

Optimizing antiemetic therapy for children undergoing chemotherapy

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ABSTRACT

Chemotherapy-induced nausea and vomiting (CINV) is a common side effect of most chemotherapy agents. Sub-optimal management of CINV impacts quality of life, nutrition, gastrointestinal (GI) integrity, and adherence to chemotherapy treatment plans. This article reviews the principles of CINV management, planning and implementation of antiemetic regimens, and pharmacology of the antiemetics currently available in the United States appropriate for pediatric use. With the advent of more targeted therapies, increased use of immunotherapy, and the effects of radiotherapy to the brain, spine, and abdomen, treatment of CINV now has a broader application than just for chemotherapeutics alone.

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Background

If you ask any patient who has undergone chemotherapy, they will tell you that one of the most undesirable side effects of treatment is nausea and vomiting. It is something parents and children most fear when starting treatment for a new diagnosis of cancer (Dupuis et al., 2018; Hematology/Oncology Pharmacy Association, 2015; Sherani et al., 2019; Sommariva et al., 2016). Management of chemotherapy-induced nausea and vomiting (CINV) requires a thoughtful, evidence-based approach to assessment, planning, implementation, and re-evaluation. With the advent of more targeted therapies, increased use of immunotherapy, and the effects of radiotherapy especially to the brain, spine, and abdomen, treatment of CINV has a broader application than for chemotherapeutics alone. POGO (Pediatric Oncology Group of Ontario) defines optimal control of CINV as no vomiting, retching, or nausea, no use of additional antiemetics, and no change in the child's usual appetite and diet (Dupuis et al., 2013).

CINV can be categorized as acute (occurring within 24 h of the medication), breakthrough (requiring rescue antiemetics to maintain control), delayed (lasting >24 h after the medication up to 120 h), and refractory (poorly responsive to intervention and persistent). Anticipatory nausea and vomiting is a learned response occurring in the days or hours leading up to chemotherapy, usually as a result of prior inadequate management of nausea and vomiting or significant anxiety about the upcoming treatment (Navari, 2017; Sherani et al., 2019).

Pathophysiology of CINV

Two areas of the brain involved in CINV are the vomiting center (VC), a network of neurons distributed throughout the medulla oblongata, and the chemotherapy trigger zone (CTZ) located in the area postrema on the dorsal surface of the fourth ventricle. The CTZ is outside of the blood-brain barrier and thus is exposed to both blood and cerebrospinal fluid. This location makes it highly sensitive for detecting noxious substances. Nausea and vomiting involve stimulation of the vomiting center via either peripheral or central pathways mediated by a variety of neurotransmitters (Baker et al., 2005). Once toxins are detected in the CTZ, the VC is then stimulated to induce salivation, and abdominal, gastrointestinal, and pharyngeal contractions which then lead to vomiting.

The peripheral pathway is triggered by mechanoreceptors and chemoreceptors in the gastrointestinal tract. The enterochromaffin cells that line the gastrointestinal (GI) tract release serotonin when exposed to toxins such as chemotherapy and increased acid production activates 5-hydroxytryptamine type 3 (5HT3) receptors that are then transmitted via vagal nerve afferents to the CTZ and on to the VC. The peripheral pathway is most associated with acute CINV occurring within the first 24 h after chemotherapy administration (Baker et al., 2005).

The central pathway occurs in the brain and is most associated with delayed nausea and vomiting (24–120 h after therapy). Nausea and vomiting can also be triggered via the cortex by sensory input such as tastes, odors, or even tactile sensations that the brain perceives as threatening. Emotions such as anxiety or dread can also be triggers. Meningeal irritation and increased intracranial pressure directly affect the VC via the cortex. The vestibular system can trigger nausea by

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motion via the afferent pathways through the vestibulocochlear nerve directly to the VC (Navari & Aapro, 2016). Known neurotransmitters involved in the emetic pathway include serotonin, dopamine, neurokinin-1 (NK1), acetylcholine, substance P (Bayo et al., 2012). Histamine, cannabinoids, and gamma-aminobutyric acid (GABA) have also been implicated (Hawkins & Grunberg, 2009; Lohr, 2008).

Assessment

Emesis is an objective symptom and can be quantified. Nausea is a subjective sensation of gastrointestinal distress that may precede emesis. Like pain, nausea is what the patient says it is when they say it is. There are two validated tools for nausea assessment currently available. The Pediatric Nausea Assessment Tool (PeNAT) was validated in children 4 years and older and has been used clinically in pediatric CINV studies (Dupuis et al., 2006; McKinnon & Jupp, 2020). The Baxter Retching Faces (BARF) scale was developed and validated in 2010 and has been used successfully in post-operative nausea and vomiting in children 6 years and older (Baxter et al., 2011; Watcha et al., 2019). Intervening when a patient first feels the sensation of nausea may prevent subsequent emesis. Currently, the use of nausea assessment tools, such as the PeNet or Baxter Retching Faces, is not commonplace. Nurses are in a prime position to lead initiatives and participate in the development of strategies for testing and implementing nausea assessment tools into practice at their institutions.

When a patient is to start chemotherapy, planning begins with ascertaining the child or adolescent's past history of nausea and vomiting and identifying the chemotherapy agents involved in the treatment to assess for risks that may increase their predilection for CINV. Risk factors in pediatric patients are not clearly defined. One study by Dupuis et al. (2019) showed that non-white race, non-central nervous system (CNS) tumors, receipt of cisplatin, and poorly controlled acute phase nausea are overall risk factors for increased CINV in pediatric patients. Assessment points that are helpful include a history of motion sickness, a history of gastroesophageal reflux disease (GERD), experience with uncontrolled nausea and vomiting in the past, and whether they are sensitive to tastes and odors that stimulate nausea or vomiting (Gregory & Ettinger, 1998; Triozzi & Laszlo, 1987).

Chemotherapy agents are ranked by their emetic potential as minimal (<10% incidence of causing CINV without antiemetics), low (10–30% incidence), moderate (31–90% incidence), and high (>90% incidence) emetic risks (Dupuis et al., 2013; Paw Cho Sing et al., 2019). Examples of common chemotherapy agents used in pediatric patients and

their associated emetogenicity are found in Table 1. Antiemetic choices are based on the drug or combination of drugs with the highest level of emetic incidence. The potential for delayed nausea and vomiting with agents such as platinum agents must also be considered in choosing an antiemetic regimen. Prophylactic antiemetic regimen choices based on emetic potentials are essential. There are several guidelines available for antiemetics including those published by the following organizations: Pediatric Oncology Group of Ontario (POGO), National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), and the Multinational Association of Supportive Care in Cancer (MASCC) (Dupuis et al., 2013; Hesketh et al., 2020; National Comprehensive Cancer Network, 2022; Patel, Robinson et al., 2017; Roila et al., 2016). Integration of institutional policies or algorithms for selecting appropriate antiemesis prophylaxis will standardize processes and help nurses provide appropriate supportive care.

Implementation

Preparing the family and patient for CINV management is a crucial step. Reassurance that the goal is CINV control and that the care team will continually assess, intervene, and reassess the patient's response to the antiemetics can go a long way in alleviating anxiety. Often the first chemotherapy experience is the most emetogenic, likely due to multifactorial influences from a larger tumor burden and a higher anxiety level related to a new and unknown experience (Dranitsaris et al., 2017). Providers and nurses can encourage the patient to eat throughout the day since keeping food in the stomach decreases excess acid production which can stimulate nausea. Small frequent meals and snacks are often better tolerated than large meals to prevent gastric distention which can worsen nausea. It is not necessary to restrict the diet; most pediatric oncology patients learn quickly what works and what doesn't in managing their nausea. For patients sensitive to certain odors, it may be helpful to utilize aromas that are pleasing to the child to minimize noxious odors which may not be entirely avoidable in the hospital or clinic setting. Simple techniques such as mental distraction and activity may be helpful in modifying the sensation of nausea (Gupta et al., 2021).

Not every person responds to the same antiemetic regimen in the same way. Frequent need for rescue medications may mean that the antiemetic regimen needs to be augmented or adjusted for better management. Fig. 1 shows the antiemetic pathway in use at our institution. Once a good regimen that is acceptable to the patient is achieved, it is important to maintain consistency with subsequent chemotherapy

Table 1
Emetogenicity classification of common chemotherapy used in pediatric patients.

High (HEC) >90%	Moderate (MEC) 31–90%	Low 10–30%	Minimal <10%
<ul style="list-style-type: none"> • Single agent • Carboplatin • Cisplatin • Cyclophosphamide (≥ 1000 mg/m²) • Cytarabine (≥ 3000 mg/m²) • Dacarbazine • Dactinomycin • Methotrexate ($\geq 12,000$ mg/m²) • Thiotepa (≥ 300 mg/m²) • Multiple agents • Cyclophosphamide + Anthracycline • Cyclophosphamide + Etoposide • Ifosfamide + Doxorubicin • Ifosfamide + Etoposide 	<ul style="list-style-type: none"> • Arsenic trioxide • Azacitidine • Bendamustine • Busulfan • Cyclophosphamide (<1000 mg/m²) • Cytarabine (200 mg/m² to <3000 mg/m²) • Daunorubicin • Doxorubicin • Ifosfamide • Imatinib • Irinotecan • Melphalan (>50 mg/m²) • Methotrexate (250 mg/m² to <12,000 mg/m²) • Temozolomide 	<ul style="list-style-type: none"> • Cytarabine (<200 mg/m²) • Etoposide • 5-Fluorouracil • Gemcitabine • Methotrexate (>50 mg/m² to <250 mg/m²) • Mitoxantrone • Paclitaxel • Topotecan 	<ul style="list-style-type: none"> • Asparaginase • Bleomycin • Dasatinib • Dexrazoxane • Fludarabine • Gemtuzumab ozogamicin • Mercaptopurine • Methotrexate (≤ 50 mg/m²) • Nelarabine • Rituximab • Temsirolimus • Thioguanine • Vinblastine • Vincristine • Vinorelbine

Note: This table shows common chemotherapy used in pediatric cancer treatment and their associated risk (high, moderate, low, or minimal) based on the Pediatric Oncology Group of Ontario (POGO) guideline for prevention of acute chemotherapy induced nausea and vomiting. The percentage listed for each is the incidence of nausea and vomiting for these agents when given without prophylactic antiemetics.

Adapted from Dupuis L, Boodhan S, Holdsworth M, Robinson P, Hain R, Portwine C, O'Shaughnessy E, Sung L & Pediatric Oncology Group of Ontario. (2013). Guideline for prevention of acute nausea and vomiting due to antineoplastic medication in pediatric cancer patients. *Pediatric Blood & Cancer*, 60, 1073–1082. <https://doi.org/10.1002/pbc.24508>

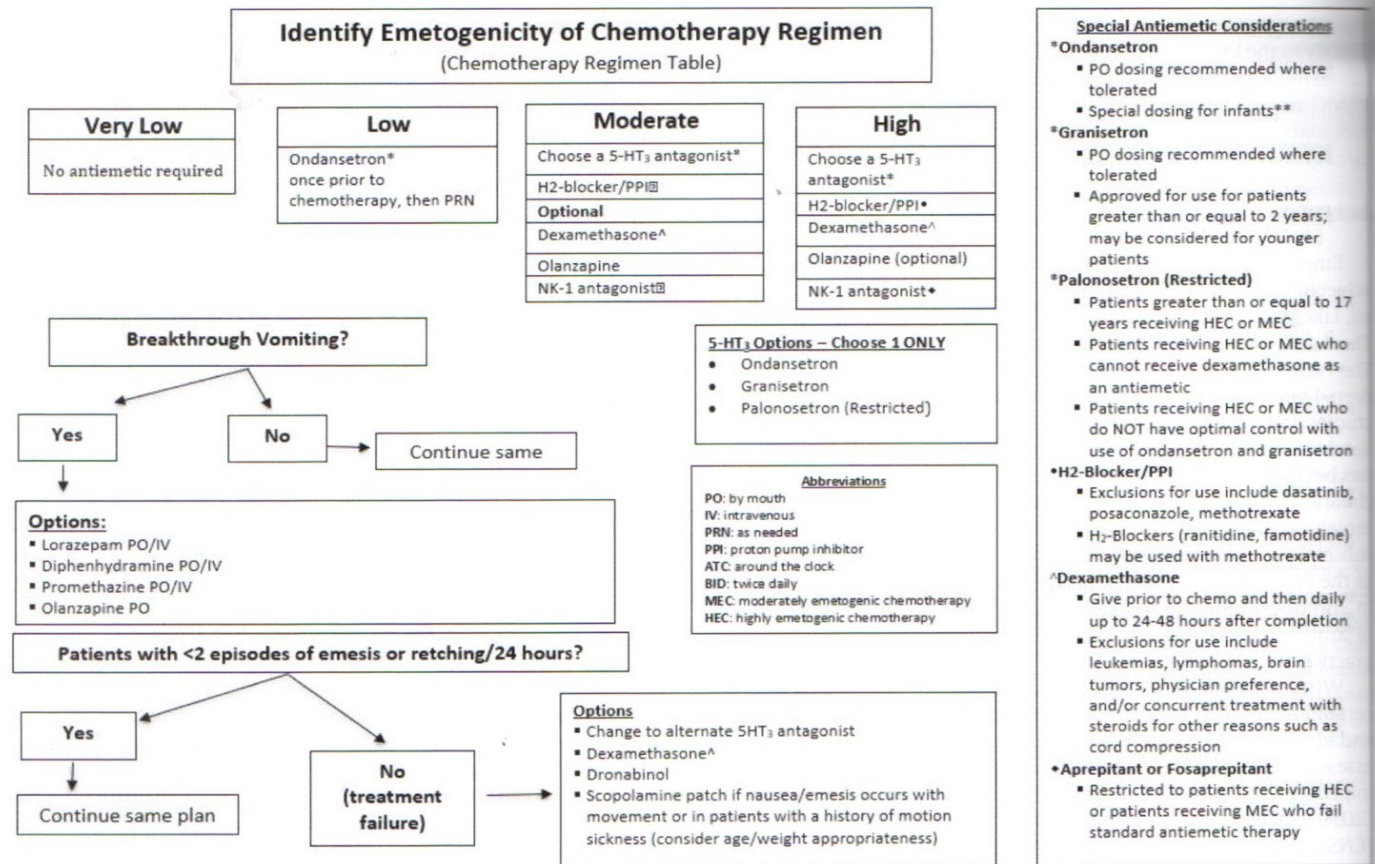


Fig. 1. Example of an institution-specific guideline.

Note: This is an author-created figure showing an institution specific guideline for prevention of CINV in pediatric patients.

treatments. Some patients will need different antiemetic plans based on the differing drug combinations in their treatment plans. Reassessment should be done for effectiveness and safety after administration of antiemetics and rescue antiemetics. Once a good regimen has been identified it should be consistently utilized in subsequent chemotherapy encounters. At our institution, we have developed a supportive care worksheet that is integrated in our electronic medical record and is accessible to the medical team to maintain consistency.

Treatment and re-assessment

The goals of therapy are to prevent nausea, to prevent emesis, and to overall improve the patient’s quality of life. Antiemetic therapy is initially selected based on the chemotherapy’s emetic risk and can be tailored to patient’s preference and past history for subsequent cycles. It is important to categorize what type of CINV the patient experienced in the past (acute, delayed, anticipatory, breakthrough, or refractory) as this can be a helpful guide to modifications (Barbour, 2017; Paw Cho Sing et al., 2019).

Nonpharmacologic interventions may be helpful to prevent nausea and vomiting including meditation or distraction techniques such as guided imagery, music therapy, self-hypnosis, ginger, and other relaxation techniques. Acupuncture and acupressure have been used as well (Figuroa-Moseley et al., 2007; Momani & Berry, 2017). These interventions likely have minimal side effects; however, there has been a lack of robust research leading integrative options to be considered a weak recommendation in the POGO guidelines (Dupuis et al., 2013; Patel, Robinson, et al., 2017).

Antiemetic prophylaxis is chosen based on the emetic risk of the chemotherapy or combination of chemotherapy. See Table 1 for examples of common agents in pediatric oncology and their emetic risk. 5HT₃ receptor antagonists such as ondansetron, granisetron, and palonosetron are the backbone of antiemetic recommendations. For regimens that meet the criteria for moderately emetic chemotherapy (MEC) or highly emetic chemotherapy (HEC), scheduled preventative antiemetics should be implemented. The recommendation for HEC regimens is to treat with a three drug prophylaxis including dexamethasone, a 5HT₃ antagonist, and a NK1 receptor antagonist. Standard prophylaxis used for MEC regimens is a 5HT₃ receptor antagonist with or without dexamethasone. Drug interactions and contraindications should be taken in consideration with antiemetic regimens. For low emetic risk regimens, premedication with a 5HT₃ receptor antagonist is recommended to be given at minimum (Dupuis et al., 2013; Ho & Gan, 2006; Patel, Leeder, et al., 2017). Patients receiving chemotherapy with minimal emetic risk do not receive routine prophylaxis. All patients should have “as needed” antiemetic choices available for any post-chemotherapy nausea.

Anticipatory nausea can be treated by giving a small dose of anti-anxiety medication such as lorazepam prior to coming for treatment (Navari & Aapro, 2016). Some patients will respond well to taking a dose at bedtime and again in the morning. Non-pharmacological measures such as mindfulness, distraction, and conscious relaxation techniques may also provide some preventive effects.

Breakthrough nausea and vomiting is best treated with rescue antiemetics as needed. Rescue antiemetics should always be available to be

given as soon as the patient perceives nausea. Patients who have frequent breakthrough nausea should have their regimen re-evaluated and will likely need either added or substituted agents to improve control.

Delayed nausea is common with agents such as cisplatin and high dose cyclophosphamide but may be experienced by some children with other agents as well. Palonosetron, olanzapine, and NK1 receptor antagonists have shown efficacy in helping prevent delayed CINV (Kang et al., 2015; Naik et al., 2020; Tan et al., 2018). Expected delayed nausea and vomiting can be treated with ongoing antiemetics for 2–3 days past the completion of the course. Children who have delayed nausea and vomiting from drugs less commonly associated with it will also require a longer duration of scheduled antiemetics for best control. Dexamethasone can be very useful in helping manage delayed nausea and vomiting in combination with a scheduled 5HT3 receptor antagonist and histamine-2 (H2) blocker when given for 2–3 days following therapy with these agents.

Refractory nausea and vomiting can be more difficult to manage. Changing to a different 5HT3 antagonist or adding dronabinol can be helpful with patients experiencing refractory nausea and vomiting. Dronabinol should be used with caution in children <12 years of age. In addition to the scheduled prophylactic antiemetics, some children find they achieve relief from alternating antiemetics around-the-clock, such as a dopamine antagonist, benzodiazepine, and/or histamine antagonist. This should be used with caution due to overlapping adverse effects. Olanzapine may also be a good choice when started at the time of chemo administration. Care must be taken to prevent oversedation when multiple sedating agents are required for control.

Review of pharmacotherapy

5HT3 receptor antagonists

5HT3 receptor antagonists work by selectively blocking serotonin both peripherally on the vagal nerve terminals and centrally in the CTZ. This class of antiemetics has revolutionized the management of CINV in pediatric and adult patients and is considered the backbone of antiemetic prophylaxis. Agents in this class are ondansetron, granisetron, and palonosetron. Dolasetron is no longer used due to its increased risk of QTc prolongation. 5HT3 receptor antagonists best prevent CINV in the acute phase; however, palonosetron has shown to prevent CINV in the delayed phase as well (Lohr, 2008; Tan et al., 2018). Class adverse effects include QTc prolongation, headache, and constipation (Tricco et al., 2016). Other factors to consider when choosing which 5HT3 receptor antagonist are cost, available dosage forms, and past history. These agents can be safely used in patients from infancy to adulthood and older. See Table 2 for comparison of agents.

Pharmacogenomic variability may contribute to efficacy variability as well. While all three agents are metabolized in the liver, ondansetron and palonosetron are metabolized by CYP2D6 into inactive metabolites. The CYP2D6 isoform is subject to genetic polymorphism where patients can be ultra-rapid, extensive (normal), intermediate, or poor metabolizers. Ultra-rapid metabolizers may see a decreased therapeutic effect of ondansetron, but this has not been confirmed for palonosetron (Bell et al., 2017). The Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends that patients who are known to be CYP2D6 ultra-rapid metabolizers should use a different agent such as

Table 2
Antiemetic summary.

Agent	Class	Age used	Role in CINV	Dosage Forms	Pertinent Adverse Reactions
Ondansetron	5HT3 Receptor Antagonist	Infants and older	Prevention for MEC, HEC, low emetic risk	IV injection, oral disintegrating tablets (ODT), oral tablets, oral liquid	Headache, constipation, QTc prolongation, fatigue, transient increase in liver function enzymes, serotonin syndrome
Granisetron	5HT3 Receptor Antagonist	Infants and older	Prevention for MEC, HEC, low emetic risk	IV injection, subcutaneous injection, transdermal patch, oral tablets	
Palonosetron	5HT3 Receptor Antagonist	Any age	Prevention for MEC, HEC	IV injection	
Aprepitant	NK1 Receptor Antagonist	Greater than or equal to 6 months of age	Prevention for MEC, HEC	Oral capsule	Fatigue, hypotension, diarrhea, constipation, anemia, neutropenia, transient increase in ALT, dizziness, hiccups
Fosaprepitant	NK1 Receptor Antagonist	Greater than or equal to 6 months of age	Prevention for MEC, HEC	IV injection	
Olanzapine	Atypical antipsychotic	4 years and older	Prevention for MEC, HEC; refractory, breakthrough	Tablets, ODT tablets (IM formulation not recommended for this indication)	Orthostatic hypotension, peripheral edema, metabolic effects (typically more with long-term use), dizziness, somnolence, weakness, tremor, leukopenia, increase in LFTs, QTc prolongation (dose-dependent)
Dexamethasone	Corticosteroid	Any age	Prevention for MEC or HEC	IV, oral tablets, oral liquid	Gastritis, peptic ulcers, hyperglycemia, sodium retention, Cushing syndrome, emotional lability, bradycardia, infection, insomnia
Lorazepam	Benzodiazepine	Any age	Anticipatory and breakthrough	IV, oral tablets, oral liquid	Sedation, respiratory depression, dizziness, amnesia, hypotension
Promethazine	Dopamine Antagonist	2 years +	Breakthrough, refractory	IV, oral tablets, oral liquid	Drowsiness, dizziness, extrapyramidal side effects, anticholinergic side effects, blood pressure changes, respiratory depression, QTc prolongation
Diphenhydramine	Antihistamine	Infants and older	Breakthrough, refractory	IV, oral tablet, oral liquid	Dizziness, drowsiness, conditional risk of QTc prolongation
Famotidine	Histamine-2 antagonist	Any age	Breakthrough, refractory	IV, oral tablet, oral liquids	Constipation, headache
Scopolamine	Anticholinergic agent	12 years and older	Refractory	Topical patch	Dizziness, drowsiness, blurred vision, dry mouth, urinary retention, constipation
Dronabinol	Cannabinoid	Avoid in children <6 years and use with caution in children between 6 and 12 years of age	Refractory	Oral capsule	Dizziness, drowsiness, hallucinations, vertigo, ataxia, dry mouth, hypotension, tachycardia

Note: This is an author created table summarizing notable information about common antiemetics used for CINV in pediatric patients. (Adapted from: Lexicomp Online, Pediatric and Hematol Lexi-Drugs Online. <https://online.lexi.com>).

granisetron (Bell et al., 2017). A study by Jacobs et al. (2022) found that about 39.3% of patients failed ondansetron initially, and of these patients 8.7% had a CYP2D6 polymorphism. Other factors they found that may contribute to CINV failure were select phenotypes on transporter genes (ABCB1) and receptor genes (5HT3RB) as well as higher body mass index (BMI) and age >12 years. If a patient experiences refractory nausea with ondansetron, switching antiemetic prophylaxis to granisetron in the next cycle may help.

Half-lives differ among these agents. Ondansetron is typically dosed every 8 h with a half-life of about 3–6 h while granisetron is typically dosed every 12 to 24 h with a half-life of about 5–9 h (Lexi-comp Online, Pediatric and Neonatal Lexi-Drugs Online, 2022a, 2022b, 2022c, 2022d, 2022e, 2022f, 2022g, 2022h, 2022i). Palonosetron is a long-acting 5HT3 receptor antagonist with a half-life of about 20–30 h in pediatrics and 40 h in adults and is typically given as a one-time intravenous injection prior to chemotherapy regimens and is the newest of the 5HT3 receptor antagonists used in pediatric patients. One study by Tan and colleagues in 2018 compared the use of palonosetron (low and high dose) and ondansetron in pediatric cancer patients receiving HEC. They found no difference between acute phase CINV control among groups but did find a statistically significant improvement of delayed CINV control with palonosetron dosed at 10 µg/kg (max 0.5 mg) indicating that palonosetron may contribute to improved CINV control in the delayed phase than ondansetron (Tan et al., 2018). Chaudhary et al. (2019) and colleagues compared CINV complete response between ondansetron and palonosetron in pediatric patients receiving their first course of MEC or HEC. There was no difference in complete response from hours 0–120 h after chemotherapy and no differences in adverse effects. This study allowed redosing of palonosetron after 72 h for 5-day chemotherapy regimens while ondansetron was dosed every 8 h during chemotherapy and 48 h afterwards. When looking at cost effectiveness, they found that the longer duration of chemotherapy correlated with cost-effectiveness for palonosetron and concluded that palonosetron may be a better choice in terms of cost-effectiveness (Chaudhary et al., 2019).

NK1 receptor antagonists

NK1 receptor antagonists prevent acute and delayed vomiting by blocking substance P and neurokinin-1 in the central pathway of CINV (Kang et al., 2015). There are several agents in this class but only aprepitant and fosaprepitant are approved for use in pediatric patients who are 6 months and older. The key role of these agents are as prophylactic antiemetics for MEC and HEC (Aapro, 2018; Lexi-comp Online, 2022a, 2022b, 2022c, 2022d, 2022e, 2022f, 2022g, 2022h, 2022i; Radhakrishnan et al., 2019; Saito et al., 2019; Willier et al., 2019). Aprepitant is available as oral capsules and an oral suspension. Fosaprepitant is a prodrug to aprepitant and is available as an intravenous injection (Lexi-comp Online, 2022a, 2022b, 2022c, 2022d, 2022e, 2022f, 2022g, 2022h, 2022i). More recently, both aprepitant and fosaprepitant have shown to be safe and effective in pediatric patients showing improved nausea control for both acute and delayed CINV. Adverse effects include fatigue, hypotension, diarrhea or constipation, and hiccups. Infusion reactions with fosaprepitant are rare but can occur due to the inactive ingredient polysorbate 80 (Cabanillas Stanchi et al., 2019, 2020; Mora et al., 2019; Radhakrishnan et al., 2019; Saito et al., 2019; Willier et al., 2019). Aprepitant is a moderate inhibitor of CYP3A4 and weak inducer of CYP2C9; therefore, drug interactions should be considered when using both aprepitant or fosaprepitant. Many antineoplastic agents are substrates to CYP3A4 and concurrent use could increase risk for toxicity and long-term outcomes. For example, at our institution, we avoid use of ifosfamide and aprepitant due to the increased risk of neurotoxicity. Although, many of these interactions are not complete contraindications, the risks and benefits should be discussed when a drug-interaction arises (Patel, Leeder, et al., 2017).

Atypical antipsychotics

Olanzapine is an atypical antipsychotic used to treat schizophrenia, mania, and bipolar disorder. Olanzapine is also used for CINV due to its inhibition on multiple neurotransmitters including dopamine, serotonin, acetylcholine, and histamine. Olanzapine is commercially available as an oral tablet, orally disintegrating tablet and intramuscular (IM) injection; however, the IM form is not recommended for CINV indication. Adverse effects include dizziness, somnolence, sedation, leukopenia, increase in liver function tests, and QTc prolongation (Lexi-comp Online, 2022a, 2022b, 2022c, 2022d, 2022e, 2022f, 2022g, 2022h, 2022i). If patients experience CNS adverse effects like somnolence or sedation, the medication can be scheduled prior to bedtime or the dose can be decreased to mitigate adverse effects (Flank et al., 2018). Historically, olanzapine was investigated as a rescue medication, but recent literature supports its use in prevention of CINV in acute and delayed phases (Bosnjak et al., 2016; Flank et al., 2018; Naik et al., 2020). Although adult CINV guidelines include the use of olanzapine, there are no recommendations for olanzapine use in pediatric CINV guidelines (Dupuis et al., 2013; Hesketh et al., 2020; National Comprehensive Cancer Network, 2022; Patel, Robinson, et al., 2017; Roila et al., 2016). A recent study by Naik and colleagues published in 2020 completed a randomized, open-label trial in children with cancer ages 5 years and older receiving first cycle of HEC. The control group received standard of care with dexamethasone, aprepitant, and ondansetron compared to the experimental group received olanzapine in addition to the standard of care. They found that the addition of olanzapine significantly improved CINV control overall and in the acute and delayed phase (Naik et al., 2020).

Corticosteroids

Of the steroid agents, dexamethasone is typically used due to its penetration into the CNS and was first used in 1981 with cisplatin. Although the mechanism is unknown for CINV control it may involve the reduction of serotonin release or activation of corticosteroid receptors in the CNS (Aapro & Alberts, 1981; Lohr, 2008). When combined with 5HT3 receptor antagonists, dexamethasone may prevent acute and delayed CINV for MEC and HEC. At our institution, we avoid dexamethasone in patients receiving steroids as part of their chemotherapy regimen (patients with leukemia and lymphoma) and in patients with CNS tumors since dexamethasone can affect permeability of the blood brain barrier. Adverse effects include gastritis, peptic ulcers, hyperglycemia, hypokalemia, sodium retention, Cushing syndrome, weight gain, bradycardia, emotional lability, and increased risk for infection (Lexi-Comp Online, 2022a, 2022b, 2022c, 2022d, 2022e, 2022f, 2022g, 2022h, 2022i).

Cannabinoids

Dronabinol prescribing has been increasing steadily in children and adolescents with cancer (Rower et al., 2021). Dronabinol is a synthetic THC which binds to the cannabinoid receptors CB1 and CB2 which may help with euphoria, appetite enhancement, analgesia, and nausea prevention. It is typically used for refractory CINV and is most effective when given around-the-clock. Dronabinol is available as oral capsules and oral solution and should be avoided in children <6 years of age and used with caution in patients 6–12 years of age. Adverse effects include dizziness, drowsiness, hallucinations, vertigo, dry mouth, hypotension and tachycardia. QTc prolongation is not associated with this antiemetic (Abrams, 2019; Lexi-Comp Online, 2022a, 2022b, 2022c, 2022d, 2022e, 2022f, 2022g, 2022h, 2022i; Lohr, 2008).

Miscellaneous agents and clinical pearls

Dopamine agonists such as promethazine, metoclopramide, and prochlorperazine can be used for breakthrough or refractory CINV. Promethazine and prochlorperazine should be avoided in children <2

years of age. QTc prolongation, extrapyramidal side effects, and anticholinergic side effects can occur with these agents (Lexi-Comp Online, 2022a, 2022b, 2022c, 2022d, 2022e, 2022f, 2022g, 2022h, 2022i; Lohr, 2008). Of note, serious tissue injury and amputation can occur if IV promethazine is inadvertently given intraarterially or extravasates peripherally. Giving smaller, diluted doses through a central line should help eliminate this risk (ISMP, 2021).

Lorazepam is a benzodiazepine that can be given intravenously or orally with a commercially available oral liquid. Its role is mainly in breakthrough and anticipatory nausea and vomiting. At our institution, we found that a lower dose (0.025 mg/kg/dose, max of 2 mg) is helpful with nausea and vomiting with decreasing risk of over-sedation. Along with sedation, lorazepam can cause respiratory depression, amnesia, and hypotension. This agent can be used in infants and older and does not cause QTc prolongation (Lexi-comp Online, 2022a, 2022b, 2022c, 2022d, 2022e, 2022f, 2022g, 2022h, 2022i; Lohr, 2008).

Antihistamines have been used for nausea and vomiting since the 1800s and are often used for breakthrough or refractory CINV. Diphenhydramine, which blocks histamine-1 (H1) receptor sites, can be given every 4 to 6 h and can cause dizziness and drowsiness and has a conditional risk of QTc prolongation. Histamine-2 (H2) blockers such as famotidine can be helpful too while receiving chemotherapy and should be given around the clock for patients receiving MEC or HEC. Scopolamine patches may be used as well due to anticholinergic activity within the vestibular input and brainstem pathways (Sanger & Andrews, 2018). At our institution, we limit the use of scopolamine patches to patients 10 years or older who are at least 35 kg and have refractory CINV.

Implications for pediatric hematology/oncology nursing

Nurses have the most sustained contact with their patients during chemotherapy. They are in a prime position to monitor and help improve emetic control in their patients. Nursing assessments and subsequent reassessment after interventions are crucial in determining what works and what doesn't for their patient as they strive together for the goal of emetic control. Ongoing communication between provider, patient, parents, and nursing together is crucial to success. Nurses have a key role in ongoing research in an effort to further improve CINV management.

Conclusion

Appropriate and effective antiemetic management can decrease patient and parent distress, offers improved quality of life, and encourages adherence to chemotherapy regimens. A sound knowledge of antiemetic principles and currently available interventions enables nurses to provide optimal care for their patients and families.

Credit authorship contribution statement

Mya Merrow: Methodology, Visualization, Validation, Writing – original draft, Writing – review & editing, Project administration.
Nancy King: Conceptualization, Writing – original draft, Writing – review & editing, Project administration, Supervision.

Declaration of Competing Interest

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