The Next Generation of Chemotherapy-Induced Nausea and Vomiting Prevention and Control: A New 5-HT₃ Antagonist Arrives

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Dramatic improvement in the control of chemotherapy-induced nausea and vomiting (CINV) came with the understanding of the role of 5-hydroxytryptamine, subtype 3 (5-HT₃), or serotonin neurotransmitters. In the 1990s, three first-generation serotonin receptor antagonists became available in oral and IV formulations and revolutionized control of emesis, including improved control of emesis experienced by patients receiving chemotherapy that is highly emetogenic. Antiemetic guidelines published beginning in 1997 emphasize the importance of 5-HT₃ receptor antagonists (in combination with a corticosteroid) as a cornerstone in preventing acute nausea and vomiting and as helpful in preventing emesis occurring after the first 24 hours following initiation of highly and moderately emetogenic chemotherapy (MEC) (“American Society of Health-System Pharmacists,” 1999; Gandara et al., 1998; Gralla et al., 1999; Hesketh, Gralla, & Marty, 1998; Kris, Roila, DuBois, & Tonato, 1998; Kris, Roila, De Mulder, & Marty, 1998; “National Comprehensive Cancer Network,” 1997).

The next advance in the quest to control CINV occurred in 2003. In March 2003, the U.S. Food and Drug Administration (FDA) approved the use of aprepitant (Emend®, Merck & Co., Inc., Whitehouse Station, NJ) in combination with other antiemetic agents for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of highly emetogenic chemotherapy (HEC), including high-dose cisplatin. Aprepitant represents a new class of antiemetic agents. It is a potent, selective, central nervous system penetrant, oral non-peptide antagonist of the neurokinin-1 receptor (Hesketh et al., 2003). A trial conducted by Cocquyt et al. (2001) and de Wit et al.’s (2003) phase III study confirmed better emetic control with the addition of aprepitant to standard “dual” therapy for acute emesis (5-HT₃ + dexamethasone) along with increased efficacy in the delayed phase and over multiple cycles. Aprepitant is an oral agent; a 125 mg dose is taken just prior to chemotherapy, and 80 mg is taken on days 2 and 3 (Merck & Co., Inc., 2003; Rittenberg, 2002).

In July 2003, a new second-generation 5-HT₃ receptor antagonist, palonosetron (Aloxi™, MGI Pharma, Bloomington, MN), was approved by the FDA. Palonosetron has greater potency, displays a higher binding affinity to the 5-HT₃ receptor, and has a much longer plasma elimination half-life than other 5-HT₃ receptor antagonists (i.e., approximately 40 hours compared to four to eight hours for the first-generation 5-HT₃ receptor antagonists, including ondansetron hydrochloride [Zofran®], GlaxoSmithKline, Research Triangle Park, NC), dolasetron mesylate [Anzemet®, Aventis, Parsippany, NJ], and granisetron hydrochloride [Kytril®, Roche, Nutley, NJ]) (Aventis, 2003; GlaxoSmithKline, 2003; MGI Pharma, 2003; Roche, 2003). The strong binding affinity for the 5-HT₃ receptors may contribute to the prolonged effect of palonosetron.

Palonosetron is administered 30 minutes before the start of chemotherapy as a single 0.25 mg IV dose infused over 30 seconds. In clinical trials, side effects included headache (9%) and constipation (5%). The drug should be administered cautiously to patients with a history of prolonged cardiac conduction intervals, similar to other 5-HT₃ agents (MGI Pharma, 2003).

The phase III clinical evaluation of palonosetron was conducted in multiple centers in North America and Europe. The primary efficacy endpoint in these trials was complete response, defined as no vomiting and no need for rescue medication in the 24 hours after chemotherapy initiation. Secondary endpoints included complete response...
FIGURE 1. COMPLETE RESPONSE: POOLED MODERATELY EMETOGENIC CHEMOTHERAPY TRIALS
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on days 2–5, safety, tolerability, and quality of life. Three studies comprised this program, two involving patients receiving MEC and one involving HEC. Patients in all three trials were randomized to receive one of two doses of palonosetron (0.25 mg or 0.75 mg) or a comparator 5-HT<sub>3</sub> receptor antagonist (ondansetron 32 mg in the HEC study and in one MEC trial, dolasetron 100 mg in the other MEC trial). All drugs were given as a single IV dose 30 minutes prior to the start of chemotherapy. A prophylactic corticosteroid was permitted in the HEC trial at the investigator’s discretion; this involved approximately 67% of patients entered in the trial.

In all three studies, palonosetron at both doses showed better control of emesis than the comparator 5-HT<sub>3</sub> receptor antagonist for acute and delayed emesis (see Figures 1 and 2). Additionally, patients receiving palonosetron had a longer length of time before their first emetic event (if they had one), superior control of nausea, and higher quality-of-life scores (Aapro, Bertoli, Lordion, Bogdanova, & Macciocchi, 2003; Eisenberg et al., 2003; Gralla et al., 2003).

As long as even one patient experiences vomiting or nausea after receiving chemotherapy, the search must continue for new agents, new combinations of existing agents, and new approaches to prevent this troublesome side effect. Although nirvana has not yet arrived, the addition of aprepitant and palonosetron is an exciting step forward in the goal of complete emetic control. Nurses are in a key position to learn about new agents and transfer what they learn to improve practice and, ultimately, patient outcomes.

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References


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