The Next Generation of Chemotherapy-Induced Nausea and Vomiting Prevention and Control: A New 5-HT_3 Antagonist Arrives

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First-generation serotonin receptor antagonists greatly improved the control of chemotherapy-induced nausea and vomiting (CINV) during the 1990s. A new class of agents, neurokinin-1 receptor antagonists, was introduced in March 2003 and produced even greater control of CINV when used in combination with a serotonin receptor antagonist and a corticosteroid. In July 2003, palonosetron, a new second-generation serotonin receptor antagonist that has greater potency and a longer half-life than first-generation serotonin receptor antagonists, was introduced. This clinical update reviews studies that were conducted to evaluate these new agents.

Key Words: nausea, vomiting, antiemetics

Dramatic improvement in the control of chemotherapy-induced nausea and vomiting (CINV) came with the understanding of the role of 5-hydroxytryptamine, sub-type 3 (5-HT_3), 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-HT_3 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, du Bois, & 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 nonpeptide 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-HT_3 + 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-HT_3 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-HT_3 receptor, and has a much longer plasma elimination half-life than other 5-HT_3 receptor antagonists (i.e., approximately 40 hours compared to four to eight hours for the first-generation 5-HT_3 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-HT_3 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-HT_3 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

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