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Review of the efficacy of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in a range of tumor types

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SUMMARY

Chemotherapy regimens differ according to the tumor type being treated and are associated with varying degrees of emetogenic potential. Since the distribution of risk factors for chemotherapy-induced nausea and vomiting differs across tumor types, it is important to understand the efficacy of antiemetic regimens in multiple patient populations. To characterize treatment response in patients with various malignancies (e.g., breast, gastrointestinal, genitourinary, and lung) treated with either highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC) regimens, a pooled analysis of patient-level data from 4 large randomized trials was performed ($N = 2813$). Patients receiving an antiemetic regimen containing aprepitant, ondansetron, and dexamethasone were compared with patients receiving an active-control antiemetic regimen containing ondansetron plus dexamethasone. In all tumor types analyzed, complete responses were observed in a higher proportion of HEC-treated patients receiving aprepitant compared with active-control patients (genitourinary [61.5% vs 40.6%, $P < 0.001$], gastrointestinal [68.2% vs 44.7%, $P = 0.013$], and lung cancers [73.5% vs 52.8%, $P < 0.001$]). For MEC-treated patients, complete response rates were also higher for aprepitant patients than active-control patients for all tumor types, with a significant difference noted among patients with breast cancer (54.9% vs 43.9%, $P < 0.0001$). The proportion of patients with no vomiting was higher in both HEC- and MEC-treated patients. While results of previous studies provide support for the use of antiemetic regimens that include aprepitant, a selective 5-hydroxytryptamine-3 receptor antagonist, and dexamethasone, this analysis demonstrates the consistent efficacy of aprepitant as part of an antiemetic regimen across different tumor types and chemotherapy regimens.

Introduction

As several patient-related risk factors—including age, sex, alcohol use, and history of motion sickness—are predictive of chemotherapy-induced nausea and vomiting (CINV), certain patient populations may be at higher inherent risk for CINV (e.g., patients with breast cancer who are primarily female and of relatively younger age).[1] In addition, chemotherapy regimens vary according to the type of tumor being treated, with varying degrees of emetogenic potential (e.g., cisplatin is widely used for the treatment of gastrointestinal and genitourinary cancers, and is highly emetogenic).[2–6] Because the distribution of these risk factors for CINV differs across tumor types, it is important to understand the efficacy of antiemetic regimens in multiple patient populations.[1]

Based on data from three phase 3 studies,[7–9] some but not all antiemetic guidelines for patients receiving moderately emetogenic chemotherapy (MEC) and highly emetogenic chemotherapy (HEC) recommend the use of the oral neurokinin 1 (NK1) antagonist aprepitant as part of a standard regimen that also includes a selective 5-hydroxytryptamine-3 (5-HT_3) receptor antagonist and a corticosteroid.[10–12] All antiemetic guidelines for patients receiving anthracycline plus cyclophosphamide (AC)-based MEC recommend the addition of an NK1 antagonist to a standard regimen.[10–12] Another recent phase 3 trial has demonstrated the efficacy of aprepitant in preventing CINV in patients with a wide range of tumor types who received AC and non–AC-based MEC regimens.[13] However, despite these results, the evidence for tumor-related response rates with aprepitant treatment regimens remains insufficient.

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Therefore, we conducted post hoc subgroup analyses to examine treatment response in patients with various malignancies receiving either HEC or MEC regimens in a series of large randomized trials evaluating the efficacy and safety of antiemetic therapy with aprepitant.[7–9,13] Patients in these trials received an active-control antiemetic regimen comprising ondansetron plus dexamethasone or an aprepitant regimen consisting of aprepitant, ondansetron, and dexamethasone. In this article, we summarize response data of patients with different tumor types (e.g., breast, gastrointestinal, genitourinary, lung, and other cancers) treated with aprepitant for the prevention of CINV.

Patients and study design

Detailed study design descriptions for the 4 double-blind, randomized, phase 3 trials investigating aprepitant-containing regimens for the prevention of CINV have previously been published.[7–9,13] Two studies, protocol 052 and protocol 054 (ClinicalTrails.gov identifiers unavailable because these trials were conducted prior to September 2007), were identically designed trials that enrolled patients who received cisplatin-containing HEC regimens for treatment of a variety of tumor types (e.g., lung, genitourinary, and gastrointestinal).[7,8,14] Two other studies enrolled patients who received MEC regimens: protocol 071 (ClinicalTrials.gov identifier: NCT00092196; http://www.clinicaltrials.gov/ct2/show/NCT00092196) enrolled patients with breast cancer[9] and protocol 130 (ClinicalTrials.gov identifier: NCT00337727; http://www.clinicaltrials.gov/ct2/show/NCT00337727) enrolled patients with various types of cancer, including breast, colon, lung, and ovarian.[13] Patients in all studies received either an aprepitant regimen (comprising aprepitant, ondansetron, and dexamethasone) or an active-control regimen (consisting of ondansetron plus dexamethasone). Treatment schedules for the active and control arms in the 4 trials are summarized in Table 1.

Inclusion/exclusion criteria for patients enrolled in the 4 trials were also previously published and are summarized in Table 2.[7–9,13] Patients in studies 052 and 054 were cisplatin-naive and were scheduled to receive their first cycle of chemotherapy, including at least 70 mg/m^2 of cisplatin. Patients in study 071 received MEC regimens containing cyclophosphamide, with or without the addition of doxorubicin or epirubicin, while patients in study 130 received MEC regimens that included 1 or more of the following agents: oxaliplatin, carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, daunorubicin, doxorubicin, cyclophosphamide (<1500 mg/m^2 intravenously [IV]), or cytarabine (>1 g/m^2 IV). In addition, at the time of this trial, although patients who received AC-based regimens were considered as MEC-treated patients, on the basis of new guidelines, these patients can now be categorized as HEC-treated.[15]

Study end points and subgroup analyses by tumor types

Efficacy end points and statistical analyses for the 4 phase 3 studies have also been published previously.[7–9,13] The primary efficacy end point in studies 052, 054, and 071 was complete response, defined as no vomiting and no use of rescue therapy during the overall (5-day) period following the first cycle of chemotherapy. Secondary end points for studies 052 and 054 included no vomiting and no use of rescue therapy. For study 071, mean functional living index-emesis score greater than 6 (on a 7-point scale) was the secondary end point. In study 130, the primary efficacy end point was the proportion of patients with no vomiting in the overall period following chemotherapy; the secondary efficacy end point was complete response (Table 2).

Subgroup analyses by tumor type (breast, lung, gastrointestinal, genitourinary, other) were performed for patients pooled from the 4 trials. Combined analyses were performed using complete response (defined as no vomiting and no use of rescue medication) data during the overall phase for HEC-treated (studies 052/054) and MEC-treated (studies 071/130) patient groups. A multivariate logistic regression model was used with no adjustment for multiple comparisons, and nominal *P* values were reported. The reported *P* values are intended for interpretation of trends, rather than for claims of significance. Time to first emesis was an exploratory end point for 4 trials, and Kaplan–Meier estimates were conducted for time to first emesis for MEC-treated breast cancer patients.

Results

Patients evaluated in subgroup analyses

Baseline characteristics for patients from studies 052/054, 071, and 130 are shown in Table 3. A total of 1099 patients were enrolled in the 052/054 studies,[14] 866 patients in the 071 study,[9] and 848 patients in the 130 study.[13] The proportions of patients receiving aprepitant or control regimens were balanced across all tumor subgroups. Efficacy analyses included all patients who

Table 1
Treatment schedule for studies 052, 054, 071, and 130.

Study	Regimen	Medication	Dose (qd unless otherwise noted)			
			Day 1	Day 2	Day 3	Day 4
052/054[a]	Aprepitant	Aprepitant	125 mg po 1 h before chemotherapy	80 mg po	80 mg po	
		Ondansetron	32 mg IV 30 min before chemotherapy			
		Dexamethasone	12 mg po 30 min before chemotherapy[b]	8 mg po	8 mg po	8 mg po
	Control	Placebo	Placebo po 1 h before chemotherapy	Placebo po	Placebo po	
		Ondansetron	32 mg IV 30 min before chemotherapy			
		Dexamethasone	20 mg po 30 min before chemotherapy[b]	8 mg po bid	8 mg po bid	8 mg po bid
071/130[c]	Aprepitant	Aprepitant	125 mg po 1 h before chemotherapy	80 mg po	80 mg po	
		Ondansetron	8 mg po 30–60 min before chemotherapy; 8 mg po 8 h after first dose	Placebo po bid	Placebo po bid	
		Dexamethasone	12 mg po 30 min before chemotherapy			
	Control	Placebo	Placebo po 1 h before chemotherapy	Placebo po	Placebo po	
		Ondansetron	8 mg po 30–60 min before chemotherapy; 8 mg po 8 h after first dose	8 mg po bid	8 mg po bid	
		Dexamethasone	20 mg po 30 min before chemotherapy			

bid = twice daily; IV = intravenously; qd = once daily; po = orally.
[a] Study designs were identical for 052 and 054.
[b] Patients treated with docetaxel or paclitaxel in addition to cisplatin received dexamethasone 20 mg at 12 h and 6 h before docetaxel/paclitaxel infusion; these patients did not receive dexamethasone 20 mg 30 min before cisplatin.
[c] Medication schedules were identical in studies 071 and 130.