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ORIGINAL ARTICLE

Efficacy and safety of aprepitant for the prevention of chemotherapy-induced nausea and vomiting during the first cycle of moderately emetogenic chemotherapy in Korean patients with a broad range of tumor types

Jeong Eun Kim[1] · Joung-Soon Jang[2] · Jae-Weon Kim[3] · Yong Lee Sung[4] · Chi-Heum Cho[5] · Myung-Ah Lee[6] · Do-Jin Kim[7] · Myung-Ju Ahn[8] · Kil Yeon Lee[9] · Sun Jin Sym[10] · Myong Choel Lim[11] · Hun Jung[12] · Eun Kim Cho[12] · Kyung Wan Min[12]

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Abstract

Purpose This study evaluated the efficacy and safety of a 3-day aprepitant regimen for the prevention of chemotherapy-induced nausea and vomiting (CINV) during the first cycle of non-anthracycline plus cyclophosphamide (AC)-based moderately emetogenic chemotherapy (MEC) based on government guidelines in Korean patients.

Methods This multicenter, randomized, double-blind, phase IV trial (NCT01636947) enrolled adult South Korean patients with a broad range of tumor types who were scheduled to receive a single dose of ≥1 MEC agent. Patients were randomized to a 3-day regimen of aprepitant (aprepitant regimen) or placebo (control regimen) on top of ondansetron plus dexamethasone. The primary and key secondary efficacy endpoints were the proportions of subjects who achieved no vomiting and complete response (CR) during the overall phase.

Results Of the 494 randomized subjects, 480 were included in the modified intent-to-treat population. Response rates for no vomiting and CR in the overall phase were numerically higher

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✉ Joung-Soon Jang
alsaba@hanmail.net

[1] Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic ro 43 gil, Sonpa-gu, Seoul, South Korea

[2] Department of Internal Medicine, Chung-Ang University College of Medicine, 101 Heukseok-ro, Dongjak-gu, Seoul, South Korea

[3] Department of Obstetrics and Gynecology, Seoul National University College of Medicine, 101 Daehak-ro Jongno-gu, Seoul, South Korea

[4] Division of Respiratory and Critical Care Medicine, Department of Internal Medicine, Korea University College of Medicine, 73 Inchon-ro, Seongbuk-gu, Seoul, South Korea

[5] Department of Obstetrics and Gynecology, School of Medicine, Keimyung University, 56 Dalseungro Jungku, Daegu, South Korea

[6] Department of Medical Oncology, Seoul St. Mary's Hospital, The Catholic University of Korea, 90 1 Hyehwa-dong, Jongno-gu, Seoul, South Korea

[7] Division of Allergy and Respiratory Medicine, Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, 170 Jomaru-ro, Wonmi-gu, Bucheon, South Korea

[8] Division of Hematology-Oncology, Department of Medicine, The Samsung Medical Center, Sungkyunkwan University School of Medicine, 135-710 Irwon-dong, Gangnam-gu, Seoul, South Korea

[9] Department of Surgery, Kyung Hee University School of Medicine, 26 Kyungheedae-ro, Dongdaemun-gu, Seoul, South Korea

[10] Division of Hematology and Medical Oncology, Department of Internal Medicine, Gachon University Gil Medical Center, Incheon Regional Cancer Center, Gachon University School of Medicine, 1198 Guwol-dong, Namdong-Gu, Incheon, South Korea

[11] Gynecologic Cancer Branch, Research Institute and Hospital, National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang-si, Gyeonggi-do, South Korea

[12] Merck Sharp & Dohme, 942-10 Daechi-dong, Gangnam-gu, Seoul, South Korea

for the aprepitant regimen compared with the control regimen groups, but failed to reach statistical significance (no vomiting 77.2 vs 72.0%; $p = 0.191$; CR 73.4 vs 70.4%; $p = 0.458$). Both the aprepitant and control regimens were generally well tolerated.

Conclusion A 3-day aprepitant regimen was numerically better but not statistically superior to a control regimen with respect to the achievement of no vomiting or CR during the overall phase in a non-AC MEC Korean population based on government reimbursement guidelines.

Trial registration ClinicalTrials.gov NCT01636947 (https://clinicaltrials.Gov/ct2/show/NCT01636947)

Keywords Aprepitant · Neurokinin-1 receptor antagonists · Moderately emetogenic chemotherapy, · Chemotherapy-induced nausea and vomiting

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a common side effect of chemotherapy [1, 2] that can have a negative impact on patients' well-being and quality of life (QOL), adversely affecting their daily lives [3–5]. This detrimental effect on QOL may also impede or interrupt anticancer treatment schedules, potentially resulting in poor compliance and subsequent adverse effects on overall response to chemotherapy, particularly in patients with early-stage disease [4–6].

The type (s) of chemotherapeutic agent used plays an important role in the development of CINV, with the risk of emesis in the absence of antiemetic prophylaxis ranging from 30 to 90% for antineoplastic agents classified as moderately emetogenic chemotherapy (MEC), and >90% for highly emetogenic chemotherapy (HEC) [7]. During chemotherapy, CINV can occur in both the acute (0–24 h after chemotherapy initiation) and delayed (25–120 h) phases of chemotherapy [4, 5]. Therefore, antiemetic prophylaxis plays an important role in cancer treatment management.

Aprepitant is a potent and highly selective neurokinin-1 (NK_1) receptor antagonist (RA) that has been shown to effectively prevent CINV in both the acute and delayed phases when administered over 3 days in combination with the standard antiemetic regimen of a serotonin ($5\text{-}HT_3$) RA and dexamethasone in patients receiving HEC and anthracycline plus cyclophosphamide (AC)–based chemotherapy [8–12]. Based on these results, a 3-day aprepitant-based regimen is considered the standard of care in the HEC setting according to the Multinational Association of Supportive Cancer Care (MASCC)/European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), and international guideline recommendations [5, 13–15]. NCCN guidelines also recommend the use of this aprepitant regimen in selected patients receiving MEC [5], while MASCC/ESMO guidelines recommend its use in recipients of AC-based chemotherapy [13].

In Korea, aprepitant has been approved for the prevention of acute and delayed CINV associated with initial and repeated courses of both HEC and MEC [16]. However, due to a lack of prospective clinical data in Korean patient populations, medical insurance in Korea does not cover the initiation of aprepitant in the first cycle of MEC. It is also important to note that AC-based chemotherapy regimens are now categorized as HEC per health insurance emetogenicity classification based on Health Insurance Review and Assessment Service (HIRA) guidelines [16].

To date, the use of NK_1 RAs in patients receiving non-AC MEC has been debated, which may in part be due to the broad emetic heterogeneity of MEC populations [17]. Therefore, the purpose of this study was to evaluate the efficacy and safety of a 3-day aprepitant-based triple-drug regimen, administered in the first cycle of non-AC MEC regimens to patients with a broad range of tumor types.

Methods

Patients

Male and female patients were eligible for inclusion in this study if they had histologically or cytologically confirmed malignant disease and were scheduled to receive a single dose of ≥1 MEC agent (Online Resource 1) during cycle 1, on treatment day 1. Additional eligibility criteria included an age of at least 20 years, Eastern Cooperative Oncology Group (ECOG) performance status 0–2 or Karnofsky score ≥ 60, and predicted life expectancy ≥4 months. The use of oxaliplatin- or irinotecan-based regimens were limited to approximately 35% of the total enrolment. Major exclusion criteria were receipt of chemotherapy within 6 months prior to treatment day 1; scheduled receipt of subsequent treatment due to refractory response to first- or second-line chemotherapy; known hypersensitivity to aprepitant, dexamethasone, or $5\text{-}HT_3$ RAs; vomiting in the 24 h prior to treatment day 1; symptomatic primary or metastatic central nervous system malignancy (asymptomatic patients were allowed); chronic use of systemic corticosteroid therapy at any dose; and pregnancy or lactation.

Study design

This was a randomized, double-blind, active-comparator, multicenter, phase IV trial (MK-0869-225) conducted at 20 sites across South Korea. The study comprised a screening period, followed by a double-blind study treatment period of 3 days,

and a follow-up period of 3 days. Eligible patients were randomized (1:1) to receive either a 3-day aprepitant or control regimen. Patients were assigned a unique, sequential baseline allocation number, and were randomly assigned in sequence to 1 of the 2 study treatment regimens. Randomization was stratified by chemotherapy regimen. Blinding of study medications was maintained for the investigator, study coordinator, and patient. Supplies were provided with blinded envelopes containing drug disclosure information.

The study protocol was reviewed and approved by all Ethical Review Committees/Institutional Review Boards. This study was conducted in full accordance with Good Clinical Practice with standards established by the Declaration of Helsinki and in compliance with all applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. Written informed consent was obtained from all individual participants included in this study.

Study treatments

Participants received aprepitant (aprepitant regimen) or placebo (control regimen) on top of ondansetron plus dexamethasone (Table 1). For the aprepitant regimen, aprepitant capsules were taken 60 min prior to initiation of MEC on day 1 (125 mg), and in the mornings on days 2 and 3 (80 mg). Open-label ondansetron 16 mg was also administered intravenously on day 1, 30–60 min before initiation of MEC on day 1, followed by placebo capsules twice daily (every 12 h) on days 2 and 3. In the control regimen group, matching aprepitant placebo capsules were taken 60 min before initiation of MEC on day 1, and in the mornings on days 2 and 3. Open-label ondansetron 16 mg was also administered intravenously on day 1, 30–60 min before initiation of MEC on day 1, followed by blinded 8-mg capsules twice daily (every 12 h) on days 2 and 3. Both study groups received oral dexamethasone capsules (12 and 20 mg for the aprepitant and control regimens, respectively), which were taken 30 min before initiation of MEC on day 1.

The use of investigator-prescribed rescue therapy for nausea or vomiting was permitted throughout the study, which included other 5-HT_3 RAs (granisetron, dolasetron, tropisetron, or ondansetron), benzodiazepines, and benzamides (e.g., metoclopramide or alizapride).

Outcome assessment

Efficacy

The primary efficacy endpoint was the proportion of patients who achieved no vomiting during the overall phase (0–120 h following initiation of MEC [i.e., days 1–5]). The key secondary efficacy endpoint was the proportion of patients with a complete response (CR; defined as no vomiting and no use of rescue therapy) during the overall phase. Additional secondary efficacy endpoints included the time to first vomiting event during the overall phase; the proportion of patients who achieved no vomiting during the acute (0–24 h following initiation of MEC [i.e., day 1]) and delayed (25–120 h following initiation of MEC [i.e., days 2–5]) phases; the proportion of patients who achieved a CR during the acute and delayed phases; and subgroup analysis of CR rates according to chemotherapy regimen. Subgroup analysis of no vomiting according to chemotherapy regimen was also assessed as an exploratory endpoint.

Safety

Safety and tolerability of the aprepitant and control regimens were assessed. Clinical adverse events (AEs) were graded according to the National Cancer Institute (NCI) Common Terminology Criteria (CTC), version 3.0. Vomiting and nausea were also reported as AEs if they occurred outside of the efficacy assessment period or met the definition of a serious adverse event (SAE; any AE that results in death, is life threatening, results in persistent/significant disability/incapacity, or results in or prolongs an existing inpatient hospitalization). Additional safety evaluations included the assessment of vital signs, physical examination, and clinical laboratory tests.

Statistical analysis

Assuming a no vomiting response rate of 65% for the control regimen, approximately 492 participants (246 per treatment group) were required to detect a 12% difference with 80% power and a 1-sided alpha level at 0.025 (2-sided 5% significance).

The modified intent-to-treat (mITT) population (patients who received chemotherapy and a dose of study drug on day 1) was used to analyze patient demographic and baseline characteristics, as well as all efficacy analyses. The all-patients-as-treated (APaT) population was used for safety analyses. Differences between treatment groups for efficacy endpoints were analyzed by Pearson's χ^2 test or Fisher's exact test, with the exception of time to first vomiting event, which was estimated using Kaplan-Meier curves and analyzed by log-rank test. The primary and key secondary efficacy endpoints were evaluated at a 2-sided level of significance of 0.05. For all other secondary efficacy endpoints, Hochberg procedure was used to control the type I error at the 0.05 level; a sequential procedure was used to control multiplicity, such that subsequent groups of efficacy endpoints would not be tested unless the prior groups' testing had revealed at least 1 statistically significant finding. Risk differences between treatment groups

Table. 1 Treatment regimens

Regimen	Study medication	Day 1 dose	Day 2 dose	Day 3 dose
Aprepitant	Aprepitant	125-mg capsule orally, 60 min before MEC	80-mg capsule	80-mg capsule
	Ondansetron	16 mg, IV, 30–60 min before MEC	1 placebo capsule q12h	1 placebo capsule q12h
	Dexamethasone 12 mg[a]	3 capsules of 4 mg + 2 placebo capsules, 30 min before MEC	None	None
Control	Placebo	125-mg capsule	80-mg capsule	80-mg capsule
	Ondansetron	16 mg, IV, 30–60 min before MEC	8-mg capsule, q12h	8-mg capsule, q12h
	Dexamethasone 20 mg[a]	5 capsules of 4 mg, 30 min before MEC	None	None

IV intravenous, *MEC* moderately emetogenic chemotherapy, *q12h* every 12 h

[a] Premedication procedures were different for patients receiving paclitaxel or docetaxel (followed each institutional protocol, based on investigator's decision); these patients did not receive dexamethasone on day 1; however, after day 1, the dosing regimen for patients treated with paclitaxel and docetaxel was the same

and corresponding 95% confidence intervals (CIs) were calculated for specific AEs occurring in ≥5% of participants.

Results

Baseline characteristics

The study was conducted between December 28, 2012 and August 4, 2014. Of the 510 screened patients, 494 were randomly assigned to the aprepitant (n = 244) or control (n = 250) regimens, and 471 completed the study (Fig. 1). The main reasons for study discontinuation after randomization were withdrawal of consent, reported in three (1.2%) patients each in the aprepitant and control regimen groups; not meeting eligibility criteria in one (0.4%) and four (1.6%) patients, respectively; and loss to follow-up in four (1.6%) patients in the aprepitant regimen group. Overall, 490 and 480 participants were included in the APaT and mITT populations, respectively.

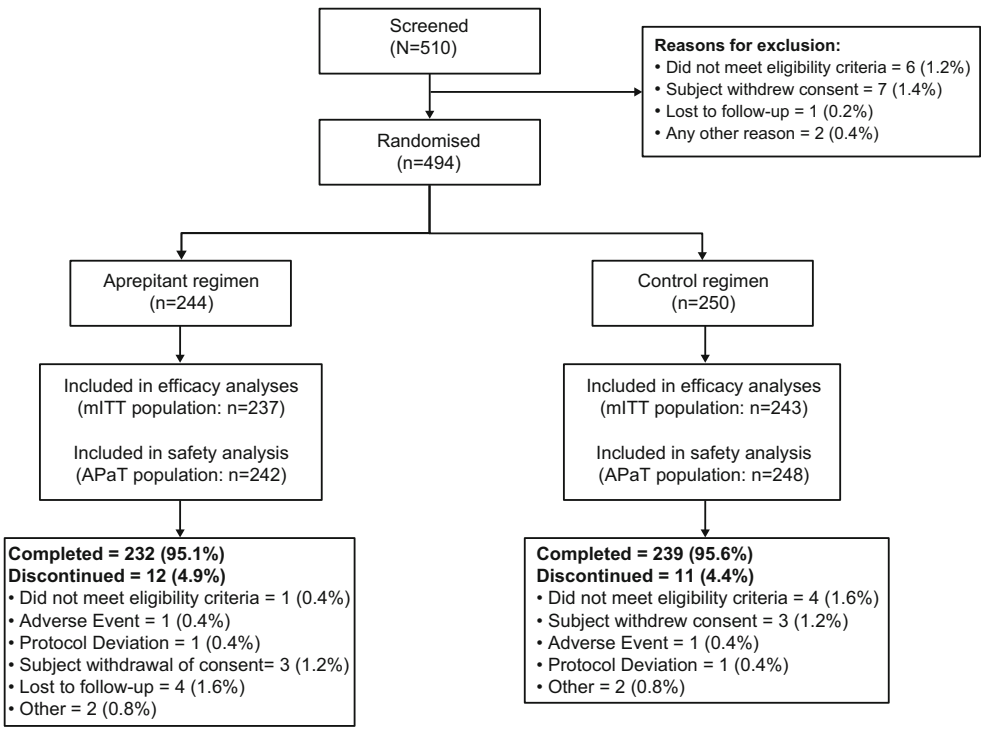

Fig. 1 Study flow diagram. *APaT* all-patients-as-treated, *mITT* modified intent-to-treat

Patient demographics and baseline characteristics were generally similar between the two study treatment groups in the mITT population and balanced with respect to the malignancy type being treated (Table 2). In the overall mITT population, 54.8% of participants were male, with an overall mean (standard deviation) age of 60.3 (11.4) years. The majority of patients received either carboplatin- (65% of all subjects) or oxaliplatin-based (28%) chemotherapeutic regimens; 6.7% of patients were treated with an irinotecan-based regimen.

Efficacy

Analysis of the primary efficacy endpoint in the mITT population demonstrated a numerical, but not statistically significant, difference in proportion of patients with no vomiting during the overall phase between the aprepitant and control regimen groups (77.2 vs 72.0%; $p = 0.191$) (Fig. 2). Similarly, the key secondary efficacy endpoint of CR achievement during the overall phase was not statistically significant between the aprepitant and control regimen groups (73.4 vs 70.4%; $p = 0.458$) (Fig. 3).

Sequential testing of statistical significance for the additional secondary efficacy endpoints was not conducted because the key secondary hypothesis was not met. During the overall phase, 54 and 68 vomiting events were reported in the aprepitant and control regimen groups, respectively. For the aprepitant versus control regimen, no vomiting was reported in 95.8 versus 98.8% of participants during the acute phase, and 78.5 versus 72.4% during the delayed phase (Fig. 2). Similar findings were also reported for CR, which was reported in 95.8 versus 97.9% of subjects during the acute phase, and 74.3 versus 71.2% during the delayed phase (Fig. 3).

Subgroup analysis of CR achievement for the aprepitant versus control regimen by chemotherapeutic regimen reported numerically higher rates of CR in the aprepitant regimen group in patients receiving carboplatin- (71.8 vs 67.9%) and oxaliplatin-based (79.1 vs 73.9%) regimens; in contrast, a lower CR rate was observed with aprepitant in the irinotecan-based subgroup (64.3 vs 77.8%). Exploratory analysis of no vomiting for the aprepitant versus control regimen by chemotherapy regimen also showed numerically higher (but nonsignificant) rates of no vomiting in favor of the aprepitant regimen in the oxaliplatin- (83.6 vs 76.8%) and carboplatin-based (74.4 vs 69.2%) subgroups; similar rates of no vomiting were seen in the irinotecan-based subgroup (78.6 vs 77.8%).

Table. 2 Baseline demographics (mITT population)

	Aprepitant regimen ($n = 237$)	Control regimen ($n = 243$)
Age, years		
Mean (SD)	59.7 (11.4)	60.9 (11.5)
Range	23–84	28–85
Sex, *n* (%)		
Male	129 (54.4)	134 (55.1)
Female	108 (45.6)	109 (44.9)
Type of malignancy, *n* (%)		
Gastrointestinal	81 (34.2)	87 (35.8)
Lung	83 (35.0)	82 (33.7)
Gynecologic	69 (29.1)	68 (28.0)
Other	4 (1.7)	4 (1.6)
Chemotherapeutic regimen, *n* (%)		
Carboplatin-based	156 (50.0)	156 (50.0)
Oxaliplatin-based	67 (49.3)	69 (50.7)
Irinotecan-based	14 (43.8)	18 (56.3)
ECOG performance status, *n* (%)		
0–1	234 (98.7)	239 (98.4)
2	3 (1.3)	4 (1.6)
Karnofsky score[a], mean (SD)	90.8 (7.1)	89.8 (7.9)
Spread of tumor to other organs, *n* (%)	163 (68.8)	147 (60.5)
History of motion sickness, *n* (%)	33 (13.9)	20 (8.2)
History of morning sickness during pregnancy[b], *n* (%)	41 (38.0)	43 (39.4)
History of alcohol use, *n* (%)	38 (16.0)	41 (16.9)

ECOG European Cooperative Oncology Group, *mITT* modified intent-to-treat, *SD* standard deviation

[a] Evaluable patients; $n = 153$ aprepitant, $n = 158$ control

[b] Out of female patients only; $n = 108$ aprepitant, $n = 109$ control

Safety and tolerability

In the APaT population, at least 1 AE was reported in 56.2 and 53.2% of participants in the aprepitant and control regimen groups, respectively (Table 3). However, drug-related AEs were rare, occurring in 3.7 and 3.6% of patients in the aprepitant and control regimen groups, respectively. The most commonly reported all-grade AEs were gastrointestinal disorders, including nausea (9.1 and 8.1%, respectively), diarrhea (6.6 and 7.3%), and constipation (0 and 8.9%), with most AEs being grade 1 or 2 in severity in both the aprepitant (66.9%) and control (66.1%) groups. Overall, SAEs were reported in 37 participants (7.6%; 22 in the aprepitant group and 15 in the control group), the most commonly reported being asthenia, pyrexia, and dyspnea (1.2% each) in the aprepitant group, and pyrexia (1.2%) in the control group. All SAEs were considered by the investigator to be "not related" to study treatment, with the exception of 1 case of rash in the aprepitant group. One patient in the APaT population discontinued the study

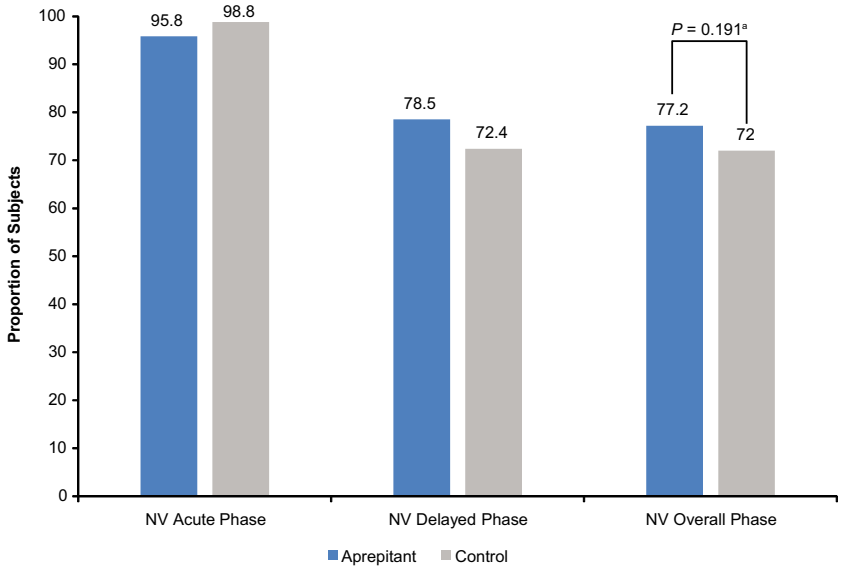

Fig. 2 Proportion of patients achieving no vomiting (NV) during the acute (0–24 h), delayed (25–120 h), and overall phase (0–120 h) following initiation of first cycle of moderately emetogenic chemotherapy (modified intent-to-treat population). [a]Primary endpoint, comparison based on Pearson's chi square test

because of an adverse event (headache, not related to study treatment).

Three deaths were reported during the study period (1 and 2 participants in the aprepitant and control groups, respectively). However, all cases appeared to be attributable to patients' underlying malignancy or other preexisting conditions, and none were considered by investigators to be related to the study drug.

No clinically meaningful changes or statistically significant differences in vital signs, physical examination, or clinical laboratory tests were seen between the aprepitant and control regimen groups during the study.

Discussion

The current double-blind, randomized, multicenter, phase IV study was conducted to provide clinical data supporting the use of a 3-day aprepitant regimen from the first cycle of non-AC MEC for the prevention of CINV in a Korean population with a broad range of tumor types. Our findings did not demonstrate superiority for the aprepitant regimen over the control regimen with respect to both the primary and key secondary efficacy endpoints, but numerical trends were noted in favor of the aprepitant regimen.

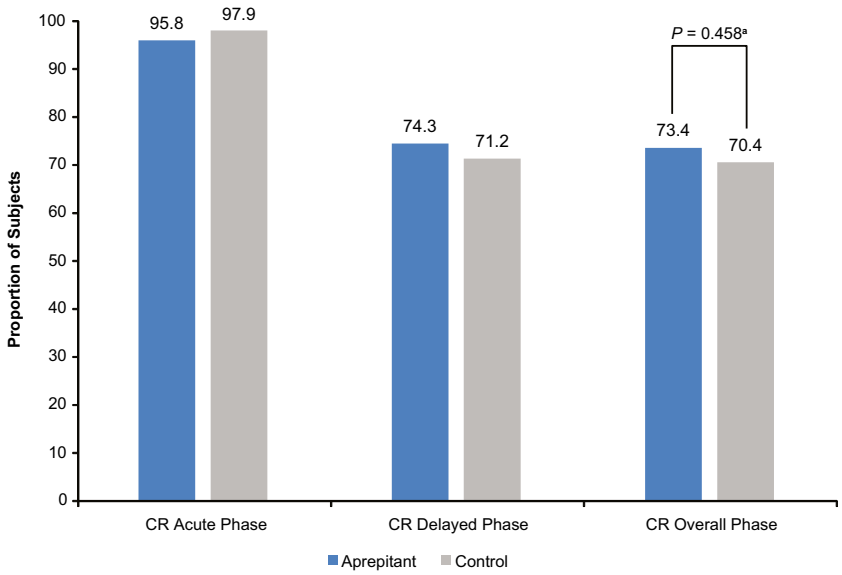

Fig. 3 Proportion of patients achieving a complete response (CR; no vomiting and no rescue therapy) during the acute (0–24 h), delayed (25–120 h), and overall phase (0–120 h) following initiation of the first cycle of moderately emetogenic chemotherapy (modified intent-to-treat population). [a]Key secondary endpoint, comparison based on Pearson's chi square test

Table. 3 Summary of adverse events (all-patients-as-treated population)

n (%)	Aprepitant regimen (*n* = 242)	Control regimen (*n* = 248)	95% CI
≥1 AE	136 (56.2)	132 (53.2)	−5.8, 11.8
Drug-related AEs[a]	9 (3.7)	9 (3.6)	−3.2, 3.4
Serious AEs	22 (9.1)	15 (6.0)	−1.6, 7.7
Serious drug-related AEs[a]	1 (0.4)	0	−0.4, 1.2
Death	1 (0.4)	2 (0.8)	−1.8, 1.0
Discontinuation due to AE	1 (0.4)	0	−0.4, 1.2
Commonly reported AEs (>5% of patients)			
Nausea	22 (9.1)	20 (8.1)	–
Constipation	0	22 (8.9)	–
Diarrhea	16 (6.6)	18 (7.3)	–
Myalgia	0	18 (7.3)	–
Alopecia	0	17 (6.9)	–
Hiccups	15 (6.2)	0	–
Decreased appetite	14 (5.8)	15 (6.1)	–

AE adverse event, *CI* confidence interval

[a] Determined by the investigator to be possibly, probably, or definitely study drug related

The effect of adding an NK_1 RA on response in the overall phase (0–120 h) may have been driven in part by the high response to ondansetron during the acute phase. Indeed, the ability of 5-HT_3 RAs (e.g., ondansetron, granisetron, dolasetron, and palonosetron) to effectively prevent and control CINV during the acute phase in patients receiving MEC or HEC is well established [5, 13, 14]. However, 5-HT_3 RAs have been shown to be generally less effective at preventing CINV in the delayed phase [18], which can be challenging to manage and is often underestimated by physicians and nurses in patients receiving MEC or HEC [19]. Although no statistically significant improvements in efficacy were demonstrated for the aprepitant regimen in this study, the benefits of aprepitant appeared to be more apparent during the delayed phase. Therefore, future studies are needed to confirm the potential benefits of aprepitant in the delayed setting in patients receiving non-AC MEC.

MEC agents have a highly heterogeneous emetogenicity (30 to 90%) relative to that of HEC agents (>90%) [7]. As a result, certain MEC subpopulations may be more likely to respond to antiemetic treatment with the addition of an NK_1 RA, such as aprepitant, during the first cycle of MEC. Numerically higher no vomiting and CR rates were seen with the aprepitant regimen in the subgroups of patients receiving oxaliplatin- and carboplatin-based chemotherapy, but not for the irinotecan-based subgroup. The findings of these subgroup analyses are supported by a post hoc analysis of phase III trials that reported higher rates of complete control of emesis during the overall phase (i.e., likelihood of 5-day no vomiting) with the aprepitant regimen in patients receiving carboplatin; higher rates were also seen in patients receiving oxaliplatin, but this did not reach statistical significance [20]. Furthermore, the control of CINV with prevention strategies may be less effective in recipients of irinotecan, which is considered to be a strong CINV inducer and has been indicated by NCCN guidelines to be highly emetogenic in select patients [5]. These findings highlight the need for additional, adequately powered subgroup analyses to better define the role of NK_1 RAs, such as aprepitant, in the non-AC MEC setting.

Previous studies of non-AC MEC populations have demonstrated mixed results. The findings of this study are in contrast to a retrospective analysis of Korean colon cancer patients who reported significantly higher rates of CR and no vomiting during the overall phase with administration of the aprepitant regimen in the first cycle of non-AC MEC [21]. In addition, an international, phase III, randomized controlled study in patients with confirmed malignancies receiving non-AC based chemotherapy showed benefits of the triple-therapy aprepitant regimen over control in terms of higher CR and no vomiting rates across all phases [9]. However, a multicenter phase II study of aprepitant versus control regimens in nondrinking women with ovarian/peritoneal cancer or uterine endometrial cancer receiving non-AC MEC (performed in Japan) reported a nonsignificant improvement in the overall CR rate (10.1%) [22]. Additionally, the findings of a recent multicenter, phase II study evaluating the aprepitant regimen in patients with advanced non-small cell lung cancer demonstrated that triple antiemetic therapy with aprepitant was associated with nonsignificant improvement of the CR rate in both the overall and delayed phases [23]. Taken together, further research is needed to establish the role that aprepitant plays in non-AC MEC populations.

The reasons for differences in efficacy findings between this study and historical data are not clear. High-response rates in the control regimen group (i.e., patients receiving ondansetron + dexamethasone alone had good response) may have contributed to the lack of benefit for the aprepitant regimen relative to the findings of previous studies. This was the case with studies conducted by Rapoport et al. and Ito et al., which reported lower rates of CR in the control group compared with the current study (65.5 and 67.2 vs 70.4%) [9, 23]. The wide variety of cancer types in the current study population may have also affected the outcomes seen in the current study, given that a recent history of gynecological or gastrointestinal surgery may increase the risk of CINV because of abdominal pain or discomfort. The subjective nature of patient-reported CINV may also be a contributing factor, giving rise to the potential for underreporting of symptoms due to cultural bias in Asian participants or the long distances that patients had to commute to receive treatment, which may have also translated to downplaying CINV symptoms. Additionally, the results of this study may have been

confounded by the lack of strict compliance to steroid premedication, in particular for taxanes.

The 3-day aprepitant regimen was generally well tolerated in the current study—no difference in the overall incidence of AEs was seen between the two study arms. AE profiles were consistent with AEs generally reported in patients receiving emetogenic chemotherapy. Furthermore, the AE profile of the aprepitant regimen in the current study was generally similar to that of previous studies, with no new safety signals [8–11, 22].

Conclusion

In summary, this study showed that a 3-day aprepitant regimen was generally well tolerated but did not demonstrate statistical superiority over a standard regimen with respect to the achievement of no vomiting or CR during the overall phase in a non-AC MEC Korean population based on HIRA reimbursement guidelines; however, numerical benefits were seen with the aprepitant regimen. The findings highlight the need for further studies to define the role that aprepitant plays in the non-AC MEC regimen.

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Author contributions Jeong Eun Kim, Joung-Soon Jang, and Kyung Wan Min are responsible for the work described in this paper. All authors were involved in at least one of the following: conception, design, acquisition, analysis, statistical analysis, interpretation of data and drafting the manuscript and/or revising the manuscript for important intellectual content. Jae-Weon Kim, Myong Choel Lim, Kil Yeon Lee, and Sun Jin Sym were also responsible for provision of study materials or patients. All authors provided final approval of the version to be published.

Compliance with ethical standards

Conflict of interest Hun Jung, Cho Eun Kim, and Kyung Wan Min are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., who may potentially own stock and/or hold stock options in the company. The remainder of the authors has nothing to disclose.

Ethical approval 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.

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