

# Antiemetics in children receiving chemotherapy. MASCC/ESMO guideline update 2009

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Received: 25 March 2010 / Accepted: 23 August 2010 / Published online: 9 September 2010  
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**Abstract** Only a few studies have been carried out in children on the prevention of chemotherapy-induced nausea and vomiting (CINV). 5-HT<sub>3</sub> receptor antagonists have been shown to be more efficacious and less toxic than metoclopramide, phenothiazines and cannabinoids. Most dose studies are available for the 5-HT<sub>3</sub> receptor antago-

nists ondansetron and granisetron. The new 5-HT<sub>3</sub> receptor antagonist palonosetron was evaluated in one comparative study so far showing promising activity. Combinations of a 5-HT<sub>3</sub> receptor antagonist and dexamethasone showed increased efficacy with respect to a 5-HT<sub>3</sub> receptor antagonist alone. All paediatric patients receiving chemotherapy of high or moderate emetogenic potential should receive a combination of a 5-HT<sub>3</sub> receptor antagonist and dexamethasone to prevent acute emesis. No studies have specifically evaluated antiemetic drugs in the prevention of chemotherapy-induced delayed and anticipatory emesis in children. The role of the NK1 receptor antagonists in children has to be further investigated, although one small study is published so far, showing promising activity in the prevention of CINV with aprepitant. The new proposed guideline from the Multinational Association of Supportive Care in Cancer and the European Society of Clinical Oncology summarises the updated data from the literature and takes into consideration the existing guidelines.

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**Keywords** Antiemetics for children submitted to chemotherapy · Dexamethasone · 5-HT<sub>3</sub> receptor antagonists

## Introduction

Not every child receiving chemotherapy will experience nausea and vomiting. However, it has been estimated that these symptoms will occur in up to 70% of patients [15, 17, 24]. It is also well recognised that children (above the age of 5 years) are more prone to vomiting than adults [27, 30].

Despite recent significant advances, problems in the control of chemotherapy-induced emesis in children and adolescents remain [2]. Still, only a few studies have been carried out in children on the prevention of chemotherapy-

induced emesis, and it is inappropriate to assume that all results obtained in adults can be directly applied to children, since metabolism and side effects of drugs may be different [12, 19, 27]. Furthermore, a cross-comparison of the studies is sometimes difficult because of the significantly different definitions of response rates and nausea rates.

The purpose of this updated Multinational Association of Supportive Care in Cancer (MASCC)/European Society of Medical Oncology (ESMO) guideline is to provide a consensus statement derived from published articles as well as expert opinion about antiemetic therapy in children. This guideline refers to children and young people (<18 years).

### Literature search strategy

Pertinent information from the published literature as of 2004 to June 2009 was retrieved and reviewed for the creation of this guideline. MEDLINE (National Library of Medicine) was searched for pertinent articles. The following keywords or phrases were used: antiemetics, chemotherapy-induced emesis, children, neoplasms, nausea, vomiting, serotonin antagonists, neurokinin-1 receptor antagonists, phenothiazines, butyrophenones, cannabinoids, corticosteroids and metoclopramide. Abstracts were reviewed and articles were excluded, if they possessed any of the following characteristics: review articles and cause for emesis other than chemotherapy.

Between 2004 and June 2009, the following articles could be identified:

- 5-HT<sub>3</sub> receptor-antagonists
  - Safety issues: two studies
  - Dose-finding/optimising studies: four studies
  - Comparative studies: two studies
- NK-1 receptor antagonist, aprepitant: one randomised study, two case reports (one in French), one study on liquid formulation of aprepitant
- Miscellaneous: two studies, impact of an antiemetic pump and value of metopimazine when added to ondansetron

### 5-HT<sub>3</sub> receptor antagonists as monotherapy

#### Dose-finding studies

The optimal dose and scheduling of the 5-HT<sub>3</sub> receptor antagonists have been evaluated in several trials, and since the last consensus conference, three dose-finding studies have been published, whereas one by Hasler and others [4, 7, 13] is retrospective. Unfortunately, almost all of the published studies are small, and it is difficult to identify the

absolute optimal oral and intravenous doses of the 5-HT<sub>3</sub> receptor antagonists in children [4, 7, 13, 16, 27]. However, most dose studies are available for the 5-HT<sub>3</sub> receptor antagonists ondansetron and granisetron. In clinical practice, established doses for ondansetron are 5 mg/m<sup>2</sup> or 0.15 mg/kg every 8 h and for granisetron 0.01 mg/kg or 10 µg/kg once a day [5, 18].

The new 5-HT<sub>3</sub> receptor antagonist palonosetron was evaluated in one comparative study and so far it showed promising activity [29].

#### Ondansetron

Since the last update, two studies were published [8, 13]. One study compared the antiemetic efficacy of an intravenous (IV) and orally disintegrating tablet (ODT) of ondansetron in a prospective randomised fashion in 22 children [8]. Complete and major control of emesis was obtained in 92% of patients in the IV group and in 93% of patients in the ODT group. In the other study, the safety of an ondansetron loading dose (16 mg/m<sup>2</sup>, top 24 mg) was studied in 37 patients. The authors concluded that an IV ondansetron loading seemed to be safe in infants, children and adolescents. However, as this study was retrospective, no firm conclusion can be drawn [13].

#### Granisetron

Since 2004, one additional study has been published [4]. In this small study including 18 patients (225 cycles), 10 versus 40 µg/kg granisetron were compared in a double-blind crossover, randomised study in acute and delayed nausea/emesis [4]. No significant differences in antiemetic efficacy in terms of nausea and emesis between the dose groups in the first 5 days after the chemotherapy could be detected.

#### Tropisetron

In the updated literature search, one study including 50 children evaluated the efficacy of tropisetron with a dose of 5 mg in patients weighing less than 20 kg and 10 mg in patients weighing greater than 20 kg [7]. Acute emesis control was achieved overall in 92% of the treated patients. None of the treated patients experienced any adverse events with the used dose of tropisetron.

#### New comparative studies of 5-HT<sub>3</sub> receptor antagonists

##### *Ondansetron versus granisetron*

One study compared a single-dose oral granisetron (0.5 mg: 25–50 kg; 1 mg > 50 kg) versus multidose IV ondansetron (0.15 mg/kg tid) for moderately emetogenic cyclophosphamide-based chemotherapy in 33 children (66 cycles) [16]. Complete

efficacy defined as no emesis and no use of rescue medication was obtained in 60.6% in the granisetron arm and in 45.5% in the ondansetron arm. Boys were noted to experience a greater rate of vomiting than did girls.

#### *Palonosetron versus granisetron*

One small study so far compared ondansetron (8 mg/m<sup>2</sup> every 8 h while receiving chemotherapy) versus palonosetron 0.25 mg once (all patients independent of weight) [29]. In this study, 100 cycles were evaluated in patients receiving highly or moderately emetogenic chemotherapy over several days (slightly more cisplatin in the ondansetron group). Complete control of emesis during chemotherapy in the first 24 h, on day 2 and on day 3 was obtained in 92%, 72% and 78% of patients in the palonosetron group and in 72%, 46% and 54% of patients in the ondansetron group. Regarding the delayed phase (days 4–7), complete control of emesis on days 4, 5, 6 and 7 was obtained in 88%, 98% and 100% on days 6 and 7 in the palonosetron group and in 84%, 90%, 94% and 96% in the ondansetron group. In summary, a significant reduction of emesis and nausea was achieved with palonosetron in the first 3 days (defined here as acute phase) in comparison to ondansetron. The antiemetic protection of emesis and nausea in the delayed phase was similar in both arms.

#### Corticosteroids

Since the last update, no study specifically addressing the dosing, safety or efficacy of corticosteroids has been published. Corticosteroids are more effective antiemetics in chemotherapy-induced nausea and vomiting (CINV) than chlorpromazine or metoclopramide [3, 23]. The combination of a steroid and metoclopramide is more effective than chlorpromazine alone [22]. The combination of ondansetron and dexamethasone was superior to ondansetron alone in controlling emetic episodes in children receiving moderately or highly emetogenic chemotherapy [1]. Similar results were obtained by Hirota et al [14]. The optimal dose of steroids in children has to be determined. In clinical practice, a dexamethasone dose ranging from 10 to 14 mg/m<sup>2</sup> is usually used [2, 15, 28]. In regard to the safety of corticosteroids, it has to be considered that corticosteroid treatment, especially in children older than 10 years, increases the risk of aseptic osteonecrosis [6, 20, 28]. Furthermore, laboratory studies suggest steroids may interfere with response to chemotherapy in osteosarcoma cell lines, but this has not been shown in vivo [9].

#### NK1 receptor antagonists

So far, one randomised small study ( $n=50$ , age 11–19 years) is available on the additional use of the NK1 receptor

antagonist aprepitant in adolescents [10]. The used dose (125 mg d1, 80 mg days 2–3) of aprepitant was the same as the dose used in adult patients. Blood samples for analysis of aprepitant pharmacokinetic parameters were collected from 17 patients who received aprepitant. The mean plasma aprepitant concentration–time profiles were generally similar between adolescent and historical data from adult subjects. No details about the emetogenicity of the chemotherapy administered were discussed in the paper. In terms of efficacy, the aprepitant regimen (aprepitant, ondansetron, dexamethasone) when compared to the control regimen (ondansetron, dexamethasone) showed a complete response rate defined as no emesis and no use of rescue medication of 60.7% vs. 38.9% (acute phase), 35.7% vs. 5.6% (delayed phase) and 28.6% vs. 5.6% (overall phase). Although the complete response rate was improved with the aprepitant regimen, statistical significance was not reached, which may be attributed to the small patient number. The parallel pharmacokinetic study conducted suggested that the adult dose regimen was appropriate for adolescents.

#### Comparative studies with agents of low therapeutic index

Overall, metoclopramide, phenothiazines and cannabinoids have only moderate efficacy and significant side effects, most notably marked sedation and extrapyramidal reactions [11, 26]. As in adults, lorazepam did not show convincing antiemetic efficacy [26]. Ondansetron and granisetron have been shown to be superior to chlorpromazine, dimenhydrinate and to metoclopramide combined with dexamethasone and are less toxic [21, 27].

Two studies have been published since the last update [21, 25]. In the first small pilot study, ondansetron versus ondansetron plus metopimazine was studied in ten patients receiving highly emetogenic chemotherapy [25]. The combination antiemetic therapy of ondansetron and metopimazine was more effective especially in the delayed phase than the monotherapy without additional toxicity. In the second study, single dose of granisetron (50 µg/kg) was compared to metoclopramide (2 mg/kg) plus dimenhydrinate (5 mg/kg) in 26 patients receiving 80 cycles of moderate emetogenic chemotherapy [21]. As a result of this study, granisetron as monotherapy was superior to the combination of metoclopramide and dimenhydrinate.

#### Updated recommendations for the prophylaxis of CINV in children

After the last MASCC Consensus Conference in 2004, new data on CINV suggested a need to update the existing guidelines. Therefore, MASCC convened an

Expert Panel for a new International Antiemetic Consensus Conference which was held in Perugia, Italy, 20–22 June 2009. Data from the literature were evaluated, and relevant data were included. These provided the basis for the new proposed MASCC/ESMO guidelines discussed by the experts and described below. The following recommendations refer only to the acute phase of CINV, because no appropriate studies are available for the delayed phase, and therefore no formal recommendation is possible.

### 5-HT<sub>3</sub> receptor antagonists

No designated 5-HT<sub>3</sub> receptor antagonist can be recommended (MASCC level of confidence: moderate, level of consensus: high/ESMO level of evidence: II, grade of recommendation: B).

No verifiable high-level evidence-based consensus was possible on the dose of the individual 5-HT<sub>3</sub> receptor antagonists.

### Corticosteroids

Corticosteroids are effective antiemetics for CINV especially when combined with a 5-HT<sub>3</sub> receptor antagonist (MASCC level of confidence: moderate, level of consensus: high/ESMO level of evidence: II, grade of recommendation: B). No recommendation of an optimal dose of dexamethasone or methylprednisolone is possible. Safety issues (e.g., osteonecrosis) when administering corticosteroids in children must be strongly considered.

### NK-1 receptor antagonists

Although there is only one study with the NK-1 receptor antagonist aprepitant in combination with ondansetron and dexamethasone in adolescents, the NK-1 so far has shown promising additional activity. However, the guideline panel will wish to see more well-conducted three-agent trials testing the addition of a NK-1 receptor antagonist to draw firm conclusions for a recommendation.

### High emetogenic chemotherapy, acute phase

All paediatric patients should receive antiemetic prophylaxis with a combination of a 5-HT<sub>3</sub> receptor antagonist and dexamethasone (Table 1) (MASCC level of confidence: moderate, level of consensus: high/ESMO level of evidence: III, grade of recommendation: B).

**Table 1** Comparison of the new guidelines of chemotherapy-induced emesis in adults and children

Emesis risk level	Antiemetic guidelines in adults	MASCC level of scientific confidence/level of consensus	Antiemetic guidelines in children	MASCC level of scientific confidence/level of consensus
High (>90%)	Day 1: 5-HT <sub>3</sub> antagonist + DEX + (fos)aprepitant Days 2–3: DEX + aprepitant Day 4: DEX	High/high	Day 1: 5-HT <sub>3</sub> antagonist + DEX Days 2–4: No recommendation possible	Moderate/high Not applicable
Moderate AC-based	Day 1: 5-HT <sub>3</sub> antagonist + DEX + (fos) aprepitant Days 2–3: Aprepitant	High/high	Not applicable	Not applicable
Moderate (30–90%)	Day 1: Palonosetron + DEX Days 2–3: DEX days 2–3	Moderate/moderate Moderate/moderate	Day 1: 5-HT <sub>3</sub> antagonist + DEX Days 2–4: No recommendation possible	Moderate/high Not applicable
Low (10–30%)	Day 1: DEX or 5-HT <sub>3</sub> or dopamine antagonist Days 2–3: No routine prophylaxis	Moderate/moderate No confidence possible/moderate	No recommendation possible	Not applicable
Minimal (<10)	Day 1: No routine prophylaxis Days 2–3: No routine prophylaxis	No confidence possible/high	No recommendation possible	Not applicable

DEX Dexamethasone, AC combination of an anthracycline (doxorubicin or epirubicin) and cyclophosphamide

### Moderate emetogenic chemotherapy, acute phase

All paediatric patients should receive antiemetic prophylaxis with a combination of a 5-HT<sub>3</sub> receptor antagonist and dexamethasone (MASCC level of confidence: moderate, level of consensus: high/ESMO level of evidence: II, grade of recommendation: B).

### Low and minimal emetogenic chemotherapy, acute phase

No recommendation is possible due to a lack of studies in children in this setting.

## Conclusions

In the last few years, not enough attention has been paid to the problem of chemotherapy-induced emesis in children. With some exceptions, published studies continue to present so many methodological problems (few patients, nonoptimal design, etc.) that it is impossible to draw firm conclusions. It seems likely that children receiving chemotherapy of minimal emetic potential do not need prophylactic antiemetics, but this is not yet shown; children probably tend to underreport nausea. Furthermore, there is an additional need to investigate the potential role of NK-1 receptor antagonists and the 5-HT<sub>3</sub> receptor antagonists palonosetron and transdermal granisetron in well-designed studies. Finally, optimal management of delayed and anticipatory CINV in children is not yet clear.

**Conflicts of interest** Karin Jordan receives compensation for: Advisory Board—Merck Sharp and Dhome (MSD), Glaxo Smith Kline (GSK); and Speakers Bureau—MSD, GSK, Helsinn.

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### Note

*MASCC evidence:* Level of confidence (high–low) and grade of consensus (high–low) as used by the Multinational Association of Supportive Care are given in brackets.

*ESMO evidence:* Levels of evidence (I–V) and grades of recommendation (A–D) as used by the American Society of Clinical Oncology are in given in brackets.