REVIEW ARTICLE

Management of Chemotherapy-Induced Nausea and Vomiting

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Context: Chemotherapy-induced nausea and vomiting (CINV) is a significant problem in the treatment of children with cancer. The last decade has seen a variety of newer antiemetics being evaluated for CINV; their efficacy and side-effects need to be assessed in children. This article attempts to highlight this revised management of CINV.

Evidence acquisition: Online search; journals. Search period: 6 months.

Results: Newer drugs (aprepitant, fosapritant and newer 5HT3 antagonists) have been found to be effective in CINV: both acute and delayed phases. Most of the available literature is, however, based on adult oncology patients, with a few trials on adolescent patients.

Conclusion: Every child receiving treatment for cancer should be evaluated for possible CINV. Their treatment should take into account the emetogenic potential of the chemotherapeutic drugs. Newer antiemetic drugs have good efficacy and can be tried in pediatric patients, especially in children > 11 years of age.

Keywords: Antiemetics, Cancer, Chemotherapy, Nausea, Vomiting.

Chemotherapy is a common modality for treatment of cancer. Regardless of the fact that chemotherapy improves survival; it has its own toxicity and side-effects, which have a negative impact on the quality of life of children with cancer. Severe side-effects, and non-compliance because of those side-effects, can lead to loss of time at school for the child, loss of time at work for the caregiver, and additional office visits to the doctor; all of which contribute both to death and disability, and to the annual costs of cancer. It is therefore imperative to optimize chemotherapy and ensure minimum side-effects. Nausea and vomiting continue to be significant side-effects of cancer therapy and can affect patient compliance(1). To avoid the clinical sequelae of chemotherapy-induced nausea and vomiting (CINV) like malnutrition, dehydration, dyselectrolytemias, anorexia, stress, esophageal tears, and anxiety, it is imperative to provide prophylaxis and treatment for CINV.

CLASSIFICATION

Chemotherapy-induced nausea and vomiting (CINV) is broadly classified into acute, delayed or anticipatory type depending upon the time period of vomiting(2). Vomiting occurring in the first 24 hours of administering chemotherapy is labeled as acute CINV and in the absence of effective prophylaxis, it most commonly begins within one to two hours of chemotherapy and usually peaks in the first four to six hours. Vomiting occurring later is called delayed CINV. Classically, this phenomenon was described with cisplatin. While the frequency and number of episodes of emesis may be less during the delayed period compared to acute emesis, the delayed form is less well controlled with current antiemetic medications. Anticipatory

emetic episodes are triggered by taste, odor, sight, thoughts, or anxiety secondary to a history of poor response to antiemetic agents or inadequate antiemetic prophylaxis in the previous cycle of chemotherapy. It usually starts 1 to 4 hours before chemotherapy but can sometimes occur days before chemotherapy(3,4).

PREDISPOSING FACTORS

Risk factors for CINV include patient gender (females >males), age (>3 years), past history of CINV, the emetogenic potential of the drug, and administration schedule of chemotherapy(5).

The American Society of Clinical Oncology has classified the cancer chemotherapeutic drugs in four categories of high, moderate, low, and minimal emetogenecity, depending on their emetogenic potential (***Table* I**)(1,2).

PATHOPHYSIOLOGY

Chemotherapeutic drugs can cause nausea and vomiting by several mechanisms. They act by causing irritation of the mucosal lining of the stomach and duodenum, which stimulates certain nerves that activate the vomiting center (VC) and the chemoreceptor trigger zone (CTZ) in the brain which leads to vomiting. They can also activate the CTZ by causing intestinal obstruction, delayed gastric emptying, or inflammation. Therefore, CINV involves coordination of several organs of the gastrointestinal tract, the peripheral and central nervous systems(5). Historically, there were only two neurotransmitter receptors (dopamine D2 and cannabinoid-1) that were the known targets for antiemetic therapy. Major advances in the management of chemotherapy-induced emesis were seen with the introduction of 5-hydroxytryptamine-3 receptor antagonists, which included ondansetron, tropisetron, dolasetron, and granisetron. However, these agents offer limited protection in the acute phase of chemotherapy-induced nausea and vomiting, with little or no effect over the delayed phase. Recently, selective inhibitors of substance P (Neurokinin1 (NK1) receptor antagonists) and also some newer 5-HT3 receptor antagonists have shown promising activity in the management of delayed phase of CINV(6). Among the NK1 receptor antagonists, aprepitant has been approved for the treatment of CINV. Currently, several other NK1 receptor antagonists, including casopitant, vestipitant, netupitant, and SCH619734 are undergoing clinical evaluation for

TABLE I RISK OF EMESIS WITH CHEMOTHERAPEUTIC DRUGS AND RECOMMENDED TREATMENT FOR CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING(1)

Emetic Risk	Chemotherapeutic Drug	Anti-emetic Schedule
High (> 90%)	Cisplatin, Mechlorethamine, Streptozotocin, Dacarbazine, Carmustine, Dactinomycin Cyclophosphamide (>1500 mg/m^2)	5-HT$_3$ serotonin receptor antagonist: Day 1 Dexamethasone: Days 1-4 Aprepitant: Days 1-3
Moderate (30 to 90%)	Oxaliplatin, Cytarabine (> 1000 mg/m^2), Carboplatin, Ifosfamide, Cyclophosphamide < 1500 mg/m^2, Doxorubicin, Daunorubicin, Epirubicin, Idarubicin, Irinotecan	5-HT$_3$ serotonin receptor antagonist: Day 1 Dexamethasone: Day 1 (2, 3)* (Aprepitant: Days 1, 2, 3)
Low (10% to 30%)	Paclitaxel, Docetaxel, Mitoxantrone, Topotecan, Etoposide, Pemetrexed, Methotrexate, Mitomycin, Gemcitabine, Cytarabine (< 1000 mg/m^2), Fluorouracil, Bortezomib, Cetuximab, Trastuzumab	Dexamethasone: Day 1
Minimal (< 10%)	Bevacizumab, Bleomycin, Busulfan, Fludarabine, Vincristine, Vinorelbine, Vinblastine, 2-Chlorodeoxyadenosine, Rituximab	Prescribe as needed

* *May omit days 2 and 3 if aprepitant is given; for patients receiving a combination of an anthracycline and cyclophosphamide.*

the prevention of CINV in patients with a variety of malignancies.

TRADITIONAL DRUGS FOR CINV MANAGEMENT

The key to effective control of nausea and vomiting is to prevent it before it occurs whenever possible. That is why medicines for nausea and vomiting are started before the chemotherapy is given. Anti-emetic drugs may be used alone or in combination. The traditional drugs for management of CINV have been the dopamine antagonists (metoclopramide); steroids (dexamethasone), the 5-HT3 antagonists (ondansetron) and cannabinoids(5-7).

Dopamine antagonists

The prototype of dopamine receptor antagonist group of drugs is metoclopramide; other drugs being domperidone, haloperidol, chlorpromazine, and prochlorperazine. At higher doses, metoclopramide also acts as a serotonin receptor antagonist. Antiemetic efficacy with metoclopramide is slightly less than that seen with the selective serotonin receptor antagonists. Side-effects include acute dystonic reactions, akathisia, and sedation. Domperidone does not cause dystonia as it does not cross the blood brain barrier. Haloperidol is rarely used in children for CINV.

Corticosteroids

Dexamethasone (0.05-0.2 mg/kg) and methylprednisolone (100 mg/m^2) have a high therapeutic index when used to prevent chemotherapy-induced emesis. They are among the most frequently used antiemetics. The American Society of Clinical Oncology has proposed its single-agent use in patients receiving chemotherapies of low-emetic potential. Dexamethasone is especially valuable when administered in combination with 5-HT$_3$ serotonin receptor antagonists. It acts by decreasing inflammatory effects on intestinal mucosa, blocking 5-HT3 release, and by decreasing the permeability of blood-brain barrier. Adverse effects of single dexamethasone doses are rare, although elevations of serum glucose levels, epigastric burning, and sleep disturbances have been reported.

Serotonin (5-HT3) Antagonists

The traditional 5-HT3 antagonist agents are granisetron, ondansetron, and tropisetron. They are highly selective agents sharing the same side-effect pattern, with mild headache, flushing, and constipation, being among the most commonly reported adverse events. In conjunction with steroids, they have been found to be very useful for the acute phase of CINV in association with moderate and high emetogenic schedules. They are effective orally as well as parenterally, the effective dose being 5 mg/m^2 for Ondansetron (maximum dose: 8 mg). Dolasetron is another effective drug though not yet established for pediatric use.

Benzodiazepines

Short acting benzodiazepines including lorazepam (0.025-0.05 mg/kg) and midazolam (0.1 mg/kg) can act as adjuncts to treatment of CINV, especially anticipatory, by reducing anxiety and causing sedation.

Others

Cannabinoids, both as plant extracts (dronabinol) and as semisynthetic agents (nabilone and levonantradol), have been found to have antiemetic activity when used alone or in combination with other agents. These agents cause frequent dizziness, sedation, hypotension, and dysphoria, especially in older adults.

In view of limited control of CINV by the traditional group of drugs, there was a need to discover newer and better drugs(8). The discovery of neurokinin 1 receptor antagonists, and also some newer 5-HT3 antagonists has led to a better control of CINV. This review highlights some of these drugs.

NEUROKININ 1 RECEPTOR ANTAGONISTS

Aprepitant

Aprepitant is the most widely studied and the most commonly used drug of all the NK1 receptor antagonists(8). Aprepitant has been shown to inhibit both the acute and delayed emesis induced by cytotoxic chemotherapeutic such as cisplatin by

blocking substance P landing on receptors in the neurons. It was first approved by the FDA in 2003 as an oral antiemetic drug.

Pharmacokinetics: Aprepitant has an average bioavailability of 60-65% when consumed orally, with 95% of the drug being bound to plasma proteins. Its peak plasma concentration is achieved about 4 hours after administration and is mainly eliminated from body by phase I metabolism. *In vitro* studies using human liver microsomes indicate that aprepitant is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. The half-life ranged from approximately 9 to 13 hours. No dose adjustment is needed in renal disease or mild to moderate hepatic insufficiency (Child-Pugh score 5-9)(8,9).

Regimens and efficacy: It is mainly used as a preventive add-on drug for CINV. Many case series are available that prove the efficacy of aprepitant in the delayed phase of CINV, especially of the highly emetogenic chemotherapeutic group. Aprepitant is available commercially as capsules in bottles or blister pack (Emend, Merck, 125 mg and 80 mg capsules, INR 1150 for a pack of 3 capsules). It is given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist. The recommended dose of Aprepitant is 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg once daily in the morning on Days 2 and 3. Capsules can be stored at 20-25°C. Most of the aprepitant studies have been conducted in adult patients(10-15). A pilot, single-institution, randomized, double-blind, placebo-controlled trial by Herrington, *et al*.(15) found that in patients who were receiving palonosetron, aprepitant, and dexamethasone for highly emetogenic chemotherapy, a single dose of aprepitant displayed similar effectiveness compared with 3-day aprepitant. Only a few adolescent studies are available(16,17). A clinical regimen tried effectively in adolescents by Gore, *et al*.(17) is shown in ***Table* II**. Pediatric studies are required to establish the role of this drug in management of CINV.

Side effects and drug interactions: The main reported side effects of aprepitant are constipation, fatigue and diarrhea. In view of its induction of various enzymes, there is a possibility of drug interactions. Aprepitant may interfere with the metabolism of ifosfamide as it inhibits CYP3A4. A retrospective study of 45 patients conducted by Howell, *et al*.(18) has shown an increase in the incidence of neurotoxicity of ifosfamide with the concomitant use of aprepitant. It should not be used with cisapride and pimozide.

Fosaprepitant

Fosaprepitant dimeglumine (MK-0517 or L-758,298), a prodrug of aprepitant, was developed to provide a parenteral alternative to the orally administered aprepitant(19, 20). Fosaprepitant is rapidly converted to aprepitant via the action of ubiquitous phosphatases. Based on equivalence studies, 115 mg fosaprepitant seems to be the substitute for 125 mg orally administrated aprepitant. Tolerability of the prodrug is no different from the active drug. In phase I and II trials, fosaprepitant shows efficacy, but most of the large randomized efficacy studies have utilized aprepitant. Fosaprepitant has recently been approved by FDA and EMEA as an intravenous substitute for oral aprepitant on day 1 of the standard 3-day CINV prevention regimen, which also includes dexamethasone and a 5-HT3 antagonist. Side effects are similar to aprepitant with the addition of mild venous irritation and headache. Further studies are needed to clarify the utility of fosaprepitant in the prevention of CINV and to clarify optimal dosing regimens that may be

TABLE II NEWER REGIMEN USING COMBINATION OF ANTI-EMETIC DRUGS FOR CINV

	Day 1	Day 2	Day 3	Day 4
Aprepitant*	125 mg	80 mg	80 mg	-
Dexamethasone**	8 mg, oral	4 mg, oral	4 mg, oral	4 mg, oral
Ondansetron†	0.15 mg/kg, IV, tid	0.15 mg/kg, IV, tid	–	–

**Administered orally 1 hour prior to chemotherapy treatment on Day 1 and in the morning on Days 2 and 3; **Administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4; †Administered 30 minutes prior to chemotherapy treatment on Day 1.*

appropriate substitutes for oral aprepitant. It is not yet available commercially.

Casopitant

It is a novel NK1 antagonist which is scheduled to be marketed having completed phase II and phase III trials(5). It can be administered orally or intravenously.

PALONOSETRON

Palonosetron is different from conventional serotonin receptor antagonists as it has a longer half-life (40 hours) and also a higher affinity for serotonin receptors(21). It is the first agent in the class which is approved for preventing both delayed and acute emesis induced by moderately emetogenic chemotherapy.

In a study by Grunberg, *et al*.(22), a single-dose regimen of palonosetron in combination with dexamethasone and aprepitant was found highly effective in preventing acute and delayed emesis following administration of moderately emetogenic chemotherapy. In another study by Grote, *et al*.(23) patients received a single intravenous dose of palonosetron (0.25 mg on day 1 of chemotherapy), along with 3 daily oral doses of aprepitant (125 mg on day 1, 80 mg on days 2 and 3) and dexamethasone (12 mg on day 1, 8 mg on days 2 and 3). The proportion of patients with complete response (no emesis and no rescue medication) was 88% during the acute (0-24 hours) interval, 78% during the delayed (> 24-120 hours) interval, and 78% during the overall (0-120 hours post chemotherapy) interval. More than 90% of patients during all time intervals had no emetic episodes, and between 57% and 71% of patients reported no nausea during each of the 5 days post chemotherapy. Multiple-day dosing of palonosetron plus dexamethasone was safe and effective for prevention of emesis induced by 5-day cisplatin-based chemotherapy. There was no evidence of cumulative toxicity when palonosetron was given three times over 5 days.

Palonosetron represents a useful addition to the therapeutic armamentarium for the management of chemotherapy-induced nausea and vomiting. Further studies are needed to assess the effectiveness of palonosetron in combination with dexamethasone compared with that of older serotonin receptor antagonists combined with dexamethasone, However, palonosetron may offer advantages of convenience over the short-acting older antagonists due to its ability to be given as a single intravenous dose prior to chemotherapy.

RECOMMENDATIONS FOR PREVENTING CINV

The choice of antiemetic drug to be used in a chemotherapy regimen should include not only the chemotherapeutic drug being used but also the possible patient characteristics and etiology of emesis. Emphasis should be on the primary prevention of CINV rather than its treatment. Further, the selection of the route of administration needs to be proper as oral drugs may be ineffective in a child who is vomiting actively. Therefore, 24-48 hours of parenteral drugs may help to attain good control till such time that oral treatment can be instituted. Recommended antiemetic regimens for

TABLE III DOSE AND SCHEDULE OF ANTIEMETICS USED TO PREVENT EMESIS INDUCED BY ANTINEOPLASTIC THERAPY OF HIGH EMETIC RISK (2)

Antiemetic drug	Single dose administered before chemotherapy
5HT3 Receptor Antagonists	
Dolasetron	Oral: 100mg; IV: 100 mg or 1.8 mg/kg
Granisetron	Oral: 2 mg; IV: 1 mg or 0.01 mg/kg
Ondansetron	Oral: 24 mg; IV: 8 mg or 0.15 mg/kg
Palonosetron	IV: 0.25 mg
Tropisetron	Oral or IV: 5 mg
Corticosteroids	
Dexamethasone*	Oral: 12 mg
NK1 Receptor Antagonists	
Aprepitant*	Oral: 125 mg

**These drugs can be administered as a single oral daily dose as 8 mg on days 2-4 for Dexamethasone and 80 mg on days 2-3 for aprepitant. For antineoplastic drugs of moderate risk: Dexamethasone can be used as 12 mg oral when used with aprepitant or 8 mg IV when used without aprepitant. Alternately Ondansetron may be used orally in a dose of 16 mg (8 mg BD).Rest of the drug schedule is same as for high risk. 5HT3: 5-Hydroxytryptamine; NK1: Neurokinin 1; IV: intravenous.*

KEY MESSAGES

- Antiemetics can be used alone or in combination depending upon the total emetic potential of the chemotherapeutic regimen.
- Newer antiemetic drugs such as Aprepitant have showed good potential in adult cancer patients but more trials are needed in children.

highly emetogenic chemotherapy include a 5-HT3 antagonist, and dexamethasone. (***Table* III)**. Moderately emetogenic chemotherapy requires a 5-HT3 antagonist or corticosteroid and the various drugs and their dose schedule is depicted in ***Table* III**. Options for treatment of refractory CINV include aprepitant, olanzapine, dronabinol, nabilone, gabapentin, and casopitant; however, their efficacy and safety needs to be established in pediatric cancer patients.

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