A New Class of Antiemetic Agents on the Horizon

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Until recently, attempts to ameliorate chemotherapy-induced nausea and vomiting (CINV) focused on blocking dopamine receptors located in the vomiting center in the brain stem. The vomiting center receives impulses from the chemoreceptor trigger zone after administration of emetogenic antineoplastic agents, such as cisplatin. Dramatic improvement in the control of CINV occurred during the 1990s with the advent of the serotonin receptor antagonists that target sites of emetic action in the gut and brain. Additionally, studies have shown even better control when a corticosteroid is included with the antiemetic regimen (Gralla et al., 1999; Herrstedt, Aapro, Smyth, & Del Favero, 1998). Although control of acute phase CINV has improved, the agents that currently are available are not as effective in the delayed phase of CINV (days 2–5).

A new class of agents, the neurokinin-1 (NK-1) receptor antagonists (RAs), is being studied. Substance P, one of the four types of peptides called tachykinins, acts through the NK-1 receptor pathways involved in nausea and vomiting (N&V) and is thought to be implicated in the pathophysiology of emesis. In preclinical studies, NK-1 receptor antagonists inhibited emesis induced by cytotoxic chemotherapy. Clinical studies of the oral NK-1 RAs suggest that they improve control of acute phase CINV when used with standard antiemetic regimens (a serotonin RA + dexamethasone). They also appear to be promising agents in the control of CINV in the delayed phase when used alone or with dexamethasone (Campos et al., 2001; Navari et al., 1999). Additionally, patients who received monotherapy with an NK-1 RA alone prior to cisplatin had better delayed phase CINV control than those who received a serotonin RA (Coquyt et al., 2001). Phase III studies of an NK-1 RA, aprepitant (MK-869) (Merck & Co., Inc., West Point, PA), are ongoing. Results of three published phase II studies concerning this agent follow.

Navari et al. (1999) conducted a randomized, double-blind, three-arm study in which all 159 patients received standard acute CINV prophylaxis (in this case, granisetron and dexamethasone) prior to administration of cisplatin. Groups 1 and 2 also received the NK-1 RA; group 3 received a placebo. In the delayed phase, only group 1 received the NK-1 RA on days 2–5; the other two groups received a placebo. Complete response rates during the acute phase, defined as “no emesis and no rescue antiemetic use in a daily diary. Onset of emesis was determined to be within one hour of the dose,” were 77%, 52%, and 57%, respectively (p < 0.004, groups 1 and 2 combined versus group 3). Complete response rates observed during the delayed CINV phase were 58%, 8%, and 16%, respectively (p < 0.001, groups 1 and 2 versus group 3).

To determine if an NK-1 RA was effective as monotherapy, Coquyt et al. (2001) conducted a randomized, double-blind study (N = 53). Patients in groups 1 and 2 received the NK-1 RA in two different doses. Group 3 received 32 mg of ondansetron prior to cisplatin therapy. In both NK-1 RA groups, acute phase emesis control was achieved in only 37% of patients, whereas 52% of patients treated with ondansetron experienced no vomiting. However, over the next six days, 72% of those who received only a single dose of the NK-1 RA reported no emesis, versus 7% of those patients who received only ondansetron (p < 0.005). Given the poor performance of NK-1 in preventing acute emesis, control of delayed emesis in these groups was an unexpected finding in this study. The researchers concluded that different underlying mechanisms of acute and delayed emesis may exist. Also, patients receiving the NK-1 RA had less delayed nausea in addition to experiencing less delayed vomiting.

A large (N = 351), four-arm, antiemetic study was conducted by Campos et al. (2001). Table 1 illustrates the study design. Triple antiemetic therapy administered before cisplatin chemotherapy on day 1 (received by group 2) provided the best control of acute phase emesis. The addition of the NK-1 RA enhanced emesis control by 23% (80% to 57%, groups 1 and 2, respectively). During the delayed period, optimum control of emesis was achieved in patients who received NK-869 (groups 2, 3, and 4). In the acute period, triple antiemetic therapy significantly reduced nausea when compared to standard therapy. Over the entire treatment period, triple therapy on day 1 followed by daily MK-869 resulted in superior nausea control (Campos et al.).

Nausea has a measurable negative impact on patients’ self-reported ability to enjoy meals, maintain daily functions, and avoid personal hardships (Martin, Cai, Pearson, Horgan, Wittreich, et al., 2001). As part of the study conducted by Campos et al. (2001), 228 cisplatin-naïve patients recorded emetic events, nausea ratings, and rescue antiemetic use in a daily diary. On