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Symptom Management and Supportive Care

A Nationwide, Multicenter Registry Study of Antiemesis for Carboplatin-Based Chemotherapy-Induced Nausea and Vomiting in Japan

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Antiemetic • Carboplatin • Chemotherapy • Nausea • Risk factor • Vomiting

Abstract

Background. We previously reported the results of a prospective study of chemotherapy-induced nausea and vomiting (CINV) in a cohort of patients who received carboplatin-based chemotherapy and were selected from a nationwide registry of those scheduled for moderately (MEC) or highly emetogenic chemotherapy (HEC) by the CINV Study Group of Japan. Of 1,910 previously registered patients (HEC: 1,195; MEC: 715), 400 patients received carboplatin-based chemotherapy. The frequency of CINV was determined, and the risk factors for CINV were assessed.

Materials and Methods. CINV data were collected from 7-day diaries. Risk factors for CINV were identified using logistic regression models.

Results. Of 400 patients scheduled for carboplatin-based chemotherapy, 267 patients received two antiemetics (5-hydroxytryptamine-3 receptor antagonist [5-HT_3 RA] and dexamethasone [DEX]), 118 patients received three antiemetics (5-HT_3 RA, DEX, and neurokinin-1 receptor antagonist [NK_1 RA]), and 15 were nonadherent to the treatment. In these patients, the CINV overall, acute, and delayed phase rates of complete response (CR), defined as no vomiting with no rescue medication, were 67.0%, 98.2%, and 67.5%, respectively. The rates of no nausea were 55.6%, 94.0%, and 56.1%, respectively, and those of no vomiting were 81.3%, 99.0%, and 81.8%, respectively. Older age was associated with a decreased non-CR, whereas female sex, history of pregnancy-related emesis, and dual antiemetic therapy were associated with an increased non-CR during the overall period.

Conclusion. In a clinical practice setting, in patients who received carboplatin-based chemotherapy, adherence is quite high and appropriate antiemetic prophylaxis requires a triple antiemetic regimen including NK_1 RA. ***The Oncologist*** 2020;25:e373–e380

Implications for Practice: For patients receiving carboplatin-based chemotherapy, triple antiemetic therapy with 5-hydroxytryptamine-3 receptor antagonist, dexamethasone, and neurokinin-1 receptor antagonist should be given prophylactically regardless of risk factor status.

Introduction

In patients undergoing chemotherapy, chemotherapy-induced nausea and vomiting (CINV) often reduces quality of life (QOL), treatment adherence, treatment efficacy, and curability. It is therefore important to minimize the incidence of CINV so that patients' QOL is well maintained and the chemotherapy can be continued. In recent guidelines, including those of the

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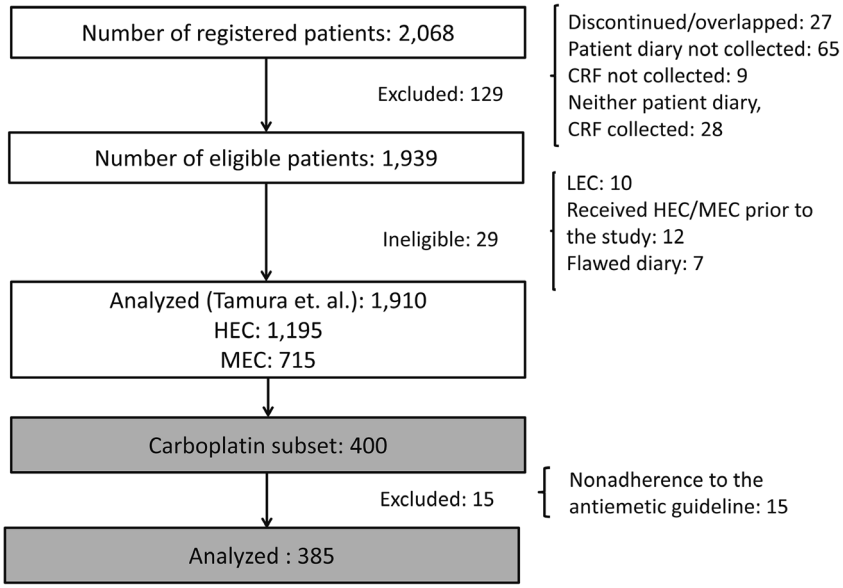

Figure 1. Flowchart showing the patient enrollment process. Reproduced, with permission, from Tamura et al., Testing the effectiveness of antiemetic guidelines: Results of a prospective registry by the CINV Study Group of Japan. Int J Clin Oncol 2015;20:855–865. [12]. © 2015 Japan Society of Clinical Oncology.
Abbreviations: CRF, case report form; HEC, highly emetogenic chemotherapy; LEC, low emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy.

American Society of Clinical Oncology [1], Multinational Association of Supportive Care in Cancer-European Society for Medical Oncology [2], and Japanese Society of Clinical Oncology (JSCO) [3], administration of carboplatin (CBDCA) at an area under the curve (AUC) dosage of 4 mg/mL per minute or more is classified as the highest risk factor for CINV in those receiving moderately emetogenic chemotherapy (MEC). In the National Comprehensive Cancer Network guideline [4], CBDCA at an AUC of 4 mg/mL per minute or more is classified as highly emetogenic chemotherapy (HEC). All guidelines recommend a triple prophylactic antiemetic therapy with 5-hydroxytryptamine-3 receptor antagonist (5-HT_3 RA), dexamethasone (DEX), and neurokinin-1 receptor antagonist (NK_1 RA).

The changed classifications of CBDCA are, however, based on results from patients receiving CBDCA in several clinical trials of MEC or small sample studies [5–11]. For this reason, very little diary-collected data are available on which to base the incidence of CBDCA-induced CINV in chemotherapy-naive patients.

In our previous study, we enrolled patients after the first cycle of MEC or HEC in a nationwide prospective survey of CINV in Japan [12]. The survey was conducted at 108 institutions that included cancer centers, university hospitals, and cancer treatment hospitals certified by the Ministry of Health, Labour and Welfare in Japan. The strength of this prospective observational study was its use of 7-day diaries for collection of CINV data that began on day 1 after chemotherapy. Well-known high-risk factors for CINV include young age, female sex, prior pregnancy-related morning or motion sickness, no prior alcohol consumption, and a poor performance status [13–16]. Previously, pooled analyses of HEC, including cisplatin, were carried out to identify risk factors for CINV; however, it is thought that they interact with each other, and therefore, such results of previous studies are not applicable to CBDCA.

Therefore, this study was carried out to clarify the incidence of CINV and identify the risk factors for CINV in a nationwide registry of patients who underwent CBDCA-based chemotherapy.

Materials and Methods

A prospective, observational multicenter study was carried out at 108 institutions by the CINV Study Group of Japan [12]. Overall, 2,068 patients enrolled from April 2011 to December 2012 were included. This study analyzed registry data on patients who received CBDCA. Of 2,068 registered patients, data for 1,910 (HEC: 1,195; MEC: 715) patients were analyzed. In total, 400 patients received CBDCA-based chemotherapy; 15 of these patients were excluded because of nonadherence to the antiemetic guideline. In all, 385 patients were included in the analyses.

Data Collection and Evaluation of the Control of CINV

The data were collected from patients' diaries. Patients recorded nausea severity graded on a visual analog scale, frequency of vomiting, amount of food intake, and use of rescue medication. The daily diary began on day 1 of chemotherapy and entries were made over a 7-day period.

The control of nausea and vomiting, achievement of complete response (CR; no vomiting without any rescue medication), and use of rescue medication were assessed during the acute (0–24 hours after CBDCA), delayed (24 hours–7 days), and overall (0 hours–7 days) periods.

Antiemetic Drugs

The JSCO antiemetic guideline recommended two antiemetics for MEC: $5HT_3$ RA and DEX. For CBDCA-based

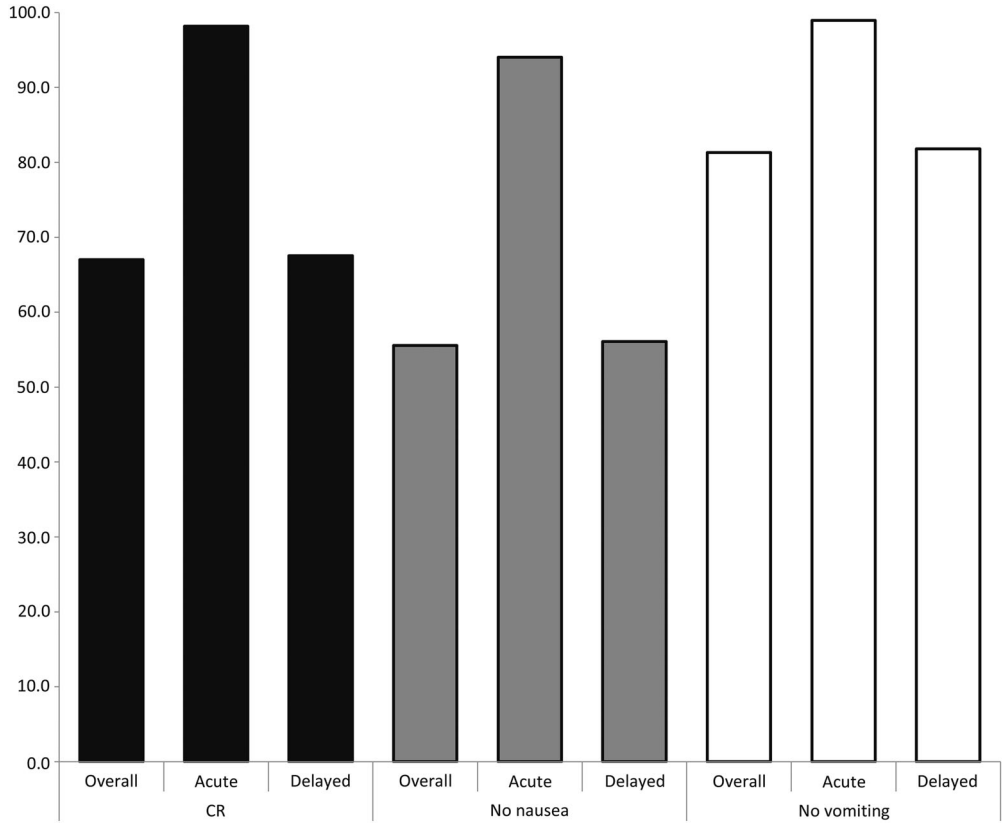

Figure 2. Percentage of complete response, no nausea, and no vomiting during the overall, acute, and delayed phases of chemotherapy-induced nausea and vomiting in patients who complied with the guideline.
Abbreviation: CR, complete response.

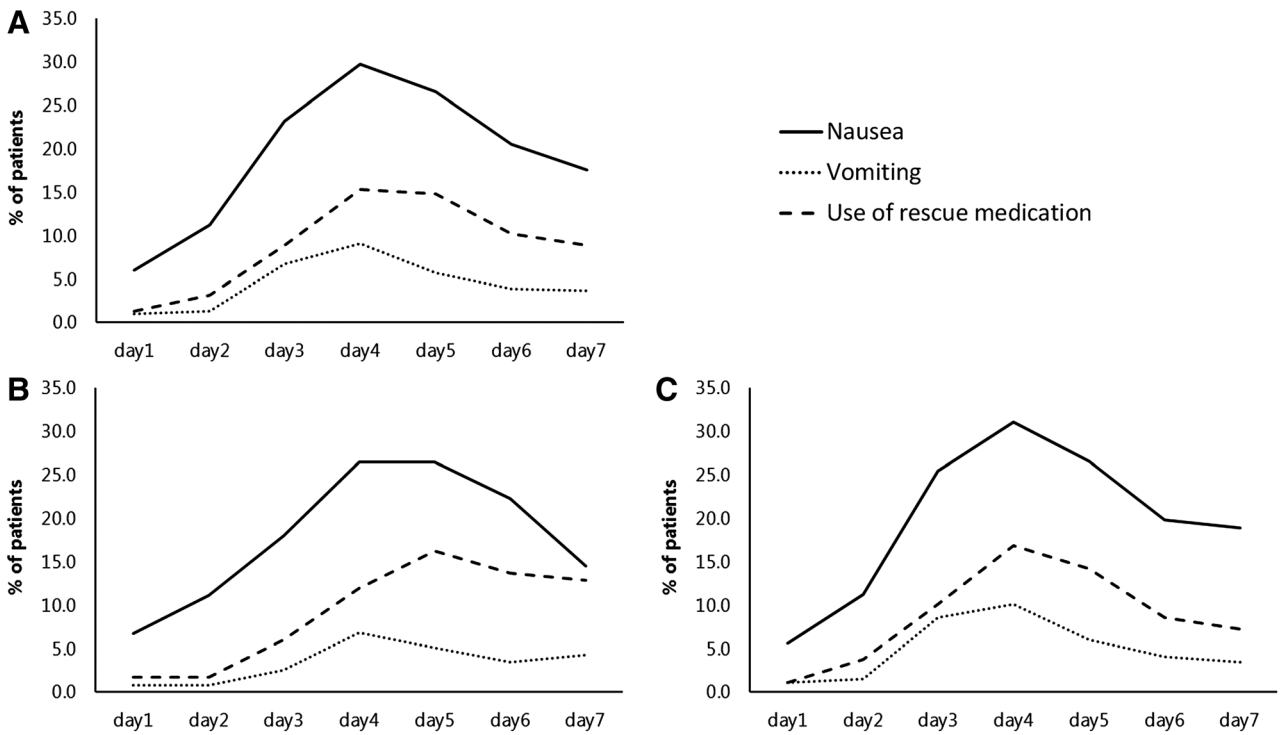

Figure 3. The incidence of nausea, vomiting, and rescue medication use over 7 days starting on the first day of chemotherapy in patients who complied with the guideline. **(A):** All patients (*n* = 385). **(B):** Patients with aprepitant use (*n* = 118). **(C):** Patients without aprepitant use (*n* = 267).

Table 1. Patients' characteristics

Characteristics	*n* (%)
Number of patients	385
Median age (range)	64 (28–85)
Sex	
Male	162 (42.1)
Female	223 (57.9)
Cancer type	
Breast	8 (2.1)
Gastrointestinal	2 (0.5)
Gynecologic	155 (40.3)
Lung	216 (56.1)
Hematologic	4 (1.0)
Disease status	
Primary	356 (92.5)
Recurrent	29 (7.5)
Stage	
I	74 (19.2)
II	28 (7.3)
III	101 (26.2)
IV	153 (39.7)
Recurrence	29 (7.5)
ECOG PS	
0	201 (52.2)
1	168 (43.6)
2	14 (3.6)
3	2 (0.5)
Motion sickness	
No	326 (84.7)
Yes	59 (15.3)
History of pregnancy	
No	45 (11.7)
Yes	178 (46.2)
Unknown	162 (42.1)
History of pregnancy-related emesis	
No	89 (23.1)
Yes	87 (22.6)
Unknown	209 (54.3)
Habitual alcohol consumption	
No	294 (76.4)
Yes	91 (23.6)
Antiemetics	
2 antiemetics	267 (69.4)
3 antiemetics	118 (30.6)
Palonosetron	
No	233 (60.5)
Yes	152 (39.5)

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Chemotherapy regimen

Chemotherapy regimen	*n* (%)
Brest	
TRZ + CBDCA+DOC	8 (2.1)
Gastrointestinal	
CBDCA+GEM	1 (0.3)
CBDCA+PTX	1 (0.3)
Gynecologic	
CBDCA+PTX	138 (35.8)
CBDCA+DOC	16 (4.2)
CBDCA+DXR	1 (0.3)
Lung	
CBDCA+PEM	87 (22.6)
CBDCA+PTX	46 (11.9)
CBDCA+ETP	40 (10.4)
CBDCA+GEM	17 (4.4)
CBDCA+S-1	15 (3.9)
CBDCA+CPT-11	8 (2.1)
CBDCA+AMR	2 (0.5)
CBDCA+DOC	1 (0.3)
Hematologic	
DeVIC	4 (1.0)

Abbreviations: AMR, amrubicin; CPT-11, irinotecan; DeVIC, ifosfamide, carboplatin, etoposide, and dexamethasone; DOC, docetaxel; DXR, doxorubicin; ETP, etoposide; GEM, gemcitabine; PEM, pemetrexed; PTX, paclitaxel; S-1, tegafur-gimeracil-oteracil potassium; TRZ, trastuzumab.

chemotherapy, addition of the antiemetic NK_1 RA to $5HT_3$ RA and DEX was considered optional for prophylaxis. In this study, patients who received either two antiemetics or three antiemetics were considered to be in compliance with the guideline.

Statistical Analysis

Patients' characteristics were summarized using descriptive statistics or contingency tables. Logistic regression analyses were carried out to identify risk factors associated with non-CR during the overall period. The baseline variables used for this evaluation were age, sex, motion sickness, habitual alcohol consumption, no use of NK_1 RA, performance status, and cancer type. The patterns for CINV and use of rescue medication were evaluated on days 1–7 after the start of chemotherapy.

Two-sided p values <.05 were determined as statistically significant. In this study, SAS 9.4 (SAS Institute, Cary, NC) was used for the analyses.

Ethical Considerations

The study protocol was approved by the institutional review board at each participating institute. All patients provided written informed consent prior to study initiation.

Table 3. Prognostic factors of noncomplete response during the overall period

	Univariate		Multivariate	
Prognostic factors	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
Age	0.966 (0.948–0.985)	.0005	0.968 (0.947–0.990)	.0040
Sex: female vs. male	2.167 (1.380–3.404)	.0008	2.326 (1.190–4.546)	.0135
Motion sickness: yes vs. no	1.251 (0.703–2.227)	.4457	0.935 (0.503–1.738)	.8320
Habitual alcohol consumption: yes vs. no	0.454 (0.260–0.794)	.0056	0.555 (0.300–1.027)	.0609
Antiemetics: 2 antiemetics vs. 3 antiemetics	1.575 (0.975–2.546)	.0635	1.766 (1.053–2.962)	.0311
ECOG PS: 0–1 vs. 2–3	2.193 (0.614–7.840)	.2269	1.769 (0.481–6.502)	.3905
Cancer type: other vs. lung	2.484 (0.836–7.375)	.1013	1.045 (0.306–3.565)	.9439
Cancer type: gynecologic vs. lung	1.485 (0.957–2.304)	.0774	0.470 (0.237–0.931)	.0305

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; OR, odds ratio.

Table 4. Control of chemotherapy-induced nausea and vomiting (CINV) during the overall, acute, and delayed periods of CINV analyzed according to sex, antiemetics, and cancer type

	Complete responses			No nausea			No vomiting		
Subgroups	**Overall period, *n* (%)**	**Acute period, *n* (%)**	**Delayed period, *n* (%)**	**Overall period, *n* (%)**	**Acute period, *n* (%)**	**Delayed period, *n* (%)**	**Overall period, *n* (%)**	**Acute period, *n* (%)**	**Delayed period, *n* (%)**
Sex									
Female (*n* = 223)	134 (60.1)	218 (97.8)	135 (60.5)	105 (47.1)	208 (93.3)	107 (48.0)	165 (74.0)	221 (99.1)	165 (74.0)
Male (*n* = 162)	124 (76.5)	160 (98.8)	125 (77.2)	109 (67.3)	154 (95.1)	109 (67.3)	148 (91.4)	160 (98.8)	150 (92.6)
Antiemetics (all subjects)									
2 antiemetics (*n* = 267)	171 (64.0)	262 (98.1)	173 (64.8)	139 (52.1)	252 (94.4)	141 (52.8)	208 (77.9)	264 (98.9)	210 (78.7)
3 antiemetics (*n* = 118)	87 (73.7)	116 (98.3)	87 (73.7)	75 (63.6)	110 (93.2)	75 (63.6)	105 (89.0)	117 (99.2)	105 (89.0)
Antiemetics (using 1st generation $5HT_3RA$)									
2 antiemetics (*n* = 181)	118 (65.2)	177 (97.8)	119 (65.8)	94 (51.9)	170 (93.9)	95 (52.5)	139 (76.8)	179 (98.9)	140 (77.4)
3 antiemetics (*n* = 52)	37 (71.2)	51 (98.1)	38 (73.1)	30 (57.7)	51 (98.1)	30 (57.7)	47 (90.4)	52 (100)	47 (90.4)
Antiemetics (using palonosetron)									
2 antiemetics (*n* = 84)	51 (60.7)	83 (98.8)	52 (61.9)	43 (51.2)	80 (95.2)	44 (52.4)	67 (79.8)	83 (98.8)	68 (81.0)
3 antiemetics (*n* = 66)	50 (75.8)	65 (98.5)	49 (74.2)	45 (68.2)	59 (89.4)	45 (68.2)	58 (87.9)	65 (98.5)	58 (87.9)
Antiemetics (all subjects)									
1st generation $5HT_3RA$ (*n* = 233)	155 (66.5)	228 (97.9)	157 (67.4)	124 (53.2)	221 (94.9)	125 (53.7)	186 (79.8)	231 (99.1)	187 (80.3)
Palonosetron (*n* = 150)	101 (67.3)	148 (98.7)	101 (67.3)	88 (58.7)	139 (92.7)	89 (59.3)	125 (83.3)	148 (98.7)	126 (84.0)
Antiemetics (using 2 antiemetics)									
1st generation $5HT_3RA$ (*n* = 181)	118 (65.2)	177 (97.8)	119 (65.8)	94 (51.9)	170 (93.9)	95 (52.5)	139 (76.8)	179 (98.9)	140 (77.4)
Palonosetron (*n* = 84)	51 (60.7)	83 (98.8)	52 (61.9)	43 (51.2)	80 (95.2)	44 (52.4)	67 (79.8)	83 (98.8)	68 (81.0)
Antiemetics (using 3 antiemetics)									
1st generation $5HT_3RA$ (*n* = 52)	37 (71.2)	51 (98.1)	38 (73.1)	30 (57.7)	51 (98.1)	30 (57.7)	47 (90.4)	52 (100)	47 (90.4)
Palonosetron (*n* = 66)	50 (75.8)	65 (98.5)	49 (74.2)	45 (68.2)	59 (89.4)	45 (68.2)	58 (87.9)	65 (98.5)	58 (87.9)
Cancer type									
Gynecologic (*n* = 155)	97 (62.6)	151 (97.4)	97 (62.6)	73 (47.1)	144 (92.9)	74 (47.7)	117 (75.5)	154 (99.4)	116 (74.8)
Lung (*n* = 216)	154 (71.3)	213 (98.6)	156 (72.2)	136 (63.0)	204 (94.4)	137 (63.4)	185 (85.7)	213 (98.6)	188 (87.0)

Abbreviation: $5HT_3RA$, 5-hydroxytryptamine-3 receptor antagonist.

Results

Characteristics of Patients

Four hundred patients in the registry were scheduled for CBDCA-based chemotherapy. Among these patients, 267 patients were treated with two antiemetics and 118 with three antiemetics. This result shows that 96% of patients underwent treatment with antiemetic therapy in compliance with the JSCO antiemesis guideline. The selection of the final 385 patients targeted for further analysis, their characteristics, and chemotherapy regimens are described in Figure 1, Table 1, and Table 2, respectively.

Regarding antiemetic prophylaxis of delayed CINV, 35.0% of patients who received 5-HT_3 RA without NK_1 RA required administration of DEX during the delayed phase. However, 77.0% of these patients were receiving high-dose DEX as premedication for paclitaxel allergy prevention on day 1. As a result, these patients did not receive DEX for delayed CINV, but the average DEX dose for the overall period was 16.2 mg.

Control of CINV

As shown in Figure 2, during the overall period and the acute and delayed phases of CINV, antiemetic therapy resulted in a CR rate of 67.0%, 98.2%, and 67.5%, respectively, no-nausea rate of 55.6%, 94.0%, and 56.1%, respectively, and no-vomiting rate of 81.3%, 99.0%, and 81.8%, respectively. Except rescue medication administration for patients with aprepitant, the incidences of CINV and rescue medication administration after chemotherapy (as shown in Fig. 3) were the highest on day 4 after chemotherapy. The incidence of rescue use for patients with aprepitant was the highest on day 5 after chemotherapy.

Risk Factor Analysis of Antiemetic Non-CR During the Overall Period

In the logistic regression analysis (Table 3), we identified four independent risk factors. Older age (odds ratios [OR], 0.968; 95% confidence interval [CI], 0.947–0.990; p = .0040) and gynecologic cancer (OR, 0.470; 95% CI, 0.237–0.931; p = .0305) were associated with a decrease of non-CR, whereas female sex (OR, 2.326; 95% CI, 1.190–4.546; p = .0135) and dual antiemetic therapy (OR, 1.766; 95% CI, 1.053–2.962; p = .0311) were associated with an increase of non-CR. However, there was an interaction between the type of antiemetic regimen and the type of disease in the logistic regression model.

NK_1 RA was used in 26.4% of patients with lung cancer and 17.4% of patients with gynecologic cancer. The CR rate was 71.9% and 70.4% for patients with lung cancer receiving two antiemetics and three antiemetics, respectively, whereas it was 57.4% and 81.8% for patients with gynecologic cancer receiving two antiemetics and three antiemetics, respectively.

For female patients, a logistic regression analysis including history of pregnancy-related emesis identified the same risk factors as the overall analysis. And, history of pregnancy-related emesis was recognized as a new factor (OR, 2.777; 95% CI, 1.428–5.401; p = .0026).

Control of CINV in Subgroups by Sex, Antiemetic Combination, and Cancer Type

The antiemetic effects during the overall period and the acute and delayed phases of CINV in various subgroups are shown in Table 4. During the overall period, the rate of CINV control was numerically greater in male than female patients, patients treated with three antiemetics than patients treated with two antiemetics, and patients with lung cancer than those with gynecologic cancer.

Discussion

CINV in real world settings was evaluated for the first time by using data gathered from the 7-day self-report diaries of patients enrolled in a large-scale prospective registry who received CBDCA-based chemotherapy. Since the publication of guidelines in 2010 in Japan, antiemetic prophylaxis with a combination of $5HT_3$ RA and DEX or combination of $5HT_3$ RA, DEX, and NK_1 RA has been recommended for CBDCA-based regimens [3]. Therefore, it is thought that use of both antiemetic regimens during the study period comply with the JSCO guideline. The present study recruited 400 patients, 96% of whom received antiemetics in compliance with the antiemesis guidelines. Even in those receiving MEC regimens, the rate of compliance in our study was quite high compared with rates in previous reports, which ranged from 30% to 60% depending on geographic region [17–19]. This is partly because, in Japan, the first cancer control law was enacted in 2006, and the first and second action plans to implement the cancer control act were defined in 2007 and 2012, respectively [20]. The action plans included establishment of a system of standard chemotherapy, formulation of guidelines, and promotion of team-based care in oncology. These policies may have influenced compliance with the guidelines. We previously reported that pharmacist participation in the oncology team helps to improve and maintain compliance with antiemetic therapy guidelines [21–23].

The rates of CR, no nausea, and no vomiting during the overall period were 67.0%, 55.6%, and 81.3%, respectively. In the triple antiemetic (including NK_1 RA) subgroup, the rate of CR during the overall period was 73.7%. This was comparable to the rates found by Weinstein et al. (77.8%) and Hesketh et al. (80.2%) in CBDCA subgroup analysis of large phase III trials that evaluated fosaprepitant and rolapitant, respectively [5, 6]. The rates of no nausea and no vomiting during the overall period in those receiving the 3 antiemetics were 63.6% and 89.0%, respectively, and comparable to the rates reported by Hesketh et al. (no nausea 62.5%, no vomiting 87.5%) [5].

It is important to know the patterns of CINV incidence and rescue medication use. Regarding patients receiving CBDCA regimens but no antiemetic prophylaxis, Martin et al. reported that vomiting began 48 hours after the start of chemotherapy [24]. The incidence and mean period of latency of vomiting were 82% and 6.25 hours, respectively. In contrast, in our study with prophylactic administration of antiemetic agents, after excluding rescue medication administration for patients with aprepitant, the peak incidence of nausea, vomiting, and rescue medication use

occurred on day 4 regardless of the use of NK_1 RA. This incidence pattern is quite similar to that of cisplatin [12]. Most previous studies monitored the incidence of CINV for only 5 days after chemotherapy, whereas we investigated it for 7 days after chemotherapy. Notably on day 7, the incidences of nausea, vomiting, and rescue medication use were 17.6%, 3.7%, and 8.9%, respectively. Therefore, particular attention should be paid to symptoms after day 6, and, in future research on CINV, the investigation period should be at least 7 days.

Female sex, younger age, low performance status, and nonhabitual alcohol consumption, are known risk factors for CINV [13–16]. In a risk factor analysis for non-CR during the overall period, we found that younger age, female sex, history of pregnancy-related emesis, and dual antiemetic therapy were significant and independent non-CR risk factors. Recent studies have revealed that the combined use of $5HT_3$ RA and DEX with NK_1 RA improves CBDCA-induced CINV [5–11]. The identification of dual antiemetic therapy as a risk factor in the present study is consistent with the results of these studies. However, there was an interaction between the type of antiemetic regimen and the type of disease in the logistic regression model. In patients with lung cancer, the CR rate was around 70% whether or not NK_1 RA was administered. Thus, in patients with lung cancer who do not have other risk factors, the combination of NK_1 RA may not be necessary. Younger age, female sex, and history of pregnancy-related emesis are well-known risk factors in patients with various backgrounds [13–16]. The present study in patients receiving CBDCA also identified these three factors as important independent risk factors. Therefore, improved antiemetic treatment during chemotherapy is needed in these patients to optimize their care. Olanzapine also appears to reduce the incidence of CINV during chemotherapy, although it is a multiacting receptor-targeted antipsychotic that blocks not only dopaminergic D_1, D_2, D_3, and D_4 receptors but also serotonergic 5-TH_{2A}, 5-HT_{2B}, 5-HT_3, and 5-HT_6 receptors, histamine H_1 receptors, and muscarinic acetylcholine receptors M_1, M_2, M_3, and M_4 [25]. The efficacy and safety of 10 mg olanzapine and standard triple antiemetic therapy have been shown in a randomized, double-blind phase III study in patients given HEC, including anthracycline-cyclophosphamide and cisplatin [26]. Four antiemetics, including olanzapine, may be recommended for younger and female CBDCA-administered patients. However, it is important to know that 10 mg of olanzapine causes drowsiness and unsteadiness especially in elderly patients at risk of falls.

Although this prospective observational study is well designed and has produced very valuable results, it is limited by the lack of treatment randomization, controls, and face-to-face comparison of two antiemetics with three antiemetics. Although the present results were preliminary and obtained in the Japanese population, they are likely applicable to other Asian populations. Further research in this area is needed to verify the applicability of these results.

Conclusion

Our large-scale nationwide prospective registry study revealed that three antiemetics including NK_1 RA are needed for appropriate antiemetic prophylaxis of CBDCA-induced CINV. This reasonable conclusion is consistent with the recommendations of various guidelines. Nevertheless, there are still patients whose CBDCA-induced CINV is insufficiently controlled by antiemetic therapy consistent with these guidelines. Younger age, female sex, history of pregnancy-related emesis, and double antiemetic prophylaxis were identified as risk factors for non-CR during the overall period. Therefore, triplet antiemetic therapy with NK_1 RA should be prescribed when a CBDCA-based regimen is scheduled. Improvement in prophylactic antiemetic therapy combining antiemetic agents with different mechanisms of action such as olanzapine is needed for patients who have these risk factors.

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Disclosures

Hitoshi Kawazoe: Ono Pharmaceutical (H), Merck, Sanofi, Merck Sharp & Dohme, Astellas Pharma, Daiichi Sankyo, Chugai Pharmaceutical (RF); **Toshiaki Saeki:** Cyugai Pharmaceutics, Ono Pharmaceutics, Taiho Pharma, Kyowa Hakko Kirin, Eisai (RF); **Kazuo Tamura:** Ono Pharmaceutical Co. (H). The other authors indicated no financial relationships.

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