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Review Article

Chemotherapy induced nausea & vomiting (CINV)

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ABSTRACT

Chemotherapy is the first line treatment in management of many cancers, both for cure and palliation; hence it's crucial to minimize the unpleasant side effects of chemotherapy to increase tolerability to chemotherapy. Most of the conventional anti cancer drugs are emetogenic. Patients receiving chemotherapy experience different degrees of nausea and vomiting depending on the emetogenic potential of the anti cancer drugs given and the patient characteristics. With a better understanding of the pathophysiology, distinct phases of chemotherapy-induced nausea and vomiting (CINV) i.e., acute emesis, delayed emesis and anticipatory emesis have been identified. Identification of various mediators has led to the development of different drugs acting through different mechanisms which are useful in the prevention and treatment of CINV. Serotonin receptor three (5-HT3) antagonists, corticosteroids and neurokinin type one receptor (NK-1) antagonists are of proven usefulness and have wide therapeutic indexes in the prevention of CINV. Other drugs like dopamine receptor antagonists & benzodiazepines are not routinely used because of their narrow therapeutic index. Practice guidelines for prevention of CINV will not only improve patient's tolerability to chemotherapy & wellbeing, but also decrease hospital stay and overall cost of treatment of the patient.

Keywords: Chemotherapy Induced Nausea and Vomiting (CINV), 5-HT₃ receptor antagonist, Neurokinin type one receptor antagonist, Corticosteroids

INTRODUCTION

Since chemotherapy is emerging as an important mode of treating cancer, both for cure and palliation; preventing and minimizing its unpleasant side effects have become an important aspect of cancer chemotherapy. Nausea and vomiting are the frequently observed unpleasant and inseparable aspects of cancer chemotherapy, which can be prevented by efficient use of antiemetic agents. Chemotherapy-induced nausea and vomiting (CINV) may jeopardize the nutritional status of patients, thereby it may reduce the performance status and ability to tolerate further cycles of chemotherapy. 1,2 The duration and severity of CINV depends on the emetogenic potential of drugs used, dose, route of administration, duration of treatment, patient characteristics and effectiveness of the antiemetic regimen employed.^{3,4} Patient factors associated with increased risk for CINV include female sex, younger age, history of CINV, emesis during pregnancy, motion sickness and impaired quality of life.5,6,7

CLASSIFICATION OF ANTI-CANCER DRUGS ACCORDING TO EMETOGENICITY

Intrinsic emetogenic potential and dose are the two important aspects determining the risk of CINV and its severity. Anti-cancer drugs are classified into four classes depending on their emetogenicity (Table 1).

ETIOLOGY & CLASSIFICATION OF CINV

CINV can be classified into 3 distinct clinical syndromes.

Acute emesis: Occurs within 24 hours of initial administration of chemotherapy and usually peaks within 1-2 hrs. It may be due to direct stimulation of chemoreceptor trigger zone by chemotherapeutic agents and serotonin & other mediators released by enterochromaffin cells stimulated by cytotoxic drugs, or stimulation of vagal afferent fibers by serotonin & other mediators released by enterochromaffin cells.¹⁰

Table 1: Classification of anti-cancer drugs according to Emetogenicity.^{8,9}

Level of Emetogenicity	Agents		
1. High	Cisplatin> 50 mg/m ² , Carmustine>250 mg/m ² , Cyclophosphamide		
(>90% of patients will have	(>1.5 g/m ²), Pentostatin, Actinomycin D, Dacarbazine, Mechlorethamine &		
emesis when no prophylactic	Streptozocin		
antiemetic is given)			
2. Moderate	Carboplatin, Cyclophosphamide ($\leq 1.5 \text{ g/m}^2$), Cytarabine ($> 1 \text{ g/m}^2$), Daunorubicin,		
(31-90% of patients will have	Doxorubicin>60 g/m², Cisplatin<50 mg/m², Epirubicin, Idarubicin, Carmustine<250		
emesis when no prophylactic	mg/m ² , Ifosfamide, Irinotecan, Oxaliplatin, Methotrexate>1 mg/m ² , Temozolomide,		
antiemetic is given)	Trabectedin & Treosulfan		
3. Low	Bortezomib, Cetuximab, Cytarabine (≤100 mg/m² of body-surface area), Docetaxel,		
(10-30% of patients will have	Capecitabine, Etoposide, Fluorouracil< 1 mg/m ² , Gemcitabine, Ixabepilone,		
emesis when no prophylactic	Lapatinib, Methotrexate, (50-250 mg/m ²), Mitomycin, Mitoxantrone, Paclitaxel,		
antiemetic is given)	Pemetrexed, Temsirolimus, Topotecan, Trastuzumab & L-Asperaginase		
4. Minimal	Methotrexate (< 50 mg/m ²), Estrogen, Progesterone, Hydroxyurea, Bevacizumab,		
(< 10% of patients will have	Bleomycin, Busulfan, Cladribine, Fludarabine, Vinblastine, Vincristine,		
emesis when no prophylactic	Vinorelbine, Melphalan & Mercaptopurine		
antiemetic is given)			

Delayed emesis: Occurs after 24 hours to several days after initial treatment. Classically seen after administration of cisplatin; also seen with carboplatin, anthracyclines (doxorubicin & daunorubicin) and cyclophosphamide. It may be due to the effect of released serotonin, substance P & other mediators on CTZ & vagal afferent fibers.

Anticipatory emesis: A conditioned response observed in patients with a history of poor response to antiemetic agents or inadequate antiemetic prophylaxis in the previous cycle of chemotherapy. Emetic reflex is triggered by taste, anxiety, odor, sight, or thoughts of previous cycle of chemotherapy. 12

ANTI EMETIC AGENTS USED IN PREVENTION & TREATMENT OF CINV

As different mechanisms are responsible for acute and delayed CINV, combination of antiemetic drugs of different classes will prevent CINV efficiently through out the duration of chemotherapy. Currently 5HT-3 receptor antagonists, corticosteroids and substance P antagonists are mainly used in prevention of CINV.

5-Hydroxytryptamine Type-3 Receptor Antagonists

Introduction of 5-HT3 receptor antagonists (5-HT3 RAs) was a major advance in the prevention & treatment of acute CINV as it significantly improved patient tolerance to emetogenic chemotherapy. Ondansetron was the first 5-HT3 Receptor antagonist approved by the US FDA for prevention of CINV. Soon its congeners dolasetron, tropisetron, granisetron & palonosetron were approved. Classically, ondansetron, dolasetron, tropisetron & granisetron are considered as first-generation 5-HT3 receptor antagonists and palonosetron as a second

generation 5-HT3 receptor antagonist. Single-agent therapy with a 5-HT 3 receptor antagonist prevents acute emesis in 40–60% of patients receiving highly emetogenic chemotherapy. Addition of dexamethasone increases the protection to 60-90%. The plasma half-life of first generation 5-HT3 receptor antagonists is less than 24 hours (ondansetron [4-6 h], granisetron [5-8 h], tropisetron [7 h] and dolasetron [7 h]). All are metabolized in liver and excreted through the kidney. Headache and constipation are the most commonly reported adverse events. All first generation 5-HT3 receptor antagonists demonstrate equivalent efficacy and safety. All first generation 5-HT3 receptor antagonists demonstrate equivalent efficacy and safety.

Palonosetron is considered as second generation 5-HT3 Receptor antagonist because of its distinct pharmacokinetic and receptor binding affinity. In contrast to other 5-HT3 antagonists that exist as racemic mixtures, palonosetron exists as a single stereoisomer. 18 Its plasma half-life is approximately 40 hours & receptor binding affinity is 30-fold higher than ondansetron. These properties make it more efficacious & compliant than antagonists. 19 generation 5-HT3 receptor first Palonosetron has a similar safety profile as that of firstgeneration 5-HT3 RAs. Headache and constipation are most commonly reported adverse events. Palonosetron is more effective at 0.25 mg than 0.75 mg, perhaps due to the formation of less effective enantiomers. 5-HT3 RAs undergo extensive metabolism in liver and are eliminated through urine, however dose adjustment is not needed in the elderly & in patients with decreased renal function.

Neurokinin type one receptor antagonists

Aprepitant is a potent and selective non-peptide Neurokinin type one receptor antagonist, which freely crosses the blood brain barrier and effectively

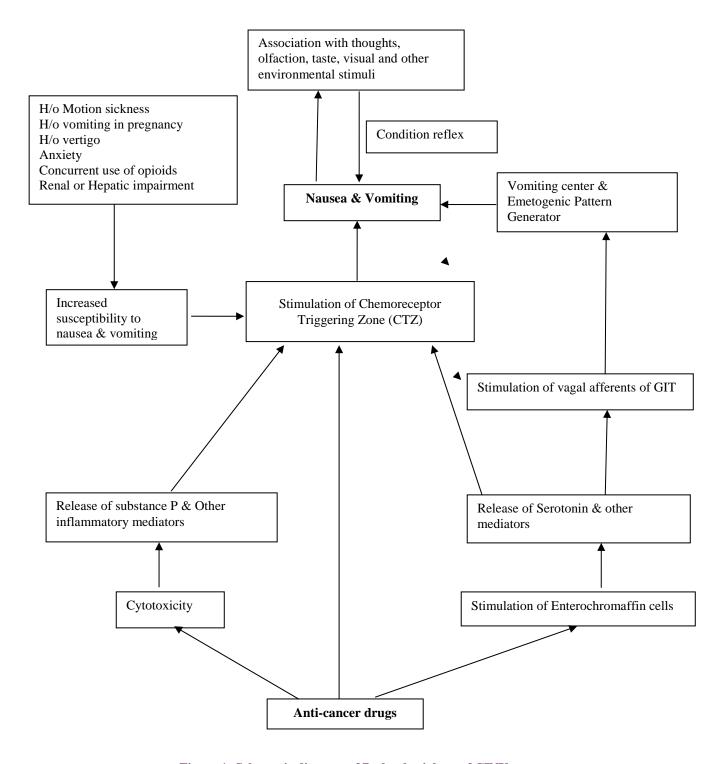


Figure 1: Schematic diagram of Pathophysiology of CINV.

antagonizes the central actions of substance P.^{20,21} Aprepitant is especially useful in preventing delayed emesis which is not effectively prevented by 5-HT 3 RAs.²² It is effective both as monotherapy and in combination with dexamethasone, and 5-HT3 RAs. Addition of aprepitant improves protection against acute emesis by more than 10% and delayed emesis by about 20%.²³⁻²⁵ Co-administration of aprepitant provides a

sustained protection against emesis over multiple cycles of chemotherapy^{26,27} and enhances the protection provided by combination of 5-HT3 RAs and dexamethasone.^{28,29} Dosing with aprepitant prior to initiation of cisplatin-based chemotherapy provided particularly good control of delayed vomiting, and continued dosing with aprepitant on subsequent days improved control of both vomiting and nausea.^{30,31}

Aprepitant is absorbed orally with an oral bioavailability of 60-65%. Its t1/2 is nine-thirteen hours. Food does not interfere with its oral absorption. Fosaprepitant is a water-soluble prodrug of aprepitant which is converted into the active form within 30 minutes of parenteral administration. It is metabolized in the liver primarily by CYP3A4 and also partly by CYP1A2 & CYP2C19. It exhibits first order elimination, with increase in dose it is eliminated by zero order elimination.32 Hundred and twenty five mg is given on day one before initiation of chemotherapy followed by 80 mg twice daily in subsequent days. At therapeutic doses it significantly inhibits CYP3A4 leading to drug interactions with drugs like corticosteroids, benzodiazepines, ketoconazole, oral contraceptives etc. 33-35 It has been shown to increase dexamethasone levels approximately two-fold. This suggests that oral corticosteroid doses should be reduced by 50% when co-administered with aprepitant. However it has no significant interaction with important anticancer drugs like cyclophosphamide, taxanes, etoposide and vinca alkaloids.³⁶ No dose adjustment is needed in patients with renal insufficiency.³⁷ A single oral dose of 125 mg has most favorable risk:benefit profile.³⁸

Corticosteroids

Studies have shown that a combination of steroids either with 5-HT-3 RAs or both 5-HT-3 RAs and aprepitant improves protection against both acute and delayed CINV. 39-41 As monotherapy, steroids are also effective in prevention of CINV in patients receiving chemotherapy of low emetic potential. Though the exact mechanism of the anti emetic action of corticosteroids is not known it may be due to reduced inflammatory damage to mucosal cells, depletion of tryptophan which is the precursor of serotonin⁴², & reduction of 5-HT release from the gut, or due to release of endorphins, resulting in mood elevation, a sense of well-being, and appetite stimulation.⁴³ Dexamethasone has a biological half life of 36-72 hrs, which is favorable in effective prevention of delayed emesis. At doses used to prevent CINV, i.e., 12 mg on day one and 8-12 mg/day from two-five days, dexamethasone does not cause dysfunction of the hypothalamic-pituitary-adrenal axis and hence tapering is not required. 44,45

Others

Dopaminergic antagonists: Dopaminergic antagonists such as phenothiazines and butyrophenones were the first agents found to be useful in the treatment of vomiting. 46,47 They act through inhibition of dopamine two receptor in the stomach (thereby promoting gastric emptying) and the chemoreceptor trigger zone (CTZ). At higher doses drugs such as metoclopramide also inhibit 5-HT3 receptors. The side effects due to inhibition of dopamine two receptors such as extrapyramidal symptoms, hyperprolactinemia, galactorrhea & gynecomastia, are inseparable from its therapeutic effects. Due to their narrow therapeutic index dopamine

antagonists are not used routinely for prevention/treatment of CINV. They are used only in resistant cases. Examples of clinically used dopamine 2 receptor antagonists for treatment of CINV are

- Phenothiazines: Chlorpromazine & prochlorperazine
- Butyrophenones: Haloperidol & domperidone
- Substituted benzamides: Metoclopramide & trimethobenzamide

Olanzapine is an atypical antipsychotic drug. Phase two clinical trials have shown that olanzapine is useful in prevention of both acute and delayed CINV, when given either with dexamethasone or palonosetron⁴⁹; this may be due to its 5-HT & dopamine antagonistic action. However careful monitoring is required due to its propensity to cause aplastic anemia and seizures.

Benzodiazepines: Diazepam, lorazepam & alprazolam are used in the prevention of CINV, especially anticipatory vomiting.^{50,51} The anti-emetic action of benzodiazepines may be due to its sedative, anxiolytic & amnesic properties.

Cannabinoids: Though the anti-emetic action of cannabis has been known for a long time, their usefulness is clinically limited due to undesirable effects, especially hallucinations and paranoia. Though some of its effects like drowsiness, sedation & increasing appetite may be in patients receiving chemotherapy, hallucinogenic properties and potential for abuse limits its usefulness. Compared to commonly used drugs in treatment of nausea and vomiting, cannabinoids act different mechanism through i.e., through endocannabinoid system, hence they may be useful in treatment of CINV refractory to conventional treatment modalities. Drugs acting on Cannabinoid receptors like nabilone & dronabinol (one of the main ingredients in cannabis) have shown to be effective in CINV^{52,53} some medical establishments have appealed for legalization of cannabis for this indication^{54,55} and these are sometimes used to treat CINV not controlled by other agents. 56-58

Levetiracetam: Recently levetiracetam has been found to be useful in prevention of CINV especially in patients with brain tumors in whom it was used to prevent seizures. It was well tolerated and had no interaction with chemotherapeutic drugs.⁵⁹

Others: Complementary medicine interventions such as acupuncture, hypnosis, behavioral therapy (especially for anticipatory vomiting) and herbal drugs (especially garlic and ginger) are known to be useful in prevention and treatment of CINV. However randomized controlled trials are needed to firmly establish their usefulness in prevention and treatment of CINV.

Table 2: Guidelines for Antiemetic Treatment. ⁶⁰

American Society of Clinical Oncology (ASCO) Guidelines for prevention of CINV					
Type (Day) Emetogenicity	Acute emesis (Day 1)	Delayed emesis (Day 2)	Delayed emesis (Day 3)	Delayed emesis (Day 4)	
High	5-HT3 receptor antagonists + Dexamethasone + Aprepitant	Dexamethasone + Aprepitant	Dexamethasone + Aprepitant	Dexamethasone	
Moderate	5-HT3 receptor antagonists + Dexamethasone (+ Aprepitant for anthracyclin & cyclophosphamide combination)	Dexamethasone (+ Aprepitant for anthracyclin & cyclophosphamide combination)	Dexamethasone (+ Aprepitant for anthracyclin & cyclophosphamide combination)		
Low	Dexamethasone	No routine prophylaxis, prescribe if needed			
Minimal	No routine prophylaxis, prescribe if needed	No routine prophylaxis, prescribe if needed	No routine prophylaxis		

CINV is also partly because of underestimation of the problem by treating staff. Strict compliance with guidelines to prevent CINV will not only improve the well being of patient by minimizing the side effects of chemotherapy but also will reduce the duration of stay in hospital and hence cost of treatment.

CONCLUSION

Better understanding of the pathophysiology of CINV has led to the development of many effective anti emetic drugs, thereby improving the tolerability of emetogenic chemotherapy and quality of life. However CINV is still a significant problem in cancer chemotherapy. CINV can be effectively controlled by understanding the emetogenic potential of the cytotoxic drugs used and the patient characteristics, especially for preventing anticipatory vomiting. Guidelines should be followed. There is need for drugs acting through different mechanisms (like cannabinoid receptors) with good safety profile as they can increase the protection against CINV when given in combination with presently used drugs.

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