Management of Nausea and Vomiting

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Overview

Although marked progress in controlling chemotherapy-induced emesis has occurred over the past 25 years, nausea and vomiting remain among the most distressing side effects of cancer chemotherapy. With the increased use of chemotherapy in primary and adjuvant treatment settings, the need for improved control of emesis remains an important consideration in both medical oncology and supportive care.

Several major oncology groups have published consensus reports or guidelines on the prevention of chemotherapy-induced emesis. However, the introduction of new agents may change these paradigms. In addition, an understanding of the neuropharmacology of this problem is valuable in planning patient care.

Pathophysiology of Emesis

Stimulation of Neurotransmitter Receptors

The emetic reflex arc is activated by stimulation of receptors in the central nervous system (CNS) and/or gastrointestinal (GI) tract. These receptor areas relay information to the vomiting center in the medulla, which then coordinates the act of vomiting. The chemoreceptor trigger zone, also located in the medulla, serves as a "chemosensor" and is exposed to blood and cerebrospinal fluid. These areas are rich in a variety of neurotransmitter receptors.

Dopamine

For many years, the dopamine receptors were the main focus of interest in antiemetic research. Available antiemetics, such as phenothiazines (chlorpromazine and prochlorperazine) and substituted benzamides (metoclopramide), were known to affect these receptors, as were butyrophenones (haloperidol and droperidol).

Serotonin

The role of the neurotransmitter serotonin (5-hydroxytryptamine [5-HT]) has also been elucidated. The improved antiemetic activity of higher doses of metoclopramide was not explained by its dopamine-binding properties but by the fact that it also affects serotonin receptors. This finding led to the development of several highly specific compounds that interact solely with serotonin receptors, specifically the type 3, or 5-HT3, receptor subtype. Several compounds (ondansetron, granisetron, palonosetron) from this family are currently available in the United States. The 5-HT3 receptor, which is found in both the GI tract and CNS, is an important mediator of the emetic reflex arc. Molecular studies have suggested that mutation of the 5-HT3B receptor subunit may affect antiemetic efficacy.

Substance P

Tachykinins, such as substance P, play an important role in emesis, as well as in pain and a variety of inflammatory conditions. These neurotransmitters are 11-amino acid molecules that bind to specific receptors. Substance P binds to the neurokinin type 1, or NK1, receptor. Several NK1 receptor antagonists have been synthesized and used both preclinically and in clinical trials in patients receiving cancer chemotherapy. Results indicate that these agents are effective against a broad range of causes of emesis, particularly delayed emesis. The oral agent aprepitant and its intravenous prodrug fosaprepitant have been approved for clinical use. Clinical trials of
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netupitant and rolapitant have recently been completed. Phase III clinical trials of netupitant and rolapitant have been reported in 2014.

**Sidebar:** In a recent large randomized, double-blind, parallel-group study, Hesketh et al assessed the efficacy and safety of NEPA, a new fixed-dose oral combination of the NK₁ antagonist netupitant and the 5-hydroxytryptamine receptor antagonist (5-HT₃RA) palonosetron, for prevention of chemotherapy-induced nausea and vomiting (CINV) following highly emetogenic chemotherapy. The aim of the study was to determine the appropriate clinical dose of netupitant to combine with palonosetron for evaluation in a phase III NEPA program. A total of 694 chemotherapy-naive patients undergoing cisplatin-based chemotherapy for solid tumors were randomized to three different oral doses of netupitant (100, 200, and 300 mg) plus 0.50 mg palonosetron, or to oral palonosetron at 0.50 mg, all given on day 1. A standard regimen of 3-day aprepitant plus IV ondansetron at 32 mg was included as an exploratory arm. All patients received oral dexamethasone on days 1–4. The primary efficacy endpoint was complete response (CR; no emesis, no rescue medication) during the overall phase (0–120 hours).

At each dose, prevention of CINV with NEPA was superior to that with palonosetron following highly emetogenic chemotherapy (87.4%, 87.6%, and 89.6% CR for NEPA100, NEPA200, and NEPA300, respectively, vs 76.5% CR with palonosetron; P < .05); however, NEPA300 had an advantage over lower doses for all efficacy endpoints. The combination of NEPA was well tolerated, with a safety profile (eg, percentage of patients developing echocardiogram changes) similar to that of palonosetron and the combination of aprepitant plus ondansetron (Hesketh PJ et al: Ann Oncol 25:1340–1346, 2014).

**Sidebar:** An additional study using NEPA has recently been reported. In a multinational, randomized, double-blind, parallel-group phase III trial in 1,455 chemotherapy-naive patients receiving mitoxantrone, etoposide, and intermediate-dose cytarabine (MEC; the trial included patients receiving anthracycline and cyclophosphamide), patients were randomized to a single oral dose of NEPA (300 mg netupitant plus 0.50 mg palonosetron) or a single oral dose of palonosetron (0.50 mg) prior to chemotherapy, on day 1. All patients received oral dexamethasone on day 1 only (12 mg in the NEPA arm; 20 mg in the palonosetron arm). The primary efficacy endpoint was CR during the delayed (24–120 hours) period. The CR during the delayed period was significantly higher for the NEPA group compared with the palonosetron group. NEPA was well tolerated, with a safety profile similar to that of palonosetron (Aapro M et al: Ann Oncol 25:1328–1333, 2014).

**Sidebar:** In recently completed phase III clinical trials, rolapitant, an NK1 antagonist, was evaluated for the prophylactic treatment of CINV. In three global, randomized, double-blind, active-controlled, parallel-group, phase III studies, cancer patients received a 200-mg rolapitant dose or placebo prior to administration of moderately emetogenic chemotherapy (mitoxantrone, etoposide, and intermediate-dose cytarabine [MEC], N = 1,344) or highly emetogenic chemotherapy (HEC-1 and HEC-2, N = 1,072 [pooled]). All patients also received granisetron and dexamethasone. The primary objective was the CR rate (no emesis or rescue medication) in the delayed phase (24–120 hours), while key secondary endpoints were CR rate in the acute (0–24 hours) and overall (0–120 hours) phases. The studies were registered with ClinicalTrials.gov: NCT01500226, NCT01499849, and NCT01500213. Patients receiving rolapitant had a significantly higher CR rate in the delayed phase in the MEC (71.3% vs 61.6%, P < .001) or pooled HEC studies (71.4% vs 60.2%, P < .001). The CR rate was significantly higher in the acute phase in the pooled HEC studies (83.6% vs 76.6%, P = .004) and in the overall phase in both the pooled HEC (66.8% vs 58.5%, P < .001) and the MEC (68.6 vs 57.8, P < .001) studies. The incidence of adverse events was similar across treatment groups. Rolaupilant in combination with granisetron and dexamethasone was safe and effective for the prevention of CINV during the 5-day at-risk period across a spectrum of emetogenic cancer chemotherapies (Urban L et al: J Clin Oncol. 32[Suppl 5]: abstract 9636, 2014).

**Emetic Problems**

**Emesis Related to Chemotherapy**

Both nausea and vomiting are seen in patients receiving cancer chemotherapy. Nausea occurs at a higher frequency than vomiting and is more difficult to control. The control of vomiting is strongly correlated with the control of nausea, although some patients experience nausea without vomiting. The three most common emetic patterns in patients receiving chemotherapy are outlined below.

**Acute chemotherapy-induced emesis**

Acute chemotherapy-induced emesis is defined as nausea or vomiting that occurs within the initial
24 hours of chemotherapy administration. The time of greatest risk is from 1 to 6 hours after chemotherapy with most agents.

**Delayed emesis**

Delayed emesis is emesis that begins 24 hours or more after chemotherapy administration. Delayed emesis is particularly likely in patients who have received cisplatin, carboplatin, or cyclophosphamide. However, this problem may begin somewhat earlier than 24 hours in some patients, with peak incidence and severity occurring 48–72 hours post chemotherapy.

**Anticipatory emesis**

Anticipatory emesis is defined as a conditioned vomiting response following inadequate antiemetic protection with prior courses of chemotherapy.

**Emesis Unrelated to Chemotherapy**

Patients receiving anticancer drugs may also develop emesis for other reasons. Emesis can be induced by concomitant medications (such as analgesics, anti-infectives, or bronchodilators) or by tumor-related complications (such as intestinal obstruction or brain metastases). In these instances, adjustment of medication or treatment of tumor-related complications is more important than selecting an antiemetic agent.

**Patient Characteristics and Emesis**

**History of Poor Emetic Control**

Poor control of emesis with past courses of chemotherapy predisposes a patient to unsatisfactory antiemetic results with any subsequent treatment, regardless of the emetic stimulus or antiemetic employed. Both delayed and conditioned anticipatory emesis are more likely to occur in such patients, and there is likely to be greater difficulty in controlling acute emesis.

**History of Alcohol Intake**

Emesis is easier to control in patients with a history of chronic, high alcohol intake (> 100 g/day of alcohol [approximately five alcohol units, or drinks]). In a prospective evaluation of 52 patients receiving high-dose cisplatin and an effective combination antiemetic regimen, 93% of those with a history of high alcohol intake had no emesis, as opposed to 61% of those without such a history. This difference in emesis control is independent of the patient's current alcohol intake.

**Age**

Most trials have found that it is easier to control emesis in older patients than in younger ones. Younger patients have a predilection for developing acute dystonic reactions when dopamine-blocking antiemetics are administered (see section on "Antiemetic agents for high–emetic-risk chemotherapy"). Younger patients also have a greater tendency to develop anticipatory emesis than do older patients.

**Gender**

It is more difficult to control emesis in women than in men given the same chemotherapy and antiemetic regimen.

**Motion Sickness/Morning Sickness**

Patients with a history of motion sickness or morning sickness are more likely to develop CINV than are those without such a history. The above predisposing factors appear to be additive. One can identify patients at particularly high risk for emesis, such as younger women without a history of high alcohol intake. Awareness of these factors is helpful in monitoring individual patients and interpreting the results of clinical trials.

**Chemotherapeutic Agents and Emesis**
Emetic Potential

The most accurate predictor of the risk of emesis is the chemotherapeutic agent that a patient is receiving. Several different classifications of commonly used chemotherapy agents have been devised. Table 1 is based on the consensus report of the Multinational Association of Supportive Care in Cancer (MASCC) as updated in April 2011.

The emetic potential of a chemotherapeutic combination is determined by identifying the most emetic agent in the combination. Other agents in a combination may also increase the risk. In general, agents associated with the highest incidence of emesis also induce the most severe emesis. Differences occur among patients and even between identical treatment courses in the same patient. The dose, route, and schedule of administration of the chemotherapeutic agent can affect the incidence of nausea and vomiting.

Time of Onset of Emesis

In patients receiving initial chemotherapy of high emetic risk, nausea or vomiting typically begins between 1 and 2 hours after chemotherapy administration. Cyclophosphamide and carboplatin may be associated with a late onset of emesis (ie, 8 to 18 hours following chemotherapy administration).

Antiemetic Agents for High-Emetic-Risk Chemotherapy

Careful antiemetic research has shown that numerous agents are safe and effective. Dosage and administration schedules for some of these agents are given in Table 2. Antiemetic therapy is commonly administered either orally or intravenously. Among the best-studied agents are ondansetron, granisetron, palonosetron, metoclopramide, haloperidol, dexamethasone, aprepitant, fosaprepitant, lorazepam, dronabinol, prochlorperazine, and chlorpromazine.

The combination of a single prechemotherapy dose of a 5-HT3 antagonist and dexamethasone is the
most commonly used therapy to prevent emesis in patients receiving chemotherapy of high emetic risk (both cisplatin and noncisplatin) as listed in Table 1. Addition of an NK₁ antagonist such as aprepitant will increase the rate of antiemetic protection.

**Serotonin Antagonists: Ondansetron, Granisetron, and Palonosetron**

Ondansetron, granisetron, and palonosetron are highly selective 5-HT₃ receptor antagonists. Doses of these agents are given in Table 2. All are effective in controlling emesis induced by a variety of chemotherapeutic agents. Oral and intravenous routes of administration available for ondansetron, granisetron, and palonosetron are effective, as demonstrated in large randomized trials. Granisetron is also now available as a transdermal patch (Sancuso). Single-dose regimens given before chemotherapy appear to be as effective as more cumbersome multiple- or continuous-dose regimens. Palonosetron has a significantly longer half-life (of approximately 40 hours) compared with the other serotonin antagonists, it and may exhibit more noncompetitive binding and greater efficacy against delayed emesis.

**Side effects**

Ondansetron, granisetron, and palonosetron have all demonstrated excellent safety characteristics over a large dosing range. Toxicities have been minor and have included headache, mild transient elevation of hepatic enzyme levels, constipation and, with some agents, prolongation of cardiac conduction intervals (particularly QT₉ intervals). Dystonic reactions and akathisia (restlessness), which may be treatment-limiting with antiemetic agents known to block dopamine receptors, are not seen with serotonin antagonists, even when given on consecutive days. This finding is of particular importance for younger patients, in that several regimens used to treat malignancies in this age group use a schedule of daily chemotherapy.

**Efficacy**

The serotonin antagonists have been reported to achieve complete control of acute emesis in 30% to 50% of patients receiving cisplatin. These agents have also proved to be at least as effective against other chemotherapeutic agents, with acute-emesis control rates of about 50% to 56%. Many trials have examined the benefit of adding corticosteroids to a serotonin antagonist. Typically, the control of acute emesis is improved by 10% in patients receiving highly emetic chemotherapy. Both the American Society of Clinical Oncology and the MASCC guidelines recommend that a corticosteroid be added whenever a serotonin antagonist is indicated (ie, in all patients receiving chemotherapy associated with high emetic risk).

**Sidebar:** In a systematic review and meta-analysis of 16 randomized trials of approximately 6,000 patients treated with either palonosetron (n = 2,896) or another 5-HT3RA (n = 3,187) for prophylaxis of CINV, Popovic et al found palonosetron to be consistently statistically superior to other agents in achieving complete response, complete control, no emesis, or no nausea, and sometimes superior in enabling patients to avoid taking rescue medication. Palonosetron also was statistically significantly safer in terms of 5-HT3RA-related adverse events including dizziness and mean QTc interval change. The investigators recommended consideration of palonosetron as first-line therapy in future antiemetic guidelines (Popovic M et al: Support Care Cancer 22:1685–1697, 2014).

**Dexamethasone**

The antiemetic mechanism of action of dexamethasone remains unclear. Several randomized trials and a meta-analysis have all confirmed both its effectiveness in controlling emesis and its safety. Other corticosteroids, such as methylprednisolone, are also effective; however, dexamethasone is the most widely studied corticosteroid and it is available in oral and parenteral dosage forms as an inexpensive generic product. Dexamethasone is an excellent agent for use in combination antiemetic regimens and as a single agent for patients receiving chemotherapy of low emetic risk (<30% incidence).

**Dosage**

Dexamethasone dosages have generally ranged from 4 to 20 mg/day. In a randomized trial in patients receiving chemotherapy of high emetic risk, a single 20-mg dose prior to chemotherapy was superior in completely controlling both nausea and vomiting. Thus, the 20-mg dose is recommended in this setting. For patients receiving chemotherapy of moderate emetic risk, a single 8-mg dose may be used. In patients receiving aprepitant, which inhibits dexamethasone metabolism, a lower dose of...
Dexamethasone may be sufficient.

**Side effects**

Toxicities associated with short courses of dexamethasone used for antiemetic therapy have been mild and generally consist of insomnia and mild epigastric burning. Care using this agent is particularly warranted in patients with diabetes.

**Metoclopramide**

Metoclopramide has proved to be generally safe and effective when given in high intravenous doses prior to chemotherapy. Metoclopramide was thought to function as an antiemetic through blockade of dopamine receptors. However, high concentrations of this agent effectively block 5-HT₃ receptors as well.

**Efficacy**

High-dose metoclopramide is a second-choice agent, after the serotonin antagonists, in patients receiving cisplatin and other chemotherapy agents.

**Side effects**

Commonly observed side effects with metoclopramide include mild sedation, dystonic reactions, akathisia, anxiety, and depression. Dystonic reactions are age-related and route-related. In a report summarizing the experience of nearly 500 patients receiving metoclopramide, the incidence of trismus or torticollis was only 2% in those older than 30 years; in contrast, a 27% occurrence was reported in younger patients. Also, such reactions are more common when metoclopramide is administered by the oral route or is given over several consecutive days. It should not be used for more than 3 consecutive days. Acute dystonic reactions are not allergic in nature. Dystonic reactions and akathisia can be prevented or controlled by administering diphenhydramine, benztropine (Cogentin), or a benzodiazepine. These reactions should not be viewed as a contraindication to further use of dopamine-blocking drugs.

**Haloperidol**

Haloperidol exerts its antiemetic action through dopaminergic blockade. A formal study comparing haloperidol with metoclopramide in patients receiving cisplatin found both agents to be effective, although metoclopramide afforded better emetic control. Haloperidol should therefore only be used as a salvage agent.

**Dosage**

Haloperidol in doses of 1 to 3 mg given intravenously every 4 to 6 hours has been used.

**Side effects**

Toxicities of haloperidol include sedation, dystonic reactions, akathisia, occasional hypotension, and cardiac conduction defects.

**Benzodiazepines**

Lorazepam is an antianxiety agent and is not considered an antiemetic. Lorazepam and other benzodiazepines are potent anxiolytic agents that can be useful additions to antiemetic therapy. They should not be used as single agents for chemotherapy-induced emesis. Lorazepam has been shown to achieve a high degree of patient acceptance and subjective benefit. The anxiolytic properties of benzodiazepines may be particularly useful in the treatment of anticipatory nausea and vomiting.

**Dosage**

Lorazepam is usually given in doses of 0.5 to 1.5 mg/m² intravenously or 0.5 to 2 mg orally. These doses, especially the higher intravenous doses, can be associated with marked sedation lasting for several hours.

**Cannabinoids**

Many trials have tested the antiemetic effects of dronabinol (delta-9-tetrahydrocannabinol), a component of marijuana. Dronabinol has modest antiemetic activity, similar to that seen with oral prochlorperazine, but it may have a greater effect against nausea.
Semisynthetic cannabinoids such as nabilone have been tested but appear to have no clear advantage over dronabinol. The modest antiemetic activity and significant toxicity of cannabinoids make them a relatively poor choice for the control of chemotherapy-related emesis.

**Dosage**

Dronabinol has been tried in many doses and schedules. The most useful doses have ranged from 5 to 10 mg/m² orally every 3 to 4 hours. The usual dose of nabilone is 1 to 2 mg orally twice daily.

**Side effects**

Side effects frequently associated with cannabinoids, particularly in older adults, include dry mouth, sedation, orthostatic hypotension, ataxia, dizziness, euphoria, and dysphoria.

**Phenothiazines**

Although phenothiazines were the first effective antiemetics, the results of antiemetic trials with this class of agents against highly emetogenic chemotherapy have been poor. Randomized trials have found standard-dose prochlorperazine, given orally or intramuscularly, to be less effective than metoclopramide or dexamethasone and equivalent to or less effective than dronabinol. Intravenous administration is more effective than oral administration but can rarely cause profound hypotension (unlike serotonin antagonists or metoclopramide). Phenothiazines are seldom used as first-line antiemetic agents for highly or moderately emetogenic chemotherapy.

**Side effects**

Side effects of phenothiazines include sedation, akathisia, hypotension, and dystonic reactions.

**NK₁ Antagonists**

Aprepitant and fosaprepitant are two NK₁ antagonist antiemetics currently in common use. NK₁ antagonists have demonstrated activity against a wide range of emetogenic stimuli. Although less effective than serotonin antagonists as single agents against acute emesis, NK₁ antagonists have shown superior activity against delayed emesis, suggesting the value of combination therapy. In a multicenter, randomized, double-blind, phase III trial, 866 breast cancer patients being treated with cyclophosphamide with or without doxorubicin or epirubicin were randomized to receive either a regimen of aprepitant (125 mg), ondansetron (8 mg bid), and dexamethasone (12 mg) on day 1 with aprepitant (80 mg/day) on days 2 and 3 or a standard regimen of ondansetron (8 mg bid) on days 1 to 3 and dexamethasone (20 mg) on day 1. Of the 857 evaluable patients, 50.8% in the aprepitant arm vs 42.5% in the standard-regimen arm achieved a complete response (P = .015). In addition, more patients in the aprepitant arm achieved a complete response during both acute (75.7% vs 69%; P = .034) and delayed (55.4% vs 49.1%; P = .064) phases. Both treatments were generally well tolerated.

In a recent randomized, double-blind, phase III trial, a single 150-mg dose of intravenous fosaprepitant was found to be equivalent to a 3-day oral aprepitant regimen when administered with ondansetron and dexamethasone against highly emetogenic chemotherapy. On October 10th, 2014, the US Food and Drug Administration (FDA) approved NEPA to treat nausea and vomiting in patients undergoing cancer chemotherapy. Recent phase III clinical trials of rolapitant have been submitted to the FDA, with anticipated approval in 2015.

**Combination Antiemetic Regimens**

**Table 3** summarizes recommended antiemetic regimens, according to the emetic potential of the chemotherapy regimen.

**Serotonin Antagonist Plus Dexamethasone**

Combinations of a 5-HT₃ antagonist and dexamethasone form the basis of the most effective regimens for controlling acute chemotherapy-induced emesis. Use of these two agents combined has proved to be more effective than treatment with either agent alone. Addition of an NK₁ antagonist results in increased activity against highly emetogenic chemotherapy. However, inhibition by aprepitant or fosaprepitant of the cytochrome P-450 3A4 metabolic pathway may require a decrease in the dose of concomitantly administered dexamethasone. The atypical antipsychotic agent olanzapine has shown promise in phase II and III clinical trials for prevention and treatment of CINV. A thiobenzodiazepine, it exhibits activity at multiple receptors,
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notably at the D2, 5-HT2c, and 5-HT3 receptors which appear to be involved in nausea and emesis, thus prompting investigation of its use in the treatment of nausea and vomiting refractory to standard antiemetics.

In a 2011 randomized phase III study, olanzapine combined with a single dose of palonosetron and a single dose of dexamethasone (OPD) effectively controlled acute and delayed CINV in patients receiving highly emetogenic chemotherapy. Rates of CR (with CR defined as no emesis or rescue treatment) with OPD were not significantly different from those of a similar group of patients receiving highly emetogenic chemotherapy and an antiemetic regimen of aprepitant, palonosetron, and dexamethasone (APD). For 121 patients randomized to OPD, the CR was 97% for the acute period (24 hours post chemotherapy), 77% for the delayed period (days 2–5 post chemotherapy), and 77% for the overall period (0–120 hours). CR rates for the 120 patients receiving APD were 87%, 73%, and 73%, respectively. Patients were much more likely to have no nausea with the OPD regimen (69%), however, than with the APD regimen (38%) over the 5-day post-chemotherapy period.

Sidebar: In a phase III double-blind randomized trial, Navari et al investigated olanzapine (10 mg orally daily for 3 days) vs the dopamine-2 receptor antagonist metoclopramide (10 mg orally tid for 3 days) for prevention of breakthrough CINV in chemotherapy-naive patients being treated with highly emetogenic chemotherapy (cisplatin or doxorubicin, plus cyclophosphamide) who were refractory to prophylactic dexamethasone, palonosetron, and fosaprepitant (Emend) pre-chemotherapy and dexamethasone post-chemotherapy. Among the 276 enrolled patients, a total of 112 developed breakthrough CINV; 108 were evaluable and were monitored for nausea and emesis during a 72-hour observation period. During the 72-hour observation period, 70% of patients (39 of 56) randomized to olanzapine had no emesis vs 31% (16 of 52) of patients treated with metoclopramide (P < .01). There were no grade 3 or 4 toxicities (Navari RM et al: Support Care Cancer 21:1655–1663, 2013). When used for several months, common side effects of olanzapine include weight gain and an association with the onset of diabetes mellitus, but, according to a 2014 study by Navari et al, these effects have not been seen with short-term use of daily doses of < 1 week. Because of these effects, however, and given that the 10 mg dose of olanzapine has been associated with grade 1/2 sedation, lower doses are under investigation in the setting of CINV. For example, in a recent randomized, placebo-controlled study from Japan, Mizukami et al assessed the benefit of addition of 5 mg/day of oral olanzapine to standard therapy from the day before chemotherapy to treatment day 5 for patients receiving highly or moderately emetogenic chemotherapy. A total of 44 patients were enrolled. All patients received a 5-HT3RA and NK1 receptor antagonist. Patients were randomly assigned to receive olanzapine (n = 22) or placebo (n = 22). More patients achieved total control (no vomiting, no rescue medications) on olanzapine (86% and 64% in the acute and delayed phases, respectively) vs the control group (55% [P = .045] and 23% [P = .014]). Patients randomized to olanzapine also experienced a better quality of life than the controls, based on their responses to the Functional Living Index–Emesis questionnaire (P = .0004).

Treatment of Emesis

Acute Emesis

A management strategy to prevent acute chemotherapy-induced emesis is outlined in Table 3. All patients should receive education and reassurance, as well as antiemetics tailored to the chemotherapy regimen. For regimens that commonly cause emesis (> 30%), antiemetic combinations are recommended; for regimens of low emetic risk (10% to 30% incidence), a single agent will usually suffice. As stated in Table 3, chemotherapy of minimal emetic risk typically does
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not require preventive treatment.

Delayed Emesis

Delayed emesis is defined as nausea or vomiting beginning or persisting 24 hours or more after chemotherapy administration. The pathophysiology of this problem is unclear, but it is particularly common after high-dose cisplatin (≥ 50 mg/m²), carboplatin (≥ 300 mg/m²), cyclophosphamide (≥ 600 mg/m²), or doxorubicin (≥ 50 mg/m²).

In one natural history study, 89% of patients experienced some delayed emesis from 24 to 120 hours after receiving high-dose cisplatin, with a peak incidence occurring between 48 and 72 hours. With anthracyclines or cyclophosphamide, the rate of delayed emesis without preventive antiemetics is about 30%.

Some observations suggest that delayed emesis may begin earlier. When combination antiemetic regimens for acute emesis "fail," the initial emetic episode is often at 17 to 23 hours following chemotherapy. In some trials, antiemetics to prevent delayed emesis have been initiated at 16 to 17 hours.

Treatment options

The combination of dexamethasone and an NK₁ antagonist has demonstrated efficacy. Activity of palonosetron may also continue for several days. The recommended doses and schedules for the prevention of delayed emesis are given in Table 4.

Treatment regimens for prevention of delayed emesis

Anticipatory Emesis

This problem is defined as nausea or vomiting beginning before the administration of chemotherapy in patients with poor emetic control during previous chemotherapy. Because this problem is a conditioned response, the hospital environment or other treatment-related associations may trigger the onset of emesis unrelated to chemotherapy. Strong emetic stimuli combined with poor emetic control increase the likelihood that anticipatory emesis will occur.

Treatment approach

Behavioral therapy involving systematic desensitization can be helpful in managing anticipatory emesis. Also, benzodiazepines appear to be useful. However, the best approach to anticipatory emesis is prevention of prior emesis, which underscores the need to provide the most effective and appropriate antiemetic regimens with the initial course of emesis-producing chemotherapy.

Radiation-induced nausea and vomiting

Emetogenicity of radiation therapy is dependent on anatomic site and dose. For example, total body irradiation is highly emetogenic, while upper abdominal irradiation is moderately emetogenic. Serotonin antagonists remain the mainstay of antiemetic therapy for highly or moderately emetogenic radiotherapy.

Comparative Efficacy and Cost of Recommended Antiemetic Agents

The recommended first-generation serotonin receptor antagonists ondansetron and granisetron are equivalent in efficacy and compete on an economic basis. Both of these agents are available as generics. The recommended second-generation serotonin receptor antagonist palonosetron has documented higher efficacy than ondansetron and granisetron, but it is not available as a generic and has a higher cost. If the use of palonosetron can prevent return visits to the clinic, a visit to the...
emergency department, or a hospital admission for the treatment of chemotherapy-induced nausea and vomiting, the higher initial cost may be cost-effective. Aprepitant has been the recommended NK1 receptor antagonist since its approval in 2003. There have been no published comparative-efficacy studies among the NK1 receptor antagonists aprepitant, netupitant, and rolapitant. Comparative cost information between aprepitant and netupitant (approved by the FDA) should be available in the near future. If rolapitant is approved by the FDA in 2015, comparative cost information about the three available NK1 receptor antagonists should become readily available.

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