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ORIGINAL ARTICLE

Controlling chemotherapy-induced nausea requires further improvement: symptom experience and risk factors among Korean patients

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Abstract
Purpose The purpose of the present study is to describe the incidence and intensity of chemotherapy-induced nausea and vomiting (CINV) and patterns of symptom change after chemotherapy among Korean cancer patients for whom antiemetic guidelines were widely utilized and guideline-consistent antiemetics were available. The study also aimed to determine the contribution of known risk factors for CINV to the incidence and intensity of CINV, as well as patterns of symptom change.
Methods A prospective observational descriptive study was conducted. A total of 332 adult cancer patients starting their first adjuvant chemotherapy participated in this study. Items of the Multinational Association of Supportive Care in Cancer Antiemesis Tool were utilized to generate a symptom diary. Descriptive statistics, logistic regression analyses, repeated measures ANOVA, and hierarchical generalized linear models were applied to analyze the data.
Results Vomiting occurred, on average, less than once in the acute and delayed phases, and its frequency remained similar throughout 5 days after chemotherapy infusion in the first and second cycles. A quadratic pattern of nausea change was found. Nausea intensity increased to a peak on the third day after chemotherapy infusion (first-cycle incidence rate ratio (IRR) = 1.40 and second-cycle IRR = 1.27, both $p < .001$) and then changed gradually (first-cycle IRR = 0.69 and second-cycle and IRR = 0.76, both $p < .001$). Nausea experience in the previous cycle contributed to the subsequent nausea intensity (IRR = 2.78, $p < .001$). Younger age, consuming less alcohol, and expecting nausea were identified as risk factors for chemotherapy-induced nausea that needed to be considered from the start of the chemotherapy.
Conclusions Nausea control, especially in the delayed phase, has room for improvement. As the first chemotherapy-induced nausea experience contributes to subsequent symptom experience, intense control from the start of chemotherapy is necessary while considering patient-related risk factors. Future studies should evaluate the contribution of risk factors when antiemetic prophylaxis is fully provided in multiple settings.

Keywords Chemotherapy · Nausea · Vomiting · Risk factors · Antiemetic

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) has been considered among the most distressful side effect of chemotherapy, affecting the functional status and quality of life of cancer patients. Poorly controlled CINV leads to unscheduled clinic visits, emergency room visits, and even hospitalization

[1]. An increased understanding of the mechanisms underlying CINV and the corresponding development of antiemetics and their guidelines [2–4] have significantly improved symptom control. Following antiemetic guidelines when chemotherapy begins is recommended for the prevention of CINV [2–4].

Actual clinical practice and subsequent symptom control are not currently optimal. An investigation of community-hospital-based clinical practices during 2005–2007 in the Netherlands [5] found that acute and delayed nausea occurred in 39 and 68 % of patients, respectively, with lower rates of acute (12 %) and delayed (23 %) vomiting. Suboptimal antiemetic coverage, with only 15 % receiving a triple-antiemetic regimen after highly emetogenic chemotherapy (HEC), might have contributed to the poor symptom control observed in the study. An investigation of CINV in clinical practices in the Asia-Pacific region during 2011 and 2012 [6] also found a high occurrence rate of nausea (61.6 %), while the rate of emesis was relatively low (25.2 %) among patients receiving HEC. Again, the proportion of patients receiving a triple-antiemetic regimen for HEC was limited to 38.7 % [1]. Improved nausea control after moderately emetogenic chemotherapy (MEC) was demonstrated by occurrence rates of acute and delayed nausea of 23.3 and 38.5 %, respectively [7]. This study reflected improvements in clinical practice during 2012 and 2013, although more than half of the participants did not receive antiemetic prophylaxis for the delayed phase, which limited the generalizability of the findings. These studies used clinical data through 2012 and then data limited to CINV after MEC from 2012, demonstrating nonoptimal antiemetic prophylaxis. Clinical data from 2012, reflecting symptoms after both HEC and MEC, could provide information about the current status of CINV management and areas that require further attention.

Patients who suffer from symptoms despite the continuous improvements in antiemetic prophylaxis require special attention. Patients with personal risk factors reportedly have a higher risk of nausea even when advanced symptom control is applied with antiemetics, including aprepitant, extended-duration dexamethasone, or olanzapine [8]. Previously reported key risk factors, such as chemotherapy emetogenicity, are no longer risk factors when sufficient antiemetics are applied for prophylaxis [9]. Clinical data regarding CINV experiences when the best available antiemetic prophylaxis is administered would facilitate risk factor analysis of CINV.

Antiemetic guidelines are well adapted, and antiemetics are fully available through reimbursement in the Republic of Korea, making an evaluation of current antiemetic practice appropriate. This study investigated the current status of CINV management among Korean cancer patients in a setting in which antiemetic guidelines were widely utilized and guideline-consistent antiemetics were available. This prospective observational study aimed to describe the actual experiences with CINV of patients receiving prophylactic, as well as p.r.n. (as needed) antiemetics. Whether the known risk factors for CINV remained influential risk factors with current antiemesis was also evaluated.

Purpose

The purpose of this study was to describe the incidence and intensity of CINV and the patterns of symptom changes after chemotherapy among Korean cancer patients for whom antiemetic guidelines were widely utilized and guideline-consistent antiemetics were available. The study also aimed to determine the contribution of known risk factors for CINV to the incidence and intensity of CINV, as well as patterns of symptom changes.

Methods

Design

This study was a prospective, observational, descriptive study.

Sample

A total of 332 adult cancer patients diagnosed as having stomach, lung, breast, or colorectal cancer and who were starting their first adjuvant chemotherapy participated in this study. The patients were recruited from outpatient clinics and inpatient wards of a university hospital in Seoul, Republic of Korea. Patients who were expected to receive at least three cycles of HEC or MEC in single-day chemotherapy were eligible for inclusion. Patients with colorectal cancer were included if they were receiving continuous infusion of 5-FU for 2 days. The exclusion criteria were receiving concurrent radiotherapy or the presence of health issues that could cause nausea or vomiting (e.g., bowel obstruction), cognitive problems, or a history of psychiatric problems. Of the 332 participants, 313 and 284 patients provided data regarding CINV experiences during the first and second cycles of chemotherapy, respectively. Data were available at all data collection points for 274 cancer patients (77.6 % retention rate) (Table 1). Those subjects who dropped out of the study before completing the first symptom diary ($n = 40$) were significantly older than the remaining participants ($t = -2.914$, $p = .004$). The types of cancer were evenly distributed among the dropouts (8–12 patients for each cancer), while a large proportion of the remaining participants had breast cancer. There were no differences in terms of sex, cancer stage, ECOG status, emetogenicity of the chemotherapy regimen, or treatment setting.

Table 1 General characteristics of patients

	Total (N = 332)	First cycle (n = 313)	Second cycle (n = 284)
Age	52.12 ± 9.96	52.03 ± 9.93	51.96 ± 9.54
Gender			
Male	109 (32.8)	101 (32.3)	93 (32.7)
Female	223 (67.2)	212 (67.7)	191 (67.3)
Cancer Dx			
Breast	154 (46.4)	148 (47.3)	137 (48.2)
Colorectal	62 (18.7)	59 (18.8)	53 (18.7)
Stomach	60 (18.1)	56 (17.9)	51 (18.0)
Lung	56 (16.9)	50 (16.0)	43 (15.1)
Stage			
0	1 (0.3)	1 (0.3)	1 (0.4)
1	79 (23.8)	76 (24.3)	71 (25.0)
2	120 (36.1)	113 (36.1)	103 (36.3)
3	122 (36.7)	113 (36.1)	99 (34.9)
4	10 (3.0)	10 (3.2)	10 (3.5)
ECOG			
0	329 (99.1)	310 (99.0)	282 (99.3)
1	3 (0.9)	3 (1.0)	2 (0.7)
CTx			
HEC	211 (63.6)	199 (63.6)	180 (63.4)
MEC	121 (36.4)	114 (36.4)	104 (36.6)
Setting			
Outpatient	235 (70.8)	223 (71.2)	203 (71.5)
Inpatient	97 (29.2)	90 (28.8)	81 (28.5)

n(%)

Measurements

Items of the Multinational Association of Supportive Care in Cancer Antiemesis Tool [10] were utilized to generate a symptom diary. The participating patients were asked to log incidences of vomiting, the severity of nausea, and the use of p.r.n. antiemetics. A list of CINV risk factors was included as survey questions. Demographic characteristics were obtained from the patients using structured questionnaires, while clinical characteristics, such as the type of cancer diagnosis, chemotherapy regimen, and antiemetic prescription, were retrieved from electronic medical records.

Procedures

The study was approved by the Institutional Review Board (IRB approval number 4-2012-0504). The purpose and details of the study protocol were explained to the patients, who then provided written informed consent. Patient data were collected between December 2012 and February 2015. Consistency with inclusion and exclusion criteria was confirmed by research nurses. The participants were asked to log their CINV experiences in the symptom diary for 5 days, including the frequency of vomiting, intensity of nausea, and use and effects of p.r.n. antiemetics. The participants were asked to return their diaries when they next visited the hospital. Research nurses reviewed the diaries to confirm the use of p.r.n. antiemetics and to find any erroneous remarks. CINV risk factors were inquired about at the end of the study because some of the risk factors for CINV, such as expectations regarding symptoms, might evoke CINV. This was an observational study and thus did not involve providing or changing the chemotherapy or antiemetic regimen.

Analysis

Standard statistical software (SPSS 22 and STATA 14) was used to analyze the data. Descriptive statistics were utilized to provide general information about the characteristics of the participants and key values of CINV. To describe the overall symptom experience of CINV, patients receiving both HEC and MEC were included in the analyses. The evaluation of antiemetic use included the entire group while incorporating emetogenicity-specific criteria (Table 2). For example, the use of a triple antiemetic regimen ($5HT_3$ RA + NK1 RA + dexamethasone) was considered to adhere to HEC, whereas it was

Table 2 Chemotherapy regimen and antiemetic use

	Total (N = 332)	First cycle (n = 313)	Second cycle (n = 284)
Chemotherapy regimen			
AC	150 (45.2)	144 (46.0)	133 (46.8)
AC + F	1 (0.3)	1 (0.3)	1 (0.4)
CMF	3 (0.9)	3 (1.0)	3 (1.1)
Carboplatin + Navelbin	1 (0.3)	1 (0.3)	1 (0.4)
Cisplatin +5-FU	4 (1.2)	3 (1.0)	2 (0.7)
Cisplatin + Navelbin	54 (16.3)	49 (15.6)	42 (14.8)
Cisplatin + TS1	2 (0.6)	2 (0.6)	2 (0.7)
FOLFOX	55 (16.6)	52 (16.6)	48 (17.9)
Oxaliplatin + Xeloda	62 (18.7)	58 (18.5)	53 (18.3)
Antiemetic prescription			
5HT3RA	330 (99.4)	311 (99.4)	276 (97.2)
NK1RA	213 (64.2)	200 (63.9)	202 (71.1)
Dexamethasone	273 (82.3)	256 (81.8)	234 (82.4)
Metoclopramide (prn)	215 (64.8)	202 (64.5)	153 (53.9)
Benzodiazepine (prn)	135 (40.7)	128 (40.9)	132 (46.5)
Antiemetic regimen			
$5HT_3RA$ + NK1RA + dexa	210 (63.3)	197 (62.9)	197 (69.4)
$5HT_3RA$ + dexa	61 (18.4)	57 (18.2)	33 (11.6)
Antiemetic guideline adherence			
Adhere	41 (12.3)	37 (11.8)	41 (14.4)
Adhere + alpha	31 (9.3)	30 (9.6)	24 (8.5)
Adhere + PRN	100 (30.1)	95 (30.4)	84 (29.6)
Adhere + alpha + PRN	90 (27.1)	84 (26.8)	67 (23.6)
Not adhere	70 (21.1)	67 (21.4)	71 (25.0)

n(%)

considered to utilize additional antiemetics (+ alpha) for MEC. In the evaluation of risk factors for CINV, the emetogenicity of chemotherapy regimens (HEC or MEC) was considered one of the risk factors for CINV; thus, the whole patient group was evaluated. Exceptions were the analyses that yielded results specific to the emetogenicity of the chemotherapy regimen: incidence of CINV and rates of emetogenicity-specific antiemetic adherence (Table 3 and the "Results" section). When specific patient groups were utilized for the analysis, subgroup membership was identified with "HEC" or "MEC" in the sentence. Risk factors were identified through logistic regression analyses. For the analysis of age as a risk factor, age as a continuous variable as well as a dichotomized variable (age <55 vs age ≥55) was utilized based on previous studies [11–13]. Repeated measures ANOVA evaluted CINV change over time. Hierarchical generalized linear models (HGLMs) involving multilevel negative binomial regression and Poisson regression analyses were applied to analyze the experience of chemotherapy-induced nausea (CIN) over two cycles of chemotherapy while considering individual variance, as well as risk factors for CIN.

Results

General characteristics

The participants were aged 52.12 ± 9.96 years, 67.2 % of them were female, and they had the following types of cancer: breast (46.4 %), colorectal (18.7 %), stomach (18.1 %), and lung (16.9 %). All of the patients were cared for by medical oncologists, and most of them received chemotherapy on an outpatient basis (71 %). More than half of the patients were receiving HEC (63.6 %). In the second cycle of chemotherapy, 14 patients received a reduced dose of the chemotherapy regimen, mainly due to CINV. One patient started chemotherapy with a reduced dose but received the standard dose in the second chemotherapy cycle (Table 1).

Antiemetic use

During the first cycle of chemotherapy, most of the patients received $5HT_3RA$ (99.4 %) and dexamethasone (81.8 %). NK1RA was prescribed to 63.9 % of the patients. A triple-antiemetic regimen consisting of $5HT_3RA$ + NK1RA + dexamethasone was prescribed to 62.9 % of the patients, while a two-drug regimen of $5HT_3RA$ + dexamethasone was provided to 18.2 % of the patients. In terms of guideline adherence, 78.6 % of the patients received guideline-recommended antiemetics, although only 11.8 % strictly adhered to the type and dose of the antiemetics without taking additional or prn antiemetics. A major change in the antiemetic prescription occurred in the second cycle in 18.0 % of the patients. The most frequent changes were adding aprepitant + dexamethasone (4.9 %), excluding dexamethasone (4.6 %), or adding aprepitant (2.8 %). Four patients did not receive antiemetic prophylaxis during the second cycle of chemotherapy. Metoclopramide was frequently prescribed as an additional and/or prn antiemetic (Table 2).

Among the patients who received HEC in the first cycle, 99 % received a guideline-recommended antiemetic regimen ($5HT_3RA$ + NK1RA + dexamethasone), whereas 50 % received the recommended $5HT_3RA$ + dexamethasone after MEC. In the second cycle, 98.9 % received guideline-recommended antiemetics for HEC, whereas only 31.7 % received them after MEC, and 18.3 % received a triple regimen for MEC in the second cycle.

CINV incidence

During the first cycle, 74.4 % of the patients did not vomit. However, nausea (defined as a nausea intensity of ≥1 out of 10) was experienced by 81.5 % of participants, with 64.9 % experiencing significant nausea (nausea intensity of ≥3 out of 10) [14]. In the second cycle, fewer patients experienced

Table 3 CINV incidence

	Cycle 1			Cycle 2		
	HEC (n = 199)	MEC (n = 114)	Total (n = 313)	HEC (n = 180)	MEC (n = 104)	Total (n = 284)
Overall						
No vomiting	80.4	64.0	74.4	82.8	66.3	76.8
No nausea	17.1	13.2	15.7	12.2	14.4	13.0
No sig nausea	32.7	31.6	32.3	28.9	26.9	28.2
Acute phase						
No vomiting	93.5	88.6	91.7	95.6	90.4	93.7
No nausea	50.3	60.5	54.0	37.8	44.2	40.1
No sig nausea	73.4	79.8	75.7	70.6	57.7	65.8
Delayed phase						
No vomiting	82.4	67.5	77.0	85.0	69.2	79.2
No nausea	19.6	14.0	17.3	12.2	16.3	13.7
No sig nausea	35.2	32.5	34.2	31.7	29.8	31.0

(%)

vomiting (76.8 %), and more patients experienced nausea (86.3 %) and significant nausea (71.1 %) (Table 3).

Frequency of chemotherapy-induced vomiting and intensity of CIN

The vomiting frequency and nausea intensity of each cycle are depicted in Fig. 1. Vomiting occurred, on average, less than once during the acute and delayed phases, and its frequency remained similar throughout 5 days after chemotherapy infusion in both cycles (p = .363 for the first cycle and p = .174 for the second cycle). The nausea intensities in the acute and delayed phases during the first cycle were 1.65 ± 2.43 and 2.91 ± 2.50, respectively; the corresponding ratings during the second cycle were 2.11 ± 2.59 and 3.23 ± 2.48. A quadratic pattern of nausea change was found in repeated measures ANOVA (p < .001 for both cycles). The HGLM analysis predicted the change in the CIN intensity (estimated nausea intensity in Fig. 1) accounting for individual variance in the CIN experience; the nausea intensity increased to a peak on the third day after chemotherapy infusion (first-cycle incidence rate ratio [IRR] = 1.40 and second-cycle IRR = 1.27, both p < .001) and then gradually changed (first-cycle IRR = .69 and second-cycle IRR = .76, both p < .001).

Prevalence of known risk factors for CINV

A history of morning sickness was reported in 30.7 % (n = 65) of the female participants. Approximately one quarter of the patients (n = 77, 24.6 %) had a history of motion sickness, and

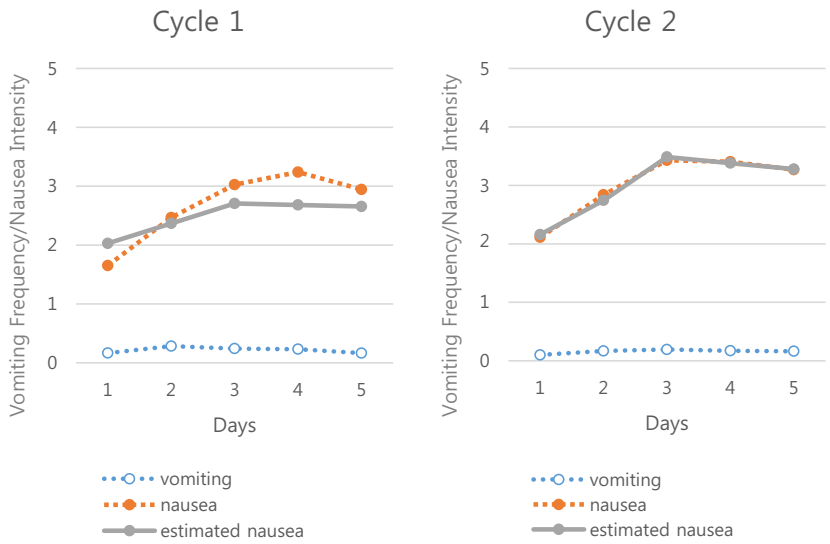

Fig. 1 Chemotherapy-induced vomiting frequency and nausea intensity

20.4 % (n = 64) reported a history of nausea and vomiting (NV) with stress. More than half (61.3 %, n = 192) consumed fewer than four glasses of alcoholic beverages per week. Approximately three quarters (70.6 %, n = 221) of the patients expected nausea with chemotherapy (with an intensity of 4.10 ± 3.23, range 0–10), and 62.3 % (n = 195) expected to vomit (with a frequency of 3.57 ± 3.30, range 0–10).

Logistic regression analyses: risk factors for NV and significant NV

The only risk factor that contributed to NV and significant NV during the first cycle was less alcohol consumption. Consuming fewer than four drinks per week increased the odds for NV (OR = 2.27, p = .010) and significant NV (OR = 1.87, p = .016). NV in the first cycle was a contributing factor to NV in the second cycle (OR = 7.45, p < .001). First-cycle significant NV (OR = 8.99, p < .001) and expecting nausea (OR = 2.57, p = .006) were contributing factors to significant NV in multiple logistic regression analysis (Table 4 and Appendix).

Logistic regression analyses: risk factors for vomiting, nausea, and significant nausea overall and in the acute and delayed phases

In the first cycle, having a history of morning sickness increased the odds for overall vomiting (OR = 2.39, p = .017) and delayed vomiting (OR = 2.93, p = .005), whereas receiving HEC decreased the odds for overall vomiting (OR = .35, p = .035) and delayed vomiting (OR = .33, p = .037) among female patients in multiple logistic regression analysis. Being younger than 55 years old (OR = 1.90, p = .018), consuming less alcohol (OR = 1.85, p = .029), and expecting nausea (OR = 2.45, p = .003) were the factors with greater odds for acute nausea.

In the second cycle, experiencing symptoms in the previous cycle was the strongest predictor of vomiting, nausea, and significant nausea, overall and in the acute and delayed phases (all p < .05). In multiple logistic regression analysis, HEC decreased the odds for overall, acute, and delayed vomiting (OR = .31, p = .005; OR = .18, p = .015; and OR = .38, p = .005, respectively). A history of morning sickness increased the odds for overall vomiting (OR = 2.49, p = .035) and delayed vomiting (OR = 2.61, p = .034) among female patients. Expecting nausea increased the odds for acute nausea (OR = 2.21, p = .011), overall significant nausea (OR = 2.49, p = .009), and delayed significant nausea (OR = 2.95, p = .001). Not adhering to antiemetic guidelines increased the odds for acute significant nausea (OR = 3.02, p = .014) (Table 4 and Appendix).

HGLM analysis of risk factors for nausea intensity

There was no significant change in vomiting frequency for 5 days in either cycle. Single risk factor analysis identified aging (as well as age ≥55) as a protective factor for nausea intensity in both cycles. Expecting nausea contributed to nausea intensity in both cycles. In multiple risk factor analyses, being younger than 55 years old and expecting nausea contributed to the nausea intensity of the first cycle (IRR = 1.36, p = .033 and IRR = 1.40, p = .038) and the second cycle (IRR = 1.12, p < .001 and IRR = 1.20, p < .001). Nausea experience in the previous cycle (IRR = 2.78, p < .001) was the most important factor contributing to nausea in the second cycle. Other risk factors were a history of motion sickness (IRR = 0.89, p = .004), a history of NV associated with stress (IRR = 1.18, p < .001), and receiving MEC (IRR = 1.23, p < .001). For female patients, a history of morning sickness (IRR = 1.14, p = .001) was the main risk factor, while histories of motion sickness and NV associated with stress were not significant (Table 5).

Discussion

Vomiting in the acute phase was better controlled in the present study than in previous studies [5, 6]. The 23 % incidence rate of delayed vomiting was similar to that found by Hilarius et al. but higher than that reported by Heish et al. (19.2 % after HEC and 16.1 % after MEC). Half of the patients received the recommended $5HT_3RA$ + dexamethasone regimen after MEC in the first cycle, which might explain the less satisfactory symptom control. CINV after HEC has long been the focus of symptom management. However, an improved understanding of the mechanisms underlying emesis after HEC and the adaptation of the triple-antiemetic regimen have changed CINV experiences. Vomiting occurred, on average, less than once over 5 days during the two cycles of chemotherapy in this study. As depicted in Fig. 1, the traditional biphasic pattern of emesis after cisplatin or a gradual peak in vomiting incidence after cyclophosphamide/carboplatin [15] was no longer observed. Notably, antiemetic prophylaxis according to antiemetic guidelines also improved the control of CINV after MEC [16]. Although the emetogenic potential of MEC is lower than that of HEC, poor antiemetic prophylaxis, especially in the delayed phase, can increase the symptoms experienced. In an era when a triple-antiemetic regimen provides good control of CINV after HEC [13, 17, 18], patients might suffer more CINV from MEC when antiemetic prophylaxis continues to be less satisfactory.

The control of nausea, especially in the delayed phase, continues to be problematic [19–21], including in the current study, because more than 65 % of the patients experienced significant nausea. The mechanisms underlying nausea are

Table 4 Simple logistic regression analyses regarding risk factors for CINV incidence

	age (< 55)				female				history of morning sickness (female only)				history of motion sickness				history of nausea and vomiting with stress			
	OR	95% CI		*p*-value	OR	95% CI		*p*-value	OR	95% CI		*p*-value	OR	95% CI		*p*-value	OR	95% CI		*p*-value
1st cycle																				
nausea and vomiting																				
cinv (vomiting & nausea ≥1)	1.75	0.95	3.24	.073	1.25	0.66	2.36	.497	1.41	.593	3.362	.437	1.22	0.59	2.53	.600	1.44	0.63	3.25	.385
significant cinv (vomiting & nausea ≥3)	1.34	0.82	2.19	.236	1.35	0.81	2.24	.247	1.81	.905	3.630	.093	1.10	0.62	1.94	.744	1.20	0.65	2.21	.564
vomiting																				
overall	1.40	0.80	2.46	.241	1.48	0.81	2.70	.200	2.06	1.048	4.054	.036*	1.59	0.87	2.88	.131	0.89	0.45	1.76	.737
acute	1.08	0.38	3.06	.881	2.14	0.60	7.71	.243	2.27	.701	7.340	.172	1.93	0.66	5.63	.226	0.55	0.12	2.50	.438
delayed	1.49	0.82	2.69	.186	1.48	0.79	2.78	.219	2.45	1.226	4.893	.011*	1.57	0.85	2.91	.150	0.92	0.45	1.86	.813
nausea																				
overall	1.75	0.95	3.24	.073	1.25	0.66	2.36	.497	1.41	.593	3.362	.437	1.22	0.59	2.53	.600	1.44	0.63	3.25	.385
acute	2.24	1.40	3.59	.001*	1.96	1.20	3.20	.007*	1.07	.588	1.929	.837	1.41	0.84	2.38	.195	1.58	0.90	2.75	.108
delayed	1.59	0.86	2.82	.143	1.17	0.63	2.17	.623	1.64	.696	3.866	.258	1.21	0.60	2.46	.591	1.38	0.63	3.00	.423
significant nausea																				
overall	1.29	0.79	2.10	.304	1.32	0.80	2.17	.286	1.57	.803	3.073	.187	1.10	0.63	1.93	.739	1.30	0.70	2.39	.407
acute	1.71	0.98	2.97	.058	1.56	0.87	2.80	.137	1.24	.640	2.399	.525	1.62	0.91	2.89	.101	1.93	1.05	3.52	.033*
delayed	1.20	0.74	1.93	.464	1.25	0.76	2.06	.384	1.47	.768	2.824	.244	1.07	0.61	1.85	.818	1.33	0.73	2.43	.355
2nd cycle																				
nausea and vomiting																				
cinv (vomiting & nausea ≥1)	1.53	0.75	3.11	.243	1.44	0.69	2.97	.330	5.47	1.23	24.27	.026*	1.48	0.62	3.56	.377	2.87	0.85	9.76	.091
significant cinv (vomiting & nausea ≥3)	1.03	0.60	1.77	.918	1.13	0.64	1.97	.678	1.79	0.86	3.73	.123	0.80	0.45	1.45	.466	1.23	0.62	2.44	.557
vomiting																				
overall	0.75	0.42	1.34	.332	1.27	0.68	2.39	.451	2.40	1.19	4.82	.014*	1.39	0.74	2.60	.302	1.52	0.77	3.00	.226
acute	1.17	0.38	3.60	.779	0.86	0.28	2.64	.792	0.99	0.24	4.10	.991	0.76	0.20	2.79	.674	1.68	0.51	5.57	.397
delayed	0.68	0.37	1.24	.210	1.27	0.66	2.45	.482	2.47	1.19	5.10	.015*	1.41	0.73	2.70	.303	1.45	0.71	2.95	.305
nausea																				
overall	1.37	0.68	2.74	.380	1.49	0.73	3.02	.273	3.65	1.04	12.82	.044*	1.60	0.67	3.81	.291	2.23	0.76	6.59	.145
acute	1.58	0.97	2.57	.067	1.61	0.97	2.66	.067	1.47	0.77	2.78	.240	1.25	0.72	2.16	.434	1.58	0.85	2.94	.146
delayed	1.55	0.79	3.06	.207	1.72	0.86	3.43	.123	3.59	1.02	12.62	.047*	1.70	0.71	4.04	.231	2.35	0.80	6.91	.121
significant nausea																				
overall	1.04	0.61	1.76	.890	1.26	0.73	2.16	.414	1.71	0.84	3.51	.142	0.83	0.46	1.48	.519	1.25	0.64	2.43	.521
acute	1.13	0.68	1.88	.642	1.03	0.61	1.76	.905	0.84	0.44	1.59	.587	1.25	0.71	2.18	.441	1.13	0.61	2.08	.704
delayed	1.09	0.65	1.82	.745	1.27	0.75	2.15	.383	1.56	0.78	3.11	.205	0.70	0.40	1.22	.208	1.15	0.60	2.19	.677

* $p < .05$

	alcohol less than 4 drinks per week				expecting nausea				expecting vomiting				highly emetogenic chemotherapy				not adhering to antiemetic guideline			
	OR	95% CI		*p*-value	OR	95% CI		*p*-value	OR	95% CI		*p*-value	OR	95% CI		*p*-value	OR	95% CI		*p*-value
1st cycle																				
nausea and vomiting																				
cinv (vomiting & nausea ≥1)	2.27	1.21	4.25	.010*	1.89	0.98	3.64	.056	1.44	0.76	2.71	.261	0.74	0.38	1.44	.377	2.11	0.86	5.21	.105
significant cinv (vomiting & nausea ≥3)	1.87	1.13	3.12	.016*	1.44	0.83	2.48	.195	1.22	0.73	2.03	.456	0.99	0.60	1.64	.980	0.95	0.53	1.71	.861
vomiting																				
overall	1.38	0.77	2.50	.282	1.41	0.73	2.73	.306	1.69	0.91	3.12	.097	0.42	0.24	0.72	.002*	2.57	1.41	4.69	.002*
acute	2.35	0.65	8.52	.194	0.53	0.18	1.53	.236	0.60	0.21	1.70	.333	0.42	0.15	1.17	.097	4.04	1.45	11.21	.007*
delayed	1.15	0.63	2.09	.659	1.52	0.76	3.05	.239	1.97	1.02	3.80	.043*	0.44	0.25	0.78	.005*	2.36	1.27	4.39	.007*
nausea																				
overall	2.27	1.21	4.25	.010*	1.89	0.98	3.64	.056	1.44	0.76	2.71	.261	0.74	0.39	1.44	.377	2.11	0.86	5.21	.105
acute	1.99	1.22	3.24	.006*	2.71	1.55	4.76	<.001*	2.08	1.27	3.42	.004*	1.49	0.93	2.38	.096	0.89	0.51	1.53	.660
delayed	1.88	1.02	3.44	.043*	1.63	0.85	3.09	.139	1.22	0.66	2.27	.532	0.71	0.37	1.34	.285	1.99	0.85	4.65	.111
significant nausea																				
overall	1.80	1.09	2.98	.023*	1.45	0.84	2.50	.179	1.29	0.78	2.15	.321	0.97	0.59	1.59	.890	0.94	0.52	1.68	.826
acute	1.47	0.83	2.62	.186	1.61	0.84	3.09	.152	1.82	1.00	3.31	.049*	1.41	0.81	2.46	.227	0.99	0.52	1.86	.973
delayed	1.63	0.99	2.69	.054	1.37	0.80	2.35	.255	1.27	0.77	2.10	.354	0.91	0.56	1.49	.709	0.97	0.54	1.72	.906
2nd cycle																				
nausea and vomiting																				
cinv (vomiting & nausea ≥1)	1.80	0.88	3.67	.107	2.19	1.05	4.58	.038*	1.54	0.75	3.16	.242	1.16	0.56	2.38	.696	0.70	0.33	1.52	.372
significant cinv (vomiting & nausea ≥3)	1.19	0.69	2.06	.533	2.43	1.37	4.32	.002*	1.54	0.89	2.66	.121	0.80	0.46	1.40	.442	1.10	0.59	2.03	.768
vomiting																				
overall	1.40	0.76	2.59	.285	2.56	1.15	5.70	.022*	1.90	0.98	3.66	.057	0.38	0.21	0.68	.001*	1.86	1.00	3.45	.050*
acute	0.74	0.25	2.19	.583	4.60	0.59	35.82	.145	3.21	0.70	14.65	.132	0.30	0.10	0.93	.037*	3.16	1.07	9.34	.038*
delayed	1.37	0.72	2.62	.339	2.12	0.94	4.75	.069	1.72	0.87	3.41	.119	0.36	0.20	0.66	.001*	1.71	0.90	3.27	.104
nausea																				
overall	2.04	1.01	4.09	.046*	2.22	1.08	4.57	.030*	1.77	0.88	3.55	.112	1.20	0.59	2.42	.621	0.66	0.31	1.40	.278
acute	1.70	1.04	2.78	.036*	3.10	1.78	5.39	<.001*	2.66	1.60	4.41	<.001*	1.27	0.78	2.08	.338	0.99	0.57	1.70	.956
delayed	2.15	1.08	4.30	.029*	2.29	1.13	4.62	.021*	1.78	0.90	3.53	.099	1.38	0.69	2.73	.360	0.63	0.30	1.31	.214
significant nausea																				
overall	1.27	0.75	2.18	.375	2.26	1.28	3.98	.005*	1.65	0.96	2.81	.068	0.89	0.52	1.53	.681	1.01	0.56	1.84	.966
acute	1.18	0.70	1.98	.534	1.73	0.94	3.16	.076	1.58	0.92	2.71	.098	0.54	0.32	0.89	.016*	2.49	1.43	4.33	.001*
delayed	1.26	0.75	2.11	.392	2.54	1.45	4.43	.001*	1.87	1.11	3.16	.019	0.89	0.53	1.51	.676	1.02	0.57	1.83	.945

* $p < .05$

	cinv in previous cycle				significant cinv in previous cycle				vomiting in the previous cycle				nausea in the previous cycle				significant nausea in the previous cycle			
	OR	95% CI		*p*-value	OR	95% CI		*p*-value	OR	95% CI		*p*-value	OR	95% CI		*p*-value	OR	95% CI		*p*-value
2nd cycle																				
nausea and vomiting																				
cinv (vomiting & nausea ≥1)	7.82	3.55	17.20	<.001*	10.30	4.26	24.93	<.001*												
significant cinv (vomiting & nausea ≥3)	7.33	3.66	14.68	<.001*	8.92	4.86	16.39	<.001*												
vomiting																				
overall									6.44	3.33	12.43	<.001*								
acute									11.16	2.85	43.60	0.001*								
delayed									5.30	2.70	10.36	<.001*								
nausea																				
overall													8.28	3.79	18.07	<.001*				
acute													4.83	2.43	9.61	<.001*				
delayed													7.25	3.38	15.56	<.001*				
significant nausea																				
overall																	10.34	5.61	19.05	<.001*
acute																	3.89	2.07	7.30	<.001*
delayed																	7.78	4.36	13.87	<.001*

* $p < .05$

poorly understood; thus, controlling CINV has been largely focused on vomiting, based on the belief that vomiting and nausea are closely related. However, as depicted in Fig. 1, NV demonstrated different patterns of change with the applied antiemetic prophylaxis. Reported patterns of nausea changes have remained similar despite the evolution of antiemetics over several decades. Nausea gradually increased up to day 3 in an evaluation of CINV using the Index of Nausea Vomiting and Retching among breast cancer patients [22]. This pattern of nausea has also been observed among breast cancer patients using a numeric rating scale [23]. The rate of nausea occurrence in the current study was higher than previously reported [21] for patients receiving $5HT_3RA$ + dexamethasone after MEC in the acute phase while not receiving antiemetic prophylaxis in the delayed phase, which resulted in 54 % of patients experiencing delayed nausea. Acute-phase symptom control might have contributed to delayed nausea control. In an investigation of CINV after MEC [7], most patients (95.3 %) received $5HT_3RA$ + corticosteroids in the acute phase, and approximately half did not receive antiemetics in the delayed phase. With satisfactory antiemetic prophylaxis in the acute phase, nausea was experienced by 23.3 and 38.5 % in the acute and delayed phases, respectively. However, great variations remain in delayed-phase antiemetic prophylaxis after MEC, and corticosteroids are often underprescribed (37.3 %).

Clinicians are concerned about the potential side effects of steroids [1]. A regimen of single-day corticosteroid + palonosetron could be considered for controlling delayed nausea after MEC [24–27]. Olanzapine has promising effects in nausea control after HEC [28, 29], and a recent phase III trial found that nausea control was significantly improved by adding olanzapine (74 and 43 % with no acute and delayed nausea, respectively) [30]. There is a greater room for further improving delayed nausea than acute nausea. Adhering to the current antiemetic guideline ($5HT_3RA$ + corticosteroids) in the acute phase, combining single-dose corticosteroid + palonosetron (considering the side effects of steroids) after MEC and utilizing olanzapine (as an adjunct to the antiemetic regimen) after HEC, could improve symptom control. Evidence-based nonpharmacological approaches, such as progressive muscle relaxation, could also improve symptom control [31].

Different risk factors for CINV have been identified for NV [5, 11] and for acute and delayed symptoms [9, 32], with the results also being inconsistent across different patient groups [5, 9, 11, 33]. These differences could be due to differences in the antiemetic coverage for chemotherapy and to the risk factors included in the analyses. Warr [34] suggested that the risk factors for emesis found in at least two clinical trials of substantial size were vomiting in the previous cycle, receiving HEC, not receiving guideline-recommended antiemetics, being younger, being female sex, drinking less alcohol, and having a history of pregnancy-associated emesis and of motion sickness. Experiencing symptoms in the previous cycle, not using antiemetics in accordance with international guidelines, younger age, and nausea before chemotherapy were found to be key factors for CINV [9]. Clinically significant nausea in the previous cycle and younger age were also previously found to be important predictors of clinically significant nausea [35]. The risk factors for CIN identified in the current study (i.e., symptom experience in the previous cycle, younger age, and less alcohol intake) were congruent with these previous reports.

Preventing CINV is the goal of antiemesis because symptom experience serves as a key risk factor for further symptom experience [4], especially given that experiencing CINV in the previous cycle resulted in patient characteristics no longer playing a major role in determining the subsequent risk of CINV [34]. The appropriate use of antiemetics provides good control of the risk of NV from emetogenic chemotherapy agents. Compared to emetogenicity itself [9], adhering to antiemetic guidelines is more important for controlling CINV [1, 36]. Receiving MEC was a risk factor for CINV in the current study in which antiemetic prophylaxis was unsatisfactory. This finding indicates the need to optimize antiemetic prophylaxis.

Younger age is considered a risk factor for CIN. Age is reportedly a significant predictor of the intensity [23] and the frequency and duration [37] of nausea. Lee et al. [23] and the current study evaluated age as a continuous variable contributing to CIN, whereas various age cutoffs (50, 55, and 65 years old) have also been identified as a risk factor for CINV [33, 35, 37–39], vomiting [11], and nausea [12]. Future studies should attempt to determine the optimal cutoff age.

Drinking less alcohol increased the odds for experiencing nausea and significant nausea in this study. Chronic alcohol intake exceeding 100 g/day has been reported as a protective factor against CINV [40, 41]. Consuming five or more alcoholic drinks per week was also found to be significantly associated with improved complete response (no vomiting and no rescue medication) [33]. Alcohol consumption therefore should be considered in risk assessments. Expecting nausea also increases the risk of developing nausea [42], although nausea expectations were significant only in certain phases and cycles [9]. Managing the expectations of patients is a viable approach for controlling CIN [43, 44]. The data analyzed in this study were collected in a single institution, which could have limited the generalizability of the findings. Considering that the institution was one of the five hospitals that treat 20 to 30 % of cancer patients in the Republic of Korea [45] and that guideline-recommended antiemetics were fully utilized, the results of this study should reflect the current CINV experience of Korean patients. To include colorectal cancer patients, patients receiving multiday chemotherapy were included. Although administered 5-FU was considered

Table 5 HGLM analysis of CIN risk factors

HGLM contribution of single risk factor to nausea intensity	IRR	*p*- value
First cycle (negative binomial regression)		
Age	0.98	.005*
Age (<55)	1.43	.009*
Female	1.25	.119
History of morning sickness (female only)	1.36	.074
History of motion sickness	1.16	.340
History of nausea and vomiting with stress	1.37	.054
Less alcohol consumption	1.21	.176
Nausea expectation	1.50	.011*
MEC	0.96	.777
Not adhering antiemetic guideline	1.06	.715
Second cycle (Poisson regression)		
Nausea in the first cycle	2.92	<.001*
Age	0.99	<.001*
Age (<55)	1.16	<.001*
Female	1.02	.479
History of morning sickness (female only)	1.09	.023*
History of motion sickness	0.93	.032*
History of nausea and vomiting with stress	1.26	<.001*
Less alcohol consumption	1.07	.033*
Nausea expectation	1.34	<.001*
MEC	1.27	<.001*
Not adhering antiemetic guideline	1.21	<.001*
HGLM contribution of multiple risk factors to nausea intensity IRR *p*- value is necessary	IRR	*p*- value
First cycle (negative binomial regression)		
Age (<55)	1.36	.033*
Nausea expectation	1.40	.038*
*First cycle - female only analysis was not significant for change in nausea intensity		
Second cycle (Poisson regression)		
Nausea in the first cycle	2.78	<.001*
Age (<55)	1.12	.001*
History of motion sickness	0.89	.004*
History of nausea and vomiting with stress	1.18	<.001*
Less alcohol consumption	1.00	.914
Nausea expectation	1.20	<.001*
MEC	1.23	<.001*
Not adhering antiemetic guideline	0.96	.371
Second cycle—female only (Poisson regression)		
Nausea in the first cycle	2.97	<.001*
Age (<55)	1.27	<.001*
History of morning sickness	1.14	.001*
History of motion sickness	0.92	.051
History of nausea and vomiting with stress	1.03	.505
Less alcohol consumption	0.98	.687
Nausea expectation	1.19	.001*
MEC	1.52	<.001*
Not adhering antiemetic guideline	0.82	.004*

*$p < .05$

to have low emetogenic potential, including multiday chemotherapy might have influenced symptom control.

Conclusion

Advances in antiemetics targeting emesis mechanisms allow for good control of vomiting, especially after HEC. However, the control of CINV after MEC requires further improvement, with an emphasis on antiemetic prophylaxis. Nausea control also has room for further improvement, especially in the delayed phase. The first chemotherapy-induced experience of nausea contributes to subsequent symptom experience, making intense control from the start of chemotherapy necessary when considering patient-related risk factors. Being younger, consuming less alcohol, and expecting nausea were identified risk factors for CIN, which should be considered at the start of chemotherapy. Future studies should evaluate the contribution of risk factors when antiemetic prophylaxis is fully provided in multiple settings.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest. They state that they have full control of all of the primary data and that they agree to allow the journal to review their data if requested.

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