Pediatric Hematology Oncology Journal 1 (2016) 50–55

Contents lists available at ScienceDirect

Pediatric Hematology Oncology Journal

journal homepage: https://www.elsevier.com/journals/pediatric-hematology-oncology-journal/

Prophylaxis and management of antineoplastic drug induced nausea and vomiting in children with cancer

Sidharth Totadri

Medical Oncology Unit (Pediatric Oncology Division), Cancer Institute, Adyar, Chennai, India

ARTICLE INFO

Article history:
Received 9 August 2016
Received in revised form
4 September 2016
Accepted 26 September 2016
Available online 30 September 2016

Keywords:
Antiemetics
Emesis
India
Antineoplastic-induced nausea and vomiting
Emetogenic potential

ABSTRACT

Antineoplastic drug induced nausea and vomiting (AINV) is a major adverse event which deeply impacts the quality of life of children with cancer. It additionally causes distress to parents and negatively impacts compliance to therapy. A robust AINV prophylaxis regimen is essential to achieve complete control; and prevent anticipatory, breakthrough and refractory AINV. With a wide array of available anti-emetics, standard guidelines for their use are crucial to ensure uniform and optimum prophylaxis. Chemotherapeutic agents are classified as having high, moderate, low or minimal emetic risk based on their potential to cause emesis in the absence of prophylaxis. Three drug regimen with aprepitant, ondansetron/granisetron and dexamethasone is recommended for protocols with high emetic risk. Although approved in children ≥12 years, there is mounting evidence for the use of aprepitant in younger children too. In protocols with moderate and low emetic risk, combination of ondansetron/granisetron and dexamethasone; and single agent ondansetron/granisetron are recommended, respectively. Metoclopramide is an alternative when steroids are contraindicated. Olanzapine and lorazepam are useful drugs for breakthrough AINV and anticipatory AINV. Knowledge of pediatric dosage, salient adverse events, drug interactions as well as cost of drugs is essential to prescribe anti-emetics accurately and safely in resource constrained settings. Non pharmacological interventions such as hypnosis, acupressure and psychological interventions can benefit a sub-group of patients without significant risk of adverse events.

1. Introduction

Antineoplastic drug induced nausea and vomiting (AINV) constitutes an undesirable adverse event which profoundly impacts the quality of life of children with cancer, as well as their caregivers [1–3]. The entity is also referred to as chemotherapy induced nausea and vomiting [2–4]. Additionally, it can compromise compliance to chemotherapy and disease free survival [2,3]. AINV is best prevented with an optimal antiemetic regimen [3]. Inadequate control often leads to a vicious cycle of breakthrough, anticipatory and sometimes refractory AINV [3–5]. Uncontrolled vomiting can result in potentially life threatening complications such as dehydration, dyselectrolytemias, aspiration pneumonia, wound dehiscence, upper gastrointestinal tract injury/bleeding, malnutrition and psychological stress [3,6,7]. In resource limited settings, AINV further adds to the cost of therapy, increased need of hospital visits and prolongation of hospital stay [3].

2. Literature review

There is a paucity of guidelines for anti-emetic prophylaxis in children with cancer. The American Society of Clinical Oncology published updated clinical practice guidelines in 2011 followed by a focused clinical update in 2015 [8,9]. However, these do not specifically address pediatric patients [8,9]. The Pediatric Oncology Group of Ontario (POGO) published a series of guidelines addressing management of AINV in children. The first outlined classification of antineoplastic agents based on their emetogenic potential [10]. This was followed by guidelines for prevention of acute AINV; prevention and treatment of anticipatory AINV; as well as prevention and treatment of breakthrough and refractory AINV [4,5,11]. These guidelines have been utilized as the backbone of this review. Further inputs regarding formulations available in the Indian market and their cost have been obtained from the current index of medical specialties (CIMS) website [12].

E-mail address: totadri86@yahoo.com.

Peer review under responsibility of Pediatric Hematology Oncology Chapter of Indian Academy of Pediatrics.

http://dx.doi.org/10.1016/j.phoj.2016.09.001

3. Salient definitions

Acute AINV is defined as nausea, vomiting and/or retching occurring within 24 h of administration of chemotherapy. Acute AINV excludes delayed, anticipatory or breakthrough AINV; as well as nausea/vomiting secondary to other therapeutic modalities such as radiotherapy and palliative medications, primary disease and co-incident conditions [7,11]. Delayed AINV occurs after 24 h of administration, and usually within 7 days [7]. AINV ensuing in any phase despite adequate antiemetic prophylaxis with the usual standard of care is termed breakthrough [4,7]. Refractory AINV fails to respond to changing prophylaxis or treatment [4]. Further, nausea/vomiting may develop within 24 h prior to antineoplastic therapy, termed as anticipatory AINV [5,7]. Optimum control of AINV is identified by absence of nausea, vomiting, retching and AINV induced anorexia; from start of the chemotherapy block till 24 h after administration of last chemotherapeutic agent; without requirement of additional anti-emetics outside the prescribed prophylaxis [11].

The first step in prescribing an antiemetic regimen for preventing AINV entails assessment of the emetogenic potential of the chemotherapy scheduled to be administered [10]. Emetic risk is measured by the frequency of emesis in the absence of prophylaxis [10]. Based on emetic risk, chemotherapeutic agents are classified as: highly emetogenic chemotherapy (HEC) if risk > 90%, moderately emetogenic chemotherapy (MEC) if risk 30–90%, chemotherapy with low emetic risk (LEC) if 10–30% and minimally emetogenic chemotherapy if < 10% [10]. Table 1 illustrates the emetogenic potential of chemotherapeutic agents commonly used in the day to day practice of pediatric oncology. Besides emetogenicity of antineoplastic therapy, additional risk factors for AINV include older age (>3 years), female gender and prior history of AINV [3]. It is evident from this classification that almost all treatment protocols administered in pediatric malignancies such as sarcomas, Wilms tumor, neuroblastoma, hepatoblastoma, medulloblastoma, lymphomas and myeloid leukemia possess high emetic risk. Chemotherapy administered during the intensive phases of management of acute lymphoblastic leukemia which include anthracyclines, cyclophosphamide and high dose methotrexate would qualify as at least moderately emetic. This reiterates the importance of AINV prophylaxis in pediatric oncology.

A multi-national cross sectional survey of children and adults with cancer receiving chemotherapy/radiotherapy revealed that physicians/nurses may significantly underestimate the impact of AINV on the quality of life of patients [13]. While 76% physicians adhered to guidelines while prescribing anti-emetics in HEC, merely 15% followed guidelines for MEC [13]. Lesser than 40% patients reported complete adherence to self-administered anti-emetic drugs as advised by their physician/nurse [13]. This underscores the importance of thorough understanding of current recommendations by physicians/nurses; as well as the need for reinforcement of compliance to anti-emetic drugs among patients and their caregivers.

Table 1
Classification of chemotherapeutic agents based on their emetogenicity.

Category (frequency of emesis in the absence of antiemetic prophylaxis in %)	Chemotherapeutic agents
Highly emetic (>90%)	Cisplatin, carboplatin Cyclophosphamide $\geq$ 1 g/m^2 Dacarbazine Actinomycin-D Methotrexate $\geq$ 12 g/m^2 Cyclophosphamide + Anthracycline Cyclophosphamide + Etoposide Cytarabine 150–200 mg/m^2 + Daunorubicin Cytarabine 300 mg/m^2 + Etoposide Doxorubicin + Ifosfamide Doxorubicin + Methotrexate 5 g/m^2 Etoposide + Ifosfamide Oral: Procarbazine
Moderately emetic (30–90%)	Arsenic trioxide Busulfan Carmustine $\leq$ 250 mg/m^2 Cyclophosphamide < 1 g/m^2, Ifosfamide Cytarabine > 200 mg/m^2 to < 3 g/m^2 Daunorubicin, doxorubicin, idarubicin, epirubicin IT therapy (Methotrexate, hydrocortisone, cytarabine) Irinotecan Lomustine Melphalan > 50 mg/m^2 Methotrexate $\geq$ 250 mg/m^2 to < 12 g/m^2 Oral: Cyclophosphamide, etoposide, temozolomide, imatinib
Low level emetic (10 to < 30%)	Cytarabine $\leq$ 200 mg/m^2 Etoposide 5-Fluorouracil Gemcitabine Methotrexate > 50 mg/m^2 to < 250 mg/m^2 Mitoxantrone Topotecan Oral: Busulfan
Minimally emetic (<10%)	L-Asparaginase (IM and IV) Bevacizumab Bleomycin Cladribine Fludarabine Methotrexate $\leq$ 50 mg/m^2 Nelarabine Rituximab Vincristine, vinblastine, vindesine, vinorelbine Oral: 6-MP, 6-TG, dasatinib, hydroxyurea, sorafenib

Drugs to be assumed as intravenously administered unless specified otherwise; IT: Intrathecal; IM: Intramuscular; IV: Intravenous; 6-MP: 6-mercaptopurine; 6-TG: 6-thioguanine. Adapted from: Dupuis LL, Boodhan S, Sung L, Portwine C, Hain R, McCarthy P et al. Guideline for the classification of the acute emetogenic potential of antineoplastic medication in pediatric cancer patients. Pediatr Blood Cancer. 2011 Aug; 57(2):191–8.

4. Antiemetic armamentarium in children

AINV results from the stimulation of the centrally located emetic center and chemoreceptor trigger zone in the brain as well as the peripherally located vagal afferents in the gastrointestinal tract [14]. The mediators and respective receptors involved in this process include dopamine acting on dopamine receptor D2; serotonin acting on 5-hydroxytryptamine receptor 5-HT3; prostaglandins; and substance P acting on Neurokinin (NK-1) receptors [3,14]. Cholinergic, cannabinoid (CB-1) and α-adrenergic receptors are additional receptors involved in the emetic mechanism [3,14]. Consequently, antiemetic drugs have been developed to target these receptors. Classification of these drugs based on their mechanism of action, and adverse events are outlined in Table 2. Dosing schedules and cost of commonly used drugs are described in Table 3.

5. Anti-emetic prophylaxis for AINV: case based approach

5.1. Anti-emetic prophylaxis for acute AINV

Case 1. *A 7-year-old girl with weight of 19 kg and body surface area (BSA) of 0.76 was diagnosed with non-metastatic Ewing sarcoma of*

Table 2
Anti-emetics available for use in children with their pharmacological profile.

Class of drugs based on mechanism of action	Drugs available	Adverse events
5HT3 receptor antagonists	Ondansetron Granisetron Palonosetron	Mild headache, flushing, constipation, QT prolongation
NK-1 antagonists	Aprepitant Fosaprepitant	Constipation, fatigue, diarrhea, Inhibition of cytochrome P-450 leading to drug interactions
Corticosteroids (Inhibition of prostaglandin synthesis in hypothalamus)	Dexamethasone	Hyperglycemia, epigastric pain, sleep disturbance
Dopamine antagonists	Metoclopromide Chlorpromazine Levomepromazine	Sedation, akathisia, acute dystonic reactions
Benzodiazepines (Sedation, anxiolysis, depression of emetic center)	Lorazepam	Respiratory depression, hypotension, syncope, dependency
Cannabinoids	Dronabinol Nabilone	Dizziness, sedation, dysphoria, hypotension, hallucinations

5-HT3: 5 hydroxytryptamine3; NK-1: Neurokinin-1.

Table 3
Dosing schedule and cost of commonly used anti-emetic drugs.

Name	Dose	Available formulations with approximate maximum retail price in Indian market
Ondansetron	5 mg/m^2/dose IV/PO q 8–12 hourly (max. 8 mg/dose) in HEC/MEC 10 mg/m^2 IV/PO stat dose in LEC	Tab. 4 mg × 10 – Rs 50 Syr. 2 mg/5 ml × 30 ml – Rs 35 Inj. 2 mg/ml × 4 ml – Rs 30
Granisetron	40 μg/kg PO q 12 hourly (or) 40 μg/kg IV q 24 hourly in HEC/MEC/LEC (max. 3 mg/dose)	Tab. 1 mg × 4 – Rs 80 Syr. 1 mg/5 ml × 30 ml – Rs 35 Inj. 1 mg/ml × 3 ml – Rs 60
Palonosetron	20 μg/kg IV stat (max. 1.5 mg)	Inj. 0.25 mg/5 ml × 5 ml – Rs 140
Aprepitant	125 mg PO on day1, 80 mg on days 2 & 3, q 24 hourly in HEC*	Blister pack of 3 capsules (125 mg × 1 and 80 mg × 2) – Rs 1215
Dexamethasone#	6 mg/m^2/dose IV/PO q 6 hourly in HEC, 2 mg (BSA < 0.6) or 4 mg (BSA ≥ 0.6) IV/PO q 12 hourly in MEC	Tab. 4 mg × 4 – Rs 16 Inj. 4 mg/ml × 2 ml – Rs 8
Metoclopromide	1–5 mg IV/PO q 8 hourly in settings where steroids are not permitted	Tab. 5 mg × 10 – Rs 8 Syr. 1 mg/ml × 30 ml – Rs 20 Inj. 5 mg/ml × 10 ml – Rs 12
Olanzapine	0.1 mg/kg PO q 24 hourly (max. 10 mg) in breakthrough AINV	Tab. 5 mg × 10 – Rs 50
Lorazepam	0.04–0.08 mg/kg PO (max. 2 mg) night prior and morning of chemo for anticipatory AINV	Tab. 2 mg × 10 – Rs 25

IV: intravenous; PO: per oral; HEC: highly emetogenic chemotherapy; MEC: moderately emetogenic chemotherapy; LEC: chemotherapy with low emetic risk; Tab: Tablet; Inj: Injection; Rs: Rupees; *Consider dose of 80 mg on all 3 days if age <12 years and weight 15–40 kg; #50% dose dexamethasone if simultaneously giving aprepitant.

the humerus. Neoadjuvant chemotherapy was planned with the first cycle comprising vincristine (1.5 mg/m^2), cyclophosphamide (1.2 g/m^2) and doxorubicin (50 mg/m^2). What would be the ideal antiemetic schedule for AINV prophylaxis?

5.1.1. Prophylaxis for acute AINV in chemotherapy regimens with high emetic risk (HEC)

The child described in Case 1 is about to receive a HEC as it contains cyclophosphamide in combination with doxorubicin. The emetic risk of a multi-agent chemotherapy block is contributed by the most emetogenic single drug or combination of drugs as illustrated in Table 1 [8,10]. Further in multiple day schedules, the risk for each day would be contributed by the most emetogenic single drug/drug combination administered on that day [8,10]. The POGO guideline for acute AINV prophylaxis recommends a combination of three drugs: aprepitant, dexamethasone and 5HT3-receptor antagonist (ondansetron/granisetron) for HEC [11]. In children aged <12 years in whom aprepitant is not currently approved, as well as patients receiving chemotherapeutic drugs which have the potential to interact with aprepitant (See Table 2), dexamethasone and ondansetron/granisetron alone are recommended [11]. The ASCO guideline recommends aprepitant/5-HT3-receptor blocker/dexamethasone in adults for HEC [8,9]. However it continues to recommend 5-HT3-receptor blocker/dexamethasone for pediatric patients receiving HEC, with higher weight based dosing [8,9]. For multi-day chemotherapy, anti-emetics appropriate for the emetogenic risk class of the chemotherapy are to be administered for each day of the chemotherapy and for 2 days afterward, if appropriate [8].

Aprepitant is solely available as oral capsules of 125 mg and 80 mg strength. Standard dose is 125 mg 1 h prior to chemotherapy administration on day 1, followed by 80 mg once daily on the morning of days 2 and 3 [11]. Dexamethasone is recommended at a dose of 6 mg/m^2 every 6 hourly administered orally (PO) or intravenous (IV) (dose halved if aprepitant is being used concomitantly, as it doubles the area under the curve of dexamethasone) [11,15]. Ondansetron is administered at a dose of 5 mg/m^2 (0.15 mg/kg) PO/IV 30 min prior to chemotherapy followed by 8 hourly doses [11]. Alternatively, granisetron can replace ondansetron as a once daily IV dose of 40 μg/kg [11]. Although, the guideline recommends aprepitant in children aged >12 years, two recently published randomized control trials (RCT) have shed new light on the use of aprepitant in younger children [16,17]. Kang et al. performed a multicenter phase-3 randomized control trial in 307 children aged between 6 months and 17 years [16]. Oral suspensions of aprepitant were prepared for the trial, and doses of 3 mg/kg on day 1 and 2 mg/kg on day 2 were used in children aged <12 years, while standard dose with 125 mg/80 mg capsules was used in older children [16]. Complete response in the delayed phase was 51% as compared to 26% in the control arm ($p < 0.0001$) [16]. Grade 3–4 events such as febrile neutropenia did not differ between the two

arms [16]. Bakhshi et al. performed a phase-3 RCT in 96 children aged 5–18 years [17]. Children weighing 15–40 kg were administered 80 mg on all 3 days, while standard dosing was followed in heavier children [17]. Complete response was 48% as compared to 12% in patients receiving ondansetron/dexamethasone alone ($p < 0.0001$) with no increase in adverse events [17]. Currently aprepitant is approved for all children older than 12 years as well as those who are younger but weighing >30 kg and with ability to swallow capsules [18].

With current evidence of superiority and safety of aprepitant as prophylaxis for acute AINV in children, it may be prudent to offer the drug in all children receiving HEC, who are old enough to swallow capsules. As practiced by Bakhshi et al., 80 mg dose on all 3 days can be utilized for younger children who weigh 15–40 kg [17]. Besides age, drug interactions potentially limit the use of aprepitant. Aprepitant, being an inhibitor of the CYP3A4 isoenzyme, can potentially interact with several antineoplastic drugs which are metabolized by CYP3A4. These include vinca alkaloids, taxanes, etoposide, irinotecan, ifosfamide, thiotepa and tyrosine kinase inhibitors such as imatinib and dasatinib [11,15]. However, the following reasons offset the concern arising from such potential interactions. Firstly, aprepitant induced CYP3A4 may be more relevant for oral drugs rather than intravenously administered drugs [15]. The enzyme inhibitory effect of aprepitant is moderate and only marginally significant in comparison to other inhibitors such as rifampin and ketoconazole [15]. Further, there is paucity of evidence demonstrating clinically significant interaction between aprepitant and the above mentioned antineoplastic drugs [15]. The interaction of aprepitant with ifosfamide and cyclophosphamide is noteworthy. While CYP3A4 does not play a major role in the metabolism of cyclophosphamide, it is involved in the metabolism and activation of ifosfamide. Therefore, while the former drug is not affected by aprepitant, combination with ifosfamide is associated with risk of precipitating neurotoxicity by interfering with its metabolism [15,19,20]. ASCO guideline recommends use of aprepitant in all HEC protocols, in adults [8]. Other drugs which merit caution while being simultaneously administered with aprepitant include warfarin (requires close monitoring of international normalized ratio for two weeks after aprepitant administration) and oral contraceptives (necessitates secondary method of contraception) [15]. Fosaprepitant, a single dose IV pro-drug which has been approved in patients >18 years, is yet to be validated in children.

Antiemetic schedule in Case 1: Capsule aprepitant 80 mg 1 h was administered PO prior to chemotherapy on day 1, followed by 80 mg once daily on days 2 and 3. Ondansetron 4 mg IV (5 mg × BSA 0.76) was given 30 min prior to chemotherapy followed by 8 hourly doses (Alternatively, granisetron 0.8 mg (40 μg × body weight 19 kg) can be administered as a single dose). Dexamethasone 2 mg (6 × BSA 0.76 = 4 mg, halved as aprepitant being given) was administered every 6 hourly.

5.1.2. Prophylaxis for acute AINV in chemotherapy regimens with moderate emetic risk (MEC)

Case 2. *An 8-year-old boy weighing 22 kg and having BSA of 0.84 receiving treatment for metastatic neuroblastoma failed to respond to conventional chemotherapy and was planned for salvage chemotherapy with topotecan/cyclophosphamide regimen. The regimen scheduled was as follows: topotecan (0.75 mg/m^2/day) and cyclophosphamide (250 mg/m^2/day) for 5 days. Plan antiemetic prophylaxis.*

The regimen described in Case 2 is MEC (topotecan has low emetic risk while cyclophosphamide daily dose of 250 mg/m^2 has moderate emetic risk). Recommended combination for MEC includes ondansetron/granisetron and dexamethasone [11]. This is mirrored by the ASCO guideline, which additionally mentions palonosetron as the preferred 5-HT3-receptor blocker for MEC [8,9]. Ondansetron is administered at a dose of 5 mg/m^2 (0.15 mg/kg) PO/IV 30 min prior to chemotherapy followed by 12 hourly doses [11]. Alternatively, granisetron can replace ondansetron as a once daily IV dose or twice daily oral dose of 40 μg/kg [11]. Dexamethasone is recommended at the following dose: 2 mg/dose IV/PO q 12 hourly for BSA <0.6 and 4 mg/dose IV/PO q 12 hourly for BSA ≥0.6 [11].

Antiemetic schedule in Case 2: Granisetron was administered as a single daily dose of 0.9 mg (40 μg × body weight 22 kg) IV prior to chemotherapy and dexamethasone was administered at a dose 4 mg every 12 hourly (BSA > 0.6).

5.1.3. AINV prophylaxis in HEC/MEC where dexamethasone is contraindicated

Case 3. *A 2.5-year-old boy weighing 12 kg and BSA 0.54 with medulloblastoma underwent complete resection of tumor. The pediatric oncologist decided to proceed with chemotherapy as the child was too young for craniospinal irradiation. The chemotherapy cycle scheduled included cisplatin (3.5 mg/kg) on day 1; vincristine (0.05 mg/kg) on days 1, 8, and 15; etoposide (4 mg/kg/d) followed by cyclophosphamide (65 mg/kg/d) with mesna on days 2 and 3 and methotrexate (400 mg/kg) on day 4 with leucovorin rescue. How should one go about charting an antiemetic prophylaxis schedule?*

Certain chemotherapy protocols discourage use of dexamethasone, such as those used in acute myeloid leukemia where steroids can cause additional immunosuppression and increased invasive fungal infections; and brain tumors where steroids can interfere with distribution of chemotherapeutic drugs into the CNS compartment [21]. Further, physician discretion, parental preference, and steroid already being an integral component of the chemotherapy regimen can inhibit the use of dexamethasone as an antiemetic [21]. The POGO guideline recommends combination of 5HT3-receptor antagonist along with either of chlorpromazine/nabilone for HEC and either of metoclopramide/chlorpromazine/nabilone for MEC [11].

Chlorpromazine is recommended at a starting dose of 0.5 mg/kg (may be increased up to 1 mg/kg) IV every 6 hourly [11]. It is safer to be administered in-patient due to risk of sedation and hypotension [11]. Diphenhydramine/benztropine can be added to prevent extrapyramidal effects [11]. Nabilone is an alternative drug for combining with 5HT3 receptor blocker with the following dose: <18 kg body weight: 0.5 mg/dose PO twice daily; 18–30 kg: 1 mg/dose PO twice daily; >30 kg: 1 mg/dose PO three times daily [Maximum daily dose: 0.06 mg/kg/day] [11]. Its use is however off set by adverse effects such as dysphoria, dizziness and hallucinations [14]. Metoclopramide is recommended for MEC rather than HEC, as an RCT demonstrated superior control in low to moderate emetic risk as compared to high risk (74% versus 11%) [22]. A meta-analysis of studies evaluating pediatric use of metoclopramide concluded that commonest adverse effects were extrapyramidal symptoms, sedation and diarrhea which were completely reversible [23]. Recommended dose in the POGO guideline is 1 mg/kg IV pre-chemotherapy followed by 0.0375 mg/kg PO every 6 hourly [11]. The author prefers to use metoclopramide over chlorpromazine and nabilone even in regimens with high emetic risk due to paucity of experience of using chlorpromazine/nabilone in children. The recommended dose in children is: 1–3 yr (10–14 kg)–1 mg TDS; >3–5 yr (15–19 kg)–2 mg TDS; >5–9 yr (20–29 kg)–2.5 mg TDS; >9–18 yr (30–60 kg): 5 mg TDS [maximum duration: 48 h] [24]. The POGO guideline discourages use of metoclopramide in children aged less than 1 year due to concern of extrapyramidal symptoms [4].

Antiemetic schedule in Case 3: Protocol is HEC as it contains cisplatin. Steroids were avoided as it was a CNS malignancy. Ondansetron was administered at a dose of 2.5 mg (5 × BSA 0.54) IV prior to chemotherapy on day 1 and 8 hourly subsequently. Metoclopramide was administered at a dose of 1 mg TDS PO [as per CIMS dosing recommendation].

5.1.4. Prophylaxis for AINV in chemotherapy regimens with low and minimal emetic risk

Single agent prophylaxis with 5HT3-receptor antagonist is sufficient for chemotherapy with low emetic risk: ondansetron 10 mg/m^2 [0.3 mg/kg, maximum 16 mg/day] single dose IV/PO prior to chemotherapy [8,11]. Granisetron can be used alternatively in the same dose as for MEC [11]. There is no need for routine prophylaxis for chemotherapy with minimal emetic risk [8,11].

5.2. Management of breakthrough and refractory AINV

Case 4 part 1. *A 15-year-old boy weighing 35 kg (BSA 1.2) with osteosarcoma of femur was planned for first cycle of neoadjuvant chemotherapy with methotrexate, doxorubicin and cisplatin. The cycle involved administration of cisplatin and doxorubicin on days 1 and 2 followed 3 weeks later by high-dose methotrexate. He received cap. aprepitant 125 mg on day and 80 mg on days 2 and 3; Inj. granisteron 1.4 mg IV once daily as well as Inj. dexamethasone 4 mg 6 hourly during the chemotherapy block. Despite prophylaxis, he developed debilitating vomiting from night of day 1. He remained admitted for 2 days after completion of chemotherapy for intravenous hydration as he had continuous vomiting and almost nil oral intake.*

Case 4 exemplifies a case of breakthrough AINV, that occurs in the acute/delayed phase despite adequate prophylaxis and not attributable to any other pathological case. The most important aspect of AINV management is prevention by providing an adequate and robust antiemetic prophylaxis [3]. Options for managing breakthrough and refractory AINV are limited. For patients who experience breakthrough AINV after prophylaxis for LEC/MEC, the prophylaxis can be escalated to the next higher risk (e.g. prophylaxis recommended for HEC can be given to a child who develops breakthrough AINV after prophylaxis recommended for MEC) [4]. If a patient has already received complete prophylaxis as recommended for HEC, olanzapine is a reasonable option [4]. An adult phase 2 trial has demonstrated safety and effectiveness of olanzapine in breakthrough AINV [25]. Although prospective data is lacking, a retrospective multi-centric review of pediatric use of olanzapine for AINV demonstrated up to 65% control of AINV with a single daily dose of 0.1 mg/kg/day and no major adverse events other than dose related sedation [26]. Other less frequent adverse events which are reversible and minor include extrapyramidal symptoms and ECG changes [4]. IV administration is not recommended. Due to metabolism by CYP1A2 enzyme, its use is discouraged in patients receiving drugs which inhibit/induce the enzyme such as carbamazepine, rifampicin and ciprofloxacin [4]. Alternatives for patients who are not eligible to receive olanzapine include levomepromazine and metoclopramide [4]. Levomepromazine is recommended at a dose of 0.25 mg/kg/day in 2–3 divided doses [maximum 40 mg/day] but experience in children is lacking [4]. Metoclopramide is a reasonable option in children who have completed 1 year of age (Dose described earlier) [4].

AINV is said to be refractory if AINV ensues in a patient during acute/delayed phase subsequent to an episode of breakthrough AINV in the prior block of chemotherapy. In other words, AINV occurs despite prophylaxis as well as prior management of breakthrough AINV [4]. Once again, the option of escalating prophylaxis is available for patients who have received prophylaxis for MEC/LEC [4]. If prophylaxis has already been for HEC, the POGO guideline recommends changing 5HT3-R antagonist from ondansetron/granisetron to palonosetron [4]. Palonosetron is approved for children aged >1 month at a single stat dose of 20 μg/kg (maximum 1.5 mg) infused IV over 15 min, 30 min prior to start of chemotherapy [27]. If palonosetron is unavailable, one can consider switching from ondansetron to granisetron, as some individuals may have rapid metabolism of ondansetron due to enzyme polymorphisms [4].

Case 4 part 1 *management: The boy had already received complete prophylaxis for HEC. Olanzapine was added at dose of 5 mg PO daily. Vomiting reduced significantly albeit with some drowsiness after starting the drug. After 3 days, olanzapine was stopped and he was discharged.*

5.3. Management of anticipatory AINV

Case 4 part 2. *The same patient described in Case 4 was scheduled for next cycle of chemotherapy. He developed nausea and retching from the evening previous to hospital visit. Vomiting ensued even as he entered the hospital premises and prior to starting chemotherapy.*

The scenario presented above is characteristic of anticipatory AINV which precedes administration of chemotherapy, and is predominantly attributed to the AINV experienced in acute/delayed phase of the prior chemotherapy blocks [5,7]. It may be triggered by sights, sounds, odors, thoughts and anxiety associated with the prior chemotherapy experience, similar to a conditioned response [3]. It is evident that, greater the control of AINV during acute/delayed phase, lesser would be the chance of developing anticipatory AINV. An important aspect of ensuring optimal antiemetic prophylaxis is following a standard guideline for all patients. A recently published survey which evaluated the practice of prescribing antiemetic prophylaxis within the Children's oncology group (COG), reported significant diversity among the COG sites [28]. Differences were especially noted in dosing of dexamethasone, choice of anti-emetics when steroids were contraindicated, aprepitant use in children <12 years and use of aprepitant concomitantly with drugs with known interactions [28].

Once anticipatory AINV ensues, limited options include two doses of lorazepam 0.04–0.08 mg/kg PO (maximum 2 mg) administered the night prior to the day of chemotherapy as well as the next day morning prior to start of chemotherapy [5]. Though evidence for its use in AINV is lacking, there is extensive experience for the safe use of lorazepam in pediatric patients [5]. Non pharmacological measures such as hypnosis and systemic desensitization have also shown benefit, and may be attempted in centers possessing necessary resources and skills [5].

6. Non pharmacological interventions in AINV

Pharmacological intervention does not constitute the sole aspect of managing AINV. Dietary counseling is important. Some useful dietary advice includes: consumption of 'mini meals' (frequent and small quantities); avoiding strong aromas/odors in food; drinking liquids from closed containers through straws; avoiding excessively salty, sweet, spicy or greasy food; sitting for at least an hour after eating and timing anti-emetics prior to meals [11,29]. Favorite food items are better avoided during chemotherapy blocks. Adult studies have shown role for citrus extracts and ginger in reducing AINV [30].

Several non-pharmacological interventions can be tried in children, especially in those who have anticipatory and refractory AINV. These include: hypnosis, acupuncture, acupressure, guided imagery, music therapy, progressive muscle relaxation techniques and psychoeducational support [5,11,30]. These may benefit only a proportion of children but carry minimal risk of adverse events.

7. Conclusion

Accurate prescription of anti-emetics is critical to ensure optimum control of AINV in children. Encouraging evidence for the use of aprepitant in younger children is emerging. Adherence to standard guidelines can facilitate adequate prophylaxis and prevent breakthrough and anticipatory AINV.

Source of funding

Nil.

Competing interest

Nil.

Acknowledgements

Dr. Deepak Bansal (Professor, Hematology-Oncology, Advanced Pediatric Center, PGIMER, Chandigarh) is gratefully acknowledged for his suggestions and contribution of literature for the review.

References

[1] Dupuis LL, Milne-Wren C, Cassidy M, Barrera M, Portwine C, Johnston DL, et al. Symptom assessment in children receiving cancer therapy: the parents' perspective. Support Care Cancer 2010;18:281–99.

[2] Jordan K, Sippel C, Schmoll H-J. Guidelines for antiemetic treatment of chemotherapy-induced nausea and vomiting: past, present, and future recommendations. Oncol 2007;12:1143–50.

[3] Dewan P, Singhal S, Harit D. Management of chemotherapy-induced nausea and vomiting. Indian Pediatr 2010;47:149–55.

[4] Flank J, Robinson PD, Holdsworth M, Phillips R, Portwine C, Gibson P, et al. Guideline for the treatment of breakthrough and the prevention of refractory chemotherapy-induced nausea and vomiting in children with cancer. Pediatr Blood Cancer 2016;63:1144–51.

[5] Dupuis LL, Robinson PD, Boodhan S, Holdsworth M, Portwine C, Gibson P, et al. Guideline for the prevention and treatment of anticipatory nausea and vomiting due to chemotherapy in pediatric cancer patients. Pediatr Blood Cancer 2014;61:1506–12.

[6] Lohr L. Chemotherapy-induced nausea and vomiting. Cancer J 2008;14:85–93.

[7] Flank J, Dupuis LL. Comparative effectiveness research in antineoplastic-induced nausea and vomiting control in children. J Comp Eff Res 2014;3:185–96.

[8] Basch E, Hesketh PJ, Kris MG, Prestrud AA, Temin S, Lyman GH. Antiemetics: American society of clinical oncology clinical practice guideline update. J Oncol Pract 2011;7:395–8.

[9] Hesketh PJ, Bohlke K, Lyman GH, Basch E, Chesney M, Clark-Snow RA, et al. Antiemetics: American society of clinical oncology focused guideline update. J Clin Oncol 2016;34:381–6.

[10] Dupuis LL, Boodhan S, Sung L, Portwine C, Hain R, McCarthy P, et al. Guideline for the classification of the acute emetogenic potential of antineoplastic medication in pediatric cancer patients. Pediatr Blood Cancer 2011;57:191–8.

[11] Dupuis LL, Boodhan S, Holdsworth M, Robinson PD, Hain R, Portwine C, et al. Guideline for the prevention of acute nausea and vomiting due to antineoplastic medication in pediatric cancer patients. Pediatr Blood Cancer 2013;60:1073–82.

[12] Search Drug Information, Interactions, Images, Dosage & Side Effects | CIMS India [Internet]. [cited 2016 Aug 8]. Available from: http://www.mims.com/.

[13] Vidall C, Fernández-Ortega P, Cortinovis D, Jahn P, Amlani B, Scotté F. Impact and management of chemotherapy/radiotherapy-induced nausea and vomiting and the perceptual gap between oncologists/oncology nurses and patients: a cross-sectional multinational survey. Support Care Cancer 2015;23:3297–305.

[14] Perwitasari DA, Gelderblom H, Atthobari J, Mustofa M, Dwiprahasto I, Nortier JWR, et al. Anti-emetic drugs in oncology: pharmacology and individualization by pharmacogenetics. Int J Clin Pharm 2011;33:33–43.

[15] Aapro MS, Walko CM. Aprepitant: drug-drug interactions in perspective. Ann Oncol Off J Eur Soc Med Oncol ESMO 2010;21:2316–23.

[16] Kang HJ, Loftus S, Taylor A, DiCristina C, Green S, Zwaan CM. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting in children: a randomised, double-blind, phase 3 trial. Lancet Oncol 2015;16:385–94.

[17] Bakhshi S, Batra A, Biswas B, Dhawan D, Paul R, Sreenivas V. Aprepitant as an add-on therapy in children receiving highly emetogenic chemotherapy: a randomized, double-blind, placebo-controlled trial. Support Care Cancer 2015;23:3229–37.

[18] FDA approval for oral suspension of aprepitant.pdf [Internet]; [cited 2016 Aug 4]. Available from: http://www.accessdata.fda.gov/drug satfda_docs/label/2015/207865lbl.pdf.

[19] Howell JE, Szabatura AH, Hatfield Seung A, Nesbit SA. Characterization of the occurrence of ifosfamide-induced neurotoxicity with concomitant aprepitant. J Oncol Pharm Pract 2008;14:157–62.

[20] Durand J-P, Gourmel B, Mir O, Goldwasser F. Antiemetic neurokinin-1 antagonist aprepitant and ifosfamide-induced encephalopathy. Ann Oncol 2007;18:808–9.

[21] POGO_Acute_AINV_Full_Guideline_Feb_28_2013pdf [Internet]. [cited 2016 Aug 4]. Available from: http://www.pogo.ca/_media/File/guidelines/POGO_Acute_AINV_Full_Guideline_Feb_28_2013.pdf.

[22] Köseoglu V, Kürekçi AE, Sarici U, Atay AA, Ozcan O, Sorici U. Comparison of the efficacy and side-effects of ondansetron and metoclopramide-diphenhydramine administered to control nausea and vomiting in children treated with antineoplastic chemotherapy: a prospective randomized study. Eur J Pediatr 1998;157:806–10.

[23] Lau Moon Lin M, Robinson PD, Flank J, Sung L, Dupuis LL. The safety of metoclopramide in children: a systematic review and meta-analysis. Drug Saf 2016;39:675–87.

[24] Metoclopramide Full Prescribing Information, Dosage & Side Effects | CIMS India [Internet]. [cited 2016 Aug 4]. Available from: http://www.mims.com/india/drug/info/metoclopramide/?type=full&mtype=generic#Dosage.

[25] Chanthawong S, Subongkot S, Sookprasert A. Effectiveness of olanzapine for the treatment of breakthrough chemotherapy induced nausea and vomiting. J Med Assoc Thai 2014;97:349–55.

[26] Flank J, Thackray J, Nielson D, August A, Schechter T, Alexander S, et al. Olanzapine for treatment and prevention of acute chemotherapy-induced vomiting in children: a retrospective, multi-center review. Pediatr Blood Cancer 2015;62:496–501.

[27] aloxi - pipdf [Internet]. [cited 2016 Aug 5]. Available from: http://www.aloxi.com/docs/pdf/pi.pdf.

[28] Patel P, Robinson PD, Orsey A, Freedman JL, Langevin A-M, Woods D, et al. Chemotherapy-induced nausea and vomiting prophylaxis: practice within the Children's oncology group. Pediatr Blood Cancer 2016;63:887–92.

[29] Nutrition for Children with Cancer [Internet]. [cited 2016 Aug 5]. Available from: http://www.cancer.org/treatment/childrenandcancer/whenyourchildhascancer/nutritionforchildrenwithcancer/index.

[30] Sheikhi MA, Ebadi A, Talaeizadeh A, Rahmani H. Alternative methods to treat nausea and vomiting from Cancer chemotherapy. 818759 Chemother Res Pract 2015;2015. http://dx.doi.org/10.1155/2015/818759. Epub 2015 Nov 8.