Abstract 9626

Sustainability of Antiemetic Complete Responses (CRs) With APF530 (Sustained-Release Granisetron) During Multiple Cycles of Moderately (MEC) and Highly (HEC) Emetogenic Chemotherapy: Results of a Randomized Phase 3 Trial

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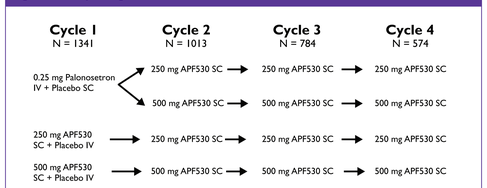
BACKGROUND

- Greater than 30% of chemotherapy patients experience chemotherapy-induced nausea and vomiting (CINV) despite use of the latest generation of antiemetics. Improved approaches to prevent CINV (especially delayed) are still needed
- APF530 is a new polymeric formulation of 2% granisetron and a biodegradable triethylene glycol poly (ortho ester) vehicle designed to provide slow, controlled, and sustained release of granisetron for the prevention of both acute (0-24 hours) and delayed (24-120 hours) CINV associated with emetogenic chemotherapy[1]
- In clinical studies in patients undergoing chemotherapy, a single dose of subcutaneously (SC) administered APF530 provided sustained therapeutic drug levels for over 5 days (> 120 hours)[1,2]
- In a phase 3 trial, APF530 500 mg SC (containing 10 mg granisetron) was demonstrated to be non-inferior to palonosetron 0.25 mg IV in the control of acute and delayed CINV in patients who had received MEC and acute CINV in patients who had received HEC[1]
- Although not statistically significant, APF530 500 mg compared with palonosetron achieved numerically superior CR rates in the setting of delayed CINV with HEC[1]
- The sustainability of responses in the phase 3 trial with APF530 through 4 cycles of chemotherapy was evaluated

METHODS

- 1428 patients scheduled to receive single doses of MEC or HEC in cycle 1 were randomized to APF530 250 mg or 500 mg SC (5 or 10 mg granisetron) or palonosetron 0.25 mg IV. Standard doses of IV dexamethasone (8 mg MEC, 20 mg HEC) were administered per protocol prior to chemotherapy on day 1; oral dexamethasone (8 mg, bid) was given to HEC patients on days 2, 3, and 4
- In cycles 2 to 4, patients who received palonosetron in cycle 1 were re-randomized to APF530 250 or 500 mg; those who received APF530 in cycle 1 continued with their APF530 dose (**Figure 1**)
- Treatment cycles were separated by 7 to 28 days
- Rates of CR (no emetic episodes and no use of rescue medications) were evaluated across each cycle
- Data shown are for the 1341 patients (634 MEC, 707 HEC) in the modified intent-to-treat population (treated patients with post-baseline efficacy data) (**Tables 1** and **2**)

Figure 1. Study Design



RESULTS

Table 1. Patient Demographics

	MEC			HEC		
	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
Age, mean (SD), y	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)
ECOG PS 0-1, n (%)	203 (94.9)	208 (98.1)	199 (95.7)	220 (96.1)	229 (95.4)	228 (95.8)
Time since diagnosis, mean (SD), y	0.7 (1.7)	0.9 (2.1)	0.8 (1.9)	0.7 (1.8)	0.7 (1.7)	0.5 (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)

Palo = palonosetron.

Table 2. Current Chemotherapy Regimens

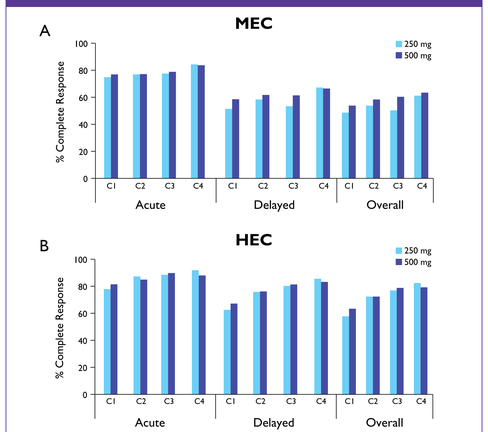
	Hesketh	APF530 250 mg N (%)	APF530 500 mg N (%)	Palo 0.25 mg N (%)
MEC Regimens		N = 214	N = 212	N = 208
Cyclophosphamide/doxorubicin or epirubicin	4	129 (60.2)	117 (55.2)	109 (52.4)
Carboplatin	4	27 (12.6)	21 (9.9)	24 (11.5)
Cyclophosphamide-based combinations excluding AC	4	19 (8.9)	20 (9.4)	24 (11.5)
Irinotecan-based combinations	4	3 (1.4)	10 (4.7)	8 (3.9)
Doxorubicin or epirubicin combinations excluding AC	4	7 (3.3)	7 (3.3)	7 (3.4)
Other regimens	4	1 (0.5)	1 (0.5)	3 (1.4)
Doxorubicin or daunorubicin	3	9 (4.2)	9 (4.3)	11 (5.3)
Other	2, 3	19 (8.9)	27 (12.7)	22 (10.6)
HEC Regimens		N = 229	N = 240	N = 238
Carboplatin + paclitaxel or other combinations	5	114 (49.8)	118 (49.2)	117 (49.2)
Cisplatin-based combinations	5	51 (22.3)	53 (22.1)	53 (22.3)
Cyclophosphamide/doxorubicin or epirubicin combinations	5	47 (20.5)	47 (19.6)	43 (18.1)
Dacarbazine	5	10 (4.4)	10 (4.2)	12 (5.0)
Other	5	2 (0.9)	6 (2.5)	10 (4.2)
Other	2, 3, or 4	5 (2.2)	6 (2.5)	3 (1.3)

AC = doxorubicin-cyclophosphamide; Palo = palonosetron.

CR Rates During the Acute-Onset, Delayed-Onset, and Overall Phases in Cycles 1, 2, 3, and 4 (Figure 2A and B)

- No significant differences were seen in within-cycle CR rates between the 250-mg and 500-mg doses of APF530 during the acute-onset, delayed-onset, and overall phases in cycle 1 to cycle 4 for MEC (**Figure 2A**) and HEC (**Figure 2B**) regimens
- There was a trend toward higher rates of CR with successive cycles in the acute-onset, delayed-onset, and overall periods
- Overall higher CR rates were obtained with HEC regimens compared with MEC regimens

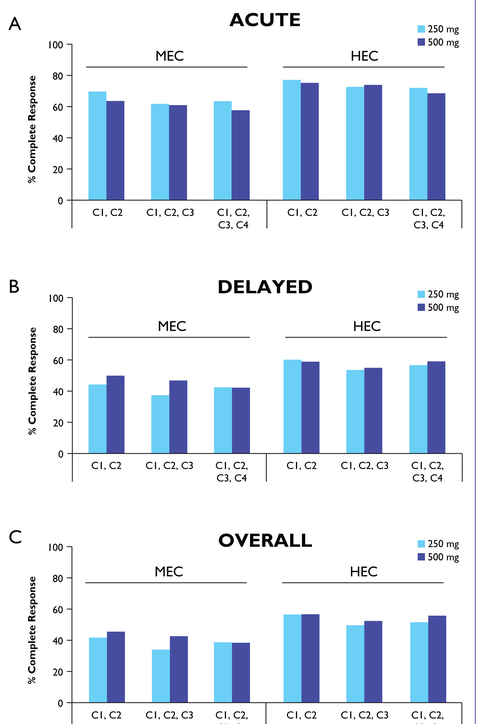
Figure 2. CR Rates for Cycles 1, 2, 3, and 4: MEC Regimens (A) and HEC Regimens (B)



Sustainability of CR Rates Through Cycles 1 and 2; Cycles 1, 2, and 3; and Cycles 1, 2, 3, and 4 (Figure 3A-C)

- Acute-onset CRs (**Figure 3A**) were maintained across all 4 cycles with APF530 250 mg and 500 mg in MEC and HEC regimens
  - CR rates of 63% (250 mg) and 57% (500 mg) with MEC and 72% (250 mg) and 68% (500 mg) with HEC in all 4 cycles
- Among 92 patients who received APF530 500 mg and completed 4 cycles of MEC: 57, 38, and 34 had a CR in the acute-onset, delayed-onset, and overall phases, respectively
- Among 95 patients who received APF530 500 mg and completed 4 cycles of HEC: 65, 55, and 52 had a CR in the acute-onset, delayed-onset, and overall phases, respectively
- The 500-mg dose generally sustained a higher CR in the delayed-onset (**Figure 3B**) and overall (**Figure 3C**) phases for all cycles compared to the 250-mg dose

Figure 3. Sustainability of CR Over Multiple Cycles—Acute-Onset (A), Delayed-Onset (B), and Overall (C)



Sustainability of CR During the Acute-Onset Phase: Comparison of Cycle 1 Response With Response in Cycles 2, 3, and 4

- CRs were sustained from cycle 1 to cycles 2, 3, and 4 for both the 250-mg and 500-mg doses of APF530 in patients receiving MEC or HEC regimens
- For MEC patients receiving APF530 250 mg or 500 mg with an acute-onset CR in cycle 1 and receiving APF530 in cycles 2, 3, and 4, 84% to 90% had a CR in subsequent cycles
- For HEC patients receiving APF530 250 mg or 500 mg with an acute-onset CR in cycle 1 and receiving APF530 in cycles 2, 3, and 4, 91% to 97% had a CR in subsequent cycles
- Similar levels of sustainability of CR were seen during the delayed-onset phase and among patients who received palonosetron in cycle 1
- The proportion of patients with no CR in cycle 1 but CR in later cycles was consistently higher than that of patients with CR in cycle 1 but no CR in later cycles across all treatment groups

CONCLUSIONS

- APF530 500 mg demonstrated non-inferiority to palonosetron in the prevention of CINV in the acute-onset and delayed-onset phases following administration of emetogenic chemotherapy (MEC or HEC)[1]
- In this subset analysis, sustainability of CR rates over multiple cycles, there were no differences between APF530 250 mg and 500 mg in terms of within-cycle CR rates in any phase for patients receiving MEC or HEC regimens
- Acute-onset, delayed-onset, and overall CR rates were sustained across 4 cycles of chemotherapy with MEC and HEC regimens with both APF530 250 mg and 500 mg
- CR rates in cycle 1 were maintained at high rates in cycles 2, 3, and 4
- CR rates tended to improve with subsequent cycles. A consistently higher proportion of patients who did not have a CR in cycle 1 achieved a CR in later cycles, compared to those with a CR in cycle 1 and no CR in later cycles
- APF530 has shown substantial sustained activity in the prevention of CINV in first and subsequent cycles of chemotherapy in patients receiving MEC and HEC regimens

REFERENCES

1. Grous et al. ASCO 2009. Abstract 9627.
2. Gabrail et al. ASCO 2013. Abstract e20518.