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REVIEW ARTICLE

Prevention of chemotherapy induced nausea and vomiting in pediatric cancer patients

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Abstract

Despite the relevant progress achieved in the last 20 years, vomiting and, especially, nausea, continue to be two of the most distressing side-effects of cancer chemotherapy. The goal of antiemetic therapy is to prevent nausea and vomiting associated with chemotherapy administration. The appropriate pharmacologic treatment should be chosen by evaluating the emetogenic risk of chemotherapy as a single agent or as combination therapy. For most children, receiving any chemotherapy that has emetogenic potential, a 5-hydroxytryptamine-3 (5-HT3) receptor antagonist should form the backbone of antiemetic therapy.Nausea and vomiting in pediatric cancer patients can be multi-factorial. Evaluation of symptoms should reflect this. Nausea and vomiting can have structural, psychological, chemical, and metabolic or a combination of origins. Nausea and vomiting is a troublesome side effects of chemotherapy and when antiemetic prophylaxis is not adequate, it affects the compliance of the treatment. This is a mini review on different aspects of chemotherapy induced nausea and vomiting in pediatric patients.

Keywords: Chemotherapy, Nausea, Vomiting, Pediatric cancer

Introduction

Despite the relevant progress achieved in the last 20 years, vomiting and, especially, nausea, continue to be two of the most distressing side-effects of cancer chemotherapy. These side effects have a significant impact on quality of life and can interfere with the ability to deliver intensive care. Fortunately, improvements in supportive and adjunctive care have also been attained, and current treatments for nausea and vomiting are effective in mitigating these adverse effects in most patients [1].

Vomiting were classified into acute and delayed depending on the onset of symptoms after chemotherapy. In acute vomiting, symptoms occur within 24 hours of the administration of chemotherapy and delayed vomiting refers to vomiting 2-5 days after the administration of chemotherapy. Anticipatory vomiting, which is a particularly challenging phenomenon in children and teenagers, is vomiting prior to the administration of chemotherapy.

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Anticipatory CINV can occur in up to 25% of patients and is a result of classic operant conditioning from stimuli associated with chemotherapy; usually occurring within 12 hours prior to treatment administration [2]. Also, this type of vomiting is more likely in children who have a history of motion sickness or who have had particularly negative post-chemotherapy nausea or vomiting experience [3]. In addition to acute, delayed and anticipatory CINV, patients can also experience breakthrough or refractory CINV, which occurs despite prophylactic antiemetic administrations.

According to Cohen et al. (2007), 38% of patients receiving a new chemotherapy regimen develop acute CINV and as many as 64% develop delayed CINV. He also showed that the risk of developing CINV was highly related to having CINV in the previous cycle, illustrating the importance of proper management of CINV at initial treatment. Ballatori et al. [5] found that more than 90% of patients who experience acute or delayed CINV also reported an impact on their daily activities.

The goal of each antiemetic therapy is to prevent chemotherapy - induced nausea and vomiting [6]. Twenty years ago, these were inevitable adverse events of chemotherapy and forced up to 20% of patients to postpone or refuse potentially curative treatment [7].

Pathophysiology of CINV

The chemotherapy trigger zone (CTZ) is located in a medullary center located in the area postrema, which is susceptible to emetic stimuli delivered through the blood system or cerebrospinal fluid (CSF). The chemotherapy trigger zone stimulates the vomiting center, an area of the medulla oblongata that acts by stimulating the phrenic, spinal, and visceral nerves. These efferent signals induce vomiting by their effects on the diaphragm, abdominal muscles, and stomach. The vomiting center also receives signals of increased intracranial pressure from visceral organs, the inner ear labyrinthine apparatus, and higher CNS structures. The most important transmitters and their receptors include serotonin and the 5-HT3 receptor, dopamine, dopamine receptor and substance P, and the neurokinin 1 (NK1) receptor. Most antiemetics function as competitors of the emetogenic transmitters; therefore, by binding to the receptors, they prevent binding of the emetogenic transmitters. For this reason, using antiemetics prior to administration of emetogenic chemotherapy is important. It was Wang and Borison who first proposed the idea of a vomiting centre [8].

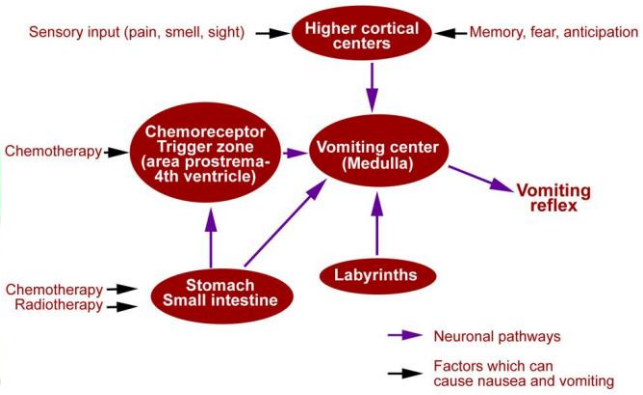

Fig 1: Vomiting Reflex

Epidemiology

Frequency: In order to determine the emetogenic potential of combination chemotherapy regimens, the following must be considered:

- Determine the category of the most emetogenic agent in the regimen.
- Add one level for all level 2 agents or each level 3 agent included in the regimen.
- Level 1 agents do not contribute to the emetogenicity of a given regimen.

Mortality/Morbidity: Nausea and vomiting are a significant cause of morbidity in pediatric patients.

Sex: Although both sexes are affected by chemotherapy-induced nausea and vomiting, some studies have suggested that females are somewhat more susceptible.

Age: Chemotherapy-induced nausea and vomiting affects children of all ages; however, children younger than 6 years have been shown to have a lower incidence than older children when receiving similar agents. By contrast, adolescents appear to be more susceptible.

Differential Diagnoses

Nausea and vomiting in pediatric cancer patients can be multi-factorial. Evaluation of symptoms should reflect this. Nausea and vomiting can have structural, psychological, chemical, metabolic or a combination of origins. When evaluating pediatric cancer patients with suspected CINV, causes such as pain, anxiety, hepatosplenomegaly, bowel obstruction, metastasis or increased ICP should also be considered. These include the following:

- Direct effects of tumor by stretching organs of the GI system or causing obstruction.
- Postoperative obstruction (in patients who have had abdominal surgery).
- Increased intracranial pressure.
- Opioid-induced vomiting.

The goal of antiemetic therapy is to prevent nausea and vomiting associated with chemotherapy administration. The appropriate pharmacologic treatment should be chosen by evaluating the emetogenic risk of chemotherapy as a single agent or as combination therapy (see the Tables and specific recommendations below). In the event of uncontrolled nausea or vomiting, several medical complications may arise, including fluid and electrolyte imbalances, poor nutrition status, prolonged hospitalization, and delay in subsequent chemotherapy administration cycles.

Differential Diagnoses	
Structural: Bowel Obstruction Hepatosplenomegaly Brain metastasis	**Psychological:** Anxiety Depression Uncontrolled pain
Chemical: Opiods Antidepressants Antiobiotics	**Metabolic:** Hypo/Hypernatremia Hypo/Hyperkalemia Hypercalcemia

For most children, receiving any chemotherapy that has emetogenic potential (ie, any agents except those in level 1), a 5-hydroxytryptamine-3 ($5\text{-}HT_3$) receptor antagonist should form the backbone of antiemetic therapy. No studies have demonstrated superiority of any $5\text{-}HT_3$ antagonist over another when used optimally (see Medication for dosing guidelines). For maximum efficacy, these agents should be started 30 minutes prior to chemotherapy, continued throughout chemotherapy, and continued for several days after completion.

Children who are receiving highly emetogenic chemotherapy may benefit from additional antiemetics. If no contraindications to dexamethasone are noted, adding this agent to a $5\text{-}HT_3$ agonist may be beneficial, particularly in those patients receiving cisplatin-containing chemotherapy regimens. This can help with both acute and delayed nausea. Relative contraindications to dexamethasone include hyperglycemia, systemic infection, and hypertension. Dexamethasone should generally be avoided in patients receiving chemotherapy regimens that include corticosteroids and was recently found to increase the risk of postoperative bleeding in

Table 1. Emetogencity of Chemotherapeutic Agents [3,9]

Emetogenic Risk level	Antineoplastic Agents	Antiemetic Regimen
Level 4 (High): More than 90% of patients who receive these agents experience nausea and vomiting.	Carmustine, cisplatin, cyclophosphamide (>1500 mg/m^2), dacarbazine, dactinomycin, mechlorethamine, streptozotocin	Serotonin-receptor antagonist, dexamethasone, and aprepitant
Level 3 (Moderate): Nausea and vomiting occurs in 30-90% of patients who receive these agents.	Carboplatin, cyclophosphamide (< 1500 mg/m^2), cytarabine (>1 g/m^2), daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin	Serotonin-receptor antagonist and dexamethasone
Level 2 (Low): Nausea and vomiting occurs in 10-30% of patients who receive these agents.	Bortezomib, cetuximab, cytarabine (< 1 g/m^2), docetaxel, etoposide, fluorouracil, gemcitabine, methotrexate, mitomycin, mitoxantrone, paclitaxel, pemetrexed, topotecan, trastuzumab	Serotonin-receptor antagonist
Level 1 (Minimal): Less than 10% of patients who receive these agents experience nausea and vomiting.	Bevacizumab, bleomycin, busulfan, 2-chlorodeoxyadenosine, fludarabine, rituximab, vinblastine, vincristine, vinorelbine	No antiemetic routinely administered*

**If antiemetic required for individual patients, may use a single dose of serotonin-receptor antagonist*

patients after tonsillectomy [10]. Aprepitant is a neurokinin receptor (NK)-1 antagonist that is indicated in combination with other antiemetic agents for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic and highly emetogenic cancer chemotherapy (including high-dose cisplatin) [11]. In September 2015, its indication for CINV was expanded to include children aged ≥12 years or children <12 years who weigh at least 30 kg. In December 2015, the indication was expanded to include children aged 6 months or older.

Approval of aprepitant in children was based on findings from a randomized, double-blind, active-comparator-controlled trial in children aged 6 months to 17 years that compared aprepitant plus ondansetron with ondansetron alone (control group). Each group was allowed to receive IV dexamethasone at the discretion of the physician. The primary endpoint was complete response (no vomiting, retching and no use of rescue medication) in the acute phase (0 to 24 hours) and in the delayed phase (25 to 120 hours following initiation of chemotherapy). Seventy-seven (51%) of 152 patients in the aprepitant group and 39 (26%) of 150 in the control group achieved a complete response in the delayed phase ($p<0.0001$). For patients aged 12-17 years and patients <12 years who weighed at least 30 kg (n=132), a higher complete response was observed in the acute and delayed phases with the aprepitant regimen (55.6% and 49.2%) compared with the control regimen (37.7% and 18.8%) [12]. (Kang et al, 2015).

Table 2. Emetogenic risk of oral chemotherapeutic agents. [13, http://www.nccn.org]

High (emesis risk, >90% without antiemetics)	
Hexamethylmelamine	Procarbazine
Moderate (emesis risk, 30%–90% without antiemetics)	
Cyclophosphamide	Etoposide
Temozolomide	Vinorelbine
Imatinib	
Low (emesis risk, 10%–30% without antiemetics)	
Capecitabine	Fludarabine
Minimal (emesis risk , <10% without anti emetics)	
Chlorambucil	Melphalan
Erlotinib	Methotrexate
Methotrexate	L-Phenylalanine mustard
Sorafenib	6-Thioguanine
Geftinib	Sunitinib

Lorazepam is particularly useful when anticipatory nausea is a contributing factor. Dronabinol is most useful when started prior to chemotherapy (started in anticipation of a second cycle of chemotherapy in a patient who experienced significant nausea or emesis during the first cycle). Diphenhydramine, promethazine, and lorazepam may cause drowsiness, and, in some cases, a balance must be reached by the patient in terms of emesis relief and sleepiness.

Acute and delayed nausea and vomiting

- Monitor serum electrolytes, with special attention to sodium, potassium and bicarbonate status. In patients with uncontrolled vomiting and poor oral intake, replacement with intravenous fluids that contain sodium chloride and potassium chloride may be necessary.

- Monitor the number of vomiting episodes and quantify fluid loss. Encourage oral intake of liquids.
- If unable to tolerate oral intake, replace losses with intravenous fluids to prevent dehydration.
- If unable to maintain appropriate caloric intake enterally, consider initiation of parenteral nutrition.
- Acupuncture, as an addition to standard antiemetic medication, is associated with a reduction in the need for subsequent rescue antiemetic medications [14, 15].

Anticipatory nausea and vomiting: Hypnosis is a behavioral intervention technique that reduces anticipatory and post chemotherapy nausea and vomiting [http://www.cancer.org/ , 16].

Specific recommendations are as follows:

- Anticipatory nausea, emesis, or both: Add lorazepam (0.02-0.05 mg/kg/dose intravenously every 6 h as needed) to the regimen.
- Breakthrough and refractory emesis: If nausea and vomiting is controlled, continue breakthrough medication on a scheduled regimen (ie, not "as needed").

- 5-HT3 serotonin-receptor antagonist (eg, ondansetron [0.15 mg/kg/dose IV for 3 doses; not to exceed 16 mg/dose]) with or without promethazine (0.25-1 mg/kg/dose

IV q4-6h prn [with or without diphenhydramine])

- Prochlorperazine: 0.1 mg/kg/dose intravenously every 8-12 h as needed (with or without diphenhydramine to decrease risk of extrapyramidal adverse effects), and with or without the following:

- Metoclopramide (plus diphenhydramine to decrease risk of extrapyramidal adverse effects): 1 mg/kg/dose intravenously or orally every 6 h as needed.
- Lorazepam: 0.02-0.05mg/kg/dose intravenously or orally every 6 h as needed.
- Diphenhydramine: 1mg/kg/dose intravenously or orally every 6 h as needed.
- Dronabinol: 5 mg/m^2/dose orally every 4-6 h as needed.

Instruct patients as follows:

- Eat small, frequent meals or snacks.
- Drink plenty of water and non caffeinated liquids to avoid dehydration.
- Avoid greasy or spicy foods.
- Eat dry foods such as crackers, toast, or dry cereals.
- Eat soft, bland foods that are easy to digest

Refractory Nausea and Vomiting and Rescue Antiemetic Therapy

Antiemetics are most effective when used prophylactically, since emesis in progress is much more difficult to suppress and raises the spectre of an added component of anticipatory nausea or vomiting on future treatment cycles. It is therefore preferable to use maximally effective antiemetics as first-line therapy rather than withholding more effective antiemetics for later use at the time of antiemetic failure.

There are no clear-cut definitions of the terms 'rescue antiemetic therapy' and 'refractory emesis'. Rescue antiemetic treatment is generally understood to be antiemetics given on demand to a patient with breakthrough emesis. No randomized double-blind trials have investigated antiemetics in this setting.
A few trials have investigated patients with refractory emesis defined as emesis in the previous cycle of chemotherapy, but without emesis before the subsequent cycle of chemotherapy. A number of approaches have been utilized including switching to a different 5-HT_3 receptor antagonist or adding other agents such as dopamine antagonists or benzodiazepines.

In two randomized trials, metopimazine improved the efficacy of ondansetron and of ondansetron plus methylprednisolone. Both pharmacological interventions such as cannabinoids and olanzapine, which act in multiple dopaminergic, serotonergic, muscarinic and histaminic receptor sites, and non-pharmacologic interventions, such as acupuncture, could be considered (Choo et al, 2006).More recently, some studies have documented antiemetic activity of the NK_1 receptor antagonists in patients who did not achieve complete protection from emesis when treated with dexamethasone and a serotonin receptor antagonist alone.

Prevention of Anticipatory Nausea and Vomiting

Anticipatory nausea and vomiting is widely believed to be a learned response to chemotherapy that develops in up to 20% of patients by the fourth treatment cycle. More recent studies showed that the rate of anticipatory nausea and vomiting is much less than observed in older studies that used less satisfactory antiemetic prophylactic treatments (<10% of anticipatory nausea and <2% of anticipatory vomiting). The risk of

anticipatory nausea and vomiting tends to increase with the number of cycles received and the symptoms may persist for a long time after the completion of chemotherapy. If postchemotherapy nausea and vomiting do not occur then anticipatory nausea and vomiting are unlikely to develop.

Once it develops, anticipatory nausea and vomiting is difficult to control by pharmacological means. Therefore, the panel recommended that the best approach to the treatment of anticipatory emesis is the best possible control of acute and delayed emesis. Behavioural therapies, in particular progressive muscle relaxation training, systematic desensitization and hypnosis, can be used to effectively treat anticipatory nausea and vomiting but unfortunately their use will remain difficult to implement as most patients are treated in settings where the needed expertise is not available.

Benzodiazepines are the only drugs that reduced the occurrence of anticipatory nausea and vomiting but their efficacy tended to decrease as chemotherapy treatment continued.

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