

ADVANCES IN SUPPORTIVE CARE

Current Developments in Side Effect Management, Palliative Care, and Quality of Life

Update on the Management of Chemotherapy-related Nausea and Vomiting: An Emphasis on the New Class of Agents—Neurokinin-1 Receptor Antagonists

Richard Gralla, MD
President, New York Lung Cancer Alliance

H&O What is the current standard of care for chemotherapy-related nausea and vomiting?

RG Until recently, the standard of care for preventing nausea and vomiting in patients receiving highly and moderately emetic chemotherapy was a combination of a serotonin antagonist and a corticosteroid. In 2003, the first drug in a new class of agents was approved by the US Food and Drug Administration (FDA). This has changed the standard approach, as is seen in both the new Multinational Association of Supportive Care in Cancer (MASCC) and American Society of Clinical Oncology (ASCO) antiemetic guidelines in highly emetic settings and in some moderately emetic presentations.

The new class of agents, neurokinin type 1 (NK1) receptor antagonists, were found to be additive to the combination of a 5HT₃ antagonist plus a corticosteroid. The only currently available agent of this class is aprepitant (Emend, Merck). It is now advised that aprepitant (one capsule daily for 3 days) be added to a regimen of a 5HT₃ antagonist plus a corticosteroid in highly emetic settings and in patients receiving combination chemotherapy containing an anthracycline plus cyclophosphamide.

Prevention, by using the most effective appropriate antiemetics with the initial chemotherapy and with each subsequent cycle, remains the best strategy in antiemetic care. This approach reduces emesis and prevents the onset of conditioned or anticipatory emesis. In determining which regimen is appropriate for individual patients, the single greatest risk factor for chemotherapy-related emesis is the type of chemotherapy being given. Other risk factors (such as gender, age, and past alcohol intake

history) are all important, but they do not determine the recommended antiemetic regimen. The guidelines for chemotherapeutic agents generally list four categories of risk if useful antiemetics are not given: high (nearly all patients at risk), moderate (the risk associated with a large heterogeneous group of chemotherapy drugs, varying from a 30% to 90% chance of emesis), low (10–30% risk, generally requiring only a single antiemetic agent), and minimal (<10% risk, with no antiemetic agent usually advised). A list of the agents corresponding with these risk categories can be found on the MASCC Web site (www.mascc.org).

H&O How do the NK1 antagonists work?

RG The NK1 receptor antagonists block the action of substance P on the receptor. Substance P, an 11-amino-acid neuroregulatory protein, is the natural ligand for the NK1 receptor. In animal models, NK1 receptor antagonists have the broadest spectrum of antiemetic activity of any available agents. Substance P occurs naturally in humans and is released in response to a variety of stimuli, including as a neurotransmitter in various emetic conditions.

H&O Has aprepitant been compared directly to the 5HT₃ antagonists?

RG Small clinical trials have found that aprepitant has activity similar to the 5HT₃ antagonists against acute emesis when given as a single agent in patients receiving chemotherapy. However, greater activity is seen in the delayed emesis period when aprepitant is given on the day of chemotherapy. The greatest benefit of aprepitant is in adding it to a 5HT₃ antagonist and a corticosteroid, which leads to significantly better control of both acute and delayed emesis; thus, aprepitant is an additive agent and not a replacement for either of the older drugs. The effect in delayed emesis is particularly strong when aprepitant therapy is continued on days 2 and 3.

H&O Is the three-drug combination appropriate for all types of chemotherapy?

RG Aprepitant regimens were initially approved for highly emetic chemotherapy, specifically for patients receiving cisplatin. However, a subsequent large random-

ized study found the three-drug combination to have a significant benefit in preventing nausea and vomiting in patients receiving anthracyclines plus cyclophosphamide for breast cancer. In that combination, chemotherapy for many malignancies uses these agents. The guideline groups addressed regimens containing anthracyclines and cyclophosphamide separately and recommended the addition of aprepitant.

Interestingly, a recent study by Herrstedt and colleagues demonstrated that the three-drug combination compared with the prior two-drug combination is particularly beneficial over subsequent cycles of treatment with anthracycline plus cyclophosphamide chemotherapy. In this study, patients who were being treated for breast cancer were randomized to receive antiemetic therapy with ondansetron plus dexamethasone with or without aprepitant. By the fourth cycle of therapy, nearly two thirds of the patients receiving the three-drug combination had remained free of vomiting throughout their chemotherapy experience, whereas fewer than 40% of the women receiving the two-drug combination had the same level of control.

H&O What are other recent findings regarding the NK1 receptor antagonists?

RG For reasons that are unclear, emesis has consistently been more difficult to control in women than in men receiving serotonin antagonist–based antiemetics. Surprisingly, though the benefit of adding aprepitant to the standard two-drug combination among men treated with cisplatin was certainly noteworthy, the benefit among women was even greater. For the first time in large randomized trials, the control among both men and women was equal. This same pattern was seen in delayed emesis as well.

In summary, the addition of aprepitant to the combination of a 5HT₃ receptor antagonist plus a corticosteroid leads to better control of nausea and vomiting associated with moderate (anthracycline + cyclophosphamide) and highly emetic chemotherapy, better control over multiple cycles, especially better control among women, and better control for both acute and delayed emesis.

H&O Are other NK1 antagonists being developed?

RG Yes, several investigative agents in this class are being evaluated in various clinical trial settings. An intravenous form of aprepitant is now under regulatory review by the FDA. Several pharmaceutical companies have NK1 antagonists currently about to enter or in clinical trials. The most advanced of these agents is casopitant (GlaxoSmithKline). Encouraging antiemetic activity and

interesting dose-comparison data were presented at the recent ASCO annual meeting in large randomized phase II trials in both highly and moderately emetic settings. This company also has another NK1 antagonist (vestipitant), which is likely being developed in other emetic circumstances. The NK1 antagonist netupitant (Helsinn) also continues in clinical trials, and SCH-619734 (Schering-Plough) is in early clinical development.

H&O Are the NK1 antagonists associated with any noteworthy side effects?

RG To date, the side effects associated with the NK1 receptor antagonists appear to be very minor, and it is difficult to identify specific side effects. Patients appear to experience a greater incidence of hiccups with the three-drug combination compared with the prior two-drug combination, but serious or clearly identifiable side effects have not been observed.

Because aprepitant is metabolized by the cytochrome P450 system CYP3A4, it has the potential to interact with many different agents, as this is a common metabolic pathway. However, a recent pharmacokinetic study in which patients received docetaxel (which is metabolized by CYP3A4), with or without aprepitant, showed no change in the metabolism of docetaxel among patients receiving aprepitant. It may be that the effect of aprepitant would be more relevant with oral chemotherapy than with intravenous administration.

Suggested Reading

Apornwirat W, Albert I, Hansen V, et al. Multicenter, randomized, double-blind, ondansetron controlled, dose-ranging parallel group trial of the neurokinin-1 receptor antagonist casopitant mesylate for chemotherapy-induced nausea/vomiting in patients receiving moderately emetogenic chemotherapy [abstract]. *J Clin Oncol*. 2006;24:471s.

Gralla RJ, de Wit R, Herrstedt J, et al. Antiemetic efficacy of the neurokinin-1 antagonist aprepitant, plus a 5HT₃ antagonist and a corticosteroid in patients receiving anthracyclines or cyclophosphamide in addition to high-dose cisplatin. *Cancer*. 2005;104:864-868.

Herrstedt J, Muss HB, Warr DG, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and emesis over multiple cycles of moderately emetogenic chemotherapy. *Cancer*. 2005;104:1548-1555.

Hesketh PJ, Grunberg SM, Herrstedt J, et al. Combined data from two phase III trials of the NK(1) antagonist aprepitant plus a 5HT(3) antagonist and a corticosteroid for prevention of chemotherapy-induced nausea and vomiting: effect of gender on treatment response. *Support Care Cancer*. 2006;14:354-360.

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;21:4112-4119.

Rolski J, Ramlau R, Dediou M, et al. Randomized phase II trial of the neurokinin-1 receptor antagonist casopitant mesylate with ondansetron / dexamethasone for chemotherapy-induced nausea/vomiting in patients receiving highly emetogenic chemotherapy [abstract]. *J Clin Oncol*. 2006;24:471s.