

Controlling Nausea & Vomiting Related to Cancer Treatment

BY BETH EABY-SANDY, MSN, CRNP

Chemotherapy-induced nausea and vomiting (CINV) has been an ongoing problem since the beginning of cancer treatment. While there have been vast improvements in CINV in the past decades, it is often multifactorial. Several challenges with patients still remain. Further complicating nausea and vomiting in cancer treatment is the oral chemotherapies or oral targeted therapies.

Pathophysiology

Our understanding of the pathophysiology of CINV and how it relates to management has evolved over the past 2 decades. The emetic reflex is complex and is a result of activation from either the gastrointestinal (GI) tract or the central nervous system (CNS) through stimulation of vagal afferents. These interactions activate the dorsal vagal complex which coordinates neurons to produce the physical aspects of CINV (*Chem Rev* 2009;109:3158-3199). The two major neurotransmitters involved are serotonin and substance P.

In the GI tract, enterochromaffin cells display 5HT₃ receptors which bind with serotonin to stimulate vagal afferents within the GI tract and CNS to produce nausea and vomiting (*Pharmacogenomics* 2015;16(2):149-160). The CNS plays a huge role as well in the pathophysiology of CINV. The area postrema and chemoreceptor trigger zone, located in the medulla, respond to toxic stimuli and activate the dorsal vagal complex (*Chem Rev* 2009;109:3158-3199). NK-1 receptors are dense in the CNS. Substance P is released in response to noxious stimuli and has a very high binding affinity for NK-1 receptors. This binding also accounts for several downstream signals which activate the emetic reflex (*Pharmacogenomics* 2015;16(2):149-160).

Risk Factors

There are two key categories of risk factors for patients receiving chemotherapy: 1) patient-specific risk factors, and 2) chemotherapy drug risk factors. For chemotherapy drug risk factors, there have been a few recent updates to the National Comprehensive Cancer Network (NCCN) guidelines in recent years. One of the main updates was that carboplatin at an area under the curve (AUC) of 4 or greater is now considered highly emetogenic. Others like cisplatin and regimens con-

Table 1. NCCN Antiemesis Guidelines V3.2018 Highly Emetogenic Chemotherapy

- Cisplatin any dose
- Carboplatin ≥ AUC 4
- Any regimen containing an anthracycline plus cyclophosphamide
- Cyclophosphamide > 1,500mg/m²
- Doxorubicin ≥ 60mg/m²
- Epirubicin > 90mg/m²
- Dacarbazine
- Streptozocin
- Carmustine > 250mg/m²
- Ifosfamide ≥ 2g/m²
- Mechlorethamine

Source: NCCN Antiemesis Guidelines V3.2018;
https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf



BETH EABY-SANDY, MSN, CRNP, OCN, is a nurse practitioner specializing in thoracic medical oncology at the Abramson Cancer Center, University of Pennsylvania, Philadelphia.

Table 2. Risk Factors for CINV in Dranitsaris Study

- Nausea or vomiting in prior chemotherapy cycle
- Use of non-prescribed antiemetics taken at home for CINV control
- Platinum or anthracycline-based chemotherapy
- Age ≤ to 60 years
- Anticipatory nausea and vomiting
- < 7 hours of sleep the night before chemotherapy
- History of morning sickness
- First cycle of chemotherapy

Source: *Ann Oncol* 2017;28:1260-1267

taining an anthracycline plus cyclophosphamide are long considered to be highly emetogenic.

See Table 1 for a list of highly emetogenic chemotherapy regimens according to the NCCN guidelines. Also it is important to be knowledgeable about newer oral chemotherapies and targeted therapies that may have significant nausea or vomiting as a side effect.

Patient-specific risk factors should also be considered. The typical patient risk factors that are associated with increased CINV are females, younger age, and history of little or no alcohol intake (*Cancer Sci* 2013;104:711-717, *Support Care Cancer* 2010;18:1171-1177). A more recent study identified some of the same risk factors, but other new risk factors listed in Table 2. One of the interesting findings in the Dranitsaris study is that it did not find that females were more at risk than males, which had been seen in studies before. However, in general, it is important to evaluate each patient and their risk factors prior to administering chemotherapy to ensure an appropriately aggressive antiemetic plan.

Treatments

In recent years, there have been several newer antiemetic agents and combinations that have been studied and approved. There are different drug classes that may be of use for prevention listed in Table 3.

Of the newer agents, some are just new routes of administration and some are new medications to the market. For example, granisetron has been around for many years; however, a new long-acting subcutaneous injection was approved for use in 2016. Also, rolapitant is a newer NK-1 receptor antagonist (RA) approved in 2015 initially as an oral drug, then with an IV indication. However, the IV formulation is not currently available due to a higher rate of anaphylactic reactions than anticipated. The oral rolapitant remains available and offers a

Continued on page 8



NAUSEA & VOMITING

continued from page 7

180-hour half-life as well as no CYP3A4 interactions, which is a common class effect of other NK-1 RAs.

There is also a newer version of aprepitant that is IV (not the pro-drug fosaprepitant), that is not mixed in polysorbate 80, thus should reduce the risk of infusion reactions. And finally, there is the newer agent often referred to as NEPA, which is netupitant and palonosetron in a combination capsule. It was first approved back in 2015, and the IV formulation fosnetupitant and palonestron approved in 2018. This

Read This Article and Earn CME or CNE!

Earn continuing education credit by completing a quiz about this article. You may read the article here or on our website, then complete the quiz, answering at least 70 percent of the questions correctly to earn credit.

CONTINUING MEDICAL EDUCATION INFORMATION FOR PHYSICIANS

Visit <http://CME.LWW.com> for more information about this educational offering and to complete the CME activity. This enduring material is available to physicians in all specialties. Lippincott Continuing Medical Education Institute, Inc., is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Lippincott Continuing Medical Education Institute, Inc., designates this enduring material for a maximum of 1 *AMA PRA Category 1 Credit™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity. This activity expires February 28, 2021.

PROVIDER ACCREDITATION INFORMATION FOR NURSES
Lippincott Professional Development (LPD) will award 1.0 contact hour for this continuing nursing education activity. LPD is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. This activity is also provider approved by the California Board of Registered Nursing, Provider Number CEP 11749 for 1.0 contact hour. LWW is also an approved provider by the District of Columbia, Georgia, and Florida CE Broker #50-1223. Visit www.nursingcenter.com/ce for more information and to complete the CNE activity.

Fee: \$12.95.

Deadline: March 5, 2021

For nurses who wish to take the test for CE contact hours, visit www.nursingcenter.com/ce.

Learning Objectives for This Month's CME Activity:

After participating in this CME/CNE activity, readers should be better able to: 1. Describe the pathophysiology of and risk factors for chemotherapy-induced nausea and vomiting (CINV). 2. Summarize current guidelines for the management of CINV.

Disclosure: The author(s), faculty, staff, and planners, including spouses/partners (if any), in any position to control the content of this activity have disclosed that they have no financial relationships with, or financial interests in, any commercial companies relevant to this educational activity.

Table 3. Drug Classes for Prevention of CINV

NK-1 Receptor Antagonists	5HT ₃ Receptor Antagonists	Corticosteroids	Anti-psychotics
Aprepitant or Fosaprepitant	Palonosetron	Dexamethasone	Olanzapine
Rolapitant	Ondansetron		
Netupitant or Fosnetupitant	Granisetron		
	Dolasetron		

Table 4. General Recommendations for Prevention of CINV on Day 1 According to NCCN Guidelines

Prevention of Highly Emetogenic Chemotherapy	Prevention of Moderately Emetogenic Chemotherapy
NK-1 RA + 5HT ₃ RA + Dexamethasone +/- Olanzapine OR	5HT ₃ RA + Dexamethasone OR 5HT ₃ RA + Dexamethasone + NK-1 RA* OR
5HT ₃ RA + Dexamethasone + Olanzapine	5HT ₃ RA + Dexamethasone + Olanzapine

*in selected patients at higher risk to develop CINV

Source: NCCN Antiemesis Guidelines V3.2018; https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf

drug offers the obvious convenience to have an NK-1 RA and a 5HT₃ RA together in one drug, whether an IV or a capsule.

There are many other drugs used to manage CINV, usually in the delayed or breakthrough settings at home. When using dexamethasone and/or olanzapine as prevention, the NCCN guidelines usually recommend using them as prevention in the delayed setting at home for about 3-4 days after chemotherapy depending on the regimen. Also, the benzodiazepines such as lorazepam can be useful, especially in those patients who seem to have anxiety associated with CINV or anticipatory CINV. Dopamine RAs such as prochlorperazine, haloperidol, and metoclopramide are also useful mostly in the breakthrough setting at home. Cannabinoids have been used, but their results are at variable in patients and side effects and cost may prohibit usage.

Guidelines

Following guidelines is the best way to ensure that patients get the maximum control of their CINV (*Ann Oncol* 2012;23:1986-1992). The NCCN, as well as several other organizations, have put forth anti-emetic treatment guidelines. For highly emetogenic chemotherapy, the NCCN guidelines recommend using an NK-1 RA plus a 5HT₃ RA plus dexamethasone. There is also a 4-drug regimen indicated for highly emetogenic chemotherapy regimens that utilizes aprepitant or fosaprepitant, a 5HT₃ RA, dexamethasone, and olanzapine for prevention of CINV (*N Engl J Med* 2016;375:134-142).

Table 4 represents the general recommendations of the NCCN guidelines for management of highly and moderately emetogenic chemotherapy regimens.

To summarize, CINV is still a prevalent side effect of chemotherapy. Scientists have discovered some pathways that cause the emetic reflex. There are several risk factors that can predict for CINV. There are several drugs approved for the prevention and management of CINV, with strong data to support their use. Guidelines are published to guide oncology providers in the proper CINV prevention. Oncology nurses and pharmacists are often the primary educators for patients. Patients need to know when to take antiemetics and when to call the office. It is important for all oncology providers to be aware of the CINV guidelines and regimens to use in the appropriate population of oncology patients. **OT**