Updates on the Understanding and Management of Chemotherapy-Induced Nausea and Vomiting

BETH EABY-SANDY, MSN, CRNP, OCN®, and VICTORIA SHERRY, MSN, CRNP, AOCNP®

From Abramson Cancer Center, Hospital of the University of Pennsylvania, and University of Pennsylvania School of Nursing, Philadelphia, Pennsylvania

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Correspondence to: Beth Eaby-Sandy, MSN, CRNP, OCN®, 3400 Civic Center Boulevard, 2nd Floor West, Perelman Center for Advanced Medicine, Philadelphia, PA 19104. E-mail: eabyb@uphs.upenn.edu

Abstract

Chemotherapy-induced nausea and vomiting (CINV) is a common adverse event for patients with cancer. Many advances over the past 2 decades have improved the treatment of CINV, thus increasing the quality of life of cancer patients. Understanding the pathophysiology and risk factors for CINV helps clinicians develop better treatments and strategies for prevention. Updates to the understanding and management of CINV occur very often due to intense study and interest in this common toxicity associated with cancer therapy. As a result, the optimal management of CINV changes continually, impacting patient care. Oncology advanced practitioners (APs) are often the primary contact and treating providers of CINV. This article will review the most recent updates in risk factors, pathophysiology, classifications, treatments, and changes incorporated into guidelines for the management of CINV, providing opportunities for APs to better understand and treat CINV.

J Adv Pract Oncol 2011;2:373–380

Chemotherapy-induced nausea and vomiting (CINV) is one of the most common and widely investigated adverse events (AEs) associated with cancer treatment. Although CINV remains a significant problem for patients undergoing chemotherapy, there have been many advances in the treatment of CINV as well as changes in the way we assess both the risk for CINV and CINV itself. As these changes occur frequently, it is difficult for oncology advanced practitioners (APs) to stay up to date on the optimal assessment and treatment strategies. This article will highlight the most recent updates in the assessment and treatment of CINV over the past 2 to 3 years.

Risk Factors

The most important risk factor for CINV is the level of emetogenic potential of the chemotherapeutic agents (Ettinger et al., 2007); see Table 1. Other risk factors for increased CINV are younger age, female sex, and history of low alcohol intake (≤ 4 drinks per week). There is no specific age identified in clinical trials when assessing risk for CINV, but the consensus in these trials has correlated that the younger the age, the greater the risk of CINV. A history of morning sickness with pregnancy, motion sick-

Table 1. Emetic Risk of Intravenously Administered Antineoplastic Agents

Emetic risk[a]	Agent
High (> 90%)	Carmustine Cisplatin Cyclophosphamide ≥ 1,500 mg/m^2 Dacarbazine Dactinomycin Mechlorethamine Streptozocin
Moderate (> 30%–90%)	Carboplatin Cyclophosphamide < 1,500 mg/m^2 Cytarabine > 1 g/m^2 Daunorubicin Doxorubicin Epirubicin Idarubicin Ifosfamide Irinotecan Oxaliplatin
Low (10%–30%)	Bortezomib Cetuximab Cytarabine ≤ 1,000 mg/m^2 Docetaxel Etoposide Fluorouracil Gemcitabine Methotrexate Mitomycin Mitoxantrone Paclitaxel Pemetrexed Topotecan Trastuzumab
Minimal (< 10%)	Bevacizumab Bleomycin Busulfan 2-Chlorodeoxyadenosine Fludarabine Rituximab Vinblastine Vincristine Vinorelbine

Note. [a]Incidence of emesis without antiemetics.

ness, and anxiety has also been associated with a higher risk of CINV (Eckert, 2001; Stricker & Eaby, 2010). Studies from 2009–2010 evaluating for risk factors of CINV are as follows:

- In a study of over 1,000 patients receiving cisplatin-based chemotherapy, a triple-drug antiemetic regimen of aprepitant (Emend), dexamethasone, and ondansetron improved complete response (defined as no emesis and no use of rescue therapy) in preventing CINV regardless of risk factors and eliminated the increased risk of CINV associated with female sex (Hesketh, Aapro, Street, & Carides, 2010).
- In patients with breast cancer who have one or more risk factors for CINV, the addition of aprepitant to a 5-hydroxytryptamine-3 (5-HT$_3$) receptor antagonist plus dexamethasone improved control of CINV from 38% to 66% no emesis in the control arm to 70% to 82% no emesis in the aprepitant-containing arm. In the small group of patients (3%) in this study who had no risk factors for CINV, aprepitant provided little clinical benefit (Warr, Street, & Carides, 2011).
- A study of Asian patients with breast cancer determined that while most (65%) of the patients adhered to their antiemetic regimens, severe nausea still affected 14.3% of patients, mostly in the delayed setting. Anxiety as a risk factor was not well established when only asking a single question of whether the patient is anxious, as opposed to a more comprehensive assessment. However, it was determined that when anxiety is present, it is a major risk factor contributing to CINV. Clinicians need to communicate with their patients and accurately assess for anxiety to help improve CINV control (Shih, Wan, & Chan, 2009).
- Two recent articles concurred that age is a major risk factor for CINV (Jakobsen & Herrstedt, 2009; Roscoe et al., 2010). In Jakobsen & Herrstedt, increased risk was observed in patients under the age of 65. In Roscoe et al., there were over 1,600 patients analyzed; in each decade of life category, the older the age, the less CINV reported. In addition, patients who perceived that they were more susceptible to nausea than their friends and family reported severe nausea 2.85 times more often than those who did not believe that they were more susceptible to nausea (Roscoe et al., 2010).

Pathophysiology

The pathophysiology of CINV has been better understood since the identification of the neurotransmitters and receptors involved in the process and the medications that target these pathways (Table 2). Chemotherapy activates receptors via neurotransmitters in three areas: the gastrointestinal (GI) tract, the chemoreceptor trigger zone, and the vomiting center (VC). Once activated by neurotrans-

mitters, the VC sends signals to the abdominal muscles and GI tract, respiratory tract, and the cranial nerves to cause vomiting or the feeling of nausea (Cunningham, 1997). There are two separate neurologic pathways involved in the process of nausea and vomiting: the peripheral pathway and the central pathway. The peripheral pathway is innervated primarily by the 5-HT_3 receptors binding with serotonin in the GI tract (Cunningham, 1997), and the central pathway is activated by substance P binding with neurokinin-1 (NK-1) receptors found in the central nervous system (Hesketh et al., 2003). Recent reviews and studies of this process suggest the following:

Table 2. Neurotransmitters and Pathways Involved in the Control of Chemotherapy-Induced Nausea and Vomiting

	CINV pathway and receptor	
Drug	**Central NK-1**	**Peripheral 5-HT_3**
Aprepitant	✓	
Fosaprepitant	✓	
Palonosetron		✓
Dolasetron		✓
Granisetron		✓
Granisetron transdermal system		✓
Ondansetron		✓

Note. 5-HT_3 = 5-hydroxytryptamine-1; CINV = chemotherapy-induced nausea and vomiting; NK-1 = neurokinin-1.

- The key neurotransmitters involved in emesis are serotonin, dopamine, and substance P, and the main way to treat CINV is by deactivating their corresponding receptors by blocking them from binding with these neurotransmitters (Navari, 2009).
- Additional neurotransmitters and receptors play roles in CINV other than 5-HT_3 receptors and NK-1 receptors; understanding their importance requires further study. There is a need to better understand the relationships between receptors and neurotransmitters involved in the process of CINV. Also, physicians and scientists could consider developing drugs that target multiple receptors in the CINV process (Frame, 2010).

Assessment and Classification

Chemotherapy-induced nausea and vomiting is commonly categorized as acute, delayed, or anticipatory. Each category can have different triggers and should be treated differently. Acute CINV occurs within the first 24 hours of receiving chemotherapy; delayed CINV occurs 24 to 120 hours after chemotherapy (Martin, 1996); anticipatory CINV occurs when a patient feels nausea or vomits prior to chemotherapy based on a past experience, which may be heightened by anxiety. In addition to these three main categories, CINV can also be refractory (or breakthrough), in which the patient experiences CINV because of inadequate or ineffective antiemetic treatments (Tipton et al., 2007). The most recent literature relating to assessment of CINV suggests the following:

- The specific cutoff time between acute and delayed CINV (24 hours) originated in cisplatin-based trials and may be somewhat arbitrary when applied to other chemotherapeutic agents (Feyer & Jordan, 2011). This may be important when clinicians observe a longer acute CINV phase or conversely, a delayed CINV phase, which may begin prior to the 24 hours, and are trying to utilize medication regimens that are recommended for each category.
- Acute CINV is likely mediated by the peripheral serotonin pathway; delayed CINV is likely mediated by the action of substance P at NK-1 receptors in the central pathway. Treatments should be geared toward the corresponding receptors (Langford & Chrisp, 2010).

Treatment

A wide array of antiemetic agents are available for the prevention and treatment of CINV.

5-HT_3 RECEPTOR ANTAGONISTS

5-HT_3 receptor antagonists dramatically improved acute CINV in the 1990s. Granisetron is available in both oral and transdermal formulations, and there are no significant differences in complete response rates between formulations (Grunberg, Gabrial, & Clark, 2007). Another 5-HT_3 receptor antagonist, palonosetron, has a

long half-life (approximately 40 hours) and minimal toxicity profile, which may make it more appealing than other 5-HT_3 receptor antagonists (Feyer & Jordan, 2011). Ondansetron and dolasetron are the other 5-HT_3 receptor antagonists available for use in the United States. The most recent studies of 5-HT_3 receptor antagonists suggest the following:

- A transdermal formulation may be preferable for patients with CINV for whom oral administration is difficult and extended duration is desired (Frame, 2010).
- A large, multicenter Japanese trial of over 1,100 patients demonstrated that palonosetron was noninferior to granisetron for acute CINV in patients receiving highly emetogenic chemotherapy (HEC) when given with dexamethasone. Palonosetron was more efficacious at preventing delayed CINV than was granisetron, but there was no use of prophylactic granisetron given in the delayed setting (Saito et al., 2009). Although it has been assumed that 5-HT_3 receptor antagonists do not play a significant role in preventing delayed CINV, this study calls for further study into this concept.

NK-1 RECEPTOR ANTAGONISTS

In 2003, oral aprepitant was the first NK-1 receptor antagonist to be approved by the US Food and Drug Administration (FDA) for CINV. When combined with a corticosteroid and a 5-HT_3 receptor antagonist, aprepitant has been shown to prevent acute and delayed CINV in patients receiving HEC. The IV formulation fosaprepitant received approval from both the FDA and the European Medicines Agency in January 2008 for the treatment of CINV in patients receiving HEC and moderately emetogenic chemotherapy (MEC) when given with the aprepitant bi-pack on days 2 and 3. The most recent changes and updates for NK-1 receptor antagonists include the following:

- A study was conducted to compare aprepitant vs. placebo in addition to a 5-HT_3 receptor antagonist and dexamethasone for MEC regimens including doxorubicin and cyclophosphamide (AC), as well as non–AC-containing chemotherapy drugs considered to be moderately emetogenic (Rapoport et al., 2010). There were slightly more patients in both arms of the study who received the non–AC-containing chemotherapy regimens. Results indicated that in both the AC- and non–AC-containing MEC regimens, there was improvement in the rate of vomiting and complete response in acute and delayed CINV (Rapoport et al., 2010).
- A single-day dosing regimen of fosaprepitant 150 mg was shown to be noninferior to the 3-day dosing regimen of aprepitant, and has recently gained FDA approval in combination with dexamethasone and a 5-HT_3 receptor antagonist in HEC regimens (Grunberg et al., 2010).

OTHER PHARMACOLOGIC INTERVENTIONS

Corticosteroids are effective antiemetics when combined with a 5-HT_3 receptor antagonist and NK-1 receptor antagonist. Their mechanism of action is unknown, and the optimal dose for the control of emesis has not been determined (Navari, 2009; Roila, Herrstedt, Gralla, & Tonato, 2010); however, numerous clinical trials have confirmed superior outcomes (improved control by 15% to 20%) when corticosteroids are used in antiemetic regimens compared with a 5-HT_3 antagonist alone (Frame, 2010). Dexamethasone is the most widely used corticosteroid; however, no study reports the superiority of one corticosteroid over another in terms of efficacy (Feyer & Jordan, 2011). Adverse events associated with dexamethasone include insomnia, GI symptoms, agitation, increased appetite, weight gain, rash, depression on cessation of treatment, hiccups, and oral candidiasis (Tan et al., 2009).

Olanzapine is an antipsychotic that blocks multiple neurotransmitters. Several phase II studies (Navari et al., 2005; Navari et al., 2007; Tan et al., 2009) showed that olanzapine can improve complete response rates of delayed CINV in patients receiving MEC or HEC, as well as improve the quality of life of cancer patients during chemotherapy administration. Common AEs with olanzapine are sedation and weight gain.

Dopamine receptor antagonists (e.g., metoclopramide, prochlorperazine, droperidol, and haloperidol) were the core of antiemetic therapy before the introduction of 5-HT_3 receptor antagonists. Current guidelines recommend that dopamine receptor antagonists be reserved for patients intolerant of or refractory to 5-HT_3 receptor antagonists, NK-1 receptor antagonists, and corticosteroids. Because of the high level of blockade of the dopamine receptors, they can cause extrapyramidal symptoms that can limit the use of these

agents (Navari, 2009). Benzodiazepines are effective accompaniments to antiemetic regimens to treat anxiety and reduce anticipatory CINV. Cannabinoids (dronabinol and nabilone [Cesamet]) are also recommended in the recent guidelines to be reserved for patients intolerant of or refractory to 5-HT_3 receptor antagonists, NK-1 receptor antagonists, and corticosteroids. They possess weak antiemetic effects and have a high incidence of AEs, such as dizziness, dysphoria, and hallucinations (Feyer & Jordan, 2011).

NONPHARMACOLOGIC INTERVENTIONS

Nonpharmacologic interventions for the treatment of CINV include acupuncture, acupressure, guided imagery, music therapy, psychoeducational support, and progressive muscle relaxation. Exercise, hypnosis, yoga, Chinese herbal medicine, massage and aromatherapy, acustimulation with a wristband device, and consumption of ginger have been studied for use in the prevention of nausea and vomiting, but further investigation is needed to ascertain their effectiveness (Eaton & Tipton, 2009).

- Progressive muscle relaxation was found to be effective in treating anticipatory CINV (Eaton & Tipton, 2009).
- Virtual reality interventions were researched by Eaton and Tipton (2009) and found to be helpful in combination with antiemetics.

Guidelines

Several cancer organizations (American Society for Clinical Oncology [ASCO], Multinational Association of Supportive Care in Cancer [MASCC], the National Comprehensive Cancer Network [NCCN]) and the Oncology Nursing Society (ONS) have published nationally recognized guidelines for managing CINV. The most recent updates to these guidelines are summarized in Table 3 and listed below:

- MASCC 2010 (Roila et al., 2010)
- NCCN 2011 (NCCN, 2011)
- ONS 2009 (Tipton et al., 2007)
- ASCO 2011 (Basch et al., 2011)

All four guidelines unanimously suggest a combination of a 5-HT_3 receptor antagonist, dexamethasone, and aprepitant or fosaprepitant on day 1 for acute CINV with HEC. The guidelines for MEC vary more throughout the different organizations (see Table 3). None of the four organizations recommend a 5-HT_3 receptor antagonist or an NK-1 receptor antagonist for use with low emetogenic chemotherapy. Prophylaxis is not recommended by ASCO, MASCC, NCCN, or ONS for patients receiving chemotherapy regimens associated with minimal emetic risk (< 10%).

Barriers to Management

As with many treatments that cancer patients receive, there are often barriers that both providers and patients face when trying to achieve optimal medical management. Cost of medications, education of patients and providers, perceptions of CINV, and fear of missing treatment are all reasons why patients may not receive the most efficacious antiemetic regimen. When oncologists, nurses, and patients were interviewed separately to determine the experience of CINV, the oncologists and nurses clearly underestimated the amount of delayed CINV patients experienced (Grunberg et al., 2004). The recent literature identifies the following barriers to treating CINV:

- Delayed CINV remains a poorly managed symptom that is not well understood. The best current treatment recommendations are centered around corticosteroids, which are not approved for CINV. Future study into the pathophysiology and treatment of delayed CINV is warranted (Nevidjon & Chaudhary, 2010).
- Current guidelines do not provide guidance on how to treat patients who have significant CINV while receiving lower-risk chemotherapy agents. There is also ambiguity regarding 5-HT_3 receptor antagonists and serotonin and their role in delayed CINV (Wickham, 2010).
- Many patients with cancer are older and may have difficulty with comorbidities or following instructions. In addition, they may be taking many medications, some of which may interact with antiemetic therapy. Cost and reimbursement are further reasons that a patient may not remain compliant with the prescribed antiemetic regimen. Nonadherence, lack of education, depression, and language or cultural issues are all barriers that patients face. Challenges for healthcare professionals include communication, empathy, education with respect to the ever-changing guidelines, and delivery systems of antiemetics (Grunberg, Clark-Snow, & Koeller, 2010).
- A large retrospective analysis of more than

Table 3. Antiemetic Guidelines Summarized by Emetic Risk Category

	Emetic Risk							
	High		Moderate		Low		Minimal	
Group	Acute CINV	Delayed CINV	Acute CINV	Delayed CINV	Acute CINV	Delayed CINV	Acute CINV	Delayed CINV
ONS (Tipton et al., 2007)	5-HT_3RA + dexamethasone + aprepitant ± lorazepam	Dexamethasone + aprepitant ± lorazepam	5-HT_3RA + dexamethasone + aprepitant ± lorazepam On days 2–4 consider: dexamethasone *or* 5-HT_3RA *or* metoclopramide ± diphenhydramine	Aprepitant ± lorazepam On days 2–4 consider: dexamethasone *or* 5-HT_3RA *or* metoclopramide ± diphenhydramine	No antiemetic agent *or* dexamethasone *or* prochlorperazine *or* metoclopramide ± diphenhydramine, *or* lorazepam	NRP	N/A	N/A
ASCO (Basch et al., 2011)	5-HT_3RA + dexamethasone + (fos)aprepitant	Dexamethasone + aprepitant, if fosaprepitant not used	5-HT_3RA (palonesetron recommended) + dexamethasone. Limited evidence to consider adding aprepitant	Dexamethasone	Dexamethasone	NRP	NRP	NRP
MASCC (Roila et al., 2010)	5-HT_3RA + dexamethasone + (fos)aprepitant	Dexamethasone + aprepitant	AC regimen: 5-HT_3RA + dexamethasone + (fos)aprepitant Non-AC regimen: palonosetron + dexamethasone	Aprepitant Non-AC regimen: Dexamethasone	5-HT_3RA *or* dexamethasone *or* dopamine RA	NRP	NRP	NRP
NCCN (NCCN Clinical Practice Guidelines in Oncology: Antiemesis v3.2011, 2011)	5-HT_3RA + dexamethasone + (fos)aprepitant ± lorazepam ± H2 blocker or PPI	Dexamethasone + aprepitant ± lorazepam ± H2 blocker or PPI	5-HT_3RA + dexamethasone + (fos)aprepitant ± lorazepam ± H2 blocker or PPI	5-HT_3RA or dexamethasone aprepitant, each ± lorazepam ± H2 blocker or PPI	Dexamethasone *or* metoclopramide *or* prochlorperazine ± lorazepam ± H2 blocker or PPI	NRP	NRP	NRP

Note. 5-HT_3RA = 5-hydroxytryptamine-3 receptor antagonist; AC = anthracycline/cyclophosphamide; ASCO = American Society for Clinical Oncology; CINV = chemotherapy-induced nausea and vomiting; MASCC = Multinational Association of Supportive Care in Cancer; NCCN = National Comprehensive Cancer Network; NRP = no routine prophylaxis; ONS = Oncology Nursing Society; PPI = proton pump inhibitor.

19,000 patients who received HEC or MEC showed that 1 in 8 patients required a follow-up hospital visit, mostly inpatient stays, for complications of CINV. These visits were exceedingly costly, with a mean CINV event cost of $4,043 in the first cycle of chemotherapy when CINV was the primary diagnosis (Burke, Wisniewski, & Ernst, 2011).

- The costs of treatment (Table 4) may also present a barrier, particularly in uninsured or underinsured patients. In addition, many brand name drugs are tiered and may carry exorbitant copays when they occupy a higher tier in a patient's prescription plan.

Considerations for the AP

Oncology APs make a significant impact on the quality of life and treatment of patients undergoing chemotherapy. Acute, delayed, and anticipatory CINV can negatively affect a patient's outcome. Performing a thorough history, review of systems, and physical exam and assessment can help identify treatment-related risk factors for CINV. Advanced practitioners should educate patients about the AEs associated with antiemetic therapy, communicate concerns to prescribing clinicians (if applicable), and advocate for changes in therapy when appropriate. Advanced practitioners are ideally positioned to work toward the goals of prevention, early diagnosis, and prompt management of CINV, allowing for substantially improved outcomes.

Conclusions

Significant advances have been made in the pharmacologic and nonpharmacologic treatment of CINV, as well as in our understanding of its pathophysiology and risk factors. Despite this progress, CINV continues to be one of the most feared AEs of cancer treatment. By understanding the current CINV guidelines and recognizing patients at high risk, APs can prescribe the best available antiemetic regimen to allow for maximal control of CINV. Paying special attention to patient barriers, including cost of medications or the need for prior authorizations, can also improve compliance with antiemetic regimens. Being knowledgeable about the most up-to-date literature and clinical trials can aid APs in quelling the myths about CINV and in reassuring patients that they will have significantly improved outcomes in the prevention and management of CINV if they adhere to the guidelines.

Table 4. Pricing Comparison of Agents Approved for the Prevention of Emesis

Antiemetics	AWP (USD)[a]
5-HT_3 receptor antagonists	
Ondansetron 8 mg IV	$1.64
Ondansetron 8 mg tablet	$39.36/tablet
Palonosetron 0.25 mg vial	$445.20
Granisetron 1 mg IV	$12.00
Granisetron 3.1 mg patch	$358.80
NK-1 receptor antagonists	
Aprepitant (Emend Tri-Pack)	$408.76
Fosaprepitant 150 mg	$307.20

Note. AWP = average wholesale price; 5-HT_3 = 5-hydroxytryptamine-3; NK-1 = neurokinin-1; USD = US dollars.
[a]Average wholesale price per Red Book.

DISCLOSURE

Beth Eaby-Sandy discloses that she is on the speakers bureau for Merck & Co. Victoria Sherry has no financial disclosures to report. Beth Eaby-Sandy and Victoria Sherry authored 100% of this publication. Editing and formatting support was provided by Complete Healthcare Communications, Inc., funded by Merck & Co.

REFERENCES

Basch, E., Prestrud, A. A., Hesketh, P. J., Kris, M., Feyer, P. C., Somerfield, M. R.,...Lyman, G. H. (2011). Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *Journal of Clinical Oncology.* E-pub ahead of print, September 26, 2011. doi:10.1200/JCO.2010.34.4614

Burke, T. A., Wisniewski, T., & Ernst, F. R. (2011). Resource utilization and costs associated with chemotherapy-induced nausea and vomiting (CINV) following highly or moderately emetogenic chemotherapy administered in the US outpatient hospital setting. *Supportive Care in Cancer, 19*(1), 131–140. doi: 10.1007/s00520-009-0797-x

Cunningham, R. S. (1997). 5-HT3-receptor antagonists: A review of pharmacology and clinical efficacy. *Oncology Nursing Forum, 24*(7 suppl), 33–40.

Eaton, L. H., & Tipton, J. M. (2009). *Putting evidence into practice: Improving oncology patient outcomes.* Pittsburgh, PA: Oncology Nursing Society.

Eckert, R. M. (2001). Understanding anticipatory nausea. *Oncology Nursing Forum, 28*(10), 1553–1558; quiz 1559–1560.

Ettinger, D. S., Bierman, P. J., Bradbury, B., Comish, C. C., Ellis, G., & Ignoffo, R. J. (2007). Antiemesis. *Journal of the National Comprehensive Cancer Network, 5*(1), 12–33.

Feyer, P., & Jordan, K. (2011). Update and new trends in antiemetic therapy: The continuing need for novel therapies. *Annals of Oncology, 22*(1), 30–38.

Frame, D. G. (2010). Best practice management of CINV in

oncology patients: I. Physiology and treatment of CINV. Multiple neurotransmitters and receptors and the need for combination therapeutic approaches. *Journal of Supportive Oncology, 8*(2 suppl 1), 5–9.

Grunberg, S., Chua, D., Maru, A., DeVandry, S., Boice, J., & Hardwick, J. (2010). Phase III randomized double-blind study of single-dose fosaprepitant for prevention of cisplatin-induced nausea and vomiting [Abstract 9021]. *Journal of Clinical Oncology, 28*(15 suppl).

Grunberg, S., Clark-Snow, R. A., & Koeller, J. (2010). Chemotherapy-induced nausea and vomiting: Contemporary approaches to optimal management. Proceedings from a symposium at the 2008 Multinational Association of Supportive Care in Cancer (MASCC) Annual Meeting. *Supportive Care in Cancer, 18*(suppl 1), 1–10.

Grunberg, S. M., Deuson, R. R., Mavros, P., Geling, O., Hansen, M., & Cruciani, G. (2004). Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. *Cancer, 100*(10), 2261–2268.

Grunberg, S. M., Gabrial, N., & Clark, G. (2007, June 27-30). Phase III trial of transdermal granisetron patch (Sancuso) compared to oral granisetron (OG) for chemotherapy-induced nasuea and vomiting (CINV) after muti-day moderately emetogenic (MEC) or highly emetogenic (HEC) chemotherapy. Paper presented at the International MASCC/ISOO Symposium, St. Gallen, Switzerland.

Hesketh, P. J., Aapro, M., Street, J. C., & Carides, A. D. (2010). Evaluation of risk factors predictive of nausea and vomiting with current standard-of-care antiemetic treatment: Analysis of two phase III trials of aprepitant in patients receiving cisplatin-based chemotherapy. *Supportive Care in Cancer, 18*(9), 1171–1177. doi:10.1007/s00520-009-0737-9

Hesketh, P. J., Grunberg, S. M., Gralla, R. J., Warr, D. G., Roila, F., & de Wit, R. (2003). The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: A multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin—the Aprepitant Protocol 052 Study Group. *Journal of Clinical Oncology, 21*(22), 4112–4119. doi:10.1200/JCO.2003.01.095

Jakobsen, J. N., & Herrstedt, J. (2009). Prevention of chemotherapy-induced nausea and vomiting in elderly cancer patients. *Critical Reviews in Oncology/Hematology, 71*(3), 214–221.

Langford, P., & Chrisp, P. (2010). Fosaprepitant and aprepitant: An update of the evidence for their place in the prevention of chemotherapy-induced nausea and vomiting. *Core Evidence, 5*, 77–90.

Martin, M. (1996). The severity and pattern of emesis following different cytotoxic agents. *Oncology, 53*(suppl 1), 26–31.

Navari, R. M. (2009). Pharmacological management of chemotherapy-induced nausea and vomiting: Focus on recent developments. *Drugs, 69*(5), 515–533. doi:10.2165/00003495-200969050-00002

Navari, R. M., Einhorn, L. H., Loehrer, P. J., Sr., Passik, S. D., Vinson, J., & McClean, J. (2007). A phase II trial of olanzapine, dexamethasone, and palonosetron for the prevention of chemotherapy-induced nausea and vomiting: A Hoosier oncology group study. *Supportive Care in Cancer, 15*(11), 1285–1291.

Navari, R. M., Einhorn, L. H., Passik, S. D., Loehrer, P. J., Sr., Johnson, C., & Mayer, M. L. (2005). A phase II trial of olanzapine for the prevention of chemotherapy-induced nausea and vomiting: A Hoosier Oncology Group study. *Supportive Care in Cancer, 13*(7), 529–534.

NCCN. (2011). Clinical Practice Guidelines in Oncology: Antiemesis v3.2011. Fort Washington, PA: National Comprehensive Cancer Network.

Nevidjon, B., & Chaudhary, R. (2010). Controlling emesis: Evolving challenges, novel strategies. *Journal of Supportive Oncology, 8*(4 suppl 2), 1–10.

Rapoport, B. L., Jordan, K., Boice, J. A., Taylor, A., Brown, C., & Hardwick, J. S. (2010). Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: A randomized, double-blind study. *Supportive Care in Cancer, 18*(4), 423–431. doi:10.1007/s00520-009-0680-9

Roila, F., Herrstedt, J., Aapro, M., Gralla, R. J., Einhorn, L. H., & Ballatori, E. (2010). Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: Results of the Perugia consensus conference. *Annals of Oncology, 21*(suppl 5), v232–v243.

Roila, F., Herrstedt, J., Gralla, R. J., & Tonato, M. (2010). Prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: Guideline update and results of the Perugia consensus conference. *Supportive Care in Cancer, 19*(suppl 1):S63-S65. doi:10.1007/s00520-010-1044-1

Roscoe, J. A., Morrow, G. R., Colagiuri, B., Heckler, C. E., Pudlo, B. D., & Colman, L. (2010). Insight in the prediction of chemotherapy-induced nausea. *Supportive Care in Cancer, 18*(7), 869–876.

Saito, M., Aogi, K., Sekine, I., Yoshizawa, H., Yanagita, Y., & Sakai, H. (2009). Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: A double-blind, double-dummy, randomised, comparative phase III trial. *Lancet Oncology, 10*(2), 115–124.

Shih, V., Wan, H. S., & Chan, A. (2009). Clinical predictors of chemotherapy-induced nausea and vomiting in breast cancer patients receiving adjuvant doxorubicin and cyclophosphamide. *Annals of Pharmacotherapy, 43*(3), 444–452. doi:10.1345/aph.1L437

Stricker, C. T., & Eaby, B. (2010). Chemotherapy induced nausea and vomiting. In C. Brown (Ed.), *A guide to oncology symptom management* (pp. 91–121). Pittsburgh, PA: Oncology Nursing Society.

Tan, L., Liu, J., Liu, X., Chen, J., Yan, Z., & Yang, H. (2009). Clinical research of olanzapine for prevention of chemotherapy-induced nausea and vomiting. *Journal of Experimental and Clinical Cancer Research, 28*, 131.

Tipton, J. M., McDaniel, R. W., Barbour, L., Johnston, M. P., Kayne, M., & LeRoy, P. (2007). Putting evidence into practice: Evidence-based interventions to prevent, manage, and treat chemotherapy-induced nausea and vomiting. *Clinical Journal of Oncology Nursing, 11*(1), 69–78.

Warr, D. G., Street, J. C., & Carides, A. D. (2011). Evaluation of risk factors predictive of nausea and vomiting with current standard-of-care antiemetic treatment: Analysis of phase 3 trial of aprepitant in patients receiving adriamycin-cyclophosphamide-based chemotherapy. *Supportive Care in Cancer, 19*(6), 807–813.

Wickham, R. (2010). Best practice management of CINV in oncology patients: II. Antiemetic guidelines and rationale for use. *Journal of Supportive Oncology, 8*(2 suppl 1), 10–15.