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Acute chemotherapy-induced nausea and vomiting in children with cancer: Still waiting for a common consensus on treatment

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Abstract

Chemotherapy-induced nausea and vomiting (CINV) is one of the most common treatment side-effects, and remains a significant concern, in children undergoing chemotherapy. Although adult patients receive chemotherapy regimens combined with appropriate standardized antiemetic treatment, children can receive markedly varying antiemetic treatments. A narrative review of CINV was performed regarding CINV definition, scoring system, prevention and treatment, specifically focussing on studies conducted with paediatric oncology patients. The review highlighted a lack of rigorously developed CINV scoring systems and standardized CINV pharmacological treatment for paediatric oncology patients. Different scoring systems were found to identify potential risk factors for CINV associated with the use of several different antiemetic drugs, however, few studies have been performed in children undergoing chemotherapy. Thus, CINV remains a distressing and partially controlled side-effect in the paediatric patient population. To reduce emesis and improve quality of life in paediatric oncology patients, standardized antiemetic treatment may be preferred, using a unique CINV scoring system that accounts for the emetogenic level of the chemotherapy regimen adopted and the children's clinical characteristics.

Keywords

CINV, children, chemotherapy, cancer, paediatric

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Introduction

The adoption of more intensive chemotherapeutic regimens has greatly contributed to the successful treatment of childhood cancers, leading to a marked increase in the cure rate of most tumours occurring during childhood.[1]

Despite significant advances in antiemetic therapies, chemotherapy-induced nausea and vomiting (CINV) continues to be one of the most distressing symptoms in children undergoing chemotherapy, associated with a significant deterioration in quality of life and perceived by patients as a major adverse treatment effect.[2,3] CINV has been estimated to occur in up to 70% of the paediatric population undergoing chemotherapy,[4] which is similar to prevalence rates described in adult patients, for whom nausea and vomiting are described as the first and third most distressing chemotherapy adverse effects, with a prevalence of approximately 60% and 72%, respectively.[5,6]

Although international evidence-based guidelines have been drafted for CINV in the adult population,[7] their direct application in children seems to be inappropriate, as individual antiemetic treatment should be based on metabolic features peculiar to paediatric age,[8,5] in addition to the emetogenic level of the antineoplastic drugs.[9] The occurrence of CINV in children is also influenced by psychological and behavioural characteristics, such as parent and child state and trait anxiety scores, and child behaviour problems, although these features have not been well defined as specific CINV predictors.[10,11]

A rigorously developed scoring system and guidelines for antiemetic regimens based on the paediatric population, founded on research-based evidence and not on personal preference or experience, may facilitate the optimization of CINV control in children with cancer.[12,13]

The present article reviews studies and guidelines for CINV in children and adolescents, published over the past 15 years. The review focuses on paediatric CINV definitions, scoring system, prevention and treatment, with the aim of providing useful information for clinicians.

Definitions

Nausea is a subjective experience characterized by a feeling of impending vomiting (emesis). Although nausea may precede the act of vomiting, severe nausea can be present without vomiting. Vomiting is characterized by retching and expulsion of the stomach's contents through the mouth accompanied by shivering and salivation. In terms of chemotherapy, vomiting can be classified according to five distinct CINV syndromes depending on onset and any prior patient response to antiemetic treatment.[14]

Acute CINV appears within a few minutes of chemotherapy treatment onset and disappears within 24 h of its occurrence. In 2016, the Multinational Association of Supportive Care in Cancer (MASCC) and the European Society for Medical Oncology (ESMO) proposed new practice guidelines for use of antiemetics in children receiving chemotherapy, updating the 2009 MASCC/ESMO recommendations.[4] Also in 2016, the International Society of Paediatric Oncology (SIOP) and the American Society of Paediatric Haematology/Oncology (ASPHO) provided an update of the 2013 clinical practice guideline for preventing acute CINV in children.[15]

Delayed CINV occurs 24 h following the start of chemotherapy and can be present in up to 80% of patients. It is usually most severe on the 3rd day and can last up to 7 days, and delayed nausea and emesis is more prevalent in patients with uncontrolled acute CINV. It has been extensively

studied in patients who have received anthracycline, cisplatin, carboplatin and cyclophosphamide, however, the prevalence of delayed CINV is less clear for other agents, such as those classified as moderately emetogenic.[16]

Anticipatory nausea and emesis can be present before treatment is started in patients, depending on the patient's emotional distress or expectations. It is present in approximately 25% of paediatric patients and appears to be a conditioned response to the occurrence of uncontrolled CINV during previous chemotherapy courses. Thus, the best method to avoid anticipatory CINV would be to avoid CINV from the first exposure to chemotherapy.[17]

Breakthrough CINV refers to the occurrence of nausea and emesis during previous courses of chemotherapy despite the administration of appropriate CINV prophylaxis.[18]

Refractory CINV is defined as nausea and emesis that recurs during subsequent chemotherapy courses and does not respond to antiemetic treatment or changes in prophylactics. In 2016, a clinical practice guideline was proposed for the treatment of breakthrough and refractory CINV, recommending evidence-based interventions developed by a systematic literature review.[18]

CINV scoring system

Nausea and vomiting were initially coded by the World Health Organisation (WHO) in 1979 as a unique entity and graded according to vomiting severity.[19] In the 1988 Common Toxicity Criteria system, nausea and vomiting were considered separately.[20] The system was elaborated by the Intergroup Toxicity Criteria, composed by the Eastern Cooperative Oncology Group (ECOG), the Southwest Oncology Group (SWOG), the Cancer and Acute Leukaemia Group B (CALGB), and the North Central Cancer Treatment Group (NCCTG), and was updated in 2009. Although nausea and vomiting were classified as distinct entities, antiemetic treatment was not included as an assessment parameter (Table 1).[14,20]

Numerous attempts have been made to identify predictive risk factors for CINV

Table 1 Coding systems used to score nausea and vomiting

	WHO 1979[19]	CTC 2009[20]	
Grade	Nausea-Vomiting	Nausea	Vomiting
0	None	–	–
1	Nausea	Loss of appetite without alteration in eating habits	1–2 episodes (separated by 5 min) in 24 h
2	Transient vomiting	Oral intake decreased without significant weight loss, dehydration or malnutrition	3–5 episodes (separated by 5 min) in 24 h
3	Vomiting requiring therapy	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	≥6 episodes (separated by 5 min) in 24 h; tube feeding, TPN or hospitalization indicated
4	Intractable vomiting	–	Life-threatening consequences; urgent intervention indicated
5		–	Death

WHO, World Health Organisation; CTC, Common Toxicity Criteria; TPN, Total Parenteral Nutrition.

in adults and children. Clinical studies have highlighted that, even with the same antineoplastic drugs, there are some patient-related factors such as age or sex that can alter the risk of emesis.[21] In adult patients, the most important risk factors for CINV include age <50 years, female sex, chemotherapy regimen, alcohol consumption, emesis in earlier cycles of chemotherapy, and previous history of morning sickness or pregnancy-induced emesis.[22]

The most significant factor observed in a prospective European study[23] was the complete control of CINV in the first or second chemotherapy course: patients without complete CINV control during the first course had greater risk of incomplete response in the subsequent course. In children, only a few studies have been performed to investigate factors influencing the risk of CINV. For example, a review of trials conducted between 2000 and 2004 identified different risk factors that were associated with CINV control, such as chemotherapy regimen, age, sex, anxiety and patient perception, and cortisol activity. The review found that the complete protection rate against CINV, obtained using intravenous ondansetron administered alone for moderately emetogenic chemotherapy, or in combination with dexamethasone for a severely emetogenic regimen, varied among children, and was associated with patient age: children aged less than 3 years showed complete CINV control rates that were significantly superior compared with older children and adolescents.[24] Another study showed that in paediatric patients with acute myeloid leukaemia, patient age is one of the most important clinical factors influencing the lack of control of CINV.[25]

Although the different scoring systems identify potential risk factors for CINV, there remains a gap between clinical and therapeutic practice, particularly in terms of treating children. None of the scoring systems include evidence-based suggestions for acute and delayed antiemetic treatment in children, thus CINV remains a distressing and partially controlled side effect.

Pharmacological treatment

An in-depth knowledge of different antiemetic drugs and their administration schedule (e.g. oral versus parenteral, or single versus multiple doses) is mandatory for adequate and evidence-based paediatric CINV management.

Dopamine antagonists (metoclopramide, chlorpromazine and prochlorperazine) are widely used, but a high level of blockade of the dopamine receptors can result in extrapyramidal reactions, as well as disorientation and sedation.[26] Phenothiazines and butyrophenones have also been used in CINV, but their use, particularly when administered at a high dose, is limited by the risk of major extrapyramidal reactions (dystonia, parkinsonism and oculogyric crisis).[27,28]

Antagonists of 5-hydroxytryptamine3 (5-HT3) receptors (ondansetron, granisetron, tropisetron, palonosetron) are used in CINV control.[29] Palonosetron is a second-generation 5-HT3 receptor antagonist that has been shown to achieve better control of emesis compared with ondansetron, in children receiving highly or moderately emetogenic chemotherapy over several days.[30] Dolasetron can no longer be used to prevent CINV in any patient, due to potential serious cardiovascular adverse events.[31]

A relatively new antiemetic drug, aprepitant (a neurokinin 1 receptor antagonist), has been approved in the USA and Europe for the treatment of moderately and highly emetogenic chemotherapy. Aprepitant appears to be well tolerated but, due to its inhibitory effect on cytochrome P450 isoenzyme 3A4, it can lead to significant drug interactions, resulting

in the need for dose modification of concomitant therapy.[32–34]

Corticosteroids, such as dexamethasone, are widely used in paediatric patients for the prevention of acute and late CINV, but long-term use can result in moderate to severe problems with insomnia, hyperglycaemia, epigastric discomfort, agitation, increased appetite, weight gain and acne.[35] In 2016, MASCC/ESMO recommended acute CINV prophylaxis using a 5-HT3 antagonist for children receiving low emetogenic chemotherapy, and using a 5-HT3 antagonist ± dexamethasone ± aprepitant for children receiving highly or moderately emetogenic chemotherapy.[4]

Some adjuvant drugs (e.g., benzodiazepines and cannabinoids) have a role in CINV control, particularly in the management of anticipatory symptoms and anxiety,[36,37] however, the wide spectrum of toxicity (sedation, dizziness, dysphoria, disorientation and hallucinations) limits their routine use in paediatric patients.[38,39]

Finally, in CINV control and prevention, a series of complementary, non-pharmacological interventions (e.g. acustimulation, acupuncture, hypnosis, massage, and relaxation techniques) should be considered, aimed at controlling the psychological and emotional components peculiar to the age of paediatric patients.[40–42]

Discussion

Despite the introduction of new agents for the treatment of CINV, nausea and emesis continue to be the most important adverse side-effects in children receiving chemotherapy. These distressing symptoms negatively affect the patients' quality of life and can be responsible for poor adherence to treatment sometimes causing treatment suspension.[43] In paediatric patients, care can be even more complex, as disease-specific and treatment-specific emotional and psychological factors have to be considered when antiemetic treatment is planned. In adult patients, the adoption of consensus-based recommendations and guidelines for antiemetic treatment appear to optimize CINV control. Most clinical studies and suggestions for pharmacologic CINV treatment are focused on the adult patient population, and their findings are extrapolated for use in the paediatric patient population (Table 2). Existing guidelines for the prevention of CINV in children are characterized by a lack of robust evidence, resulting in inadequate symptom control in paediatric patients receiving antineoplastic drugs with high emetogenic potential.[12,44] Thus, newer antiemetic drugs that are in clinical use for the control of CINV in adult patients with cancer remain absent from most paediatric guidelines. Children are

Table 2 MASCC/ESMO guidelines for chemotherapy-induced nausea and vomiting in children[4]

Emesis risk level	Antiemetic treatment	Level of scientific consensus
High, > 90%	Day 1: 5-HT_3 antagonist + DEX	Moderate/high
	Days 2–4: No recommendation possible	Not applicable
Moderate, 30–90%	Day 1: 5-HT_3 antagonist + DEX	Moderate/high
	Days 2–4: No recommendation possible	Not applicable
Low, 10–30%	No recommendation possible	Moderate/high
Minimal, < 10%	No recommendation possible	Not applicable

MASCC, Multinational Association Supportive Care in Cancer; ESMO, European Society for Medical Oncology; DEX, Dexamethasone; 5-HT3, 5-hydroxytryptamine3.

not small adults, and metabolic and pharmacological findings may be quite different regarding efficacy and risk of side-effects. Some clinical studies have shown that each child's emetic behaviour evolves according to a singular pattern due to different influencing factors such as sex, age, or previous chemotherapy, and requires adequate monitoring and personalization throughout antineoplastic therapy.[45] Moreover, paediatric guidelines and recommendations for CINV treatment regimens should refer to an established CINV scoring system that includes the clinical characteristics of the paediatric patient and any previous antiemetic history before considering the most appropriate CINV treatment based on the emetogenic level of the chemotherapeutic regimen. In addition, physicians involved in chemotherapy administration should take into account the fact that patients may experience acute and delayed CINV more frequently than is perceived by practitioners, with the consequence that patients don't receive appropriate prophylaxis and treatment for their nausea and vomiting.[46]

In conclusion, standardizing paediatric antiemetic treatment based on a unique CINV scoring system that incorporates the emetogenic level of the adopted chemotherapy regimen and the child's clinical characteristics, is desirable to reduce emesis and improve quality of life in paediatric oncology patients.

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