Support Care Cancer (2017) 25:323–331
DOI 10.1007/s00520-016-3384-y

SPECIAL ARTICLE

2016 updated MASCC/ESMO consensus recommendations: Prevention of acute chemotherapy-induced nausea and vomiting in children

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Received: 17 May 2016 / Accepted: 16 August 2016 / Published online: 26 August 2016

Abstract
Purpose To update the 2009 recommendations for the prevention of acute chemotherapy-induced emesis in children.
Methods We updated the original systematic literature search. Randomized studies were included in the evidence to support this guideline if they were primary studies fully published in full text in English or French; included only children less than 18 years old or, for mixed studies of adults and children, reported the pediatric results separately or the median or mean age was no more than 13 years; evaluated acute chemotherapy-induced nausea and vomiting (CINV) prophylaxis; provided sufficient information to permit determination of the emetogenicity of the antineoplastic therapy administered or the study investigators stated the emetogenicity of the chemotherapy administered; included an implicit or explicit definition of complete acute CINV response; described the antiemetic regimen in full; and reported the complete acute CINV response rate as a proportion.
Results Twenty-five randomized studies, including eight published since 2009, met the criteria for inclusion in this systematic review. Prophylaxis with a 5-HT3 antagonist (granisetron or ondansetron or palonosetron or tropisetron) ± dexamethasone ± aprepitant is recommended for children receiving highly or moderately emetogenic chemotherapy. For children receiving chemotherapy of low emetogenicity, a 5-HT3 antagonist is recommended.
Conclusions The findings of several randomized trials were used to update recommendations for the prevention of acute CINV. However, significant research gaps remain and must be addressed before CINV control in children can be optimized.

Keywords Pediatrics · Antiemetics · Chemotherapy-induced vomiting · Chemotherapy-induced nausea · Supportive care

Introduction

In previous iterations of the Multinational Association of Supportive Care in Cancer (MASCC) pediatric guideline for

Electronic supplementary material The online version of this article (doi:10.1007/s00520-016-3384-y) contains supplementary material, which is available to authorized users.

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prevention of chemotherapy-induced nausea and vomiting (CINV), little or no randomized pediatric evidence was identified [1–4]. Thus, previous MASCC pediatric guideline panels were unable to offer recommendations in certain situations or were only able to offer recommendations based on indirect evidence from studies in adult cancer patients. Although many evidence gaps remain, more direct pediatric evidence regarding the efficacy of antiemetic regimens now exists and pediatric recommendations for acute CINV prophylaxis may be made with more confidence.

In formulating the recommendations presented here, the guideline panel intended to improve acute CINV control in children receiving chemotherapy. The recommendations are aimed at all health care providers, including but not exclusive to physicians, advanced practice nurses, nurses, pharmacists, psychologists, and child life workers, caring for children (1 months to less than 18 years of age) receiving chemotherapy for the treatment of cancer. They are most applicable to children who are chemotherapy-naïve since it is expected that the CINV prophylaxis provided in subsequent chemotherapy blocks would be tailored based on the child's experience with CINV. The recommendations are applicable only to prevention of CINV in the acute phase (starting with the first chemotherapy dose of the chemotherapy block and continuing until 24 h after the last dose of the chemotherapy block). Prevention of delayed phase CINV and radiotherapy-induced nausea and vomiting were not within the scope of this guideline update. The updated MASCC consensus guideline for the prevention of anticipatory nausea and vomiting in children is presented separately.

Since the influence of age, sex, and other factors on the risk of CINV in children has yet to be conclusively determined, chemotherapy emetogenicity is the strongest known determinant of chemotherapy-induced vomiting in children. Since chemotherapy doses and regimens are different in pediatric and adult oncology and the risk factors for CINV in children may well be different than in adults, a pediatric chemotherapy emetogenicity classification system [5] was used in developing the 2016 MASCC pediatric recommendations.

This guideline builds on the systematic reviews and evidence summaries that underpin the Guideline for the Prevention of Acute Antineoplastic-induced Nausea and Vomiting in Pediatric Cancer Patients [6] and on previous MASCC recommendations [1–4] for antiemetics in children receiving chemotherapy.

Methods

Guideline development panel

The current MASCC Pediatric Antiemesis Committee was formed in March 2015. Clinicians with expertise in the supportive care of children with cancer were invited to participate in the guideline update. Members were selected so as to obtain international and interprofessional representation in pediatric oncology. Panel members completed conflict of interest forms; no members had conflicts of interest that precluded participation in the panel.

Evidence identification and selection

The panel was able to capitalize on the update of the Pediatric Oncology Group of Ontario (POGO) Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients [6] that is currently in progress. With the assistance of a library scientist, the systematic literature search created during the development of the 2013 POGO guideline was initially updated through May 8, 2015 and was again updated through April 7, 2016. The following databases were searched: Medline (including in-process and other non-indexed citations), Embase, CCTR, AMED, HTA, NHSEED, and CINHAL. The search strategies are available at http://www.pogo.ca/healthcare/practiceguidelines/.

For the MASCC pediatric guideline, we included studies which met the following criteria to inform this guideline: were fully published, primary randomized studies published in full text in English or French; included only children less than 18 years old or, for mixed studies of adults and children, reported the pediatric results separately or the median or mean age was no more than 13 years; evaluated CINV prophylaxis over the entire acute phase or over the first 24 h of the acute phase; provided sufficient information to permit determination of the emetogenicity of the chemotherapy administered as per the pediatric classification or stated the emetogenicity of the chemotherapy administered as per the study authors; included an implicit or explicit definition of complete acute CINV response; described the antiemetic regimen in full; and reported the complete acute CINV response rate as a proportion. Studies were excluded if they did not have a randomized design. Studies evaluating dolasetron were excluded due to reports of fatal arrhythmia [7].

Two reviewers independently reviewed the titles and abstracts of all citations identified by the updated search strategy. Publications considered to be potentially relevant by both reviewers were reviewed in full text by the two independent reviewers. Publications which met the inclusion criteria listed above from both the original POGO guideline evidence tables and the updated search were included in the evidence tables. Thus, the literature search encompassed the period from database inception to April 7, 2016.

Decision-making process

Chemotherapy emetogenicity was defined using the POGO Guideline for the Classification of the Acute Emetic Potential of Antineoplastic Medication in Children [5]. If insufficient information was provided to independently classify the emetogenicity of the chemotherapy administered, the authors' assessment of the emetogenicity of the chemotherapy administered was accepted. If a study included children receiving chemotherapies of mixed emetogenicity and it was not possible to determine the complete response rates for each group separately, the study findings were presented in the evidence tables under the lowest emetogenicity classification included in the study to ensure that we were conservative in our recommendations and optimized the chances of CINV control. The findings of all studies with respect to complete CINV control were evaluated based on the definition applied by the authors of each study.

The MASCC consensus guideline development process [8–10] has been described in full elsewhere. In brief, decisions were made through panel discussions after review of the evidence summaries during teleconferences and at a face-to-face meeting in June 2015. In April 2016, the guideline panel discussed the results of the updated systematic literature review and revised the recommendations during a teleconference. Differences in interpretation were resolved by consensus. Draft recommendations were then brought to the full MASCC Antiemesis Committee for development of overall consensus. Agreement among at least 67 % of the members of the full panel was required before a recommendation was changed. Recommendations will be reviewed and revised periodically as warranted by the publication of new information.

Results

Figure 1 depicts the study identification, selection, and reasons for exclusion. Of the 21,132 citations identified in the literature searches, 6686 represented papers published since the POGO Guideline for the Prevention of Acute

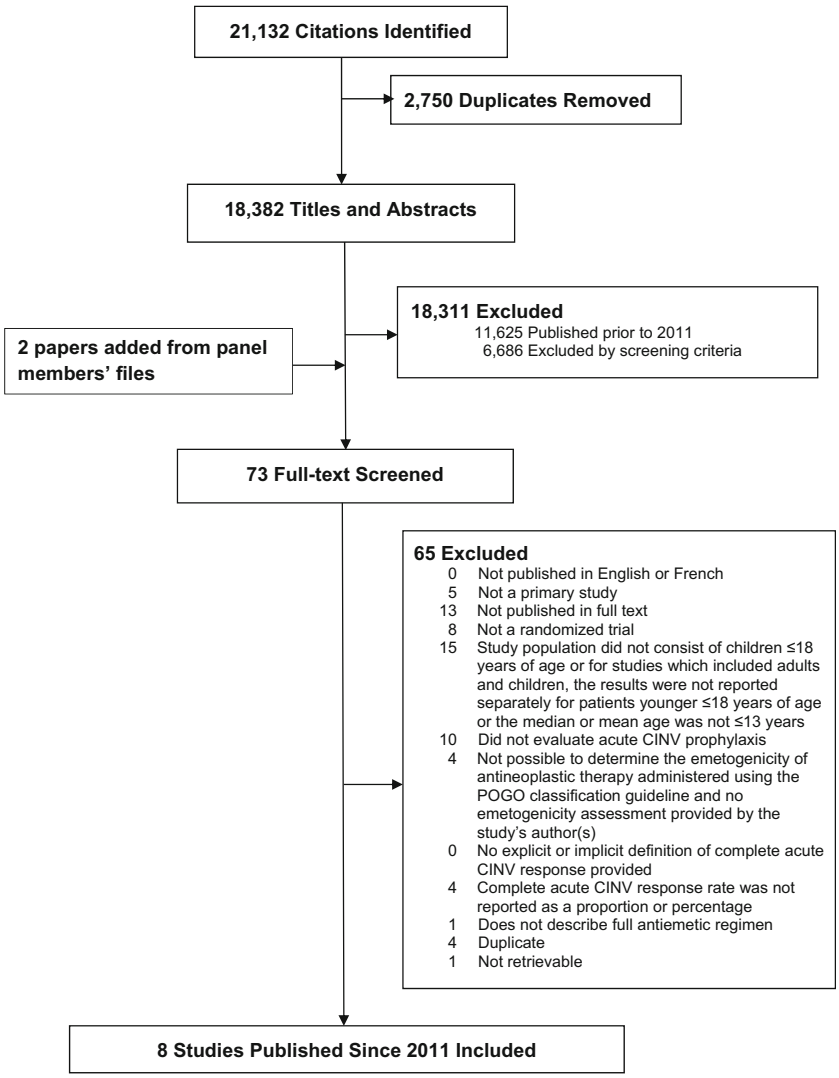

Fig. 1 MASCC guideline for chemotherapy-induced nausea and vomiting prevention in children: literature screening and identification flowchart to April 7, 2016

Antineoplastic-induced Nausea and Vomiting in Children [6]. Of these, 73 publications were screened at full text. Eight publications available since November 1, 2011 met the criteria for inclusion in this guideline update [11–18]. Another publication [19], published prior to November 1, 2011, was included due to a change from the study inclusion criteria of the POGO guideline to include studies which assessed CINV control during the first 24 h of the acute phase. When combined with the randomized studies which had been identified in the POGO guideline [6] evidence summary, a total of 25 randomized studies were included in the evidence to support this guideline update (Supplementary Tables) [11–35]. The 2009 and 2016 MASCC recommendations for CINV prophylaxis in children are presented in Table 1 together with the levels of confidence and consensus.

Acute CINV: high emetic risk chemotherapy (>90 % risk of emesis in the absence of prophylaxis)

Eleven studies evaluated antiemetic interventions in 914 children receiving 990 blocks of highly emetogenic chemotherapy [11–15, 19–24]. Four were published subsequent to the previous version of the guideline [11–13, 15]. Sufficient detail was available in six studies to determine the emetogenicity of the chemotherapy using the pediatric classification. The definition of complete control varied among studies. Two studies defined acute phase complete control as no vomiting; three as no vomiting or retching; two as no vomiting, no nausea, and no use of breakthrough antiemetic agents; and four as no vomiting and no nausea. Among studies that assessed nausea, no study used a validated pediatric nausea assessment tool [36, 37] to evaluate nausea severity.

Ten studies included a first-generation 5-HT3 antagonist (ondansetron 8; granisetron 2; tropisetron 1) in at least one study arm [11–15, 19–21, 23, 24] and two included palonosetron in at least one study arm [14, 19]. Seven studies included dexamethasone [11–15, 20, 22], although in two, its use was not controlled [13, 14] and two studies included aprepitant [11, 13] in one or both study arms. Other antiemetic agents evaluated were chlorpromazine (one study) [22], chlorpromazine plus dexamethasone (one study) [38], midazolam plus diphenhydramine (one study) [12], metoclopramide plus diphenhydramine (one study) [21], metoclopramide plus benztropine plus lorazepam (one study) [22], and ginger root powder (one study) [15]. Since no difference in complete CINV control rates was observed with the addition of ginger root powder to ondansetron plus dexamethasone [15], the addition of midazolam plus diphenhydramine to ondansetron plus dexamethasone [12], or with the use of an ondansetron loading dose compared to no loading dose [24], these interventions will not be discussed further. Complete CINV control rates reported with prophylaxis with single-agent chlorpromazine [22], with metoclopramide plus diphenhydramine [21], and with metoclopramide plus dexamethasone plus benztropine plus lorazepam [22] were lower than those generally achieved with CINV prophylaxis that includes a 5-HT3 antagonist plus dexamethasone. Thus, these regimens will also not be discussed further.

Studies of first-generation 5-HT3 antagonists included in this systematic review, granisetron [12, 23], ondansetron [11, 13, 15, 19–21, 24], and tropisetron [23], indicate that these agents achieve comparable complete CIV control rates in children receiving highly emetogenic chemotherapy. However, these rates vary widely (single-agent 5-HT3 agents, 23 to 72 %). Sepulveda-Vildosola observed complete CIV control in a significantly higher proportion of children who received palonosetron 0.25 mg IV compared to ondansetron [19]. Kovacs et al. recently demonstrated the non-inferiority of palonosetron 20 μg/kg/dose IV with/without dexamethasone compared to ondansetron with/without dexamethasone in achieving complete CIV control in children [14]. The same was found in the subset of children included in this study who did not receive dexamethasone.

Two studies have evaluated the benefit of adding aprepitant to ondansetron-containing CIV prophylaxis. Bakshi et al. reported a significantly higher complete response rate in children receiving highly emetogenic chemotherapy who received ondansetron plus dexamethasone plus aprepitant for CINV prophylaxis compared to the group who received ondansetron plus dexamethasone (48 vs. 12 %; $p < 0.001$) [11]. It is important to appreciate that this trial evaluated CIV control from administration of the first chemotherapy dose of the chemotherapy block to 24 h after the last dose of the block in children receiving multiday chemotherapy. The second trial compared ondansetron plus aprepitant with/without dexamethasone vs. ondansetron plus placebo with/without dexamethasone [13]. A complete response rate of 68 % was reported in the ondansetron plus aprepitant arm for the first 24 h after administration of the first chemotherapy dose of the chemotherapy block. However, the number of children in this group who received dexamethasone is unknown and the dose of dexamethasone, when given, was uncontrolled and varied widely. As a result, it is difficult to ascertain the contribution of aprepitant itself to CIV control in this trial. Interestingly, these authors reported a reduced rate of CIV control in children who received dexamethasone. Poor CIV control may have been observed in children receiving highly emetogenic chemotherapy and given dexamethasone at inadequate doses.

The guideline panel recommends that children receiving highly emetogenic chemotherapy receive CINV prophylaxis with a 5-HT3 antagonist (granisetron, ondansetron, tropisetron, or palonosetron) plus dexamethasone plus aprepitant. Changes to the 2009 recommendations were based primarily on the findings of Bakshi et al., Sepulveda et al., and Kovacs et al. [11, 14, 19]. The use of dexamethasone is

Table 1 Prevention of CINV in children: 2009 and 2016 MASCC recommendations

2009 MASCC recommendation	2016 MASCC recommendation
Acute CINV, high emetic risk chemotherapy	
All pediatric patients should receive antiemetic prophylaxis with a combination of a 5-HT3 receptor antagonist and dexamethasone Level of confidence, moderate Level of consensus, high	Children receiving chemotherapy of high emetic risk should receive antiemetic prophylaxis with a 5-HT3 antagonist[a] plus dexamethasone plus aprepitant MASCC level of confidence, high MASCC level of consensus, high ESMO level of evidence II ESMO grade of recommendation B Children who cannot receive dexamethasone should receive a 5-HT3 antagonist[a] plus aprepitant MASCC level of confidence, moderate MASCC level of consensus, high ESMO level of evidence II ESMO grade of recommendation B Children who cannot receive aprepitant should receive a 5-HT3 antagonist[a] plus dexamethasone MASCC level of confidence, moderate MASCC level of consensus, high ESMO level of evidence II ESMO grade of recommendation B
Acute CINV, moderate emetic risk chemotherapy	
All pediatric patients should receive antiemetic prophylaxis with a combination of a 5-HT3 receptor antagonist and dexamethasone Level of confidence, moderate Level of consensus, high	Children receiving moderately emetogenic chemotherapy should receive antiemetic prophylaxis with a 5-HT3 antagonist[a] plus dexamethasone MASCC level of confidence, moderate MASCC level of consensus, high ESMO level of evidence II ESMO grade of recommendation B Children who cannot receive dexamethasone should receive a 5-HT3 antagonist[a] and aprepitant MASCC level of confidence, moderate MASCC level of consensus, high ESMO level of evidence II ESMO grade of recommendation B
Acute CINV, low emetic risk chemotherapy	
No appropriate studies are available in this setting for children, and therefore, no formal recommendation is possible. Many panelists feel that in the absence of studies, children should be treated in a manner similar to that of adults receiving chemotherapy of this risk. Doses should be adjusted appropriately for children	Children receiving chemotherapy of low emetogenicity should receive antiemetic prophylaxis with a 5-HT3 antagonist[a] MASCC level of confidence, moderate MASCC level of consensus, moderate ESMO level of evidence II ESMO grade of recommendation B
Acute CINV, minimal emetic risk chemotherapy	
No appropriate studies are available in this setting for children, and therefore, no formal recommendation is possible. Many panelists feel that in the absence of studies, children should be treated in a manner similar to that of adults receiving chemotherapy of this risk. Doses should be adjusted appropriately for children	Children receiving chemotherapy of minimal emetogenicity should receive no antiemetic prophylaxis MASCC level of confidence, moderate MASCC level of consensus, high ESMO level of evidence V ESMO grade of recommendation D
Delayed CINV following chemotherapy of high and moderate emetic risk	
No appropriate studies are available for the prevention of delayed nausea and vomiting in children, and therefore, no formal recommendation is possible. Many panelists feel that in the absence of studies, children should be treated in a manner similar to that of adults receiving chemotherapy of this risk. Doses should be adjusted appropriately for children	Delayed CINV was not addressed in the 2015 update. The panel supports the 2009 recommendation

[a] 5-HT3 antagonist granisetron, ondansetron, palonosetron, or tropisetron

supported by a meta-analysis of pediatric studies which reports improved complete vomiting control in children who received a 5-HT3 antagonist together with dexamethasone compared to a 5-HT3 antagonist alone (RR 2.03; 95 % CI 1.35 to 3.04) [39].

Clinicians are counseled to avoid the use of dexamethasone in many pediatric oncology protocols (e.g., leukemia and brain tumors) due to concerns regarding potential interference with apoptosis [40], fungal infection [41], and distribution of chemotherapy across the blood-brain barrier [42]. In situations where clinicians wish to avoid using dexamethasone for CINV prophylaxis, the combination of a 5-HT3 antagonist (granisetron, ondansetron, tropisetron, or palonosetron) plus aprepitant is recommended based primarily on the findings of Sepulveda et al. and Kang et al. [13, 19].

Aprepitant may not be an option for all children receiving highly emetogenic chemotherapy. An oral liquid aprepitant formulation is not available in all jurisdictions. A stable, extemporaneous oral liquid formulation is available, but its bioavailability is unknown [43]. Young children who cannot swallow oral solid dosage forms or children whose weight does not allow appropriate dosing with the oral solid dosage forms available may be unable to receive aprepitant. The IV fosaprepitant cannot be routinely recommended currently since pediatric experience is scant. Furthermore, aprepitant is a moderate inhibitor of CYP3A4 and a weak inhibitor of CYP1A2, 2C8, 2C9, and 2E1 [44]. By definition, a moderate inhibitor increases the area under the concentration vs. time curve (AUC) of a sensitive substrate by 2- to less than 5-fold, whereas a weak inhibitor increases the AUC of a sensitive substrate by 1.25- to less than 2-fold [45]. Aprepitant consequently may decrease the clearance of many chemotherapy agents commonly used in pediatric oncology [6]. Thus, potentially increased cumulative chemotherapy exposure may pose concerns regarding a heightened risk of late effects in children, although there is currently no direct evidence to support this. Many pediatric oncology protocols advise against the use of aprepitant for this reason. When aprepitant administration is not feasible or desirable, the guideline panel recommends a 5-HT3 antagonist plus dexamethasone be given to children receiving highly emetogenic chemotherapy. Clinicians who wish to consider alternatives to aprepitant for certain patients are directed to other resources, which provide recommendations based on evidence from both randomized and non-randomized studies [6].

Acute CINV: moderate emetic risk chemotherapy (30 to 90 % risk of emesis in the absence of prophylaxis)

Fourteen randomized studies [13, 14, 16–18, 25–27, 30–33, 35, 38], five new to this update [13, 14, 16–18], were identified that met the criteria for inclusion in this systematic review. These studies involved 1492 children aged 0.5 to 22 years who received 1885 chemotherapy blocks. Chemotherapy emetogenicity was defined using the pediatric classification in five studies [26, 31–33, 38]. The definition of complete response used by each study again varied. Four studies included no nausea in the definition of complete response and six included no use of rescue antiemetic medications. Three reported no nausea and no vomiting separately. No study used a validated pediatric nausea assessment tool [36, 46] to evaluate nausea severity.

All but three studies included either ondansetron or granisetron in at least one study arm. Interventions that were compared to a 5-HT3 antagonist-containing regimen were chlorpromazine plus dexamethasone [38] and metoclopramide plus dexamethasone plus procyclidine [27]. These regimens will not be discussed further since the 5-HT3 antagonist study arm performed better than either of these regimens. Similarly, single-agent CINV prophylaxis with methylprednisolone [32], chlorpromazine [32], nabilone [25], or prochlorperazine [25] achieved complete control rates below those expected with CINV prophylaxis with 5-HT3 antagonists and therefore will not be discussed further.

Reported complete control rates achieved with single-agent CINV prophylaxis with ondansetron or granisetron ranged from 22 to 85 % [26, 27, 30, 31, 33, 38] and from 45 to 81 % [13, 35] when combined with dexamethasone. The addition of auricular acupressure to CINV prophylaxis with ondansetron with or without dexamethasone did not result in increased complete control rates [16]. A single study evaluated the addition of aprepitant to ondansetron alone or to ondansetron plus dexamethasone [13]. The number of patients who received dexamethasone in this study is unknown, and when given, the dexamethasone dose was uncontrolled. A complete response rate of 65 % was reported in children receiving moderately to very highly emetogenic chemotherapy, given ondansetron plus aprepitant and 71 % with ondansetron plus aprepitant plus dexamethasone [13]. Interestingly, Traivaree et al. reported a complete response rate of 85 % in children receiving dexamethasone alone for CINV prophylaxis after administration of intrathecal chemotherapy [18].

The complete response rates reported with single-agent dexamethasone (85 %), single-agent ondansetron or granisetron (22 to 85 %), ondansetron or granisetron plus dexamethasone (45 to 81 %), ondansetron plus aprepitant (65 %), and ondansetron plus aprepitant plus dexamethasone (71 %) overlap substantially. This may be explained by the wide disparity in emetic risk between agents within this classification band. Acknowledging this and the evidence in adult cancer patients receiving moderately emetogenic chemotherapy, the panel therefore recommends that children receiving moderately emetogenic chemotherapy receive CINV prophylaxis with a 5-HT3 antagonist plus dexamethasone. For

children who cannot receive dexamethasone, aprepitant may be used as an alternative.

Acute CINV: low emetic risk chemotherapy (10 to 30 % risk of emesis in the absence of prophylaxis)

Three publications [21, 29, 34] were identified, which described CINV control in children receiving 97 chemotherapy blocks and which met the criteria for inclusion in this systematic review. In the two studies which provided this information, patient age arranged from 0.25 to 18 years. One of these studies was an ondansetron dose comparison study [34]. The other two studies compared single-agent ondansetron or granisetron to metoclopramide plus diphenhydramine [21] or granisetron plus methylprednisolone [29].

Reported complete control rates in children receiving single-agent ondansetron or granisetron ranged from 50 to 91 %. The lowest complete response rate was reported in a trial which enrolled children receiving chemotherapy of low to high emetogenicity and did not report their findings stratified by the emetogenicity of the chemotherapy received [29].

The guideline panel recommends that children receiving chemotherapy of low emetogenicity receive single-agent CINV prophylaxis with a 5-HT3 antagonist. The decision to include palonosetron is based on the evidence of its demonstrated non-inferiority to ondansetron in children receiving highly and moderately emetogenic chemotherapy and the published experience in adult cancer patients.

Acute CINV: minimal emetic risk chemotherapy (<10 % risk of emesis in the absence of prophylaxis)

No randomized studies were identified, which described the complete CINV rates associated with antiemetic interventions in children receiving chemotherapy of minimal emetogenicity. Based on indirect evidence from findings in adult cancer patients, the panel recommended that children receiving chemotherapy of minimal emetogenicity receive no CINV prophylaxis.

Conclusions

Evidence published since the last MASCC guideline update permits the development of recommendations for acute CINV prophylaxis for children with increased confidence. However, the number of children studied is small, the standard antiemetic backbone varies between studies, the definition of complete response is not standardized, and nausea has not been evaluated using a validated method. Future studies must address these methodological concerns so that acute CINV prophylaxis in children with cancer can be improved. With appropriately designed studies, the use of older antiemetic agents can be optimized and the role of promising new pharmacological (e.g., olanzapine [47], rolapitant [48], and palonosetron [19, 39]) and non-pharmacological (e.g., acupressure [49] and relaxation training and psycho-education [50]) antiemetic interventions in the supportive care of children with cancer can be determined.

Acknowledgments The MASCC Pediatric Guideline Development Panel is grateful to the Pediatric Oncology Group of Ontario (POGO) for granting permission to edit and update the evidence tables prepared for the 2013 POGO Guideline for the Prevention of Acute Nausea and Vomiting Due to Antineoplastic Medication in Pediatric Cancer Patients. The guidance of Dr. P.D. Robinson with respect to clinical practice guideline methods is acknowledged with thanks. The assistance of Ms. Elizabeth Uleryk, Library Scientist, with the literature search is also gratefully acknowledged as is the assistance of Dr. Priya Patel and Ms. Mila Khanna.

Compliance with ethical standards

Conflict of interest L.L. Dupuis has participated in research partially supported by Sea-Band Ltd. A. Molassiotis has received honoraria and support from MSD Merck, Helsinn, Tesaro, Norgine, and Acacia Pharma. A. Orsey holds stock in Pfizer. Other authors had no disclosures to declare.

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