Sustained antiemetic responses with APF530 (sustained-release granisetron) during multiple cycles of emetogenic chemotherapy

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Background A phase 3 trial in patients with cancer who received chemotherapy has shown that subcutaneous (SC) APF530, a sustained-delivery formulation of granisetron, is noninferior to palonosetron in preventing acute (0-24 hours) and delayed (>24-120 hours) chemotherapy-induced nausea and vomiting (CINV).

Objective To investigate the sustainability of APF530 antiemetic responses during multiple chemotherapy cycles.

Methods 1,395 patients receiving moderately or highly emetogenic chemotherapy (MEC and HEC, respectively) were randomized either to APF530 250 or 500 mg SC (containing granisetron 5 or 10 mg, respectively) or palonosetron 0.25 mg intravenously before cycle 1 of chemotherapy. Patients who received palonosetron in cycle 1 were rerandomized in cycles 2-4 to APF530 250 or 500 mg; those who received APF530 in cycle 1 continued their APF530 dose. Between-group response rates were compared using the Fisher exact test.

Results Complete response (CR; no emesis, no rescue medication) for APF530 500 mg with HEC increased from 81.3% to 87.8% over 4 cycles in the acute phase of CINV, and from 67.1% to 83.1% in the delayed phase. Rates were slightly lower with MEC. Within-cycle CR rates between APF530 doses showed no significant differences. With HEC, APF530 500 mg provided sustained CRs through 4 cycles of chemotherapy in 68.4% of patients in the acute phase and in 57.9% in the delayed phase; with MEC, corresponding CRs were 56.5% and 41.3%. Nausea prevention was nearly as effective as emesis prevention.

Limitations Chemotherapy emetogenicity was classified according to Hesketh criteria during the time of this study. However, subsequent post hoc analyses indicate that reclassification according to newer ASCO emetogenicity guidelines did not alter the original study noninferiority conclusions.

Conclusion CR rates with APF530 during the acute and delayed phases of CINV in MEC and HEC were maintained over multiple cycles.

Funding/sponsors Heron Therapeutics Inc

Preventing chemotherapy-induced toxicities is as important as any other aspect of chemotherapy in allowing for effective treatment and maintaining patient quality of life. For many patients, chemotherapy-induced nausea and vomiting (CINV) not only is particularly uncomfortable but often affects the patient's ability to receive adequate chemotherapy.[1-3] Combinations of 5-hydroxytryptamine type 3 (5-HT_3) receptor inhibitors and corticosteroids, with a neurokinin 1 (NK-1) receptor inhibitor added when needed, effectively prevent both acute (0-24 hours) and delayed (>24-120 hours) CINV in most patients who receive moderately emetogenic chemotherapy (MEC); but prevention of emesis, particularly delayed emesis, associated with many widely used and highly effective regimens remains a problem. Regimens that contain cisplatin and cyclophosphamide-anthracycline combinations are among the most effective and the most highly emetogenic therapies and are most likely to be curtailed by failure to prevent delayed emesis.[2-4]

The 4 available 5-HT_3 inhibitors are structurally different. Because of these differences and those among individual patients, unsuccessful treatment with one does not preclude benefit with another.[5-8] All of the agents are approved for prevention of CINV after initial and repeat courses of chemotherapy.[9-12] Palonosetron is specifically approved for prevention of delayed CINV associated with

Accepted for publication January 21, 2015. Correspondence: Ralph Boccia, MD; rboccia@ccbdmd.com. Disclosures: Mr Cooper is an employee of TFS International, which contracted with Heron Therapeutics Inc (formerly AP Pharma Inc) to provide statistical analysis, during the study conduct. Ms O'Boyle was an employee of and consulted for AP Pharma (now Heron Therapeutics Inc). Dr Boccia has no conflicts of interest to report. ClinicalTrials.gov identifier: NCT00343460. JCSO 2015;13:38-46. DOI 10.12788/jcso.0107.

MEC regimens. No agent is recognized as effective in prevention of delayed CINV associated with highly emetogenic chemotherapy (HEC). Further, although the agents are indicated for use in repeat courses of chemotherapy, there have been reports that 5-HT_3 inhibitors may lose activity over multiple cycles.[13-15] The ability to adequately prevent delayed CINV with HEC is the greatest need in chemotherapy management, and the ability to maintain response over multiple cycles is an essential aspect of this need.[3,13-15]

APF530 is a tri(ethylene glycol) poly(orthoester) bioerodible polymer containing 2% granisetron.[16] It is designed to provide slow, controlled, and sustained release of granisetron for at least 5 days to control acute and delayed CINV associated with initial and repeat courses of MEC and HEC.[17] APF530 is administered as a subcutaneous (SC) injection in the abdomen 30 minutes before a patient receives chemotherapy. A series of phase 1 and 2 studies has defined the dosing, safety, and pharmacokinetic properties of APF530.[18,19] After a patient receives an SC injection, therapeutic levels of granisetron are maintained in the plasma for more than 168 hours.[19,20] The safety profile of APF530 is consistent with published data on granisetron.[18] A study of cardiac safety in normal volunteers found no clinically significant cardiac arrhythmias associated with high doses of APF530.[20] Noninferiority of APF530 compared with palonosetron was demonstrated in the prevention of acute and delayed CINV in association with MEC and acute CINV in association with HEC in a phase 3 trial.[17,21] Across all groups, including prevention of delayed CINV in association with HEC, the rates of complete response (CR; no emesis, no rescue medication) with APF530 500 mg were numerically superior to those obtained with palonosetron. In this trial, patients were randomized to receive APF530 250 mg SC, APF530 500 mg SC, or palonosetron 0.25 mg intravenously (IV) in cycle 1. All of the patients had the option to stay on study and continue treatment with only APF530 in cycles 2-4. In this report, we describe results with APF530 in prevention of CINV in cycles 2-4.

Methods

Patients

Study inclusion and exclusion criteria have been previously described.[17] Patients were adult (aged ≥ 18 years) men or women with histologically or cytologically confirmed malignancy, scheduled to receive a single-day MEC (Hesketh score 3 or 4) or HEC (Hesketh score 5) regimen. Emetogenicity of the chemotherapy regimens was defined according to the then-applicable Hesketh criteria.[22,23]

Study design

The trial was a prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 3 trial (NCT00343460), with stratification according to emetogenicity (MEC or HEC) of the regimen. The study was approved by the institutional review board or independent ethics committee at each participating center and conducted in accordance with the Declaration of Helsinki. All of the patients provided signed informed consent.

Treatment

In cycle 1, patients received APF530 250 mg SC (containing granisetron 5 mg) plus IV saline placebo, or APF530 500 mg SC (containing granisetron 10 mg) plus IV saline placebo, or palonosetron 0.25 mg IV plus SC saline placebo (Figure 1). After cycle 1, palonosetron was discontinued. All of the patients were offered the opportunity to continue in the study if they met the eligibility requirements; that is, they had not completed therapy, were receiving qualifying therapy, and met the dosing criteria. If they consented, those in the palonosetron group were rerandomized 1:1 to receive APF530 250 mg SC or 500 mg SC, and the APF530 groups continued with the same treatment. Patients could receive up to 3 subsequent chemotherapy cycles. In each cycle, APF530 was administered SC in the abdomen on Day 1, 30 minutes before receiving single-day MEC or HEC; a local anesthetic was applied to the area of the injection site before the study drug was administered. Standard doses of dexamethasone were administered per protocol 30 to 90 minutes before the start of chemotherapy, either 8 mg IV for MEC or 20 mg IV for HEC. On days 2, 3, and 4, oral dexamethasone was prescribed at a dose of 8 mg twice daily to all patients treated with HEC. Treatment cycles were separated by 7-28 days (± 3 days). Rescue medications were allowed as needed.

Objectives and assessments

The objective in cycles 2-4 was to evaluate the efficacy and safety of APF530 for the prevention of acute and delayed CINV during multiple chemotherapy cycles. Efficacy was assessed as the percentage of patients achieving CR (no emetic episodes, no rescue medications) during the acute (0-24 hours) and delayed (>24-120 hours) phases during chemotherapy cycles 1-4. Other efficacy measures included defining the sustainability of a CR over 4 cycles of chemotherapy, the proportion of patients with complete control (CC; CR with no more than mild nausea) and total response (TR; CR with no nausea) during the acute and delayed phases in cycles 2-4, time to first emetic episode, time to first rescue medication, and time to first treatment failure in cycles 2-4 (defined as time

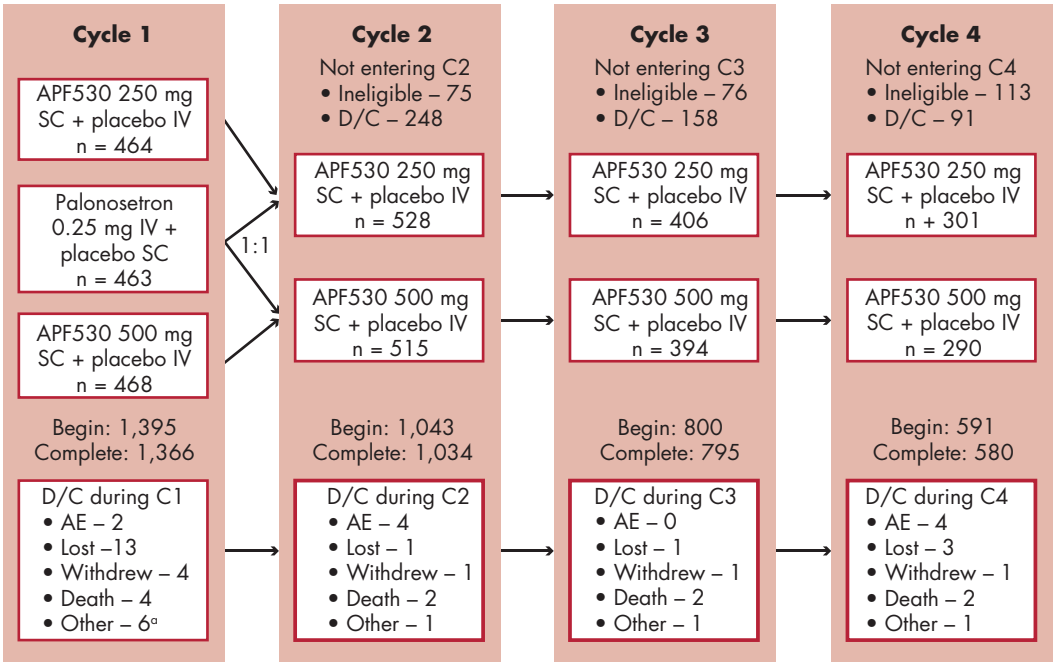

FIGURE 1 Study design
AE, adverse event; C, cycle; D/C, discontinued therapy; IV, intravenous; lost, lost to follow-up; SC, subcutaneous
[a]Protocol violations and study termination.

to first emetic episode or rescue medication, whichever occurs first). These efficacy measures were assessed from patient diaries recording emetic episodes, use of rescue medication, and severity of nausea for each 24-hour period after chemotherapy.

Adverse events (AEs) and serious AEs were assessed during each treatment cycle on the basis of standard toxicity criteria; assessments included type of AE, duration, severity (ie, mild, moderate, or severe), and relation to study drug. Physical examination, vital signs, and clinical laboratory parameters were also assessed.

Statistical analysis

The planned sample size was 1,389 patients, 669 in the MEC stratum and 735 in the HEC stratum. Sample sizes for cycle 1 were determined to provide adequate power for 4 simultaneous tests of noninferiority with respect to CR in the MEC group and 4 simultaneous tests (2 for noninferiority and 2 for superiority) in the HEC group. The noninferiority margin was defined as 15%. Within each emetogenicity stratum, each dose of APF530 was compared with palonosetron for both acute and delayed CR. Sample sizes in cycles 2-4 were determined by the number of patients in cycle 1 who elected to stay on study. Efficacy analyses were performed separately for MEC and HEC strata and were based on a modified intent-to-treat population, comprising all randomized patients who received study drug and had postbaseline efficacy data. This population is distinct from the intent-to-treat population, which comprises all randomized patients. The safety population comprised all patients (MEC and HEC strata) who were randomized and received study drug. Treatment comparisons were based on the Fisher exact test. Quantitative variables were summarized by sample size, mean, median, standard deviation, minimum, and maximum. Qualitative variables were summarized by number and percentage of patients. Unless otherwise indicated, statistical significance was reached if the 2-sided P value was $< .05$.

Results

Demographics

Patient characteristics were balanced among the 3 treatment arms in the MEC and HEC groups, with women constituting a somewhat higher proportion of MEC patients than HEC patients. Cancer types and chemotherapy regimens are shown in Tables 1 and 2.

Disposition

In all, 1,428 patients were randomized to 3 treatment arms at 103 centers in the United States, India, and Poland during June 2006-August 2008. Of those, 1,395 patients (653 MEC, 742 HEC) received treatment in cycle 1. Among the patients who completed cycle 1,

1,291 were eligible to receive APF530 in cycle 2 and 81% elected to stay in the study. Likewise, 84% and 87% of eligible patients elected to continue to cycles 3 and 4, respectively. The disposition of patients in cycles 1-4 and reasons for discontinuation during a cycle or for not entering the next cycle are shown in Figure 1. None of the deaths ocurring on study were related to the study drugs. Four cycles of treatment were completed by 580 patients: 270 received MEC (136 APF530 250 mg, 134 APF530 500 mg), and 310 received HEC (160 APF530 250 mg, 150 APF530 500 mg).

Efficacy

CR rates for APF530 250 mg and APF530 500 mg in each cycle of chemotherapy for patients receiving MEC or HEC are shown in Figure 2A. In cycle 1, ≥ 75% of patients had a CR during the acute phase and ≥ 50% had a CR in the delayed phase, with somewhat higher rates among HEC patients than among MEC patients. This pattern was maintained across all cycles. Within-cycle CR rates tended to be higher in the group receiving the 500-mg dose, although differences between the 250-mg and 500-mg doses were not significantly different in any

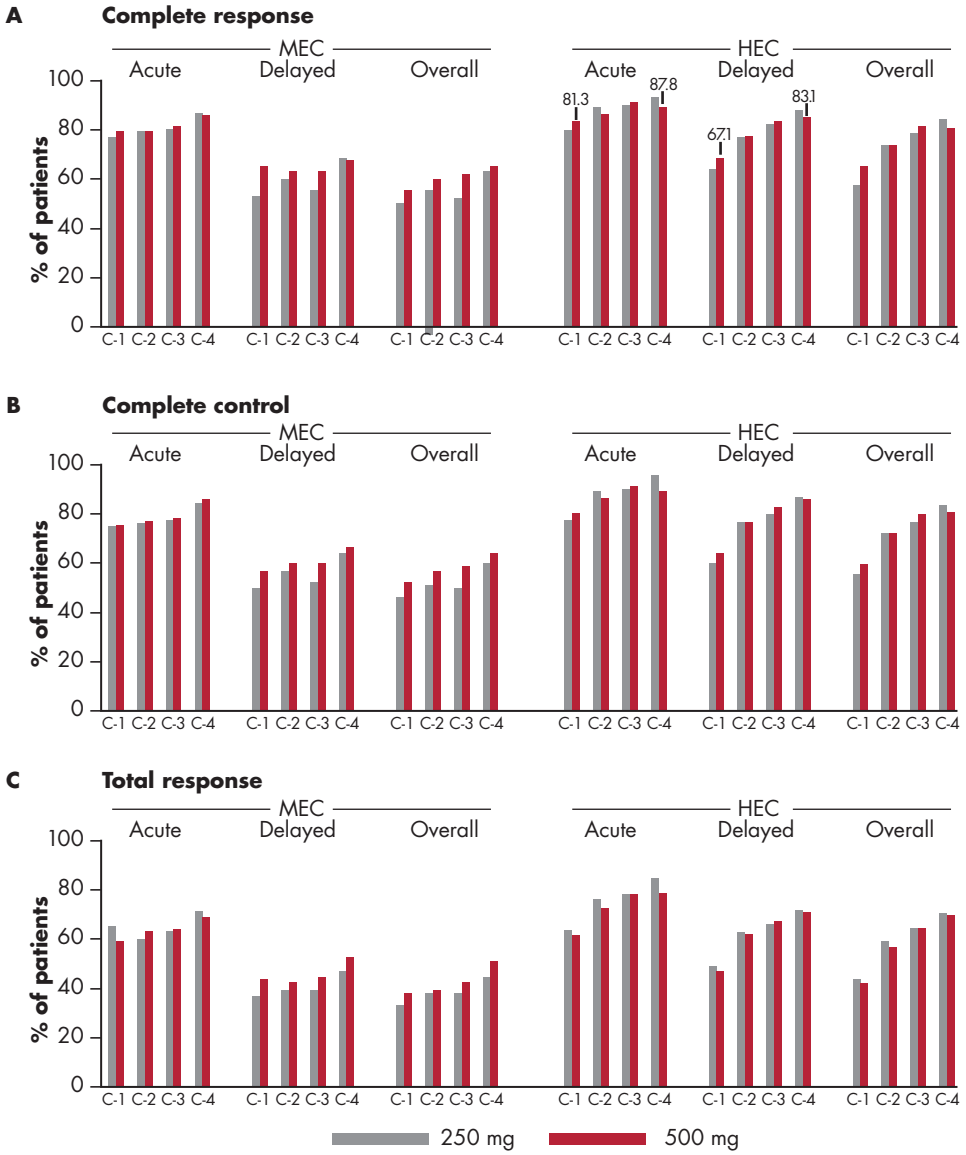

FIGURE 2 A, complete response; B, complete control; and C, total response rates for cycles 1, 2, 3, and 4 during the acute phase (0-24 hours), delayed phase (>24-120 hours), and overall (0-120 hours) for patients receiving MEC and HEC regimens.
C, cycle; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy

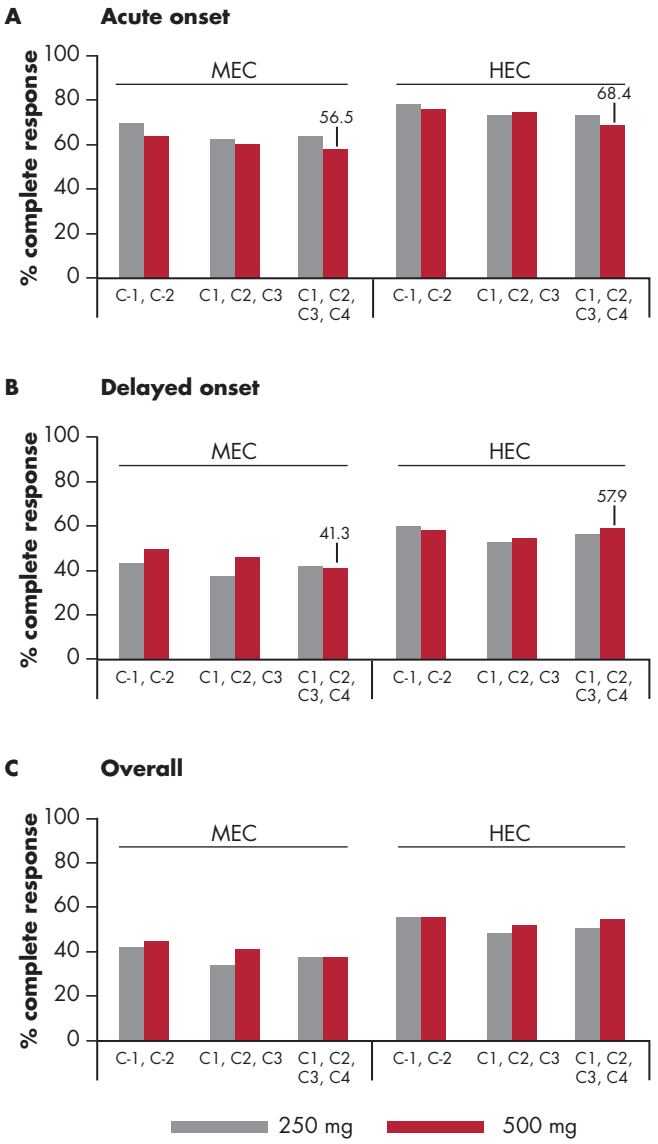

FIGURE 3 Sustainability of complete response during cycles 1 and 2; cycles 1, 2, and 3; and cycles 1, 2, 3, and 4 during A, the acute phase (0-24 hours); B, the delayed phase (>24-120 hours); and C, overall (0-120 hours). Numbers of patients evaluated in all phases (250 mg/500 mg) were 165/160 (MEC) and 178/171 (HEC) for cycles 1 and 2; 125/120 (MEC) and 141/129 (HEC) for cycles 1, 2, and 3; and 91/92 (MEC) and 106/95 (HEC) for cycles 1, 2, 3, and 4.
C, cycle; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy

phase of any cycle with MEC or HEC. Higher CR rates were seen during the 24-hour acute phase than during the more difficult to control delayed phase, and this difference was greater with MEC regimens. There was an apparent trend toward higher CR rates with successive cycles; for example, more than 80% of HEC patients had a CR during the acute and delayed phases in cycles 3 and 4 with both doses of APF530.

Prevention of moderate or worse nausea and vomiting (CC; Figure 2B) and complete prevention of nausea and vomiting (TR; Figure 2C) showed patterns very similar to those for CR. The rate of CC indicated prevention of moderate to severe nausea in a high proportion of patients, as well as prevention of vomiting with APF530. Nausea was mostly mild, with prevention seeming to improve with subsequent chemotherapy cycles. Among HEC patients, overall CC was achieved in > 70% of patients in cycles 3 and 4, and acute-phase CC was achieved in > 80%. Overall TRs (no emesis, no nausea, and no use of rescue medication) during the acute and delayed phases were achieved with APF530 500 mg in cycle 1 in 37% of MEC patients and 41% of HEC patients, and in cycle 4 in 49% of MEC patients and 68% of HEC patients.

Sustainabilty of response was assessed as the proportions of patients with CR in cycles 1 and 2; cycles 1, 2, and 3; and cycles 1, 2, 3, and 4 (Figure 3). The data showed, for example, that HEC patients receiving APF530 500 mg sustained acute-phase and delayed-phase CRs through 4 cycles of chemotherapy in 68% and 58% of patients, respectively. Results were similar for HEC patients who received APF530 250 mg; MEC patients had slightly lower rates of sustained CR across the 4 cycles.

In both APF530 dose groups, ≥ 83% of MEC patients and ≥ 90% of HEC patients with an acute-phase CR in cycle 1 had an acute-phase CR in at least 1 subsequent cycle. In the delayed phase, ≥ 70% of MEC patients and ≥ 85% of HEC patients with a CR in cycle 1 had a delayed-phase CR in a subsequent cycle. Many patients with no CR in cycle 1 responded in later cycles, with the proportions appearing to increase with each cycle. For example, among MEC patients receiving APF530 500 mg, although the numbers are small, 64% of 25 patients with no acute-phase CR in cycle 1 had acute-phase CR in cycle 4; similarly, 44% of 36 patients with no delayed-phase CR in cycle 1 had a delayed-phase CR in cycle 4. Among HEC patients receiving APF530 500 mg, 64% of 14 patients with no acute-phase CR in cycle 1 and 63% of 24 patients with no delayed-phase CR in cycle 1 achieved CR in cycle 4 (Online Table S1).

It is also of interest that acute-phase CR rates with palonosetron in cycle 1, 75% with MEC and 81% with HEC, were well maintained, with ≥ 90% of those patients also achieving CR in cycle 2; among 40 MEC patients who had no CR with palonosetron in cycle 1 and were evaluated in cycle 2, 20 achieved CR. Failure to repond to palonosetron in cycle 1 did not preclude successful prevention of CINV with APF530 in later cycles.

Time to first emetic episode, time to first use of rescue

TABLE 1 Baseline characteristics of patients treated in Cycle 1 (modified ITT population)

	MEC			HEC		
Characteristic	**APF530 250 mg (n = 214)**	**APF530 500 mg (n = 212)**	**Palo 0.25 mg (n = 208)**	**APF530 250 mg (n = 229)**	**APF530 500 mg (n = 240)**	**Palo 0.25 mg (n = 238)**
Mean age, y (SD)	55.0 (12.8)	55.2 (12.8)	57.2 (12.4)	57.6 (13.4)	56.8 (13.2)	58.1 (13.7)
Female, n (%)	189 (88.3)	177 (83.5)	177 (85.1)	153 (66.8)	152 (63.3)	158 (66.4)
Race, n (%)						
White	123 (57.5)	122 (57.5)	141 (67.8)	133 (58.1)	154 (64.2)	147 (61.8)
Asian	63 (29.4)	54 (25.5)	43 (20.7)	56 (24.5)	61 (25.4)	55 (23.1)
ECOG PS 0-1, n (%)	203 (94.9)	208 (98.1)	199 (95.7)	220 (96.1)	229 (95.4)	228 (95.8)
Mean time since diagnosis, y (n, SD)	0.7 (207,1.7)	0.9 (206,2.1)	0.8 (200,1.9)	0.7 (223,1.8)	0.7 (232,1.7)	0.5 (225,1.0)
Hesketh class, n (%)						
1-2	1 (0.5)	1 (0.5)	2 (1.0)	0	0	1 (0.4)
3	25 (11.7)	35 (16.5)	31 (14.9)	1 (0.4)	2 (0.8)	0
4	186 (86.9)	173 (81.6)	173 (83.2)	4 (1.7)	4 (1.7)	1 (0.4)
5	2 (0.9)	3 (1.4)	2 (1.0)	224 (97.8)	234 (97.5)	236 (99.2)
Cancer history, n (%)						
Breast	149 (69.6)	140 (66.0)	134 (64.2)	60 (26.2)	67 (27.9)	58 (24.4)
Lung	17 (7.9)	11 (5.2)	14 (6.7)	65 (28.4)	77 (32.1)	59 (24.8)
Ovarian	17 (7.9)	16 (7.6)	21 (10.1)	34 (14.9)	33 (13.8)	39 (16.4)
Lymphoma	10 (4.7)	10 (4.7)	7 (3.4)	12 (5.2)	12 (5.0)	12 (5.0)
Uterine	3 (1.4)	0	2 (1.0)	20 (8.7)	5 (2.1)	21 (8.8)
Other	18 (8.4)	35 (16.5)	30 (14.4)	38 (16.6)	46 (19.2)	49 (20.6)

ECOG PS, Eastern Cooperative Oncology Group performance status; HEC, highly emetogenic chemotherapy; ITT, intent-to-treat; MEC, moderately emetogenic chemotherapy; Palo, palonosetron

medication, and time to treatment failure showed no significant differences between the APF530 250 mg and 500 mg groups for MEC or HEC patients in any cycle, and there were no apparent differences in these parameters over cycles 1-4 for the MEC and HEC patients.

Safety

In cycles 2-4, 528 patients received APF530 250 mg and 515 patients received APF530 500 mg. Each patient received up to 3 doses, for a total of 1,236 doses of 250 mg and 1,199 doses of 500 mg. No treatment-related serious AEs were seen. The most commonly reported treatment-related AEs, excluding injection-site reactions, in the 250-mg and 500-mg groups were mild constipation (2.5%, 2.3%, respectively), moderate constipation (2.1%, 1.4%), mild headache (1.5%, 1.2%), mild fatigue (0%, 1.6%), and mild diarrhea (0.4%, 1.4%; OnlineTable S2). All other treatment-related AEs occurred in ≤0.6% of patients. There were 8 treatment-related severe AEs: 2 patients had constipation, and individual patients had dyspepsia, upper abdominal pain, headache, insomnia, thrombocytopenia, and pain; none were considered serious, and only dyspepsia led to treatment discontinuation. Comparing AEs in cycles 2-4 with those in patients who received APF530 in cycle 1, the 4 most common AEs across all 4 cycles were constipation, headache, fatigue, and diarrhea, and they were similar in severity and overall frequency.

Injection-site reactions in the APF530 250-mg and 500-mg groups included bruising (23.5%, 29.7%, respectively), nodules (10.8%, 17.5%), erythema (11.0%, 11.8%), pain (6.4%, 7.2%), and bleeding (6.0%, 6.6%). Most of the injection-site reactions were mild in severity; reactions of moderate severity occurred in fewer than 3% of patients. One patient in each group reported severe bruising, and 1 patient discontinued because of injection-site pain and erythema.

TABLE 2 Current chemotherapy regimens (modified ITT population)

Regimen	APF530 250 mg	APF530 500 mg	Palo 0.25 mg
MEC, n (%)	214	212	208
Cyclophosphamide-anthracycline	129 (60.3)	117 (55.2)	109 (52.4)
Cyclophosphamide combinations (others)	28 (13.1)	29 (13.7)	29 (13.9)
Carboplatin, carboplatin combinations	26 (12.2)	21 (9.9)	24 (11.5)
Doxorubicin, other anthracycline combinations	16 (7.5)	16 (7.6)	18 (8.7)
Other	15 (7.0)	29 (13.7)	28 (13.5)
HEC, n (%)	229	240	238
Carboplatin combinations	114 (49.8)	118 (49.2)	117 (49.2)
Cisplatin, cisplatin combinations	51 (22.3)	53 (22.1)	54 (22.7)
Cyclophosphamide-anthracycline	49 (21.4)	51 (21.3)	43 (18.1)
Other	15 (6.6)	18 (7.5)	24 (10.1)

HEC, highly emetogenic chemotherapy; ITT, intent-to-treat; MEC, moderately emetogenic chemotherapy

Discussion

Previously reported data from the phase 3 trial have established the noninferiority of APF530 500 mg SC to palonosetron 0.25 mg IV in the prevention of acute and delayed phase CINV associated with MEC and acute-phase CINV associated with HEC.[17] Superiority of APF530 500 mg SC compared with palonosetron for preventing delayed CINV after HEC was not demonstrated, but CR rates for this dose of APF530 were numerically superior to those for palonosetron in this setting. A phase 3 randomized trial designed to demonstrate the superiority of APF530 compared with ondansetron in delayed CINV in patients receiving HEC is currently ongoing (NCT02106494).

Conflicting reports about the efficacy of IV granisetron over multiple cycles of MEC or HEC contributed to the rationale for conducting this study with SC APF530. APF530 releases granisetron slowly after SC administration, and granisetron exposure is equivalent regardless of whether administered SC or IV.[24] Early studies with granisetron reported on its sustained efficacy over multiple cycles, with some noting decreased efficacy[13,14] and others reporting efficacy sustained for as long as 5 cycles,[15,25] although not as well in women as in men,[26] with HEC,[15] or in the delayed phase.[14] The present study shows sustained responses with APF530 in both the acute and delayed phases over 4 cycles with both MEC and HEC regimens. It is further encouraging that successful prevention of moderate to severe nausea after MEC or HEC was nearly the same as prevention of emesis.

A high proportion of patients with a response to APF530 in cycle 1 – CR, CC, or TR – also responded to APF530 in cycles 2, 3, and 4. Rates of response seemed to increase in later cycles, although the effect of nonresponding patients who dropped out of the study likely contributed to the apparent increase. Nevertheless, more than 50% of patients treated in cycle 1 remained on study and received APF530 in cycle 4, excluding those ineligible to receive treatment in cycles 2, 3, or 4 for any reason. Many patients who did not respond in cycle 1 and remained in the study developed a response in a later cycle.

Twenty of 40 MEC patients and 12 of 23 HEC patients who did not attain acute-phase CR with palonosetron in cycle 1 achieved CR in cycle 2 with APF530, suggesting limited cross-resistance between these agents. In a previous study, the absence of absolute cross-resistance between ondansetron and granisetron in preventing acute emesis was shown by the finding that after ondansetron failure in 40 cancer patients, 1 of 21 patients who stayed on ondansetron developed CR, whereas 9 of 19 who switched to granisetron achieved acute-phase CR with granisetron.[8] Although responses to 5-HT_3 inhibitors are determined mainly by the emetogenic potential of the chemotherapy, other factors such as alcohol consumption, preexisting nausea, and the patient's age, sex, ethnicity, and genetic makeup influence response. P450 enzymes metabolize all the 5-HT_3 inhibitors: granisetron is metabolized by CYP3A4 almost exclusively, with no contribution by CYP2D6, whereas dolasetron, ondansetron, and palonosetron are metabolized by CYP2D6. Multiple CYP2D6 alleles occur in about 10% of patients, with a high degree of ethnic variation and contribute to 5-HT_3 inhibitor sensitivity.[5,27,28] Such patients might be better treated with granisetron, which is not a CYP2D6 substrate.[27] Further study of this relationship is warranted.

The greater efficacy in prevention of CINV associated with HEC regimens compared with MEC regimens was unexpected. Reasons for this difference may have been the higher exposure to dexamethasone in patients who received HEC compared with those who received MEC. Another factor to consider is that regimens that contained both cyclophosphamide and an anthracycline, classified as MEC in this trial using the Hesketh algorithm, would now be classified as HEC by more recent

guidelines.[29] A post hoc analysis of CR rates in cycle 1, in which patient emetogenicity was reclassified according to newer criteria from the American Society of Clinical Oncology, resulted in better CR rates among patients with MEC regimens and poorer CR rates among patients with HEC regimens overall.[30] However, reclassification did not alter original study conclusions regarding noninferiority of APF530 to palonosetron in acute and delayed MEC and acute HEC.[30]

AEs associated with APF530 were similar to those seen with IV granisetron,[11] except for the injection-site reactions that were unique to SC APF530, but those were mostly mild in severity.

Conclusion

High rates of CR were sustained with APF530 over 4 cycles of chemotherapy in both the acute and delayed phases of CINV, with somewhat higher rates of response seen with APF530 500 mg compared with the 250-mg dose. Higher rates were seen during the acute phase than during the more difficult to control delayed phase, and surprisingly higher rates of response were seen with HEC versus MEC regimens. Total control of nausea and vomiting was achieved in most of the patients in later cycles against regimens with high emetogenic potential. With the exception of mostly mild injection-site reactions in a few patients, the safety profile of APF530 was consistent with the known safety profile of granisetron.

Acknowledgments

The authors thank the investigators and their clinical staff who made this study possible. Medical writing support was provided by Richard McCabe of SciStrategy Communications, supported by Heron Therapeutics.

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