REVIEW

ISSN (O): 2349-5332
CODEN: IRJPHY

CINV: A Review

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Submitted on: 29.05.2022; **Revised on:** 15.06.2022; **Accepted on:** 27.07.2022

Abstract:

Background:
Cancer chemotherapy can cause serious side effects such as nausea and vomiting. These side effects in lieu can cause significant negative impacts on a care taker's quality of life and his/her ability to continue with the therapy. Despite various advancements are adopted in the prevention and management of chemotherapy-induced nausea and vomiting (CINV), these side effects stands the most distressing for patients.

Objective
To discuss CINV and ways to its management.

Discussion
This article helps to understand the mechanism of CINV followed by a review of current approaches to pharmacologic therapy and current practice guidelines from various cancer organizations. The information will help providers and patients with value-based decision-making that considers cost issues. It will also help them to understand the optimal treatment therapy that a patient with CINV can have including all the practical considerations

Conclusion
A number of prophylactic and treatment options are available to manage CINV. To understand and determine the best approach for each individual patient, administration of antiemetic regimens needs continuous ongoing patient examination and evaluation.

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Indian Research Journal of Pharmacy and Science; 32(2022)2724-2733;
Journal Home Page: https://www.irjps.in

INTRODUCTION:

The known serious and related side effects of cancer chemotherapy include nausea and vomiting. A patients' quality of life and on their ability to continue with the therapy can be significantly affected bt the adverse effects caused by these side effects.. Also, certain other effects that it can impart include anorexia, decreased performance status, metabolic imbalance, wound dehiscence, esophageal tears, and nutritional deficiency.1,2 Even though there are many advances adopted in the prevention and management of chemotherapy-induced nausea and vomiting (CINV), these side effects stands the most distressing for patients.. The use of newer antiemetic medications has helped reduce the incidence of vomiting substantially, but evaluations show that approximately 30% to 60% of patients still experience either acute or delayed nausea after chemotherapy.3 Although vomiting has gone way down on the list of side effects of cancer chemotherapy as the most severe, but nausea remains among the top in the list as the most severe side effect of chemotherapy.4–8

The risk factors for CINV can be divided into patient-specific and treatment-specific risk factors. The gender of the person and history of motion or morning sickness are clear risk factors for nausea and vomiting.5,6 Younger age can also have some correlation with increased risk, but can be explained by the fact that the more aggressive chemotherapy regimens that tend to be administered to younger patients who have more aggressive diseases.5–7 It has been seen that persons consuming alcohol tends to be less prone to develop CINV. Factors contributing to the treatment-specific risk, include (1) the emetogenicity of the agents being used, (2) dosing regimen of each agent, and (3) site of radiation or surgery in the case of radiation-induced or postoperative nausea. "Emetogenicity" refers to the tendency of various agents to cause nausea and/or vomiting. Initially the emetogenicity scale, also known as the Hesketh scale, divided chemotherapy agents and doses into 5 levels, based on their likelihood to cause CINV.9 Since then, the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) have worked on modifying the scale. It is now divided into the following 4 categories10,11:

- *Highly emetogenic:* medications or doses that cause CINV in >90% of patients
- *Moderately emetogenic:* medications that induce CINV in 30% to 90% of patients
- *Low emetogenic:* medications that are associated with CINV rates of 10% to 30%
- *Minimally emetogenic:* medications that cause CINV in <10% of patients.

"CINV" is a broad term used to describe the various types of nausea and vomiting that can occur in patients with cancer. Following are the various subtypes of it: 12–16:

- *Acute:* onset of nausea and vomiting within minutes to hours after administration of chemotherapy and resolving within 24 hours
- *Delayed:* occurs 24 hours or later after administration of chemotherapy
- *Anticipatory:* occurs before chemotherapy administration; thought to be an indicator of previous poor control of nausea and vomiting
- *Breakthrough/refractory:* nausea and vomiting that occur despite appropriate prophylaxis; requires the use of rescue medications.

Pathophysiology of Nausea and Vomitting

The reticular formation of the brain stem contains the emetic center which controls the vomiting response there are three sources from which the emetic center can receive input: the periphery, the cortex, and the chemoreceptor trigger zone. Peripheral pathways are mediated mainly by serotonin (5-hydroxytryptamine3 [5-HT_3]) and neurokinin (NK) mediates mainly the peripheral pathways; the cortical pathway, being mediated by dopamine and histamine is responsible

for anticipatory emesis. The chemoreceptor trigger zone is a collection of neurons at the base of the brain which is exposed to the body's general circulation. It mediates signals through all of the above chemokines. Once triggering of the emetic center has been initiated, signals are being sent to the salivatory, vasomotor, respiratory, and cranial centers in the brain to activate the organs involved with the vomiting reflex. The organs involved in the vomitting reflex includes the abdominal muscles, diaphragm, stomach, and esophagus.17

Pharmacologic Treatment Options for CINV

Available Agents

A number of treatment options are available for the treatment of CINV in the present day which generally targets pathways of the process. Before the 1980s, CINV was primarily managed with dopamine receptor antagonists. Today, we have a multitude of options available, targeting the various pathways of the process, to use in the prevention and management of CINV.

NK_1 receptor antagonists. They act by inhibiting substance P in peripheral and central emetic pathways. A drug called Aprepitant was the first among its type to be approved by the FDA in 2003. Aprepitant was approved at doses of 125 mg orally on day 1 and 80 mg orally on days 2 and 3 for the prevention of nausea and vomiting in patients receiving highly emetogenic or moderately emetogenic single-day chemotherapy.28 It was approved after 2 trials showed that the combination of aprepitant, ondansetron, and dexamethasone decreased emesis or decreased the use of rescue medications for patients receiving highly emetogenic chemotherapy during the acute and delayed phases.29,30 The common adverse effects include headache, anorexia, fatigue, hiccups, diarrhea and increased transaminases.

5-HT_3 receptor antagonists. Ondansetron was the first US Food and Drug Administration (FDA)-approved 5-HT_3 antagonist in 1991. Palonosetron is the newest agent and was approved in 2003. These agents are believed to prevent CINV by antagonizing 5-HT_3 receptors either peripherally on vagal nerve terminals and/or centrally in the chemoreceptor trigger zone.23–27 Since their introduction, 5-HT_3 receptor antagonists have become the most important regimen for CINV prevention especially due to their effectiveness and tolerable side-effect profile. The common adverse effects may include headache and constipation.

Corticosteroids. Corticosteroids were first shown to be efficacious for CINV in the 1980s, and they are now considered a main drug in the antiemetic regimens for the prevention of acute and delayed emesis.10,11,35 Although not approved by the FDA for CINV, corticosteroids have been found to be beneficial when used alone for the prevention of nausea and vomiting in patients receiving low emetogenic chemotherapy.36–39

The mechanism of action of corticosteroids as antiemetic agents is not known as of now, but it may be related to its activity in the peripheral nervous system or in the central nervous system (CNS), and also possibly by antagonizing serotonin receptors.40–43 Common adverse effects can be insomnia, epigastric discomfort, agitation, weight gain, and hyperglycemia.44

Other regimens:

Dopamine receptor antagonists. Dopamine receptor antagonists can be a saviour for breakthrough or refractory emesis. The dopamine antagonists are divided into phenothiazines (eg, prochlorperazine), butyrophenones (eg, haloperidol, droperidol), and substituted benzamides (eg, metoclopramide). These agents act by antagonizing the dopamine (D_2) receptor in the chemoreceptor trigger zone.45,46 Metoclopramide acts by antagonizing dopamine, but at high doses it also has activity against the 5-HT_3 receptor.47,48 Common side effects of dopamine receptor antagonists may include dystonia, extrapyramidal symptoms, and drowsiness.

Benzodiazepines. Benzodiazepines act as adjunct therapies to decrease treatment-related anxiety, and are considered as preferred agents to treat and prevent anticipatory nausea and vomiting.49–51 Even if sedation can be the most common side effect with Lorazepam and alprazolam, they are considered as the primary agents used in this class.

Olanzapine. olanzapine is considered to be a safe and effective drug for preventing acute, delayed, and refractory CINV when combined with other antiemetics in patients receiving moderately and highly emetogenic chemotherapy.52–54 Adverse effects may include weight gain, orthostatic hypotension, sedation, hyperglycemia.55

Cannabinoids. Dronabinol and nabilone are 2 cannabinoids that are currently approved by the FDA for CINV in patients who does not tend to respond to conventional antiemetics in a while. It is thought that Cannabinoids prevent nausea and vomiting by antagonizing cannabinoid receptor CB_1 in the CNS and possibly CB_2 receptors as well.56 Cannabinoids have even been shown to be slightly more effective than dopamine receptor antagonists.57,58 Vertigo, euphoria, and somnolence are adverse effects that limit the use of cannabinoids.

Current Practical Guidelines

Care providers can thake help from Current Practice guidelines from the NCCN and ASCO to determine optimal prophylaxis and the treatment of CINV.10,11 The NCCN Antiemesis Guideline™, a consensus-based guideline which incorporates evidence and expert opinion to make recommendations and is revised annually.11 ASCO guidelines are purely evidence-based guidelines. They are updated periodically; the last update was in 2011.10 **Table 1** summarizes specific recommendations for antiemesis from the NCCN and from ASCO. For CINV, both guidelines help to outline the primary prophylaxis based on the emetogenicity of the patient's chemotherapy: high, moderate, low, and minimal.

Table 1: Recommended Antiemetic Regimens for CINV prevention:

Emetic risk	Treatment for acute phase[a]	Treatment for delayed phase
High	3-drug combination treatment with an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone	NK_1 receptor antagonist if oral route was used; dexamethasone
Moderate	2-drug combination treatment with a 5-HT_3 receptor antagonist and dexamethasone	Dexamethasone
Low	Dexamethasone	
Minimal	No routine prophylaxis recommended	

[a] All patients should have with them "as needed" rescue medications

5-HT: Serotonin

CINV: Chemotherapy Induced Nausea and Vomitting

NK: Neurokinin

For patient who receive highly emetogenic chemotherapy, both guidelines recommend a 3-drug combination including a 5-HT_3 receptor antagonist, an NK_1 receptor antagonist, and dexamethasone in the CINV prophylaxis. The ASCO does not list a preferred 5-HT_3 receptor antagonist whereas NCCN specifies that the preferred 5-HT_3 receptor antagonist for highly emetogenic chemotherapy is palonosetron.11

For patients receiving moderately emetogenic chemotherapy, both the NCCN and ASCO recommend a 2-drug combination of a 5-HT_3 receptor antagonist, preferably palonosetron, with dexamethasone. Metoclopramide or prochlorperazine are listed as possible alternative bt the NCCN. No medications are recommended primarily as prophylaxis for patients receiving minimal-risk chemotherapy.

For radiation-induced nausea and vomiting, 5-HT_3 receptor antagonists are the preferred class of antiemetic. The NCCN has divided types of radiation into high risk (eg, total body irradiation), moderate risk (eg, radiation to upper abdomen), and combined radiation with chemotherapy.11 For moderate- and high-risk radiation, granisetron or ondansetron can be given before each radiation treatment, with or without dexamethasone.

For anticipatory nausea and vomiting (ANV), ASCO and the NCCN both has recommended that prevention with optimal primary prophylaxis is the best approach.10,11 The NCCN recommends the use of benzodiazepines to treat ANV.

Practical Considerations

For clinicians managing patients with CINV certain challenges cross the path even with the current published guidelines, In this article, we focus on the following 2 practical challenges.

1. what to consider if all 5-HT_3 receptor antagonists are not created equal? Currently, there are four 5-HT3 antagonists available in the US market—dolasetron, granisetron, ondansetron, and palonosetron. If we study these agents, it can be seen that they show relatively similar rates of success in the prevention of CINV in patients receiving cisplatin-based chemotherapy regimens. Equivalent doses and pharmacokinetic properties of the agents are listed in **Table 2** and **Table 3**. When used in equivalent doses, ondansetron, granisetron, and dolasetron are considered similar for the prevention of nausea and vomiting.59,60 The pharmacokinetics of ondansetron, granisetron, and dolasetron are slightly different, but not enough to result in any clinically significant differences.

Table 2: Dosing Ranges for Antiemetics Used for Primary Prophylaxis of CINV

Antiemetic	Dose	Antiemetic	Dose
NK_1 receptor antagonists		Granisetron	2 mg oral or 1 mg oral twice daily; 1 mg IV or 0.01 mg/kg IV
Fosaprepitant	150 mg IV		
Aprepitant	125 mg oral on day 1 and 80 mg oral on days 2 and 3	Dolasetron	100 mg oral
		Palonosetron	0.25 mg IV
5-HT_3 receptor antagonists		*Corticosteroid*	
Ondansetron	16–24 mg oral; 8 mg IV	Dexamethasone	8–20 mg oral IV

5-HT indicates serotonin; CINV, chemotherapy-induced nausea and vomiting; IV, intravenous; NK, neurokinin.

Table 3: Pharmacokinetic Properties of 5-HT_3 Receptor Antagonists

Agent	Ondansetron	Granisetron	Dolasetron	Palonosetron
Half-life (hrs)	3–4	7–9	7–8	40
Oral bioavailability, %	52	54	62	N/A
Renal elimination, %	4	14	61	46
Hepatic metabolism	CYP-3A, CYP-1A, CYP-2D6, CYP-2E1	CYP-3A	CYP-3A, CYP-2D6	CYP-3A4, CYP-2D6, CYP-1A2

5-HT indicates serotonin; CYP, cytochrome P; N/A, not applicable.

Palonosetron is having increased binding affinity to the 5-HT_3 receptor which differs it from the other 5-HT3 antagonists.61,62 The half-life of palonosetron is approximately 40 hours compared with the significantly lower half-lives of ondansetron, granisetron, and dolasetron.64 This results in altered dosing recommendations for palonosetron. That is why it is dosed once per cycle rather than on a daily basis.

All of these trials had significant flaws in their design. All of the trials compared a single dose of palonosetron to a single dose of the comparator 5-HT_3 receptor antagonist. Palonosetron's extended half-life of 40 hours was compared with the half-lives of between 3 and 8 hours for other 5-HT_3 receptor antagonists but comparisons at any time after 24 hours are pharmacokinetically irrelevant. In addition to it, only 1 of the trials mandated the use of corticosteroids, which are the backbone of any combination antiemetic regimen.63 Considering the flaws in design, we can question the "preferred" status of palonosetron and propose that all 5-HT_3 receptor antagonists are indeed equal only if used at same doses and interval.

2. Breakthrough/refractory nausea and vomiting. Breakthrough/refractory nausea and vomiting stands challenging to treat. In particular, refractory nausea and vomiting tends to cause significant morbidity, weight loss, metabolic imbalances, and nutritional deficiency, which may lead to the inability of patients to remain on their therapy schedule. Anticholinergic and antidopaminergic agents is very appropriately used in this setting. Poor tolerance of therapy in a patient's history can be indicative of severe or refractory nausea and accordingly, adjustments could have been made to decrease the risk of nausea and vomiting.

Conclusion

It is important to evaluate and determine a particular Antiemetic regimen for a particular patient. Then it should be reevaluated at every treatment cycle. Clinicians need to incorporate clinical decision-making with value-based considerations at every step of a patient's care to determine each patient's individual, most optimal approach to treatment. Adopting such an approach, may prove beneficial and progressive in the prevention and management of this problematic adverse effect of chemotherapy, thereby helping to improve the therapy experience and quality of life for the patients.

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CONFLICT OF INTEREST REPORTED: NIL; SOURCE OF FUNDING: NONE REPORTED