REVIEW ARTICLE

Chemotherapy-Induced Nausea and Vomiting

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Abstract

Chemotherapy-induced nausea and vomiting (CINV) is one of the most common side effects of cancer treatment. There are many receptors involved in the CINV pathophysiology, such as 5-hydroxytryptamine-3 (5-HT_3) receptor, neurokinin-1 (NK-1) receptor, and dopamine receptor. As rapid progress in research and drug development, there are many effective drugs available for CINV including 5-HT_3 receptor antagonists, NK-1 receptor antagonists, dexamethasone, and dopamine antagonists. In clinical practice, the antiemetic regimen used for CINV prophylaxis is primarily based on emetogenic risk and their mechanisms of action. This article aims at guiding healthcare providers on the appropriate management of CINV.

Keywords: Chemotherapy, nausea, vomiting

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ภาวะคลื่นไส้อาเจียนจากยาเคมีบำบัด

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บทคัดย่อ

ภาวะคลื่นไส้อาเจียนจากยาเคมีบำบัดเป็นผลข้างเคียงที่พบบ่อยที่สุดอย่างหนึ่งในการรักษาโรคมะเร็ง โดยมีตัวรับหลายชนิดที่เกี่ยวข้องในพยาธิสรีรวิทยาของภาวะดังกล่าว เช่น ตัวรับ 5-hydroxytryptamine-3 (5-HT_3), ตัวรับ neurokinin-1 (NK-1) และตัวรับ dopamine ด้วยความก้าวหน้าในการวิจัยและพัฒนายา ทำให้มียาที่มีประสิทธิภาพในการรักษาภาวะคลื่นไส้อาเจียนจากยาเคมีบำบัดหลายชนิด ได้แก่ ยากลุ่ม 5-HT_3 receptor antagonists, NK-1 receptor antagonists, dexamethasone และ dopamine receptor antagonists ในทางเวชปฏิบัติ การเลือกใช้ยาต้านอาเจียนสำหรับป้องกันภาวะคลื่นไส้อาเจียนจากยาเคมีบำบัดขึ้นกับความเสี่ยงของยาเคมีบำบัดที่ทำให้อาเจียนและกลไกการออกฤทธิ์ของยาเป็นหลัก บทความนี้มีวัตถุประสงค์เพื่อเป็นแนวทางให้บุคลากรทางการแพทย์สามารถเลือกใช้ยาเพื่อป้องกันภาวะคลื่นอาเจียนจากยาเคมีบำบัดได้อย่างเหมาะสม

คำสำคัญ: เคมีบำบัด, คลื่นไส้, อาเจียน

Introduction

Chemotherapy-induced nausea and vomiting (CINV) remains an important adverse effect that can be frequently seen during cancer treatment. It is reported that patients who received highly emetic chemotherapy (HEC) and moderately emetic chemotherapy (MEC) developed CINV approximately 62% and 50%, respectively.[1] CINV causes a decreased quality of life[2-4], resources consuming[2,4,5], poor treatment compliance[6], and complications including malnutrition and electrolyte imbalance.[2] Therefore it is essential that healthcare providers are aware of CINV and stay up-to date on the latest CINV clinical practice guideline.

Classification of CINV

CINV can be divided into 5 types as follows[7,8]:

1) Acute onset CINV occurs within 24 h after the initial chemotherapy session.

2) Delayed onset CINV occurs after 24 h of initial chemotherapy session.

3) Breakthrough CINV usually occurs within 5 days after the initial chemotherapy session. Although the patients receive appropriate prophylactic antiemesis, the breakthrough CINV still occurs and the patients need rescue antiemetic therapy.

4) Refractory CINV occurs even though the patients receive both appropriate prophylactic and rescue antiemesis.

5) Anticipatory nausea and vomiting (ANV) occurs before a chemotherapy session in a patient who experiences CINV in the previous chemotherapy cycle.

CINV associated risk factors

The patient-related risk factors that affect CINV include[9-11]:

- *Age*: Younger patients are more susceptible to CINV than older patients.
- *Sex*: CINV is often worse in females.
- *Alcohol drinking*: The lesser alcohol the patients drink, the more frequent the patients develop CINV.
- *History of previous CINV*: The patients who develop CINV in the previous chemotherapy cycle have an increased risk of CINV.
- *Onset of CINV*: The patients who experience CINV during the initiation of chemotherapy treatment cycle have an increased risk of CINV.
- *Nausea and vomiting during pregnancy*: The patients who develop emesis during pregnancy have an increased risk of CINV.
- *Anxiety*: The patients who are anxious or are concern about CINV have an increased risk of CINV.

In addition to risk factors listed above, there are many chemotherapy-related risk factors affecting CINV, including dosage, rate and route of administration, and type of chemotherapeutic agents.[12] For example, patients receiving platinum-based chemotherapy or anthracycline are at high risk of CINV.[9]

Although several factors contribute to CINV, the current CINV treatment guidelines are primarily based on the emetogenic potential of chemotherapeutic and targeted drugs, which are classified into 4 groups: high, moderate, low, and minimal emetogenicity.[12]

Pathophysiology of CINV

CINV involves numerous neurotransmitters, such as serotonin, substance P, dopamine, and endogenous opioids.[13] For acute CINV, chemotherapy induces free radical generation, resulting in stimulating the release of serotonin from entero-chromaffin cells in the human gastrointestinal tract. The released serotonin then stimulates vagal afferent nerve via 5-HT_3 receptor and NK-1 receptor, causing action potential transfer to the nucleus of solitary tract (NTS) and chemoreceptor trigger zone (CTZ) in medulla oblongata, which results in nausea and vomiting. For delayed CINV, chemotherapy induces nausea and vomiting by stimulating the release of substance P, which subsequently binds to NK-1 receptor, mainly in CTZ.[7,14-16] Notably, recent studies revealed the crosstalk mechanisms between serotonin and substance P in CINV. This highlights the importance of CINV management through multiple mechanisms.[17,18]

ANV is a conditioned response of nausea and vomiting. It mostly occurs in patients who develop CINV in previous chemotherapy treatment cycle. ANV is triggered by perception stimuli, such as sights, sounds, or smells of the treatment atmosphere or healthcare providers. For example, a patient experiencing CINV in the previous chemotherapy cycle recognizes the infusion set of chemotherapy and later becomes nauseous or even vomits when visualizing the infusion set. Therefore the most appropriate approach to management of ANV is to prevent the patients from CINV.[19,20] However, if ANV occurs, the National Comprehensive Cancer Network (NCCN) guidelines suggest the use of pharmacotherapy such as benzodiazepine, and/or behavioral therapy, such as systematic desensitization, relaxation exercises and hypnosis.[20-23]

Antiemesis in CINV management

Currently, there are many antiemetic drugs used in CINV prophylaxis and treatment. Their mechanisms of action are summarized below.

5-HT_3 receptor antagonists

5-HT_3 receptor antagonists have been used to prevent CINV since the 1990s. The drugs act as antagonists by binding to the 5-HT_3 receptor, therefore preventing receptor-mediated signaling pathway in the vomiting center. The first-generation 5-HT_3 receptor antagonists (ondansetron, granisetron, dolasetron and tropisetron) are commonly used for acute CINV rather than delayed CINV. The second-generation drug, palonosetron[24], allosterically inhibits 5-HT_3 receptor longer than the first-generations by triggering 5-HT_3 receptor internalization and inhibiting 5-HT_3/NK-1 receptor crosstalk.[25] Therefore, the drug can be used for the prevention of both acute and delayed CINV.[26,27] The side effects of 5-HT_3 receptor antagonists are headache, dizziness, flushing, muscle pain, and QT prolongation.[28]

NK-1 receptor antagonists

NK-1 receptor antagonists have been developed since the 1990s and approved in 2003. Their mechanism of action is inhibition of substance P from binding to the NK-1 receptor, so the signal transduction pathway does not occur in the vomiting center. NK-1 receptor antagonists, such as apprepitant, netupitant, rolapitant, and fosaprepitant, are mainly used to prevent both acute and delayed CINV. However, it should be noted that netupitant and apprepitant are CYP3A4 inhibitors. Hence, the patients with concomitant use of these drugs with dexamethasone, a CYP3A4 substrate, should be monitored for side effects.[24]

Dexamethasone

Dexamethasone is a synthetic glucocorticoid that has anti-inflammatory, anti-allergic, immunosuppressive and pain relief effects.[29] It has been used as an antiemesis since the 1980s. Nowadays, it is also indicated for CINV, radiation-induced nausea and vomiting (RINV), and postoperative nausea and vomiting (PONV). There are several proposed mechanisms whereby dexamethasone prevents CINV, such as suppression of inflammation mediators and downregulation of the serotonin and 5-HT_3 expression.[30] Its common side effects are gastrointestinal symptoms, anxiety, insomnia, and hyperglycemia.[28]

Olanzapine

Olanzapine, one of the antipsychotics, acts by inhibiting various receptors including dopamine receptor (D_1, D_2, D_3, and D_4), 5-HT receptor (5-HT_{2A}, 5-HT_{2C}, 5-HT_3 and 5-HT_6), α_1-adrenergic receptor, muscarinic receptor, and histamine receptor (H_1). Results from previous clinical studies have demonstrated that, when compared with placebo, olanzapine combined with dexamethasone, 5-HT_3 receptor antagonists, and NK-1 antagonists are more effective for prevention of CINV in patients receiving cisplatin or cyclophosphamide-doxorubicin regimen. Its side effects include sedation, dizziness, fatigue, weight gain, dry mouth, constipation, dyslipidemia, and increased risk of diabetes mellitus (when used more than 6 months).[31,32]

Dopamine receptor antagonists

Dopamine receptor antagonists, such as metoclopramide and prochlorperazine, have been used for the prevention of acute CINV except in patients receiving cisplatin-based regimen. It is also effective in delayed CINV when using with corticosteroids.[33] However, metoclopramide has been reported to cause several side effects, including increased risk of falling in the elderly, QT prolongation, and dystonia with extra-pyramidal effects. Additionally, other currently available drugs are more effective, therefore they are only indicated for prophylaxis of low emetic risk chemotherapy-induced CINV and breakthrough CINV.[23]

Cannabinoids

The antiemetic substance in the cannabinoid groups is Δ9-tetrahydro-cannabinol (THC). This compound directly inhibits 5-HT_3 and CB_1 receptors[34,35] that are co-expressed in the γ-aminobutyric acid (GABA)ergic neurons.[36] Thus, the anti-nausea/anti-emetic effects of cannabinoid may be mediated by the interactions between the cannabinoid and serotonergic systems at the level of GABA neuro-

transmission in brain areas. Recently, the United State Food and Drug Administration (U.S. FDA) has approved dronabinol and nabilone, two oral synthetic cannabinoids, for refractory CINV. Furthermore, the NCCN has recommended cannabinoids for the treatment of breakthrough CINV. The adverse drug effects include dizziness, sedation, feeling high, dysphoria, depression, and increased risk of falling in the elderly due to CNS depression.[23,37,38]

Practical guideline for CINV[23]

The prophylaxis of CINV is one of the objectives in cancer patient management, therefore the healthcare providers should emphasize on the appropriate utilization of antiemetic guidelines. For example, it is commonly known that ANV is associated with past experiences of CINV. Thus, successful prevention of acute and delayed CINV is the best approach to avoid the development of ANV. It should be noted that nausea and vomiting are not specific to chemotherapy and can also occur from complications of cancer, such as bowel obstruction, brain metastasis as well as opioid side effects.

The NCCN clinical practice guideline recommends that the healthcare providers should take into account the emetic risk of chemotherapy (Table 1) and choose the antiemetic regimens according to the guidelines summarized in Tables 2 and 3. If there are several types of chemotherapy in the regimen, antiemetic selection should be based on the chemotherapy with the highest emetic risk.

In the case of breakthrough CINV, the healthcare providers should add additional agent(s) from a different drug class that are not used in the standard prophylactic antiemetic regimen. As listed in Table 4, the management should be implemented using around the clock fashion. Moreover, the healthcare providers should increase the antiemetic dose or modify antiemetic regimen for the next cycle of chemotherapy.

Summary

CINV is an important adverse event in cancer patient treatment which affects the patients' quality of life and treatment process. Currently, there are many potent antiemetics available for CINV, therefore the healthcare providers should be aware and comply to the latest evidence-based antiemetic guidelines.

Table 1. The emetic risk of chemotherapy and targeted drugs (adapted from NCCN guideline with permission).[23]

Emetic risk of parenteral chemotherapy				
Emetic risk	**Chemotherapy**			
High emetic risk (>90% frequency of CINV if do not have standard prophylaxis)	• Regimen with anthracycline and cyclophosphamide • Carboplatin AUC ≥4	• Carmustine >250 mg/m^2 • Cisplatin • Cyclophosphamide >1,500 mg/m^2	• Dacarbazine • Doxorubicin ≥60 mg/m^2 • Epirubicin >90 mg/m^2	• Ifosfamide ≥2 g/m^2/dose • Mechlorethamine • Streptozocin
Moderate emetic risk (> 30%-90% frequency of CINV if do not have standard prophylaxis)	• Aldesleukin >12-15 million IU/m^2 • Amifostine >300 mg/m^2 • Bendamustine • Carboplatin AUC <4	• Carmustine ≤250 mg/m^2 • Cyclophosphamide ≤1,500 mg/m^2 • Cytarabine >200 mg/m^2 • Dactinomycin	• Daunorubicin • Doxorubicin <60 mg/m^2 • Epirubicin ≤90 mg/m^2 • Idarubicin	• Ifosfamide <2 g/m^2/dose • Irinotecan • Methotrexate ≥250 mg/m^2 • Oxaliplatin
Low emetic risk (10-30% frequency of CINV if do not have standard prophylaxis)	• Ado-trastuzumab emtansine • Aldesleukin ≤12 million IU/m^2 • Amifostine ≤300 mg/m^2 • Cytarabine 100-200 mg/m^2	• Docetaxel • Doxorubicin (liposomal) • Etoposide • 5-Fluorouracil	• Gemcitabine • Methotrexate 50-250 mg/m^2 • Mitomycin • Mitoxantrone	• Paclitaxel • Pemetrexed • Topotecan • Ziv-aflibercept
Minimal emetic risk (<10% frequency of CINV if do not have standard prophylaxis)	• Asparaginase • Bevacizumab • Bleomycin • Bortezomib	• Cetuximab • Cytarabine <100 mg/m^2 • Fludarabine • Methotrexate ≤50 mg/m^2	• Panitumumab • Pembrolizumab • Pertuzumab • Rituximab	• Temsirolimus • Trastuzumab • Vinblastine • Vincristine

Table 1. (Continued)

Emetic risk of oral chemotherapy				
Emetic Risk	**Chemotherapy**			
Moderate to high emetic risk (≥30% frequency of CINV if do not have standard prophylaxis)	• Busulfan ≥4 mg/day • Ceritinib • Crizotinib	• Cyclophosphamide >100 mg/m^2/day • Estramustine • Etoposide	• Lenvatinib • Midostaurin • Mitotane	• Niraparib • Olaparib • Procarbazine
Minimal to low emetic risk (<30% frequency of CINV if do not have standard prophylaxis)	• Busulfan <4 mg/day • Capecitabine • Cyclophosphamide <100 mg/m^2/day • Erlotinib • Everolimus	• Fludarabine • Gefitinib • Hydroxyurea • Imatinib • Mercaptopurine	• Methotrexate • Nilotinib • Osimertinib • Palbociclib • Regorafenib	• Sorafenib • Sunitinib • Thioguanine • Topotecan • Vemurafenib

Table 2. The prophylactic antiemetic regimens for parenteral anticancer agents (adapted from NCCN guideline with permission).[23]

Practical guideline of antiemetic for parenteral chemotherapy[1]		
Emetic risk	**Antiemetic drug administration**	
High emetic risk	**Day 1**	**Day 2-4**
	1.[2] Olanzapine[3, 4] NK-1 RA[5] 5-HT$_3$ RA[6] Dexamethasone[7]	Olanzapine[4, 9] Aprepitant[10] Dexamethasone[11]
	2. Olanzapine[3, 4] Palonosetron[8] Dexamethasone[7]	Olanzapine[4, 9]
	3. NK-1 RA[5] 5-HT$_3$ RA[6] Dexamethasone[7]	Aprepitant[10] Dexamethasone[11]
Moderate emetic risk	**Day 1**	**Day 2-3**
	1.[13] 5-HT$_3$ RA[6] Dexamethasone[7]	5-HT$_3$ RA (choose only 1 drug)[12] Dexamethasone[11]
	2.[13] Olanzapine[3, 4] Palonosetron[8] Dexamethasone[7]	Olanzapine[4, 9]
	3.[13] NK-1 RA[5] 5-HT$_3$ RA[6] Dexamethasone[7]	Aprepitant[10] ±Dexamethasone[11]
Low emetic risk[14]	1. Dexamethasone 8-12 mg oral or intravenous once daily	
	2. Metoclopramide 10-20 mg oral or intravenous once daily	
	3. Prochlorperazine 10 mg oral or intravenous once daily	
	4. 5-HT3 RA (choose only 1 drug)	
	• Dolasetron 100 mg oral once daily	
	• Granisetron 1-2 mg oral once daily	
	• Ondansetron 8-16 mg oral once daily	
Minimal emetic risk	No need for prophylaxis	

[1] Considering given with Lorazepam 0.5-2 mg po/IV/SL q 6 h in day 1-4 of chemotherapy, considering given with H_2 blocker or proton pump inhibitor and considering to add lorazepam po when use olanzapine in regimen; [2] Preferred regimen and preferred if having breakthrough CINV or previous using of olanzapine or NK-1 RA in regimen; [3] Olanzapine 5-10 mg po once daily; [4] Considering 5 mg in case of elderly; [5] Choose 1 drug from apprepitant 125 mg po once, apprepitant (emulsion) 130 mg IV once, fosaprepitant 150 mg IV once, netupitant 300 mg/palonosetron 0.5 mg (combined drug) po once, fosaprepitant 235 mg/palonosetron 0.25 mg (combined drug) iv once or rolapitant 180 mg po once (rolapitant should have at least 2 week interval); [6] Choose 1 drug from dolasetron 100 mg po once, ondansetron 16 mg po once or 8-16 mg iv once, palonosetron 0.25 mg iv once, granisetron (extended release) 10 mg SC once or granisetron 2 mg po once or 0.01 mg/kg (maximum 1 mg) IV once or 3.1 mg/day transdermal 1-2 day before chemotherapy (if using combined drug, it is not necessary to use 5-HT$_3$ RA); [7] Dexamethasone 12 mg po/IV once; [8] Palonosetron 0.25 mg IV once; [9] Olanzapine 5-10 mg po once daily; [10] Apprepitant 80 mg po once when use apprepitant in day 1; [11] Dexamethasone 8 mg po/IV once daily; [12] When do not use palonosetron, granisetron (extended release) and transdermal granisetron in day 1, suggest to choose 5-HT$_3$ RA 1 drug: dolasetron 100 mg po once daily, granisetron 1-2 (total dose) mg po once daily or 0.01 mg/kg (maximum 1 mg) IV once daily, ondansetron 8 mg po twice a day or 16 mg po once or 8-16 mg IV once daily; [13] Preferred regimen for high CINV risk patients or patients who are failure to treat corticosteroid and 5-HT$_3$ RA; [14] Start before chemotherapy and continue daily throughout treatment.

Table 3. The prophylactic antiemetic regimens for oral anticancer agents (adapted from NCCN guideline with permission).[23]

Practical guideline of antiemetic for enteral chemotherapy				
Emetic risk	**Antiemetic drug administration**			
Moderate to high emetic risk	Antiemetic should be started before chemotherapy and given daily			
	5-HT_3 RA (choose only 1 drug)			
	• Dolasetron	100 mg	po	once daily
	• Granisetron	1-2 mg	po (total daily dose)	once daily
	or Granisetron	3.1 mg/day	transdermal	q 7 day
	• Ondansetron	8-16 mg	po (total daily dose)	once daily
Minimal to low emetic risk	PRN treatment recommended antiemetic should be given before chemotherapy and given daily[1]			
	• Metoclopramide	10-20 mg	po	q 6 hr
	• Prochlorperazine	10 mg	po (maximum 40 mg/day)	q 6 hr
	5-HT_3 RA (choose only 1 drug)			
	• Dolasetron	100 mg	po	once daily
	• Granisetron	1-2 mg	po (total daily dose)	once daily
	• Ondansetron	8-16 mg	po (total daily dose)	once daily

[1] Considering given with Lorazepam 0.5-2 mg po or IV or sublingual q 6 h in day 1-4 of chemotherapy and considering given with H_2 blocker or proton pump inhibitor

Table 4. The antiemetic regimen for breakthrough CINV (adapted from NCCN guideline with permission).[23]

Practical guideline for breakthrough CINV
Antipsychotics • Olanzapine 5-10 mg po once daily[1]
Benzodiazepine • Lorazepam 0.5-2 mg po or sublingual or intravenous every 6 h
Cannabinoids • Dronabinol (capsule) 5-10 mg or Dronabinol (solution) 2.1-4.2 mg/m^2 po 3-4 times per day[2] • Nabilone 1-2 mg po twice a day
Others • Haloperidol 0.5-2 mg po or intravenous q 4-6 h • Metoclopramide 10-20 mg po or intravenous q 4-6 h • Scopolamine 1.5 mg transdermal patch q 72 h
Phenothiazine • Prochlorperazine 25 mg rectal suppository q 12 h or 10 mg po or IV q 6 h • Promethazine 25 mg rectal suppository q 6 h or 12.5-25 mg po q 4-6 h
5-HT$_3$ receptor antagonist • Dolasetron 100 mg po once daily • Granisetron 1-2 mg po once daily or 1 mg po twice a day or 0.01 mg/kg IV once daily (maximum 1 mg) or 3.1 mg/day transdermal once a week • Ondansetron 16-24 mg po once daily or 8-16 mg IV
Corticosteroid • Dexamethasone 12 mg po or IV once daily

[1] When not use olanzapine in previous prophylaxis regimen, for olanzapine-containing regimens, only use po lorazepam; [2] Solution has better bioavailability than capsule (2.1 mg per 2.5 mg).

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