Prevention of Delayed Nausea: A University of Rochester Cancer Center Community Clinical Oncology Program Study of Patients Receiving Chemotherapy

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ABSTRACT

Purpose

We conducted a double-blind randomized clinical trial of the following four regimens for controlling delayed nausea (DN): group 1: palonosetron + dexamethasone on day 1 with prochlorperazine on days 2 and 3; group 2: granisetron + dexamethasone on day 1 with prochlorperazine on days 2 and 3; group 3: aprepitant + palonosetron + dexamethasone on day 1 with aprepitant + dexamethasone on days 2 and 3; and group 4: palonosetron + dexamethasone on day 1 with prochlorperazine + dexamethasone on days 2 and 3.

Patients and Methods

Chemotherapy-naïve patients received doxorubicin, epirubicin, cisplatin, carboplatin, or oxaliplatin. The primary end point was average nausea assessed four times daily on days 2 and 3. Primary analyses were whether nausea control would be improved by using palonosetron versus granisetron on day 1 (group 1 v group 2); by adding dexamethasone on days 2 and 3 (group 1 v group 4); and by using aprepitant versus prochlorperazine (group 3 v group 4). Statistical significance was set at $P = .017$.

Results

Two hundred thirty-four, 234, 241, and 235 evaluable patients were accrued to groups 1, 2, 3, and 4, respectively. Adjusted mean differences for the three planned analyses were as follows: palonosetron versus granisetron: -0.01 (95% CI, -0.23 to 0.20 ; $P = .72$); adding dexamethasone on days 2 and 3: 0.20 (95% CI, -0.02 to 0.41 ; $P = .01$); and using aprepitant versus prochlorperazine: -0.03 (95% CI, -0.24 to 0.19 ; $P = .56$).

Conclusion

The addition of dexamethasone on days 2 and 3 reduced DN. Palonosetron and granisetron have similar effects on DN. The beneficial effect of adding aprepitant for control of DN was the same as adding prochlorperazine.

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INTRODUCTION

Nausea remains one of the most troublesome adverse effects associated with cancer treatment.¹⁻⁴ The introduction of the 5-hydroxytryptamine receptor antagonist (5-HT RA) class of antiemetics, including ondansetron, granisetron, and dolasetron, more than 15 years ago greatly reduced treatment-related vomiting but not treatment-related nausea.^{1,2,5} More recently, the use of palonosetron (Aloxi; MGI Pharma, Bloomington, MN), a second-generation 5-HT RA, and aprepitant (Emend; Merck, Whitehouse Station, NJ), a neurokinin-1 receptor antagonist, has further increased control of emesis.⁶⁻¹⁰ However, treatment-related nausea remains a significant issue.^{3,9,11,12}

Delayed nausea (DN) is a particular problem and often occurs at rates higher than acute nausea.^{2,3,13-15}

Patients with breast cancer receiving doxorubicin are especially vulnerable to nausea, and our prior research shows they are more likely to experience DN than patients receiving either cisplatin or carboplatin.¹⁶

The National Cancer Institute–supported University of Rochester Cancer Center (URCC) Community Clinical Oncology Program (CCOP) has just completed its second study to determine optimal antiemetic therapy for control of chemotherapy-induced DN. The first study, reported earlier,¹⁷ was conducted between June 2001 and June 2004 on 671 chemotherapy-naïve patients receiving chemotherapy containing doxorubicin. All patients were

Fig 1. CONSORT diagram.

given a first-generation 5-HT RA antiemetic plus dexamethasone on the day of treatment (day 1) and randomly assigned to one of the following three regimens for days 2 and 3: group 1: prochlorperazine 10 mg orally (PO) every 8 hours; group 2: any first-generation 5-HT RA using standard dosage; or group 3: prochlorperazine 10 mg PO as needed.

This prior study was designed to answer the following two questions: Is a 5-HT RA antiemetic more effective than prochlorperazine in controlling DN? Is prochlorperazine taken on a preventive basis more effective than prochlorperazine taken as needed in controlling treatment-related DN? In that study, no corticosteroids were given on days 2 and 3 of treatment. Occurrence and severity of nausea and occurrence of vomiting were assessed by a home record. There was no difference between the groups in mean DN severity or in the occurrence of delayed vomiting (29%). We did, however, see a difference in occurrence of DN, with 71% of patients taking prochlorperazine regularly (group 1) reporting DN compared with 79% of patients in group 2 and 82% in group 3.

We followed up with the study reported herein, testing four antiemetic regimens for control of DN from chemotherapy containing a platinum-based drug or an anthracycline. Group 1 of the prior study, because it had the lowest occurrence of DN, was carried forward and is designated as group 2 in the present study. New groups to examine regimens containing palonosetron, aprepitant, and/or dexamethasone are also included.

PATIENTS AND METHODS

Patients

Chemotherapy-naïve patients at least 18 years of age with any cancer diagnosis who were scheduled to receive their first treatment with a chemotherapy regimen containing any of the five following chemotherapy agents at any dose or schedule other than multiple-day doses were eligible: doxorubicin, epirubicin, cisplatin, carboplatin, or oxaliplatin. Patients from 15 private practice oncology groups in the United States affiliated with the URCC CCOP were enrolled by research personnel from May 2007 to September 2010. Patients scheduled to receive liposomal doxorubicin, liposomal cisplatin, dacarbazine, hexamethylmelamine, nitrosoureas, or streptozocin and patients scheduled to receive radiotherapy or interferon concurrently with chemotherapy were not eligible. Patients with clinical evidence (as judged by the treating oncologist) of current or impending bowel obstruction or symptomatic brain metastases were not eligible. Chemotherapy agents, other than those listed earlier, could be administered orally, intravenously, or by continuous infusion on 1 or several days; in an adjuvant or neoadjuvant setting; and with curative or palliative intent. The institutional review boards of the University of Rochester and each participating site approved the protocol in accordance with an assurance filed with and approved by the US Department of Health and Human Services. Patients gave written informed consent. This trial is registered with ClinicalTrials.gov (identifier: NCT00475085).

Design and Procedures

A randomized, double-blind, placebo-controlled study design was used. A computer-generated random numbers table was used to assign patients to one of four groups (Fig 1). Random assignment, stratified by CCOP site and treatment (doxorubicin, epirubicin, cisplatin, carboplatin, and oxaliplatin), was carried out centrally via a secure Internet connection. The antiemetic

Table 1. Antiemetic Medications and Dosing Schedule

Day	Group 1*†	Group 2*‡	Group 3§	Group 4†§
Day 1	Palonosetron 0.25 mg IV + dexamethasone 20 mg IV + placebo PO	Granisetron 1 mg IV + dexamethasone 20 mg IV + placebo PO	Palonosetron 0.25 mg IV + dexamethasone 12 mg IV + aprepitant 125 mg PO	Palonosetron 0.25 mg IV + dexamethasone 20 mg IV + placebo PO
Days 2 and 3, morning	Prochlorperazine¶ 10 mg PO + placebo#	Prochlorperazine¶ 10 mg PO + placebo#	Aprepitant¶ 80 mg PO + dexamethasone 8 mg PO	Prochlorperazine¶ 10 mg PO + dexamethasone 8 mg PO
Days 2 and 3, midday	Prochlorperazine¶ 10 mg PO	Prochlorperazine¶ 10 mg PO	Placebo¶ PO	Prochlorperazine¶ 10 mg PO
Days 2 and 3, evening	Prochlorperazine¶ 10 mg PO	Prochlorperazine¶ 10 mg PO	Placebo¶ PO	Prochlorperazine¶ 10 mg PO

Abbreviations: IV, intravenous; PO, oral.

*Palonosetron versus granisetron comparison.

†Adding dexamethasone on day 2 and 3 comparison.

‡Group 2 in this study is the same as group 1 in the prior study.¹⁷

§Aprepitant versus prochlorperazine comparison.

||This placebo matched aprepitant 125 mg.

¶Prochlorperazine 10 mg, aprepitant 80 mg, and a capsule containing only placebo were made to match.

#This placebo matched dexamethasone 8 mg.

medications and dosing schedule for the four groups are listed in Table 1. Palonosetron or granisetron along with the specified dose of dexamethasone were administered as an intravenous dose approximately 30 minutes before chemotherapy. Aprepitant or matching placebo was provided orally before chemotherapy. Study medications (ie, antiemetic or placebo) for days 2 and 3 were provided to patients on a specially prepared double-blinded blister pack organized by day and time of day (morning, midday, or evening) when the medications should be taken. Metoclopramide was allowed as a rescue medication for control of persistent nausea and vomiting on day 2 and subsequent days.

The study was designed to assess three primary research objectives. First, is palonosetron more effective than a first-generation 5-HT₃ RA (granisetron) in controlling DN when both are given on day 1 and prochlorperazine is provided on days 2 and 3? Second, does the addition of dexamethasone to prochlorperazine, given at a dose of 8 mg PO every morning on days 2 and 3, result in better control of DN when compared with prochlorperazine alone? Third, is aprepitant more effective than prochlorperazine for control of DN when both are combined with palonosetron and dexamethasone? Furthermore, we assessed frequency and severity of acute nausea and frequency of acute and delayed vomiting. Analyses were by intent to treat.

Assessments

On enrollment, patients completed an on-study questionnaire with questions about sex, age, race, ethnic origin, education, previous treatment, and susceptibility to motion sickness. Patients were also given a home-record questionnaire by the clinical research associate at the site, who instructed the patients on how to complete the forms. The home record was to be returned to the treatment site in a postage-paid envelope. A phone call reminder was made by clinic personnel on the third day after treatment. The home-record questionnaire enables the patient to note nausea, vomiting, and use of antiemetic drugs and was used in our prior URCC CCOP protocol examining DN (see Introduction).¹⁷ Every day is divided into four segments (morning, afternoon, evening, and night), and patients report the severity of nausea and number of vomiting episodes for the periods of that day. Severity of nausea was assessed by use of a 7-point semantic rating scale, ranging from 1 (not at all nauseated) to 7 (extremely nauseated). Mean and maximum scores of nausea severity were obtained from the afternoon, evening, and night reporting periods on day 1 (ie, for assessment of acute nausea) and from morning, afternoon, evening, and night reporting periods on days 2 and 3 (ie, for assessment of DN). The number of patients who reported vomiting (ie, any number greater than zero for any reporting period) was calculated.

We used scannable forms, the data from which were automatically entered into an Access database (Microsoft, Redmond, WA); data quality was checked by an information analyst. Missing data for nausea severity for any reporting period were excluded from the calculation of the mean and maxi-

mum. If all data for nausea severity were absent for any day, the data were classified as missing, and the patient's data were not evaluable.

Statistical Analyses

One-way analysis of variance was used for the primary analysis with contrast statements used to compare average DN severity between treatment groups 1 and 2, 1 and 4, and 3 and 4 to assess the three primary research objectives. Because the nausea distributions were skewed, Box-Cox transformations were used for the determination of *P* values, with optimum $\lambda = -1.6$ for average DN, and optimum $\lambda = -0.5$ for maximum DN.¹⁸ Because three comparisons were made, a Bonferroni correction was used, and the significance level was set to be $P = .017$ (0.05/3). An identically structured analysis that examined maximum DN severity was also conducted. Because they were stratification factors, all of the previously mentioned analyses initially controlled for type of chemotherapy, CCOP site, and arm $\times$ chemotherapy and arm $\times$ CCOP site interactions, with only covariates significant at $P \leq .05$ retained in the final models. Although not stated aims of the protocol, we also conducted several analyses to provide context for the DN analyses. These supplemental analyses, which are included in the Appendix (online only), examine between-group differences in acute nausea, vomiting, and incidence of DN. Because vomiting and nausea are often but not always linked, we also conducted exploratory analyses examining the relationship between maximum DN and vomiting. These analyses are also reported online.

Based on our prior study (see Introduction), we expected the mean DN severity to be 2.12, with a standard deviation of 1.29. We estimated that 800 evaluable patients (200 patients per group) would provide 80% power to detect a 0.42 difference in mean nausea severity between any pair of conditions adjusting for the three comparisons using the Bonferroni method at an overall significance level of $P = .05$. To account for an anticipated 10% of randomly assigned patients to have no information on the outcome variables after first-line chemotherapy, a total enrollment of 890 patients was planned. No interim analyses were conducted. Although analyses were done by intent to treat, 77 patients had no outcome data and were therefore excluded from analyses. Multiple imputation was used to evaluate the sensitivity of the results to the missing data, and the results were similar, so we present the complete case results here. We used SAS version 9.2 (SAS Institute, Cary, NC), SPSS version 12 (SPSS, Chicago, IL), and R version 2.12.2 (<http://www.r-project.org>) for analyses as appropriate.

RESULTS

One thousand twenty-one patients were enrolled onto the study and randomly assigned to one of the four groups; 944 patients had evaluable data on the primary outcome (Fig 1). Table 2 lists their baseline

Table 2. Baseline Demographic and Clinical Characteristics by Study Group

Characteristic	Group 1 (n = 234)		Group 2 (n = 234)		Group 3 (n = 241)		Group 4 (n = 235)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years								
Mean	57		57		58		58	
Standard deviation	12.5		12.7		11.4		11.5	
Sex								
Male	52	22	39	17	54	22	41	17
Female	182	78	195	83	187	78	194	83
Ethnicity								
Non-Hispanic	229	98	227	97	238	99	233	99
Hispanic	5	2	7	3	3	1	2	1
Race								
White	213	91	214	91	209	87	212	90
African American	18	8	18	8	26	11	18	8
Asian					4	2	2	1
American Indian	3	1	2	1	2	1	2	1
Education								
Beyond high school	135	58	140	60	137	57	136	58
High school or less	99	42	94	40	104	43	99	42
History of motion sickness								
Yes	175	75	148	63	180	75	171	73
No	59	25	85	37	61	25	63	27
Cancer diagnosis								
Alimentary tract	40	17	39	17	46	19	47	20
Breast	138	59	138	59	137	57	142	60
GI	1	0	1	0	2	1	0	0
Genitourinary tract	5	2	9	4	5	2	4	2
Gynecologic	9	4	10	4	7	3	14	6
Head and neck	1	0	1	0	1	0	2	1
Hematologic	12	5	11	5	10	4	8	3
Lung	24	10	22	9	29	12	16	7
Melanoma	1	0			1	0	2	1
Unknown	3	1	3	1	3	1		
Chemotherapy								
Doxorubicin	139	59	138	59	138	57	140	60
Epirubicin	2	1	2	1	5	2	2	1
Cisplatin	11	5	15	6	16	7	10	4
Carboplatin	42	18	41	17	40	17	41	17
Oxaliplatin	40	17	38	16	42	17	42	18
Previous treatment								
Surgery	182	78	180	77	184	76	189	80
Radiotherapy	10	4	5	2	12	5	9	4

NOTE. Data might not add to 100% because of rounding.

characteristics by treatment group. Mean severity of DN was 1.87 for the 234 evaluable patients in group 1, 1.88 for the 234 patients in group 2, 1.65 for the 241 patients in group 3, and 1.68 for the 235 patients in group 4 (Table 3).

Average DN

The three planned contrast statements on average DN to assess the primary objectives provided mixed results (Table 3). The group 1 to group 2 comparison to determine whether palonosetron was more effective than granisetron in controlling DN was not statistically significant (mean difference, -0.01 ; $P = .718$). The group 1 to group 4 comparison to determine whether the addition of dexamethasone on days 2 and 3 resulted in better control of DN was significant (mean difference, 0.20 ; $P = .010$). The group 3 to group 4 comparison to determine whether aprepitant was more effective than prochlorperazine for control of DN, when both were combined with palonosetron and dexamethasone, was also not statistically significant (mean difference, 0.03 ; $P = .557$).

Knowing our negative findings in both the palonosetron versus granisetron comparison and the aprepitant versus prochlorperazine comparison could be considered controversial, especially since our sample was diagnostically heterogeneous and chemotherapies with both high and moderate emetogenic potential were allowed, we replicated these two comparisons using data from only the 507 patients with breast cancer receiving doxorubicin. The findings remained the same. These analyses are reported in the Appendix.

Figure 2 shows mean and maximum severity of DN. Maximum severity of DN for groups 1, 2, 3, and 4 were 2.74, 2.89, 2.21, and 2.39, respectively.

Maximum DN

Figure 2 shows mean and maximum severity of DN. Maximum severity of DN for groups 1, 2, 3, and 4 were 2.74, 2.89, 2.21, and 2.39, respectively.

Table 3. Between-Group Differences in Average and Maximum Delayed Nausea for the Three Comparisons of Interest, Adjusted for Chemotherapy Type

Comparison	Mean Difference	95% CI	P*
Average nausea			
Group 1–group 2 (palonosetron v granisetron)	−0.013	−0.225 to 0.200	.718
Group 1–group 4 (adding dexamethasone)	0.195	−0.017 to 0.407	.010
Group 3–group 4 (aprepitant v prochlorperazine)	−0.025	−0.236 to 0.186	.557
Maximum nausea			
Group 1–group 2	−0.145	−0.480 to 0.190	.941
Group 1–group 4	0.359	0.024 to 0.693	.017
Group 3–group 4	−0.183	−0.515 to 0.149	.304

*Based on transformed responses.

respectively. An analysis of variance using the full data set with contrast statements on maximum DN identical in structure to the one detailed earlier for average DN mirrored the findings for average DN (Table 3). The palonosetron versus granisetron comparison was not statistically significant (mean difference, −0.15; $P = .941$). The comparison examining dexamethasone reached significance (mean difference, 0.36; $P = .017$). The comparison of aprepitant to prochlorperazine was also not statistically significant (mean difference, −0.18; $P = .304$).

DISCUSSION

Our study findings are clear in regard to all three of our primary research objectives. Our data provided no evidence that palonosetron was more effective in controlling DN than a first-generation 5-HT RA (granisetron) when both were provided with dexamethasone on the day of treatment and prochlorperazine on days 2 and 3. There was no statistically significant difference between these two treatment conditions (group 1 v group 2) in average or maximum DN severity. Similarly, our data did not support the conclusion that aprepitant was more effective than prochlorperazine in controlling DN when both were combined with palonosetron and dexamethasone (group 3 compared with group 4). We saw no statistically significant differences in average or maximum DN severity in this comparison. Also clear was our finding that the addition of dexamethasone to prochlorperazine on days 2 and 3 resulted in better control of DN than the same dose of prochlorperazine without dexamethasone. Patients receiving dexa-

methasone had significantly lower average and maximum DN (group 1 v group 4).

At first glance, our finding that palonosetron provided on day 1 was no more effective in controlling DN than a first-generation 5-HT RA provided on day 1 is at variance with a recent report by Saito et al¹⁹ that showed that palonosetron was more effective than a first-generation 5-HT RA in preventing the occurrence of DN and delayed vomiting in patients receiving highly emetogenic chemotherapy. We believe the differences in outcomes between the two studies can be attributed to differences in the antiemetic regimen provided on days 2 and 3.¹⁹ All patients in the study by Saito et al¹⁹ received only dexamethasone during that time period. In contrast, all patients assigned to the relevant groups in our study (ie, groups 1 and 2) received prochlorperazine on days 2 and 3. Our earlier study¹⁷ showed that a first-generation 5-HT RA was no better than prochlorperazine in controlling DN, and one interpretation of the present data is that the combination of a 5-HT RA and prochlorperazine is no better than prochlorperazine alone (ie, the effects are not additive). If this is the case, it explains why the benefit of having a longer lasting 5-HT RA compared with a shorter lasting one for control of DN, as shown in the study by Saito et al,¹⁹ disappears when prochlorperazine is provided. A reasonable interpretation for the combined findings of the study by Saito et al¹⁹ and our study is that the effects of a 5-HT RA and dexamethasone are additive in regard to controlling DN, whereas those of a 5-HT RA and prochlorperazine are not.

Our ability to meaningfully compare our study findings regarding aprepitant to prior research is limited, because seven of the eight randomized controlled studies that have reported on the efficacy of aprepitant-based antiemetic regimens in controlling DN have not used a comparator group that received the strongest available alternative antiemetic regimen (ie, dexamethasone with either prochlorperazine or a 5-HT RA) in the delayed phase of the trial. These seven studies used either placebo alone, a 5-HT RA alone, or dexamethasone alone.^{10,12,20–24} The one study comparable to ours in terms of the antiemetic efficacy of the comparator group during the delayed phase was conducted by Schmoll et al.²⁵ They provided both ondansetron and dexamethasone to the comparison group during the delayed phase, and similar to our study, no significant differences in DN were observed between groups.

Our finding that dexamethasone on days 2 and 3 enhances control of DN is in keeping with both prior research^{26,27} and current antiemetic guidelines.^{7,28,29} Despite this, the finding is in seeming contradiction with two recent studies. The first is a study by Aapro et

Fig 2. Mean and maximum severity of delayed nausea. Vertical bars are upper limit of the 95% CI.

al²⁴ of 300 chemotherapy-naïve patients with breast cancer receiving palonosetron and dexamethasone on day 1, randomly assigned to receive placebo or dexamethasone on days 2 and 3. The investigators reported that most nausea and vomiting parameters showed no difference between the two treatment groups. We believe the findings of our study differ from the study by Aapro et al²⁴ because we reported on nausea severity averaged across days 2 and 3, whereas they reported mostly on prevalence of nausea calculated across days 2 through 5. The apparent differences in the findings of the two studies disappears when similar metrics are examined; their findings on DN severity show that on days 2 and 3, patients receiving dexamethasone had less severe nausea than patients not receiving dexamethasone and that this difference was statistically significant on day 3. The second study, by Celio et al,³¹ was a randomized, open-label trial evaluating differences between two treatment conditions for control of delayed nausea and vomiting in 332 chemotherapy-naïve patients receiving moderately emetogenic chemotherapy. Both groups received palonosetron and dexamethasone before chemotherapy. In addition, group 2 patients, but not group 1 patients, received dexamethasone 8 mg PO on days 2 and 3. The authors reported no overall difference between groups in complete response, which was defined as no emetic episodes and no rescue medication, during days 2 through 5. An imbalance in the number of patients receiving anthracycline plus cyclophosphamide (AC)-based regimens in the two treatment groups, a regimen associated with high rates of DN,¹⁶ provides a possible explanation for why their reported results are different from ours. Thirty-eight percent of patients in group 2 in their study received an AC-based regimen compared with only 32.5% of group 1 patients. Indeed, their subgroup analyses selecting only patients receiving AC-based regimens showed that the antiemetic regimen providing dexamethasone on days 2 and 3 was significantly better at controlling delayed nausea and vomiting than the regimen providing dexamethasone only on day 1, a finding consistent with our own results.

Our study shows that DN remains a significant problem and that more effective regimens for controlling DN are needed. Over half of the patients studied experienced DN, and control afforded by all of the

antiemetic regimens examined was inadequate. The finding that a second-generation 5-HT RA, palonosetron, showed no greater efficacy in controlling DN than a first-generation 5-HT RA was disappointing. We were similarly disappointed that aprepitant provided no significant benefit over prochlorperazine in controlling DN. More effective regimens for controlling DN are needed and should include the addition of prolonged dexamethasone.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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