

Phase 2 Trial Results With the Novel Neurokinin-1 Receptor Antagonist Casopitant in Combination With Ondansetron and Dexamethasone for the Prevention of Chemotherapy-Induced Nausea and Vomiting in Cancer Patients Receiving Moderately Emetogenic Chemotherapy

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BACKGROUND: This randomized, double-blind, dose-ranging, placebo-controlled, phase 2 trial evaluated the neurokinin-1 receptor antagonist casopitant mesylate in combination with ondansetron/dexamethasone (ond/dex) for the prevention of chemotherapy-induced nausea and vomiting (CINV) related to moderately emetogenic chemotherapy (MEC). **METHODS:** Chemotherapy-naive patients who were receiving MEC (N = 723) were randomized to receive either oral placebo or casopitant at doses of 50 mg, 100 mg, or 150 mg daily (on Days 1-3) plus ondansetron (on Days 1-3) and dexamethasone (Day 1). Two exploratory arms evaluated single-dose casopitant (150 mg) plus ond/dex and a 3-day casopitant regimen with once-daily ondansetron and dexamethasone. Primary endpoints were rates of complete response (CR) (no vomiting, retching, rescue therapy, or premature discontinuation) and significant nausea (SN) (≥ 25 mm on a visual analog scale) over the first 120 hours after Cycle 1 of MEC. Secondary endpoints included acute and delayed CR and SN rates, rates of nausea, vomiting, and safety. **RESULTS:** All casopitant doses that were tested significantly increased the proportion of patients with CR: The CR rates were 80.8% with casopitant 50 mg, 78.5% with casopitant 100 mg, and 84.2% with casopitant 150 mg compared with 69.4% in the control group ($P = .0127$); casopitant 150 mg was identified as the minimally effective dose. In exploratory analyses, single-dose casopitant demonstrated a 79.2% CR rate, and once-daily ondansetron plus casopitant produced an 83.5% CR rate. Vomiting rates in the first 5 days after MEC were reduced with casopitant-containing regimens (from 23% to 10%-16%). Rates of SN did not differ among treatment arms (range, 28%-

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29%). Casopitant appeared to be well tolerated with no notable differences in overall adverse event frequency. **CONCLUSIONS:** Casopitant plus ond/dex was more effective than ond/dex alone for the prevention of CINV. *Cancer* 2009;115:5807-16. © 2009 American Cancer Society.

KEY WORDS: antiemetics, antineoplastic combined chemotherapy protocols, combination drug therapy, nausea, neoplasms, neurokinin-1 receptors, vomiting.

The introduction of 5-hydroxytryptamine 3 (5-HT₃) receptor antagonists into standard therapy for the prevention of chemotherapy-induced nausea and vomiting (CINV) represented a significant advance; however, the prevention and treatment of CINV remain clinically challenging. In a prospective multinational study, 27.9% of patients who received moderately emetogenic chemotherapy (MEC) experienced delayed vomiting despite antiemetic prophylaxis.¹ In the community, patients' quality of life and daily functioning continue to be affected adversely by CINV even when antiemetics are prescribed in accordance with current clinical practice guidelines.² There remains room for improvement in the prevention of CINV in both the acute phase (0-24 hours) and the delayed phase (24-120 hours).

Casopitant is a potent, selective neurokinin-1 (NK-1) receptor antagonist with demonstrated antiemetic activity.³⁻⁶ In ferret models, a combination of casopitant and ondansetron was superior to either agent alone for the prevention of acute cisplatin-induced emesis, but only casopitant was effective as a rescue treatment for established cisplatin-induced emesis.^{3,4} Casopitant has been well tolerated in phase 1 clinical trials in single doses up to 150 mg and in phase 2 trials in combination with ondansetron.⁵⁻⁷ In a phase 2 trial, patients who received highly emetogenic, cisplatin-based chemotherapy experienced significantly higher complete response rates, lower rates of vomiting, and a longer median time to first emesis when casopitant was added to the prophylactic regimen relative to ondansetron/dexamethasone alone.⁶ The current trial was designed to evaluate the efficacy and side-effect profile of several casopitant doses when administered with ondansetron and dexamethasone for the prevention of CINV over the first 5 days after administration of MEC.

MATERIALS AND METHODS

Inclusion Criteria

Chemotherapy-naive patients aged >18 years with a malignant solid tumor who were scheduled to receive their

first course of MEC were eligible for the trial. Eligible regimens included at least 1 of the following agents: cyclophosphamide from 500 mg/m² to 1500 mg/m² if given with other MEC or from 750 mg/m² to 1500 mg/m² if given alone or with agents that had minimal or low emetogenic potential, oxaliplatin \geq 85 mg/m², doxorubicin \geq 60 mg/m², epirubicin \geq 90 mg/m², irinotecan (dosed as part of an irinotecan, leucovorin, 5-fluorouracil [FOLFIRI] regimen), or carboplatin at an area under the curve (AUC) \geq 5. Other inclusion criteria included a Karnofsky performance status score \geq 70 and adequate hematologic and metabolic status, which we defined as white blood cells >3000/mm³, absolute neutrophils >1500/mm³, platelets >100,000/mm³, and serum creatinine <1.5 mg/dL. Eligible patients were required to have adequate liver function, as demonstrated by laboratory values for aspartate aminotransferase and/or alanine aminotransferase \leq 2.5 times the upper limit of normal in patients without known liver metastases or \leq 5 times the upper limit of normal in patients with liver metastases. All patients of childbearing potential were required to use birth control.

Exclusion Criteria

Patients were not eligible if they had previously received cytotoxic chemotherapy or an NK-1 receptor antagonist or if they were scheduled to receive 1) highly emetogenic chemotherapy, 2) adjuvant cyclophosphamide-based chemotherapy, 3) bone marrow transplantation and/or stem cell rescue with the current chemotherapy course, or 4) any medication of moderate or high emetogenic risk within 48 hours of receiving study medication. Abdominal or pelvic radiation was not allowed from 7 days before to 6 days after the initiation of study medication. Patients who had known central nervous system metastases were ineligible unless they were treated successfully with excision or radiation and had been stable for at least 1 week before they received the first dose of study medication.

Patients who were receiving other antiemetics and those who experienced emesis or clinically significant

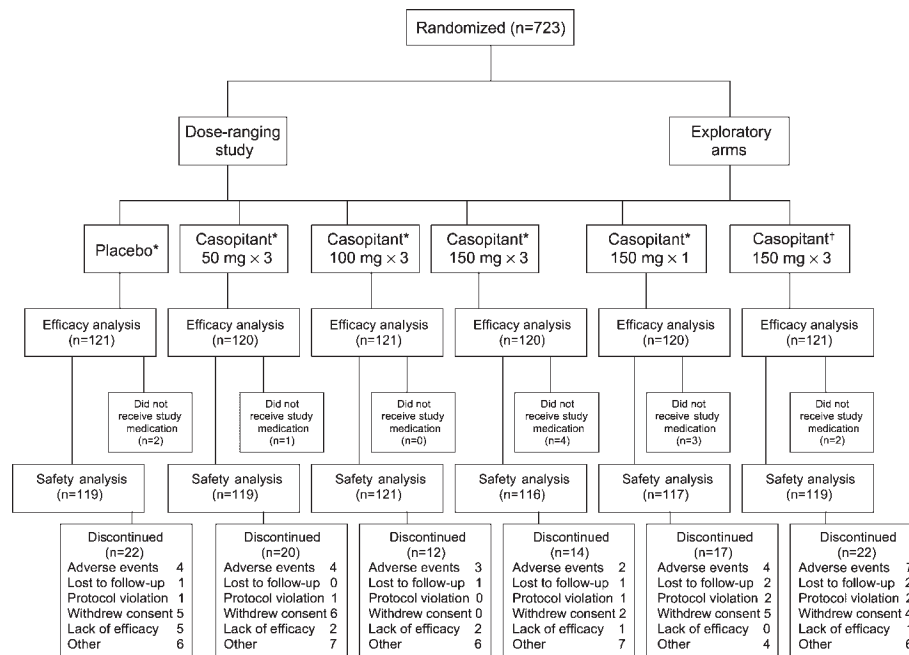


FIGURE 1. Consolidated Standards of Reporting Trials (CONSORT) diagram is shown. The efficacy population (full ITT) is defined as all subjects who were randomized to any treatment group. The safety population is defined as all subjects who received any study medication. *Plus ondansetron 8 mg twice daily + dexamethasone. †Plus ondansetron 16 mg every day + dexamethasone.

nausea (SN) within 24 hours before the initiation of study medication or with another etiology for emesis and nausea (eg, gastrointestinal obstruction, increased intracranial pressure, hypercalcemia, active peptic ulcer) were excluded from the study. Systemic corticosteroid therapy other than for taxane premedication was not to be initiated within 72 hours before the first dose of study medication. Opioid narcotics for cancer pain were permitted if the dose had been stable for at least 7 days and if the patient had not experienced nausea or emesis as a side effect. Patients were ineligible if they had taken strong or moderate inhibitors of cytochrome P450 3A4 (CYP3A4) and CYP3A5 within 2 to 14 days of the first dose of study medication or inducers of CYP3A4 within 14 days of the first dose of study medication. The use of other investigational drugs within 30 days before study drug initiation or during the study was not allowed.

Study Design

The current randomized, double-blind, placebo-controlled, dose-ranging trial was conducted at 99 centers in 24 countries (Fig. 1). Patients were randomized to 1 of 6 treatment groups (Table 1) by a centralized, automated

randomization system and were stratified by sex and chemotherapy treatment (taxane-based or nontaxane-based). Patients in Group 1, the control arm, did not receive casopitant. Groups 2, 3, and 4 (primary treatment arms) and Group 6 (exploratory arm) received casopitant for 3 consecutive days, whereas Group 5 (exploratory arm) received casopitant only on Day 1. Groups 1 through 5 received ondansetron 8 mg orally twice daily, whereas Group 6 received ondansetron 16 mg once daily. All patients who did not receive steroid premedication for taxane therapy received a single intravenous dose of dexamethasone 8 mg before MEC on Day 1.

All patients provided written informed consent before participation in the trial. The study was conducted in accordance with good clinical practice, all applicable regulatory requirements, and the guiding principles of the Declaration of Helsinki.

Assessments

Patients recorded the incidence of vomiting, retching, and use of any rescue medications in a study diary daily throughout the 120-hour evaluation period. They also completed a visual analog scale (VAS) daily to grade the

Table 1. Dosing Regimens by Treatment Group

Study Arm	Day 1, 30 Minutes Before MEC	Day 1, 8 Hours Later	Day 2	Day 3
Group 1: Control	Ond 8 mg PO, Dex 8 mg IV,* Cas PBO	Ond 8 mg PO	Ond 8 mg PO BID, Cas PBO	Ond 8 mg PO BID, Cas PBO
Group 2: Primary treatment	Ond 8 mg PO, Dex 8 mg IV,* Cas 50 mg	Ond 8 mg PO	Ond 8 mg PO BID, Cas 50 mg	Ond 8 mg PO BID, Cas 50 mg
Group 3: Primary treatment	Ond 8 mg PO, Dex 8 mg IV,* Cas 100 mg	Ond 8 mg PO	Ond 8 mg PO BID, Cas 100 mg	Ond 8 mg PO BID, Cas 100 mg
Group 4: Primary treatment	Ond 8 mg PO, Dex 8 mg IV,* Cas 150 mg	Ond 8 mg PO	Ond 8 mg PO BID, Cas 150 mg	Ond 8 mg PO BID, Cas 150 mg
Group 5: Exploratory arm	Ond 8 mg PO, Dex 8 mg IV,* Cas 150 mg	Ond 8 mg PO	Ond 8 mg PO BID, Cas PBO	Ond 8 mg PO BID, Cas PBO
Group 6: Exploratory arm	Ond 16 mg PO, Dex 8 mg IV,* Cas 150 mg	Ond PBO	Ond 16 mg QAM, Ond PBO QPM, Cas 150 mg	Ond 16 mg QAM, Ond PBO QPM, Cas 150 mg

MEC indicates moderately emetogenic chemotherapy; Ond, ondansetron; PO, orally; Dex, dexamethasone; IV, intravenously; Cas, casopitant; PBO, placebo; BID; twice daily; QAM, in the morning; QPM, in the evening.

* Patients who received steroid premedication for taxane therapy did not receive protocol-defined Dex on Day 1.

severity of nausea, if present. The Functional Living Index-Emesis (FLIE) questionnaire was administered on Day 1 and Day 6 of the trial to assess the impact of CINV on activities of daily living during the 120-hour evaluation phase. Patient satisfaction was assessed on Day 6 with a 5-point Likert scale ranging from “very satisfied” to “very dissatisfied.” Safety assessments were performed until the end of the first cycle of MEC (Days 20-30) and included the results of routine physical examination, vital signs, electrocardiogram monitoring, routine clinical laboratory tests, clinical monitoring and/or observation, and adverse event reporting. Adverse events were captured by the study personnel, who telephoned patients daily on Days 2 through 5 and graded events according to the National Cancer Institute Common Toxicity Criteria (version 3).

Statistical Analysis

The primary endpoints of the study were 1) the proportion of patients achieving a complete response (CR), which was defined as no vomiting, no retching, no rescue therapy, and no premature discontinuation from the study, during the 120-hour evaluation period after the first cycle of MEC; and 2) the proportion with SN, which was defined as a maximum nausea score ≥ 25 mm on the VAS, during the same period. Both endpoints were assessed in the intent-to-treat (ITT) population.

The study had 90% power to detect a 20% difference in the overall CR rate between the control group

(Group 1) and the group that received the highest dose of casopitant (Group 4) with a 2-sided significance level of .05 and assuming a predicted CR rate of 52% (Group 1) and 72% (Group 4), which would require 100 evaluable patients per arm. However, a 15% dropout rate was assumed, and, in total, 118 patients were to be enrolled in each study arm.

The 2 primary endpoints in this study were to be tested hierarchically as follows: First, the dose-response for CR was tested using a Cochran-Armitage test.⁸ If this test was statistically significant, then the dose response for SN (defined as a maximum nausea score ≥ 25 mm on the VAS) would be tested.

Once a dose response had been determined for the primary endpoint of CR at 120 hours, ordinal contrasts were fit by excluding the highest dose until the test for linear trend was no longer statistically significant; the highest dose at which the ordinal contrasts retained statistical significance was to be considered the “minimally effective dose.” This analysis was repeated for SN at 120 hours. For secondary endpoints, the primary treatment groups were compared with Group 1 in a similar fashion. The study was not powered based on secondary endpoints; thus, there was no adjustment for multiplicity. Time-to-event endpoints were summarized by using quartiles and the associated 95% confidence intervals, and log-rank *P* values comparing all groups together and comparing each treatment arm with placebo were calculated. Scores on the FLIE were compared by using the Kruskal-Wallis test for differences between treatments.

Table 2. Patient Disposition

Variable	No. of Patients (%)					
	Primary Analysis				Exploratory Analyses	
	Dex Plus Ond 8 mg BID Plus				Dex/Ond 16 mg QD Plus	
	Group 1: Placebo, n=121	Group 2: Cas 50 mg ×3, n=120	Group 3: Cas 100 mg ×3, n=121	Group 4: Cas 150 mg ×3, n=120	Group 5: Cas 150 mg ×1, n=120	Group 6: Cas 150 mg ×3, n=121
Mean age [range], y	57 [22-83]	58.5 [33-88]	57.4 [20-85]	59.2 [26-82]	57.9 [22-84]	57.9 [28-88]
Sex						
Men	47 (39)	46 (38)	49 (40)	48 (40)	48 (40)	49 (40)
Women	74 (61)	74 (62)	72 (60)	72 (60)	72 (60)	72 (60)
Primary tumor type						
Breast	26 (21)	38 (32)	32 (26)	23 (19)	30 (25)	27 (22)
NSCLC	29 (24)	29 (24)	35 (29)	24 (20)	26 (22)	30 (25)
Colon/rectum	20 (17)	17 (14)	24 (20)	23 (19)	14 (12)	20 (17)
Ovary	16 (13)	14 (12)	15 (12)	22 (18)	14 (12)	12 (10)
Other	30 (25)	22 (18)	15 (12)	28 (23)	36 (30)	32 (26)
Median time since diagnosis, d	35	32	35	36.5	35	30
Chemotherapy administration*						
Carboplatin	68 (56)	60 (50)	60 (50)	65 (54)	66 (55)	65 (54)
5-Fluorouracil	29 (24)	36 (30)	40 (33)	36 (30)	28 (23)	32 (26)
Paclitaxel	28 (23)	26 (22)	36 (30)	30 (25)	30 (25)	32 (26)
Oxaliplatin	23 (19)	18 (15)	25 (21)	22 (18)	16 (13)	20 (17)
Doxorubicin	21 (17)	28 (23)	29 (24)	18 (15)	29 (24)	25 (21)
Cyclophosphamide	18 (15)	22 (18)	25 (21)	18 (15)	21 (18)	19 (16)
Gemcitabine	16 (13)	7 (6)	7 (6)	8 (7)	5 (4)	9 (7)
Docetaxel	12 (10)	14 (12)	6 (5)	12 (10)	12 (10)	12 (10)
Etoposide	12 (10)	11 (9)	7 (6)	10 (8)	16 (13)	12 (10)
Epirubicin	11 (9)	11 (10)	8 (7)	7 (6)	8 (7)	8 (7)

Dex indicates dexamethasone; Ond, ondansetron; BID, twice daily; QD, once daily; Cas, casopitant; NSCLC, nonsmall cell lung cancer.

* Reported for at least 5% of patients in any treatment arm.

Secondary endpoints included CR rates and SN rates during the acute phase (0-24 hours) and the delayed phase (24-120 hours), and the rates of complete protection (CR plus maximum nausea <25 mm on the VAS), total control (CR plus maximum nausea <5 mm on the VAS), vomiting, and rescue medication use. The median times to emesis and rescue medication use were determined.

RESULTS

Population demographics were similar across all treatment groups (Table 2). The most common diagnoses were breast cancer, nonsmall cell lung cancer, colorectal cancer, and ovarian cancer. More women were enrolled than men (60% and 40%, respectively). The average age of all patients was 58 years, and the median time since diagnosis was 30 days. Carboplatin, which was the most fre-

quently administered, moderately emetogenic agent, was received by 384 patients (53%) overall. Dexamethasone used as a premedication for paclitaxel or docetaxel or as a rescue medication was balanced across treatment arms.

Efficacy

The proportion of patients in the ITT population who achieved a CR at 120 hours ranged from 69.4% in Group 1 (control arm) to 84.2% in Group 4 (casopitant 150 mg daily for 3 days), and a significant overall dose response was established through Cochran-Armitage trend testing ($P = .0127$). Testing for a linear trend for doses from 0 mg to 100 mg did not achieve significance ($P = .0846$), thereby establishing the 3-day 150 mg daily dose as the minimally effective dose (ordinal contrast; $P = .0127$).

Table 3. Proportion of Patients With Complete Response (Intent-to-Treat Population)*

	No. of Patients (%)					
	Primary Analysis				Exploratory Analyses	
		Dex Plus Ond 8 mg BID Plus				Dex/Ond 16 mg QD Plus
Complete Response	Group 1: Placebo, n=121	Group 2: Cas 50 mg ×3, n=120	Group 3: Cas 100 mg ×3, n=121	Group 4: Cas 150 mg ×3, n=120	Group 5: Cas 150 mg×1, n=120	Group 6: Cas 150 mg ×3, n=121
Overall	84 (69.4)	97 (80.8)	95 (78.5)	101 (84.2)	95 (79.2)	101 (83.5)
<i>P</i> , trend test	.0127					
<i>P</i> , ordinal contrast		.0305	.0846	.0127	ND	ND
Acute phase	108 (89.3)	110 (91.7)	108 (89.3)	110 (91.7)	108 (90)	113 (93.4)
<i>P</i> , trend test	.6850					
<i>P</i> , ordinal contrast		ND	ND	ND	ND	ND
Delayed phase	84 (69.4)	97 (80.8)	95 (78.5)	101 (84.2)	95 (79.2)	101 (83.5)
<i>P</i> , trend test	.0127					
<i>P</i> , ordinal contrast		.0305	.0846	.0127	ND	ND

Dex indicates dexamethasone; Ond, ondansetron; BID, twice daily; QD, once daily; Cas, casopitant; ND, not determined.

* Patients who did not have a CR in the acute phase were considered as not having a CR in the delayed phase.

The greatest benefit from the addition of casopitant to the prophylactic regimen was observed in the delayed phase, in which the CR rate was 69.4% for Group 1 versus 80.8% for Group 2, 78.5% for Group 3, and 84.2% for Group 4 ($P = .0127$). There were no differences among Groups 1 through 4 for the second primary endpoint, SN. From 0 hours to 120 hours, the rates of SN were 28.9% in Group 1, 27.5% in Group 2, 29.8% in Group 3, and 28.3% in Group 4 ($P = .0983$).

In the exploratory analyses, Group 5 (single-dose casopitant regimen) produced a numerically higher CR rate relative to Group 1 (control) overall and in the delayed phase (Table 3). The absolute treatment benefit approached 10%, and the lower limit of the 95% confidence interval approached zero for each time point (mean difference, 9.7%; 95% confidence interval, -1.2 to 20.7). Results in Group 6 were similar to those in Group 4, suggesting that ondansetron 16 mg given once daily with casopitant could be a convenient alternative to twice-daily dosing. For SN, the 34.2% overall incidence rate in Group 5 was not significantly different from that in Group 1 (28.9%), and the 30.6% rate in Group 6 was consistent with the rates in both Group 1 and Group 4 (28.9% and 28.3%, respectively).

Significant dose-response relations were not observed for rates of complete protection, total control, or nausea (Table 4). However, there was a significant dose-response relation for vomiting both overall and in the delayed phase ($P = .0251$ and $P = .0069$, respectively) (Table 4). Each ordinal contrast was statistically significant, indicating the effectiveness of all casopitant regimens in the reduction of vomiting relative to Group 1 in the delayed phase. There also was a significant difference in favor of casopitant in the time to first emesis ($P = .0401$) (Fig. 2). Hazard ratios for first emesis relative to Group 1 were 0.487 for Group 2 (pairwise Wald test; $P = .0278$), 0.668 for Group 3 ($P = .1752$), and 0.448 for Group 4 ($P = .0169$).

Less than 10% of patients on each arm received rescue medication during the evaluation period (7.4% in Group 1 vs 5.8% in Group 2, 3.3% in Group 3, and 5% in Group 4). There were no differences in the time to first rescue medication use across groups ($P = .5466$). Rescue medication was received by 5 patients in Group 5 (4.2%) and by 7 patients in Group 6 (5.8%) over 0 to 120 hours.

There were no significant differences on FLIE scores for CINV, nausea, or vomiting in the ITT population for Groups 1 through 4 (data not shown). For all 6 treatment

Table 4. Secondary Endpoints (Intent-to-Treat Population)

Endpoint	No. of Patients (%)					
	Primary Analysis				Exploratory Analyses	
	Dex Plus Ond 8 mg BID Plus				Dex/Ond 16 mg QD Plus	
Group 1: Control, n=121	Group 2: Cas 50 mg ×3, n=120	Group 3: Cas 100 mg ×3, n=121	Group 4: Cas 150 mg ×3, n=120	Group 5: Cas 150 mg ×1, n=120	Group 6: Cas 150 mg ×3, n=121	
Complete protection						
Overall	73 (60.3)	80 (66.7)	76 (62.8)	77 (64.2)	73 (60.8)	78 (64.5)
Acute phase	104 (86)	103 (85.8)	99 (81.8)	104 (86.7)	98 (81.7)	103 (85.1)
Delayed phase	73 (60.3)	80 (66.7)	76 (62.8)	77 (64.2)	73 (60.8)	78 (64.5)
Total control						
Overall	60 (49.6)	68 (56.7)	55 (45.5)	64 (53.3)	59 (49.2)	63 (52.1)
Acute phase	96 (79.3)	90 (75)	85 (70.2)	97 (80.8)	87 (72.5)	98 (81)
Delayed phase	60 (49.6)	68 (56.7)	55 (45.5)	64 (53.3)	59 (49.2)	63 (52.1)
Vomiting						
Overall	28 (23.1)*	14 (11.7)†	19 (15.7)‡	13 (10.8)§	19 (15.8)	12 (9.9)
Acute phase	7 (5.8)	6 (5)	8 (6.6)	6 (5)	8 (6.7)	5 (4.1)
Delayed phase	26 (21.5)¶	12 (10)¶	15 (12.4)#	10 (8.3)**	14 (11.7)	8 (6.6)
Nausea						
Overall	55 (45.5)	50 (41.7)	62 (51.2)	52 (43.3)	60 (50)	56 (46.3)
Acute phase	20 (16.5)	30 (25)	34 (28.1)	19 (15.8)	31 (25.8)	21 (17.4)
Delayed phase	52 (43)	45 (37.5)	55 (45.5)	48 (40)	56 (46.7)	54 (44.6)
Rescue medication use						
Overall	9 (7.4)	7 (5.8)	4 (3.3)	6 (5)	5 (4.2)	7 (5.8)
Acute phase	3 (2.5)	2 (1.7)	2 (1.7)	2 (1.7)	—	—
Delayed phase	6 (5)	5 (4.2)	2 (1.7)	4 (3.3)	—	—

Dex indicates dexamethasone; Ond, ondansetron; BID, twice daily; QD, once daily; Cas, casopitant.

* $P = .0251$ for monotonic trend.

† $P = .0130$ for comparison with Group 1.

‡ $P = .1072$ for comparison with Group 1.

§ $P = .0251$ for comparison with Group 1.

¶ $P = .0069$ for monotonic trend.

¶ $P = .0077$ for comparison with Group 1.

$P = .0349$ for comparison with Group 1.

** $P = .0069$ for comparison with Group 1.

groups, the majority of patients (>60%) described themselves as “very satisfied” with the antiemetic prophylactic regimen in the patient satisfaction questionnaire.

Subgroup analyses were specified in the protocol to examine the results by sex and by type of chemotherapy (taxane-based vs nontaxane-based). The results of these analyses generally were consistent with the overall results. Rates of CR at 120 hours among men were 70.8% in Group 1, 83% in Group 2, 87.5% in Group 3, and 83.3% in Group 4, whereas, among women, the rates were 68.5%, 79.5%, 72.6%, and 84.7%, respectively. Efficacy appeared to be similar for patients who received taxane-based therapy and patients

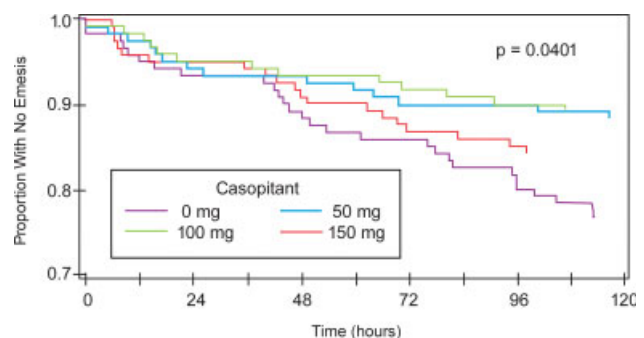


FIGURE 2. The time to first emesis is illustrated in an intent-to-treat population. These Kaplan-Meier survival curves illustrate the time to the first emetic episode.

Table 5. Adverse Events (>10%) Reported in the Safety Population (N=711)

Event	No. of Patients (%)					
	Primary Analysis				Exploratory Analyses	
	Dex Plus Ond 8 mg BID Plus Dex Plus				Dex/Ond 16 mg QD Plus	
Group 1: Control, n=119	Group 2: Cas 50 mg ×3, n=119	Group 3: Cas 100 mg ×3, n=121	Group 4: Cas 150 mg ×3, n=116	Group 5: Cas 150 mg ×1, n=117	Group 6: Cas 150 mg ×3, n=119	
Any AE	85 (71)	82 (69)	92 (76)	90 (78)	75 (64)	90 (76)
Nausea	22 (18)	22 (18)	36 (30)	25 (22)	21 (18)	21 (18)
Anemia	20 (17)	17 (14)	16 (13)	19 (16)	14 (12)	15 (13)
Fatigue	20 (17)	14 (12)	28 (23)	25 (22)	21 (18)	25 (21)
Constipation	16 (13)	16 (13)	15 (12)	14 (12)	18 (15)	17 (14)
Neutropenia	14 (12)	17 (14)	18 (15)	15 (13)	16 (14)	17 (14)
Vomiting	14 (12)	5 (4)	9 (7)	5 (4)	8 (7)	5 (4)
Alopecia	11 (9)	12 (10)	21 (17)	18 (16)	14 (12)	15 (13)
Diarrhea	8 (7)	15 (13)	10 (8)	17 (15)	13 (11)	17 (14)
Anorexia	7 (6)	8 (7)	23 (19)	8 (7)	14 (12)	9 (8)
Dizziness	5 (4)	10 (8)	9 (7)	12 (10)	10 (9)	7 (6)

Dex indicates dexamethasone; Ond, ondansetron; BID, twice daily; AE, adverse event.

who received nontaxane-based regimens. In those who received taxane-based therapy, a CR was reported in 71.4% of Group 1, 85.4% of Group 2, 80.5% of Group 3, and 82.9% of Group 4. Those who received nontaxane-based regimens experienced similar complete responses: 68.4% of Group 1, 78.5% of Group 2, 77.5% of Group 3, and 84.8% of Group 4.

Safety

The safety population consisted of the 711 patients who received at least 1 dose of study medication in any treatment cycle. The most frequently reported adverse events—nausea, anemia, fatigue, constipation, neutropenia, and vomiting—generally appeared to be balanced across study arms. Fewer patients in Groups 2 through 6 reported vomiting than in Group 1, and more patients in Group 3 reported nausea and anorexia than in the other groups; however, there were no notable differences among treatment arms for overall adverse event frequency. Seventy-eight patients experienced at least 1 serious adverse event, and there were 20 deaths in this study, none of which were considered by the investigator to be related to study medication (Table 5). The incidence of adverse events leading to discontinuation was low and was balanced across the study arms.

DISCUSSION

This large international trial was conducted to assess the efficacy and side-effect profile of different doses of the NK-1 antagonist casopitant when added to a standard antiemetic regimen for the prevention of CINV in chemotherapy-naïve patients who were receiving MEC. At the time that this trial was initiated, the standard of care for the prevention of CINV was a combination of a 5-HT₃ receptor antagonist plus a corticosteroid; therefore, the dual regimen was used as a control.⁹⁻¹¹ Since that time, both the American Society of Clinical Oncology and the Multinational Association for Supportive Care in Cancer have revised their guidelines to reflect a triple-drug regimen with a 5-HT₃ receptor antagonist, a corticosteroid, and the NK-1 antagonist aprepitant as the standard of care for patients who are receiving certain MECs.¹¹⁻¹³

The population in the current trial comprised patients with a broad range of tumor types (breast cancer, nonsmall cell lung cancer, colorectal cancer, and ovarian cancer) who were receiving a variety of chemotherapeutic regimens with moderate emetogenicity. In the primary analysis, a statistically significant dose-response relation was demonstrated for the primary endpoint: the CR rate over the first 5 days after chemotherapy administration.

This composite endpoint was defined rigorously as no vomiting, no retching, no rescue therapy, and no premature discontinuation from the study. Each casopitant dose demonstrated clinical activity, and absolute improvements in CR at 120 hours ranged from approximately 10% to 15% relative to the control arm. Clinical activity was not affected by sex or by the type of chemotherapy (taxane-based vs nontaxane-based). Although it was active in the acute phase, the greatest clinical benefit related to casopitant was observed in the delayed phase. In an exploratory arm, a single dose of casopitant added to the prophylactic regimen on Day 1 appeared to be as effective as the 3-day regimens.

A significant dose-response relation was not noted for SN (maximum score ≥ 25 on the VAS), which was the other primary endpoint of the trial. In addition, rates of nausea (score ≥ 5 on the VAS) did not differ among the 6 treatment arms overall or in the acute phase. Approximately 40% to 50% of patients in this study experienced nausea at some point after chemotherapy administration, highlighting the need for further research into the pathogenesis of chemotherapy-induced nausea.

Rates of vomiting were reduced significantly with casopitant treatment both overall and in the delayed phase. Approximately 90% of patients who were randomized to receive casopitant therapy did not vomit in the delayed phase, and there was an absolute improvement over the control arm of approximately 10%. Each 3-day casopitant regimen produced a statistically significant improvement in vomiting rates relative to control in the delayed phase. Statistical comparisons were not made between the exploratory arms and controls; however, the vomiting rates in Groups 5 and 6 were consistent with the rates in the other casopitant arms.

Treatment with casopitant generally was well tolerated. The most commonly reported adverse events generally were consistent with side effects related to chemotherapy, such as fatigue, anemia, neutropenia, and alopecia.

In summary, across the different doses that we studied, an antiemetic regimen of combined casopitant, ondansetron, and dexamethasone provided a significant reduction in the number of patients who experienced CINV events over the first 5 days after MEC relative to the ondansetron/dexamethasone regimen alone and appeared to be well tolerated. It is noteworthy that casopi-

tant produced significant improvements in the prevention of CINV in this broad population of men and women with different tumor types who received a variety of chemotherapeutic regimens. A single-day casopitant regimen provided benefit in the prevention of CINV equal to the benefit that was provided by the 3-day regimens that were evaluated in this trial. These regimens are being evaluated in recently completed phase 3 trials.

Conflict of Interest Disclosures

Financial support was provided by GlaxoSmithKline.

Dr. Grunberg has acted as a consultant and provided expert testimony for GlaxoSmithKline.

Dr. Levin is a full-time employee of GlaxoSmithKline.

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