

# Effectiveness of a single-day three-drug regimen of dexamethasone, palonosetron, and aprepitant for the prevention of acute and delayed nausea and vomiting caused by moderately emetogenic chemotherapy

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Received: 7 September 2008 / Accepted: 7 November 2008 / Published online: 27 November 2008  
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## Abstract

**Purpose** Chemotherapy-induced nausea and vomiting includes both Acute (0–24 h) and Delayed (24–120 h) components with different physiologic mechanisms. A combination of a serotonin antagonist, a corticosteroid, and an NK-1 antagonist has proven effective against this problem. However, standard antiemetic regimens require administration over 3–4 days after chemotherapy. The present study evaluated a more convenient single-day three-drug antiemetic regimen for patients receiving moderately emetogenic chemotherapy.

**Materials and methods** Chemotherapy-naïve patients with solid tumors receiving cyclophosphamide and/or doxorubicin were eligible. Patients could not have pre-existing etiologies for vomiting. Prior to chemotherapy, patients

received a single dose of aprepitant 285 mg p.o., dexamethasone 20 mg p.o., and palonosetron 0.25 mg i.v. A daily patient diary recording episodes of emesis and severity of nausea was then kept for 5 days. Any further antiemetics were considered rescue medication.

**Results** Forty-one eligible and evaluable patients (40 women, one man) with breast cancer were entered on study. Most were receiving adjuvant chemotherapy. Complete Response (no vomiting, no rescue medication) was seen in 51% of patients, including 76% with Complete Response for the Acute period and 66% for the Delayed period. No emesis was reported for 100% of patients in the Acute period and 95% in the Delayed period. No Nausea was seen in 32% of patients. No untoward toxicities were seen.

**Conclusion** A single-day three-drug antiemetic regimen is feasible and effective for protection against both Acute and Delayed vomiting after moderately emetogenic chemotherapy. Formal comparison to a standard multi-day antiemetic regimen is warranted.

Presented in part at the 43rd Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 2007.

Supported in part by Grant Number P30CA022435 from the National Cancer Institute and by an unrestricted grant from MGI Pharma.

Dr. Grunberg has served as a consultant to MGI Pharma and Merck.

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**Keywords** Palonosetron · Aprepitant · Dexamethasone · Antiemetic

## Introduction

Nausea and vomiting have consistently been considered to be the toxicities of chemotherapy most feared by the cancer patient [13]. Chemotherapy-induced nausea and vomiting is a complex phenomenon consisting of both acute (0–24 h) and delayed (24–120 h) components which may have different physiologic mechanisms [33]. However, the incidence of delayed nausea and vomiting, particularly in

patients receiving moderately emetogenic chemotherapy, continues to be severely underestimated by physicians and nurses [15]. It is thus imperative that feasible and effective regimens be developed that address both acute and delayed nausea and vomiting.

Effective antiemetic regimens for highly and moderately emetogenic chemotherapy or radiotherapy have historically been based on the combination of a serotonin antagonist and a corticosteroid, as reflected in numerous antiemetic treatment guidelines [1, 11, 22, 25]. This combination is highly effective for the control of acute emesis but less so for delayed emesis, and the contribution of serotonin antagonists to the management of delayed emesis has been questioned. More recently, the role of NK-1 receptor antagonists, particularly in the control of delayed emesis, has been appreciated [5]. The NK-1 receptor antagonist aprepitant has been shown to markedly improve control of delayed emesis after both highly and moderately emetogenic chemotherapy [18, 31, 35]. Of interest, aprepitant also improves control of acute emesis when used in combination with a serotonin antagonist and a corticosteroid [18, 31, 35], while Phase III studies of the long-acting serotonin antagonist palonosetron have suggested that this agent may still have some role in the control of delayed emesis, particularly after moderately emetogenic chemotherapy [9, 12].

Presently, a three-drug combination of a serotonin antagonist, a corticosteroid, and an NK-1 antagonist is approved for the prevention of nausea and vomiting after cisplatin-containing regimens [18, 31] and also after moderately emetogenic chemotherapy [35]. However, such regimens tend to be inconvenient and cumbersome since continued treatment with oral antiemetic agents for at least 3 days is generally required. An extended serotonin antagonist effect can be obtained using a single dose of palonosetron [9, 12], and a three-drug antiemetic regimen including this serotonin antagonist showed promising preliminary results [14]. However, this reported regimen continued to use extended oral administration of dexamethasone and aprepitant, negating the schedule advantage of palonosetron.

A simpler single-day antiemetic regimen providing protection for the entire period of major risk for acute and delayed emesis with all three antiemetic agents administered as single doses at the time of chemotherapy should be possible. A single dose of palonosetron will provide antiemetic protection for at least 3 days [9, 12]. Since aprepitant inhibits the metabolism of dexamethasone and doubles the systemic exposure (AUC) of this agent [26], reduced doses of dexamethasone when given over 3 days are already recommended if such agents are given together. This systemic exposure could be approximated with a single 20-mg dose of dexamethasone, a commonly used dose for other indications. Although aprepitant has usually

been given as part of 3 to 5 day regimens, administration of a single dose of 285 mg (the equivalent of a standard aprepitant tri-pack) provides systemic exposure over the first several days similar to a split-dose regimen [19] and is well below single doses given safely in earlier clinical studies [4]. The present study was therefore designed as a preliminary exploration of the safety and efficacy of such a simplified and convenient single-day three-drug antiemetic regimen.

## Materials and methods

### Eligibility

Patients eligible for this study were adults with a histologically or cytologically documented solid tumor receiving chemotherapy for the first time with regimens including cyclophosphamide  $\leq 1,500$  mg/m<sup>2</sup> i.v. and/or doxorubicin  $\geq 40$  mg/m<sup>2</sup> i.v. given as single doses on Day 1. Patients were required to have adequate hematologic, renal, and hepatic reserve for administration of chemotherapy, good performance status (Performance Status 0–2), and a life expectancy of at least 3 months. The study was approved by Institutional Review Boards at Fletcher Allen Health Care/University of Vermont and at Maine Medical Center, and all patients provided written informed consent. Patients were ineligible if they had received prior chemotherapy or were scheduled to receive highly emetogenic chemotherapy (Hesketh Level 5) during the 5-day study period or moderately emetogenic chemotherapy (Hesketh Level 3–4) after Day 1 of the 5-day study period. Patients could not receive corticosteroids or antiemetic agents other than the study drug doses immediately before or during the study period and could not receive cranial, abdominal, or pelvic irradiation during the study period. Patients were considered ineligible if they had an uncontrolled primary or metastatic CNS malignancy or another physical cause for nausea or vomiting (such as bowel obstruction) not related to chemotherapy administration. Vomiting or nausea within 24 h prior to initiation of study chemotherapy also led to exclusion. Patients were ineligible if they had had a previous hypersensitivity reaction to any of the study agents, if simultaneous administration of any other investigational agent was planned, if there was an active infection for which administration of a corticosteroid would be contra-indicated, or if they were taking antiarrhythmic agents. Pregnant or nursing women could not participate in the study and patients of child-bearing potential were required to use adequate contraception.

### Treatment plan

Patients received aprepitant 285 mg p.o. and dexamethasone 20 mg p.o. 1 h prior and palonosetron 0.25 mg i.v.

30 min prior to scheduled Day 1 chemotherapy, which had to include cyclophosphamide and/or doxorubicin and was delivered over no more than 4 h. Patients could receive scheduled mildly or minimally emetogenic chemotherapy (Hesketh Level 1–2) during the remainder of the study period. The Study Diary, which recorded frequency and intensity of nausea and vomiting and use of rescue medication, was completed just prior to initiation of therapy and then daily for 5 days. Patients were contacted at least twice during the 5-day study period and once a week after initiation of therapy by the research nurse to re-enforce the importance of completing the Study Diary and to screen for any additional concerns and for toxicities.

### Endpoints

The primary study endpoint was Complete Response (no vomiting and no rescue therapy) during the Overall (0–120 h) period during the first chemotherapy cycle. Secondary endpoints included No Vomiting, No Nausea (Nausea Visual Analogue Scale (VAS) <5 mm), and No Significant Nausea (Nausea VAS <25 mm) during the Acute (0–24 h), Delayed (24–120 h), and Overall periods. Nausea VAS >25 mm was considered to represent Significant Nausea. Complete Response was also evaluated during the Acute and Delayed periods. Toxicities were summarized descriptively.

### Statistical analysis

A Complete Response rate of at least 50% would make these results comparable to other studies using triplet antiemetic therapy for moderately emetogenic chemotherapy [35] and would justify formal evaluation of the regimen in a Phase III trial, while a Complete Response rate of 30% would be unacceptable and should lead to termination of the trial. A three-stage MiniMax design [34] was used testing the null hypothesis that  $P_0=30\%$  with a one-sided alternative hypothesis of  $P_a=50\%$  for a single proportion using an exact binomial test of proportions with early stopping for futility with a Type I error level of 5% and power of 80%. Complete Response in more than two of the first ten and eight of the first 25 patients was therefore required to continue the study, with Complete Response in more than 16 of 39 patients as the final checkpoint. To account for the possibility of ineligible or inevaluable patients, accrual of up to 45 patients was anticipated. Secondary endpoints for efficacy and reporting of toxicity were explored using descriptive statistics. All patients, with the exception of those who received no study medication, were considered evaluable for efficacy and toxicity.

## Results

### Patient demographics

Between December 2004 and March 2007, a total of 42 patients were screened for protocol eligibility and provided written informed consent. One patient took a benzodiazepine for anxiety immediately prior to initiation of therapy. She was therefore considered ineligible and did not receive protocol antiemetic therapy or evaluation. The remaining 41 eligible and evaluable patients who were entered on study had a median age of 51 years (Table 1). All patients but one were female and all patients but one were receiving adjuvant chemotherapy. Most patients (38 patients) had Performance Status 0. All patients received cyclophosphamide. Thirty-seven patients received cyclophosphamide/doxorubicin doublet chemotherapy alone.

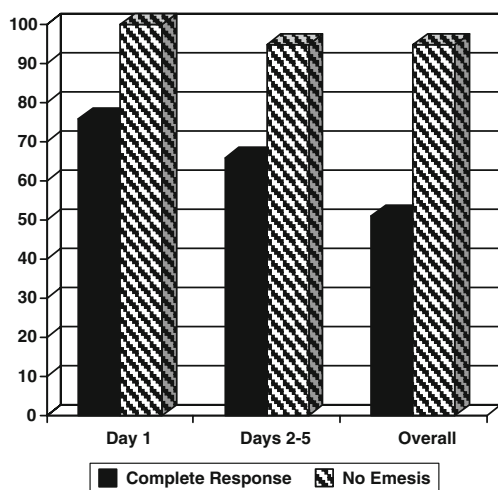
### Efficacy

The study was continued to full accrual based on the pre-designated futility checkpoints. The goal for the primary endpoint was reached with 21 of the 41 patients (51%) achieving Complete Response for the Overall period (Fig. 1). This included 31 patients (76%) who achieved Complete Response during the Acute period and 27 patients (66%) who achieved Complete Response during the Delayed period.

Additional secondary endpoints were also evaluated. No Emesis was seen in 39 patients (95%) for the Overall period, including 41 patients (100%) for the Acute period and 39 patients (95%) for the Delayed period. Nausea was evaluated on a daily basis (Fig. 2). For the full 5-day period, 13 patients (32%) had No Nausea and 23 patients

**Table 1** Patient demographics ( $n=41$ )

Median age (range)	51 (33–74)
Gender	
Male	1
Female	40
Performance status	
0	38
1	3
Chemotherapy agents	
Cyclophosphamide	41
Doxorubicin/epirubicin	38/1
Docetaxel	3
5-Fluorouracil	1
Trastuzumab	1
Triptorelin	1
Chemotherapy setting	
Adjuvant	40
Advanced disease	1

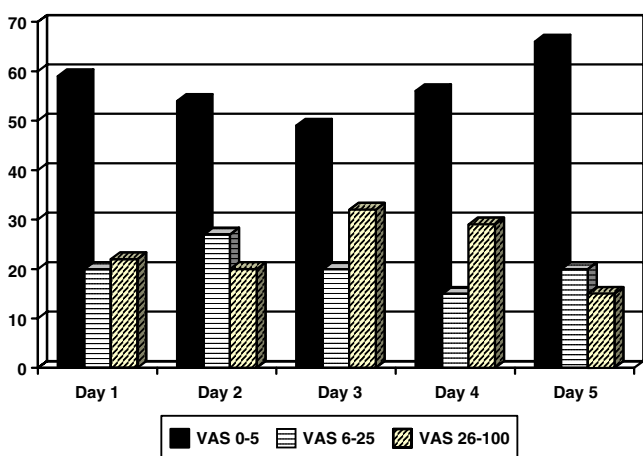


**Fig. 1** Percent of patients with Complete Response (no vomiting episodes and no rescue medication) or No Emesis (no vomiting episodes) during the acute (Day 1) and delayed (Days 2–5) periods

(56%) had No Significant Nausea. During the Acute period, 24 patients (59%) had No Nausea and 32 patients (79%) had No Significant Nausea. During the Delayed period, 17 patients (41%) had No Nausea and 24 patients (59%) had No Significant Nausea. The greatest degree of nausea was seen on Day 3 when only 20 patients (49%) had No Nausea while 13 patients (32%) had Significant Nausea. However, it should be noted that only 11 patients (27%) had more than 1 day of Significant Nausea during the study period.

**Adverse events**

No unexpected major adverse events were seen (Table 2). Myelosuppression, mucositis, and alopecia were considered to be related to cytotoxic chemotherapy rather than to antiemetic



**Fig. 2** Percent of patients with various levels of nausea during each day of the study period as determined using a 100-mm Nausea Visual Analogue Scale (VAS). VAS≤5 is considered to represent No Nausea, VAS≤25 is considered to represent No Significant Nausea, and VAS>25 is considered to represent Significant Nausea

**Table 2** Common drug related adverse events (n=41)

	Grade 1	Grade 2	Grade 3
Fatigue	18	12	2
Headache	23	6	2
Anorexia	15	5	0
Insomnia	9	6	0
Constipation	12	2	0
Hot flash	5	4	0
Diarrhea	9	0	0
Bone pain	3	1	2
Dyspnea	4	2	0
ALT elevation	5	1	0
Dyspepsia	5	1	0

Common adverse events were those seen in 6 or more patients. Myelosuppression, mucositis, and alopecia were not considered to be drug related adverse events for antiemetics

therapy. The most common adverse events noted were those expected to be seen with cytotoxic chemotherapy and a serotonin antagonist based antiemetic regimen, particularly fatigue, headache, and anorexia. Almost all of the adverse events noted were minor in nature (Grade 1 or Grade 2).

**Discussion**

Administration of effective supportive care measures during chemotherapy is a continuing challenge, since numerous prerequisites must be met. First, it is necessary that the problem itself be recognized as significant and persistent. Although the significance of chemotherapy-induced nausea and vomiting has not been questioned, successful development of antiemetics during the last 25 years can lead to the assumption that this is no longer a major problem. However, numerous patient surveys have now demonstrated that chemotherapy-induced nausea and vomiting continues to exist, particularly during the delayed period and particularly in patients receiving moderately emetogenic chemotherapy such as cyclophosphamide/doxorubicin, and that the incidence of this problem in the delayed period is markedly underestimated by healthcare professionals [7, 10, 15, 23]. Second, it is necessary to have appropriate remedies to address the problem. The development of serotonin antagonists, recognition of the antiemetic properties of corticosteroids, and recent development of the NK-1 antagonists, has markedly improved management of this problem [8, 35]. However, new strategies continue to be required for delayed vomiting, where complete response rates have lagged behind acute complete response rates even if appropriate guidelines are followed [6]. Third, drug–drug interactions must be considered so that the supportive care remedies do not interfere with treatment of the underlying neoplasm or with other supportive care

measures. Although the NK-1 antagonists inhibit CYP 3A4 metabolic pathways, meaningful alterations in the metabolism of agents such as vinorelbine [24] or docetaxel [29], which utilize these pathways, have not been demonstrated. In addition, the NK-1 antagonists do not cause significant changes in the metabolism of serotonin antagonists [3, 33]. A decrease in the metabolism of corticosteroids leading to a two-fold increase in exposure has been seen [26] but can be easily addressed with appropriate corticosteroid dose modifications.

Even if all of these conditions are met, the question of adherence must be addressed. Adherence with supportive care guidelines by physicians and by patients is modest at best. Particularly in a curative setting, physicians are more likely to follow therapeutic guidelines to treat a cancer than supportive care guidelines designed to ameliorate the toxicities of the antineoplastic therapy being given [16]. Numerous factors can then affect patient adherence to the prescribed regimen. Socioeconomic factors may impact the patient's willingness and ability to obtain oral medications and comply with the regimen [20]. Although a good physician–patient relationship may be helpful in encouraging adherence [36], the lack of an improvement in adherence with prescribed regimens in the days before physician visits (“white-coat compliance”) demonstrates the limitations of physician influence [27]. Even with a therapeutic intervention as straightforward as oral administration of an aromatase inhibitor, adherence of only about 85% can be expected [30].

One promising strategy to improve adherence is to simplify the treatment regimen and thereby minimize the scheduled medication administration that patients must remember at home. Simplification of the regimen has proven to be possible with several of the antiemetic families. The serotonin antagonist ondansetron was originally given in hospital in three doses 2 h apart, an inconvenient regimen in the outpatient setting [21]. However, the excellent toxicity profile of this agent allowed higher single doses to be given that would provide protection for the entire acute emesis period of risk [2, 32], and the later development of agents such as palonosetron with an extended half-life of 40 h allowed drug exposure to continue for multiple days even after a single dose [9, 12]. Prevention of delayed emesis was originally assumed to require treatment throughout the delayed period (days 2–5 after chemotherapy). However, this may not be necessary if the initiating event for delayed emesis occurs shortly after administration of chemotherapy or if antiemetic agents can be given which are retained throughout the period of risk. Inhibition of corticosteroid metabolism by the NK-1 antagonists [26] will provide such extended exposure. Development of the NK-1 antagonist regimens themselves has followed a path similar to that of the serotonin

antagonists. Initial trials of a 5-day course of treatment were found to be no more effective than a shorter course of treatment. Even in these early studies, the differences between a 5-day course and a single day of treatment were minimal [28]. In the present study, we have taken advantage of the excellent toxicity profile of these agents to provide extended exposure with a single higher dose of aprepitant. As Horgan [19] has demonstrated, such a dose will provide similar drug exposure over a 3-day period as compared to a standard 3-day regimen.

Efficacy of the palonosetron/dexamethasone/aprepitant combination has now been demonstrated by several groups. Grote [14] administered a single dose of palonosetron with a 4-day course of dexamethasone and a 3-day course of aprepitant. Herrington [17] administered a single dose of palonosetron and a 4-day course of dexamethasone with patients randomized to receive a 1- or a 3-day course of aprepitant. The Grote regimen [14], both arms of the Herrington study [17], and the present single-day regimen all achieved similar results, with prevention of virtually all emetic episodes. Excellent control of nausea was also achieved. Rates of complete response, as evidenced by lack of use of rescue medication, were numerically superior to the present study with the Grote regimen [14] but similar with both of the Herrington regimens [17]. However, any difference from the present regimen in complete response could reflect the provision of scheduled antiemetic medication throughout most of the 5-day study period with these other regimens, while any antiemetic medication taken after Day 1 in the present study would be considered to be rescue medication. Identification of effective antiemetic drug families has now been complemented by insights into appropriate schedules of antiemetic administration based on pharmacokinetic and pharmacodynamic principles. Direct comparison of brief and extended antiemetic regimens to determine the most convenient and feasible strategy for obtaining maximal antiemetic efficacy could lead to improved patient adherence and improved quality of life.

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