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Current Management of CINV

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ABSTRACT

Chemotherapy-induced nausea and vomiting (CINV) prevention is important to reduce overall morbidity and financial burden in patients receiving chemotherapy. Severe symptoms reduce the patient's quality of life and can interfere with further treatment. The five major forms of CINV (ie, acute, delayed, predicted, breakthrough, and refractory) often include 5-HT3 receptor antagonists, NK1 receptor antagonists, and various treatments that often include corticosteroids. Despite significant research and development efforts on antiemetics, treatment of CINV remains a major challenge, waiting for many needs to be adequately addressed, including those that are vulnerable to CINV despite adequately treated. This review hope to raise awareness and discuss current the current CINV management.

Keywords: Chemotherapy, nausea and vomiting, NK1 receptor antagonist, 5-HT3 receptor antagonist.

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I. Introduction

Chemotherapy induced nausea and vomiting (CINV) is one of most feared and common adverse effects affecting up to 40% of cancer patients receiving chemotherapy [1]. Despite the development of new antiemetics, CINV remains a problem for many patients [2], [3]. If left untreated, complications such as early discontinuation, poor quality of life, dehydration and electrolyte imbalances may occur [4]. Ultimately, it is associated with lower treatment response and higher treatment costs [5]. Prevention of CINV is important to reduce morbidity and overall medical costs and improve the quality of care for patients receiving high and / or moderate emetic inducing chemotherapy.

Different patterns of vomiting in terms of intensity, duration, and peak are induced by different antitumor drugs. Drugs that induce vomiting in more than 90% of patients who are not emetically prevented are called "highly emetic chemotherapy" (HEC), and drugs with a 30% to 90% incidence of nausea and vomiting are called "moderate emetic chemotherapy" (MEC) [6]. Five terms are used to group CINV based on the pathophysiology of which nausea and vomiting (NV) happened. Acute emesis most commonly begins within 1 to 2 hours after chemotherapy and usually peaks after 4 to 6 hours; delayed emesis occurred more than 24 hours after chemotherapy; anticipatory emesis, which occurred as a pretreatment conditional response in patients who develop significant nausea and vomiting during the previous chemotherapy cycle; breakthrough CINV occurs within 5 days of chemotherapy, despite appropriate precautions; and refractory CINV occurs after breakthrough CINV occurs in the cycle prior, excluding predicted CINV [7]-[9].

Overall, there is still room for improvement in the control of nausea and vomiting associated with cancer chemotherapy. In addition, current antiemetics are associated with serious side effects related to dopamine antagonists such as hypotension and extrapyramidal side effects, sedation, and adverse effect related to 5-HT3 receptor antagonists such as constipation, diarrhea, and headache. A desirable feature of alternative or supplemental antiemetics is the absence of clinically significant side effects [10]-[14]. Eventually, a patient's quality of life is heavily affected by CINV. CINV causes enormous financial burden for patients and is one of the main reasons for refusing to continue the chemotherapy cycle which impairs the therapeutic effect. This review hopes to raise awareness and discuss current the current CINV management [15].

II. Risk Factor

Risk factors for CINV can be divided into patient-related factors and chemotherapeutic drug-related factors [1]. To assess appropriate CINV prophylaxis, it is essential to correctly assess the emetic potential of the drug in combination with individual risk factors that can be assessed prior to the start of treatment [6].

A. Chemotherapy-Related Risk Factors

The type of antitumor drug given as part of chemotherapy is the first risk factor to evaluate. Regimen containing highly emetic drugs have a higher risk of inducing CINV than regimens containing fewer emetic compounds. However, most chemotherapeutic protocols consist of a combination of different drugs that produce different emetic stimuli that

Intravenous Anticancer Agents		
High Emetic Risk (>90% frequency of emesis)		
• Any regimen that contains an anthracycline and cyclophosphamide • Carboplatin AUC ≥4 • Carmustine >250 mg/m²	• Cisplatin • Cyclophosphamide >1500 mg/m² • Dacarbazine • Doxorubicin ≥60 mg/m²	• Epirubicin >90 mg/m² • Ifosfamide ≥2 g/m² per dose • Mechlorethamine • Streptozocin
Moderate Emetic Risk (>30%-90% frequency of emesis)[a]		
• Aldesleukin >12-15 million IU/m² • Amifostine >300 mg/m² • Arsenic trioxide • Azacitidine • Bendamustine • Busulfan • **Carboplatin AUC <4** • **Carmustine ≤250 mg/m²** • Clofarabine	• Cyclophosphamide ≤1500 mg/m² • Cytarabine >200 mg/m² • **Dactinomycin** • **Daunorubicin** • Dual-drug liposomal encapsulation of cytarabine and daunorubicin • Dinutuximab • **Doxorubicin <60 mg/m²** • **Epirubicin ≤90 mg/m²**	• Idarubicin • **Ifosfamide <2 g/m² per dose** • Interferon alfa ≥10 million IU/m² • **Irinotecan** • Melphalan • **Methotrexate ≥250 mg/m²** • **Oxaliplatin** • Temozolomide • **Trabectedin**
Oral Anticancer Agents		
Moderate to High Emetic Risk (≥30% frequency of emesis)[b]		
• Altretamine • Bosutinib • Busulfan (>4 mg/day) • Cabozantinib • Ceritinib • Crizotinib • Cyclophosphamide (≥100 mg/m²/dose) • Enasidenib	• Estramustine • Etoposide • Hexamethylmelamine • Lenvatinib • Lomustine (single day) • Midostaurin • Mitotane • Niraparib	• Olaparib • Panobinostat • Procarbazine • Rucaparib • Temozolomide (>75 mg/m²/dose) • Trifluridine/tipiracil • Vinorelbine (oral vinorelbine not available in United States)

AUC indicates area under the curve.

[a] Bolded agents may be highly emetogenic in some patients.

[b] Underlined agents considered by other guidelines to be highly emetic (>90% frequency of emesis).

Fig. 1. Emetogenicity level of Chemotherapy [9].

can vary not only in intensity but also in duration and peak. Therefore, while current international guidelines classify recommended CINV prophylaxis only according to the highest emetogenic drug chemotherapy, it is clear that proper assessment of CINV is more complex. In addition, different dosing regimens (ie, aprepitant which is an NK1-RA must be given within 3 days) can affect adherence to prophylactic treatment [6].

B. Patient-Related Risk Factors

Several researches have shown that the development of CINV is strongly correlated with patient characteristics and medical history. Gender, age, drinking, sleep restrictions, number of previous chemotherapy cycles, nausea during pregnancy, motion sickness are one of such risk factors. In addition, few other researches suggest other risk factors, especially anxiety, anticipation, and associated use of serotonin-specific reuptake inhibitors or opioids [6]. Female gender is an established risk factor for developing CINV through a mechanism that is not fully understood. In addition, these patients may develop nausea and vomiting during pregnancy, increasing their risk of CINV.

All patients who previously had episodes of nausea and vomiting are also at particularly high risk of CINV. These include nausea and/or vomiting during pregnancy, motion sickness, and previous chemotherapeutic treatment. The chances of developing CINV in subsequent cycles increases by more than a factor of five if there is an uncontrolled CINV prior. Thus, the best prophylactic treatment available from the first chemotherapy cycle is of a surmountable importance, especially in patients with multiple risk factors, as recommended by international guidelines [6].

Patient age and alcohol consumption are also predictors of CINV development. Low alcohol consumption (less than 44 mL / day) also correlates with increased CINV sensitivity [6].

III. Chemotherapy Agent

Management of CINV was greatly facilitated by the development of a classification scheme that reflects the likelihood of developing vomiting after treatment with a particular drug. The classification scheme dating back to 1997 was widely accepted and used by the Guidelines Panel as the basis for treatment recommendations. Amendments to this scheme were proposed at the 2004 Perugia Antiemetic Consensus Guidelines Conference, and many chemotherapeutic agents are still available, but are relevant. Chemotherapeutic agents have been divided into four categories based on the risk of vomiting without antiemetic prophylaxis. High emetogenic chemotherapy (HEC) in which risk of vomiting exceeds 90%. Moderate emetogenic chemotherapy (MEC) > 30-90% risk of vomiting. Drug which has risk of vomiting lower than 10-30% is classified in low emetogenic & minimal emetogenic is drug which has 10% risk of emesis [6].

IV. Pathophysiology of CINV

The etiology of CINV includes multiple organ systems, central and peripheral signaling pathways, and neurotransmitters. It depends on several factors, including the

emetic properties of the chemotherapeutic regimen, the dose and rate of the chemotherapeutic drug, various patient related factors, and environmental triggers (i.e., odor, location, or location related to previous experience with CINV) [3]. The CINV process involves communication between the the gastrointestinal (GI) tract and the higher central nervous system. Target neurotransmitters involved in CINV and related receptors include dopamine and dopamine receptor, substance P and neurokinin-1 (NK1) receptors, serotonin (5-hydroxytryptamine [5-HT]) and serotonin receptors [5].

Vomiting center (VC) of the brain in the medulla oblongata regulates the emetic response [13], [14]. VC integrates various peripheral and central inputs, known as peripheral and central pathways, respectively, and induces the emetic reflex accordingly. Abdominal vagus nerve afferents carry the stimulation from the pharynx and gastric or duodenal distension into the VC via peripheral pathway [15]. Abdominal vagal afferent fibers express various receptors that can provoke an emetic response when stimulated (5-HT3, neurokinin (NK) 1, cholecystokinin-1, etc.), 5-HT3 is the main mediator [15]. These fibers terminate in the dorsal vagal complex, which consists of the area postrema, solitary tract nucleus (NTS), and the dorsal motor nucleus. The area postrema and, to a greater extendt, the NTS (also known as the "chemoreceptor trigger zone") relay the input to the VC. This pathway is primarily associated with acute vomiting [16].

On the other hand, the central vomiting pathway represents brain input to the VC that elicits an emetic response. VC receives direct input of cholinergic agonists and histamine and induces vomiting in response to pain, vestibular disorders, or emotional factors. In response to endogenous toxins and other chemical stimuli (eg, chemotherapy or other drugs), VCs also receive input from the chemoreceptor trigger zone or the last field on the floor of the fourth ventricle [14]. Neurochemical mediators of the latter signaling pathway include the neurotransmitter serotonin (5-HT) and its receptors. Substance P and NK1 receptors; dopamine and its receptors, especially NTS, dorsal motor nucleus and D3 in the posterior area [16], [17]. Certain drugs, such as opioids and dopamine agonists, act directly on receptors in the last area because there is no blood-brain barrier surrounding this periventricular sensory organ [18].

The pathophysiology of nausea is not well understood. Nausea is a subjective sensation that is difficult to explain, but it usually occurs in the stomach and is perceived as preceded by vomiting. It is unclear whether the same neurotransmitters and receptors that cause vomiting, such as serotonin and substance P, are associated with nausea. However, histaminergic, dopaminergic, and muscarinic receptors may be involved [19].

V. Therapy and Prevention for CINV

Because different types of CINV are regulated by the coordinated functioning of different signaling pathways and neurotransmitters, pharmacological approaches to prevention and treatment use these to maximize results.

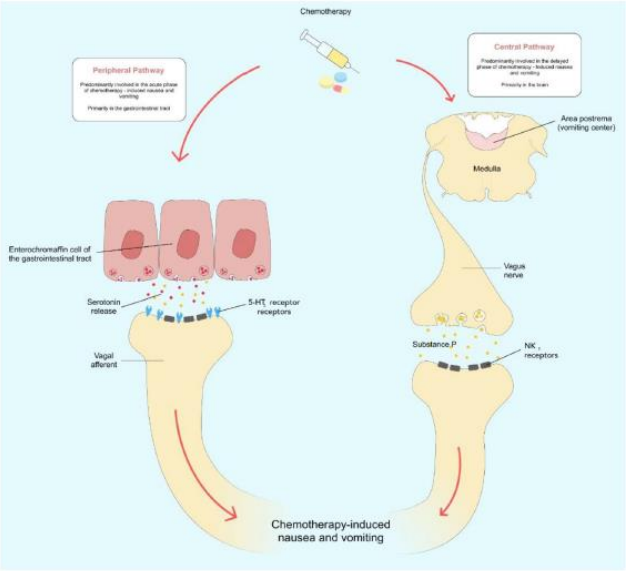

Fig 2. The interplay of the peripheral and central pathways for triggering emesis [15].

Drugs that target each of the signaling pathways and neurotransmitters should be used. The use of antiemetics has been shown to be valuable in preventing late-onset vomiting. The major drug classes were neurokinin-1 receptor (NK1R) antagonists, corticosteroids, and more recently olanzapine. The data supporting the latter treatment for delayed vomiting are described in the section above. Additional drugs that may be of some value in some delayed emesis situations include metoclopramide and type 3 5-hydroxytryptamine (5-HT3) receptor antagonist [20].

A. Dexamethasone

Dexamethasone is a corticosteroid commonly used in combination with two, three, or four doses with other drugs. According to six-country guidelines, dexamethasone delays CINV in patients undergoing acute and HEC and / or MEC. Dexamethasone may reduce its effectiveness and should not be used with most immunotherapies and cell therapies. Unwanted side effects such as immunosuppression that occur with long-term use should be carefully considered on a patient-by-patient basis. Be careful with diabetics, as dexamethasone can increase serum glucose levels. Dexamethasone can cause dyspepsia and may require the use of H2 antagonists or proton pump inhibitors. In addition, if possible, insomnia can be minimized by giving dexamethasone in the morning [21].

B. 5-HT$_3$ Receptor Antagonists

Since serotonin is a major mediator of acute CINV, 5-HT3 receptor antagonists (5-HT3 RAs) play an essential role in prophylaxis. 5-HT3-RA should be planned prior to administration of HEC and / or MEC, not as needed. In clinical studies, 5-HT3-RA has shown excellent results in the prevention of acute CINV [22].

South Indian prospective observational study on patients receiving cancer chemotherapy found that palonosetron was clinically more effective in controlling CINV than ondansetron. Statistically significant differences in antiemetic responses to these two types of prophylaxis were observed, with palonosetron being more effective, especially in late-onset and overall CINV (p = 0.006 in late-onset phase,

overall response). Then p = 0.008). Complete response was observed in 82.1% and 65.1% of patients in the palonosetron and ondansetron groups, respectively [22].

However, it is appropriate to identify the cardiac side effects of these drugs. Long QT syndrome is a side effect of this drug class. In light of the evidence, special attention should be paid to patients with heart disease or older cancers with multiple drugs. NCCN guidelines recommend intravenous palonosetron as the preferred 5-HT3 antagonist [22].

C. NK_1 Receptor Antagonists

These drugs reduce substance P activity by blocking the NK1 receptor. This is primarily useful for delayed CINV, but it is also useful for acute CINV. The addition of NKRA1 to 5-HT3RA / dexamethasone has been shown to be more effective than 5-HTRA / dexamethasone alone in the prevention of acute and delayed CINV in patients undergoing HEC. These agents, along with dexamethasone and 5-HT3-RA, are associated with first-line therapy to prevent CINV in HEC and MEC with coexisting risk factors, prior prevention / treatment failure, or higher emetic risk. In recent years, three other NK1-RAs have been approved for use in CINV: fixed-dose combination with paronosetron (netupitant / palonosetron capsules (NEPA)) [23].

Currently, NK1-RA is approved only for the prevention of CINV and not for the treatment. In addition, most NK-RA, except lorapitant, inhibit dexamethasone metabolism, so lower doses of dexamethasone should be used when co-administered. This is not the only drug interaction known to occur in most NK1-RA. Other important interactions include various other non-chemotherapeutic agents (eg, walfarin and oral contraceptives) and various chemotherapeutic agents (eg, vinca alkaloids, taxanes, and etoposide), but these Not limited to. These interactions differ in importance and dose adjustment or monitoring recommendations. In addition, lorapitant has a long half-life and should not be given more often than every two weeks [23].

D. Olanzapine

Olanzapine is drug that initially approved for depression, bipolar disorder and mainly treats schizophrenia; however, olanzapine also has antiemetic effect by inhibiting 5-HT3, 5-HT2, and dopamine receptors.

Olanzapine plus palonosetron and dexamethasone (OPD) demonstrated efficacy in controlling acute and delayed CINV in patients receiving HEC, with complete response (CR) (no emesis, no rescue) rates of 97%, 77%, and 77% for the acute, delayed, and overall phases, respectively in a phase 3 trial, When compared with the OPD regimen, aprepitant plus palonosetron and dexamethasone (APD) demonstrated a similar CR (87%, 73%, 73% for the acute, delayed, and overall phases, respectively), but the differences in nausea control are favoring the OPD group (OPD: 87% acute, 69% delayed, and 69% overall; APD: 87% acute, 38% delayed, and 38% overall). Fatigue, disturbed sleep, somnolence, and dry mouth are some common side effects that associated with olanzapine antiemetic regimens [24].

E. Miscellaneous Agents

In addition to the most commonly used drugs in the first-line treatment of CINV, healthcare providers should be aware of antiemetic alternatives such as dopamine antagonists, cannabinoids, and complementary and alternative medicines. Dopamine antagonists, including phenothiazines (eg, metoclopramide, prochlorperazine) and butyrophenones (eg, droperidol, haloperidol) have historically been the basis of antiemetic therapy. However, strong blockade at dopamine receptors causes extrapyramidal reactions, disorientation, and sedation. With the advent of new therapies with less dose-restricted AE, dopamine antagonists are usually reserved for CINV resistant to other treatments or chemotherapy with a low risk of vomiting [24].

Cannabinoids have been found to be superior to placebo and other antiemetics in that they have no NV similarity by the meta-analysis conducted by Smith *et al*. In addition, patients prefer cannabinoid therapy over other antiemetic regimens (risk ratio [RR], 2.8; 95% CI, 1.9-4.0; RR> 1 favors cannabinoids); however, for some reason the likelihood of discontinuing cannabinoid therapy increase in some patients (RR, 3.5; 95% CI, 1.4-9.0; RR <1 supports cannabinoids) and adverse events increase (RR, 3.2; 95% CI, 1.3-8.0; RR <1 favor cannabinoids). Other alternatives to conventional treatments include ginger, which had no benefit in controlling CINV; acupuncture, which had limited evidence due to lack of standardization of treatment and high risk of bias; and non-pharmacological therapy which has limited support includes cognitive distraction (e.g., video games), exercise, systematic desensitization, transcutaneous electrical nerve stimulation, and hypnosis [24].

VI. Current Guideline Recommendations for Management of CINV

Various national guidelines provide recommendations for the prevention and treatment of CINV [8], [11]. Two of the most well-known and followed guidelines are the American Society of Clinical Oncology Guidelines (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines, which was updated in October 2017 and June 2018 respectively. Four agents of NK1-RA, 5-HT3-RA, dexamethasone, and olanzapine are currently recommended by both guidelines for the prevention of CINV in HEC [8], [11]. It needs to be noted that the NCCN guidelines specify options for HEC's 3- or 4-drug combinations. In addition, NEPA is included as a first-line drug for the HEC and MEC regimens of the NCCN guidelines and the HEC regimens of the ASCO guidelines.

VII. Conclusion

Treatment has made significant progress over the last 40 years, but more than 40% of patients suffer from CINV in addition to chemotherapy. New drugs such as rolapitant and NEPA improve control of acute and delayed CINV, along with four-drug combination therapy, and improved prevention also improves the incidence of predictive, refractory, and breakthrough CINV. rice field. Healthcare providers need to be aware of the recommendations and safety and efficacy data of the new antiemetic guidelines. The successful integration of these evidence-based strategies and effective treatments into clinical practice is important for

improving morbidity and quality of life in patients undergoing MEC and / or HEC.

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