5-Hydroxytryptamine-3 Receptor Antagonist and Dexamethasone as Prophylaxis for Chemotherapy Induced Nausea and Vomiting during Moderately Emetic Chemotherapy for Solid Tumors: A Multicenter, Prospective, Observational Study

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Abstract

Background Patients receiving moderate emetic risk chemotherapy (MEC) occurs chemotherapy-induced nausea and vomiting (CINV) in 30–90%, however the optimal antiemetic treatment remains controversial. Methods In this multicenter, prospective, observational study of adults treated with MEC for various cancer types in Japan, We enrolled patients kept diaries documenting CINV. All participants received a 5-HT3 receptor antagonist(5HT3RAs) and dexamethasone. We assessed various possible risk factors for complete response (CR; no emetic events and no antiemetic measures), total control (TC; no emetic events , no antiemetic measures and no nausea) and complete control (CC; no emetic events, no antiemetic measures and less than mild nausea) by univariate and multivariate analysis. Results Of the 400 patients enrolled from May 2013 to January 2015, 386 were eligible for evaluation. The overall CR rate was 64%, CBDCA-based chemotherapy and oxaliplatin-based chemotherapy were particularly low. However, we showed that the CR rates in men were high in CBDCA(AUC5)□ETP (80%), CapeOX (78%) and CBDCA+PTX for lung cancer(73%). Emesis occurred significantly more women (30%) than men (16%) of patients overall. TC and CC were achieved by 51% and 61% of patients. Logistic regression analysis revealed that age <65 years and history of motion sickness or pregnancy-associated vomiting were risk factors for nausea and being women for vomiting. Conclusions Our data support triplet regimen including NK1 receptor antagonist with woman receiving CBDCA-based chemotherapy or oxaliplatin-based chemotherapy. However, it became clear that two antiemetics for men received CBDCA(AUC5)□ETP, CBDCA□PTX for lung cancer and CAPOX may be sufficiently effective. Further individualization of antiemetic regimens for patients receiving MEC on the basis of both type of chemotherapy regimen and sex is needed.

Background

Chemotherapy-induced nausea and vomiting (CINV) are major adverse effects of cancer chemotherapy, impair patients' quality of life, and often causes delay in or refusal of potentially curative chemotherapy. Over the past decade, antiemetic treatment has been greatly improved by development of new antiemetic agents and international guidelines for antiemetic therapy prepared by well-known organizations such as the American Society of Clinical Oncology (ASCO)[1], the Multinational Association of Supportive Care in Cancer (MASCC)/European Society of Medical Oncology (ESMO)[2], and the National Comprehensive Cancer Network (NCCN)[3] are now available. The Japanese guidelines for CINV published in 2010 recommend two antiemetics for moderate emetic risk chemotherapy (MEC): 5-hydroxytryptamine-3 receptor antagonists (5HT3RAs) and dexamethasone. However, both the Japanese and international guidelines recommend a three-drug combination of a neurokinin 1 receptor antagonist (NK1RA), a 5HT3RA, and dexamethasone for patients receiving carboplatin, which is classified as MEC. However, whether addition of an NK1RA to a 5HT3RA and steroid combination is beneficial in patients receiving MEC other than carboplatin -based regimens remains controversial. Providing a single recommendation for antiemetic treatment for the entire broad range of expected CINV in the moderate level (30–90%) is problematic. Furthermore, the recommendations of international guidelines are based on the emetic

potential of anticancer agents when given in the absence of antiemetic prophylaxis and show minimal consideration for patient-related factors. Few studies have compared the incidence of CINV for different MEC regimens. Different antiemetic treatment strategies may be optimal for different regimens and risk factors. Risk factors reportedly associated with CINV include younger age, female sex, history of CINV, and low alcohol consumption for several solid tumors[4–6]. Identification of risk factors for CINV is important in selecting appropriate care for various MEC regimens.

Despite advances in prophylactic antiemetics, many aspects of CINV in MEC remain unclear. In the present study, we clarified regimens and risk factors that are associated with poor control of CINV associated with MEC.

Methods

Study design

This was a multicenter, prospective, observational study in which seven institutions throughout Japan participated. We selected university hospitals, cancer centers, and cancer treatment hospitals certified by the MHLW and asked them to participate in this study. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by National Cancer Center Institutional Review Board (2012 − 324) and the Institutional Review Board of each participating hospital.

Enrollment Of Patients

Written informed consent was obtained from all participants prior to registration. The primary inclusion criteria were ≥ 20 years of age, diagnosis of solid tumors, no prior chemotherapy, and planned administration of combination therapy with a 5-HT3 receptor antagonist and dexamethasone. The combinations administered were as follows: for lung cancer, carboplatin plus etoposide (CBDCA + ETP), carboplatin plus paclitaxel (CBDCA + PTX), or carboplatin plus pemetrexed therapy (CBDCA + PEM); for breast cancer, cyclophosphamide plus docetaxel therapy (DTX□CPA); for colon cancer: oxaliplatin with fluorouracil and folinic acid chemotherapy(FOLFOX)or capecitabine plus oxaliplatin (CAPOX); and for ovarian cancer: carboplatin plus paclitaxel therapy (CBDCA + PTX). Patients with any of the following conditions were not included in the study: 1) gastrointestinal obstruction; 2) ascites or pleural effusion; 3) symptomatic brain metastasis; and 4) current radiotherapy directed toward the abdomen/pelvis.

Management Of Patient Diaries And Collection Of Required Data

Before commencing cancer chemotherapy, patients were provided with 7 day diaries in which to recording their symptoms of CINV. They were asked to record digestive symptoms, that is, development and severity of nausea, frequency of vomiting, and number of salvage treatments, including use of antiemetic medications such as metoclopramide, domperidone, and olanzapine. Nausea was assessed by patients themselves with the 4-point Likert Scale (0: No Nausea, 1: Mild, 2: Moderate, 3: Severe) and the results were recorded in daily diaries. Patients were required to write their symptoms in the diary every day for 7 days from commencement of anticancer MEC. The investigators and/or their colleagues recorded background patient information, including sex, age, treatment history (history of radiotherapy, use of anticancer drugs, use of anxiolytic drugs before administration of the anticancer drug), alcohol intake history, smoking history, risk factors for CINV (history of motion sickness or vomiting related to pregnancy), performance status, cancer chemotherapy regimen (type and dose of drug and timing of administration), and details of antiemetic therapy and salvage treatment for CINV as extracted from the patients' diaries. The patients were requested to fill in their diaries and hand over them to the person in charge of this study at the end of the observation period. The diaries were also sent to the secretariat by the investigators after extraction of required data.

Antiemetic Regimen

Patients received a guideline-based combination of a 5-HT_3 receptor antagonist ($5HT_3RA$) and dexamethasone for MEC. The 5HT3RA was 0.75 mg of either palonosetron or a first generation 5HT3RA.

Outcomes

Evaluation items comprised the complete response (CR), total control (TC) and complete control (CC) rates over the entire observation period (0–168 h), the acute phase (0–24 h), and the delayed phase (24–168 h) of the first cycle of treatment. We also evaluated emetic event rate over the entire observation period and time to treatment failure.

The CR rate was defined as the proportion of participants in the analysis set with no emetic events and no antiemetic measures, the TC rate as the proportion of participants with no emetic episodes, no antiemetic measures, and no nausea, and the CC rate as the proportion of participants with no emetic episodes, no antiemetic measures, and less than mild nausea. Severity of nausea was measured by the 4-point Likert Scale. Time to treatment failure was defined as time to the first emetic episode or use of rescue medications.

Data analysis

Patient characteristics, CR, TC, and CC rates were summarized using descriptive statistics or contingency tables. Independent risk factors for delayed nausea and vomiting incidence (dependent variable) were evaluated using logistic regression analysis with backward elimination method. The following

independent factors were included in the model: Gender, Age, Motion sickness, Drinking habit, Smorking History, Pregnancy associated vomiting and type of 5HT3RA. For all analysis, p-values correspond to two-sided tests, and $p < 0.05$ was considered to denote statistical significance. All statistical analyses were performed with SAS 9.2.

Results

Patient selection and characteristics

Between May 2013 and January 2015, 400 patients were registered in the study, 386 of whom were eligible for evaluation. Those 14 patients were withdrawn from analyses for the following reasons: three withdrew consent, four met discontinuation criteria before the start of study treatment, one met the exclusion criteria, three lacked efficacy data because of serious adverse effects, and three had not completed their diary correctly(Fig. 1). Table 1 summarizes the eligible patients' characteristics. Patients with breast cancer and ovarian cancer were almost exclusively female, and younger than those with other malignancies. Patients with other malignancies were on average older and predominantly male. Only four patients received the FOLFIRI regimen because this is mainly used as second-line chemotherapy, thus not fulfilling the enrolment criteria.

Table 1
Patient characteristics

	All Patients (n = 386)	Colorectal cancer (n = 161)	Lung cancer (n = 140)	Ovarian cancer (n = 45)	Breast cancer (n = 40)
Age,n (%) ≧ 65 years	178 (46.1)	66 (41.0)	92 (65.7)	9 (20.0)	11 (27.5)
< 65 years	208 (53.9)	95 (59.0)	48 (34.3)	36 (80.0)	29 (72.5)
Gender (%) Female	185 (47.9)	71 (44.1)	29 (20.7)	45 (100.0)	40 (100.0)
Motion sickness (%) Yes	59 (15.3)	22 (13.7)	12 (8.6)	13 (28.9)	12 (30.0)
Drinking habit (%) Yes	203 (52.6)	79 (49.1)	83 (59.3)	23 (51.1)	18 (45.0)
Smoking habit (%) Yes	150 (38.9)	56 (34.8)	88 (62.9)	2 (4.4)	4 (10.0)
Pregnancy associated vomiting (%) Yes	95 (51.4)	34 (47.9)	20 (69.0)	20 (44.4)	21 (52.5)
Regimen	34 (8.8)	-	34 (24.3)	-	-
CBDCA(AUC5) + ETP	103 (26.7)	-	58 (41.4)	45 (100.0)	-
CBDCA + PTX	20	-	2	18	-
CBDCA(AUC5)	83	-	56	27	-
CBDCA(AUC6)	48 (12.4)	-	48 (34.3)	-	-
CBDCA + PEM	11	-	11	-	-
CBDCA(AUC5)	37	-	37	-	40 (100.0)
CBDCA(AUC6)	40 (10.4)	-	-	-	-
DTX + CPA	79 (20.5)	79 (49.1)	-	-	-
FOLFOX	4 (1.0)	4 (2.5)	-	-	-
FOLFIRI	78 (20.2)	78 (48.4)	-	-	
CAPOX					

CBDCA, carboplatin; ETP, etoposide; PTX, paclitaxel; PEM, pemetrexed; CPA, cyclophosphamide; DTX, docetaxel; FOLFOX, oxaliplatin with fluorouracil and folinic acid; FOLFIRI, irinotecan with fluorouracil and folinic acid; CAPOX, capecitabine plus oxaliplatin therapy

Control Of Cinv

CR was achieved by 64% of patients over the entire observation period (0–168 h), the details being as follows: FOLFOX, 63% and CAPOX, 64% for colon cancer; CBDCA + ETP, 77%, CBDCA + PTX, 67%, and

CBDCA + PEM, 54% for lung cancer; CBDCA + PTX, 51% for ovarian cancer; and DTX□CPA, 70% for breast cancer (Fig. 2). The proportions were similar for the overall and delayed phases. We consider the most likely explanation is that good control was achieved during the acute phase. Of the patients who received MEC regimen, 51% and 61% and achieved TC and CC, respectively, over the entire observation period (Fig. 3). The overall CR rates for CAPOX occurred significantly more frequently in men (78%) than in women (46%)□We showed that the overall CR rates in men were high in CBDCA□ETP (80%), CAPOX (78%) and CBDCA + PTX for lung cancer(73%) (Fig. 4).

Emetic events occurred in 23% of participants overall, with unexpectedly high incidences of emetic episodes in those with colorectal cancer (19%), lung cancer (24%), ovarian cancer (33%) and breast cancer (25%). Emetic episodes occurred significantly more frequently in women (30%) than in men (16%) (Fig .5).

Analysis Of Risk Factors

The results of univariate and multivariate logistic regression analysis, shown in Table 2, indicate the degree of CINV risk arising from possible CINV-related factors. Female sex, abstinence from alcohol, and history of pregnancy-associated vomiting were identified as risk factors for nausea and vomiting in the delayed phase, whereas age < 65 years and history of motion sickness were identified as risk factors for nausea alone in the delayed phase.

Logistic regression analysis revealed age < 65 years (OR 0.542 [95% CI: 0.354–0.830], p = 0.005), motion sickness (OR 2.138 [95% CI: 1.160–3.939], p = 0.015) and pregnancy-associated vomiting (OR 2.419 [95%CI: 1.447–4.045], p = 0.001) as risk factors for delayed nausea and being female (OR 0.479 [95% CI: 0.286–0.803], p = 0.005) for delayed vomiting. Effects of palonosetron versus first generation 5HT3RA on CINV did not differ significantly during any phase of treatment.

Study Observation Period

Comparison of rates of CC over 5-day and 7 day observation periods revealed the following: CBDCA + ETP (82%, 77%, respectively), CBDCA + PTX: (69%, 67%, respectively), CBDCA + PEM: (58%, 54%, respectively) for lung cancer; DTX□CPA: (75%, 70%, respectively) for breast cancer; FOLFOX: (63%, 63%, respectively) and CAPOX: (67%, 64%, respectively) for colon cancer, and CBDCA + PTX: (53%, 51%, respectively) for ovarian cancer. The maximum range was 5.9% for CBDCA + ETP and the average range 3.3%.

Nausea in delayed phase

	Univariate analysis			multivariate analysis		
	p value	OR(95%CI)		*p* value	OR(95%CI)	
Gender：Male vs Female	<0.001	0.473	[0.315-0.711]			
Age：≧65 vs <65	0.001	0.510	[0.339-0.766]	0.005	0.542	[0.354-0.830]
Motion sickness：Yes vs No	0.001	2.742	[1.523-4.938]	0.015	2.138	[1.160-3.939]
Drinking habit：Yes vs No	0.005	0.562	[0.376-0.843]	0.096	0.691	[0.447-1.068]
Smorking History：Yes vs No	0.160	0.744	[0.493-1.124]			
Pregnancy associated vomiting：Yes vs Others	<0.001	3.026	[1.857-4.933]	0.001	2.419	[1.447-4.045]
palonosetron vs 1st generation 5HT3RA	0.674	0.916	[0.610-1.377]			

Vomiting in delayed phase

	Univariate analysis			multivariate analysis		
	p value	OR(95%CI)		*p* value	OR(95%CI)	
Gender：Male vs Female	0.001	0.426	[0.258-0.702]	0.005	0.479	[0.286-0.803]
Age：≧65 vs <65	0.948	1.016	[0.626-1.650]			
Motion sickness：Yes vs No	0.156	1.571	[0.842-2.933]			
Drinking habit：Yes vs No	0.013	0.535	[0.327-0.875]	0.068	0.621	[0.373-1.037]
Smorking History：Yes vs No	0.155	0.689	[0.413-1.151]			
Pregnancy associated vomiting：Yes vs Others	0.004	2.175	[1.290-3.666]			
palonosetron vs 1st generation 5HT3RA	0.196	0.717	[0.433-1.187]	0.184	0.705	[0.421-1.180]

Backward selection method with an entry and exit criteria of 0.2

Table 2. Risk factors by univariate and multivariate analysis

Discussion

In this study, we demonstrated differences in the incidence of CINV between MEC regimens and sexes. The overall CR rate was 64%, the CR rates for CBDCA + PEM for lung cancer (54%) and CBDCA + PTX for ovarian cancer (51%) being particularly low, followed by FOLFOX (63%) and CAPOX (64%).The CR rate in the acute phase was more than 90% for all evaluated regimens. Thus, the poorer overall CR rate reflects the CR rate in the delayed phase. Risk factor analysis revealed that female sex is an independent risk factor for vomiting and age, motion sickness, and pregnancy-associated vomiting are independent risk factors for nausea alone.

In our previous study, Suzuki et al. reported a CR rate for palonosetron combined with dexamethasone and aprepitant in patients receiving high emetic risk chemotherapy (HEC) of 68%[7]. We insist that it is necessary to improve control of CINV in patients receiving CBDCA- or oxaliplatin-based chemotherapy.

We recommend a combination of three antiemetics to minimize CINV in patients receiving CBDCA- or oxaliplatin-based chemotherapy because our data indicate that these regimens carry a higher emetic risk than other MEC. Tsuji et al. reported that three antiemetics are more effective than two for prophylaxis of delayed vomiting in patients with colorectal cancer treated with CAPOX or FOLFOX[8]. However, we also found that patients treated with CBDCA + ETP(AUC5) and for men treated with CBDCA + ETP(AUC5) or CBDCA + PTX for lung cancer or CAPOX had good control for CINV. The CR rate for CBDCA + ETP was 77%, which was much higher than for other such regimens. The dose of CBDCA in all patients who

received CBDCA + ETP was carboplatin AUC5. Current international guidelines recommend a three-drug combination (NK1RA, a 5HT3RA, and dexamethasone) for patients receiving carboplatin AUC 4 or higher; however, there is insufficient evidence concerning carboplatin AUC 4. We believe that further research is necessary. In patients receiving CBDCA-based chemotherapy, we found high overall CR rates for men receiving CBDCA ETP (80%) or CBDCA + PTX for lung cancer (73%). A combination of two antiemetics appears to achieve good control of CINV in men with lung cancer. Recent international antiemetic guidelines consistently recommend antiemetic prophylaxis with three antiemetics (5HT3RAs, steroids, and NK1RAs) for patients receiving carboplatin-containing regimens, similar to that recommended for HEC. The present results generally support these recommendations. However, a combination of two antiemetics appears to achieve control of CINV in men with lung cancer receiving CBDCA (AUC5) ETP or CBDCA + PTX. On the other hand, we found low overall CR rates for men receiving CBDCA PEM (60.6%). In previous study, it has been suggested that control of CINV in patients treated with CBDCA + PEM received two antiemetics was poor. It is necessary to consider prophylaxis for CINV for each drug used in combination with CBDCA[9]. In patients receiving oxaliplatin-based chemotherapy, the CR rate for CAPOX therapy was significantly higher in men (78%) than in women (46%) The CR rate was notably lower in women with colorectal cancer receiving CAPOX than in those with ovarian cancer receiving CBDCA + PTX. We found that female sex contributes strongly to the low CR rate. Although antiemetic guidelines do not always recommend three antiemetics for oxaliplatin-based regimens, we consider that addition of NK1RA to two antiemetics is necessary for women with colorectal cancer receiving CAPOX. In contrast, a combination of two antiemetics achieved high overall CR rates in men receiving CAPOX and appeared to adequately control CINV. When treating patients with MEC, we need to further individualize antiemetic regimens for both type of chemotherapy regimen and sex.

In a similar observational study of CINV in Japan, Tamura et al. did not report CR, TC, or CC rates and gender comparisons of CR rates [10]. They reported a 16% emetic events rate in the delayed phase in 715 patients receiving MEC, which is notably lower than in our study (23%), likely because patients in their study received a triplet antiemetic regimen that included aprepitant, which apparently further reduced the rate of CINV. There is some evidence that adding an NK1RA improves control of vomiting[11]. Thus, adding an NK1RA to 5HT3RA and dexamethasone may increase effectiveness.

The risk factors identified in this study are similar to those reported previously: younger age, female sex, history of CINV, and low alcohol consumption, all being well-known risk factors[4–6]. However, most of the patients in those studies had breast cancer. In the present study, which also included patients with lung and colorectal cancers, we identified female sex as a strong risk factor for vomiting. We found no significant difference in rates of CINV between first-generation 5HT3RA and palonosetron in this study. In a previous study, an open-label, crossover trial was designed to compare the efficacy of palonosetron and ondansetron for MEC[12]. Furthermore, the SENRI trial reported similar results for oxaliplatin-based chemotherapy (FOLFOX or CAPOX)[13].

The observation period in this study was 7 days (168 h); however, it has only been 5 days (120 h) in many studies of CINV. We found that 5 days of observation resulted in underestimation by up to 5.9% compared

with 7 days observation. We therefore recommend that assessment should continue for around 7 days in future observational studies.

The present study had some limitations. First, its design was neither randomized nor blinded; thus, the present findings should be interpreted within the limitations of an observational study design. Second, there was a bias in the number of patients receiving different chemotherapeutic regimens. Third, NK1RA was not a component of the evaluated antiemetic treatment. Despite these limitations, we identified the incidence of CINV and its associated risk factors in routine clinical practice, rather than in a controlled trial. Additionally, we have presented characteristics of CINV for different chemotherapeutic regimens.

It has not yet been conclusively demonstrated that a combination of three antiemetics is indicated for all patients receiving MEC. More randomized trials exclusively testing MEC regimens that do not include carboplatin are warranted.

Conclusion

Our data support a triplet regimen including a NK1RA for woman receiving CBDCA- or oxaliplatin-based chemotherapy. However, it became clear from two antiemetics may be sufficiently effective for men receiving CBDCA(AUC5) + ETP, CBDCA + PTX for lung cancer, or CAPOX. Randomized controlled studies with a 7 day observation period are needed to verify our findings. Further individualization of antiemetic regimens for patients receiving MEC on the basis of both type of chemotherapy regimen and sex is needed. Identified individual risk factors in this study will assist in the development of personalized antiemetic treatments.

Abbreviations

CINV : Chemotherapy-induced nausea and vomiting

ASCO : American Society of Clinical Oncology

MASCC : Multinational Association of Supportive Care in Cancer

ESMO : European Society of Medical Oncology

NCCN : National Comprehensive Cancer Network

MEC : moderate emetic risk chemotherapy

5HT3RAs : 5-hydroxytryptamine-3 receptor antagonists

NK1RA : neurokinin 1 receptor antagonist

CBDCA : carboplatin

ETP : etoposide

PTX : paclitaxel

PEM : pemetrexed

CPA : cyclophosphamide

DTX : docetaxel

FOLFOX : oxaliplatin with fluorouracil and folinic acid

FOLFIRI : irinotecan with fluorouracil and folinic acid

CAPOX : capecitabine plus oxaliplatin therapy

CR : complete response

TC : total control

CC : complete control

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by National Cancer Center Institutional Review Board (2012-324) and the Institutional Review Board of each participating hospital. Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

Koichi Goto has received a speaker honorarium fees from AstraZeneca,Bristol-Myers Squibb,ONO, Chugai,Eli Lilly,MSD,Pfizer and research grants from Dainippon Sumitomo Pharma, MSD, Astellas,AstraZeneca, ONO, Kyowa Hakko Kirin, Daiichi Sankyo, TAIHO, Takeda, Chugai, Eli Lilly,Novartis,

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Authors' contributions

RM designed the study, and wrote the initial draft of the manuscript. KS , TH ,MS, KG designed the study,contributed to analysis, interpretation of data, and assisted in the preparation of the manuscript. RM, KS , TH, KG ,TT, MN, TK, TS, YK, NN, KF, HK, TH, SS, MK and HK have contributed to data collection and interpretation. All authors critically reviewed the manuscript. All authors approved the final version of the manuscript.

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Figures

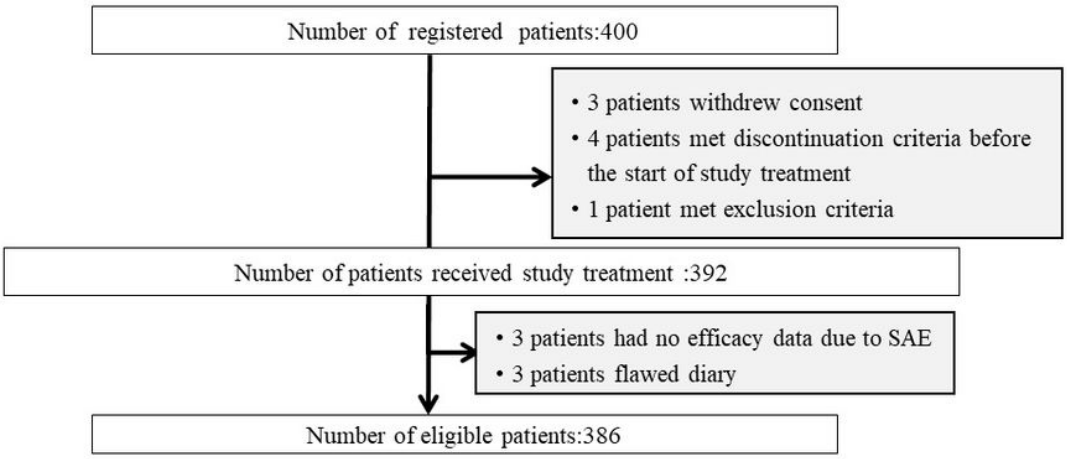

Figure 1

Flow chart showing enrollment of patients

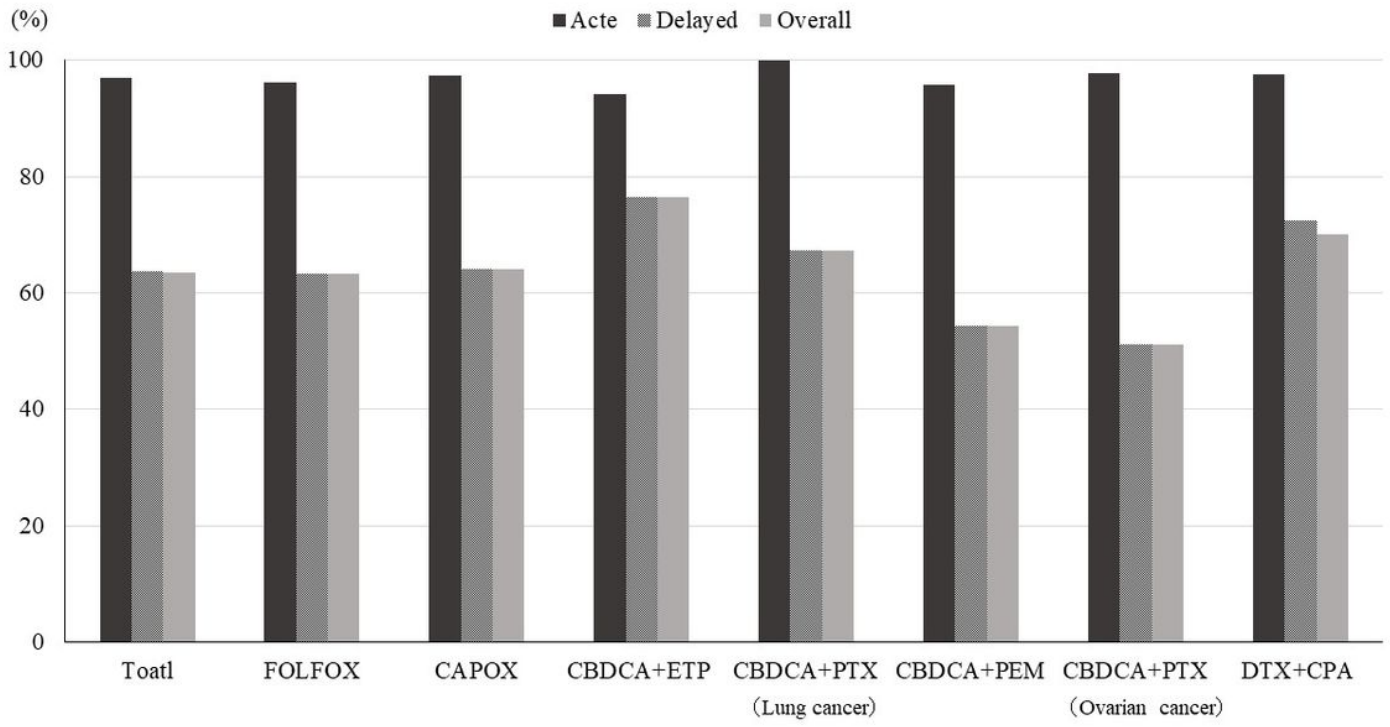

Figure 2

Complete response rate

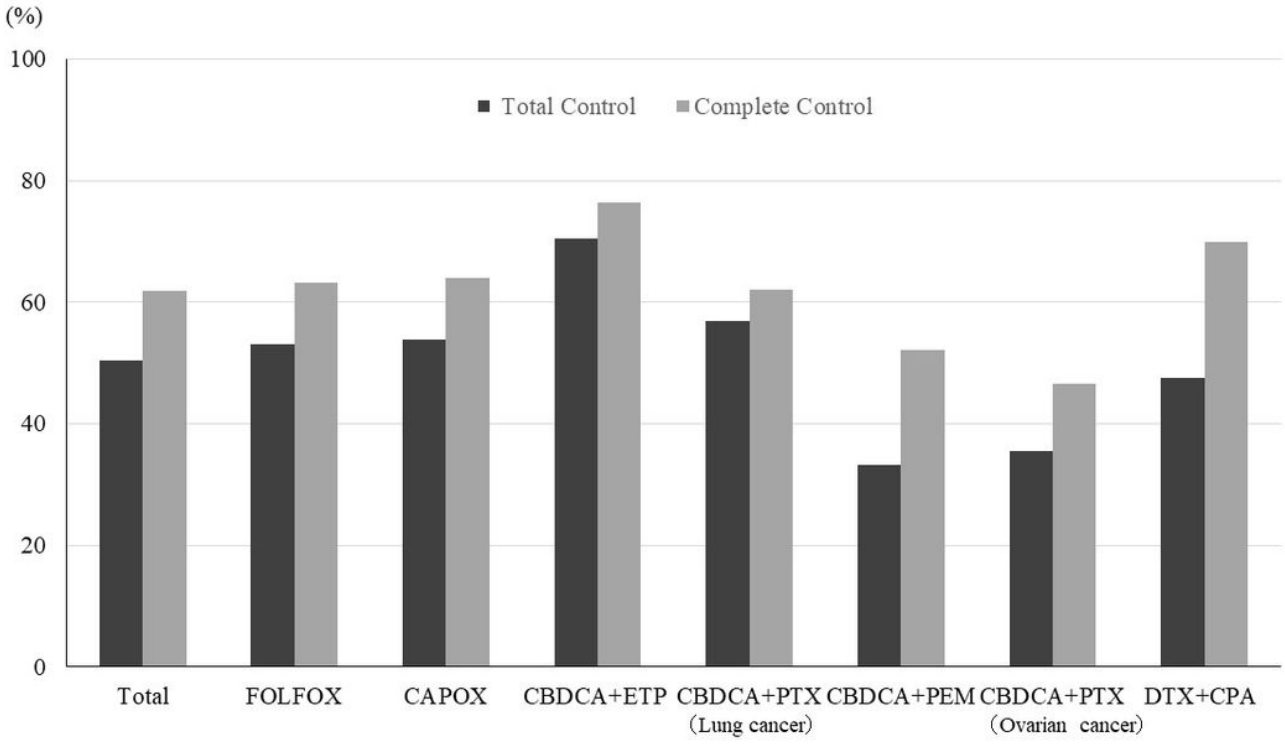

Figure 3

Total Control rate and Complete Control rate during the overall phase

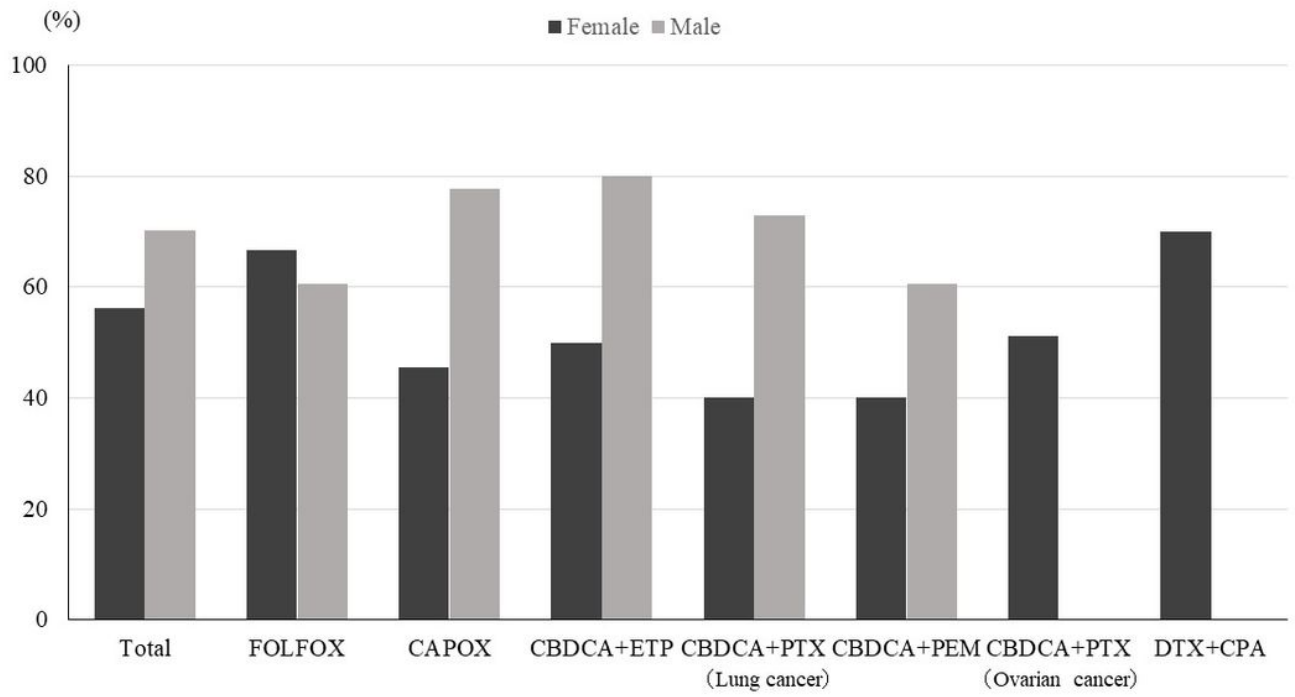

Figure 4

Complete response rate during the overall phase

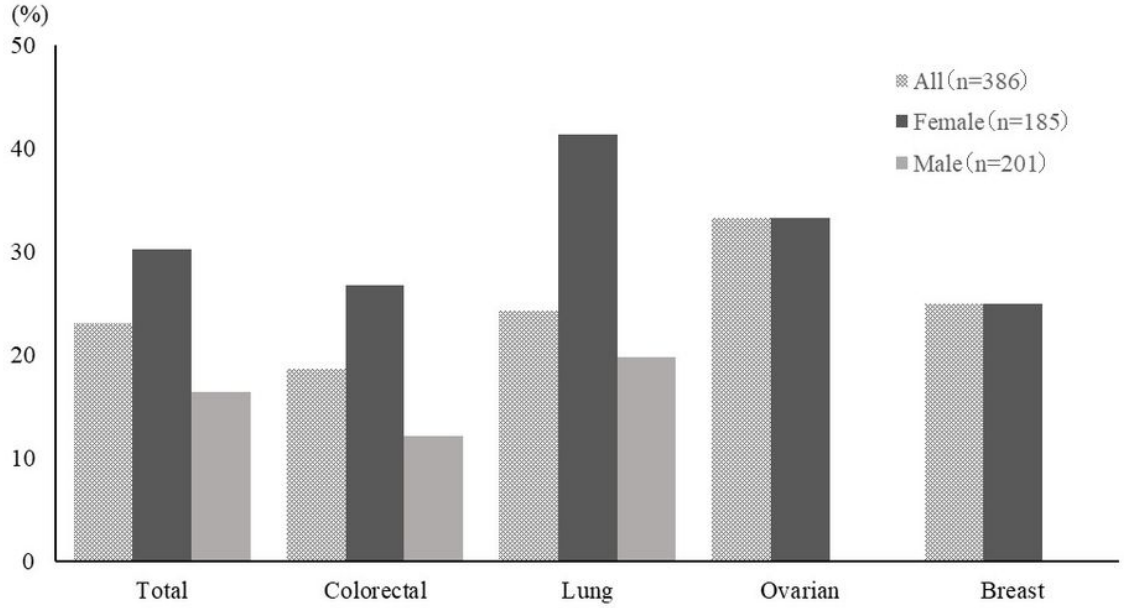

Figure 5

Emetic event rate during the overall phase