

# Olanzapine Versus Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting: A Randomized Phase III Trial

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**C**hemotherapy-induced nausea and vomiting (CINV) is associated with a significant deterioration in quality of life and is perceived by patients as a major adverse effect of the treatment.<sup>1</sup> The use of 5-hydroxytryptamine<sub>3</sub> (5-HT<sub>3</sub>) receptor antagonists plus dexamethasone has significantly improved the control of acute CINV.<sup>2</sup> Recent studies have demonstrated additional improvement in the control of acute CINV and delayed CINV with the use of three new agents: palonosetron, a second-generation 5-HT<sub>3</sub> receptor antagonist;<sup>3</sup> aprepitant, the first agent available in the drug class of neurokinin-1 (NK-1) receptor antagonists;<sup>4,5</sup> and olanzapine, an antipsychotic which blocks multiple neurotransmitters in the central nervous system.<sup>6–8</sup>

Palonosetron is a second-generation 5-HT<sub>3</sub> receptor antagonist which has antiemetic activity at both central and gastrointestinal sites. In comparison to the first-generation 5-HT<sub>3</sub> receptor antagonists, it has a higher potency, a significantly longer half-life, and a different molecular interaction with 5-HT<sub>3</sub> receptors.<sup>9,10</sup> These differences may explain palonosetron's efficacy in delayed CINV compared to the first-generation receptor antagonists.<sup>3</sup> A high level of efficacy and an excellent safety profile have been demonstrated in a number of studies.<sup>3,9,11–14</sup> Based on these studies, palonosetron is recommended by multiple international antiemetic guidelines<sup>15–17</sup> for the prevention of acute nausea

## Abstract

**BACKGROUND:** The purpose of the study was to compare the effectiveness of olanzapine (OLN) and aprepitant (APR) for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving highly emetogenic chemotherapy.

**METHODS:** A phase III trial was performed in chemotherapy-naive patients receiving cisplatin  $\geq 70$  mg/m<sup>2</sup> or cyclophosphamide  $\geq 500$  mg/m<sup>2</sup> and doxorubicin  $\geq 50$  mg/m<sup>2</sup>, comparing OLN to APR in combination with palonosetron (PAL) and dexamethasone (DEX). The OLN, PAL, DEX (OPD) regimen was 10 mg of oral OLN, 0.25 mg of IV PAL, and 20 mg of IV DEX prechemotherapy, day 1, and 10 mg/day of oral OLN alone on days 2–4 postchemotherapy. The APR, PAL, DEX (APD) regimen was 125 mg of oral APR, 0.25 mg of IV PAL, and 12 mg of IV DEX, day 1, and 80 mg of oral APR, days 2 and 3, and 4 mg of DEX BID, days 2–4. Two hundred fifty-one patients consented to the protocol and were randomized. Two hundred forty-one patients were evaluable.

**RESULTS:** Complete response (CR) (no emesis, no rescue) was 97% for the acute period (24 hours postchemotherapy), 77% for the delayed period (days 2–5 postchemotherapy), and 77% for the overall period (0–120 hours) for 121 patients receiving the OPD regimen. CR was 87% for the acute period, 73% for the delayed period, and 73% for the overall period in 120 patients receiving the APD regimen. Patients without nausea (0, scale 0–10, MD Anderson Symptom Inventory) were OPD: 87% acute, 69% delayed, and 69% overall; APD: 87% acute, 38% delayed, and 38% overall. There were no grade 3 or 4 toxicities. CR and control of nausea in subsequent chemotherapy cycles were equal to or greater than cycle 1 for both regimens. OPD was comparable to APD in the control of CINV. Nausea was better controlled with OPD.

**DISCUSSION:** In this study, OLN combined with a single dose of DEX and a single dose of PAL was very effective at controlling acute and delayed CINV in patients receiving highly emetogenic chemotherapy. CR rates were not significantly different from a similar group of patients receiving highly emetogenic chemotherapy and an antiemetic regimen consisting of APR, PAL, and DEX.

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and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy (HEC) and for the preven-

tion of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

Aprepitant is an NK-1 receptor antagonist which blocks the emetic effects of substance P.<sup>4,5,18</sup> When combined with a standard regimen of the corticosteroid dexamethasone and a 5-HT<sub>3</sub> receptor antagonist, aprepitant is effective at preventing CINV in patients receiving HEC.<sup>5,18</sup> This regimen is recommended in the guidelines of multiple international groups for the control of CINV in patients receiving HEC.<sup>15-17</sup>

Palonosetron and aprepitant have been combined with dexamethasone for the prevention of CINV in a phase II study of 58 patients who received MEC.<sup>19</sup> This three-drug antiemetic regimen was found to be safe and highly effective at preventing CINV in the acute, delayed, and overall periods.

Olanzapine is a Food and Drug Administration–approved antipsychotic that blocks multiple neurotransmitters: dopamine at D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub> brain receptors; serotonin at 5-HT<sub>2a</sub>, 5-HT<sub>2c</sub>, 5-HT<sub>3</sub>, and 5-HT<sub>6</sub> receptors; catecholamines at  $\alpha_1$ -adrenergic receptors; acetylcholine at muscarinic receptors; and histamine at H<sub>1</sub> receptors.<sup>20,21</sup> Common side effects are sedation and weight gain,<sup>22,23</sup> as well as an association with the onset of diabetes mellitus.<sup>24</sup> Olanzapine's activity at multiple receptors—particularly at the D<sub>2</sub>, 5-HT<sub>2c</sub>, and 5-HT<sub>3</sub> receptors, which appear to be involved in nausea and emesis—suggests that it may have significant antiemetic properties.

A recent phase II trial demonstrated that olanzapine, when combined with a single dose of dexamethasone and a single dose of palonosetron, was very effective at controlling acute and delayed CINV in patients receiving both HEC and MEC.<sup>7</sup> There was excellent control of nausea without the use of multiple days of dexamethasone. A recent phase III study showed that addition of olanzapine to the 5-HT<sub>3</sub> receptor antagonist azasetron and dexamethasone improved delayed CINV in patients receiving HEC or MEC.<sup>8</sup>

Dexamethasone has been a very effective antiemetic at controlling both acute and delayed CINV, but concern has been expressed over the potential toxicity of the use of multiple-day dexamethasone to control CINV.<sup>25</sup> Patients receiving dexamethasone as a prophylactic treatment for CINV reported moderate to severe problems with insomnia, hyperglycemia, indigestion–epigastric discomfort, agitation, increased appetite, weight gain, and acne.<sup>25</sup> Dexamethasone might be decreased or eliminated in an antiemetic regime if other agents effective in both the acute and delayed periods are employed.

The purpose of this study was to compare the efficacy of olanzapine vs. aprepitant, each combined with palonosetron and dexamethasone, in the prevention of CINV in patients receiving HEC.

## Patients and Methods

### PATIENT SELECTION

Eligible patients were  $\geq 18$  years of age with histologically or cytologically confirmed malignant disease who were chemotherapy-naïve and scheduled to receive HEC (cisplatin

$\geq 70$  mg/m<sup>2</sup>, cyclophosphamide  $\geq 600$ – $1,000$  mg/m<sup>2</sup> and doxorubicin  $\geq 50$ – $60$  mg/m<sup>2</sup>). Patients were treated at three outpatient oncology treatment centers with three participating medical oncologists at each site. A similar number of patients in each arm were seen at each site.

### INCLUSION/EXCLUSION CRITERIA

The inclusion/exclusion criteria consisted of the following: patients had to be without nausea in the 24 hours prior to beginning chemotherapy; serum creatinine  $\leq 2.0$  mg/dL; serum bilirubin  $\geq 2.0$  mg/dL; serum glutamic-oxaloacetic transaminase (SGOT) or serum glutamic-pyruvic transaminase (SGPT) less than or equal to three or more times the upper limits of normal; absolute neutrophil count  $\geq 1,500$  mm<sup>3</sup>; patients of childbearing potential (male and female) had to consent to use adequate contraception throughout the protocol therapy; females of childbearing potential had to have a negative urine pregnancy test; no severe cognitive compromise; no known history of central nervous system disease (e.g., brain metastases, seizure disorder); no treatment with another antipsychotic agent such as risperidone, quetiapine, clozapine, phenothiazine, or butyrophenone for 30 days prior to or during the protocol therapy; chronic phenothiazine administration as an antipsychotic agent was not allowed, but patients may receive prochlorperazine and other phenothiazines as rescue antiemetic therapy; no concurrent use of amifostine (Ethyol); no concurrent abdominal radiotherapy; no concurrent use of quinolone antibiotic therapy; no chronic alcoholism (as determined by the investigator); no known hypersensitivity to olanzapine; no known cardiac arrhythmia, uncontrolled congestive heart failure, or acute myocardial infarction within the previous six months; and no history of uncontrolled diabetes mellitus.

### INFORMED CONSENT

All patients gave written informed consent, and the study was approved by the institutional review committee of each participating site.

### STUDY DESIGN AND TREATMENT REGIMEN

All patients eligible for the study were randomized to either the olanzapine, palonosetron, and dexamethasone (OPD) regimen or the aprepitant, palonosetron, dexamethasone (APD) regimen according to a computer-generated random assignment schedule created by a statistician not involved with the study. Patients were further stratified according to gender and to the chemotherapy regimen (cisplatin or doxorubicin/cyclophosphamide).

All patients who received the OPD regime received on the day of chemotherapy, day 1, an antiemetic regimen consisting of dexamethasone 20 mg IV and palonosetron, 0.25 mg IV, 30–60 minutes prior to chemotherapy administration. Patients also began olanzapine 10 mg PO on the day of chemotherapy (day 1) and continued 10 mg PO daily for days 2–4 following chemotherapy administration. Patients received no other antiemetic treatment on days 2–4.

All patients who received the APD regimen received on the day of chemotherapy, day 1, an antiemetic regimen consisting of dexamethasone 12 mg IV, palonosetron 0.25 mg IV, and aprepitant 125 mg PO, 30–60 minutes prior to chemotherapy. Postchemotherapy, patients received oral aprepitant 80 mg/day on days 2 and 3 and oral dexamethasone 4 mg BID on days 2–4.

Protocol therapy continued with each chemotherapy cycle until discontinuation of the same regimen of chemotherapy or at the discretion of the treating investigator up to a maximum of six cycles. Patients were permitted to take rescue therapy of the treating investigator's choice for nausea and/or emesis or retching based on clinical circumstances. Patients who required rescue therapy were permitted to continue on the study at the discretion of the treating investigator in consultation with the patient.

### STUDY VISITS AND ASSESSMENT PROCEDURES

In the prestudy period, all pertinent demographics (age, gender, height, weight) and medical data (site and stage of disease, Eastern Cooperative Oncology Group [ECOG] rating, laboratory values, medications and present therapies including present oncologic therapy) were recorded. For the purposes of this study, the M.D. Anderson Symptom Inventory (MDASI)<sup>26</sup> was utilized to allow for simple, expedient measures of key symptom variables being examined daily for the entire study period. The main purpose of the use of the MDASI in this study was to determine if there were any major or minor toxicities related to the antiemetic regimens.

The MDASI is a flexible system for the assessment of symptoms experienced by patients with cancer. It consists of 13 core symptom items that are rated based on their presence and severity and six symptom interference items that are rated based on the level of symptom interference with function.<sup>26</sup>

Beginning with the first day of chemotherapy (day 1) and daily through day 5, patients were asked to record daily episodes of vomiting/retching (number and time), the daily intensity of symptoms utilizing the MDASI, and the utilization of rescue therapy.

Patients were also asked to record daily episodes of nausea using a visual analogue scale from 0 to 10, with 0 indicating no nausea and 10 indicating a maximal level of nausea. A nurse/research coordinator contacted each patient each day (days 2–5) to remind the patient to complete forms and to query toxicities.

### STATISTICAL METHODS

The primary end point in the study was complete response (CR) (no emetic episodes and no use of rescue medication) for the overall period (0–120 hours postchemotherapy). Secondary end points were CR in the acute (0–24 hours postchemotherapy) and delayed (days 2–5 postchemotherapy) periods and no nausea in the acute, delayed, and overall periods. The study was powered with a sample size to detect a 15% difference between the two antiemetic regimens. With a tol-

erance of 15%, 111 subjects were needed in each arm to obtain a 0.80 power at a Type I error level of 0.05.

The total number of patients was elevated to account for a 10% dropout rate.

Demographic data and patient characteristics were examined descriptively.

The frequencies of severe toxicities and adverse events were calculated.

The percentage of patients with CR for the acute period, the delayed period, and the overall period was calculated. The percentage of patients with no nausea (MDASI score 0) was calculated.

The mean, median, and standard deviation of the maximum MDASI symptom scores over days 1–5 were calculated for cycle 1. A repeated-measures analysis of variance was performed to test for a change in symptom scores across cycles and over days within cycles. Since 19 analyses of variance were performed, the level of significance was lowered to 0.01 as an adjustment for multiple comparisons.

## Results

Figure 1 is a flow diagram of the distribution and randomization of the study patients. Two hundred fifty-one patients were assessed for eligibility; four were excluded due to nausea 24 hours prior to treatment. Two hundred forty-seven patients were randomized. Three patients were excluded in each arm due to loss to follow-up or not completing or discontinuing the assigned treatment. A very small and equal number of patients in each arm was lost to analysis after randomization. The remaining patients in each arm were adequate in number to complete the planned analysis.

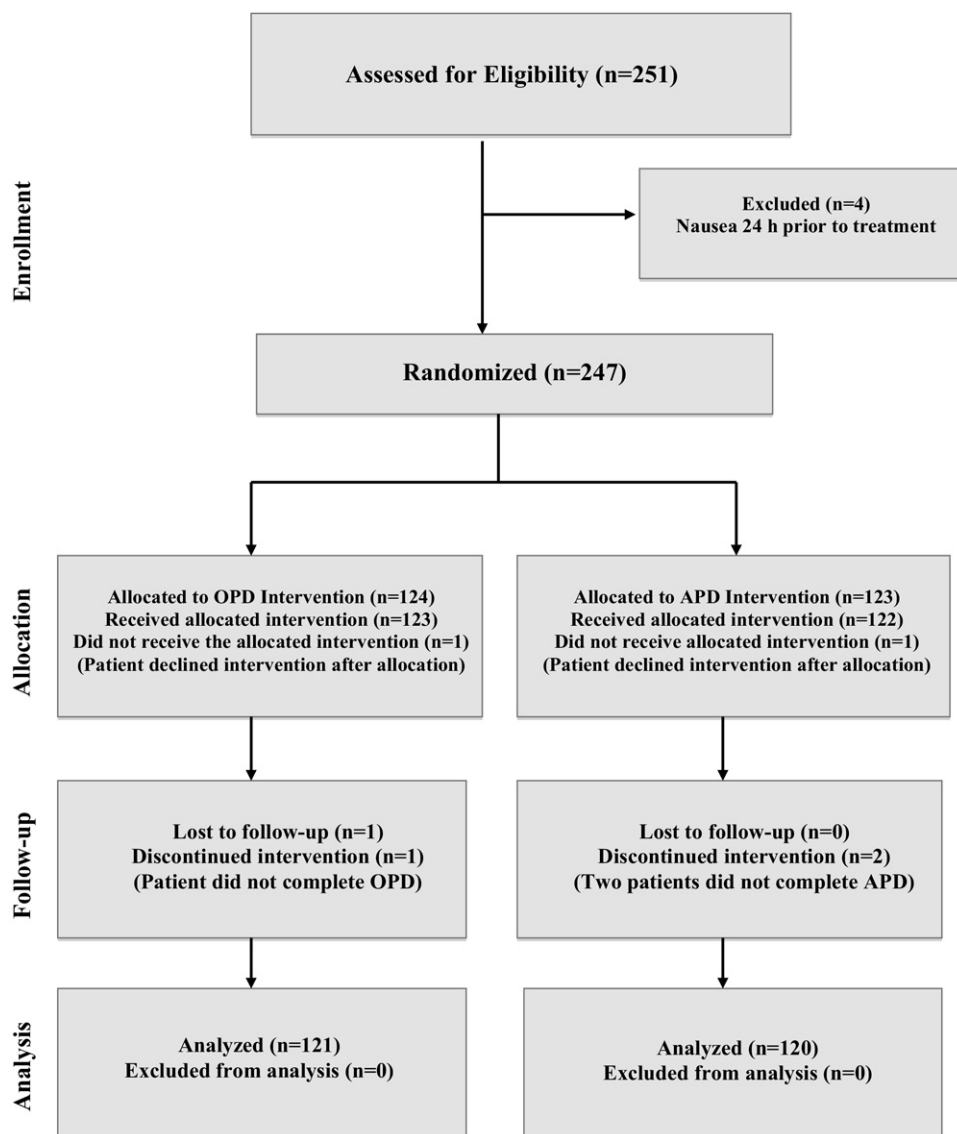
### PATIENT CHARACTERISTICS

Demographic data and patient characteristics are presented in Table 1. Two hundred forty-one patients received at least one cycle of chemotherapy and completed the assigned antiemetic regimen; 217 patients (90.1%) received two cycles, 197 (81.7%) received three cycles, 157 (65.1%) received four cycles, 92 (38.2%) received five cycles, and 88 (36.5%) received six cycles. There were very few patients who experienced weight gain or glucose elevation from day 1 to day 5 in cycle 1, and there was no difference in the study groups.

### PRIMARY EFFICACY PARAMETERS

The CR for the acute period, the delayed period, and the overall period in 121 patients receiving the OPD regimen and in 120 patients receiving the APD regimen is shown in Figure 2. The four patients in the OPD group who did not have a CR in the acute period required rescue without emesis. Twenty-eight patients in the OPD group did not have a CR in the delayed period. Eighteen had emesis on days 2 and 3, and all required rescue. Nine had emesis on day 4, and two required rescue. One patient had emesis without rescue on day 5.

The 16 patients in the APD group who did not have a CR in the acute period all had emesis, and three required rescue in the first 24 hours postchemotherapy. There were 32 patients in the APD group who did not have a CR in the delayed period.



**Figure 1** Distribution and Randomization of Study Patients

OPD, olanzapine + palonosetron + dexamethasone; APD, aprepitant + palonosetron + dexamethasone

On day 2, 10 patients had emesis without rescue and four patients had emesis with rescue. On day 3, eight patients had emesis without rescue and six patients had rescue without emesis. On day 4, two patients had rescue without emesis; and on day 5, two patients had emesis with rescue.

There were no significant differences ( $P > 0.05$ ) in the CR between the OPD regimen and the APD regimen for the acute, delayed, and overall periods.

The control of nausea for the acute period, the delayed period, and the overall period in 121 patients receiving the OPD regimen and in 120 patients receiving the APD regimen is shown in Figure 3. There were 16 patients in the OPD group who experienced nausea ( $>0$ , scale 0–10, MDASI) in the acute period. The 37 patients in the OPD group who experienced nausea in the delayed period consisted of 18 on day 2, 17 on day 3, and two on day 4. Sixteen patients in the APD group had nausea in the acute period. The occurrence of nausea in the

delayed period for the APD group was 32 patients on day 2, 28 on day 3, 10 on day 4, and four on day 5.

There was no significant difference ( $P > 0.05$ ) for the control of nausea between the OPD regimen and the APD regimen for the acute period. There were significant differences ( $P < 0.01$ ) between the OPD regimen and the APD regimen for the delayed and overall periods.

The CR and control of nausea for patients receiving either the OPD regimen or the APD regimen in subsequent cycles of chemotherapy were not significantly different from cycle 1 and were not significantly different for gender or type or stage of disease.

#### ADVERSE EVENTS

There were no grade 3 or 4 toxicities attributable to the study drugs in any of the patients for any of the cycles of chemotherapy.

**Table 1**  
Demographic Data and Patient Characteristics

	OPD	APD
Patients (n)	121	120
Age range (years)	39–77	42–81
Median age (years)	63	61
Gender (n)		
Female	81	83
Male	40	37
ECOG (n)		
0	93	94
1	23	22
2	5	4
Diagnosis (n)		
Bladder	8	4
Breast	60	66
Lung (non-small cell)	42	40
Malignant lymphoma	11	10
Chemotherapy regimen (n)		
Cisplatin ( $\geq 70$ mg/m <sup>2</sup> )	50	44
Doxorubicin ( $\geq 50$ – $60$ mg/m <sup>2</sup> ) and cyclophosphamide ( $\geq 600$ – $1,000$ mg/m <sup>2</sup> )	71	76
Initial measurements (mean)		
Height (inches)	68	69
Weight (lb)	145	149
Body mass index	23.0	23.3
Weight gain, day 1 to day 5, cycle 1 (n)		
>5%	5	6
>10%	1	2
Glucose elevation, day 1 to day 5, cycle 1 (n)		
>5%	10	11
>10%	5	7

OPD, olanzapine + palonosetron + dexamethasone; APD, aprepitant + palonosetron + dexamethasone.

The symptom scores as measured by the MDASI for cycle 1 are recorded in Table 2. Nine of the 17 symptom scores significantly differed between cycles at the 0.01 level of significance. Pain, fatigue, disturbed sleep, distress, shortness of breath, lack of appetite, sadness, general activity, and mood significantly decreased over the cycles.

Problems remembering, drowsiness, and dry mouth significantly increased over days in some individual cycles but were not increased among cycles and did not result in any grade 3 or 4 toxicities. There were no significant changes between the OPD and the APD regimens for any of the symptom scores.

## Discussion

In this study, olanzapine combined with a single dose of dexamethasone and a single dose of palonosetron was very effective at controlling acute and delayed CINV in patients receiving HEC. The CR rates were not significantly different from a similar group of patients receiving HEC and an antiemetic regimen consisting of aprepitant, palonosetron, and dexamethasone. The two antiemetic regimens were compa-

table in CR in the acute, delayed, and overall periods. In addition, the CR rates were similar to previous studies which used the same olanzapine antiemetic regimen<sup>7</sup> and the commonly employed aprepitant regimen.<sup>27–31</sup> This aprepitant antiemetic regimen has been the recommended regimen of various international associations' antiemetic guidelines for patients receiving HEC.<sup>15–17</sup> The OPD and APD antiemetic regimens were very well tolerated with no grade 3 or 4 toxicities, and there was no major severity noted among a wide range of 17 symptoms as measured by the MDASI.

A dexamethasone dose of 20 mg was used in the OPD regimen since this is the recommended dose for patients receiving HEC by the various antiemetic guidelines.<sup>15–17</sup> A dexamethasone dose of 12 mg was used in the APD regimen since this is the recommended dose to be used with aprepitant due to the possibility of hyperglycemia.<sup>27,29</sup>

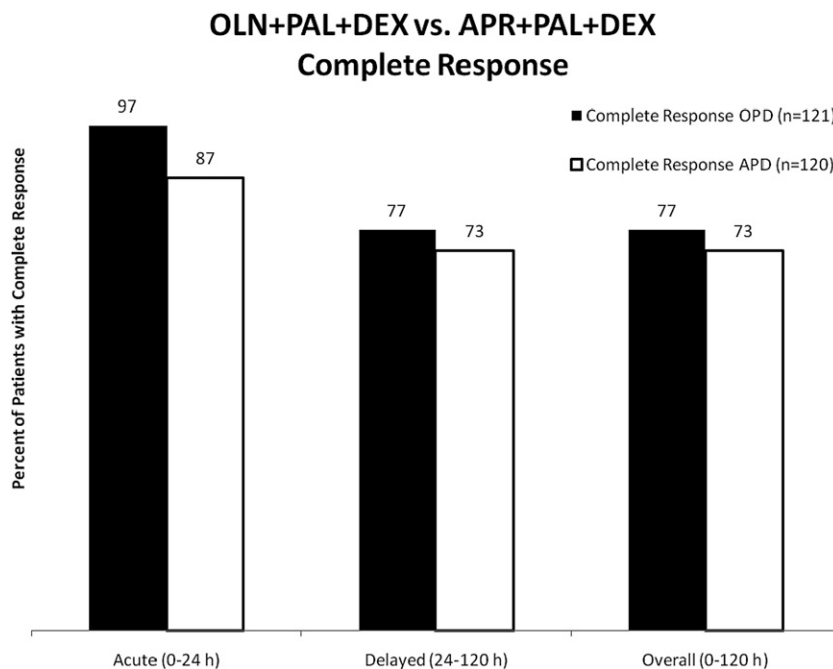
The control of nausea was also similar for the two antiemetic regimens in the acute period for this group of patients but was significantly better for the OPD regimen in the delayed and overall periods. The effectiveness of olanzapine in the control of nausea has been demonstrated in one recent phase III study,<sup>8</sup> two previous phase II studies,<sup>6,7</sup> a retrospective study<sup>32</sup> and a case report.<sup>33</sup> Nausea has not been significantly improved by the use of aprepitant in two phase III studies of patients receiving cisplatin<sup>27,34</sup> and in two phase III studies of patients receiving an anthracycline and cyclophosphamide.<sup>31,35</sup>

The high level of CR in the acute period for patients receiving HEC observed in this study was most likely an important aspect in controlling delayed CINV. The importance of the control of acute nausea and vomiting on the control of delayed nausea and vomiting has been discussed in detail in the literature.<sup>36</sup>

There were patients, however, who had a CR and good control of nausea in the acute period and subsequently developed emesis and nausea in the delayed period, suggesting differences in the mechanisms of acute and delayed CINV. The main period of failure in CR or control of nausea in the delayed period in this study was day 2 or 3, which is consistent with a number of previous studies.<sup>18,28</sup>

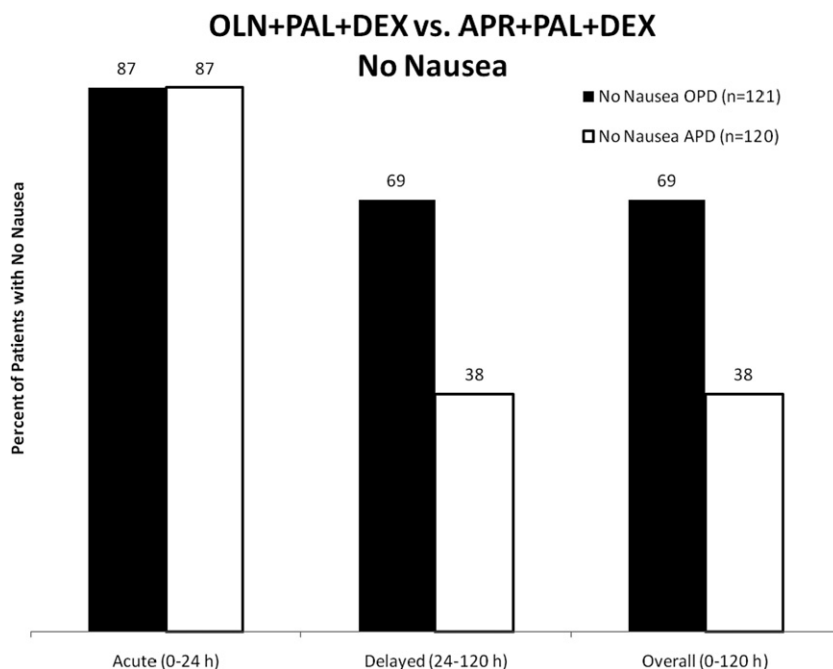
One hundred fifty-seven of the 241 patients received at least four cycles of chemotherapy, and the high level of CR, the level of control of nausea, and the lack of adverse events noted in cycle 1 were maintained over the multiple cycles of chemotherapy for each of the antiemetic regimens.

The high level of control of CINV in the delayed period in this study appears to be due to the combination of olanzapine and palonosetron. Olanzapine has been shown in previous studies to be an effective agent at controlling delayed CINV.<sup>6–8</sup> A recent study<sup>14</sup> demonstrated that when administered with dexamethasone before HEC, palonosetron exerts better efficacy against CINV than granisetron in the delayed phase. The high level of control of delayed CINV in this study was achieved without the use of dexamethasone in the delayed period, potentially eliminating the short- and long-term toxicities of dexamethasone experienced by some patients.<sup>25</sup>



**Figure 2** Percent of Patients with a Complete Response (No Emetic Episodes and No Use of Rescue Medication) for Patients Receiving Highly Emetogenic Chemotherapy in Cycle 1

OLN, olanzapine; PAL, palonosetron; DEX, dexamethasone; APR, aprepitant; OPD, OLN + PAL + DEX; APD, APR + PAL + DEX;  $P > 0.05$  for acute, delayed, and overall



**Figure 3** Percent of Patients with No Nausea (No Nausea, 0 on Scale of 0–10, MDASI) for Patients Receiving Highly Emetogenic Chemotherapy in Cycle 1

OLN, olanzapine; PAL, palonosetron; DEX, dexamethasone; APR, aprepitant; OPD, OLN + PAL + DEX; APD, APR + PAL + DEX;  $P > 0.05$  for acute,  $P \leq 0.01$  for delayed and overall

Olanzapine blocks the neurotransmitters dopamine and serotonin, which are known mediators of CINV.<sup>20,21</sup> Olanzapine appears to have activity in controlling both acute and delayed emesis and nausea and may exert much of its anti-

emetic effect in the central nervous system at multiple cortical receptors, although a peripheral effect may also exist. Olanzapine blocks the serotonin-mediated 5-HT<sub>2C</sub> receptor, which has been shown to mediate antiemetic activity in

**Table 2**  
**MDASI Scores (0–10) Over Days 1–5 in Patients Receiving Highly Emetogenic Chemotherapy in Chemotherapy Cycle 1**

SYMPTOM	OPD REGIMEN (N = 121)		APD REGIMEN (N = 120)	
	DAY 1	DAY 5*	DAY 1	DAY 5**
Pain	1.5	1.2	1.1	1.6
Fatigue	4.1	4.2	3.0	3.5
Disturbed sleep	2.1	2.6	3.3	3.0
Distress	1.5	2.0	2.2	2.4
Problems remembering	1.5	1.6	2.1	2.2
Shortness of breath	1.9	2.2	2.5	2.3
Lack of appetite	1.9	1.8	2.2	1.9
Feeling drowsy	3.3	3.7	2.8	2.6
Dry mouth	3.5	3.8	3.3	3.5
Feeling sad	1.9	2.2	3.0	2.8
Numbness	0.9	1.2	2.1	1.7
General activity	2.1	2.2	2.1	2.3
Mood	0.5	1.3	2.0	1.7
Work	2.3	3.0	3.0	2.7
Relations	1.8	1.7	1.7	1.5
Walking	1.9	2.1	2.1	2.3
Enjoyment	1.5	2.1	3.1	2.8
Sedation	1.1	1.9	1.3	2.1

OPD, olanzapine + palonosetron + dexamethasone; APD, aprepitant + palonosetron + dexamethasone.

\*P > 0.05 for all symptoms in OPD regimen, \*\*P > 0.05 for all symptoms in APD regimen.

animal models (ferret cisplatin-induced emesis and cisplatin-induced anorexia in the hypothalamus of rats).<sup>37,38</sup> The effect of olanzapine on this receptor as well as other dopamine and serotonin receptors may explain its efficacy in CINV.

The relative contribution of the effects of various antiemetics at central and peripheral sites to the control of acute and delayed nausea and emesis cannot be determined at this time based on available studies.<sup>2,4</sup> In this study, for the doses given (10 mg daily for 4 days), olanzapine was not associated with significant sedation, weight gain, or induction of significant hyperglycemia. These effects have been associated with olanzapine given for longer periods of time.

There are also economic benefits of olanzapine. The 4-day treatment with olanzapine is approximately 10%–20% of the cost of the 3-day aprepitant treatment.<sup>39</sup>

The results of this study demonstrate that in patients receiving HEC, the OPD regimen is equivalent to the APD regimen in controlling emesis and the use of rescue medication but that the OPD regimen is significantly better at controlling nausea.

The trial arms in the study were not blinded. It is unlikely that the lack of blinding in the trial would affect the trial outcome since all of the patients in the study were chemotherapy-naive and none had previously received either of the antiemetic regimens.

Future investigations may explore the efficacy of olanzapine with or without dexamethasone in the delayed period for clinical situations such as multiday chemotherapy or high-dose chemotherapy and stem cell transplantation.

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*Conflict of Interest Disclosures:* All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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