Aprepitant plus palonosetron as salvage therapy for CINV induced by moderately emetogenic chemotherapy in cancer patients

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Abstract

Background Despite the efficacy of prophylaxis with serotonin type 3 (5-HT_3) receptor antagonists, nausea and vomiting are still among the most common chemotherapy-induced toxicities. The aim of this study was to evaluate the efficacy of adding aprepitant in patients with chemotherapy-induced nausea and vomiting (CINV) refractory to prophylaxis with 5-HT_3 receptor antagonists and dexamethasone.

Patients and Methods Between January 2008 and November 2010, 51 patients (median age 59 years) with a variety of malignancies (breast cancer: 23; lung cancer: 12; sarcoma: 6; ovarian cancer: 3; other: 7) were enrolled. All patients were refractory to antiemetic therapy according to ASCO guidelines and developed at least grade 2 nausea and/or vomiting after the first chemotherapy course. Aprepitant was given at 125 mg on day 1 and 80 mg on days 2–3. Patients also received a single dose of palonosetron 250 µg on day 1 plus dexamethasone 12–20 mg at a constant dose.

Results After addition of aprepitant, the number of patients with grade 3/4 nausea decreased from 31 (61%) to 4 (8%), and those with grade 2 nausea from 20 (39%) to 6 (12%) [both p<0.0001]. All patients received aprepitant for more then two courses (range 3–8) and efficacy was maintained during all chemotherapy cycles.

Conclusions This study showed that aprepitant was effective as salvage therapy in patients with CINV refractory to prophylaxis with 5-HT_3 receptor antagonists and dexamethasone following platinum- or nonplatinum-based chemotherapy, and that the efficacy of aprepitant persists over multiple cycles.

Key words: aprepitant, chemotherapy-induced nausea and vomiting, dexamethasone, palonosetron

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is one of the most feared side effects in patients with cancer [1, 2]. Failure to adequately control CINV and radiation-induced nausea and vomiting (RINV) can precipitate a number of life-threatening medical complications, such as dehydration, electrolyte imbalances, and physical damage (e.g. Mallory-Weiss tear of the esophagus). Therefore, minimization or avoidance of CINV is very important. Furthermore, because CINV can significantly influence all the aspects of quality of life for patients and their caregivers and the distress resulting from these symptoms can escalate over time [3, 4], CINV could potentially lead patients to refusing cancer treatment [5-7]. In addition, CINV and its complications have a significant impact on the public health budget by extending hospitalization, and increasing the requirement for medical and nursing assistance and pharmacy resources.

The incidence and severity of CINV are affected by numerous factors, including the specific chemotherapeutic agents used, dosages administered, therapeutic schedule, route of administration and patient factors (e.g. age, gender, history of alcohol use) [8, 9].

Before the advent of serotonin type 3 (5-HT_3) receptor antagonists, available antiemetic agents included phenothiazines [10], substituted benzamides [11, 12], antihistamines [13], butyrophenones [14], corticosteroids [15, 16], benzodiazepines [17, 18], and cannabinoids [19]. Development of the 5-HT_3 receptor antagonists (i.e. dolasetron mesylate, granisetron, ondansetron, palonosetron) was a significant advance in antiemetic therapy,

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and all of these agents have been shown to be effective in controlling acute nausea and vomiting associated with cancer chemotherapy [20, 21].

Palonosetron is a 5-HT_3 receptor antagonist with significantly higher binding affinity and a longer half-life compared with other agents in the same class [20]. In addition, data suggest that palonosetron also differs from other 5-HT_3 antagonists in the duration of 5-HT_3 receptor inhibition [22].

Aprepitant is the newest agent introduced for the management of CINV. It acts by selectively blocking the binding of substance P to the neurokinin (NK)-1 receptor in the central nervous system [23]. Thus, aprepitant provides a different and complementary mechanism of action to all other commercially-available antiemetics [24]. Interesting data show how aprepitant augments the antiemetic activity of 5-HT_3 receptor antagonists and dexamethasone, thus contributing to inhibition of both acute and delayed CINV [25].

The aim of this study was to investigate the effectiveness of adding aprepitant to palonosetron and dexamethasone, for the prevention of both acute and delayed CINV in cancer patients receiving moderately emetogenic chemotherapy and refractory to palonosetron plus dexamethasone alone.

Methods

This single center, non-randomized, prospective study was carried out at the University Campus Bio-Medico (Rome) from January 2008 to November 2010. It was conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and all patients signed a written consent form prior to enrolment.

Patients were eligible for inclusion if they were being treated with moderately emetogenic chemotherapy, were refractory to existing antiemetic therapy according to the ASCO guidelines and developed at least grade 2 nausea and/or vomiting during the first chemotherapy course (as assessed using the NCI-Common Terminology Criteria for Adverse Events version 3) after initial premedication with a single intravenous (IV) doses of palonosetron 250 µg and dexamethasone 12–20 mg on day 1 of chemotherapy. In this study, all patients had aprepitant 125 mg on day 1 and 80 mg on days 2 and 3 added to their existing antiemetic regimen (palonosetron 250 µg IV and dexamethasone 12–20 mg IV) for at least 2 cycles of chemotherapy. Although the dexamethasone dose differed between patients, it remained constant for each patient throughout the study. Patients who presented with a history of drug allergies were given dexamethasone 20 mg to prevent chemotherapy-induced allergies.

The main study endpoint was the proportion of patients with nausea and vomiting (grade 3/4 or grade 1/2). In addition, patients rated nausea and vomiting severity using a 100-mm visual analog scale (VAS) from 0 (least severe) to 100 (most severe) [25].

Results

A total of 51 consecutive chemotherapy-naïve patients were enrolled in this study. Patient demographic and clinical data at baseline are shown in Table 1. Patients received aprepitant for 3–8 courses of chemotherapy, and use was consistent across all cycles.

There was a significant reduction in the number of patients

Table 1. Patient demographic and clinical characteristics at baseline.

Characteristics	Patients (n=51)
Median age, years	59
Gender, n (%)	19 (37)
ECOG PS, n (%)	
0-1	46 (90)
2	5 (10)
Tumor subtype, n (%)	
Breast cancer	23 (45)
Lung cancer	12 (24)
Ovarian cancer	3 (6)
Soft tissue sarcoma	6 (12)
Other	7 (14)
Current chemotherapy regimen, n (%)	
Carboplatin	14 (27)
Paclitaxel	16 (32)
Cyclophosphamide	12 (24)
Anthracycline	14 (27)
Oxaliplatin	7 (14)
Irinotecan	4 (8)
Other	11 (22)
Clinical features, n (%)	
History of motion sickness	4 (8)
Pregnancy-induced vomiting	
Yes	9 (18)
No	13 (25)
Not applicable or not available	29 (57)
Alcohol intake history	
None	25 (49)
1–5 drinks per month	15 (29)
6–14 drinks per month	9 (18)
>14 drinks per month	2 (4)

ECOG PS: European Co-operative Oncology Group performance status.

Table 2. Chemotherapy-induced nausea and vomiting (CINV) development after standard premedication (palonosetron and dexamethasone) and after the addition of aprepitant.

	Palonosetron + dexamethasone		P-value
	Alone	+ Aprepitant	
CINV, n (%)			
G0	0 (0)	41 (80)	<0.0001
G1-G2	20 (39)	6 (12)	
G3-G4	31 (61)	4 (8)	

Table 3. Severity of nausea during aprepitant treatment.

Chemotherapy cycle day	Nausea severity score*	
	Mean±SD	Median (range)
1	11.5±10.5	0 (0–90)
2	15.2±14.3	5.0 (0–80)
3	15.0±12.4	3.5 (0–90)
4	14.5±11.0	3.5 (0–60)
5	7.0±10.2	0 (0–60)

*On a 100-mm visual analog scale from 0 (least severe) to 100 (most severe).
SD: standard deviation.

with nausea and vomiting after the addition of aprepitant ($p<0.0001$) (Table 2). VAS scores for nausea severity during treatment with aprepitant are shown in Table 3. Overall, 48 patients (94%) did not experienced acute emesis during aprepitant treatment. However, a complete response in terms of preventing delayed emesis was observed in fewer patients (n=34, 67%). Only 3 patients (6%) needed rescue therapy for the treatment of nausea and vomiting after the addition of aprepitant to existing CINV prophylaxis therapy. None of the clinical features shown in Table 1 were predictive of the response to aprepitant.

Discussion

Despite progress in treatment over recent years, nausea and vomiting remain among the most common chemotherapy-associated side effects. The management of CINV represents a key topic in the field of oncology supportive care because the resulting metabolic imbalances, anorexia, loss of weight, and decline in performance status can contribute to poor compliance with later cycles of chemotherapy.

CINV occurs via a multistep reflex pathway controlled by the brain; the main neurotransmitters and receptors involved are in the dopaminergic and serotonergic pathways. The introduction of 5-HT_3 receptor antagonists in the mid-1980s was an important turning point in the treatment of CINV and this class of agents today represents standard therapy for the prevention of CINV during highly and moderately emetogenic chemotherapy [26, 27]. The first-generation 5-HT_3 receptor antagonists, ondansetron, granisetron, dolasetron, and tropisetron, have been shown to be effective in the prevention of CINV, with acute response rates ranging from 50% to 70%. Nevertheless, a significant proportion of patient still experiences CINV. For example, data from an observational study showed that 63% of patients receiving doxorubicin, cisplatin or carboplatin reported acute nausea in spite of ondasetron premedication, and 73% developed delayed nausea [28].

Another advance in the control of CINV was achieved with the addiction of dexamethasone to antiemetic regimens containing 5-HT_3 receptor antagonists. The first study published by the Italian Group for Antiemetic Research showed that premedication with both granisetron and dexamethasone increased the rate of complete protection from nausea and vomiting compared with granisetron alone (92.6% *vs* 72.3% and 71.9% *vs* 48.2%, respectively) [29]. These preliminary data were later confirmed by following randomized study, especially for highly emetogenic regimens [7].

Palonosetron is a second-generation 5-HT_3 receptor antagonist characterized by a 100-fold higher affinity for 5-HT_3-receptor compared with other agents in this class and a half-life of approximately 40 hours [30]. Data from a randomized clinical trial in patients undergoing highly emetogenic chemotherapy showed that the complete acute response rate in palonosetron recipients was non-inferior to that with granisetron (73.3% *vs* 75.3%), and that the activity of palonosetron in the delayed phase was superior to that of granisetron (56.8% *vs* 44.5% with a complete response); the safety profile of the two treatments was similar [31]. The results of a phase III showed that palonosetron was as effective as a single dose of dolasetron in preventing acute CINV and superior to dolasetron in preventing delayed CINV after moderately emetogenic chemotherapy, with a comparable safety profile [32]. On the basis of these positive results, the US Food and Drug Administration approved palonosetron in 2008 for use as a single dose on day 1 for the prevention of acute and delayed emesis due to moderately emetogenic regimens.

More recently, studies on the role of substance P in the emetic process led to the development of aprepitant, a neurokinin-1 (NK-1) receptor antagonist that selectively blocks the binding of substance P at the NK-1 receptor in the central nervous system [23]. In combination with a standard regimen consisting of a corticosteroid (dexamethasone) and a 5-HT_3 receptor antagonist, oral aprepitant has been shown to be effective for the prevention of acute and delayed CINV associated with both highly and moderately emeto-

genic chemotherapy [24, 33-39]. Moreover, a single oral dose of aprepitant administered prior to abdominal surgery was found to be effective in the prevention of postoperative nausea and vomiting [40]. A number of phase III studies have compared the efficacy of a standard antiemetic regimen (5-HT_3 antagonist and dexamethasone) *versus* a similar regimen plus aprepitant in patients undergoing highly emetogenic chemotherapy [33, 36-39], showing a higher percentage of complete responses and an improvement in the complete response rate when aprepitant was added. In addition, differences between the aprepitant-containing and standard regimens seen in the first cycle persisted over multiple cycles, and repeated administration of aprepitant appeared to be well tolerated.

Of interest, the combination of palonosetron, dexamethasone and aprepitant seems to be particularly active in the prevention of CINV due to moderately emetogenic therapy, even if a formal comparison with a standard antiemetic regimen is still needed. A phase II study reported a complete response rate of 88% during the acute interval, 78% during the delayed interval and 78% overall [41]. A total of 90% of patients had no emetic episodes during all time intervals, and between 57% and 71% of patients reported no nausea during the 5 days post chemotherapy [41]. It was these promising data that resulting in our group investigating the usefulness of adding aprepitant to palonosetron and dexamethasone for the prevention of CINV in patients with refractory nausea and emesis during moderately emetogenic therapy in the current study. After aprepitant addition, only 4/51 patients (8%) reported grade 3/4 nausea across both the acute and delayed phases, a rate that was significantly different compared with previous standard treatment (31/59, 61%). There was also a significant reduction in grade 2 nausea (12% *vs* 39%). Of interest, all patients received aprepitant for more then two courses (range 3–8) and its efficacy was consistent across all chemotherapy cycles. Moreover, repeated administrations of aprepitant were well tolerated and no adverse reactions were recorded. These finding support previous data, but are limited by the small sample size and the absence of a control group. However, our study demonstrates for the first time a convincing activity of an aprepitant-containing regimen in patients refractory to standard antiemetic prophylaxis with palonosetron and dexamethasone, who represent approximately 25% of all patients treated with moderately emetogenic therapy. The availability of an active antiemetic regimen for this patient group can help reduce the need for rescue therapies to manage breakthrough nausea and vomiting, decrease the need for chemotherapy dose reduction and help to improve patients' compliance and quality of life. Controlled clinical trials in larger groups of patients are required to confirm these preliminary data.

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Conflicts of Interest

The Authors declare there are no conflicts of interest in relation to this article.

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