Actualizing Standards of Care for Chemotherapy-Induced Nausea and Vomiting

SALLY BARBOUR, PharmD, BCOP, CPP

From Duke University Medical Center, Durham, North Carolina

Author's disclosures of potential conflicts of interest are found on page 3 and at the end of this article.

Correspondence to: Sally Barbour, PharmD, BCOP, CPP, Duke University Medical Center, Box 3089, Durham, NC 27710.
E-mail: sally.yowell@duke.edu

Abstract

Despite the development of newer antiemetics such as serotonin ($5\text{-}HT_3$) and neurokinin-1 (NK-1) receptor antagonists, prevention of chemotherapy-induced nausea and vomiting (CINV) still presents a challenge to many patients and clinicians. This is especially true for patients with delayed CINV. Although clinicians have been aided by the availability of published evidence-based CINV guidelines from the American Society of Clinical Oncology, the National Comprehensive Cancer Network, and the Multinational Association of Supportive Care in Cancer, effective control of CINV is hampered by nonadherence to guidelines that may actually improve control of CINV by approximately 10%. The management of CINV has also been aided by estimates and categorization of the emetic potential of parenteral and oral anticancer agents, which reflect the likelihood of emesis after particular drugs are administered. Nonetheless, nausea related to chemotherapy is still a significant problem. In fact, it has been identified by patients as more distressing than chemotherapy-induced vomiting. Optimal CINV management for individual patients requires concerted, collaborative efforts among oncologists and advanced practitioners (APs) in oncology: nurse practitioners and clinical nurse specialists, pharmacists, and physician assistants. Each practitioner brings unique knowledge and insights to the table to plan, implement, and evaluate collaborative therapeutic measures. Although great strides have been made in antiemetic strategies that are incorporated into current guidelines, as oncology APs know, we must continue to work together to actualize patient-centered antiemetic care that minimizes the severity and impact of CINV on patients.

J Adv Pract Oncol 2014;5:17–30

The American Society of Clinical Oncology (ASCO; Basch et al., 2011), the National Comprehensive Cancer Network (NCCN; Ettinger et al., 2012), and the Multinational Association of Supportive Care in Cancer (Roila et al., 2010) have each developed practice guidelines for the management of chemotherapy-induced nausea and vomiting (CINV). Many hospitals and clinics

Table 1. Principles of Antiemetic Use in the Chemotherapy-Induced Nausea and Vomiting Setting

- The goal of antiemetics for CINV: Prevent vomiting and prevent nausea
- Administer antiemetics prophylactically and schedule them for duration of risk for CINV
- Match antiemetic potency to emetogenic potential of chemotherapy
- Multidrug regimen: Base antiemetics on most emetogenic agent in the combination
- Combine antiemetic agents that have different mechanisms of action
- Individualize antiemetic regimens considering:
  - Prior experience with antiemetics and CINV
  - Patient risk factors
- Use the lowest fully effective antiemetic dose(s)
- Oral and IV formulations of modern antiemetics (5-HT_3 antagonists and NK-1 antagonists) have equivalent efficacy
- Choice of particular agents may be based on cost and patient factors
- Consider side effects of each antiemetic
- Consider other nonchemotherapy causes of nausea and vomiting, as appropriate

Note. CINV = chemotherapy-induced nausea and vomiting. Information from Basch et al. (2011), Ettinger et al. (2014).

use one of these or have adapted parts of them into their own guidelines.

There are many similarities among the ASCO, MASCC, and NCCN guidelines, but they are not identical. Only the ASCO and MASCC guidelines state that their purpose is to be completely evidence-driven (Grunberg, 2009). This philosophy allows clinicians to have trust in the validity of guideline information, but it is limited by the absence of high-level evidence to support some clinical situations. The NCCN guidelines, on the other hand, do not demand that all evidence be supported by randomized, prospective, adequately powered studies. The NCCN guidelines are more practical in many instances because they allow some less stringent evidence to support recommendations, which may be the best evidence we have at the time a guideline is promulgated.

In any case, the two main goals of guidelines in general are to educate clinicians and to aid them in making treatment decisions. The focus of this article is to review and consider practical application of current antiemetic guidelines, particularly for patients receiving highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC).

DECONSTRUCTING ANTIEMETIC GUIDELINES

There are several principles that underlie all antiemetic guidelines (Table 1). The first is the importance of prophylaxis in the prevention of acute (that occurring within the first 24 hours after chemotherapy administration) *and* delayed CINV (that occurring after 24 hours for a few to several days), which requires diligent and focused assessment and application of evidence-based antiemetic use. This extends from primary prophylaxis to secondary interventions if a patient does not do as well as anticipated (perhaps because of nausea and vomiting related to their cancer, another illness, or medications).

It must be emphasized that guidelines are just that: guidelines. They aid clinicians in making evidence-based management decisions, but they are not absolute rules for individual patients. One should remember that guidelines are helpful, but guidelines do not know *your* patient. One limitation of current guidelines is that they are focused on a single-day regimen and do not provide clear direction for managing CINV with multiday chemotherapy regimens. In addition, the guidelines appear to be better geared toward initial CINV as opposed to delayed CINV, which remains a problem. Table 2 includes some pros and cons associated with the use of antiemetic guidelines.

The management of CINV has been greatly facilitated by emetogenicity classification schema, which reflect the likelihood of acute emesis after treatment with particular agents. Chemotherapeutic and targeted agents are classified as having high (> 90%), moderate (30% to 90%), low (10% to 30%), or minimal (< 10%) emetogenic potential. (Roila, Hesketh, & Herrstedt, 2006). All patients whose risk for CINV is ≥ 10% should receive prophylactic antiemetics to prevent acute CINV. On the other hand, scheduled antiemetics for delayed CINV are recommended only for patients receiving HEC or MEC. See the article by Teresa Scardino on page 7 of this supplement for more discussion of classification schema.

PERCEPTIONS VS. REALITY

As mentioned previously, currently recommended standard-of-care antiemetics are better at preventing chemotherapy-induced vomiting (CIV) than chemotherapy-induced nausea (CIN)—especially delayed nausea (Hesketh, Sanz-Altamira, Bushey, & Hesketh, 2012). We know that delayed CIV is universal after high-dose cisplatin, but it is common with other HEC and MEC agents too.

Several investigators have documented the problems of inadequate follow-up with patients after chemotherapy, starting with a widely quoted study by Grunberg and colleagues (2004). These investigators looked at 14 oncology practices in the United States and Europe and compared how oncologists' and oncology nurses' predictions of acute and delayed CINV compared with what their patients who were receiving HEC or MEC actually reported. Most patients received standard-of-care antiemetics before chemotherapy: 97% received a serotonin subtype 3 (5-HT_3) antagonist and 78% got a corticosteroid. Clinicians were rather accurate about how many of their patients would have acute CINV, but more than 75% of physicians and nurses underestimated their patients' experiences of delayed CIN and CIV—whether the patients received HEC or MEC (see Figure). Clinicians recognized that nausea was a greater problem than vomiting on the day of chemotherapy but missed the fact that 52% to 60% of patients had delayed CIN and 27% to 50% had vomiting on the days *after* chemotherapy.

Table 2. Pros and Cons of Antiemetic Guidelines

Pros
- Aid in clinical decision-making
- When followed, ensure minimal standard-of-care antiemetic coverage
- Driven by best evidence (and somewhat informed by clinical expertise)
- Frequently updated (NCCN)

Cons
- Focus on single-day chemotherapy regimens
- Do not account for patient variability
- No second-line recommendations
- "Best" antiemetics may be cost prohibitive or not allowed in institutional formulary

Note. NCCN = National Comprehensive Cancer Network.

More recent studies, even those performed after the advent of neurokinin 1 (NK-1) antagonists, have arrived at similar conclusions. Delayed CIN and CIV were more frequent than oncology clinicians predicted (Liau et al., 2005; Majem et al., 2011). Remarkably, this was more likely in patients who received regimens that did not include cisplatin than in patients who received cisplatin.

If you consider these findings in light of what patients have told us, the problem of CIN becomes even more apparent. A series of small surveys were undertaken in which patients rated which side effects and events surrounding chemotherapy that they found to be the worst. Coates and others

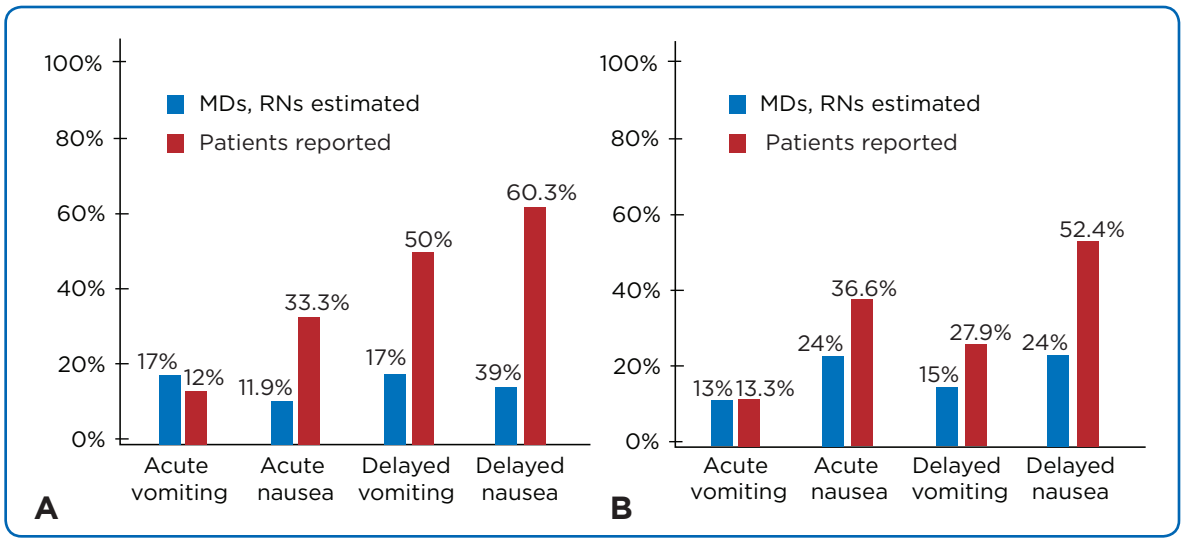

Figure. Perception vs. reality: Clinicians' predictions and patients' reports about CINV. (A) Highly emetogenic chemotherapy. (B) Moderately emetogenic chemotherapy. Adapted from Grunberg et al. (2004).

(1983) published the first such report when 5-HT_3 and NK-1 antagonists were not yet available and antiemetic research for CINV was in its infancy. As you might suspect, patients ranked vomiting as the most severe side effect and nausea as the second worst (Table 3). When the same investigators repeated the study a decade or so later, the effects of 5-HT_3 antagonists on vomiting seem clear: Patients ranked it fifth. Yet nausea was ranked as the worst side effect of chemotherapy (Griffin et al., 1996).

In two more small studies in the 1990s, patients also rated nausea to be the worst side effect (de Boer-Dennert et al., 1997; Lindley et al., 1999). In the last such study, NK-1 antagonists had become available; patients ranked nausea as the second worst side effect (Hofman et al., 2004). Although these studies can be criticized for methodologic flaws, they still give us important information that we should heed. No other studies like these have been reported since 2004, but it would be interesting to know how patients rank CIN and CIV today. All of these findings highlight the need to maximize currently available antiemetics, to continue the search for more effective antiemetic therapies for many of our patients, and to continue to improve upon follow-up with patients after chemotherapy (see the article by Teresa Scardino on page 7 of this supplement).

CONSIDERATIONS IN ANTIEMETIC MANAGEMENT

Advanced practitioners should first consider the emetogenicity of the patient's chemotherapy regimen, which is the most important factor that predicts CINV and hence antiemetic selection. Current ASCO, MASCC, and NCCN antiemetic recommendations are similar, as can be seen in Table 4.

Advanced practitioners should collect a patient history regarding prior experiences with nausea and vomiting, associated risks, and other factors before selecting an antiemetic regimen for CINV and/or considering the possible need for additional or breakthrough antiemetics. If a patient develops nausea and vomiting after chemotherapy, it may not be solely related to emetogenic chemotherapy but partly caused or exacerbated by other factors. Potential factors are GI problems (partial or complete bowel obstruction, hepatomegaly, or gastroparesis), central nervous system pathology (e.g., brain metastases or vestibular dysfunction), metabolic deficiencies (e.g., electrolyte imbalance or uremia), concomitant drugs such as opioids or other anticholinergic agents, and psychological factors such as anticipatory nausea and anxiety (Navari, 2012). An AP might discuss the use of an antianxiety medication such as lorazepam before chemotherapy, which might decrease anxiety levels and increase a sense of control.

ANTIEMETICS FOR CINV

Most APs are familiar with the commonly used antiemetics, so this section will include a few details that clinicians may not have considered. Standard-of-care antiemetics include 5-HT_3 antagonists, NK-1 antagonists, and corticosteroids. Older antiemetics may be beneficial for patients who have breakthrough nausea and vomiting.

5-HT_3 Antagonists

The US Food and Drug Administration (FDA) has approved the first-generation 5-HT_3 antagonists dolasetron, granisetron, and ondansetron; palonosetron is the only second-generation 5-HT_3

Table 3. Patient Perceptions of the Most Severe Side Effects of Chemotherapy

Rank	Coates et al. (1983)	Griffin et al. (1996)	de Boer-Dennert et al. (1997)	Lindley et al. (1999)	Hofman et al. (2004)
1	Vomiting	Nausea	Nausea	Nausea	Fatigue
2	Nausea	Constantly tired	Hair loss	Loss of hair	Nausea
3	Loss of hair	Loss of hair	Vomiting	Constantly tired	Sleep disturbances
4	Thought of coming for treatment	Effect on family	Constantly tired	Vomiting	Weight loss
5	Length of time for treatment	Vomiting	Having to have an injection	Changes in the way things taste	Hair loss

Table 4. Current Antiemetic Guideline Recommendations for Chemotherapy Induced Nausea and Vomiting

		ASCO	MASCC	NCCN
Highly Emetogenic Chemotherapy				
Acute CINV	**Before chemotherapy:** **5-HT$_3$ RA** (use 1): dolasetron, granisetron (po, IV, or transdermal patch), ondansetron (16–24 mg po or 8–16 mg IV), or palonosetron 0.25 mg IV (preferred, day 1 only) **+ NK-1 RA** aprepitant 125 mg or fosaprepitant 150 mg (day 1 only) **+ Dexamethasone** 12 mg po or IV (20 mg if with olanzapine) ***OR*** **Olanzapine** 10 mg po + **palonosetron** 0.25 mg IV + **dexamethasone** 20 mg IV or po **± lorazepam** 0.5–2 mg po, IV, or SL every 4–6 hr **± H$_2$ RA or PPI**	✓ ✓	✓	✓ ✓ ✓ ✓
Delayed CINV	• **NK-1 RA:** aprepitant 80 mg po days 2–3 (if 125 mg given day 1) ***OR*** • **Olanzapine:** 10 mg po, days 2–4 if given on day 1 ***OR*** • **Dexamethasone** 8 mg po days 2–4 (once daily on days 3 and 4 if given with aprepitant; twice, daily if given with fosaprepitant) **± lorazepam** po, IV, or SL every 4–6 hr days 2–4 **± H$_2$ RA or PPI**	✓ ✓ ✓	✓ ✓	✓ ✓ ✓ ✓ ✓
Moderately Emetogenic Chemotherapy				
Acute CINV	**Before chemotherapy:** **5-HT$_3$ RA*** (use 1): dolasetron po, granisetron (po, IV, or transdermal patch), ondansetron (16–24 mg po or 8–16 mg IV) or palonosetron 0.25 mg IV (preferred, day 1 only) **+ Dexamethasone** 12 mg po ***OR*** • **Olanzapine*:** 10 mg po + **dexamethasone** 12 mg po * **Add NK-1 RA:** aprepitant 125 mg (for select patients) **± lorazepam** 0.5–2 mg po, IV, or SL every 4–6 hr **± H$_2$ RA or PPI**	✓ ✓ ✓	✓ ✓	✓ ✓ ✓ ✓ ✓
Delayed CINV	• **5-HT$_3$ RA** if palonosetron not used day 1: dolasetron, granisetron, ondansetron days 2-3 ***OR*** • **Dexamethasone** 8 mg po or IV days 2–3 ***OR*** • **NK-1 RA:** if aprepitant given day 1; 80 mg po days 2–3 +/- dexamethasone ***OR*** • **Olanzapine:** 10 mg po days 2–4 if given on day 1 **± lorazepam** 0.5–2 mg po, IV, or SL every 4–6 hr days 2–4 **± H2 blocker or PPI**	✓ ✓ ✓	✓ ✓	✓ ✓ ✓ ✓
Low Emetogenic Chemotherapy (repeat each day of multiday chemotherapy)				
Acute CINV	• **Dexamethasone** 20 mg po or IV/day ***OR*** • **Metoclopramide** 10–40 mg po or IV; then every 4–6 hr PRN ***OR*** • **Prochlorperazine** 10 mg po, then every 6 hr PRN (max 40 mg/day) ***OR*** • **5-HT$_3$ RA** (use 1): dolasetron 100 mg po, granisetron 2 mg po once or 1 mg bid, ondansetron (16–24 mg po) **± lorazepam** 0.5–2 mg po or IV every 4–6 hr PRN **± H2 blocker or PPI**	✓ ✓ ✓ ✓ ✓	✓ ✓ ✓ ✓	✓ ✓ ✓ ✓ ✓ ✓
Delayed CINV	No routine treatment for delayed CINV; treat breakthrough as needed	✓	✓	✓
Minimal Emetogenic Potential				
	No routine prophylaxis; treat breakthrough as needed	✓	✓	✓

Note. ASCO = American Society of Clinical Oncology; MASCC = Multinational Association of Supportive Care in Cancer; NCCN = National Comprehensive Cancer Network; CINC = chemotherapy-induced nausea and vomiting; RA = receptor antagonist; PPI = proton pump inhibitor.

antagonist available (Boccia, Grunberg, Franco-Gonzales, & Voisin, 2013). All of these are highly selective for 5-HT_3 receptors and administered 30 minutes before chemotherapy. The exception is the granisetron patch, which should be applied 24 to 48 hours in advance (Keating, Duggan, & Gurran, 2012). Oral and IV formulations given at equivalent doses are equally efficacious (Basch et al., 2011).

Pharmacokinetic data are available for 5-HT_3 antagonists, which reach peak concentration within 0.5 to 2 hours of administration (Blower, 2002; McNulty, 2007; Roila & Del Favero, 1995; Stoltza, Parisib, Shahc, & Macciocchi, 2004; Yang & Scott, 2009). They have structural, binding, and half-life differences but are similarly effective when administered once a day, suggesting that half-life and duration of action are not directly related (Table 5; Blower, 2002; McNulty, 2007; Roila & Del Favero, 1995; Stoltza, Parisib, Shahc, & Macciocchi, 2004; Yang & Scott, 2009).

Palonosetron has a much higher binding affinity for 5-HT_3 receptors, a longer half-life than the first-generation 5-HT_3 antagonists, and a high oral bioavailability. Palonosetron is not better than a first-generation 5-HT_3 antagonist for acute CINV, but it has been shown to be superior for delayed CINV after MEC; it is the only 5-HT_3 antagonist FDA-approved for this use (Gonullu, Demircan, Demirag, Erdem, & Yucel, 2012; Likun, Xiang, Yi, Xin, & Tao, 2011). However, one recent prospective, randomized, double-blind study of 944 evaluable patients receiving HEC or MEC examined the effects of different combinations of antiemetics on nausea (Roscoe et al., 2012). Investigators found that palonosetron was no more effective than granisetron for delayed CIN (both were given with dexamethasone on day 1 and with prochlorperazine on days 2 and 3).

Despite receiving 5-HT_3 antagonists prescribed according to antiemetic guidelines, 20% to 30% of patients experience breakthrough CINV. This may be related to pharmacogenomic variability in 5-HT_3 receptor subunits, differences in cytochrome P450 (CYP450) metabolism, or variations in drug transport within the body (Trammel, Roederer, Patel, & McLeod, 2013). Only CYP450 2D6 (CYP2D6) has been shown to have any practical application thus far: It is involved in the metabolism of all 5-HT_3 antagonists (except granisetron).

There are numerous alleles for the *CYP2D6* gene, which is involved in the metabolism of about 25% of all drugs (Wang et al., 2009). Most people inherit two copies of "wild type" alleles, which makes them a "normal" intermediate (IM) or an extensive drug metabolizer (EM). However, if an individual inherits two inactivated *CYP2D6* genes, he or she will be a poor metabolizer (PM) with inactive enzymes that result in higher and persistent 5-HT_3 antagonist levels, more adverse effects, and perhaps drug-drug interactions. On the other hand, an ultrametabolizer (UM) inherits and expresses multiple copies of the *CYP2D6* gene, which leads to extremely rapid metabolism of 5-HT_3 antagonists (ondansetron, dolasetron, and palonosetron) and other drugs metabolized by this isoenzyme, with more severe nausea and vomiting as a result.

Table 5. Antiemetic Selection Considerations: Serotonin (5-HT_3) Antagonists

Agent[a]	Receptor binding affinity	Half-life	Oral bioavailability	Metabolism	Comments
Dolasetron	9.8 (PA_2)	7–9 hr	75%	CYP2D6[b], CYP3A	• At equivalent doses have equivalent safety, efficacy • Single doses preferred • Use interchangeably • Consider another 5-HT_3 antagonist if first not effective
Granisetron	8.42 pKi	4.91–12 hr	65%	CYP3A	
Ondansetron	8.07 pKi	3.5–5.5 hr	56%–60%	CYP2D6, CYP3A4[b], CYP1A2, CYP2E1	
Palonosetron	10.4 pKi	37–40 hr	97%	CYP2D6[b], CYP3A, CYP1A1	

Note. Information from Blower (2002), McNulty (2007), Roila & Del Favero (1995), Stoltza et al. (2004), Yang & Scott (2009).
[a]See Table 4 for doses. [b]Dominant role in metabolism.

Kaiser and colleagues (2002) confirmed that incidence of CIV and CIN was independent of chemotherapy emetogenicity level but related to the *CYP2D6* genotype. However, they concluded that about 50 patients would need to be genotyped for *CYP2D6* to protect 1 patient from severe CINV. Because gene testing is expensive and not practical for *CYP2D6*, a patient who does not have adequate control with one 5-HT_3 antagonist may benefit by switching to another (de Wit, Aapro, & Blower, 2005; Thompson & Lummis, 2006; Yavas, Dogan, Yavas, Araz, & Ata, 2012).

The most common side effects of 5-HT_3 antagonists are constipation, headache, and dizziness. Headache and constipation are less common with oral than IV palonosetron (Boccia, Grunberg, Franco-Gonzales, Rubenstein, & Voisin, 2013); this may be true for other 5-HT_3 antagonists.

There has been a great deal of study into electrocardiographic (ECG) QTc changes—a class effect of first-generation 5-HT_3 antagonists that has not been documented with transdermal granisetron. Statistically significant QTc changes have not been documented with palonosetron (Boccia et al., 2013; Likun et al., 2011; Mason et al., 2012; Smith, Cox, & Smith, 2012). Largely clinically insignificant ECG interval changes (about 5% in the QT interval) occur 1 to 2 hours after administration but return to baseline within 24 hours (Smith et al., 2012). Ondansetron and dolasetron block sodium channels that may lead to a widening of the QRS complex as well as block potassium channels with up to about 5% QT prolongation (Smith et al., 2012).

In rare instances, potentially fatal cardiac arrhythmias such as torsades de pointes have occurred with QTc prolongation (Navari & Koeller, 2003). This effect is likely related to larger doses and IV administration. In response, the FDA requested that single doses of ondansetron 32 mg IV and dolasetron 100 mg IV be removed from the market because of prolonged QT, PR, and QRS intervals and the potentially fatal cardiac arrhythmia that can occur with larger IV doses. New labeling includes recommendations limiting ondansetron to single IV doses of ≤16 mg and advising against the use of IV dolasetron for CINV. Other cautions are to avoid use in patients with congenital long-QT syndrome and to monitor ECG in certain patients (e.g., those with hypokalemia or hypomagnesemia, congestive heart failure or other heart disease, bradycardia, and renal impairment as well as those taking other medications that increase the risk for QTc prolongation). In patients with such preexisting cardiac risks, palonosetron may be the best 5-HT_3 antagonist to use (Boccia et al., 2013; Smith et al., 2012).

NK-1 Antagonists

The introduction of the oral NK-1 antagonist aprepitant, and later the IV formulation fosaprepitant (the prodrug of aprepitant), has significantly improved the prevention of acute *and* delayed CINV in patients receiving HEC and MEC—on the order of about 17% over using a 5-HT_3 antagonist plus dexamethasone—and may decrease the risk for hospitalization for intractable delayed CINV (Hesketh et al., 2003; Osorio-Sanchez, Karapetis, & Koczwara, 2007; Warr et al., 2005). This benefit was confirmed in a meta-analysis of 17 studies that included 8,173 eligible patients receiving HEC or MEC (dos Santos, Souza, Brunetto, Sasse, & da Silveira Nogueira Lima, 2012). The addition of aprepitant or another NK-1 antagonist to standard antiemetic therapy (a 5-HT_3 antagonist plus dexamethasone) significantly improved overall (1 to 120 hours after chemotherapy) complete response (no vomiting and no rescue medications), 72% vs. 54%, respectively ($p < .001$), and the likelihood of no acute or delayed CINV. The risk for severe infection was greater in patients who received the additional NK-1 antagonist vs. the standard antiemetic therapy group (6% vs. 2%, $p < .001$). The authors recognized that limitations in analyzing retrospective data do not allow conclusions to be drawn about the clinical significance of these data. Nonetheless, it may be prudent to be vigilant for respiratory and/or urinary tract infections (not associated with febrile neutropenia) in patients who are receiving aprepitant.

The most common side effects of aprepitant are diarrhea, hiccups, heartburn, dizziness, and asthenia/fatigue; neutropenia is a serious but rare adverse effect (Massaro & Lenz, 2005). Another concern with aprepitant is that it is a substrate (metabolized by) and moderate inhibitor of CYP3A4, a 2C9 inducer, and a 3A4 inhibitor, so it has several potential drug interactions (Table 6; Aapro & Walko, 2010; Massaro & Lenz, 2005; Sanchez et al., 2004).

Table 6. Antiemetic Selection Considerations: Potential Aprepitant/Fosaprepitant Drug Interactions

Agent/substance	Effect with aprepitant	Management
Corticosteroid (dexamethasone	Increases corticosteroid serum concentration	Decrease oral dexamethasone dose by 50%, IV dose by 25%
Warfarin	5 days after aprepitant dosing: 34% decrease in warfarin trough concentration, 14% decrease in PT	Monitor during this period for 7–10 days
Hormone contraceptive	Decreases efficacy	Use additional barrier contraceptive
CYP3A4 inducers • Rifampin • Carbamazepine • Phenytoin	May result in decreased plasma concentrations of aprepitant	Monitor for CINV
CYP3A4 inhibitor (ketoconazole)	Increases plasma level of aprepitant (decreases aprepitant metabolism by 98%)	Use caution with aprepitant
Diltiazem	Increases plasma concentration of both	Monitor for toxicity
Benzodiazepines	Increases benzodiazepine (e.g. midazolam, diazepam, alprazolam) plasma concentration	Monitor for toxicity
Grapefruit juice	Increases aprepitant serum concentration	• See www.rxlist.com • Avoid concurrent use
St. John's wort	May decrease plasma aprepitant levels	• See www.rxlist.com • Discuss patient's use of nutraceuticals, health food products • Instruct patient to avoid taking St. John's wort

Note. PT = prothrombin time; INR = international normalized ratio.

Oral aprepitant is administered as a 3-day regimen, starting with 125 mg 1 hour prior to chemotherapy administration and 80 mg on days 2 and 3, whereas a single dose of IV fosaprepitant 150 mg over 20 to 30 minutes is administered once before chemotherapy (Hesketh et al., 2003). Fosaprepitant may provide potential benefits for patients who are unable to tolerate oral administration of antiemetics during an episode of chemotherapy-induced nausea.

Glucocorticoids

Since the 1980s, short courses of a glucocorticoid—most often dexamethasone—have been widely used as single agents for low emetogenic risk chemotherapy regimens and in combination with 5-HT_3 antagonists (with or without NK1 receptor antagonists) for more emetogenic regimens (Joss et al., 1994). Glucocorticoids alone represent insufficient first-line therapy for patients receiving either MEC or HEC agents. However, the antiemetic efficacy of the 5-HT_3 receptor antagonists is significantly enhanced by the addition of a glucocorticoid (Joss et al., 1994). Ioannidis, Hesketh, and Lau (2000) performed a meta-analysis of previous studies that confirmed that dexamethasone (doses ranged from 8 to 100 mg, most commonly 20 mg) was superior to placebo or no treatment and increased the likelihood of complete prevention of both acute CIV and delayed CIN by 25% to 30%.

Most studies of glucocorticoids as antiemetics reported mild and tolerable side effects (Ioannidis et al., 2000; Joss et al., 1994). However, other investigators are concerned about the moderate to severe side effects of dexamethasone administered for delayed CINV (e.g., insomnia, GI symptoms, agitation, increased appetite, weight gain, skin rash, and depression) and advocate reducing the use of dexamethasone as an antiemetic for some patients or particular clinical situations (Olver et al., 2011).

To that end, one group of investigators examined the effects of two different antiemetic regimens: IV palonosetron 0.25 mg plus dexamethasone 8 mg before chemotherapy, or the same regimen with oral dexamethasone 8 mg on days 2 and 3 in chemotherapy-naive patients

with breast cancer who were to receive an anthracycline/cyclophosphamide regimen (Celio et al., 2013). Women older than 50 were more likely than younger women to have complete prevention of CINV (no vomiting episodes and no use of rescue antiemetics), but after adjusted analysis, complete prevention rates were no different for patients who got dexamethasone vs. those who did not. However, fewer than 60% of patients had complete prevention of CINV.

Another study that also included patients with breast cancer receiving anthracycline/cyclophosphamide chemotherapy asked a similar question: Would there be a difference in antiemetic control in patients who got dexamethasone (4 mg twice a day) or aprepitant 80 mg per day, each for 2 days, after all patients got IV palonosetron 0.25 mg and dexamethasone 8 mg, and oral aprepitant 125 mg before chemotherapy (Roila, Ruggeri, Ballatori, Del Favero, & Tonato, 2014)? There were no differences in complete prevention rates for acute CINV (87.6% for dexamethasone and 84.9% for aprepitant) or delayed CINV (79.5% for both groups). Insomnia and heartburn were significantly more likely in patients receiving dexamethasone, but there were no differences in quality of life as measured by the Functional Living Index–Emesis (FLIE). Thus, it seems that dexamethasone has utility for CINV, but patient ratings of intolerable side effects must be included to justify the expense of using aprepitant instead.

Other Adjunctive Agents

Because some patients with cancer report dyspepsia or heartburn after chemotherapy, the NCCN guidelines (2014) recommend a histamine type 2 (H2) blocker (e.g., cimetidine or famotidine) or a proton pump inhibitor (PPI, such as omeprazole or lansoprazole) to decrease gastric acid production. These may provide subjective relief of dyspeptic symptoms including nausea, vomiting, early satiety, and postprandial fullness, which are also symptoms of gastroparesis for which a prokinetic agent such as metoclopramide would be suggested (Haans & Masclee, 2007).

One study examined changes in gastric motility in patients with cancer who had received chemotherapy and antiemetics to control their CINV (Riezzo, Clemente, Leo, & Russo, 2005). No patients had symptoms of dyspepsia or abnormal electrogastrography (EGG) before chemotherapy, but after chemotherapy 13 of 25 had symptoms of dyspepsia or dysmotility (nausea, early satiety, and postprandial fullness) as well a significant association between tachygastria and susceptibility to nausea. The question of whether to routinely administer one of these drugs before chemotherapy or to wait until after chemotherapy to identify patients who might benefit has not been answered. Adverse effects are uncommon with short-term use of PPIs, but longer-term use is associated with osteoporosis and fractures, hypomagnesemia, enteric infections, interstitial nephritis, pneumonia, and gastric acid rebound (Vakil, 2012). There are few reports of adverse effects with H2 blockers, with the exception of an increased risk for hospital-acquired pneumonia (Eom et al., 2011).

PATIENTS REFRACTORY TO FIRST-LINE ANTIEMETICS

Two common patient scenarios include (1) the patient who does not experience acceptable antiemetic control for acute *and* delayed CINV, and (2) the patient whose control of acute CINV is adequate but delayed or breakthrough CINV occurs. For the first type of patient, the initial therapeutic approach is to consider other factors that may be magnifying the nausea and vomiting (if this was not done in the initial patient assessment). The AP also needs to determine if CINV started within a few hours of chemotherapy administration (implying that first-line antiemetics were not effective) or the next day after chemotherapy (delayed or breakthrough CINV).

If CINV occurs on the day of therapy, strategies include changing to an alternative 5-HT_3 antagonist and/or adding aprepitant or fosaprepitant (if not used) for the next chemotherapy cycle. The idea of incomplete cross-tolerance to 5-HT_3 antagonists was shown with a pilot study report that included patients who received tropisetron (a 5-HT_3 antagonist available in Europe) before cisplatin 70 mg/m^2 (de Boer, de Wit, Stoter, & Verweij, 1995). Out of 49 patients, 14 experienced 5 or more bouts of vomiting or more than 4 hours of nausea on the day of chemotherapy: 12 were switched to ondansetron for delayed CINV and 2 for acute CINV with the next cycle. Only three patients (25%) regained complete prevention of de-

layed CINV but had better control of acute CINV in the next chemotherapy cycle.

In another small phase II study, 89 patients got ondansetron 8 mg IV plus dexamethasone 8 mg IV before chemotherapy and were randomized to IV ondansetron 8 mg or oral ondansetron 16 mg for breakthrough/delayed CINV (Fabi et al., 2008). Fifty percent of patients required antiemetics for delayed CINV. It is interesting to note that even when the same antiemetic was used, about 73% of those who got oral ondansetron and 41% who got IM ondansetron experienced complete control of vomiting (p = .01), and 82% and 32%, respectively, achieved complete control of nausea (p = .001). Patients who got oral ondansetron reported greater satisfaction than those who got IM ondansetron. These results may be somewhat related to the short half-life of ondansetron, but the authors suggested that oral ondansetron might be a reasonable rescue antiemetic for patients who fail palonosetron.

Another recommended strategy for uncontrolled CINV is adding or changing to a second-line antiemetic such as oral olanzapine (10 mg/day for 3 days), a benzodiazepine such as lorazepam 0.5–2 mg every 6 hours, oral haloperidol 0.5–2 mg every 4 to 6 hours, oral metoclopramide 10–40 mg every 6 hours, or oral prochlorperazine 10 mg every 6 hours (NCCN, 2014). These were the antiemetics that were used for CINV before 5-HT_3 and NK-1 antagonists were available or are newer agents with evidence of effectiveness. For instance, oral olanzapine has been found to be superior to oral metoclopramide to control delayed CIV and CIN (70% vs. 31%, $p < .01$ and 68% vs. 23%, $p < .01$, respectively) and equivalent to aprepitant (both combined with palonosetron and dexamethasone) for acute and delayed CINV (Navari, Gray, & Kerr, 2011; Navari, Nagy, & Gray, 2013).

ADHERENCE TO ANTIEMETICS

Adherence is an important consideration for clinicians and patients. When clinicians prescribe guideline-recommended antiemetics, overall control of CINV improves by about 10% (Aapro et al., 2012; Gilmore et al., 2014). Still, even when patients receive guideline-driven antiemetics for CINV, a significant proportion of them will experience CIV or CIN. This is somewhat related to the fact that clinicians do not follow recommendations for delayed CINV as often as they follow recommendations for acute CINV (Ihbe-Heffinger et al., 2004). Similarly, patients receiving anthracycline-based chemotherapy who were adherent to antiemetics prescribed for delayed CINV as ordered were twice as likely (34% vs. 16.4%) to have complete control of delayed CINV than patients who did not take antiemetics as ordered (Chan, Low, & Yap, 2012).

Factors that may contribute to medication nonadherence among cancer patients may include side effects, inconvenience, and difficulty in swallowing tablets (Atkins & Fallowfield, 2006). Age may also play a role in nonadherence; one study found that adherence to antiemetics was lower in patients aged 49 years or younger than those aged 50 years or older (55% vs. 75%; Shih, Wan, & Chan, 2009). Misconceptions about the likelihood of side effects with corticosteroids can play a role in nonadherence as well (Chan, Low, & Yap, 2012).

ECONOMIC FACTORS

Poorly controlled CINV may lead to additional and unplanned office or emergency department visits and even hospital admissions. One study attempted to define the costs associated with uncontrolled delayed CINV between 2003 and 2007 (Burke, Wisniewski, & Ernst, 2011). One out of eight patients who received HEC or MEC in an outpatient setting made a hospital visit for delayed CINV, with an average cost of $5,300 (which would be even more substantial today). Another study found that 64.4% of patients had at least one episode of nausea or vomiting, even though all had received prophylactic antiemetics (Ihbe-Heffinger et al., 2004). Similarly, patients who experienced severe nausea had higher health-care utilization costs (emergency department visits, office visits, and hospitalizations) than patients with moderate or mild nausea (Haiderali, Menditto, Good, Teitelbaum, & Wegner, 2011). Other studies have shown similar findings, with higher costs associated with treating delayed CINV, particularly in patients who had received HEC (Craver, Gayle, Balu, & Buchner, 2011; Tina Shih, Xu, & Elting, 2007).

CLINICAL IMPLICATIONS

It is clear that interprofessional collaboration is critical to optimal antiemetic manage-

ment in patients undergoing chemotherapy that has at least low emetogenic potential. The value of having oncology APs, particularly an oncology pharmacist, as part of the care team has been recognized (Chan, Shih, & Chew, 2008). An oncology pharmacist can aid clinicians in interpreting research findings, particularly those relating to pharmacogenomics and pharmacoeconomics; monitor clinician adherence to institutional and evidence-based guidelines; and monitor and teach patients about the importance of adherence to antiemetics. Advanced practice nurses and physician assistants have similar and overlapping roles with pharmacists and physicians: teaching and monitoring patients for antiemetic adherence and intervening when antiemetics are not effective.

Oncology APs can also assist patients in weighing the risks and benefits associated with medications meant to control or prevent CINV. It is important to emphasize to patients that CINV is not a necessary part of chemotherapy to be endured, and that there is more than one option that can be explored if the first attempt does not bring about satisfactory control of acute and delayed CINV. Health literacy is crucial to patient education, as patients need to understand the relevant information before they can follow the recommended treatment regimens (Martin, Williams, Haskard, & Dimatteo, 2005; Kickbusch, 2001). To improve patient outcomes, APs in oncology should help patients to assimilate the relevant health information and align it with their own health beliefs.

Much has been learned about the etiology of CINV over the past several years, which has led to great strides in the prevention and control of CIV. However, a growing body of research substantiates the fact that chemotherapy-related acute and delayed nausea are still particularly thorny problems (Table 7). What we know is that chemotherapy-related nausea is a greater problem that chemotherapy-related vomiting (in terms of inadequate control), delayed nausea is more common than acute nausea, and nausea significantly affects patients' quality of life and daily functioning (Ballatori et al., 2007; Bloechl-Daum, Deuson, Mavros, Hansen, & Herrstedt, 2006; Cohen, de Moor, Eisenberg, Ming, & Hu, 2007; Pirri et al., 2013).

One study found that patients with breast cancer receiving doxorubicin experience significantly greater nausea ($p < .01$) than patients receiving doxorubicin for other tumors or those receiving cisplatin or carboplatin (Roscoe et al., 2010). Furthermore, Pirri and colleagues (2013) found that nausea, vomiting, and decreased appetite often occur together as a symptom cluster in patients receiving HEC and MEC, and that nausea predicts both vomiting and decreased appetite. Both CIV and CIN have negative effects on patients' quality of life, and delayed symptoms have a greater effect than acute CINV (Ballatori et al., 2007; Bloechl-Daum et al., 2006; Cohen et al., 2007; Pirri et al., 2013). Furthermore, the duration of delayed CIN and CIV was found to be more distressing to patients than the severity (Ballatori et al., 2007).

CONCLUSION

In summary, notable enhancements in understanding the physiology of emesis and beginning efforts to understand the mechanisms of nausea form the foundation of major improvements in preventing and managing CINV. Nonetheless, control of acute CIV has not been matched by similar improvements in preventing nausea—particularly delayed CIN—in the days after patients receive MEC or HEC. This is related to the fact that we continue to focus on control of vomiting in clinical trials of antiemetics despite the fact that patients tell us that inadequately controlled nausea—both acute and delayed—more negatively affects their quality of life and their ability to withstand the rigors of cancer chemotherapy.

The issues that require greater attention in the future are thus control of acute and delayed nausea, timely identification of patients who experi-

Table 7. Facts About Nausea and Quality of Life

- Nausea is a "hidden" symptom
- Delayed CINV may affect adherence to chemotherapy
- Nausea (± vomiting) affects patients' physical activities, social and emotional functioning, ability to eat or drink (as measured by the FLIE tool)
- Sustained nausea has a greater impact than vomiting on patients
- Patients characterize nausea as a hardship, distressing, overwhelming
- In terms of side effects, patients ranked CINV only better than death

Note. CINV = chemotherapy-induced nausea and vomiting; FLIE = Functional and Living Index–Emesis. Information from Ballatori et al. (2007), Bloechl-Daum et al. (2006), Cohen et al. (2007), Sun et al. (2005).

ence CINV despite standard-of-care antiemetics, and management of symptoms surrounding poor control of nausea that may actually exacerbate physical and psychological consequences such as dehydration, anorexia, and anxiety. In addition, we must all grapple with the issues of identifying structures and processes that improve professional caregiver and patient communication, as well as managing practical and ethical concerns surrounding access to extremely expensive antiemetics. All of these issues can be best addressed by APs working collaboratively with oncologists, payers, and politicians. ●

Disclosure

The author has no potential conflicts of interest to disclose.

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