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Review Article

Pharmacotherapy Considerations in Antiemetic Prophylaxis for Chemotherapy-Induced Nausea and Vomiting

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Objectives. Although several guidelines are available aiming for optimal chemotherapy-induced nausea and vomiting (CINV) control, there still remain critical therapeutic challenges: (i) recommendations are mainly drug-based, not protocol-based; (ii) the risk of antiemetics-related interactions is not highlighted; (iii) the emetogenicity of a regimen may vary over the cycle; and (iv) the impact of the underlying malignancy is overlooked. Apparently, the existing approach seems not to be generally efficient and puts patients at risk of insufficient use of antiemetics as well as poor emesis control. *Evidence Acquisition*. This study has re-evaluated the emetogenicity of chemotherapy regimens based on administered medications on each day, drug-drug interactions, combination therapy, and delayed CINV. *Results*. A literature review was done to re-evaluate the emetogenicity of the commonly accepted chemotherapy regimens based on administered medications on each day, drug interactions, combination therapy, and delayed CINV. *Conclusion*. The revised CINV prophylaxis protocols with sorted recommendations for hematologic malignancies and solid tumors have been represented, with respect to the availability of prophylactic medications.

1. Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a major and significant adverse effect of most chemotherapeutic agents [1–3]. Most of the patients undergoing chemotherapy may potentially experience CINV due to its highly reported incidence [4–6], with up to 40% of cancer patients experiencing these enervating symptoms even in the era of prophylaxis with novel antiemetics [7]. CINV may result in undesirable consequences, including treatment interruption, reduced quality of life, and suboptimal therapeutic outcomes [8–11]. Hence, ideal management of these therapy-related adverse effects will provide patients with better treatment compliance, improved daily functioning, and mitigate their fatigue, anxiety, and psychological burden of the disease [2, 12, 13].

Two major pathways are known to lead to CINV from which acute CINV (happens within the first 24 hours) is primarily affected by the peripheral pathway and the delayed form (usually happening from 2 to 5 days) is mainly affected by the central pathway. When the chemotherapeutic agent stimulates the enterochromaffin cells of the gastrointestinal tract, the serotonin release can trigger the emetic response via the abdominal vagal afferent fibers, which is known as the peripheral pathway. The central pathway includes the sensitization of the vagal nerve afferents to neuropeptide substance P via serotonin and passing the signal to the chemoreceptor trigger zone and the medulla (Figure 1) [14].

Various classes of antiemetics have been studied and approved for CINV prophylaxis and management in patients receiving chemotherapy, including 5-hydroxytryptamine 3 (5-HT3) receptor antagonists, neurokinin-1-receptor (NK-1R)

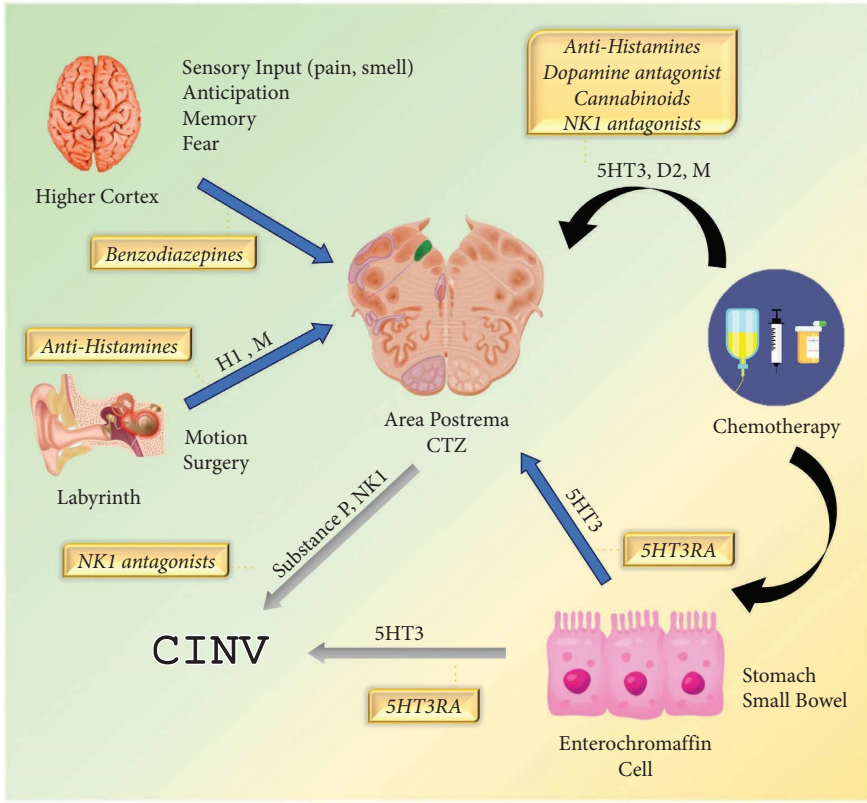

Figure 1: A schematic diagram showing main mechanisms of chemotherapy-induced nausea and vomiting. CINV: chemotherapy-induced nausea and vomiting; 5HT3: 5-hydroxytryptamine 3; CTZ: chemoreceptor trigger zone; D: dopamine; H: histamine; M: muscarine; NK: neurokinin.

antagonists, corticosteroids, and olanzapine (Table 1). In addition, several clinical guidelines are available [17–19] with the goal of the best emesis control and with key differences in approaches and suggestions [20]. These guidelines mainly recommend antiemetic management based on each medication's emetogenic risk separately, which may cause therapeutic challenges in case of combined chemotherapy regimens. Different emetogenic risks reported for a single agent per se compared with the same agent in particular combinations are one of the mentioned discrepancies [20, 21]. Notable minor differences despite fundamental similarities among various prevalent guidelines and providing general recommendations instead of applicable approaches are other obstacles medical staff face while attempting to apply those recommendations [20]. The other challenge is the potential risk of drug-drug interactions between antiemetics, antineoplastic medications, and the underlying malignancy which should be considered [22]. In addition, the emetogenic potential of a chemotherapy regimen may differ on each day of therapy due to the number and dosage of drugs administered on that day. Finally, the type of malignancy might also trigger the emetogenic pathways apart from the pharmacotherapy and affect the overall risk of nausea [23]. Apparently, the existing approach seems not to be generally efficient and puts the patient at risk of complications related to the insufficient use of antiemetic medications. These complications include significant adverse drug reactions such as intestinal obstruction and QT prolongation with some of the 5-HT3 receptor antagonists [24, 25], neutropenia with aprepitant [26], and gastrointestinal and hyperglycemic effects of dexamethasone [27–31], as well as poor emesis control, increase in hospitalization costs, and nursing workload.

This article aims to review relatively well-established antiemetic regimens to control CINV for both hematologic malignancies and solid tumors as a quick guide with the new approach of emetogenic risk assessment considering antineoplastic combinations, day-to-day differences, underlying malignancy, medication-related interactions and adverse effects, and acute and delayed phases of CINV. We determined chemotherapy protocols' emetogenicity based on single agents and combined therapies regarding each day for four-drug antiemetic combination regimens, especially for highly emetogenic protocols. In terms of emesis control and adverse reactions, the strictest approaches are considered and presented in detailed practical recommendations.

2. Emetogenicity Classification

When it comes to the prevalence of CINV, a variety of drug-related factors, environmental triggers, and patient-related factors are involved [32, 33]. Regarding chemotherapeutic agents and protocols, anticancer therapies are divided into various categories due to the risk and type of emesis. Although there is no consensus for this classification yet, three to five emetogenic levels are proposed, mostly excluding important administration-, environmental-, and patient-related variables as well as the emesis type, based on the

Table 1: Antiemetic agents for chemotherapy-induced nausea and vomiting [15, 16].

Class	Drug name	Indication	Dosing in adults
5HT-3 antagonists	Ondansetron	Acute/delayed	IV: 8–12 mg or 0.15 mg/kg Oral: 16–24 mg
	Granisetron	Acute	IV: 1 mg or 0.01 mg/kg Oral: 2 mg TOP: 34.3 mg/24 hours patch
	Dolasetron	Acute	Oral: 100 mg
	Palonosetron	Acute	IV: 0.25 mg Oral: 0.5 mg
Corticosteroids	Dexamethasone	Acute Delayed	Oral, IV: 4–20 mg Oral, IV: 8–16 mg
NK-1R antagonists	Aprepitant	Acute Delayed	Oral: 125 mg Oral: 80 mg
	Fosaprepitant	Acute	IV: 150 mg
	Rolapitant	Acute	Oral: 180 mg
5HT-3 plus NK-1R antagonists	Netupitant and palonosetron	Acute	Oral: 300 mg/0.5 mg
Second-generation antipsychotics	Olanzapine	Acute Delayed	Oral: 5–10 mg Oral: 5–10 mg
Dopamine antagonists	Metoclopramide	Acute Delayed	Oral: 10–40 mg Oral: 60–120 mg
First-generation antipsychotics	Haloperidol	Anticipatory	Oral, IV: 2–8 mg
Benzodiazepines	Lorazepam	Anticipatory	Oral, IV, sublingual: 2–8 mg

5HT-3: 5-hydroxytryptamine 3; NK-1R: neurokinin-1-receptor; IV: intravenous.

available evidence [21]. Hesketh et al. have suggested a classification schema for the acute emetogenicity of antineoplastic agents and combination chemotherapy regimens, considering the dose, rate, and route of administration dividing the antineoplastic agents into five levels (levels 1–5) based on the expected risk of emesis in the absence of prophylaxis [34].

A more applicable, modified schema has been approved in 2004 at the Perugia Antiemetic Consensus Guideline meeting classifying antineoplastic agents into four levels of emetogenicity: highly emetogenic (*H*) with ≥90% risk of emesis, moderately emetogenic (*M*) with 30–90% risk of emesis, low emetic risk (*L*) with 10–30% risk of emesis, and minimal emetic risk (min) expectedly involving ≤10% of the patients. The classification is used in the latest clinical guidelines of the American Society of Clinical Oncology (ASCO) and the Multinational Association of Supportive Care in Cancer/European Society of Medical Oncology (MASCC/ESMO) [20, 21]. There is a little conflict between the three widely accepted guidelines from ASCO, the National Comprehensive Cancer Network (NCCN), and MASCC and ESMO (the last available update for all) in the context of emetogenicity classification and management [20]. The NCCN guideline was chosen as the approach of this study due to the strictest schema.

3. Estimation of the Emetogenic Risk of the Combination Regimens

Most chemotherapeutic agents are given in combinations rather than as single agents. Estimating the emetogenicity of chemotherapy combinations is somehow difficult. The current recommended approach is to consider it the same as the medication with the highest level of risk in the regimen [34]. However, this method is not feasible enough in case of combination regimens with totally different emetogenic drugs. The following are examples of specific regimens requiring notable considerations for CINV prophylaxis.

3.1. Anthracycline plus Cyclophosphamide. The combination of cyclophosphamide (doses ≤1500 mg/m^2) and anthracyclines is highly emetogenic despite both components being at moderate risk individually [20, 35]. The nausea/vomiting (N/V) risk is considered high presumably as a distinct category for breast cancer patients receiving anthracyclines combined with cyclophosphamide (AC regimen) due to delayed phase treatment. The last updated NCCN and ASCO guidelines recommend a four-drug combination of a 5-HT3 antagonist, dexamethasone, NK-1R antagonist, and olanzapine as prevention of the acute-phase CINV with AC regimen in breast cancer patients. Olanzapine was superior in reaching the endpoint of no nausea in relevant trials both for the acute and delayed phase N/V; however, it is only recommended by ESMO's guideline in breakthrough CINV, as these reports were published after the release of this statement [20]. The delayed administration of dexamethasone or aprepitant is only recommended when the first dose of aprepitant has been given on the first day of chemotherapy [36]. Doxorubicin (Adriamycin®) is part of the anthracycline group of chemotherapeutic agents that may be used to treat many types of solid tumors and hematologic malignancies. Nausea and vomiting are the significant gastrointestinal adverse effects of doxorubicin [37].

3.2. Cisplatin-Containing Regimens. Cisplatin is a highly emetogenic agent capable of triggering both immediate and/or delayed N/V [38]. Therefore, highly effective prophylactic antiemetics with extended effects are

recommended for cisplatin-containing regimens. Four-drug combination of a 5-HT3 antagonist, dexamethasone, NK-1R antagonist, and olanzapine is recommended for the prevention of acute N/V according to the updated versions of ASCO and NCCN guidelines [20]. The use of either dexamethasone plus aprepitant, or dexamethasone plus olanzapine, or dexamethasone plus aprepitant plus olanzapine is recommended on days 2– 4 for delayed N/V prophylaxis [36].

3.3. Carboplatin-Containing Regimens. Carboplatin is classified as moderately emetogenic. Nevertheless, for combination regimens containing carboplatin with the targeted area under the curve (AUC) ≥4 mg/mL/min, both ASCO and MASCC/ESMO now recommend including an NK-1R antagonist as premedication. It should be noticed that only regimens containing carboplatin with AUC <4 mg/mL/min are classified as moderately emetogenic by NCCN. Recommendations entail three regimens of 5-HT3 antagonist plus dexamethasone, 5-HT3 antagonist plus dexamethasone plus olanzapine, or NK-1R antagonist plus 5-HT3 antagonist plus dexamethasone as acute-phase prophylaxis and three different prophylactic regimens of 5-HT3 antagonist plus olanzapine, dexamethasone plus olanzapine, or aprepitant plus dexamethasone for delayed N/V [39, 40].

3.4. Oxaliplatin-Containing Regimens. Oxaliplatin is generally categorized as moderately emetogenic but the last update of NCCN declares that sometimes it could be highly emetogenic [39] as in the FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) regimen. Antiemetic agents with moderate potency have failed to efficiently control CINV, and aprepitant-containing three-drug antiemetic combinations with continuing dexamethasone on days 2– 4 are recommended [41].

4. Advanced Cancer

Metoclopramide is recommended as an antiemetic choice for patients with advanced cancer. Alternative options include haloperidol, levomepromazine, prochlorperazine, or olanzapine [36]. The pathophysiology and pathways of N/V are partially understood, and a number of antiemetic agents have been studied for each pathway but there is no clear explanation about the various frequencies of incidence and intensity of emesis among antineoplastic agents [42].

5. Delayed CINV

Recent guidelines have also emphasized on the importance of delayed CINV [20]. Routine CINV prophylaxis is recommended when the antineoplastic regimen includes each of the following drugs: cisplatin (≥70 mg/m^2, and in combination with doxorubicin and cyclophosphamide), carboplatin (≥300 mg/m^2), cyclophosphamide (≥600 mg/m^2 in combination regimens), doxorubicin (≥40 mg/m^2 as a single agent or ≥25 mg/m^2 in combination regimens), epirubicin (≥75 mg/m^2 as a single agent or ≥50 mg/m^2 in combination regimens), oxaliplatin (in combination with 5-FU and leucovorin (FOLFOX regimen)), or to a lesser degree ifosfamide, irinotecan, or methotrexate. Dexamethasone, olanzapine, NK-1R antagonists, or a combination of them may be used according to the chemotherapy regimen. 5-HT3 antagonists are not generally recommended for delayed CINV [20].

6. Antiemetic Interactions

Drug-drug interactions are more common in cancer patients as they receive several medications concurrently. Antiemetics are well known to contribute significantly to these drug interactions. Most antiemetic agents have metabolized via the cytochrome P450 (CYP450) liver enzymes; therefore, they are usually involved in pharmacodynamics of various chemotherapeutic agents. Enzyme inhibitory effects of these medications can decrease the metabolism of competing drugs which may lead to increased serum concentrations and risk of drug toxicity [43]. Table 2 summarizes the metabolic pathway and effect of antiemetic agents used for CINV prevention. On the other hand, antiemetics adverse reactions could be intensified in simultaneous use with other drugs sharing the same metabolic pathway. Significant antiemetics adverse effects are reviewed in Table 3.

The interactions related to emesis prophylaxis in hematology-oncology practice can be classified into four categories of antiemetic-antiemetic, antiemetic-antineoplastic, antiemetic-other drugs, and antiemetic-disease interactions.

6.1. Antiemetic-Antiemetic Interactions

6.1.1. Aprepitant/Netupitant plus Dexamethasone (Risk of Increased Dexamethasone Exposure). The moderate inhibition of CYP3A4 by aprepitant, fosaprepitant, and netupitant may increase the AUC of dexamethasone or methylprednisolone leading to the increased serum concentration of the corticosteroid agent which can put patients at risk of infectious complications or mental disturbances. Therefore, it is recommended that the corticosteroid dose be reduced by 50% and 25% for dexamethasone and methylprednisolone, respectively, when coadministrated with aprepitant (>40 mg/dose), fosaprepitant, or netupitant [47, 48]. Nevertheless, if corticosteroids are given for their antitumor effect, the dose should not be reduced [49]. Rolapitant appears to have no clinically relevant effect on the pharmacokinetics of dexamethasone; thus, no dexamethasone dose adjustment is needed on concurrent use with rolapitant [43].

6.1.2. 5-HT3 Antagonists plus Olanzapine/Metoclopramide (Risk of QTc Prolongation). The Food and Drug Administration (FDA) has issued warnings about QTc prolongation and potentially fatal cardiac arrhythmias in patients receiving first-generation 5-HT3 antagonists. Among this class of medications, ondansetron has the highest risk. Hence, drugs known to create electrocardiogram (ECG) alterations

Table 2: Metabolism/transport effects of antiemetics [43, 44].

Class	Drug name	Metabolism	Effect
5HT-3 antagonists	Ondansetron	CYP1A2 (minor) CYP2C9 (minor) CYP2D6 (minor) CYP2E1 (minor) CYP3A4 (minor) Pgp-ABCB1 (minor)	Inhibits CYP1A1 (*in vivo*) Inhibits CYP1A2 (*in vivo*) Inhibits CYP2D6 (*in vivo*) Inhibits CYP3A4 (*in vivo*) Inhibits CYP3A5 (*in vivo*)
	Granisetron	CYP3A4 (minor)	—
	Dolasetron	CYP2C9 (minor) CYP3A4 (minor)	—
	Palonosetron	CYP1A2 (minor) CYP2D6 (minor) CYP3A4 (minor)	—
Corticosteroids	Dexamethasone	CYP3A4 (major) Pgp-ABCB1 (minor)	Induces CYP3A4 (weak)
NK-1R antagonists	Aprepitant	CYP1A2 (minor) CYP2C19 (minor) CYP3A4 (major)	Inhibits CYP3A4 (moderate) Induces CYP2C9 (weak)
	Fosaprepitant	CYP1A2 (minor) CYP2C19 (minor) CYP3A4 (major)	Inhibits CYP3A4 (weak) Induces CYP2C9 (weak)
	Rolapitant	CYP3A4 (major)	Inhibits BCRP-ABCG2 (weak) Inhibits CYP2D6 (moderate) Inhibits Pgp-ABCB1
Second-generation antipsychotics	Olanzapine	CYP1A2 (major) CYP2D6 (minor) UGT1A4	—

5HT-3: 5-hydroxytryptamine 3; NK-1R: neurokinin-1-receptor.

should be avoided in patients taking ondansetron, granisetron, and dolasetron. Moreover, metoclopramide and olanzapine can cause QT interval prolongation under certain conditions such as excessive dosing, electrolyte imbalance, and coadministration with other drugs. Accordingly, ECG monitoring and electrolyte assessment are necessary for the setting of the concurrent use of 5-HT3 antagonists and olanzapine or metoclopramide [36, 50].

6.1.3. Olanzapine plus Metoclopramide (Risk of Parkinson-like Symptoms). Concomitant use of olanzapine with metoclopramide, which has dopamine antagonist activity and may be used in disease-related emesis of cancer patients or failure of first-line treatments, is contraindicated due to the increased risk of extrapyramidal reactions and neuroleptic malignant syndrome [36, 43].

6.2. Antiemetic-Antineoplastic Interactions

6.2.1. Aprepitant plus Antineoplastic. Aprepitant can alter the metabolism of chemotherapeutic agents metabolized by the CYP3A4 enzyme system (e.g., paclitaxel, docetaxel, etoposide, cyclophosphamide, ifosfamide, irinotecan, imatinib, erlotinib, tamoxifen, vinca alkaloids, and tacrolimus). Worse effects may result if any of these cancer remedies are given orally rather than through single intravenous (IV) use. Evidently, some of these agents have various metabolic pathways and some must be activated via CYP3A4. However, theoretical interaction may not always be clinically significant [51–54]. For instance, concomitant administration of aprepitant with cyclophosphamide was investigated; despite increased exposure to the agent, no significant changes were reported in the serum concentration of its active metabolite. Even a reduction was seen in one of its neurotoxic metabolite levels [55–57]. Similarly, irinotecan and its active metabolite's AUC were not found to be significantly higher than coadministered with aprepitant [58]. Also, no major pharmacokinetic changes were reported with concomitant use of aprepitant and vinorelbine or docetaxel [59, 60].

6.2.2. Aprepitant/Fosaprepitant plus Ifosfamide (Risk of Neurotoxicity). The pharmacokinetic evaluation of ifosfamide has revealed a possibly significant interaction with aprepitant leading to neurotoxicity [61]. Exacerbation of ifosfamide-induced encephalopathy (IIE) has been reported by concomitant use of aprepitant in VAC-IE (vincristine, doxorubicin, and cyclophosphamide, followed by ifosfamide and etoposide) regimen for Ewing sarcoma [62, 63]. In contrast, some studies did not demonstrate an increased likelihood of IIE in the presence of aprepitant or fosaprepitant [64, 65]. Nevertheless, aprepitant needs to be given with caution in patients receiving ifosfamide.

6.2.3. Aprepitant plus Tyrosine Kinase Inhibitor (TKI) (Risk of TKI Toxicity and/or Aprepitant Toxicity). Although no investigations has yet been carried out for aprepitant

Table 3: Significant adverse effects of antiemetic agents [45, 46].

Class	Drug name	Warnings/precautions
5HT-3 antagonists	Ondansetron	(i) ECG changes/QTc prolongation (dose-dependent) (ii) Serotonin syndrome
	Granisetron	(i) ECG changes/QTc prolongation (particularly with IV formulations) (ii) Constipation/ileus (particularly with tablets and ER subcutaneous injection) (iii)Hypersensitivity reactions/anaphylaxis (iv) Injection site reactions (with subcutaneous ER formulations) (v) Serotonin syndrome
	Dolasetron	(i) ECG changes/QTc prolongation (dose-dependent) (ii) Hypersensitivity reactions/anaphylaxis (iii) Serotonin syndrome
	Palonosetron	(i) ECG changes/QTc prolongation (dose-dependent) (ii) Hypersensitivity reactions/anaphylaxis (iii) Serotonin syndrome
Corticosteroids	Dexamethasone	(i) Adrenal suppression (tertiary adrenal insufficiency) (ii) CNS and psychiatric/behavioral effects (iii) Exacerbation of heart failure and/or hypertension (iv) Gastrointestinal effects (v) Hyperglycemia (vi) Increased risk of infections (vii) Ocular effects related to the increased intraocular pressure
NK-1R antagonists	Aprepitant	(i) Hypersensitivity reactions/anaphylaxis (ii) Drug-drug interactions
	Fosaprepitant	(i)Hypersensitivity reactions/anaphylaxis (ii) Infusion site reactions
	Rolapitant	(i) Hypersensitivity reactions/anaphylaxis (ii) Drug-drug interactions
Second-generation antipsychotics	Olanzapine	(i) Hyperprolactinemia (dose-dependent) (ii) Sedation (iii) Delirium (increased mortality in elderly patients with dementia) (iv) Parkinson-like symptoms (v) Urinary retention (vi) QTc prolongation

5HT-3: 5-hydroxytryptamine 3; NK-1R: neurokinin-1-receptor; ECG: electrocardiogram; QTc: corrected QT interval; IV: intravenous; ER: extended release.

interactions with some TKIs such as gefitinib [66], a two-fold increase in erlotinib concentration is reported promoting toxicity [67]. Administration of aprepitant also showed an increase in the AUC and maximum serum concentration (C_{max}) of bosutinib with considerable clinical relevancy [68]. On the contrary, some TKIs inhibit CYP450 isoenzymes and may affect other drugs' metabolism. For example, imatinib is a moderate CYP3A4 inhibitor, and combining imatinib with the major substrates of CYP3A4 such as aprepitant should be avoided due to the risk of aprepitant toxicity [69].

6.2.4. Dexamethasone plus Imatinib (Risk of Treatment Failure). Induction of CYP3A4 by dexamethasone may decrease serum concentrations of TKIs such as imatinib, dasatinib, nilotinib, lapatinib, sunitinib, and sorafenib [70, 71]. It is recommended to avoid concurrent use of imatinib with dexamethasone whenever possible [72]. If such a combination is necessary, the imatinib dose should be increased by at least 50% while closely monitoring the clinical response [73, 74].

6.2.5. 5HT-3 Antagonist plus Arrhythmogenic Antineoplastic (Risk of QTc Prolongation). As previously mentioned, the concomitant administration of first-generation 5-HT3 antagonists with drugs capable of QT prolongation can increase the risk for torsade de pointes, a polymorphic ventricular tachycardia associated with a prolonged QT interval. A systematic review by Porta-Sánchez et al. has provided an estimated risk of drug-induced QT prolongation in patients with cancer. According to this review, arsenic trioxide (ATO), capecitabine, combretastatin (CA4P), enzastaurin, vadimezan, bosutinib, cediranib, and vorinostat are classified as high-risk chemotherapeutic agents with more than 10% incidence of long QT syndrome. Moreover, belinostat, dasatinib, dovitinib, lenvatinib, sorafenib, sunitinib, and vandetanib may increase the risk for QT prolongation with the incidence of 5–10% [75]. ECG monitoring should be performed in case of such combinations. Patients with additional risk factors may be at even greater risk. These risk factors include a past medical history of cardiac disease or congenital long QT syndrome, electrolyte imbalance, impaired hepatic and/or renal

function, advanced age, female sex, concurrent use of more than one arrhythmogenic drugs or diuretic treatment, high drug doses or concentrations, and rapid IV infusion of QT-prolonging drugs [76].

6.2.6. Ondansetron plus Antineoplastic. Ondansetron is an inhibitor of CYP1A1, CYP1A2, CYP2D6, CYP3A4, and CYP3A5 *in vivo* [77]. Concomitant use of ondansetron with cisplatin and cyclophosphamide may theoretically decrease the exposure to both medications but the importance of these interactions has not been clinically evaluated [78, 79].

6.2.7. Olanzapine plus Arrhythmogenic Antineoplastic (Risk of QTc Prolongation). Olanzapine has been associated with a mild degree of prolonged QT interval and is recommended to be used with caution and with ECG monitoring in patients with suspicious prolonged QT intervals. This drug might increase the QT prolongation risk of ATO in acute promyelocytic leukemia (APL) but there is no report of clinically significant adverse reactions [80].

6.2.8. Granisetron plus Vincristine (Risk of Intractable Constipation). Granisetron relates to a stronger incidence of iatrogenic constipation including upper colon fecal impaction among 5HT-3 antagonists which might worsen the vinca alkaloids-related intractable constipation. Vinca-induced constipation is more severe in patients receiving high dose vincristine (>2 mg). The adverse reaction reports being more incident with oral formulations of granisetron rather than the IV forms [81]. A prophylactic bowel management regimen is recommended to prevent constipation if granisetron is coadministrated with vincristine.

6.3. Antiemetic-Other Drugs Interaction

6.3.1. Aprepitant plus CYP3A4/2C9 Substrates (Risk of Drug Toxicity). Aprepitant can potentially affect the metabolism of some other supportive-care medications in cancer including CYP3A4 substrates (e.g., oxycodone, quetiapine, and contraceptives) and CYP2C9 substrates (e.g., coumarin derivatives such as warfarin). It is recommended to monitor adverse effects in concomitant use of oxycodone, changes in the international normalized ratio (INR) for warfarin, consider a dose reduction of quetiapine, and use an alternative method up to one month after the last dose of aprepitant for hormonal contraceptives [22].

6.3.2. Dexamethasone (for CINV) plus Corticosteroids in Premedication. Dexamethasone is also used to prevent hypersensitivity reactions caused by certain chemotherapeutic agents in conjunction with H1 and H2 receptor blockers. Concomitant administration of premedications including dexamethasone or equivalent doses of other corticosteroids should be considered [82].

6.4. Antiemetic-Disease Interaction

6.4.1. Dexamethasone and Breast Cancer (Risk of Cancer Progression). Dexamethasone can be used for CINV prophylaxis for drugs with various risks of emetogenicity due to the effective emesis control, but based on interactions between antiemetics and the underlying disease, the literature strongly supports that glucocorticoids can possibly promote breast cancer metastasis and progression and therefore should be used with caution in these patients' population [83].

7. Patient-Related Factors

Some other factors are involved as part of the estimation schema for choosing the strategy of intervention in CINV which are not currently considered. These include the patient's age, sex, renal and liver function, and history of alcohol consumption [84–88].

8. The Novel Daily Approach

In the context of acute emesis, CINV mostly begins during the first two hours of chemotherapy, usually peaks in four to six hours, and normally does not continue beyond one day with adequate prophylaxis [36]. For example, in the capecitabine plus oxaliplatin (XELOX) regimen, which is commonly used in colorectal cancers, oxaliplatin has a moderate and capecitabin has a low risk of emesis [21]. According to the current approach, a moderate risk of emetogenicity necessitates antiemetic prophylaxis throughout the entire 14 days of chemotherapy; though as the moderate risk of IV oxaliplatin ends by the second day, it is not required to continue the CINV prophylaxis (5-HT3 antagonist plus dexamethasone) after day 1 regarding the low risk of emesis with capecitabine alone. In fact, dexamethasone is suggested to be used with caution in colorectal cancer [89]. Likewise, in the treatment of brain tumors with PCV regimen (lomustine, procarbazine, and vincristine with moderate, high, and minimal emetogenicity, respectively), the combination is highly emetogenic due to the presence of procarbazine but as lomustine and procarbazine are administered on days 1 and 8–21, there is no need for CINV prophylaxis on days 2–7 and after day 21 as well as the vincristine-only day [90].

8.1. Multiple-Day Chemotherapy. Antiemetic prophylaxis for the four or five consecutive day cisplatin regimens used for testicular or ovarian germ cell tumors is challenging. One approach is the administration of a daily 5-HT3 receptor antagonist or one-time application of granisetron transdermal patch plus daily dexamethasone and triple-day aprepitant (or one-day other NK-1R antagonists) [36]. A three-drug combination of a 5-HT3 receptor antagonist (on chemotherapy days), dexamethasone (for 2-3 additional days after the last day of chemotherapy), and NK1 receptor antagonist (for 2 additional days after the last day of chemotherapy) is also recommended [91, 92]. Recommendations for patients with germ cell tumors treated with 5-day cisplatin-based chemotherapy protocols also include

aprepitant (125 mg day 3 and 80 mg days 4–7) with a 5-HT3 receptor antagonist (days 1–5) and dexamethasone (20 mg days 1-2) [93].

9. Recommendations: The New Insight

A literature review was done to re-evaluate the emetogenicity of the commonly accepted chemotherapy regimens based on administered medications on each day, drug interactions, combination therapy, and delayed CINV, with respect to the availability of prophylactic medications. The revised CINV prophylaxis protocols of our institute with sorted recommendations for hematologic malignancies and solid tumors have been represented in Supplementary Tables S1 and S2.

10. Key Challenges and Future Directions in CINV

As reviewed above, considering medication interactions is a necessary part of administrating CINV prophylactic regimens. These interactions have a potential effect on the efficacy of chemotherapeutic regimens, as well as safety concerns. It would be recommended that physicians consider pharmacologic aspects of therapy in the case of CINV management, and new studies would be carried out to improve future CINV prophylactic regimens.

Data Availability

No underlying data were collected or produced in this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Supplementary Materials

Table S1: the revised CINV prophylaxis protocols with sorted recommendations for hematologic malignancies. Table S2: the revised CINV prophylaxis protocols with sorted recommendations for solid tumors. (*Supplementary Materials*)

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