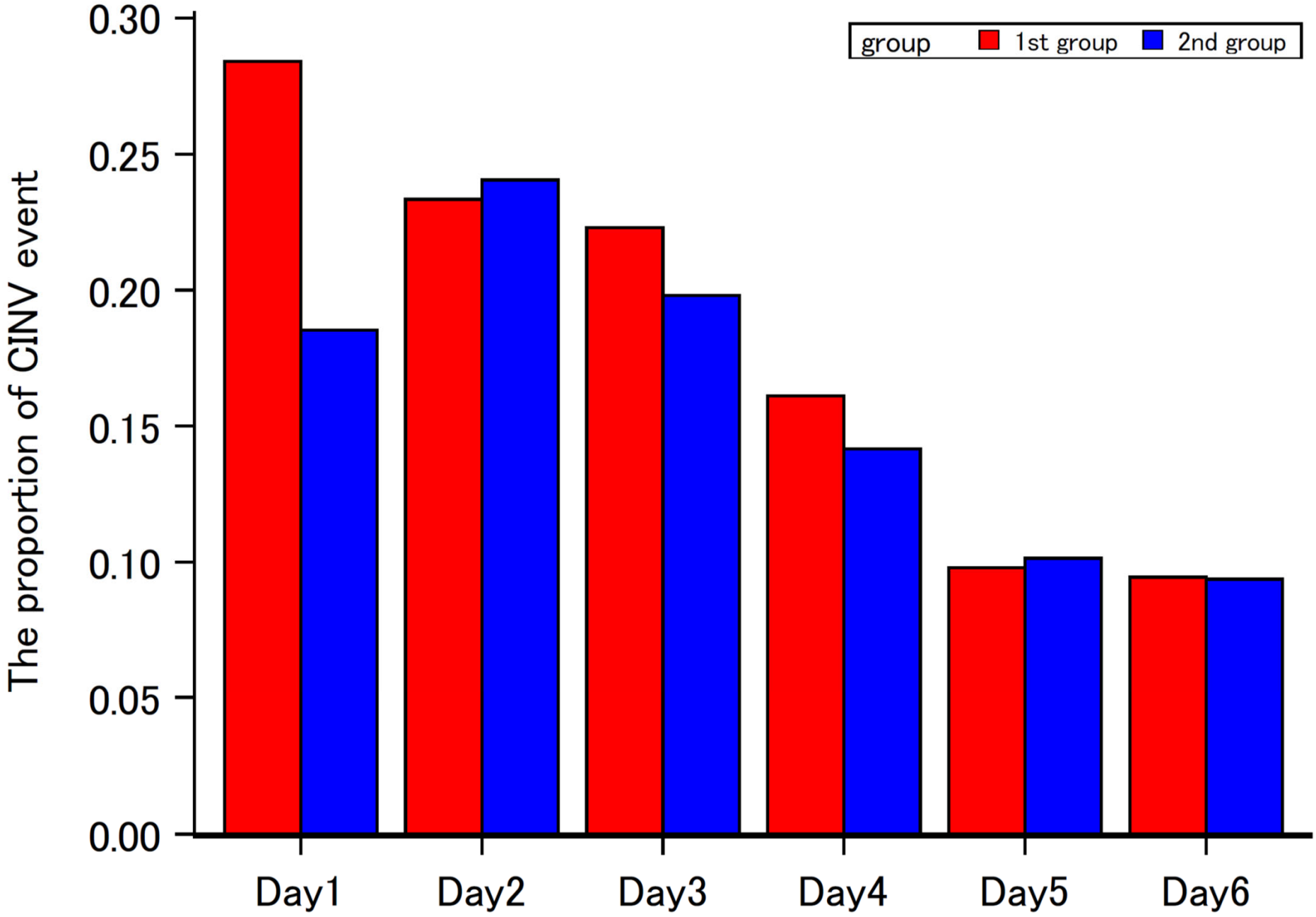
5-HT_3RA: 5-hydroxytryptamine-3 receptor antagonist,
NK1RA: neurokinin-1 receptor antagonist, DEX: dexamethasone, n: number

Figure 1. Patient selection flowchart in this study



CINV: chemotherapy-induced nausea and vomiting

Figure 2. Kaplan-Meier curves for time-to-first CINV event (first use of the additional antiemetic drug) in Cycle 1



CINV: chemotherapy-induced nausea and vomiting

Figure 3. Time course of CINV events by the day period in cycle 1

Supplementary Table 1. The use of antiemetic drugs, concomitant anticancer agents, and opioids in cycle 1 (n=3,798)

n (%)		1st group (n=1,440)	2nd group (n=2,358)
5-HT3RA (Cycle1 Day1)	Azasetron	58 (4.0)	-
	Indisetron	32 (2.2)	-
	Ondansetron	26 (1.8)	-
	Granisetron	1,311 (91.0)	-
	Ramosetron	96 (6.7)	-
	Palonosetron	-	2,358 (100.0)
NK1RA (Cycle 1 Day1)	Aprepitant	1,242 (86.3)	1,760 (74.6)
	Fosaprepitant	199 (13.8)	602 (25.5)
DEX (Cycle 1 Days 1-5)	Day 1	1440 (100.0)	2358 (100.0)
	Day 2	1142 (79.3)	1831 (77.7)
	Day 3	1046 (72.6)	1659 (70.4)
	Day 4	504 (35.0)	830 (35.2)
	Day 5	134 (9.3)	143 (6.1)
Other Concomitant anticancer drugs (Cycle 1 Days 1-6)	Trastuzumab	238 (16.5)	375 (15.9)
	Docetaxel	35 (2.4)	101 (4.3)
	Irinotecan	6 (0.4)	8 (0.3)
	other	4 (0.3)	9 (0.4)
Opioid (Cycle1 Day -29 to 1)	Fentanyl	164 (11.4)	317 (13.4)
	Oxycodone	34 (2.4)	62 (2.6)
	Morphine	23 (1.6)	30 (1.3)
	other	8 (0.6)	14 (0.6)

n: number, %: percent, 5-HT3RA: 5-hydroxytryptamine-3 receptor antagonist, NK1RA: neurokinin-1 receptor antagonist, DEX: dexamethasone

Supplementary Table 2. CINV event summary (acute (Days 1-2), delayed (Days 3-6), overall (Days 1-6)) with event proportion and unadjusted risk difference with 95% CI up to 5 cycles in the PS-matched group (n=2,874)

n (%)	n	1st group	n	2nd group	Risk difference (95%CI)
CINV Event All (Day1-Day6)					
Cycle 1	1437	744 (51.8)	1437	616 (42.9)	-8.91 (-12.54 to -5.27)
Cycle 2	1146	512 (44.7)	1161	426 (36.7)	-7.98 (-11.98 to -3.99)
Cycle 3	898	378 (42.1)	862	283 (32.8)	-9.26 (-13.76 to -4.76)
Cycle 4	706	289 (40.9)	684	216 (31.6)	-9.36 (-14.38 to -4.33)
Cycle 5	514	198 (38.5)	522	160 (30.7)	-7.87 (-13.64 to -2.10)
CINV Event Acute (Day1-2)					
Cycle 1	1437	557 (38.8)	1437	425 (29.6)	-9.19 (-12.64 to -5.73)
Cycle 2	1146	431 (37.6)	1161	311 (26.8)	-10.82 (-14.61 to -7.03)
Cycle 3	898	317 (35.3)	862	229 (26.6)	-8.73 (-13.03 to -4.44)
Cycle 4	706	250 (35.4)	684	173 (25.3)	-10.12 (-14.92 to -5.32)
Cycle 5	514	167 (32.5)	522	134 (25.7)	-6.82 (-12.34 to -1.30)
CINV Event delayed (Day3-6)					
Cycle 1	1437	515 (35.8)	1437	442 (30.8)	-5.08 (-8.52 to 1.64)
Cycle 2	1146	311 (27.1)	1161	303 (26.1)	-1.04 (-4.65 to 2.57)
Cycle 3	898	214 (23.8)	862	185 (21.4)	-2.37 (-6.28 to 1.54)
Cycle 4	706	158 (22.4)	684	140 (20.5)	-1.91 (-6.22 to 2.40)
Cycle 5	514	112 (21.8)	522	103 (19.7)	-2.06 (-7.00 to 2.88)

n: number, %: percent, CI: confidence interval, CINV: chemotherapy-induced nausea and vomiting

Supplementary Table 3. Patient demographics in PS-matched group (n=2,874)

	1st group (n=1,437)	2nd group (n=1,437)	*p*-value
Sex n (%)			0.006 *1
Male	1,075 (74.8)	1,138 (79.2)	
Female	362 (25.2)	299 (20.8)	
Smoking history n (%)			0.56 *1
Yes	685 (47.7)	705 (49.1)	
No	598 (41.6)	594 (42.3)	
Unknown	154 (10.7)	138 (9.6)	
Cancer status n (%)			0.67 *1
New-onset	1,144 (79.6)	1,160 (80.7)	
Relapse	281 (19.6)	268 (18.7)	
Unknown	12 (0.8)	9 (0.6)	
Age (mean (SD))	65.1 (9.5)	66.7 (9.4)	<.0001 *2
Charlson comorbidity index (mean (SD))	6.2 (3.1)	6.3 (3.1)	0.58 *2
Height (cm) (mean (SD))	162.5 (8.5)	162.6 (8.2)	0.62 *2
Weight (kg) (mean (SD))	56.2 (10.7)	56.5 (10.2)	0.31 *2
Body surface area (m^2) (mean (SD))	1.59 (0.17)	1.60 (0.16)	0.62 *2
Cisplatin dose (1cycle) (mg/m^2) (mean (SD))	61.7 (10.3)	62.0 (10.2)	0.36 *2
Concomitant fluoropyrimidine anticancer drug (n (%))			0.29 *1
Tegafur, Gimeracil, Oteracil Potassium	1,148 (79.9)	1,124 (78.2)	
Capecitabine	289 (20.1)	313 (21.8)	

*1: Fisher's exact test *2: Wilcoxon rank sum test

PS: propensity score, n: number, %: percent, SD: standard deviation

Supplementary Table 4. CINV event summary (acute (Days 1-2), delayed (Days 3-6), overall (Days 1-6)) with event proportion and risk difference (unadjusted, CMH) with 95% CI up to 5 cycles in the actually administered 5-HT_3RA taking into consideration the switch of generation (n=3,798)

	n	1st group event n (%)	n	2nd group event n (%)	Risk difference (% (95%CI))	CMH Adjusted Risk difference (% (95%CI))
CINV event overall (Days1-6)						
Cycle 1	1440	744 (51.7)	2358	1044 (44.3)	-7.39 (-10.66 to -4.12)	-7.40 (-10.67 to -4.14)
Cycle 2	1090	482 (44.2)	1959	736 (37.6)	-6.65 (-10.30 to -3.00)	-6.45 (-10.10 to -2.80)
Cycle 3	850	354 (41.6)	1463	511 (34.9)	-6.72 (-10.84 to -2.60)	-6.57 (-10.69 to -2.45)
Cycle 4	663	270 (40.7)	1170	397 (33.9)	-6.79 (-11.41 to -2.17)	-6.73 (-11.35 to -2.10)
Cycle 5	483	185 (38.3)	877	280 (32.8)	-5.46 (-10.80 to -0.60)	-5.29 (-10.65 to -0.06)
CINV event acute (Days 1-2)						
Cycle 1	1440	557 (38.7)	2358	712 (30.2)	-8.49 (-11.61 to -5.36)	-8.52 (-11.65 to -5.40)
Cycle 2	1090	406 (37.2)	1959	554 (28.3)	-8.97 (-12.46 to -5.47)	-8.84 (-12.34 to -5.33)
Cycle 3	850	296 (34.8)	1463	424 (29.0)	-5.84 (-9.80 to -1.88)	-5.80 (-9.77 to -1.84)
Cycle 4	663	234 (35.3)	1170	325 (27.8)	-7.52 (-11.97 to -3.06)	-7.42 (-11.89 to -2.95)
Cycle 5	483	156 (32.3)	877	242 (27.6)	-4.70 (-9.82 to 0.41)	-4.62 (-9.76 to 0.52)
CINV event delayed (Days 3-6)						
Cycle 1	1440	515 (35.8)	2358	757 (32.1)	-3.66 (-6.77 to -0.55)	-3.65 (-6.76 to -0.54)
Cycle 2	1090	291 (26.7)	1959	502 (25.6)	-1.07 (-4.33 to 2.19)	-0.91 (-4.18 to 2.36)
Cycle 3	850	206 (24.2)	1463	316 (21.6)	-2.64 (-6.21 to 0.93)	-2.38 (-5.96 to 1.19)
Cycle 4	663	149 (22.5)	1170	251 (21.5)	-1.02 (-4.97 to 2.93)	-1.03 (-4.99 to 2.94)
Cycle 5	483	107 (22.2)	877	181 (20.6)	-1.51 (-6.09 to 3.06)	-1.35 (-5.95 to 3.25)

CINV: chemotherapy-induced nausea and vomiting, CMH: Cochran-Mantel-Haenszel,

5-HT_3RA: 5-hydroxytryptamine-3 receptor antagonist, n: number, %: percent, CI: confidence interval

Supplementary Table 5. The use of additional antiemetic drugs (CINV events) in cycle 1 (n=3,798)

Category	CINV evaluated Day	Overall (Days1-6)		Acute (Days 1-2)		Delayed (Days 3-6)	
		1st group (n (%))	2nd group (n (%))	1st group (n (%))	2nd group (n (%))	1st group (n (%))	2nd group (n (%))
5-HT_3RA	2-6	84 (5.8)	85 (3.6)	64 (4.4)	32 (1.4)	54 (3.8)	57 (2.4)
Aprepitant	4-6	8 (0.6)	35 (1.5)	-	-	8 (0.6)	35 (1.5)
Fosaprepitant	2-6	1 (0.1)	0 (0)	1 (0.1)	0 (0)	0 (0)	0 (0)
DEX	6	15 (1.0)	36 (1.5)	-	-	15 (1.0)	36 (1.5)
Methylprednisolone		1 (0.1)	7 (0.3)	1 (0.1)	5 (0.2)	0 (0)	3 (0.1)
Domperidone		82 (5.7)	167 (7.1)	21 (1.5)	60 (2.5)	70 (4.9)	151 (6.4)
Metoclopramide		629 (43.7)	772 (32.7)	482 (33.5)	559 (23.7)	408 (28.3)	532 (22.6)
Alprazolam		7 (0.5)	9 (0.4)	5 (0.3)	3 (0.1)	4 (0.3)	7 (0.3)
Lorazepam		2 (0.1)	25 (1.1)	0 (0)	22 (0.9)	2 (0.1)	23 (1.0)
Prochlorperazine	1-6	52 (3.6)	65 (2.8)	12 (0.8)	25 (1.1)	45 (3.1)	51 (2.2)
Chlorpromazine		36 (2.5)	88 (3.7)	18 (1.3)	47 (2.0)	28 (1.9)	60 (2.5)
Haloperidol		6 (0.4)	4 (0.2)	1 (0.1)	1 (0.0)	6 (0.4)	3 (0.1)
Risperidone		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Olanzapine		2 (0.1)	3 (0.1)	0 (0)	0 (0)	2 (0.1)	3 (0.1)
Chlorpheniramine		15 (1.0)	52 (2.2)	15 (1.0)	48 (2.0)	1 (0.1)	6 (0.3)

CINV: chemotherapy-induced nausea and vomiting, n: number, %: percent,

5-HT_3RA: 5-hydroxytryptamine-3 receptor antagonist, DEX: dexamethasone

Supplementary Table 6. Treatment outcomes of the frequency of switch of 5-HT_3RA generation and cisplatin dose modification (discontinuation, reduction, delay, dose per BSA) up to 5 cycles (n=3,798)

	Cycle	n	Switch 5HT_3RA (1^{st} to 2^{nd} or 2^{nd} to 1^{st}) (n (%))	Cisplatin Discontinuation (n (%))	Cisplatin Dose Reduction (n (%))	Cisplatin Delay (over 43 days per cycle) (n (%))	Cisplatin Dose per BSA (mg/m^2) Mean (SD)	Cisplatin Dose per BSA (mg/m^2) Median
1^{st} group	Cycle 1	1440	-	291 (20.2)	-	-	61.8 (11.02)	59.4
	Cycle 2	1149	62 (5.4)	248 (21.6)	301 (26.2)	102 (8.9)	58.1 (11.98)	58.4
	Cycle 3	901	58 (6.4)	194 (21.5)	132 (14.7)	114 (12.7)	57.5 (13.53)	58.1
	Cycle 4	707	51 (7.2)	193 (27.3)	78 (11.0)	93 (13.2)	56.5 (11.21)	57.8
	Cycle 5	514	42 (8.2)	136 (26.5)	48 (9.3)	77 (15.0)	55.7 (10.39)	57.5
2^{nd} group	Cycle 1	2358	-	436 (18.5)	-	-	62.0 (12.68)	59.5
	Cycle 2	1922	10 (0.5)	494 (25.7)	534 (27.8)	174 (9.1)	58.2 (11.22)	58.2
	Cycle 3	1428	13 (0.9)	289 (20.2)	259 (18.1)	192 (13.4)	57.1 (12.69)	57.6
	Cycle 4	1139	12 (1.1)	282 (24.8)	158 (13.9)	157 (13.8)	55.5 (10.41)	56.6
	Cycle 5	857	17 (2.0)	184 (21.5)	108 (12.6)	115 (13.4)	54.2 (10.87)	56.0

n: number, 5HT_3RA: 5-hydroxytryptamine-3 receptor antagonist, %: percent, BSA: body surface area, SD: standard deviation