Progress in the Control of Chemotherapy-Induced Emesis: New Agents and New Studies

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The marked improvements in the prevention of emesis have become a standard of practice over the last few decades. Carefully designed and conducted studies established type 3 serotonin antagonists with corticosteroids as highly effective in most settings in which emesis was likely. Practice patterns have gradually conformed in most instances to reflect the results of these studies to the point that antiemetics are among the most commonly used drugs in medical oncology.

Background

Risk factors for emesis have been identified and utilized by guideline groups. The most important risk factor is the type of chemotherapy (such as highly or moderately emetic), while other independent factors indicating a greater risk include younger age, female gender, and a history of little consumption of alcohol. Information outlining these findings and the classification of specific antiemetic agents by risk group are easily available at a variety of sources (including www.mascc.org).

Careful review of recent progress disclosed two major findings. First, antiemetic regimens had become easy to integrate into daily oncologic practice with markedly improved efficacy when modern agents are given. The second finding was that oncologists overestimated the rate of control. In more difficult settings, such as in patients receiving frequently used chemotherapy regimens for breast or lung cancer, acute or delayed emesis still occurred in nearly half of patients. These observations were particularly valuable as new agents and new classes of antiemetics were under study.

New Agents in a New Class: Neurokinin-1 Antagonists

Over the last five years agents of the neurokinin-1 (NK₁) antagonist class have been introduced. Two agents are now commercially available: aprepitant and its intravenous prodrug fosaprepitant. Several other agents in this class are under investigation at present: casopitant has now completed phase III trials with both oral and intravenous forms.^{1,2}

Six large, randomized double-blind studies have been reported with either aprepitant or casopitant testing whether these agents add to the combination of a serotonin antagonist plus dexamethasone. Four of these studies were performed in patients receiving cisplatin^{1,3,4,5} and two in patients receiving anthracycline plus cyclophosphamide-based chemotherapy.^{2,6} In all instances, the control of emesis was significantly better in the groups of patients assigned to the NK₁ antagonist

containing regimens. This occurred in both acute and delayed emesis, as well as in the emetic control over the 5 days following chemotherapy. The magnitude of benefit generally ranged from a 10% to 20% absolute benefit (or a relative benefit of 20% to 50% in most instances). This degree of benefit exceeds that previously established by expert panels as the impact that should lead to a change in guidelines. As such, all major guideline groups (including American Society of Clinical Oncology, European Society for Medical Oncology, Multinational Association of Supportive Care in Cancer, National Comprehensive Cancer Network) have recommended the addition of NK₁ antagonists in patients receiving cisplatin or anthracycline-cyclophosphamide regimens specifically, and with other highly emetic or moderately emetic chemotherapy in several additional settings.

Analyses following the completion of these studies indicated some unexpected findings. Nearly all large trials with serotonin antagonists found that the control of emesis in men is greater than that in women. Importantly, in the aprepitant trials in patients receiving cisplatin, emetic control in both genders is improved and is equal when this NK₁ antagonist is added.⁷ In most antiemetic studies the control of vomiting exceeds that of nausea, and this too occurs with the NK₁ antagonists. This raised the question of whether this agent class actually affects nausea. A recent meta-analysis found that while the effect on nausea is less, at least in the cisplatin studies, nausea is significantly decreased with the addition of this class of antiemetic.⁸

In 2008, an intravenous form of aprepitant, its prodrug fosaprepitant, was approved for clinical use. This approval was based on the similar pharmacokinetic profile of fosaprepitant when compared with oral aprepitant.⁹ To date, clinical efficacy studies with fosaprepitant have not been published. The presentations of the results of trials with oral and intravenous forms of casopitant have demonstrated similar beneficial findings.^{1,2}

It has been difficult to identify specific NK₁ antagonist adverse effects. Both aprepitant and casopitant are metabolized via the CYP 3A4 pathway. As such they have the potential for interactions with many drugs metabolized via this route, including several chemotherapeutic agents. Published trials investigating the impact of aprepitant on the pharmacokinetics of intravenous docetaxel and with intravenous vinorelbine showed essentially no interaction.^{10,11}

Such trials are helpful in indicating that this antiemetic can be used safely with these and other similarly metabolized chemotherapeutic agents without dose adjustment. It is hypothesized that interaction would likely be greater with oral chemotherapy rather than with intravenous.

Dosing and scheduling of NK₁ antagonists have been largely based on a combination of positron emission tomography scanning results indicating 90% or greater occupancy of brain NK₁ receptors and on safety in clinical trials.¹² With the few adverse effects observed, a logical question is whether the dose or schedule of these agents is optimal for efficacy and convenience. The location and degree of receptor occupancy is based on animal observations that are for the most part hypotheses without clinical validation. Studies with casopitant imply that a single dose of that agent may be as useful as dosing over several days.^{1,2} Such a schedule would clearly make regimens containing an NK₁ antagonist maximally convenient.

NK₁ antagonists are a major step forward in the prevention of emesis. They are underutilized at present. Increasing their use as part of antiemetic regimens in guideline-indicated settings could enhance the control of emesis and lead to improvements in quality of life.

New Agents in an Established Class: Serotonin Antagonists

The selective serotonin receptor antagonists are the most commonly used modern antiemetics in chemotherapy-induced emesis. Agents such as ondansetron, granisetron, dolasetron, and tropisetron have been used for over 15 years in most countries. Recently, some of these agents have become generically available, making their use highly economical. Trials have indicated that NK₁ antagonists are additive to serotonin antagonist–corticosteroid combinations, and do not replace these drugs.

More recently introduced was the serotonin antagonist palonosetron. Palonosetron differs from other agents in this class by its longer half-life and greater binding to the type 3 serotonin antagonist receptor. While these are welcome characteristics, the issue still persisted as to whether these factors would translate into improved antiemetic control. Large single-agent studies in patients receiving chemotherapy of moderately emetic potential indicated better control when compared with older serotonin antagonists.^{13,14} These results were seen as most interesting by guideline groups; however, some doubts continued. These doubts were centered on the fact that the guideline groups recommended steroid-containing combinations rather than single-agent antiemetics in these settings.

A study recently published in *Lancet Oncology* largely addressed these concerns.¹⁵ This trial from Japan enlisted over 1,100 patients and randomly assigned patients to

treatment arms of either dexamethasone plus granisetron or dexamethasone plus palonosetron. Patients received chemotherapy with cisplatin or with an anthracycline-cyclophosphamide regimen. The primary end point was the complete control of emesis without the use of rescue medications over a 5-day period encompassing acute and delayed emesis. A highly significant difference was found, favoring the palonosetron combination. This result was found for all patients and for the subsets receiving either type of chemotherapy regimen. The Japanese investigators used higher doses of granisetron than those approved in North America (3 mg *v* 1 mg intravenously), and higher doses of palonosetron than those approved in any other country (0.75 mg *v* 0.25 mg). Prior large randomized studies comparing 0.25 mg of palonosetron with 0.75 mg had shown similar antiemetic efficacy with either dose. Two recent meta-analyses using different methodologies tested these two doses of palonosetron; both found no difference between the 0.25 mg and the 0.75 doses.^{16,17} In that the magnitude of benefit with the use of palonosetron exceeded a 10% absolute benefit in the Japanese trial, it is likely that the antiemetic guideline groups will find this trial to be compelling.

Summarizing the Results of the Role of the Addition of Corticosteroids

Multiple trials published in the 1980s and 1990s showed the highly significant benefit of the addition of corticosteroids when added to high-dose metoclopramide and to selective serotonin antagonists. These benefits were seen in both acute and delayed emesis.

Later studies outlined proper doses of corticosteroids. While it is not known if various corticosteroids have differing efficacy, most trials have used dexamethasone. In patients receiving cisplatin, a large study indicated significant benefits in controlling both nausea and vomiting with a single dose of dexamethasone at 20 mg.¹⁸ The same group also found that a single dose of 8 mg in patients receiving moderately emetic chemotherapy was as effective as 8 mg given three times a day or 24 mg given as a single dose.¹⁹

The short term use of corticosteroids (2 to 4 days) has predictable and well-described adverse effects. Specifically, heartburn and insomnia are frequently observed with dexamethasone. Both of these adverse effects are easily managed with simple over-the-counter medications and patient education. Patient education is particularly important for diabetic patients, who are likely to experience a brief increase in serum glucose with dexamethasone use. For most diabetic patients, improved emetic control with the use of dexamethasone and the adjustment of hypoglycemic agents is a reasonable strategy. This is especially noteworthy in that emesis with chemotherapy in diabetics runs additional risks associated with decreased food and fluid intake. Careful counseling for the diabetic patient can allow the use of the most effective antiemetic regimens.

Antiemetics in Delayed Emesis

A study in 2004 found surprising results when investigating the perception of physicians and nurses concerning the control of emesis when compared with what actually happened to their patients. The health care professionals accurately estimated the control rate of acute emesis, but greatly underrated the incidence of delayed nausea and vomiting. This survey illustrated why emesis may be undertreated and underestimated.²⁰

All guidelines recommend preventive treatment addressing delayed emesis in patients receiving chemotherapy of moderate and of high risk. Corticosteroids for 2 to 3 days are key agents. When dexamethasone is used, adding older serotonin antagonists gives only a minor additional benefit (< 3% in a meta-analysis). In the *Lancet Oncology* palonosetron study, a greater than 10% benefit was reported with the newer serotonin antagonist plus dexamethasone when compared with a combination using granisetron.¹⁵ Randomized studies adding NK₁ antagonists have consistently shown clear antiemetic benefit; the contribution to the control of delayed emesis exceeds the benefit in acute emesis. Here again, NK₁ antagonists offer a great opportunity to advance control in many patients.

Combination Regimens

For the best possible prevention of emesis in patients receiving chemotherapy of moderate or high risk, combinations of antiemetics are needed. Corticosteroids with serotonin antagonists have formed the basis of antiemetic regimens over nearly two decades. In the last few years, well-conducted studies have consistently demonstrated that three-drug regimens adding NK₁ antagonists provide the best control and are recommended by all guideline groups in these clinical settings.

A recently published small trial challenges current guidelines.²³ In this phase II study of 41 patients receiving their initial chemotherapy with anthracyclines plus cyclophosphamide, a three-agent antiemetic regimen was used as a single dose for both acute and delayed emesis (oral aprepitant plus intravenous palonosetron plus oral dexamethasone). In addition to using just a single

administration of these agents, the dose of aprepitant was markedly increased. Ninety-five percent of patients were free of emesis over a 5-day period, and no patient had acute emesis. Nausea was controlled in two thirds of patients, and in this preliminary trial there was no indication of an increase in adverse effects. These results indicate that studies exploring the dosing and scheduling of NK₁ antagonists are warranted, and large phase III trials are needed to see if such higher dose combinations should become standard treatment.

Emesis and Nausea

As the prevention of emesis has improved, it has been clear that the control of vomiting continues to be greater than the control of nausea. Even with the best antiemetic regimens, 33% to 50% of patients may still experience nausea. Recent analyses have shown that nausea can be accurately assessed when patients complete commonly used visual analog and categorical scales (as found with the MASCC antiemesis tool [MAT]).^{21,22} It is possible that more neurotransmitter receptors are involved with nausea than with vomiting; studies specifically addressing nausea should be emphasized.

Conclusion

New agents and new studies have demonstrated benefit in improving antiemetic therapy. Incorporating evidence-based guideline recommendations and appropriate emesis assessments are key components to achieving the best practice. Several emetic settings such as multiple day chemotherapy and nausea require further study to improve on current rates of control. (More information on antiemetics is available in related article on page 134.)

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