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Progress in preventing chemotherapy-induced nausea and vomiting

ABSTRACT

Our understanding of the pathophysiology of emesis has improved over the past 2 decades, and we now have drugs that can prevent acute emesis in most patients. Prevention and treatment of the delayed and anticipatory forms of chemotherapy-induced emesis remain a challenge.

KEY POINTS

Chemotherapy-induced emesis is difficult to control completely because the emetic process is complex and many neuroreceptors are involved.

Three distinct clinical forms of chemotherapy-induced emesis are acute, delayed, and anticipatory.

Individual patients vary considerably in the severity of nausea and vomiting they experience, depending on the drug and on specific patient characteristics.

Chemotherapy-induced emesis is easier to prevent than to treat once it has become established.

Serotonin-receptor antagonists effectively and safely prevent nausea and vomiting caused by most chemotherapy regimens and have revolutionized the management of acute chemotherapy-induced emesis.

The combination of a corticosteroid plus a serotonin-receptor antagonist should be standard treatment for patients undergoing chemotherapy with agents with moderate to high emetogenic potential.

CANCER PATIENTS and the general public fear nausea and vomiting more than nearly any other complication of chemotherapy. Fortunately, great progress has been made over the past 2 decades both in understanding the mechanism of chemotherapy-induced emesis and in preventing it.

MANY NEUROTRANSMITTERS INVOLVED

A complex series of events ultimately leads to emesis after cytotoxic chemotherapy.[1]

Multiple neurotransmitters, such as dopamine, serotonin, and neurokinin, and their receptors appear to be involved in the process by influencing the activity of several well-defined areas of the brain (eg, the chemoreceptor trigger zone and the vomiting center within the lateral reticular formation). Neuroreceptors in the gastrointestinal tract also appear to play an important role.

Given the complexity of the emetic process and the multiple neuroreceptors involved, chemotherapy-induced emesis has been extremely difficult to control completely. For example, an antiemetic agent that completely inhibits a specific neuroreceptor involved in emesis may activate another receptor that leads to nausea and vomiting by an alternative pathway. Furthermore, although the neurophysiology of acute emesis is fairly well characterized, our understanding is extremely limited of the pathways involved with either delayed or anticipatory nausea and vomiting (defined below).

An interesting question is why the human body has developed such a complex process to initiate emesis. From an evolutionary perspec-

TABLE 1

Emetogenic potential of antineoplastic agents

High risk	Moderate risk	Low risk
Altretamine	Docetaxel	Bleomycin
Carboplatin	Etoposide	Busulfan
Carmustine	Fluorouracil	Chlorambucil
Cisplatin	Gemcitabine	Fludarabine
Cyclophosphamide (high-dose)	Mitomycin	Hydroxyurea
Cytarabine	Paclitaxel	Melphalan
Dacarbazine		Vinblastine
Doxorubicin		Vincristine
Epirubicin		Vinorelbine
Ifosfamide		
Mitoxantrone		
Streptozocin		

Preventing chemotherapy-induced emesis is more effective than treating it

tive, animals that could rapidly and completely eliminate highly toxic ingested substances from the stomach would possess a survival advantage. Although this advantage has limited relevance to the survival of modern man, our bodies continue to appropriately recognize the noxious nature of most cytotoxic chemotherapeutic agents, even though these agents are usually given intravenously rather than orally.

FACTORS AFFECTING EMESIS

Drugs given

Cytotoxic antineoplastic agents vary greatly in their potential to induce emesis and in the severity of this side effect. In general, the drugs that are most likely to cause emesis also tend to cause the most severe emesis.

Different investigators have categorized specific cytotoxic chemotherapeutic agents as having a high, moderate, or low potential for inducing emesis (TABLE 1).[2–4] Generally, agents that cause emesis in more than 30% to 40% of patients are considered to have high emetogenic potential, whereas those with less than a 10% incidence are considered to have a low potential.

Patient factors

Individual patients also vary considerably in the degree of emesis they experience after chemotherapy. It is important to take a detailed history before starting a patient on chemotherapy, since certain clinical factors may increase or decrease the risk of developing treatment-induced emesis. These factors include:

Age. Younger patients are more likely than older patients to have emesis with the same agent or agents. In addition, younger patients are more likely to develop dystonic reactions to dopamine-blocking agents, which are often used to prevent and treat chemotherapy-induced emesis.[5,6]

Sex. Women experience more chemotherapy-associated emesis than men. Although the reason for this is uncertain, it may be because women are more likely than men to receive combination chemotherapy because these regimens are more commonly used for malignant diseases that mostly afflict women, such as breast cancer.

History of alcohol use. Patients with a history of chronic alcohol intake have less chemotherapy-induced emesis, particularly with highly emetogenic agents such as cisplatin.[7] Patients do not have to be current users of alcohol to experience this benefit. The reasons for this protection are not well understood.

Motion sickness. Patients with a history of motion sickness have a greater risk.

Concomitant radiation therapy and **previous exposure to chemotherapy** increase the risk.

Non–chemotherapy-related causes of emesis must be considered in patients who experience nausea and vomiting while receiving an antineoplastic drug. These include bowel obstruction, renal insufficiency, brain metastases, or other medications (eg, narcotic analgesics).

TYPES OF CHEMOTHERAPY-INDUCED EMESIS

Chemotherapy can cause several clinically distinct forms of emesis. The difference is important, since specific management strategies are based on the different pathophysiologic processes and inciting events of each form.

Acute emesis

In general, chemotherapy-induced emesis is considered acute if it begins within 1 to 2 hours after the start of chemotherapy; it may persist

for a number of hours. Notable exceptions: the commonly used chemotherapeutic agents cyclophosphamide and carboplatin may cause a more delayed acute emetic process that begins 8 to 10 hours after drug administration.

The severity of acute chemotherapy-induced emesis varies with the drug or drugs used.

Prevention is better than treatment. The most important point about managing acute chemotherapy-induced emesis is that prevention is far more effective than treatment of established nausea and vomiting. By giving effective antiemetic agents before giving cytotoxic chemotherapy, we can significantly lower the incidence of severe acute emesis, but it is very hard to stop nausea and vomiting once they have begun.

Furthermore, the incidence and severity of both delayed and anticipatory emesis (defined below) are substantially reduced if acute emesis can be prevented or minimized. It is in the prevention of acute chemotherapy-induced emesis that the currently available pharmacologic interventions have found their greatest success. Standard antiemetic regimens are discussed later in this article.

Delayed emesis can last for days and interfere with hydration and nutrition

Delayed emesis

Although the definition is somewhat arbitrary, most investigators consider emesis delayed if it develops more than 24 hours after the end of chemotherapy.

Unfortunately, the pathophysiology and neuropharmacology of delayed emesis are poorly understood. Treatment for this condition therefore has been far less successful than treatment to prevent acute chemotherapy-associated emesis.

The chemotherapeutic agent most commonly associated with delayed emesis is cisplatin.[8] When cisplatin is given in high doses (> 100 mg/m^2), most patients experience some level of delayed emesis. Other cytotoxic agents, including carboplatin, doxorubicin, and cyclophosphamide, also cause this syndrome. Overall, the greater the emetogenic potential of a chemotherapeutic agent or combination regimen, the more likely that the patient will experience delayed emesis.

One of the most distressing aspects of delayed chemotherapy-induced emesis is that it can persist for days. In addition, even a low level of persistent nausea and lack of appetite associated with this process can interfere with adequate hydration and nutrition. Patients may require intravenous fluid replacement or even hospitalization to control emesis.

Whereas the pathophysiologic processes of delayed and acute emesis differ, few patients who achieve complete control of acute nausea and vomiting experience severe delayed emesis. Therefore, the most important strategy to prevent delayed emesis may be to successfully prevent acute symptoms.

Anticipatory emesis

As the name implies, anticipatory emesis develops *before* chemotherapy is given.[9] This syndrome is generally associated with a previous episode of poorly controlled emesis during a prior treatment course.

Anticipatory emesis is a form of classic Pavlovian conditioning, in which patients are "conditioned" to associate specific sights, sounds, smells, and psychologic factors with the chemotherapy experience. Simply stepping into the chemotherapy room the morning of treatment, smelling the perfume worn on the day of the last treatment, or mentioning the name of the nurse who gave the drugs can initiate a process leading to stimulation of the vomiting center.

The manifestations of anticipatory emesis may be mild, including insomnia or anxiety several days before treatment, or severe and include intense nausea and vomiting even before the patient is given chemotherapy. It can have a devastating effect on a patient's quality of life.

We now understand that patients who have the most difficulty with both acute and delayed emesis have the greatest potential to experience anticipatory emesis.

Treatment of anticipatory emesis can be very difficult. Antianxiety medications taken several days before each chemotherapy course may help. In rare, severe cases, formal behavior-modification strategies may be required so that chemotherapy does not need to be discontinued.[10]

As with acute and delayed emesis, prevention of anticipatory nausea and vomiting is far more successful than attempting to substan-

tially alter an established, highly negative behavioral response to cytotoxic drug therapy.

ANTIEMETIC DRUGS

Serotonin-receptor antagonists

The introduction of serotonin-receptor antagonists more than a decade ago revolutionized the management of acute chemotherapy-induced emesis.[11,12] These agents are highly effective in most patients in preventing nausea and vomiting caused by even the most emetogenic chemotherapy, including cisplatin-based regimens, and they also have an extremely favorable toxicity profile.

Three serotonin-receptor antagonists are currently available in the United States for treating emesis: dolasetron (Anzemet), granisetron (Kytril), and ondansetron (Zofran; TABLE 2).[11–14] A number of trials compared the three agents and found them comparable in effectiveness and toxicity.[14,15] More recent studies found the agents highly effective when given orally, which is more convenient than parenteral administration, especially when patients must take them at home.[16]

Other important findings about serotonin-receptor antagonist antiemetic agents:

- Single-dose regimens appear to be as effective as multiple-dose regimens
- These drugs reach a plateau on their dose-response curves in preventing emesis, presumably because of blockade of all relevant receptor sites
- The effectiveness of this class of agents is potentiated by corticosteroids without increasing toxicity[17–19]
- Common side effects are headache, mild transient hepatic enzyme elevations, constipation, and minor prolongation of cardiac conduction intervals
- These agents do not produce dystonic reactions (unlike dopamine-blocking drugs).

Extensive data from randomized controlled clinical trials indicate that all patients should receive a serotonin-receptor antagonist if they are receiving a chemotherapeutic agent that has a high potential to cause nausea and vomiting.[20]

TABLE 2

Serotonin-receptor antagonists

DRUG	DOSAGE
Dolasetron	100 mg IV (single dose) 100 mg orally (single dose)
Granisetron	1–2 mg IV (single dose) 1 or 2 mg orally (single dose)
Ondansetron	8 mg IV (single dose) 16–24 mg orally (single dose) or 8 mg orally twice daily

Corticosteroids

Corticosteroids are the second most important group of drugs used to prevent chemotherapy-induced emesis.[20,21] Despite the known usefulness of this class of agents in this clinical setting, their exact mechanism of action remains unknown. The two most commonly used drugs are dexamethasone and methylprednisolone.

Several randomized trials showed that corticosteroids significantly potentiate the effects of serotonin-receptor antagonists in preventing emesis caused by agents with a high potential for serious toxicity (eg, cisplatin-based or carboplatin-based regimens).[17–19] Therefore, if patients have no contraindications to corticosteroids, the combination of a corticosteroid plus a serotonin-receptor antagonist should be standard therapy for patients undergoing chemotherapy that has moderate or high emetogenic potential.[20]

Corticosteroids potentiate serotonin-receptor antagonists

In addition, corticosteroids used alone are effective in preventing emesis produced by chemotherapeutic drugs of low or intermediate risk (eg, low-dose cyclophosphamide-based programs).[21] In this setting, more than 90% of patients can avoid emesis completely.

Although corticosteroids are well tolerated and can be given acutely in a variety of dose schedules, recent data indicate they have a dose-response curve in antiemetic action. For example, for dexamethasone, a single 20-mg dose appears to provide more protection against emesis than do lower-dose regimens.[22]

The major toxic effects of corticosteroids when given alone or in combination with other antiemetic drugs include an acute elevation in blood sugar and transient impairment

TABLE 3

Other agents used to prevent and treat chemotherapy-induced emesis

DRUG	DOSAGE
Dexamethasone	20 mg IV over 5 minutes (single dose) 20 mg orally (single dose)
Lorazepam	0.5–2 mg IV every 4–6 hours as needed 0.5–2 mg orally every 6 hours as needed
Metoclopramide	2–3 mg/kg IV every 2 hours 2–3 mg/kg orally every 2–3 hours
Haloperidol	1–2 mg IV every 4–6 hours 1–2 mg orally every 4–6 hours
Dronabinol	5 mg/m^2 orally every 4 hours
Prochlorperazine	10–20 mg IV every 3–4 hours 5–10 mg orally every 4–6 hours 25-mg suppository every 6 hours

TABLE 4

Regimens to prevent delayed chemotherapy-induced emesis

DRUG	DOSAGE
Metoclopramide plus dexamethasone	30–40 mg orally twice a day 8 mg orally twice a day (both for 3 days)
Ondansetron plus dexamethasone	8 mg orally twice a day 8 mg orally twice a day (both for 3 days)

of sleep patterns. They should be used cautiously in the presence of known or suspected infection.

Additional antiemetic agents

Other drugs occasionally used to prevent acute chemotherapy-induced emesis include **metoclopramide, prochlorperazine, chlorpromazine, haloperidol,** and **droperidol**.[23,24] Although these are active antiemetic agents, they are, in general, less effective and produce more toxicity (eg, dystonic reactions, agitation, sedation) than serotonin-receptor antagonists or corticosteroids. Use of these drugs should be limited to situations in which patients are unresponsive to serotonin-receptor antagonists or if rare excessive side effects occur (TABLE 3).

Cannabinoids are also used as antiemetic agents, particularly in younger patients, in whom their euphoric and dysphoric effects seem less common.[25,26] Other toxic effects of cannabinoids include ataxia, orthostatic hypotension, and dizziness.

Lorazepam is often used to reduce treatment-related anxiety, although it possesses limited direct antiemetic effects.[27] Its sedating effect may also decrease a patient's awareness of a low level of nausea.

Effective antiemetic therapy does not need to be prohibitively expensive, although it is important to consider the cost versus demonstrated benefit associated with individual antiemetic regimens.[28]

MANAGEMENT OF DELAYED CHEMOTHERAPY-INDUCED EMESIS

As previously noted, the effectiveness of currently available therapy to prevent or treat delayed chemotherapy-induced emesis is less than satisfactory. A number of single-agent and combination antiemetic regimens have been tested in randomized clinical trials, with conflicting results.[29–32]

Part of the difficulty in evaluating the benefits of treatment in this setting is that the symptoms can vary in severity from patient to patient, even with the same chemotherapy and the same acute antiemetic regimens. For some patients, delayed emesis may persist for days or even weeks, while for others the syndrome may be severe, but disappear after a much shorter time.

For a patient who experiences delayed emesis or who is receiving a chemotherapy regimen with high potential for causing it (eg, high-dose cisplatin), it is reasonable to consider using one of the regimens shown in TABLE 4.

Recent data suggest that a new class of agents, neurokinin-1 receptor antagonists, may be particularly effective in preventing delayed emesis due to highly emetogenic chemotherapy, such as high-dose cisplatin.[33,34] Further, these drugs appear to potentiate the effects of serotonin-receptor antagonists in preventing acute chemotherapy-induced emesis.

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