PSUMJ
PSU MEDICAL JOURNAL

Review Article

Chemotherapy Induced Nausea and Vomiting in Children: A Literature Review and Recommendation for Antiemetic Prophylaxis in Resource Limited Countries

Pornpun Sripornsawan, M.D.[1], Kwanruethai Sengnoo, Pharm.D.[2]

[1]Department of Pediatrics, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.
[2]Pharmacy Division, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.

ABSTRACT

Chemotherapy induced nausea and vomiting (CINV) are the most common side effects that impacts quality of life in children receiving cancer treatment. Inadequately controlled CINV impairs functional activity increases the health-care utilization and compromises treatment adherence. The availability of new antiemetic agents results in substantially improvement of emetic control; however, in real-world practice, many developing countries have limited access to newly-developed antiemetic agents. This is a major obstacle in achieving adequate CINV control. Recent studies have recommended the “triple therapy” regimen (a 5-HT3 antagonist, dexamethasone, and a neurokinin-1 antagonist), as the backbone for antiemetic prophylaxis. Olanzapine, an atypical antipsychotic drug that improves CINV control in adult cancer patients. Together with ‘triple therapy” olanzapine is now recommended as the first line CINV prophylaxis in adults receiving highly emetogenic chemotherapy.

Herein, we reviewed the recent published guidelines for the prevention and treatment of CINV in children. Furthermore, due to limited drug accessibility to neurokinin-1 antagonists, we proposed an institutional CINV guideline to replace the neurokinin-1 antagonist with olanzapine, which might be more reasonable in terms of economic constraints in resource limited countries.

Keywords: antiemetic agents; chemotherapy induced nausea and vomiting; childhood cancer; guidelines

Corresponding author: Pornpun Sripornsawan, M.D.
Department of Pediatrics, Faculty of Medicine, Prince of Songkla University,
Hat Yai, Songkhla 90110, Thailand.
E-mail: spornpun@medicine.psu.ac.th
doi: 10.31584/psumj.2022250660
https://he01.tci-thaijo.org/index.php/PSUMJ/

PSU Med J 2022;2(1):25-32
Received 23 July 2021
Revised 10 August 2021
Accepted 10 August 2021
Published online 22 January 2022

INTRODUCTION

Chemotherapy induced nausea and vomiting (CINV) are the most common side effects among children with cancer, who receive chemotherapy. It often causes an unpleasant experience, affects the patient's quality of life as well as their treatment adherence.

Recently, in 2017, the Pediatric Oncology Group of Ontario (POGO) published guidelines for the emetogenic classification of antineoplastic agents, prevention, and treatment of breakthrough and refractory CINV in children. Additionally, the "Antiemetics: ASCO Update", developed by the American Society of Clinical Oncology, has been endorsed by the Children's Oncology group (COG): December 2020. These guidelines comprised of series of evidence-based guidelines for children with cancer.[1,2] Therefore, as detailed below, we reviewed the published article, and the latest version of available guidelines for the prevention and treatment of chemotherapy-induced nausea and vomiting in children.

DEFINITIONS

Nausea is defined as a subjective experience of impending emesis. Vomiting is defined as expulsion of stomach contents through the mouth.[3]

1. Acute CINV is defined as nausea/vomiting, presumed to be attributable to chemotherapy that occurs within the first 24 hours (hr) after completion of chemotherapy.[3,4]

2. Delayed CINV is defined as nausea/vomiting, presumed to be attributable to chemotherapy that occurs after the first 24 hr. Delayed CINV can last for 3-5 days after completing chemotherapy. It often occurs in cases of poor control of acute CINV, or specific chemotherapeutic agents; such as cisplatin. It is recommended to administer antiemetic drugs for at least 24-48 hr for those who receive platinum-based chemotherapy, so as to prevent delayed CINV.[3,4]

3. Anticipatory CINV is defined as nausea/vomiting that occurs before receiving chemotherapy. It is usually caused by patient anxiety, and bad experiences from previous chemotherapy blocks.[5]

4. Breakthrough CINV is defined as nausea/vomiting, presumed to be attributable to chemotherapy, and with no other pathologic cause that occurs; despite CINV prophylaxis.[6]

5. Refractory CINV is defined as nausea/vomiting, presumed to be attributable to chemotherapy, and with no other pathologic cause that occurs; despite CINV prophylaxis in patients who have experienced breakthrough CINV in a previous chemotherapy block.[6]

PATHOPHYSIOLOGY OF CINV

The pathophysiology of CINV involves complex multifactorial mechanisms between several neurotransmitters and receptors in the central nervous system, and gastrointestinal tract. Current studies show the mechanism is composed of two different mechanisms.[7]

1. Peripheral pathway originates in the gastrointestinal tract, which is activated during the first 24 hr of chemotherapy administration. Therefore, it is mainly responsible for acute CINV. This process is mainly initiated by serotonin release from enterochromaffin cells located in intestinal mucosa, serotonin. These then bind to the 5-hydroxytryptamine type 3 receptors (5-HT3) on vagal afferent nerves, and send the signal through the chemotherapy trigger zone (CTZ) in the area of the postrema to the vomiting center within the medulla.

2. Central pathway occurs primarily in the brain, and it is mainly responsible for delayed CINV; although the induction of acute emesis can also occur through this pathway. Chemotherapy stimulates substance P release from both the peripheral and central nervous systems, but it mostly binds to neurokinin 1 (NK1) receptors in the neu-

ral networks of the central nervous system. This results in the direct activation of both CTZ and the vomiting center.

CLASSIFICATION OF CHEMOTHERAPY EMETOGENICITY

The classification of chemotherapy emetogenicity is very important for the appropriate selection of antiemetic prophylaxis. Especially, in chemotherapy-naive pediatric patients; wherein, the emetogenicity of chemotherapy remains the most important determinant of CINV in providing suitable CINV prophylaxis regimens. Emetogenicity classifications are based on the incidence of vomiting in the absence of antiemetic prophylaxis in chemotherapy naïve patients. Chemotherapy is classified into 4 categories[8] (Table 1).

1. Minimal emetogenic chemotherapy: the incidence of vomiting in the absence of prophylaxis less than 10%, usually not requiring antiemetic prophylaxis. Most clinical practice guidelines recommend not administrating CINV prophylaxis for this group.

2. Low emetogenic chemotherapy: the incidence of vomiting in the absence of prophylaxis at approximately 10-30%, COG supportive care-endorsed guidelines recommend a single daily dose of 5-HT3 antagonist; such as, ondansetron or granisetron as the following:

- Ondansetron 10 mg/m^2/dose (0.3 mg/kg/dose; maximum 16 mg/dose) intravenously, as a single daily dose.

- Granisetron 40 mcg/kg/dose intravenously, as a single daily dose.

3. Moderately emetogenic chemotherapy (MEC): incidence of vomiting in the absence of CINV prophylaxis of about 30-90%, COG supportive care endorsed guidelines recommend the combination of 2 drugs, comprising of: 5-HT3 antagonists (granisetron, ondansetron, or palonosetron), plus dexamethasone or 5-HT3 antagonist plus aprepitant, for children who cannot tolerate dexamethasone.

4. Highly emetogenic chemotherapy (HEC): incidence of CINV is usually more than 90%, and multiple-agent

Table 1 Classification of chemotherapy emetogenicity[8]

Groups	Minimal emetogenic	Low emetogenic	Moderately emetogenic	Highly emetogenic
Emetogenic risk	< 10%	10 – 30%	> 30 – 90%	> 90%
Example	Asparaginase	Cytarabine < 200 mg/m^2	Arsenic trioxide	Busulfan
	Bleomycin	Docetaxel	CTX < 1 g/m^2	CTX ≥ 1 g/m2
	Bevacizumab	Etoposide	Cytarabine > 200	Cytarabine ≥ 3 g/m2
	Fludarabine	5-FU	to < 3 g/m^2	Carboplatin
	Hydroxyurea	Gemcitabine	Daunorubicin	Cisplatin
	Imatinib / Dasatinib	MTX > 50 to < 250 mg/m^2	Doxorubicin	Dactinomycin
	Mercaptopurine	Mitoxantrone	Idarubicin	Dacarbazine
	MTX (oral/IT)	Paclitaxel	Ifosfamide	Melphalan
	Rituximab	Temozolomide	Irinotecan	MTX ≥ 12 g/m^2
	Sorafenib	Thiotepa < 300 mg/m^2	MTX > 250 mg	Thiotepa ≥ 300 mg/m^2
	Thioguanine	Topotecan	to < 12 g/m^2	Multiple agent
	Vinblastine		Oxaliplatin	- CTX + anthracyclin
	Vincristine		Triple IT*	- CTX + Etoposide
	Vinorelbine			- Etoposide+ Ifosfamide

5-FU = Fluorouracil; CTX = Cyclophosphamide; IT = intrathecal; MTX = Methotrexate

regimens that are commonly used in Thai-pediatric oncology group (Thai-POG) usually fall into this category. For example: Bleomycin-Etoposide-Cisplatin (BEP) regimen or Infosfamid-Carboplatin-Etoposide (ICE) regimen. Hence, COG & POGO recommends a triple-agents regimen, comprising of: 5-HT3 antagonists (granisetron, ondansetron, or palonosetron), plus dexamethasone and aprepitant. However, aprepitant should be omitted in children younger than 6 months.[9]

ANTIEMETIC AGENTS

Antiemetic agents to prevent CINV consist of a large variety and different drug classes. These agents can be classified as agents with high therapeutic index or agents with high therapeutic index.[3]

Agents with a high therapeutic index

5-HT3 antagonists

Currently, five 5-HT3 antagonists are available: ondansetron, granisetron, dolasetron, tropisetron, and palonosetron[8], and these drugs have remained the main-stay of treatment for CINV for many years. Of these, the three commonly used in pediatric populations are: ondansetron, granisetron and palonosetron. For children receiving highly emetogenic chemotherapy, POGO recommends a triple antiemetic prophylaxis; including, 5-HT3 antagonists (ondansetron, granisetron or palono-setron), dexamethasone and aprepitant (≥ 6 months of age and receiving chemotherapy, which are not known to interact with aprepitant), or a two drug combination in children age < 6 months, or receiving chemotherapy known to interact with aprepitant.[9,10] At the approved dosage, the single daily dose schedule has similar efficacy to a multiple dose schedule. However, these agents have limited efficacy to prevent delayed CINV; especially in patients receiving cisplatin. Of these palonosetron, a second generation 5-HT3 antagonist, is a highly effective agent in children. Additionally, it has a prolonged half-life (approximately 40 hr) and greater binding affinity for the 5-HT3 receptor. Furthermore, it has demonstrated its superiority to first generation 5-HT3 antagonists; including, ondansetron and granisetron, in the prevention of CINV.[11,12] Although, adverse effects include mild headaches, transient elevation of hepatic enzymes and constipation, they are usually limited and have limited toxicity at regular doses.[12]

Corticosteroids

Corticosteroids were first shown to be effective antiemetic drugs to prevent both acute and delayed CINV in children over the last three decades[2]; however, they are more beneficial when combined with other antiemetic agents. Current clinical practice guidelines for CINV prevention strongly recommend that children who received HEC should also receive dexamethasone in combination with 5-HT3 antagonist and aprepitant. However, when corticosteroid is given with a moderate cytochrome P-450 3A4 inhibitor apprepitant, doses should be reduced by approximately 50%.[10]

Dexamethasone is the corticosteroid that has most frequently been studied, and 5-HT3 antagonists with dexamethasone added are effective in patients receiving HEC.[13] Scaled pediatric dexamethasone doses, based on the recommended dose for adults (20 mg/day for HEC and 8 mg/day for MEC), suggested dexamethasone dos-ing for CINV prevention in the absent of NK-1 receptor antagonist as follows[14]

HEC age ≤ 1 yr: 0.3 mg/kg and age > 1 yr: 12 mg/m^2

MEC age ≤ 1 yr: 0.11 mg/kg and age > 1 yr: 4.6 mg/m^2

The most common adverse effects are steroid induced acne, increased appetite, insomnia and gastroin-testinal symptoms.[9]

Neurokinin-1-receptor antagonists

The neurokinin-1-receptor antagonists represent the latest class of antiemetic agents that are highly

effective for CINV prevention. Aprepitant (Emend®, Merck) was approved by the Food and Drug Administration (FDA) in 2003 in an oral formulation. Aprepitant is a moderate inhibitor of the cytochrome P-450 3A4 (CYP3A4) pathway. Corticosteroids are also metabolized by this pathway; therefore, when aprepitant was given in combination with dexamethasone, the plasma concentration of dexamethasone would be increased. The use of a NK-1 receptor antagonist was previously restricted to children 12 years and older, and only a 5-HT3 antagonist and dexamethasone was recommended as prophylaxis; even for those who were receiving HEC.[5] Not until recently, has the data been expanded for the use of aprepitant in children receiving HEC from 6 months of age,[14] as per the current updated recommendations.[9,10] The most common side effects are fatigue, hiccups, and dyspepsia.[15]

Agents with a low therapeutic index

Metoclopramide

The efficacy of metoclopramide improves with increasing doses, as it has the capacity to inhibit 5-HT3 receptors at higher blood levels. The recommend dose is 1-2 mg/kg (maximum 25 mg) before chemotherapy, and then every 6 hr after. Current guidelines recommend the use of metoclopramide as an alternative additive drug to treat breakthrough, or refractory CINV in children older than 1 year who cannot receive olanzapine.[6,16]

The most common, reported adverse effects, associated with the use of metoclopramide in children, are extrapyramidal side effects (9%), diarrhea (6%) and sedation (6%); all of which are reversible. Life threatening adverse events have been rarely associated with this drug when used in children. To prevent extrapyramidal side effects, diphenhydramine should be prescribed, and the use of metoclopramide in children < 5 years should be limited to 5 days.[17]

Olanzapine

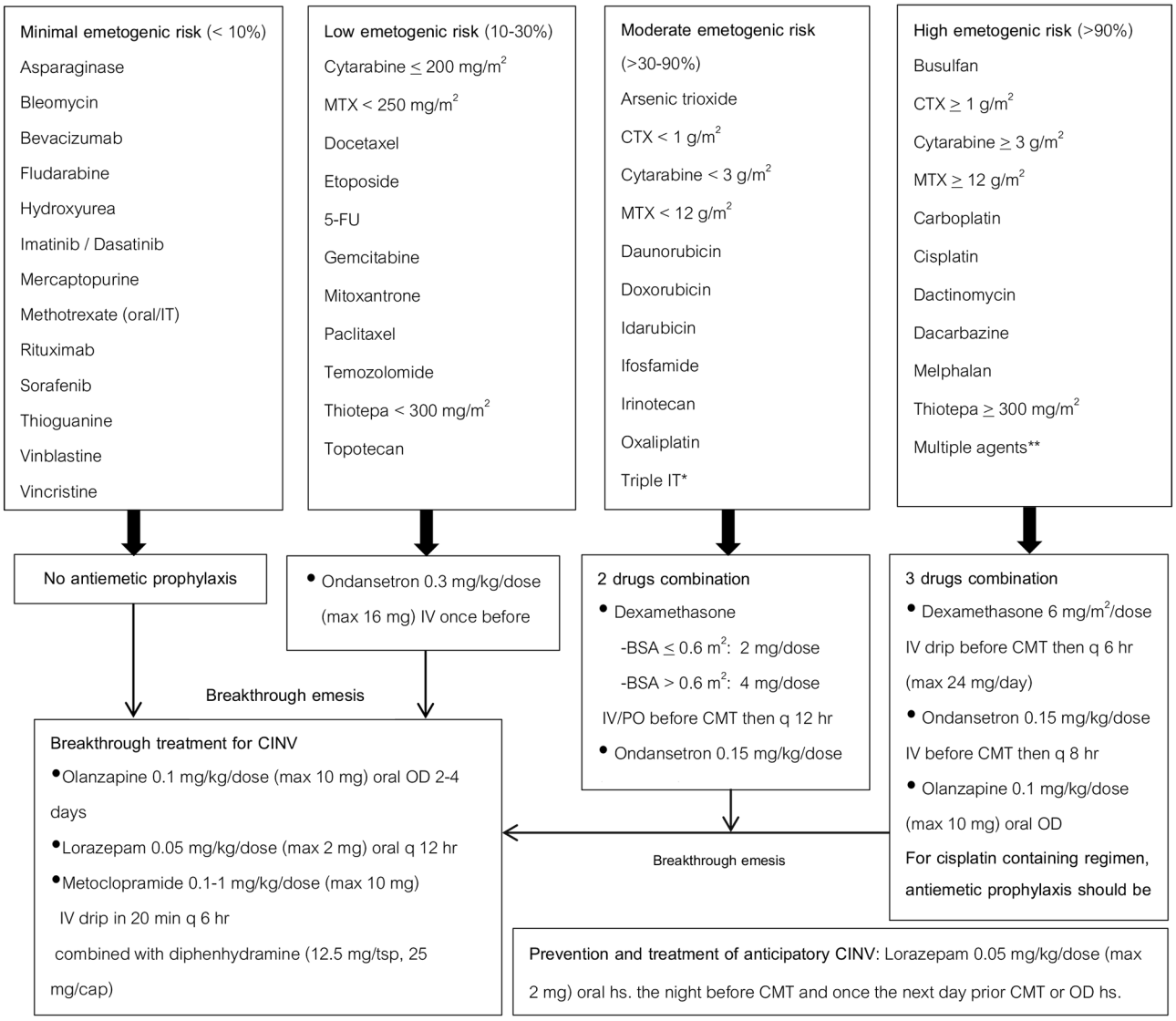
Olanzapine is approved by the FDA as an antipsychotic agent. It blocks multiple neurotransmitter receptors; including, dopaminergic (D_1-D_4 receptors; 5-HT2a, 5-HT2c, 5-HT3 and 5-HT6 serotonergic receptors; alpha-1 adrenergic, muscarinic and histaminic receptors. A large, randomized, double-bind, placebo-controlled, phase 3 trial in adults receiving HEC showed that combining olanzapine with dexamethasone and palonosetron was very effective at controlling both acute (complete response 97%) and delayed emesis (complete response 97%); and at least as effective as aprepitant, dexamethasone and palonosetron to prevent CINV.[18] Interestingly, olanzapine also has superior efficacy for controlling nausea when compared to NK1-receptor antagonists.[19]

For breakthrough CINV, olanzapine was superior to metoclopramide to treat breakthrough emesis. Therefore, olanzapine is currently recommended for the treatment of breakthrough and refractory CINV in children.[6] Olanzapine significantly improved CINV control rates in children, when administered along with ondansetron, dexamethasone and aprepitant and was well tolerated.[20] The most common adverse effects are somnolence, drowsiness and fatigue.[21]

Olanzapine at a dose of 5 mg/day has been shown to be effective in adult patients with a lower incidence of somnolence.[22] Based on 5 mg/day in adult dosing, recent studies recommended an initial pediatric dose of 0.1 mg/kg of olanzapine (max 10 mg/day).[22,23]

Benzodiazepine

Benzodiazepines have a modest antiemetic effect, but its antianxiety properties can be useful in some situations; especially for anticipatory CINV prevention.[3] The recommended dose for lorazepam is 0.04-0.08 mg/kg/dose (max 2 mg), once at bedtime the night before chemotherapy, and once the next day prior to chemotherapy administration.[5] The common adverse effects are somnolence and drowsiness.



5-FU = 5-Fluorouracil; BSA = body surface area; CMT = chemotherapy; CINV = chemotherapy induced nausea and vomiting; CTX = cyclophosphamide; hs = hora somni (at bedtime); IT = intrathecal; IV = intravenous; MTX = methrotrexate; OD = once a day; tsp = teaspoon

*Triple IT = triple intrathecal chemotherapy is the combination of 3 drugs (MTX = hydrocortisone and cytarabine) given via intrathecal route.

**Multiple agents: combination of chemotherapy that resulting increased emetogenic risk eg. CTX + anthracyclin; CTX + etoposide = etoposide + ifosfamide.

Figure 1 Recommendation for antiemetic prophylaxis for children receiving antineoplastic agents according to emetogenic risks

RECOMMENDATION FOR ANTIEMETIC PROPHYLAXIS FOR CHILDREN IN RESOURCE LIMITED COUNTRIES

In developing countries, antiemetic accessibility is one of important obstacles to achieve adequate CINV control. At present, the current antiemetic drugs recommended for children; such as, aprepitant, palonosetron or granisetron are not included in the national list of essential drugs (NLED) of Thailand.[24] The current available drugs according to NELD include: dexamethasone, ondansetron, metoclopramide, olanzapine and lorazepam. Therefore, to access NK1 receptor antagonist, patients have to pay out-of-pocket expenses; resulting in the limited use of aprepitant in Thailand.[24]

Recently, the American Society of Clinical Oncology proposed a 4-drug combination of an NK1 receptor antagonist, a serotonin (5-HT3) receptor antagonist, dexamethasone and olanzapine for adults receiving HEC.[2] Therefore, olanzapine might be a good and potential substantial agent to replace aprepitant in cases of drug accessibility being not possible, when receiving antineoplastic agents are known to interact with aprepitant or during aprepitant shortages in some countries. Here we proposed the adopted recommendation for antiemetic prophylaxis in resource limited countries.

Recommended antiemetic prophylaxis for children receiving HEC, when the access of NK1 receptor antagonist and palonosetron are possible. We suggest a 3-drug combination as the standard guideline.

Aprepitant 3 mg/kg/day day 1 (maximum 125 mg)
2 mg/kg/day day 2-3 (maximum 80 mg)

Palonosetron 20 mcg/kg IV once pre chemotherapy (maximum 1.5 mg)

Dexamethasone 6 mg/m^2/dose IV q 6 hr.

Recommended antiemetic prophylaxis for children receiving HEC, when the access of antiemetic agents outside NELD are not feasible. We recommend the usage of ondansetron instead of palonosetron, and to offer olanzapine instead of aprepitant. For other emetogenic risks, the recommendation would follow current published clinical practice guidelines.[1,4-6] **(Figure 1)**

CONCLUSION

CINV is the most common unwanted symptom for children with cancer who receive chemotherapy. Better understanding of the mechanism and current antiemetic prophylaxis available is important for improving quality of life, and treatment adherence. Although, drug accessibility remains the obstacle for CINV control in many parts of the world, the current, available data has shown a potential substitution of these unavailable drugs. Further prospective studies are needed to provide more data to support our recommendations.

REFERENCES

1. Children's Oncology Group: COG supportive care endorsed guidelines. [homepage on the Internet] Chidren's Oncology Group; [cited 2021 Mar 27] Available from: https:/children soncologygroup.org/downloads/COG_SC_Guideline_Document.pdf
2. Hesketh PJ, Kris MG, Basch E, Bohlke K, Barbour SY, Clark-Snow RA, et al. Antiemetics: ASCO guideline update. J Clin Oncol 2020;38:2782-97.
3. Hesketh PJ. Chemotherapy-induced nausea and vomiting. N Engl J Med 2008;358:2482-94.
4. 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.
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. Flank J, Robinson PD, Holdsworth M, Phillips R, Portwine C, Gibson P, et al. Guideline for the treatment of break through and prevention of refractory chemotherapy-induced nausea and vomiting in children with cancer. Pediatr Blood Cancer 2016;63:1144-51.

7. Aapro M. CINV: still troubling patients after all these years. Support Care Cancer 2018;26:5–9.
8. Paw Cho Sing E, Robinson PD, Flank J, Holdsworth M, Thackray J, Freedman J, et al. Classification of the acute emetogenicity of chemotherapy in pediatric patients: A clinical practice guideline. Pediatr Blood Cancer 2019;66:e27646
9. Sherani F, Boston C, Mba N. Latest update on prevention of acute chemotherapy– induced nausea and vomiting in pediatric cancer patients. Curr Oncol Rep 2019;21:89.
10. Patel P, Robinson PD, Thackray J, Flank J, Holdsworth MT, Gibson P, et al. Guideline for the prevention of acute chemo–therapy–induced nausea and vomiting in pediatric cancer patients: a focused update. Pediatr Blood Cancer 2017;64: e26542.
11. Kovacs G, Wachtel AE, Basharova EV, Spinelli T, Nicolas P, Kabickova. Palonosetron compared with ondansetron in pediatric cancer patients: multicycle analysis of a randomized phase III study. Future Oncol 2017;13:1685–98.
12. Jin Y, Sun W, Gu D, Yang J, Xu Z, Chen J. Comparative efficacy and safety of palonosetron with the first 5–HT3 receptor antagonists for the chemotherapy–induced nausea and vomiting: a meta–analysis. Eur J Cancer Care 2013;22: 41–50.
13. Phillips RS, Friend AJ, Gibson F, Houghton E, Gopaul S, Craig JV, et al. Antiemetic medication for prevention and treatment of chemotherapy–induced nausea and vomiting in childhood. Cochrane database of systematic review 2016.
14. Patel P, Olteanu A, Cabral S, Santesso N, Robinson PD, Dupuis LL. Dexamethasone dosing for prevention of acute chemotherapy–induced vomiting in pediatric patients: a systematic review. Pediatr Blood Cancer 2020;67:e28716.
15. 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 randomized, double–blind, phase 3 trial. Lancet Oncol 2015;16:385–94.
16. Radhakrishnan V, Pai V, Rajaraman S, Mehra N, Ganeson T, Dhanushkodi M, et al. Olanzapine versus metoclopramide for the treatment of breakthrough chemotherapy–induced vomiting in children: an open–label, randomized phase 3 trail. Pediatr Blood Cancer 2020;67:e28532.
17. 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.
18. Navari RM, Gray SE, Kerr AC. Olanzapine versus aprepitant for the prevention of chemotherapy–induced nausea and vomiting: a randomized phase III trial. J Support Oncol 2011;9:188–95.
19. Navari RM, Qin R, Ruddy KJ, Liu H, Powell SF, Bajaj M, et al. Olanzapine for the prevention of chemotherapy–induced nausea and vomiting. N Engl J Med 2016;375:134–42.
20. Naik RD, Sreenivas V, Singh V, Pillai AS, Dhawan D, Bakhshi S. Olanzapine for prevention of vomiting in children and ado–lescents Receiving Highly Emetogenic Chemotherapy: inves–tigator–initiated, randomized, open–label trial. J Clin Oncol 2020;38:3785–93.
21. Yoodee J, Permsuwan U, Nimworapan M. Efficacy and safety of olanzapine for the prevention of chemotherapy–induced nausea and vomiting: a systematic review and meta–analysis. Crit Rev Oncol Hematol 2017;112:113–25.
22. Hashimoto H, Abe M, Tokuyama O, Mizutani H, Uchitomi Y, Yamaguchi T, et al. Olanzapine 5 mg plus standard antiemetic therapy for the prevention of chemotherapy–induced nausea and vomiting (J–FORCE): A multicentre, randomised, double–blind, placebo–controlled, phase 3 trial. Lancet Oncol 2020; 21:242–49.
23. Flank J, Schechter T, Gibson P, Johnston DL, Orsey AD, Portwine C, et al. Olanzapine for prevention of chemotherapy–induced nausea and vomiting in children and adolescents: a multi–center, feasibility study. Support Care Cancer 2018; 26:549–55.
24. Dupuis LL, Sung L, Molassiotis A, Orsey AD, Tissing W, van de Wetering M. 2016 updated MASCC/ESMO consensus recommendations: prevention of acute chemotherapy induced nausea and vomiting in children. Support Care Cancer 2017; 25:323–31.
25. Yoongthong W, Hu S, Whitty JA, Wibulpolprasert S, Sukantho K, Thienthawee W, et al. National drug policies to local formulary decision in Thailand, China and Australia: drug listing changes and opportunities. Value Health 2012;15:126–31.