

Developments in antiemetic therapy

Newer agents promise more effective control of chemotherapy-induced nausea and vomiting

The recommended preventive treatment for chemotherapy-induced nausea and vomiting (CINV) for regimens with a highly emetogenic risk (which includes both cisplatin-containing and non-cisplatin regimens) consists of a 5-hydroxytryptamine type 3 receptor (5-HT₃) antagonist plus dexamethasone; for regimens with intermediate emetogenic potential, single-agent treatment (eg, with dexamethasone) currently is recommended. For prevention of delayed CINV, which is common after high-dose cisplatin treatment (as well as after carboplatin [Paraplatin], cyclophosphamide,

or doxorubicin treatment), recommendations include use of metoclopramide or a 5-HT₃ antagonist plus dexamethasone for regimens with high or moderate emetogenic risk.

Aprepitant and highly emetogenic chemotherapy

Recent phase III studies have demonstrated that the addition of the novel neurokinin-1 antagonist aprepitant (Emend) to standard antiemetic therapy results in significantly improved prevention of CINV in the setting of highly emetogenic chemotherapy. Neurokinin-1 antagonists inhibit the activity of the regulatory peptide substance P, which is involved in the emesis reflex. In a randomized, double-blind, placebo-controlled multicenter trial in Latin

America,¹ cancer patients scheduled for high-dose cisplatin treatment received either (1) standard therapy with the 5-HT₃ receptor antagonist ondansetron (Zofran) 32 mg intravenously plus dexamethasone 20 mg orally 1 day before treatment with cisplatin and dexamethasone 8 mg twice daily on days 2–4 after cisplatin therapy or (2) oral aprepitant 125 mg, ondansetron 32 mg, and dexamethasone 12 mg on day 1, aprepitant 80 mg and dexamethasone 8 mg once daily on days 2 and 3, and dexamethasone 8 mg on day 4. Complete response was defined as absence of emesis and no use of rescue therapy, as determined from patient diaries.

Among 523 evaluable patients, complete response occurred in 62.7% of the 260 patients in the aprepitant

Summary by Matt Stenger, MS; reviewed by Lee S. Schwartzberg, MD, FACP, The West Clinic, Memphis, TN.

group versus 43.3% of 263 patients in the standard therapy group during the 5 days following treatment with cisplatin ($P < 0.001$) (Figure 1). Complete response rates for day 1 were 82.8% in the aprepitant treatment group versus 68.4% in the standard therapy group and those for days 2–5 were 67.7% versus 46.8% ($P < 0.001$ for both comparisons). Overall adverse event rates were similar in the aprepitant treatment group (72.8%) and the standard therapy group (72.6%).

In a randomized, double-blind, placebo-controlled, multinational trial performed in the United States and 14 other countries,² patients receiving high-dose cisplatin for the first time were treated with the same standard therapy regimen and aprepitant-containing regimen as in the Latin American phase III trial. Among 520 evaluable patients (260 in each group), complete response was observed overall in 72.7% of the aprepitant group versus 52.3% of the standard therapy group, with response rates of 89.2% versus 78.1% on day 1 and 75.4% versus 55.8% on days 2–5 ($P < 0.001$ for

all comparisons) (Figure 1).

Female gender is an established risk factor for chemotherapy-induced nausea/vomiting. It is of interest that the proportions of females and males with a complete response overall were similar in the aprepitant group (77.6% and 69.8%), whereas a complete response was observed in a smaller proportion of females in the standard therapy group (38.8% and 60.5%). Similar proportions of patients in the aprepitant group and standard therapy group had clinical adverse events (65.1% and 61.4%) and adverse laboratory events (14.0% and 13.5%).

Overall, these findings show marked improvements in the prevention of both acute and delayed CINV with the addition of aprepitant to standard antiemetic regimens, with no significant increase in adverse events, in patients receiving chemotherapy associated with high emetogenic risk.

Aprepitant and moderately emetogenic chemotherapy

Data from the first phase III trial examining aprepitant in the setting

of non-cisplatin-based moderately emetogenic chemotherapy were reported at the 2004 Annual Meeting of the American Society of Clinical Oncology.³ In this randomized, double-blind, worldwide trial, breast cancer patients who had not received any prior emetogenic chemotherapy and who were to receive cyclophosphamide with or without doxorubicin or epirubicin were treated with either (1) aprepitant 125 mg, ondansetron 8 mg, and dexamethasone 12 mg prior to chemotherapy, ondansetron 8 mg 8 hours later on day 1, and aprepitant 80 mg/day on days 2 and 3 or (2) standard therapy consisting of ondansetron 8 mg plus dexamethasone 12 mg prior to chemotherapy, ondansetron 8 mg 8 hours later on day 1, and ondansetron 8 mg twice daily on days 2 and 3. Response was determined from patient diaries. Among the 857 evaluable patients, complete response (again, absence of emesis plus no use of rescue therapy) was observed overall in 50.8% of the aprepitant therapy group versus 42.5% of the standard therapy group ($P = 0.015$); absence of

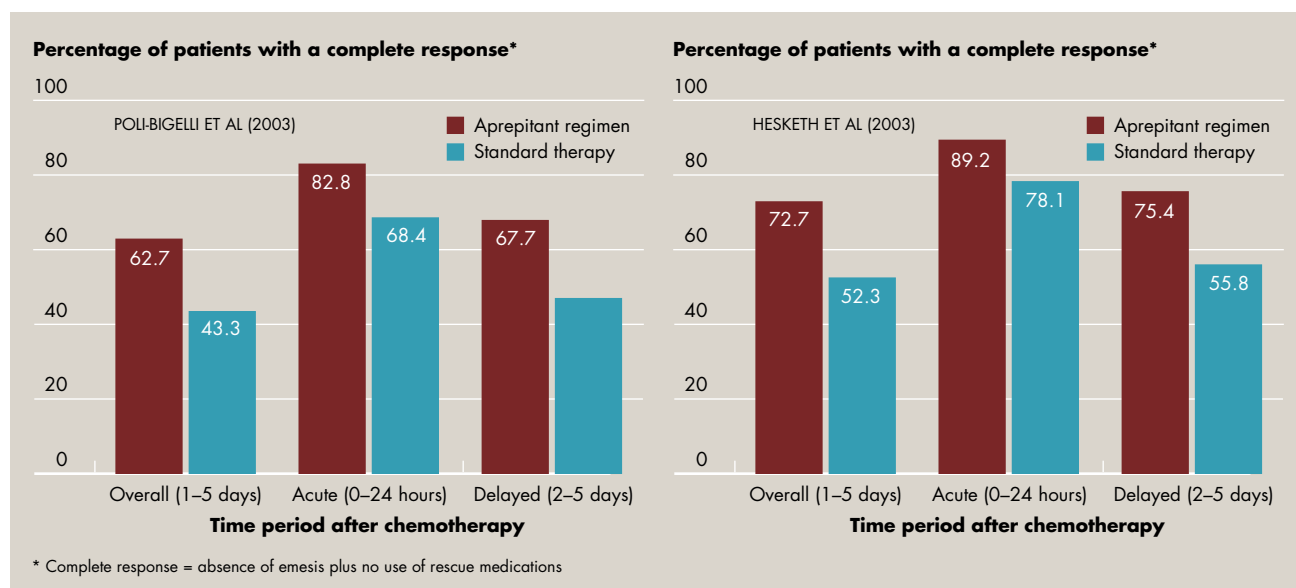


FIGURE 1 Complete response rates during the overall, acute, and delayed period in patients receiving an aprepitant-containing regimen versus standard therapy with ondansetron/dexamethasone in Latin American (left) and multinational (right) phase III trials in cancer patients undergoing treatment with highly emetogenic chemotherapy (high-dose cisplatin). All differences between the aprepitant regimen and standard therapy are statistically significant ($P < 0.001$). Adapted from Poli-Begelli et al¹ (left) and Heskent et al² (right).

TABLE 1

Response rates with palonosetron or dolasetron in patients receiving moderately emetogenic chemotherapy

Time period	Palonosetron 0.25 mg (n = 189)			Palonosetron 0.75 mg (n = 189)			Dolasetron 100 mg (n = 191)
	Response rate (%)	97.5% CI*	P value	Response rate (%)	97.5% CI*	P value	Response rate (%)
Acute (0–24 hours)	63.0	(–1.7, 21.9%)	0.049	57.1	(–7.7, 16.2%)	0.412	52.9
Delayed (24–120 hours)	54.0	(3.4, 27.1%)	0.004	56.6	(6.0, 29.7%)	< 0.001	38.7
Overall (0–120 hours)	46.0	(0.3, 23.7%)	0.021	47.1	(1.3, 24.8%)	0.012	34.0

* Palonosetron minus dolasetron

P values represent adjusted, post hoc comparison of palonosetron vs dolasetron, with a significance level = 0.025. Adapted with permission from Eisenberg et al⁵

emesis was significantly more common in the aprepitant group (75.7% vs 58.7%, $P < 0.001$), whereas similar proportions of patients in both groups reported no use of rescue therapy (58.7% vs 56.2%). Complete responses occurred in 75.7% of the aprepitant treatment group versus 69.0% of the standard therapy group during the acute phase after chemotherapy ($P = 0.034$) and in 55.4% versus 49.1% of patients during the delayed phase. Both antiemetic treatments were reported to be well tolerated.

Taken together, these trials indicate the effectiveness of aprepitant-containing antiemetic therapy in preventing acute and delayed CINV in the settings of both high and moderate emetogenic risk.

Palonosetron and moderately emetogenic chemotherapy

Two recent phase III trials compared the novel second-generation 5-HT₃ receptor antagonist palonosetron, which is characterized by strong receptor binding affinity and a prolonged plasma elimination half-life, with standard 5-HT₃ receptor antagonist therapy in the setting of moderately emetogenic chemotherapy. Although 5-HT₃ receptor antagonists have been shown to be effective in reducing acute CINV, demonstration of effectiveness in reducing delayed emesis has been lacking. In an international trial,⁴ patients were randomized to receive a single intravenous dose of palonosetron 0.25 mg, palonosetron 0.75 mg, or ondansetron 32 mg prior to chemotherapy. A total of 563 patients were evaluable for efficacy. Complete response was observed in 81.0% of the palonosetron 0.25 mg group versus 68.6% of the ondansetron group during the 24 hours after chemotherapy, 74.1% versus 55.1% during days 2–5, and 69.3% versus 50.3% overall ($P < 0.01$ for all comparisons). Complete response rates with the palonosetron 0.75 mg dose were numerically greater but not significantly greater than those observed with ondansetron at all time intervals. All treatments were well tolerated.

In another international trial,⁵ patients were randomized to receive a single intravenous dose of palonosetron 0.25 mg, palonosetron 0.75 mg, or dolasetron 100 mg prior to chemotherapy. Among 569 evaluable patients, complete response rates during the first 24 hours after chemotherapy were 63.0% in the palonosetron 0.25 mg group, 57.1% in the palonosetron 0.75 mg group, and 52.9% in the dolasetron group (no significant differences). Complete response during days 2–5 occurred in 54.0%, 56.6%, and 38.7% of patients, respectively, with rates in both palonosetron groups being significantly greater than that in the dolasetron treatment group (Table 1). The overall complete response rates in both palonosetron treatment groups were also significantly greater than that in the dolasetron treatment group.

These findings indicate that palonosetron therapy is more effective

than standard first-generation 5-HT₃ antagonist treatment in preventing delayed CINV in the setting of moderately emetogenic chemotherapy.

References

1. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting: results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer* 2003;97:3090–3098.
2. Hesketh PJ, Grunberg SM, Gralla RJ, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin. The Aprepitant Protocol 052 Study Group. *J Clin Oncol* 2003;22:4112–4119.
3. Warr DG, Eisenberg P, Hesketh PJ, et al. Effect of aprepitant for the prevention of nausea and vomiting after one cycle of moderately emetogenic chemotherapy: a randomized double-blind trial in 866 patients. Presented at the 40th Annual Meeting of the American Society of Clinical Oncology; June 5–8, 2004; New Orleans, La. Abstract 8007.
4. Gralla R, Lichinitser M, Van der Vegt S, et al. Palonosetron improves prevention of chemotherapy induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. *Ann Oncol* 2003;14:1570–1577.
5. Eisenberg P, Figueroa-Vadillo J, Zamora R, et al. Improved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a pharmacologically novel 5-HT₃ receptor antagonist: results of a phase III, single-dose trial versus dolasetron. *Cancer* 2003;98:2473–2482.

How well do these findings translate into actual community oncology practice? See the sidebar “How we do it: acute antiemetic treatment” on page 82.

How we do it: acute antiemetic treatment

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IN OUR PRACTICE, PALONOSETRON (Aloxi) has become the standard antiemetic agent of choice and is included in our practice guidelines. It is administered as an IV push 30 minutes prior to chemotherapy, followed by dexamethasone infused in a mini-bag over 10 minutes. Due to palonosetron's long half-life, our guidelines call for it to be given no more frequently than every 7 days.

For patients receiving multiple-day moderately to highly emetogenic chemotherapy, we give palonosetron on day 1 and often supplement it with another 5-hydroxytryptamine type 3 (5-HT₃) blocker on day 2. We are aware of other practices that use the reverse sequence; that is, they start with a short half-life 5-HT₃ antagonist daily until the last day of multi-day chemotherapy and then give palonosetron on the last day.

Managing delayed emesis

We first evaluate patients for risk factors that increase the likelihood of delayed emesis. These factors include female gender, age under 50 years, a negative history for alcohol intake, prior motion sickness or morning sickness, and planned highly emetogenic chemotherapy. Patients with two or more risk factors for delayed emesis or who have a history of it are usually prescribed aprepitant (Emend), given as a single 125-mg loading dose orally on day 1 of chemotherapy, followed by aprepitant 80 mg orally on days 2 and 3 and oral dexamethasone 8 mg/day on days 2–4. For breakthrough nausea and vomiting, we initially use prochlorperazine orally or in suppository form and/or thiethylperazine (Torecan). If breakthrough nausea or vomiting occurs even after all this has been done, we add a 5-HT₃ blocker.

Our sense is that the current guidelines go a long way toward reduc-

ing patient discomfort with nausea and vomiting. Emesis, in particular, is prevented with judicious use of acute and delayed antiemetic regimens. Nausea remains something of a problem, particularly for women receiving anthracycline-based chemotherapy regimens.

Cost is a factor

The cost of the newer antiemetics is a big factor in our practice. When available, we like to give an aprepitant starter pack for the first cycle of chemotherapy to see how patients respond to it. Recently, samples have been limited to the first-day, 125-mg dose, so we still have to write a prescription for the doses needed on days 2 and 3. Unfortunately, lots of our patients get "sticker shock" when they go to the pharmacy to pick up their prescription. For patients without a prescription benefit plan, the cost of the newer oral antiemetics, such as conventional 5-HT₃ blockers and aprepitant, can be a burden.

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