

Randomized, Placebo-controlled, Pilot Study Evaluating Aprepitant Single Dose Plus Palonosetron and Dexamethasone for the Prevention of Acute and Delayed Chemotherapy-induced Nausea and Vomiting

Jon D. Herrington, PharmD, BCPS, BCOP¹
 Adam D. Jaskiewicz, PharmD²
 Juhee Song, PhD³

¹ Department of Pharmacy, Scott & White Memorial Hospital, Texas A&M University Health Care System, Temple, Texas.

² Division of Pharmacy, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

³ Department of Biostatistics, Scott & White Memorial Hospital, Temple, Texas.

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Address for reprints: Jon D. Herrington, PharmD, BCPS, BCOP, Scott & White Memorial Hospital, Department of Pharmacy, 2401 South 31st Street, Temple, TX 76508; Fax: (254) 724-4829; E-mail: jherrington@swmail.sw.org

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BACKGROUND. The combination of palonosetron and aprepitant is safe and effective in the prevention of chemotherapy-induced emesis (CIE). The purpose of this pilot study was to ascertain the effectiveness of 1-day versus 3-day aprepitant in the prevention of acute and delayed nausea and vomiting in patients who were receiving highly emetogenic chemotherapy.

METHODS. This study was institutional review board-approved and informed consent was obtained before this study was begun. This was a pilot, single-institution, randomized, double-blind, placebo-controlled trial that evaluated 3 different treatment arms. All groups received palonosetron 0.25 mg intravenously on Day 1 and dexamethasone on Days 1–4. Arm A received aprepitant 125 mg orally on Day 1 followed by 80 mg on Days 2–3. Arm B received aprepitant 125 mg orally on Day 1 and placebo on Days 2–3. Arm C received placebos on Days 1–3. The primary endpoint was to evaluate the proportion of patients with acute and delayed emesis within each group.

RESULTS. Seventy-five patients were included in the analysis. The study commenced with 3 groups; however, an interim analysis displayed unacceptable emesis events in Arm C, and this group was terminated. There were no significant differences between Arms A and B for emesis, nausea, or the use of breakthrough antiemetics. In Arms A and B, 93% of patients were emesis-free from Days 1–5 compared with only 50% in Arm C.

CONCLUSIONS. From this pilot study of patients who were receiving palonosetron, aprepitant, and dexamethasone for highly emetogenic chemotherapy, a single dose of aprepitant displayed similar effectiveness compared with 3-day aprepitant. *Cancer* 2008;112:2080–7. © 2008 American Cancer Society.

KEYWORDS: serotonin antagonists, antiemetic, vomiting, nausea, receptors, neurokinin-1, dexamethasone, aprepitant, palonosetron.

With the availability of palonosetron and aprepitant, the control of acute and delayed chemotherapy-induced emesis (CIE) has improved significantly. In comparison to ondansetron and dolasetron, palonosetron appears to be similar or to have enhanced efficacy in the prevention of acute and delayed CIE.^{1–3}

Aprepitant is a substance P/neurokinin-1 (NK1)-receptor antagonist approved for use in combination with a 5-HT₃-receptor antagonist and dexamethasone for acute and delayed CIE prevention. A 3-day oral aprepitant regimen in combination with ondansetron plus dexamethasone has displayed effectiveness against acute and delayed CIE associated with anthracycline-based breast cancer

regimens or cisplatin-containing regimens compared with ondansetron antiemetics alone.^{4–9}

The original, older formulation of aprepitant, L-754,030, was evaluated in a single-day versus a 5-day regimen.¹⁰ There were no significant differences in the prevention of emesis in the acute or delayed setting. With the current United States Food and Drug Administration (FDA)-approved aprepitant formulation, there is a lack of data in a single-dose format. Therefore, our study was designed to evaluate the effectiveness of single-dose aprepitant on Day 1 of chemotherapy versus 3-day aprepitant in combination with palonosetron and dexamethasone in patients who were receiving highly emetogenic regimens.

MATERIALS AND METHODS

Study Design

The institutional review board approved this pilot, single-institution, randomized, double-blind, placebo-controlled comparative trial. Eligible patients were 18 years of age or older with histologically or cytologically confirmed malignant disease and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. The highly emetogenic regimens included cisplatin ≥ 50 mg/m² or breast cancer regimens that included anthracycline and cyclophosphamide combinations (eg, AC = doxorubicin, cyclophosphamide; FEC = fluorouracil, epirubicin, cyclophosphamide; TAC = docetaxel, doxorubicin, cyclophosphamide). Patients were either chemotherapy-naïve or chemotherapy non-naïve with the last chemotherapy separated by at least 3 weeks; however, study criteria demanded that they not have greater than grade 1 nausea. Other exclusion criteria included any patient who experienced an episode of emesis within 24 hours before the start of chemotherapy or who had documented primary or secondary brain neoplasm, and any patient who was receiving radiation to abdomen or pelvis, medications with known antiemetic activity, or medications known to induce the cytochrome P450 enzymes (eg, phenytoin, carbamazepine, rifampin).

After informed consent was obtained, the patients were randomized to receive 1 of 3 regimens. On Day 1, Arms A and B received a single dose of palonosetron 0.25 mg intravenously and dexamethasone 12 mg orally before receiving highly emetogenic chemotherapy. In Arm A, patients received the FDA-approved 3-day regimen of aprepitant 125 mg orally on Day 1 followed by 80 mg orally per day on Days 2 and 3. Patients in Arm B received aprepitant 125 mg orally on Day 1 followed by matching placebo on

Days 2 and 3. Arm C involved palonosetron 0.25 mg intravenously and dexamethasone 18 mg orally on Day 1. The dexamethasone and aprepitant were encapsulated to maintain blinding among the 3 arms. On Days 1–3, placebo resembling aprepitant was administered. All patients in the 3 study arms received dexamethasone 8 mg orally daily on Days 2–4, and all received palonosetron 30 minutes before chemotherapy and aprepitant or placebo 60 minutes before chemotherapy. The primary efficacy endpoint was the proportion of patients with emesis in the acute (Day 1) and delayed (Days 2–5) phases after chemotherapy. Secondary endpoints included assessment of prevention of acute and delayed nausea and the use of breakthrough antiemetics. Complete response was defined as no emesis nor use of breakthrough antiemetics.

Efficacy Parameters

The primary efficacy endpoint was the proportion of patients with emesis in the acute (Day 1) and delayed (Days 2–5) phases after chemotherapy. A single emetic episode was defined as emesis separated by less than a 5-minute interval. The secondary endpoints were the amount of breakthrough antiemetics administered and the severity of nausea during the 120-hour study period. Breakthrough antiemetic medications were defined as medications used to treat CIE that did not respond to the initial prophylactic antiemetic regimen. Nausea severity was evaluated by using a 100-mm visual analog scale available in the patient diary. Nausea was defined by a patient's report of a feeling in the stomach that he/she may vomit. The 100-mm visual analog scale ranged from 0, defined as "no nausea", to 100, defined as "the worst nausea possible." If patients ranked their nausea < 5 mm, it was considered "no nausea" and if ranked < 25 mm, it was considered "no significant nausea". Patients had a diary to document the number of emetic episodes, breakthrough nausea medications, and nausea severity during the 120-hour observation period after the infusion of chemotherapy. A study coordinator provided follow-up communications with the patients to ensure adherence to the required diary documentation and with the study medications.

Statistical Analyses

After the first 50 patients were randomized, an unplanned interim analysis was completed because of reports from the study coordinator that patients were experiencing severe emesis. It was found that all of the patients experiencing emesis were in Arm C ($n = 8$ of 16 experienced emesis vs none in the

TABLE 1
Baseline Demographic and Clinical Characteristics, n = 75

	Arm A Palonosetron plus 3-day arepitant	Arm B Palonosetron plus 1-day arepitant	P	Arm C Palonosetron plus placebo
No. (%)	29 (38.7%)	30 (40.0%)		16 (21.3%)
Age, y ± SD	59.6 ± 10.7	58.3 ± 10.5	.64*	56.1 ± 12.6
Sex				
Men	9 (31.0%)	9 (30.0%)	.93 [†]	2 (12.5%)
Women	20 (69.0%)	21 (70.0%)		14 (87.5%)
Weight, kg ± SD	87.5 ± 32.2	88.1 ± 33.2	.76 [‡]	86.9 ± 24.2
BSA, m ² ± SD	1.90 ± 0.18	1.89 ± 0.17	.86*	1.87 ± 0.25
ECOG Score			.43 [§]	
0	21 (72.4%)	25 (83.3%)		14 (87.5%)
1	7 (24.1%)	5 (16.7%)		1 (6.25%)
2	1 (3.5%)	—		1 (6.25%)
Cancer diagnosis			.39 [§]	
Breast	13 (44.8%)	17 (56.7%)		11 (68.75%)
Lung	6 (20.7%)	3 (10.0%)		1 (6.25%)
Head and Neck	4 (13.8%)	7 (23.3%)		3 (18.75%)
Other	6 (20.7%)	3 (10.0%)		1 (6.25%)
Positive history of motion sickness	3 (10.3%)	5 (16.7%)	.71 [§]	3 (18.75%)
Pregnancy-induced vomiting			1.00 [§]	
Yes	3 (10.3%)	3 (10.0%)		8 (50.0%)
No	16 (55.2%)	16 (53.3%)		6 (37.5%)
NA	10 (34.5%)	11 (36.7%)		2 (12.5%)
Alcohol intake history			.84 [§]	
None	22 (75.9%)	25 (83.3%)		12 (75.0%)
1–5 drinks per mo	3 (10.3%)	2 (6.7%)		1 (6.25%)
6–14 drinks per mo	1 (3.5%)	—		1 (6.25%)
>14 drinks per mo	3 (10.3%)	3 (10.0%)		2 (12.5%)
Chemotherapy naive	29 (100.0%)	28 (93.3%)	.49 [§]	14 (87.5%)

SD indicates standard deviation; BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; NA, not applicable, P-values are between Arm A and Arm B.

* Determined by using the 2 sample *t*-test.

[†] Determined by using the chi-square test.

[‡] Determined by using the Wilcoxon test.

[§] Determined by using the Fisher Exact test.

^{||} 1 drink = 12 ounces of beer, 1 ounce of liquor, or 5 ounces of wine.

other arms). Therefore, the study was temporary halted, and the protocol was amended with the removal of Arm C. The descriptive statistics of patients in Arm C will be presented, but this study group will not be included in the statistical comparison among groups.

The demographic data of study participants were reported by using descriptive statistics. Baseline comparisons of demographic data were performed using chi-square or Fisher Exact tests for categorical data and 2-sided, 2-sample *t* tests for continuous data. When the continuous data were strongly skewed, the Wilcoxon nonparametric procedure was used. To assess the main specific aim, the Fisher Exact test was used to compare the proportion of patients with no emetic episodes between the 2 treatment arms. The secondary objectives of the study were reported by using descriptive statistics

and were compared by using the 2-sided, 2-sample *t* test. When secondary outcomes data were skewed, the Wilcoxon nonparametric test was used. The designated level of statistical significance was <.05.

RESULTS

Patient Characteristics

Patients were evaluated between June 2005 and May 2007. Eighty-two patients were randomized to receive a treatment. Three patients refused or failed screening, 2 patients did not receive antiemetics as randomized, and 2 patients did not receive chemotherapy on the study day. For the study, 75 patients remained. All treatment groups received palonosetron 0.25 mg, whereas 29 patients received the 3-day arepitant regimen, 30 patients received a single-dose arepitant, and 16 patients received placebo. As

TABLE 2
Chemotherapeutic Agents Administered

	Arm A Palonosetron plus 3-day aprepitant n = 29	Arm B Palonosetron plus 1-day aprepitant n = 30	Arm C Palonosetron plus placebo n = 16
Cisplatin	16 (55.2%)	13 (43.3%)	5 (31.2%)
Dose, mg/m ² administered, median [range]	75 [50–100]	80 [50–100]	100 [75–100]
Cyclophosphamide	12 (41.4%)	17 (56.7%)	11 (68.8%)
Dose, mg/m ² administered, median [range]	500 [500–600]	600 [500–600]	600 [500–600]
Doxorubicin	11 (37.9%)	17 (56.7%)	10 (62.5%)
Dose, mg/m ² administered, median [range]	60 [24–60]	60 [30–60]	60 [50–60]
Etoposide	6 (20.7%)	2 (6.7%)	2 (12.5%)
Dose, mg/m ² administered, median [range]	90 [50–100]	90 [80–100]	100 [100–100]
Fluorouracil	4 (13.8%)	1 (3.3%)	1 (6.2%)
Dose, mg/m ² administered, median [range]	500 [500–1000]	1000 [1000–1000]	500 [500–500]
Epirubicin	3 (10.3%)	1 (3.3%)	1 (6.2%)
Dose, mg/m ² administered, median [range]	100 [100–100]	50 [50–50]	100 [100–100]
Other	6 (20.7%)	5 (16.7%)	4 (25.0%)

The total percentage is greater than 100% because all patients received more than 1 chemotherapy agent. There were no statistically significant differences between Arms A and B except the cyclophosphamide dose was statistically significantly lower in the 3-Day Arm A ($P = .04$; Fisher Exact test).

TABLE 3
Proportion of Patients With No Emesis

	Percentage with no emesis				
	Arm A Palonosetron plus 3-day aprepitant, n = 28	Arm B Palonosetron plus 1-day aprepitant, n = 27	Asymptotic 95% CI*	P^{\dagger}	Arm C Palonosetron plus placebo, n = 16
Acute phase	96.4	100	(-10.5–3.3)	1.00	93.8
Delayed phase	92.9	92.6	(-13.5–14.0)	1.00	50.0
Both phases	92.9	92.6	(-13.5–14.0)	1.00	50.0

* Difference between 3-Day and 1-Day aprepitant.

\dagger Fisher Exact test was used (3-Day vs 1-Day).

described in the statistics section, only Arms A and B were statistically compared. For the complete response endpoint, 1 patient in Arm A versus 3 patients in Arm B did not return their patient diaries; therefore, those patients were excluded. All patients included in the analysis had 100% adherence to the study's medication regimen.

Table 1 lists the demographic data for 75 patients. There were no statistically significant differences between Arms A and B. The most common malignancy types included breast carcinoma (44.8% vs 56.7% in Arms A and B, respectively), lung (20.7% vs 10%), and head and neck (13.8% vs 23.3%). The majority (100% vs 93%) of patients were chemotherapy naive. There were no differences in body surface area, ECOG scores, history of motion sickness, and

pregnancy-induced vomiting among the different patient groups. The types of chemotherapy and their median doses were similar among groups, except the cyclophosphamide dosage (Table 2). The median doses of cyclophosphamide were 500 mg/m², 600 mg/m², and 600 mg/m², respectively, for the aprepitant 3-day, aprepitant 1-day, and placebo groups ($P = .04$).

Primary Efficacy Endpoint

The proportion of patients without emesis during the first 24 hours was similar between Arms A and B (96.4% vs 100%, respectively; $P = 1.00$ (Table 3 and Fig. 1).

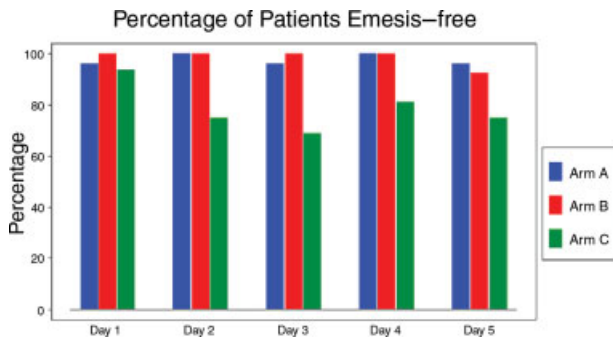


FIGURE 1. Percentage of patients without emesis during Days 1–5 after emetogenic chemotherapy. There were no statistically significant differences between Arms A and B.

TABLE 4
Severity of Nausea Using VAS

Severity of nausea using VAS (mean±SD; median, range)			
Arm A Palonosetron plus 3-day aprepitant, n = 26	Arm B Palonosetron plus 1-day aprepitant, n = 26	<i>P</i> *	Arm C Palonosetron plus placebo, n = 16
Day 1	12.6 ± 24.9 0(0–95)	.82	15.6 ± 32.1 0(0–95)
Day 2	15.2 ± 24.6 4(0–95)	.80	28.4 ± 39.2 2.5(0–100)
Day 3	15.0 ± 26.1 1.5(0–95)	.95	30.3 ± 40.4 2.5(0–100)
Day 4	10.5 ± 21.8 3.5(0–95)	.62	19.6 ± 31.5 2.5(0–95)
Day 5	12.0 ± 25.2 0(0–95)	.52	20.6 ± 34.0 0(0–95)

VAS indicates visual analog scale; SD, standard deviation.

* Wilcoxon 2-sample test, (3-Day vs 1-Day).

Other Efficacy Endpoints and Safety

The incidence of overall nausea, significant nausea (>25 mm on the 100-mm visual analog scale), and the severity of nausea was not different among the 3 arms (Table 4 and Fig. 2). In addition, the frequency of rescue antiemetics was also similar among the 3 groups (Table 5). During the first 24 hours, complete response (shown in Table 6 and Fig. 3) was similar between Arms A and B (66.7% vs 70.4%; $P = .77$). This effect carried over to the delayed phase in which 63% of Arm A and 59% of Arm B displayed no emesis or use of breakthrough medications. Only 55.6% of Arm A and 51.9% of Arm B patients displayed a complete response during both phases ($P = .78$). There were no reports of serious adverse events that were related to study medication.

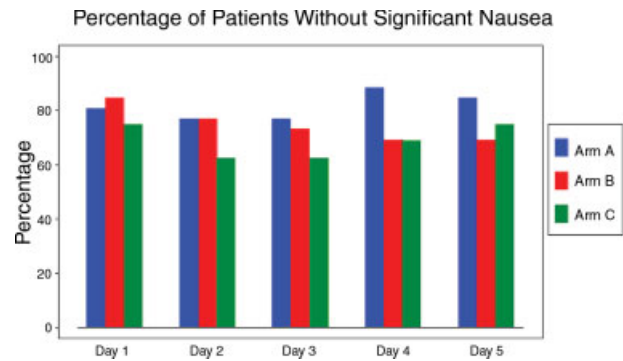


FIGURE 2. Percentage of patients without significant nausea during Days 1–5 after emetogenic chemotherapy. Significant nausea is defined as >25 mm on the visual analog scale. There were no statistically significant differences between Arms A and B.

DISCUSSION

The current pilot study suggests that a single 125-mg dose of aprepitant provides similar effectiveness compared with the traditional 3-day regimen. When aprepitant was used in combination with palonosetron and dexamethasone, it provided protection against emesis in more than 90% of patients during the 5-day study period. This finding is similar to that of other aprepitant-containing antiemetic studies.

The use of aprepitant has been shown to be effective in preventing acute and delayed emesis in patients who are receiving cisplatin and, also, anthracycline-containing therapies. In 1999, Navari and colleagues¹⁰ published a comparison trial with the original aprepitant formulation, L-754,030, combined with granisetron and dexamethasone. Their Group 1 patients received L-754,030 400 mg orally on Day 1 and then aprepitant 300 mg orally on Days 2–5, while Group 2 received only L-754,030 400 mg orally on Day 1. All groups received granisetron plus dexamethasone in which Group 3 did not receive L-754,030. There were no differences between emetic episodes or the number of rescue medications used in acute-emesis and delayed-emesis phases between Groups 1 and 2. However, compared with Group 3, the results were significantly in favor of the L-754,030 Groups 1 and 2.

Similar observations were reported by Van Belle and colleagues¹¹ who compared NK-1 receptor antagonist combinations with ondansetron and dexamethasone in patients who were receiving cisplatin-based chemotherapy regimens. Their Group 1 patients received the intravenous prodrug formulation of aprepitant (L-758,298) 100 mg on Day 1 followed by L-754,030 300 mg orally on Days 2–5. Group 2 received L-758,298 100 mg intravenously on

TABLE 5
No Breakthrough Medications Administered

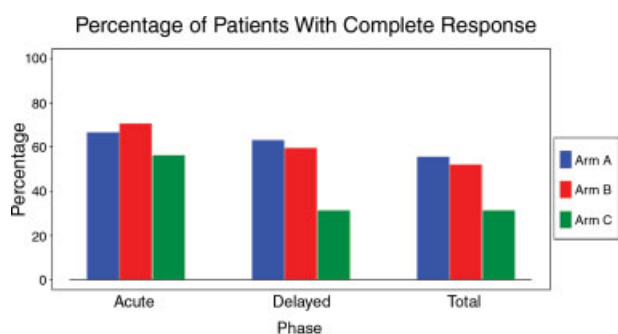
	Percentage with no breakthrough medications administered				
	Arm A Palonosetron plus 3-day aprepitant, n = 27	Arm B Palonosetron plus 1-day aprepitant, n = 27	Asymptotic 95% CI*	P	Arm C Palonosetron plus placebo, n = 16
Acute phase	81.5	85.2	(-23.6-16.2)	1.00 [†]	75
Delayed phase	55.6	70.4	(-40.3-10.6)	.26 [‡]	43.8
Both phases	55.6	63.0	(-33.5-18.7)	.58 [‡]	43.8

* Difference between 3-Day and 1-Day aprepitant.
[†] Fisher Exact test was used to compare 2 groups (3-Day vs 1-Day).
[‡] Chi-square test was used to compare 2 groups (3-Day vs 1-Day).

TABLE 6
Proportion With Complete Response

	Percentage with complete response (no emesis and no breakthrough antiemetics)				
	Arm A Palonosetron plus 3-day aprepitant, n = 27	Arm B Palonosetron plus 1-day aprepitant, n = 27	Asymptotic 95% CI	P*	Arm C Palonosetron plus placebo, n = 16
Acute phase	66.7	70.4	(-28.5-21.1)	.77	56.2
Delayed phase	63.0	59.3	(-22.3-29.7)	.78	31.2
Both phases	55.6	51.9	(-22.9-30.3)	.78	31.2

* Chi-square test was used to compare 2 groups (3-Day vs 1-Day.)

**FIGURE 3.** Percentage of patients with a complete response during the acute (Day 1), delayed (Days 2–5), and total (Days 1–5) phases after emetogenic chemotherapy. Complete response is defined as no emesis and no use of breakthrough antiemetic medications. There were no statistically significant differences between Arms A and B.

Day 1 followed by placebo on Days 2–5, while Group 3 received ondansetron 32 mg intravenously on Day 1 followed by placebo on Days 2–5. All 3 groups received dexamethasone before chemotherapy on Day 1. There was a significant decrease in the number of emetic episodes during the delayed phase

(Days 2–5) in both Groups 1 and 2 compared with Group 3. However, there was no statistical difference in the proportion of patients without emesis during the delayed phase between Groups 1 and 2.

Since the publication of both the Navari and Van Belle studies, L-754,030 (original aprepitant) has been reformulated into a nanoparticle (Nano-Crystal; Elan, Dublin, Ireland) colloidal-dispersion formulation. Unfortunately, further studies using single-dose aprepitant were not subsequently conducted using the current reformulated, FDA-approved product. A study by Wu and colleagues¹² demonstrated in a Beagle (dog model) that the nanoparticle formulation increased bioavailability, had faster absorption, and eliminated food effects on absorption compared with the original, conventional, micronized aprepitant formulation.

Recently published in abstract form, a single-arm, open-labeled study evaluated the 5-day effectiveness of aprepitant 285 mg in a single daily dose before moderately emetogenic chemotherapy.¹³ Patients received palonosetron 0.25 mg intravenously plus dexamethasone 20 mg orally and aprepitant 285 mg orally as a single dose. All 32 patients had breast

cancer and received an anthracycline-cyclophosphamide combination regimen. The complete response (no emesis and no rescue antiemetics) was 78% in the acute phase, 59% in the delayed phase, and 50% overall. Patients without emesis were 100% in the acute period and 97% for the delayed and overall periods. In addition, 75% of patients in the acute phase, 62% in the delayed phase, and 56% overall did not have significant nausea (<25 mm on visual analog scale). It is unknown if this larger aprepitant dose will have any effect on the drug-interaction profile against the potentially susceptible chemotherapy agents such as cyclophosphamide and doxorubicin.

The regimen of palonosetron and aprepitant has demonstrated effectiveness in breast cancer patients who are receiving anthracycline-containing regimens.¹⁴ Results in the current trial mirror those results published elsewhere. It would be interesting to inquire whether similar results would be seen by using another 5-HT₃-receptor antagonist. A recent abstract described the receptor-interaction differences between different 5-HT₃ receptor antagonists.¹⁵ In that trial, palonosetron exhibited competitive and allosteric interactions with the 5-HT₃ receptor. However, ondansetron and granisetron displayed only competitive antagonism of the 5-HT₃ receptor. In theory, this interaction could explain the increased efficacy in emesis control between palonosetron and other 5-HT₃ receptor antagonists.

Several design characteristics of our clinical trial are worth examining. First, this was a randomized, placebo-controlled trial, which limits the potential for bias to influence results. Second, we chose to enroll a population of high-risk patients who were receiving highly emetogenic chemotherapy. These groups of patients were mainly breast cancer patients (54.7%) and patients who were receiving high-dose cisplatin (45.3%). In the palonosetron and placebo Arm C, most patients were breast cancer patients (68.8%) and also possessed more adverse prognostic factors (eg, history of motion-induced and pregnancy-induced sicknesses) compared with the other 2 groups. The 5 patients who received cisplatin also received a higher median dose of cisplatin (100 mg vs 75 mg, 80 mg) compared with the aprepitant Groups A and B, respectively. It is unknown whether all of these disparities can explain the reason for a poorer outcome in delayed-emesis control compared with the aprepitant arms. Nevertheless, because of higher rate of failures with Arm C, this study group was subsequently closed.

It is interesting to note that there is a trend for larger complete response with the 3-day aprepitant regimen versus the single-dose regimen in the

delayed and combined phases but not in the acute phase. The differences are not statistically significant; however, this issue will have to be addressed in a larger trial. There was no significant difference in the primary objective of the trial. The prevention of emesis throughout the acute and delayed phases was achieved in 92.9% of the 3-day aprepitant versus 92.6% in the single-day aprepitant arm.

The control of nausea was achieved in similar fashion between the 2 aprepitant arms. However, there was a trend toward better significant nausea prevention on Days 4–5 with the 3-day Arm A versus the single dose. In the 3-day arm, 88.5% versus 69.2% did not have significant nausea as defined by <25 mm on the visual analog scale ($P = .09$). It is unlikely that there is a true difference present because previously published data has not found a disparity. According to its package insert, aprepitant fails to demonstrate improved efficacy over placebo for the prevention of nausea (overall and significant nausea) in acute or delayed phases.¹⁶

In conclusion, the current study has demonstrated that a single dose of aprepitant 125 mg has similar effectiveness as the 3-day aprepitant regimen. These findings are similar to previous, older formulation, aprepitant studies, which compared a single dose to 5 days of aprepitant therapy. In addition, the use of a single 125 mg dose would equate to lower drug cost with similar effectiveness for highly emetogenic chemotherapy regimens. With this combination of palonosetron and aprepitant, greater than 90% of patients can be emesis-free during Days 1–5 after chemotherapy.

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