Efficacy and Tolerability of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Emesis over Multiple Cycles of Moderately Emetogenic Chemotherapy

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BACKGROUND. An aprepitant (APR) regimen was evaluated for prevention of nausea and emesis due to moderately emetogenic chemotherapy (MEC) over multiple cycles.

METHODS. The authors performed a randomized, double-blind study. Eligible patients with breast carcinoma were naïve to emetogenic chemotherapy and treated with cyclophosphamide alone or with doxorubicin or epirubicin. Patients were randomized to receive either an APR regimen (Day 1: APR 125 mg, ondansetron [OND] 8 mg, and dexamethasone [DEX] 12 mg before chemotherapy and OND 8 mg 8 hrs later; Days 2–3: APR 80 mg every day) or a control regimen (Day 1: OND 8 mg and DEX 20 mg before chemotherapy and OND 8 mg 8 hrs later; Days 2–3: OND 8 mg twice per day). Data on nausea, emesis, and use of rescue medication were collected. The primary end point was the proportion of patients with a complete response (CR; no emesis or use of rescue therapy) in Cycle 1. Efficacy end points for the multiple-cycle extension were the probabilities of a CR in Cycles 2–4 and a sustained CR rate across multiple cycles.

RESULTS. Of 866 patients randomized, 744 (85.9%) entered the multiple-cycle extension, and 650 (75.1%) completed all 4 cycles. Overall, the CR was greater with the APR regimen over the 4 cycles: 53.8% versus 39.4% for Cycle 2, 54.1% versus 39.3% for Cycle 3, and 55.0% versus 38.4% for Cycle 4. The cumulative percentage of patients with a sustained CR over all 4 cycles was greater with the APR regimen ($P = 0.017$).

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CONCLUSIONS. The APR regimen was more effective than a control regimen for the prevention of nausea and emesis induced by MEC over multiple chemotherapy cycles. ***Cancer*** **2005;104:1548–55.** © *2005 American Cancer Society.*

KEYWORDS: antiemetic, aprepitant, breast carcinoma, multiple cycles, neurokinin-1 receptor antagonist, substance P.

A number of well-conducted trials have formed the basis of today's evidence-based antiemetic guidelines.[1–3] Some aspects of chemotherapy-induced nausea and vomiting (CINV), however, have not been as well studied as others. One such topic is antiemetic therapy in patients receiving multiple cycles of chemotherapy. Only a few studies have addressed this clinically important topic, and the interpretation of the results has been complicated by differences in trial methodology and statistical analyses between studies. A general impression from these studies is that the antiemetic effect obtained in the first cycle of chemotherapy decreases during subsequent cycles, offering patients poor protection from nausea and emesis during a major part of their chemotherapy.

In patients receiving highly emetogenic chemotherapy (HEC), aprepitant (APR), a neurokinin-1 (NK_1) receptor antagonist, improved the antiemetic effect of a control combination of the serotonin ($5\text{-}HT_3$) receptor antagonist, ondansetron (OND), and the corticosteroid, dexamethasone (DEX), as compared with OND and DEX alone.[4,5] The antiemetic effect of the APR regimen was maintained and continuously superior to OND plus DEX through six cycles of HEC.[6] Consequently, the three-drug combination including APR is now recommended as antiemetic prophylaxis in these patients.[7]

In patients receiving moderately emetogenic chemotherapy (MEC), only a few studies have addressed the antiemetic effect over several cycles of chemotherapy. These studies all showed that the antiemetic effect of a $5\text{-}HT_3$ receptor antagonist plus a corticosteroid decreases during multiple cycles of chemotherapy.[8–10] The combination of cyclophosphamide and an anthracycline (e.g., doxorubicin or epirubicin) is one of the most frequently used combination chemotherapy regimens (e.g., as adjuvant chemotherapy in patients with breast carcinoma). It is recognized that although cyclophosphamide and anthracyclines are both graded as moderately emetogenic in evidence-based guidelines, these combinations constitute particularly emetogenic regimens.[11]

The current guideline-recommended therapy for patients receiving MEC is the combination of a $5\text{-}HT_3$ receptor antagonist and DEX.[1–3] To clarify the potential role of an NK_1 receptor antagonist in patients receiving MEC, the current study compared the efficacy and tolerability of an APR regimen versus an active control regimen in preventing CINV in patients with breast carcinoma treated with cyclophosphamide-based chemotherapy. A previous report showed that the APR regimen was superior to the control regimen, as measured by the proportion of patients with a complete response (CR), defined as no emesis and no rescue therapy, throughout the acute and delayed phases (120 hrs) after the first cycle of chemotherapy.[12] All patients completing Cycle 1 were invited to continue in the study for $\leq$ 4 cycles of MEC to determine if the efficacy and tolerability observed in Cycle 1 would be sustained over multiple cycles of chemotherapy.

MATERIALS AND METHODS

Inclusion Criteria

Institutional review boards at each study site approved the study protocol, and written informed consent was obtained from all participants before enrollment. Eligible patients were $\geq$ 18 years, diagnosed with breast carcinoma, and had received a single cycle of MEC (Hesketh Level $\geq$ 3)[13] in the core protocol.[12] The following agents were administered either alone or in combination: intravenous (i.v.) cyclophosphamide 750–1500 mg/m^2 ($\pm$ 5%); i.v. cyclophosphamide 500–1500 mg/m^2 ($\pm$ 5%) and i.v. doxorubicin $\leq$ 60 mg/m^2 ($\pm$ 5%); i.v. cyclophosphamide 500–1500 mg/m^2 ($\pm$ 5%) and i.v. epirubicin $\leq$ 100 mg/m^2 ($\pm$ 5%); other chemotherapeutic agents Hesketh Level $\leq$ 2 were also permitted. Patients had a predicted life expectancy $\geq$ 4 months and a Karnofsky score $\geq$ 60. Patients were required to successfully complete each previous chemotherapy cycle before continuing to the next cycle of treatment with the same chemotherapeutic regimen. Chemotherapy cycles were separated by $\geq$ 14 days.

Study Design

This was a prospective, multicenter, randomized, double-blind, double-dummy, parallel-group study. The study design has been described in detail for Cycle 1.[12] Patients who successfully completed Cycle 1 were eligible to continue into this multiple-cycle extension study. Patients received the same antiemetic regimen to which they were randomly assigned during Cycle 1: APR regimen (Day 1: APR 125 mg, OND 8 mg, and DEX 12 mg before chemotherapy and OND 8 mg 8 hrs later;

Days 2–3: APR 80 mg every day) or a control regimen (Day 1: OND 8 mg and DEX 20 mg before chemotherapy and OND 8 mg 8 hrs later; Days 2–3: OND 8 mg twice per day) for ≤ 3 more cycles of chemotherapy, for a total of 4 cycles. During this extension study, patients reported emetic episodes and/or use of rescue therapy over the 120 hours after chemotherapy once at Day 6 and completed a daily nausea visual analog scale (VAS; 0 mm is no nausea, 100 mm is nausea as bad as it could be) during the first 5 mornings after chemotherapy. Patients were allowed to take rescue therapy throughout the study for nausea or emesis as needed. Permitted rescue medications were 5-HT_3 antagonists, phenothiazines, butyrophenones, and benzodiazepines.

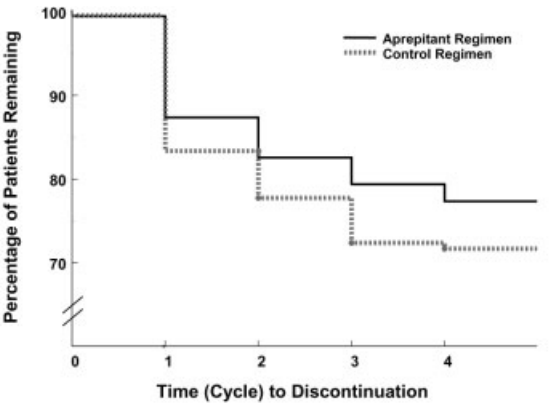
Statistical Methods

The objective of the multiple-cycle extension was to compare the APR regimen with the control regimen in terms of the proportion of patients with a CR, defined as no emesis and no use of rescue therapy, across multiple cycles of chemotherapy. The tolerability profiles for the APR and control regimens were also compared. These prospectively defined comparisons in Cycles 2–4 were based on exploratory objectives only. Thus, *P* values were reported for summary purposes only.

A modified intention-to-treat approach was used for all efficacy analyses: a patient must have entered the multiple-cycle extension, received chemotherapy, and have at least one postchemotherapy assessment during that cycle to be included in the analysis. The proportion of patients with a CR was used to evaluate efficacy across Cycles 1–4. In addition, the time (in terms of cycle) to first emetic episode or use of rescue medication was summarized.

For the current study, two analytical methods were used to compare the multiple cycle efficacy of the APR regimen and the control regimen: 1) The analysis of a sustained CR was a particularly rigorous method that evaluated the probability that a patient remains as a complete responder over four cycles of chemotherapy. This analysis was performed using Kaplan–Meier methods. Treatment groups were compared via the log-rank test. 2) The analysis of a CR by individual cycle was a more encompassing method that evaluated the probability that patients would be complete responders in a particular cycle, given their response thus far. This analysis was performed using transitional probabilities methods.[14]

Nausea was assessed on a 100-mm VAS scale on Days 1–5 in Cycles 1–4. Cycle 1 nausea results were previously reported.[12] A retrospective exploratory analysis of nausea over Cycles 2–4 using the same approach to analysis as in Cycle 1 was performed.



					Total Cycles
Aprepitant Regimen	438	385	364	350	1537
Control Regimen	428	359	335	312	1434

FIGURE 1. Time to discontinuation for Cycles 1–4. aprepitant regimen. Total number of cycles for the aprepitant regimen was 1537, and for the control regimen, the total number of cycles was 1434.

All patients who were randomized to double-blind therapy and who received at least one dose of study medication were included in the safety analyses. Safety and tolerability were assessed by statistical and clinical review of adverse experiences (AEs), vital signs, and laboratory values. The Fisher exact test was used to make treatment comparisons with respect to the incidence of AEs.

RESULTS

Of the 866 patients randomly assigned to treatment with either the APR regimen or a control regimen during Cycle 1, 744 (85.9%) entered the multiple-cycle extension, and 650 (75.1%) completed all 4 cycles. Time to discontinuation is shown in Figure 1. The number of patients who withdrew from the study before completing all 4 cycles was slightly less for the APR regimen (20.1%) compared with the control regimen (27.1%). The most common reasons for discontinuation after completing ≥ 1 cycle were lack of efficacy (33 patients [7.5%] receiving the APR regimen and 47 patients [11.0%] receiving the control regimen) and patient withdrawal of consent (20 patients [4.6%] receiving the APR regimen and 22 patients [5.1%] receiving the control regimen). Of the 744 patients who entered the multiple-cycle extension, 734 (98.7%) in Cycle 2, 683 (91.8%) in Cycle 3, and 647 (87.0%) in Cycle 4 were included in the efficacy analyses.

Patient characteristics and treatment regimens for patients entering the multiple-cycle extension are

TABLE 1
Characteristics of Patients Entering the Multiple Cycle Extension

Characteristics[a]	% Aprepitant regimen $n = 385$	% Control regimen $N = 359$
White race	79.0	76.6
History of motion sickness	16.1	18.4
History of emesis associated with pregnancy	30.9	30.1
Chemotherapy regimen		
Cyclophosphamide + doxorubicin	58.4	56.8
Cyclophosphamide + doxorubicin + docetaxel	2.1	1.9
Cyclophosphamide + doxorubicin + 5-fluorouracil	8.1	7.8
Cyclophosphamide + doxorubicin + paclitaxel	0.3	0.0
Cyclophosphamide + epirubicin	9.1	9.2
Cyclophosphamide + epirubicin + 5-fluorouracil	20.3	23.1
Cyclophosphamide + 5-fluorouracil + methotrexate	1.6	0.8

[a] Mean age for the aprepitant regimen group is 53.4 years with a standard deviation of 10.4. Mean age for the control regime group is 52.1 years with a standard deviation of 10.9. In the aprepitant regimen, 99.5% are female (2 males), and in the control regimen, 100% are female.

listed in Table 1 and are similar to those reported previously for patients in Cycle 1.[12] Treatment groups were similar with respect to baseline characteristics. The majority of patients were white (77.8%) and female (99.7%). Ninety-nine percent of patients received a combination of cyclophosphamide plus an anthracycline as their chemotherapy regimen.

Sustained Complete Response: Probability that a Patient will Complete all Four Cycles as a Complete Responder

The percentage of patients who experienced a CR in Cycle 1 and who sustained a CR over Cycles 2–4 was greater with the APR regimen than with the control regimen ($P = 0.017$, based on the log-rank test) (Fig. 2A). Analysis of the components of a CR showed a larger difference favoring the APR regimen in the percentage of patients with no emesis ($P < 0.001$) (Fig. 2B) and a smaller difference favoring the APR regimen in the percentage of patients with no use of rescue therapy (P value not significant) (Fig. 2C).

Complete Response by Individual Cycle: Probability of a Complete Response in the Next Cycle Given the Response to Chemotherapy-Induced Nausea and Emesis Prevention

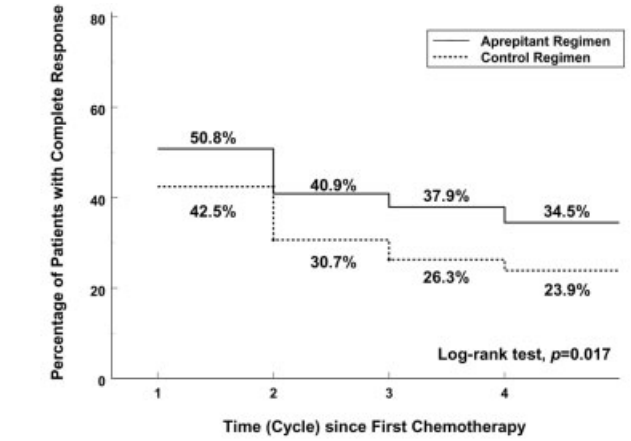
The treatment advantage seen with the APR regimen compared with the control regimen in terms of a CR in Cycle 1 (50.8% vs. 42.5%; $P = 0.015$) was maintained and increased slightly over Cycles 2–4 (Fig. 3). The CR rate differences (APR regimen − control regimen) were 8.3% in Cycle 1, 14.4% in Cycle 2, 14.8% in Cycle 3, and 16.6% in Cycle 4, all favoring the APR regimen.

Nausea

The proportion of patients reporting no nausea (peak VAS < 5 mm) as well as no significant nausea (peak VAS < 25 mm) in Cycles 1–4 are shown in Table 2. The two treatment regimens were similar with respect to the percentage of patients with no nausea over the four cycles. The proportion of patients with no significant nausea was greater with the APR regimen. This difference was most pronounced in Cycle 2 (65.5% vs. 56.9%; $P = 0.020$). As these predefined nausea end points showed only a relatively modest difference between treatment groups, a post-hoc exploratory analysis was performed comparing the distribution of nausea between treatment groups by day, by cycle, and by VAS level of nausea. This analysis did not reveal differences between treatment groups.

Tolerability

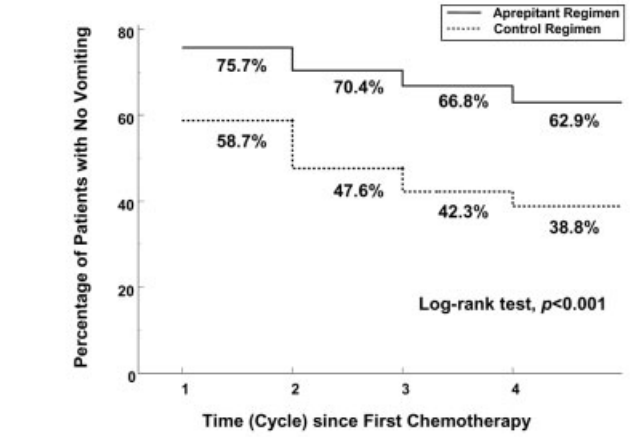
The overall percentage of patients with the most common clinical AEs (occurring in $\geq 5\%$ of patients in either treatment group) during Cycles 2–4 is shown in Table 3. The protocol specified that nausea reported after the 5 study days was categorized as an adverse experience. Both treatment regimens were generally well tolerated, and the pattern of clinical and laboratory AEs seen in both the APR and control regimens were comparable in Cycles 1–4. For neutropenia, although the incidence was similar between treatment groups in Cycle 1, a numeric difference (APR regimen, 9.1%; control regimen, 5.8%) was seen in Cycles 2–4. By the Fisher exact test, this difference was not significant ($P = 0.097$). In addition, the relative incidence of sequelae of neutropenia, such as febrile neutropenia, was balanced across treatment groups (Table 3). The National Cancer Institute (NCI) toxicity criteria Grade 3–4 neutropenia occurred in 27 patients (7.0%) in the APR regimen versus 13 patients (3.6%) in the control regimen, and the distribution of neutrophil count was balanced across treatment groups.



Number at Risk:

Aprepitant Regimen	433	207	156	141
Control Regimen	424	169	115	95

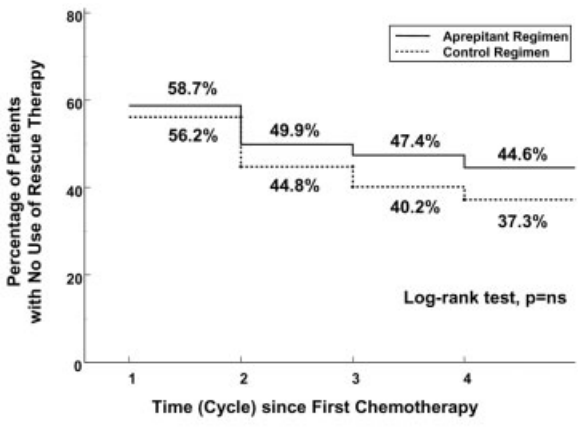
A



Number at Risk:

Aprepitant Regimen	432	296	258	234
Control Regimen	424	224	168	139

B



Number at Risk:

Aprepitant Regimen	431	239	193	178
Control Regimen	422	223	169	144

C

FIGURE 2. (A) Sustained complete response (CR) over Cycles 1–4. Kaplan–Meier curves of continued CR success rate for time (cycle) to first emetic episode or use of rescue medication by treatment group for Cycles 1–4, and (B) sustained no vomiting and (C) sustained no rescue therapy.

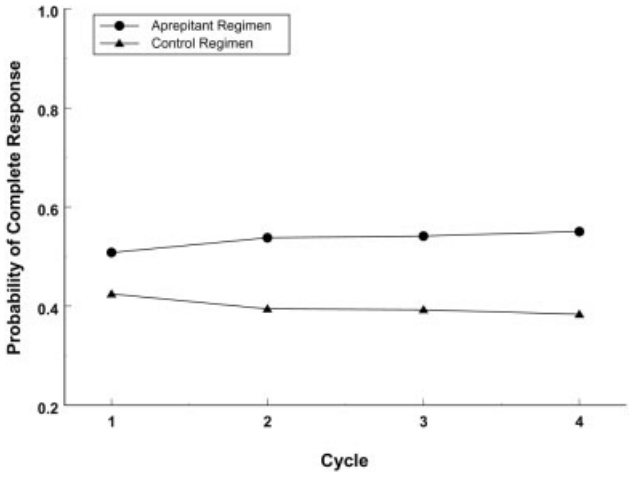


FIGURE 3. Probability of complete response by cycle and treatment group.

DISCUSSION

The results of the current study represent a significant advance in the prevention of CINV due to MEC, in that the usual decay of CR rate over multiple cycles of chemotherapy reported for a standard antiemetic regimen containing a 5-HT_3 receptor antagonist plus a corticosteroid[8–10] was not seen with the APR regimen. This study followed 866 patients during 2971 cycles of MEC. Chemotherapy consisted of cyclophosphamide (100%) plus an anthracycline (99%). This combination represents one of the most commonly prescribed chemotherapy combinations and is considered to be particularly emetogenic.[11] The study was conducted in a population of patients with breast carcinoma and, thus, almost all patients were women, further increasing the emetogenic potential of chemotherapy.[15] Given that most previous multiple-cycle CINV studies

TABLE 2
Nausea Results for Cycles 1–4

Characteristics	Aprepitant regimen (%)[a]	Control regimen (%)[a]	*P* value[b]
Cycle 1			
No nausea	142/430 (33.0)	140/424 (33.0)	0.903
No significant nausea	262/430 (60.9)	236/424 (55.7)	0.116
Cycle 2			
No nausea	137/380 (36.1)	125/357 (35.0)	0.941
No significant nausea	249/380 (65.5)	203/357 (56.9)	0.020
Cycle 3			
No nausea	134/360 (37.2)	136/328 (41.5)	0.157
No significant nausea	256/360 (71.1)	213/328 (64.9)	0.107
Cycle 4			
No nausea	155/344 (45.1)	131/307 (42.7)	0.642
No significant nausea	255/344 (74.1)	219/307 (71.3)	0.477

[a] Number of patients with desired response/number of patients included in time point.

[b] Aprepitant regimen versus control regimen based on a logistic regression model with terms for treatment group, investigator group, and age category (<55 yrs. ≥55 yrs). The *P* values shown for these end points are for summary purposes only.

TABLE 3
Summary of Adverse Events For Cycles 2–4

	Cycle 1		Cycles 2–4	
Characteristics	Aprepitant regimen *N* = 438 %	Control regimen *N* = 428 %	Aprepitant regimen *N* = 385 %	Control regimen *N* = 359 %
Alopecia	24.0	22.2	12.7	14.8
Fatigue	21.9	21.5	20.8	17.5
Headache	16.4	16.4	9.4	9.2
Constipation	12.3	18.0	9.9	13.6
Neutropenia[a]	8.9	8.4	9.1	5.8
Febrile neutropenia	2.1	2.1	2.9	2.2
Infection	9.4	11.7	17.1	16.7
Dyspepsia	8.4	4.9	0.6	7.8
Nausea	7.1	7.5	11.9	11.4
Stomatitis	5.3	4.4	8.1	7.2
Diarrhea	5.5	6.3	8.6	5.3

[a] Based on the Fisher exact test, aprepitant regimen versus control regimen with respect to the clinical adverse experience of neutropenia in Cycles 2–4 is 0.097.

incurred a large drop-out rate, it is notable that, in the current study, 75.1% of the patients completed all 4 cycles of chemotherapy.

The efficacy of an antiemetic regimen for the prevention of CINV across multiple cycles of chemotherapy may be analyzed by several different, yet complementary, methods that are useful for clinicians and patients. The initial selection of preventative antiemetic therapy is at least partially based on an assessment of efficacy across multiple cycles of chemotherapy (i.e., the probability that a patient will complete all four cycles as a complete responder). In the current study, patients receiving the APR regimen experienced a higher CR rate in Cycle 1 that was maintained through Cycle 4 compared with patients in the control therapy group. It is notable that the difference between treatment groups in this composite end point was driven by the higher rate of no emesis status in the APR group (75.7% vs. 58.7% in Cycle 1; $P < 0.001$). This 17% difference obtained in Cycle 1 increased slightly during the subsequent 3 cycles of chemotherapy, reaching a 24% absolute difference and a 62% relative difference in Cycle 4 (62.9% vs. 38.8%; $P < 0.001$) (Fig. 2B). The treatment groups were similar in terms of the percentage of patients taking rescue antiemetics.

After the initial selection of preventative antiemetic therapy, subsequent therapeutic choice is guided by a complementary assessment of efficacy

across multiple cycles of chemotherapy (i.e., the chance of a CR in the next cycle given the patient's response to CINV prevention thus far). The greater CR rate for the APR regimen seen in Cycle 1 was maintained throughout the 4 cycles of chemotherapy.

The percentage of patients experiencing no nausea in Cycles 1–4 was similar for both treatment groups, and the percentage of patients experiencing no significant nausea was numerically greater with the APR regimen compared with the active control regimen, being most pronounced in Cycle 2. Because there was a relatively modest difference between treatment groups with the symptom of nausea, an alternative analysis was performed to explore differences in the level of nausea by day, by cycle, and by VAS level of nausea. This analysis did not reveal differences between treatment groups. The Phase III trials using APR for the prevention of CINV with cisplatin-based chemotherapy may suggest that the NK_1 receptor antagonists have relatively little impact on the nausea component of CINV.[4,5] Alternatively, it has been suggested that the delayed-phase nausea and emesis resulting from high-dose cyclophosphamide is significantly mediated by 5-HT_3 receptor antagonists.[16] Thus, the absence of a 5-HT_3 receptor antagonist beyond Day 1 in the APR regimen may have hindered any potentiating effect of APR. Finally, the efficacy of corticosteroids in the prevention of delayed-phase nausea has been established, so the absence of corticosteroid therapy beyond Day 1 in either regimen may have limited any observed treatment difference between regimens that may have otherwise been seen in the context of corticosteroid therapy.[17] Further studies are needed to determine the most effective treatment regimen for nausea due to MEC.

In general, the AE profile in the current study is typical of a population of patients with breast carcinoma receiving MEC. The pattern of clinical and laboratory AEs in both the APR regimen and the control regimen was comparable in Cycle 1. This pattern continued through cycles 2–4. This is noteworthy given the slightly greater exposure to chemotherapy and study therapy for patients in the APR group. This indicates that the APR regimen was well tolerated throughout the study and that there was no evidence of clinically significant interactions between APR and the coadministered chemotherapy regimens. The incidence of anemia, neutropenia, thrombocytopenia, and febrile neutropenia was also similar in both treatment groups in Cycles 2–4. Although there was a numerically higher incidence of neutropenia associated with the APR regimen than with the control regimen, this imbalance was not statistically significant. In addition, the severity of neutropenia by the NCI toxicity grade was similar between treatment groups. The safety profile seen with MEC was generally similar to that seen with HEC.[6]

In conclusion, the results demonstrate an advance in treatment options and present recommendations[18,19] for the prevention of CINV due to MEC. It has been previously reported that the APR regimen was superior to an active control therapy, as measured by CR (no emesis and no use of rescue medication), after the first cycle of chemotherapy.[12] This study further demonstrated that the percentage of patients who experienced a CR in Cycle 1 and who sustained a CR over 4 cycles of chemotherapy was greater with the APR regimen than with the active control regimen (providing information to guide the initial selection of preventative antiemetic therapy) and that the treatment advantage seen with the APR regimen in the first cycle was maintained and increased slightly over four cycles of chemotherapy (providing information to guide subsequent therapeutic choice after the initial selection of preventative antiemetic therapy). Future studies are warranted to determine a regimen to maximally treat the nausea component of CINV.

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