Integrating Aprepitant and Palonosetron Into Clinical Practice: A Role for the New Antiemetics

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Chemotherapy-induced nausea and vomiting (CINV) can be devastating for patients with cancer; in fact, patients in several studies consistently have rated CINV as among the most common and debilitating symptoms of treatment (Coates et al., 1983; Roscoe, Morrow, Hickok, & Stern, 2000). These dismal patient ratings have persisted despite the addition of serotonin antagonists since the early 1990s (Gralla, 2002). Prior to the addition of the first serotonin antagonist, ondansetron, CINV management focused primarily on dopamine antagonist agents. Although ondansetron and subsequent serotonin antagonists played a significant role in decreasing the incidence of CINV, patients still ranked these symptoms as highly distressing. In one study of patients receiving chemotherapy and serotonin antagonists, the antiemetics led to a reduction in vomiting, yet the duration of post-treatment nausea increased (Roscoe et al.). Although management of CINV has improved, these symptoms still are a considerable challenge for many patients undergoing therapy (Kris, 2003).

The inadequate control of CINV can increase healthcare costs because of the need for hydration, repletion of electrolytes lost during vomiting, or hospital admission (Hibbe-Heffinger et al., 2004; Stewart, Dahrouge, Coyle, & Evans, 1999). The addition of the serotonin antagonists triggered worries about the potential for increased medication expenditure for hospital formulary budgets; however, improved control of CINV can lead to decreased healthcare costs (Stewart et al.). The inclusion of the most recently released antiemetics, aprepitant and palonosetron, likely will raise concern about increased antiemetic costs. The appropriate use of these agents, along with practice guidelines, will help to define their role in the armamentarium of antiemetic therapy.

Pathophysiology of Emesis

CINV can be classified as anticipatory, acute, or delayed. Treatment of these separate conditions may differ; therefore, poor control of acute nausea and vomiting plays an important role in ultimate control of delayed CINV (Dibble, Israel, Nussey, Casey, & Luce, 2003). Many different neurotransmitters have been implicated in CINV, including dopamine, acetylcholine, histamine, serotonin, and most recently substance P and the neurokinin-1 (NK-1) receptor antagonists (Hogan & Grant, 1997; Navari, 2003). Because of this, a combination approach in antiemetic therapy typically is used.

Anticipatory Emesis

Anticipatory nausea and vomiting occur prior to the...
administration of chemotherapy and most likely are stimulated by the limbic system of the brain where memories reside (Rocha do Amaral & Martins de Oliveira, 2004). When these symptoms have not been controlled adequately in past visits, nausea and vomiting may occur when patients anticipate the prior negative episode, which is believed to be the result of classic conditioning (Eckert, 2001). Anticipatory nausea and vomiting are difficult to treat; therefore, maximizing control of emesis at the beginning of therapy can lead to a reduction in its occurrence (Hesketh, 1999).

**Acute Emesis**

Acute nausea and vomiting generally occur within 24 hours of chemotherapy administration. Some researchers have further classified the acute period of nausea and vomiting as acute (within 12 hours) and late acute (12–24 hours) (Schnell, 2003). If patients do not receive adequate antiemetic coverage during the period of acute emesis, their risk for delayed nausea and vomiting increases (Dibble et al., 2003; Schnell).

**Delayed Emesis**

The phenomenon of delayed nausea and vomiting has become more prominent in the literature recently. Aprepitant and palonosetron have roles in the treatment of delayed nausea and vomiting, which are difficult to control, representing an important improvement for patients.

Delayed nausea and vomiting, generally occurring 24 hours or more after chemotherapy administration, are experienced by 40%–50% of all patients receiving emetogenic agents (Dranitsaris et al., 2001). Cisplatin has been identified frequently as a major cause of delayed CINV, but studies have found agents such as cyclophosphamide and carboplatin increase the risk for delayed CINV (Bubalo, Bierman, & Yates, 2004; Doherty, 1999). Cisplatin has a distinct curve in the measurement of CINV, with a primary peak on day 1 for acute nausea and vomiting and a second peak occurring 48–72 hours later in the delayed phase of CINV, necessitating coverage with antiemetic agents for both acute and delayed emesis (Hesketh, 1996). Evidence suggests that cisplatin-induced emesis involves dissimilar pathophysiologic mechanisms with a difference in the time course of emesis blockade (Hesketh, Van Belle, et al., 2003). The early period (8–10 hours after cisplatin administration) seems to be driven primarily by serotonin receptors, with substance P becoming more dominant in the later period. These differences account for the combined approaches in current antiemetic strategies (Hesketh, Van Belle, et al.).

Control of delayed nausea and vomiting can be problematic, and these symptoms are not always recognized in the clinical setting. Recently, Grunberg et al. (2004) studied healthcare providers’ accuracy in assessing acute and delayed nausea and vomiting in patients with breast cancer. These projections were compared to patients’ diary entries about the occurrences of nausea and vomiting; according to the results, health care providers consistently under-recognized the incidence of nausea and vomiting in this group (Grunberg et al.).

Dibble et al. (2003) examined the incidence of delayed CINV in 303 patients with breast cancer who mostly received doxorubicin and cyclophosphamide. Despite standard antiemetic therapy, including serotonin antagonists, 76% of the patients experienced delayed nausea and vomiting as measured by their diary entries (Dibble et al.).

**Breakthrough Emesis**

Defined as nausea and vomiting that occur despite the use of preventive therapy with standard antiemetics, breakthrough CINV, an uncontrolled emesis, can be a significant complication in patients with cancer and often requires additional antiemetics to attempt control of the symptom. Assessing the incidence of this breakthrough CINV is difficult because few studies have rigorously analyzed this phenomenon (Aapro, Perugia Consensus, & Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer [MASCC], 2002).

**Refractory Emesis**

Persistent or refractory emesis is an uncontrolled emesis that occurs in subsequent cycles after the failure of previous antiemetic therapy. After patterns of emesis are established, patients with this CINV can be difficult to treat (Schnell, 2003). Pharmacologic approaches may require increasing the dose of the selected antiemetic to the maximum accepted level, and the treatment regimen should be reviewed thoroughly to evaluate patient risk factors as well as chemotherapy and other medication use (Marek, 2003).

**Risk Factors**

A number of factors should be considered when deciding on an antiemetic approach for individual patients. An accurate patient history obtained prior to chemotherapy administration will help to determine the need for more aggressive antiemetic therapy.

Patients with a history of motion sickness, low alcohol intake, or anxiety or who are younger than 50 years may need more thorough treatment to prevent CINV (Doherty, 1999). Female patients who experienced nausea and vomiting while pregnant are also at risk. Patients who had increased nausea and vomiting with previous chemotherapy need aggressive antiemetic therapy; in addition, patients with a large tumor burden are at risk for increased CINV (Doherty).

Patients’ gender affects the incidence of emetic episodes; women are more likely to report severe emesis that historically is more difficult to control with current antiemetics (Roila et al., 1987). The NK-1 receptor antagonists have shown significant activity in this group of patients (Olver, 2004).

**Antiemetic Therapy: 1960s–2002**

Neurotransmitters play a major role as targets for antiemetic agents (Markman, 2002). Different medications in the treatment of CINV have various mechanisms of action; a combination approach typically is superior to single-agent therapy. These medication classes also have different side effects.

**Dopamine Antagonists**

Medications in the dopamine antagonist class have been the mainstay of antiemetic therapy in patients with cancer since the 1960s (Goodman, 1997). They are extremely useful in the treatment of other forms of nausea and vomiting as well (e.g., postoperative nausea and vomiting). These agents bind to the dopamine receptors, blocking impulses to the vomiting center. Drugs such as prochlorperazine, promethazine, and metoclopramide block dopamine and have a role in the prevention of CINV. Butyrophenones (e.g., haloperidol) also fall into this class of medications (Navari, 2003). However, these agents can cause sedation and extrapyramidal side effects, such as akathisia and oculogyric crisis (i.e., a spasmodic event in which the eyeball can become fixed in one position, often upward, and remain so for a matter of minutes or longer that has been associated with the administration of prochlorperazine) (Bubalo et al., 2004; Fast Health, 2005; Schumock & Martinez, 1991; Wickham, 2004). Although these symptoms usually resolve with administration of diphenhydramine, they can be distressing to patients taking the antiemetics (Goodman).
**Benzodiazepines**

Benzodiazepines, particularly lorazepam, can be very useful in the treatment of anxiety, a risk factor that may increase the need for more aggressive antiemetic therapy. Side effects of therapy include sedation and possible loss of short-term memory, which can be desirable during the chemotherapy experience (Wickham, 2004). However, the role of benzodiazepines is primarily an adjunctive one, rather than as a true antiemetic (Wickham).

**Serotonin Antagonists**

Serotonin antagonists block the action of serotonin both centrally and peripherally and are extremely effective in preventing acute emesis. Chemotherapy administration creates a release of 5-HT, which stimulates the vomiting center, resulting in emesis (Bender et al., 2002). The original 5-HT, antagonist agents to be marketed as antiemetics for CINV were ondansetron, dolasetron, and granisetron; all are available in parenteral or oral forms. Previous to the introduction of the NK-1 receptor antagonists, serotonin antagonists in combination with corticosteroids provided the best protection from symptoms of acute emesis (Navari, 2003; Schnell, 2003). Several large, randomized studies have shown that the use of a combination of a 5-HT, receptor antagonist with dexamethasone results in the prevention of acute emesis in 60%–70% of patients receiving highly emetogenic chemotherapy; however, serotonin antagonists are less effective against delayed emesis (de Wit et al., 2003). Serotonin antagonists are more beneficial in acute emesis, and as many as 25%–40% of patients may experience emesis or nausea from day 2–5 of chemotherapy with high-dose cisplatin (de Wit et al., 2003). Serotonin antagonists are well tolerated; therefore, patients experience few side effects. Headache and constipation are some of the most commonly reported effects of therapy, but they typically are managed easily (Anastasia, 2000).

**Corticosteroids: Role of Dexamethasone**

Although not approved by the U.S. Food and Drug Administration as an antiemetic, dexamethasone is an extremely important adjunctive agent that has shown efficacy when combined with serotonin antagonists (Ioannidis, Hesketh, & Lau, 2000). Because of dexamethasone’s efficacy, standard therapy with serotonin antagonists for acute nausea and vomiting should include concomitant therapy with steroids unless contraindicated (Bender et al., 2002). In addition, the use of dexamethasone, with or without concurrent metoclopramide, is helpful in treating delayed nausea and vomiting (Ioannidis et al.; Italian Group for Antiemetic Research, 2000; National Comprehensive Cancer Network [NCCN], 2005).

Many different doses of dexamethasone have been used historically in clinical practice in conjunction with serotonin antagonists for the control of CINV. The Italian Group for Antiemetic Research (2004) conducted a dose-finding study to determine the most appropriate dose. In this randomized, double-blind study, 585 patients (195 patients in each arm) received ondansetrons, carboplatin, or cyclophosphamide. The researchers determined that single-dose dexamethasone 8 mg via IV before chemotherapy in combination with a 5-HT, antagonist was preferred to prevent acute emesis (Italian Group for Antiemetic Research, 2004).

**New Antiemetics**

**Aprepitant**

Aprepitant represents the first in a new class of antiemetic agents, the NK-1 receptor antagonists. Substance P is a tachykinin found in vagal afferent neurons and can induce vomiting, binding to the NK-1 receptors. Blocking the NK-1 receptors reduces emesis after emetogenic chemotherapy, as well as from apomorphine, ipecac, and irradiation therapy (Navari, 2003). Aprepitant is an oral agent and effectively crosses the blood-brain barrier, penetrating into the central nervous system (Hesketh, Grunberg, et al., 2003).

In a large multicenter, randomized, double-blind, placebo-controlled phase III study, patients receiving cisplatin 70 mg/m2 or more were given either standard therapy (n = 260) (ondansetron with dexamethasone on day 1 and dexamethasone on days 2–4) or the aprepitant regimen (n = 260) (aprepitant with dexamethasone and ondansetron on day 1, aprepitant and dexamethasone on days 2–3, and dexamethasone on day 4) (Hesketh, Grunberg, et al., 2003). The primary end point was defined as a complete response (i.e., no emesis and no rescue therapy) after cisplatin administration. Patients in the aprepitant group had significantly higher complete responses from day 1–5 (72.7% versus 53.3%, p < 0.001); therefore, the researchers concluded that the aprepitant regimen was well tolerated and provided consistently higher protection against CINV with cisplatin therapy. Additionally, aprepitant’s effectiveness in the improved control of delayed emesis was significant, given the difficulties in controlling CINV in this group of patients (Hesketh, Grunberg, et al.).

Aprepitant demonstrated an improved complete response rate when examining the efficacy of preventive therapy over multiple cycles of chemotherapy (de Wit et al., 2003). The effectiveness of aprepitant in men and women was observed, despite the previously identified difficulties with control in females (Olver, 2004). In fact, Gralla et al. (2003) reviewed data from two phase III clinical trials and found that the combination of aprepitant plus standard antiemetics improved antiemetic control in men and women with delayed and acute CINV (p < 0.001 for women and p < 0.05 for men). This finding was not reported previously for any class of antiemetic in highly emetogenic therapy (Gralla et al., 2003).

Aprepitant was approved by the U.S. Food and Drug Administration in March 2003 for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin. This agent is administered for three days and requires the addition of a corticosteroid and a 5-HT, antagonist. The recommended dose is 125 mg orally once prior to chemotherapy on day 1 and 80 mg orally on days 2–3, preferably with a corticosteroid (Merck & Co., Inc., 2003).

NK-1 receptor antagonists are well tolerated, with 10% and 12.7% of patients experiencing hiccoughs or asthenia, respectively (Merck & Co., Inc., 2003). Aprepitant is a substrate, an inhibitor and inducer of CYP3A4, and an inducer of CYP2C9. CYP2C9 and CYP3A4 are enzymatic pathways of drug metabolism through the liver; therefore, caution is recommended with concomitant administration of other agents metabolized by these systems (see Figure 1). Prothrombin time or international normalized ratio (INR) should be assessed within 7–10 days of therapy in patients receiving warfarin and aprepitant because a clinically significant decrease in INR can result; in addition, oral contraceptives also may be affected. Many chemotherapy agents are metabolized throughout the CYP3A4 system; in one trial, a higher incidence of serious infection was identified in the aprepitant plus standard therapy arm versus the standard therapy plus placebo arm. However, this incidence was attributed to a pharmacokinetic interaction between aprepitant and dexamethasone and was not seen in subsequent trials when a modified dexamethasone regimen was used (Dando & Perry, 2004).
Researchers randomized 161 patients receiving highly emetogenic cisplatin-based chemotherapy to receive varying doses of palonosetron. In the phase II dose-ranging clinical study, palonosetron was well tolerated and its lowest effective doses were 3 mcg/kg and 10 mcg/kg (Eisenberg, MacKintosh, Ritch, Cornett, & Macciocchi, 2004). Three large, randomized, phase III studies all demonstrated at least equivalent and, in some cases, superior activity compared to other serotonin antagonist agents (Grunberg & Koeller, 2003). In one of the pivotal trials leading to U.S. Food and Drug Administration approval, 592 patients were randomized to receive a single IV dose of palonosetron 0.25 mg or 0.75 mg or dolasetron 100 mg 30 minutes prior to moderately emetogenic chemotherapy. The trial’s end point was the proportion of patients with a complete response during the first 24 hours after chemotherapy. Secondary end points included prevention of delayed nausea and vomiting (i.e., two to five days postchemotherapy). The complete response rates were superior for patients receiving palonosetron compared with dolasetron group (Eisenberg et al., 2003). For the primary efficacy end point, the number of patients with a complete response was higher during the first 24 hours (p = 0.049) in the 0.25 mg group, as well as the 0.75 mg group (p = 0.412). Complete control rates during the delayed period were superior for palonosetron at both doses (0.25 and 0.75 mg) compared to dolasetron (48.1%, 51.9%, and 36.1%, respectively) (Eisenberg et al., 2003).

Palonosetron was studied for its effectiveness on the prevention of CINV over multiple cycles of moderately or highly emetogenic chemotherapy at a dose of 0.75 mg in 875 patients. Seventy percent of the patients received moderately emetogenic chemotherapy, and 30% received highly emetogenic chemotherapy. In addition, 19.4% received prophylactic corticosteroids with chemotherapy. A complete response was noted in 62%, 65%, 55%, and 61% of the patients with each cycle of chemotherapy, and delayed complete response rates were maintained (Cartmell et al., 2003).

Based on the clinical trial results, the U.S. Food and Drug Administration approved palonosetron for the prevention of acute and delayed nausea and vomiting following moderately emetogenic chemotherapy and for acute nausea and vomiting only following highly emetogenic chemotherapy (see Figure 2) (Grunberg & Koeller, 2003). Palonosetron is well tolerated and eliminated through renal excretion and metabolic pathways. The potential for clinically significant drug interactions appears to be low (MGI Pharma, Inc., 2003).

### Antiemetic Guidelines

Many published guidelines are available in the literature and in practice that help to define antiemetic use in clinical settings (Koeller et al., 2002). Despite the existence of guidelines to promote effective use of antiemetic prescribing, compliance can be poor (Mertens et al., 2003). Practice guidelines can help to increase efficacy in treatment outcomes and promote cost-effectiveness (Engstrom, Hernandez, Haywood, & Lilenbaum, 1999). The MASCC (2004) guidelines, the American Society of Clinical Oncology (Gralla et al., 1999) position paper, the American Society of Hospital Pharmacists (“ASPTh Therapeutic Guidelines on the **Warfarin**

Increased patient monitoring (international normalized ratio) may be required, although changes are relatively brief in duration.

**Dexamethasone**

Area under the curve (AUC) increases were seen in the first clinical trials; therefore, reduce doses by 50%.

**Methylprednisolone**

Similar to dexamethasone

**Oral contraceptives**

Effectiveness may be reduced during aprepitant administration; barrier or other contraceptives are recommended.

**Other CYP3A4 inhibitor agents**

Ketoconazole,itraconazole, and erythromycin may lead to increased AUC of aprepitant.

**Other CYP3A4 inducer agents**

Phenytoin, rifampin, and carbamazepine administration may lead to decreased efficacy of aprepitant.

Aprepitant is contraindicated in administration with pimozide,terfenadine,astemizole, or cisapride.

**Note.** Aprepitant is a moderate CYP3A4 inhibitor, inducer of CYP2C9, and substrate for CYP3A4.

**Figure 1. Nonchemotherapy Drug-Aprepitant Interactions**

*Note. Based on information from Merck & Co., Inc., 2003.*

Oral chemotherapy agents should be used with caution. In addition, because of the small number of participants in clinical trials with docetaxel,vinblastine, vincristine, or ifosfamide, patients taking these agents should be monitored (Merck & Co., Inc., 2003). Additionally, in the original clinical trials, oral steroid doses were reduced from standard doses; the current recommendation is to reduce steroid doses by approximately half in the current three-day regimen. A recent article evaluated the potential inductive effects of aprepitant on 3A4 and 2C9 activity and concluded that, in CINV, the results are modest and transient in the two weeks following administration (Shadle et al., 2004).

**Palonosetron**

Although palonosetron is a serotonin antagonist, it is uniquely different from traditional agents. The half-life of palonosetron is approximately 40 hours, and it has a very high binding affinity (> 30 times higher) compared to other medications in this class. This long half-life contributes to the prevention of delayed nausea and vomiting that may occur after 24 hours and as many as six days after chemotherapy administration (DiVall & Cersosimo, 2003).
Pharmacologic Management of Nausea and Vomiting,” 1999), and the newly revised NCCN (2005) guidelines all offer recommendations (Bender et al., 2002).

The developers of the published guidelines met in April 2001 to unify their recommendations and offer suggestions based on information regarding the use of antiemetic agents, including that the available serotonin antagonists were equal in efficacy and side effects and that a corticosteroid should be added whenever possible (Bender et al., 2002; Koeller et al., 2002). They also recommended that single doses of serotonin antagonists are as effective as multiple doses and that oral regimens are as effective as IV ones (Bender et al.). With the addition of aprepitant and palonosetron, most of the existing guidelines have become outdated, with the exception of the NCCN guidelines. MASCC (2004) has not completely integrated the most recent clinical information about the two newest antiemetics into its guidelines but is expected to update its information soon to reflect the current state of practice and incorporate data from the 2004 American Society of Clinical Oncology meeting. The NCCN (2005) guidelines currently address the administration of aprepitant and palonosetron in antiemesis and have been updated for 2005.

The MASCC (2004) guidelines contain suggestions for the management of CINV and use of the two newest antiemetics. For the prevention of acute nausea and vomiting following chemotherapy of high emetic risk, a three-drug regimen of a 5-HT3 antagonist, dexamethasone, and aprepitant is recommended before chemotherapy. To prevent delayed nausea and vomiting in patients receiving chemotherapy of high emetic risk, a combination of dexamethasone and aprepitant is suggested. In moderately emetic chemotherapy, the MASCC guidelines have recommended a 5-HT3 receptor antagonist with dexamethasone for management of acute nausea and vomiting, which further supports the committee’s belief that no clinically relevant differences exist in the effectiveness of the 5-HT3 receptor antagonists in acute nausea and vomiting with moderately emetogenic chemotherapy. The 2004 guidelines stated that the participants in the committee believed that the comparative data with palonosetron were interesting, but that studies with the drug following guidelines for concomitant administration with dexamethasone were needed before changing the recommendation (MASCC). An update of the guidelines is expected and should include data from the most recent professional meetings and published information about further uses of the newest agents in the armamentarium of antiemetics.

National Comprehensive Cancer Network Guidelines

The NCCN (2005) guidelines include a statement of consensus opinions from the authors about currently accepted approaches to treatment. The NCCN categories of consensus are stratified into four levels (i.e., 1, 2a, 2b, and 3); uniform consensus among panel members for a recommendation is listed as 1 or 2a, 2b indicates nonuniform consensus, and 3 indicates extensive NCCN disagreement about the appropriateness of the recommendation. All recommendations in the document regarding antiemesis are level 1 or 2a unless specifically stated (NCCN). The 30-page document is a comprehensive recommendation for the practice of using antiemetics in patients receiving chemotherapy; of interest are new guidelines regarding aprepitant and palonosetron.

Guidelines for Highly Emetogenic Patients

When patients receiving chemotherapy agents are deemed highly emetogenic, NCCN (2005) recommended using aprepitant 125 mg orally on day 1, with 80 mg orally on days 2–3, and adding dexamethasone 12 mg orally or by IV on day 1, with 8 mg orally or by IV on days 2–4. The recommendations also call for the addition of a 5-HT3 antagonist (i.e., ondansetron, granisetron, dolasetron, or palonosetron) and possibly lorazepam (NCCN).

Guidelines for Moderately Emetogenic Patients

In patients receiving moderately emetogenic chemotherapy, NCCN (2005) recommended administering dexamethasone on day 1 with a 5-HT3 antagonist agent; however, palonosetron is listed as the preferred drug. Ondansetron, granisetron, or dolasetron, with the possible addition of lorazepam also may be considered. Aprepitant should be assessed for use in patients receiving moderately emetogenic chemotherapy such as carboplatin, cyclophosphamide, doxorubicin, epirubicin, ifosfamide, irinotecan, or methotrexate. From days 2–4, NCCN recommended using dexamethasone, a serotonin antagonist (if not using palonosetron on day 1), and metoclopramide with diphenhydramine. If aprepitant is used on day 1, follow with apreipant 80 mg on days 2–3.

NCCN (2005) offered recommendations for antiemetic management of minimal emetic risk agents, breakthrough treatment, and possible choices for subsequent cycles of chemotherapy in patients with breakthrough CINV. Multiday emetogenic chemotherapy regimens such as bleomycin, etoposide, and cisplatin from day 1–5 also are available. In patients receiving multiday emetogenic chemotherapy, a 5-HT3 receptor antagonist should be used each day before the first dose of moderately or highly emetogenic chemotherapy with dexamethasone. Palonosetron could be used as the designated 5-HT3. If using palonosetron, repeat administration is likely to be safe; however, in terms of efficacy, the need for repeat dosing has not been established. Aprepitant may be used for multiday regimens that are considered to be highly emetogenic and likely to cause delayed nausea and vomiting; this drug should be given as a three-day regimen with a 5-HT3 antagonist. Aprepitant 80 mg may be administered safely on days 4–5 after highly emetogenic chemotherapy, but whether this practice improves control of nausea and vomiting in this setting is unknown. Continuing aprepitant on days 4–5 or repeated doses of palonosetron would add to the total cost of antiemetic therapy.

Nursing Implications

Oncology nurses have more choices in antiemetic therapy, including the addition of a new class of antiemetic agents—the NK-1 receptor antagonist. Although aprepitant is the first drug in this class to be released, other agents are being studied. Aprepitant has shown efficacy in patients receiving high-dose cisplatin and highly emetogenic chemotherapy and is approved for treatment in both the acute and delayed setting for those agents. The longer-acting serotonin antagonist, palonosetron, has the longest drug half-life in this class of agents and has been at least as effective as the existing drugs available in this class; in some cases, it has been more effective. Palonosetron is indicated for acute and delayed CINV from moderately emetogenic chemotherapy and for acute control in highly emetogenic agents. Aprepitant and palonosetron are being studied for additional indications; their combined use may offer the best antiemetic coverage for patients with cancer on emetogenic chemotherapy, but data are not yet available. As a result, further study is needed (Flemm, 2004). The safety of the two drugs in combination first was reported in 2004 in a study of 12 patients showing a lack of effect of apreiprant on the pharmacokinetics and safety of palonosetron (Shah, Gallagher, Latimer, Cullen, & Hunt, 2004).
The combination is an appropriate choice for certain patients receiving emetogenic chemotherapy; the NCCN (2005) guidelines can help to determine which patients would benefit most from the combination (see inset).

Nurses caring for patients with cancer receiving chemotherapy should be aware of the new possibilities for antiemetic therapy and become familiar with guidelines to help establish appropriate practice changes. Knowledge of potential drug interactions with the administration of aprepitant is important. If patients are receiving warfarin therapy, check an INR within 7–10 days of therapy. If patients are taking birth control pills, alternative forms of contraceptives should be used. Aprepitant is available as an oral agent only, and palonosetron is intended for IV administration only. Appropriate dosing of palonosetron is important; although most likely safe, repeat dosing has not been proven to be more effective in the treatment of CINV because the half-life of the drug is approximately 40 hours (NCCN, 2005).

Aprepitant and palonosetron may cost more than traditional antiemetics; the 2004 average wholesale price of aprepitant in a three-day pack is $312.50 (additional 80 mg doses are $101.25), whereas a single palonosetron injection is $324 (Fleming, 2004). Both drug manufacturers, Merck & Co., Inc., and MGI Pharma, Inc., have assistance programs to help offset the cost of drugs for patients meeting their criteria. However, the cost of antiemetic therapy needs to be weighed against the potentially higher costs of untreated emesis, which can require possible hydration, extra provider visits, administration of electrolytes, or additional emetic medication (Ibhe-Heffinger et al., 2004). An abstract presented at the MASCC meeting in June 2004 reported on a cost-consequence model, including antiemetic costs (aprepitant regimen versus standard regimen), for a hypothetical cohort of 1,000 patients for a single cycle of highly emetogenic chemotherapy (Bell et al., 2004). The results indicated that 58.7% of the added cost of using aprepitant would be offset by savings in overall direct medical costs associated with CINV; in the sensitivity analyses, the cost offsets ranged from 29%–80% (Bell et al.). The other primary cost of inadequately treated emesis is ultimately to patients, who may develop anticipatory and delayed nausea and vomiting and, as a result, terminate possible lifesaving therapy.

**Conclusion**

Supportive care, including management of chemotherapy-induced emesis, is an important arena for oncology nurses; therefore, they must understand the currently available antiemetic agents, especially aprepitant and palonosetron. In addition, nurses should be aware of the potential for drug interactions with aprepitant when using the drug in patients with cancer and CINV. Incorporating the new agents into practice will require knowledge and clinical experience as healthcare providers become more familiar with these agents. Published guidelines may assist oncology nurses and healthcare providers in the appropriate use of antiemetic medications. Completely eradicating CINV may not be possible, but nurses can better control symptoms and improve the chemotherapy experience for patients.

**Case Study One**

A 54-year-old woman diagnosed with head and neck cancer was scheduled to receive high-dose cisplatin chemotherapy with infusion of 5-fluorouracil for four days. Premedication prior to chemotherapy included granisetron 2 mg orally, and decadron 10 mg orally, with prochlorperazine every four to six hours as needed for breakthrough nausea and vomiting. She also received lorazepam 1 mg orally prior to cisplatin. On day 3, the patient was sufficiently nauseated, despite the addition of decadron 8 mg orally twice daily with prochlorperazine 10 mg orally around the clock, that she complained to the staff. Lorazepam was added around the clock, as well as the oral serotonin antagonist ondansetron 8 mg three times a day. However, because of the combined sedative effects of the adjunctive medications (lorazepam and prochlorperazine), the patient fell in the hallway of the hospital and unfortunately broke her wrist. When she was admitted for her next chemotherapy treatment, the patient was placed on aprepitant because of its efficacy in highly emetogenic agents (e.g., cisplatin) and because of the newly released National Comprehensive Cancer Network’s (2005) recommendations. She also was administered palonosetron because she was scheduled to receive a serotonin antagonist on the first day of treatment and had used serotonin antagonists on subsequent days (the cost of additional days of serotonin antagonist effectively equaled the cost of adding palonosetron). The patient received aprepitant and palonosetron on her subsequent chemotherapy admissions with significantly improved emesis control.

**Case Study Two**

A 53-year-old woman with breast cancer received her first cycle of doxorubicin and cyclophosphamide (AC) with the following antiemetics ordered for her first cycle of chemotherapy: granisetron 2 mg orally, decadron 10 mg orally, and lorazepam 1 mg sublingually. For home use after chemotherapy, the patient received oral ondansetron 8 mg twice daily, with prochlorperazine 10 mg orally every four to six hours and lorazepam 1 mg. The patient reported vomiting an average of six to seven times a day, felt light-headed, and was unable to retain fluids. She was brought into the oncology clinic for IV hydration and replacement of potassium. On the next cycle of AC, palonosetron was added on day 1 with decadron 20 mg orally. Lorazepam was kept as an adjunctive agent, as well as prochlorperazine, for as-needed use at home. The oral ondansetron was discontinued because it had no proven role for further serotonin antagonist after palonosetron was added to the antiemetic regimen. The patient had significant improvement in CINV; if she had not improved, the addition of aprepitant would have been considered.

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Integrating Aprepitant and Palonosetron Into Clinical Practice: A Role for the New Antiemetics

- Chemotherapy-induced nausea and vomiting (CINV) are major side effects of chemotherapy treatments despite antiemetic therapy.
- New antiemetic agents have been approved by the U.S. Food and Drug Administration to help combat the distressing side effects of CINV.
- Palonosetron and aprepitant represent significant changes in how healthcare professionals treat CINV; oncology nurses need to know appropriate administration of these agents and how to integrate these drugs into CINV treatment.
- Practice guidelines exist and recently have been updated to assist oncology nurses with the treatment of CINV in patients receiving chemotherapy.