Neuropharmacology and Management of Chemotherapy-Induced Nausea and Vomiting in Patients with Breast Cancer

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Summary

Advances in our understanding of the pathophysiology of chemotherapy-induced nausea and vomiting (CINV), the identification of patient risk factors, and the development of new antiemetics have led to significant improvements in CINV prevention. With the correct use of antiemetic drugs, CINV can be prevented in the majority of patients. Extensive clinical data have been considered in the development of antiemetic treatment recommendations by reliable institutions such as the Multinational Association of Supportive Care in Cancer, the European Society of Medical Oncology and the American Society for Clinical Oncology. These guidelines are intended to enable physicians to incorporate the latest clinical research into their daily practice, considering CINV prevention as part of an optimal patient-centered approach to cancer management. Yet despite the availability of these guidelines, there is emerging evidence that implementation of treatment recommendations is suboptimal. Recently, guideline committees gave special consideration to patient-related risk factors (young, females) contributing to the emetogenic potential for patients receiving anthracycline and cyclophosphamide-based chemotherapy. As women with breast cancer represent a particularly challenging population regarding emesis control, it is especially important that treatment recommendations are followed. This review focuses on the content of the current antiemetic guidelines, addressing the importance of how these are intended to be implemented in routine clinical practice.

Introduction

For patients receiving chemotherapy, if not prevented, nausea and vomiting can be a significant problem. Besides being among the most distressing side effects of chemotherapy, chemotherapy-induced nausea and vomiting (CINV) may interfere with patients' daily functioning and negatively affect their quality of life. It can also have detrimental clinical implications for patients, including non-compliance with or premature discontinuation of potentially curative cancer treatment, as well as impeding patients' willingness or ability to eat and/or drink, leading to nutritional deficits. Without appropriate antiemetic prophylaxis, up to 90% of all cancer patients receiving chemotherapy may experience nausea and/or vomiting. Therefore, complete prevention of these side effects has to be the goal of all antiemetic therapy.

Over the past 25 years, continuous research has led to steady improvements in the field of supportive care for cancer patients. With the introduction of the 5-HT₃ receptor antagonists (5-HT₃ RAs) in the early 1990s and another class of antiemetics, the neurokinin-1 (NK₁) receptor antagonists 10 years ago, there have been significant improvements in the prevention and control of CINV. The first international Multinational Association of Supportive Care in Cancer (MASCC) antiemetic guidelines were published in 1998 and were immediately followed by the American Society of Clinical Oncology (ASCO) guidelines in 1999. Since that time these guidelines have been updated regularly as new data have emerged. [1, 2].

During this same time period, significant advances and a paradigm shift have occurred in the treatment of breast cancer, with research evolving toward a more molecular targeted approach. Despite these advances, the majority of breast cancer patients continue to receive emetogenic cytotoxic chemotherapy regimens, sometimes combined with novel targeted

Table 1. Emetogenic risk of selected intravenous and oral chemotherapeutic agents relevant in breast cancer treatment; adapted from [1, 2]

Risk	Chemotherapeutic agent
High (emesis risk > 90% without antiemetics)	Carmustine, BCNU Cisplatin Cyclophosphamide (> 1,500 mg/m ²)
Moderate (emesis risk 30–90% without antiemetics)	Intravenous: Carboplatin Cyclophosphamide (< 1,500 mg/m ²) Doxorubicin* Epirubicin* Ifosfamide Irinotecan Oxaliplatin Temozolomide Oral: Cyclophosphamide Temozolomide Vinorelbine
Low (emesis risk 10–30% without antiemetics)	Intravenous: Catumaxumab Docetaxel Doxorubicin liposomal Etoposide 5-Fluorouracil Gemcitabine Methotrexate (> 100 mg/m ²) Mitoxantron Paclitaxel Topotecan Trastuzumab Oral: Capecitabine Everolimus Lapatinib
Minimal (emesis risk < 10% without antiemetics)	Bevacizumab Hormones Pertuzumab Vincristine Vinorelbine
*Emetogenicity of these anthracyclines is increased when combined with cyclophosphamide.	

therapies. During the most recent review of the antiemetic guidelines, the committees gave special consideration to the patient-related risk factors that contribute to the emetogenic potential for breast cancer patients receiving the commonly used anthracycline and cyclophosphamide (AC)-based chemotherapy regimens. They acknowledged that this group is at higher risk for CINV than that expected with AC alone. It is, therefore, particularly important that efforts be made to fol-

low the guideline recommendations for antiemetic prophylaxis in patients with breast cancer.

Neuropharmacology of Emesis

While the pathophysiology of CINV is not entirely understood, it is known to be multifactorial, involving multiple pathways, neurotransmitters and receptors. CINV is believed to occur largely via 2 pathways: (1) a peripheral pathway involving neurotransmitters activated as a result of gastrointestinal irritation or damage by chemotherapy, and (2) a central pathway involving activation of neurotransmitters in the chemoreceptor trigger zone (CTZ) directly through the blood or cerebrospinal fluid.

Following exposure to radiation or cytotoxic drugs, serotonin (5-HT) is released from enterochromaffin cells in the small intestinal mucosa, which are adjacent to the vagal afferent neurons on which 5-HT₃ receptors are located. The released serotonin binds to the 5-HT₃ receptors, thereby activating vagal afferent neurons, which transmit impulses to the CTZ of the brain. At present, this vagal-dependent peripheral pathway is considered the primary mechanism by which chemotherapeutic agents initiate acute emesis. The central pathway is activated by substance P, abundant in the CTZ in the area postrema at the bottom of the fourth ventricle. Substance P induces vomiting by binding to NK₁ receptors, which are highly concentrated in the brain. In early studies it was shown that administration of substance P to dogs could induce emesis [3]. Multiple studies have suggested that substance P may be the most relevant neurotransmitter associated with delayed CINV [4].

While serotonin/5-HT₃ receptors and substance P/NK₁ receptors play the predominant role in the emesis response, other neurotransmitters and receptors are also involved. These include dopamine (D)/D₂ and D₃ receptors, cannabinoids (CBs)/CB₁ receptors, histamine (H)/H₁ receptors, and acetylcholine/muscarinic (M) acetylcholine M₃ and M₅ receptors. Although numerous other neurotransmitter and receptor systems have roles in the vomiting reflex, the relationship among them are not yet clearly understood.

Classification of CINV

The classification of CINV is widely agreed upon within the antiemetic community. CINV is categorized into 3 groups: acute onset (mostly serotonin-related), occurring within the first 24 h of initiation of chemotherapy; delayed onset (in part substance P-related), occurring 24 h to several days after chemotherapy; and anticipatory, emesis that is triggered by external factors such as taste, odor or sight, as well as thoughts or anxiety due to poor response to antiemetic agents during a previous cycle of chemotherapy.

Antiemetic	Route	Recommended dose (once daily)
5-HT ₃ RA		
Ondansetron	p.o.	8 mg twice daily
	i.v.	8 mg (0.15 mg/kg)
Granisetron	p.o.	2 mg
	i.v.	1 mg (0.01 mg/kg)
Tropisetron	p.o.	5 mg
	i.v.	
Palonosetron	p.o.	0.5 mg (only day 1)
	i.v.	0.25 mg (only day 1)
Ramosetron	i.v.	0.3 mg
Steroids		
Dexamethasone	p.o./i.v.	Highly emetogenic: 20 mg; if given with aprepitant 12 mg Moderately emetogenic: 8 mg
NK ₁ RA		
Aprepitant	p.o.	125 mg day 1, 80 mg day 2+3
Fosaprepitant	i.v.	150 mg day 1 only

Table 2. Dosage of antiemetics; adapted from [1, 2]

RA = receptor antagonist, p.o. = orally, i.v. = intravenously.

Emetogenicity of Chemotherapeutic Agents

The main risk factor linked to the development of CINV is the emetogenic potential of the administered chemotherapeutic agents. All international guidelines classify chemotherapeutic agents into 4 emetic risk groups according to their emetogenic potential: high (90%), moderate (30–90%), low (10–30%) and minimal (< 10%). The percentages represent the proportion of patients expected to have an emetic episode(s) if no prophylactic antiemetics were administered. The guideline committees continue to recognize the clinical utility of grouping chemotherapy agents into broad emetogenic categories to allow clinicians to adapt the antiemetic prophylaxis according to the emetogenicity of the chemotherapy. Table 1 highlights the emetogenic potential of chemotherapeutics most commonly administered as part of standard regimens for breast cancer.

Patient-Related Risk Factors

There are also patient-related factors that may contribute to the emetogenic risk of emesis. Risk factors known to increase the likelihood of CINV include young age, female gender, a history of low alcohol intake, motion sickness, experience of emesis during pregnancy, impaired quality of life, and previous exposure to chemotherapy. Despite these risk factors being well established, antiemetic guidelines have historically been based solely on the emetogenicity of the chemotherapy. However, when considering both the multiple patient-related risk factors inherent in many breast cancer patients and the wide range of the moderately emetogenic potential (30–90%) of the chemotherapeutics used to treat breast cancer, integrating a patient-related risk factor profile

into the guidelines may be warranted. However, further research would be needed, e.g. prospective validation studies, prior to implementation, and the feasibility of such a model in routine practice remains questionable [5]. In their most recent update, the ASCO guideline committee acknowledged that (young, female) cancer patients receiving AC-based chemotherapy represent a particularly challenging population. Consequently, they chose to re-classify AC chemotherapy from the previous category of moderately emetogenic to highly emetogenic, recognizing that the patient risk factors of those typically receiving AC were adding to the chemotherapy risk. Other guideline committees such as MASCC/European Society of Medical Oncology (ESMO) similarly acknowledged the higher risk of this group but retained the prior moderately emetogenic classification of AC.

Antiemetics

With a wide variety of modern antiemetic agents available for the prevention and treatment of CINV, vomiting can be prevented in the majority of patients [6]. However, nausea remains more difficult to control than vomiting, particularly in the delayed phase (days 2–5 after chemotherapy). As continued research strives to attain complete prevention of CINV for patients, nausea control should be a primary focus of future clinical trials.

As suggested by the antiemetic guidelines, combination antiemetic regimens targeting multiple molecular pathways have become the standard of care for the prevention of CINV.

5-HT₃ Serotonin Receptor Antagonists

Over the last 2 decades, antagonists inhibiting the actions of serotonin have been the most effective and most widely

Table 3. Antiemetic prevention based on the emesis risk category; adapted from [1, 2]

Emesis risk	Acute phase (day 1)	Followed by	Delayed phase (days 2–5)
High	5-HT ₃ RA + DEX + aprepitant (or fosaprepitant)	→	DEX (days 2–3 or 2–4) + aprepitant (days 2–3) (if fosaprepitant used day 1, then DEX only)
AC-based Moderate	5-HT ₃ RA + DEX + aprepitant (or fosaprepitant) palonosetron + DEX (alternative 5-HT ₃ RA if palonosetron is not available)	→ →	aprepitant (days 2–3)* DEX (days 2–3)
Low	DEX (or 5-HT ₃ RA or D RA)	→	None
Minimal	None	→	None

AC = anthracycline and cyclophosphamide, 5-HT₃ RA = 5-HT₃ receptor antagonist, DEX = dexamethasone, D RA = dopamine receptor antagonist.

*In the American Society of Clinical Oncology (ASCO) guideline dexamethasone is also recommended in analogy to the high emetogenic risk group.

used antiemetics for the prophylaxis and management of CINV. Currently, 5 5-HT₃ RAs are available: granisetron, ondansetron, palonosetron, ramosetron and tropisetron. When administering 5-HT₃ RAs, several points should be considered [2]:

- The lowest fully effective dose for each agent should be used; higher doses do not enhance any aspect of their activity because of receptor saturation.
- Oral and intravenous applications are equally effective.
- There is no more effective schedule than a single dose administered before chemotherapy.

The guideline-based dose recommendation is shown in table 2.

While all of the 5-HT₃ RAs form the cornerstone of therapy for the control of acute emesis caused by chemotherapy agents with moderate/high emetogenic potential, more recent data suggest that the newest 5-HT₃ RA, palonosetron, uniquely offers clinical benefit in also preventing delayed CINV [7]. This delayed benefit may be the result of pharmacologically distinct characteristics that palonosetron exhibits compared with the older 5-HT₃ RAs. As the Phase III palonosetron trials in the setting of moderately emetogenic chemotherapy (MEC) suggested superiority over older 5-HT₃ RAs, the updated MASCC/ESMO and ASCO guidelines now recommend palonosetron as the preferred agent in patients receiving MEC [1, 2]. The data and guideline recommendations are particularly relevant to a breast cancer population, as approximately half the patients in the Phase III palonosetron trials were females with breast cancer [7–9].

From the broad experience acquired with 5-HT₃ RAs in clinical practice during that time, the remarkable safety profile of these drugs has been confirmed [10]. As a class, 5-HT₃ RAs are well tolerated; common adverse events include mild headache, transient elevation of hepatic aminotransferase levels and constipation.

NK₁ Receptor Antagonists

NK₁ RAs exert their antiemetic action through the inhibition of substance P in both the central (mainly) and peripheral nervous systems. Aprepitant, approved as the first NK₁ RA in 2003, and the follow-up intravenous (i.v.) formulation,

fosaprepitant, are currently the only agents available in this class. Other NK₁ RAs such as netupitant and rolapitant are under investigation. Netupitant has been developed as a fixed-dose oral combination with palonosetron (NEPA), specifically designed to target 2 critical pathways involved in emesis with a single-dose product. In pivotal trials, NEPA has been shown to be superior to oral palonosetron in patients receiving highly emetogenic chemotherapy (HEC) [11] and in females with breast cancer receiving AC-based chemotherapy [12]. It has also been shown to be safe and highly effective over multiple cycles of MEC and HEC [13].

Aprepitant-containing regimens have been shown to significantly reduce acute and delayed emesis in patients receiving HEC [6, 14] and MEC [15, 16], compared with regimens containing 5-HT₃ RA plus dexamethasone (DEX) only. It is therefore recommended for prophylactic use in combination with a 5-HT₃ RA plus DEX therapy during the acute phase. For delayed prevention, it is to be used alone on days 2–3 in AC MEC and in combination with DEX on days 2–3 in HEC (tables 2, 3).

Aprepitant is well tolerated, with headache, anorexia, fatigue, diarrhea, hiccups and mild transaminase elevation as the most common low-grade adverse effects reported during clinical trials [6, 14, 15]. Aprepitant is metabolized by cytochrome P450 (CYP) 3A4 and is a moderate inhibitor and an inducer of CYP3A4, as well as an inducer of CYP2C9. Therefore, potential interactions between aprepitant and other drugs, especially chemotherapeutics and other antiemetics have been investigated intensively [17]. The most notable findings are that aprepitant causes a 2-fold increase in the area under the plasma concentration curve (AUC) of DEX, a sensitive substrate of CYP3A4. Consequently, DEX doses should be decreased by approximately 50% when used in combination with aprepitant. After 10 years of clinical experience with aprepitant, the clinical relevance of these potential interactions appears to be rather insignificant [17]. Reassuringly, it has had no clinically significant effect on either the pharmacokinetics or toxicity of standard doses of docetaxel in cancer patients [18], and the metabolism of cyclophosphamide is not significantly reduced in the presence of aprepitant.

Corticosteroids

Although not approved as antiemetics, corticosteroids are an integral component of most antiemetic regimens and play a major role in the prevention of both acute and delayed CINV [19, 20]. While no study has been performed to evaluate the antiemetic effectiveness of a particular corticosteroid versus another, dexamethasone remains the most frequently used. When used in combination with other antiemetics, corticosteroids exert an additive effect. Therefore, all guidelines suggest the use of DEX for the acute prevention in low emetogenic chemotherapy (LEC), MEC, and HEC settings, recommending a single dose of 4–8 mg in LEC, 8 mg in MEC and 20 mg in HEC (reduced to 12 mg when administered with aprepitant due to the CYP3A4-dependent metabolism of DEX). For delayed prevention, DEX is recommended at a dose of 8 mg twice a day for 3–4 days (8 mg once daily when used with aprepitant or fosaprepitant) and in MEC at 8 mg daily for 2–3 days. These dose recommendations are largely based on studies conducted by the Italian Group for Antiemetic Research [21].

Despite evidence of their beneficial effects, corticosteroids may be underutilized due to concerns regarding their potential side effects. In a study by Vardy et al. [22], patients receiving DEX for prevention of delayed CINV reported the following adverse events in the week following chemotherapy: moderate-to-severe insomnia (45%), indigestion and/or epigastric discomfort (27%), agitation (27%), increased appetite (19%), weight gain (16%) and acne (15%). As a result, there has been interest in minimizing the DEX dose and frequency, especially in patients who experience these DEX-related side effects. In addition, DEX should be used with caution in patients with pre-existing conditions that could be exacerbated by corticosteroid use (such as diabetes, cataracts, osteopenia/osteoporosis). In a study of chemotherapy-naïve breast cancer patients, a single dose of palonosetron plus DEX on day 1 only showed complete response rates (no emesis, no rescue medication) similar to those of palonosetron on day 1 plus DEX on days 1–3 [23]. In the recent NEPA study in breast cancer patients receiving AC chemotherapy, the complete antiemetic regimen (NEPA plus DEX) was given on day 1 only [12]. The positive results validate the guideline recommendations of a single day of DEX in patients receiving AC, and provide encouraging evidence that DEX beyond day 1 might be not necessary when using NEPA in patients at higher risk for CINV.

Olanzapine

Olanzapine is an atypical antipsychotic drug that displays antiemetic properties due to its impact on multiple receptor sites involved in the pathways controlling nausea and vomiting. In vitro and in vivo receptor binding studies showed that olanzapine exhibits a broad binding profile with high affinity for dopamine D₁-D₅, 5-HT_{2A}, 5-HT_{2C}, 5-HT₃, 5-HT₆, muscarinic, α₁-adrenergic, and histamine H₁ receptors.

There is no consistent recommendation has been given by the various guideline committees for appropriate utilization of olanzapine. It is recommended as an adjunctive drug for breakthrough CINV in the ASCO guidelines, with the general principle being to add an agent from a different drug class to the current regimen once breakthrough CINV has occurred [1]. This recommendation is supported by the study of Navari et al. [24] in which olanzapine was shown to be superior to metoclopramide when used in the rescue setting. Adverse effects reported for olanzapine are typical of those seen with other antipsychotic agents and include sleepiness, dizziness, weight gain and dry mouth.

Dopamine Receptor Antagonists

Before the introduction of 5-HT₃ RAs, dopamine-receptor antagonists formed the basis of antiemetic therapy [25]. Based on their chemical structure, these agents can be subdivided into phenothiazines, butyrophenones and substituted benzamides [10, 19]. Prior to establishing the 5-HT₃ RAs in CINV prophylaxis, metoclopramide, 1 of the most frequently used benzamides, played a primary role in the management of acute CINV, usually given at high doses and in combination with a corticosteroid.

However, in patients receiving cisplatin-based chemotherapy, conventional high doses of metoclopramide are not significantly different from placebo. Consequently, metoclopramide is not recommended for the prevention of acute CINV by current guidelines. In addition, in 2013, in an effort to reduce the risk of neurological side effects, the European Medicines Agency recommended (1) removal of the high-strength formulation of metoclopramide from the market, (2) restriction of the maximum recommended dose, and (3) limited use to ≤ 5 days.

Similar to the recommendations for olanzapine, ASCO guidelines recommend that metoclopramide be reserved for patients refractory to or intolerant of 5-HT₃ RAs, DEX and aprepitant [1].

Benzodiazepines

As a valuable addition to antiemetic regimens, benzodiazepines may be used to treat certain conditions such as anxiety and to reduce the risk of anticipatory CINV. Benzodiazepines may also be effective in patients with refractory and breakthrough emesis [1].

Ginger

Ginger has long been known to exhibit efficacy in reducing nausea and is used in the treatment of hyperemesis gravidarum. Only recently it was shown that the antiemetic activity of ginger is based on the inhibition of human 5-HT₃ receptors. In a study (of predominantly females with breast cancer) comparing the effectiveness of ginger when given in combination with a 5-HT₃ RA, ginger was shown to significantly reduce acute nausea compared to placebo [26]. There-

fore, an ‘add on’ ginger supplementation (500–1000 mg daily for 6 days, starting day –3) might be considered.

Antiemetic Studies in Breast Cancer Patients

As cisplatin is viewed as the most emetogenic chemotherapeutic agent, early antiemetic trials focused on this agent in assessing the efficacy of various agents. However, with growing interest in establishing good CINV control in the MEC setting, combined with growing awareness that women receiving AC or a similar combination are at a high risk of emesis, anthracycline-based chemotherapy has become the standard emetic stimulus in clinical trials assessing antiemetic agents among breast cancer patients. In fact, up to now AC has served as the predominant setting in which currently available 5-HT₃ RA and aprepitant MEC-approved indications have been based.

Some of the most recent and relevant large trials in breast cancer patients include: (1) the study of Saito et al. [7] demonstrating of superiority of palonosetron over granisetron in preventing delayed CINV in patients receiving MEC (43% breast cancer patients receiving anthracycline-based chemotherapy); (2) the trial of Warr et al. [27] establishing superiority of the triplet aprepitant/ondansetron/ DEX regimen over a doublet ondansetron/DEX regimen in 857 breast cancer patients; (3) the follow-up study of Rapoport et al. [16] affirming the aprepitant triplet superiority over the 5-HT₃ RA/DEX doublet in 848 patients receiving MEC (~50% of whom had breast cancer); and (4) the recent study by Aapro et al. [12] showing superiority of the new fixed- and single-dose NEPA/ DEX regimen over palonosetron/DEX in 1,449 patients (97% breast cancer) receiving AC chemotherapy.

Summary of Antiemetic Guideline Based Management of CINV

Highly Emetogenic Chemotherapy

For acute CINV, a combination of a 5-HT₃ RA, DEX and aprepitant/fosaprepitant given prior to chemotherapy is recommended unanimously by all guidelines (table 3).

For delayed CINV, the necessity of appropriate prophylaxis for prevention of delayed CINV in HEC settings is based on studies showing that without any preventive agents, 60% to nearly 90% of patients receiving cisplatin will experience delayed emesis. All guidelines recommend a combination of DEX and aprepitant. If fosaprepitant is given on day 1, no repetition of fosaprepitant on the consecutive days is necessary.

AC-Based Chemotherapy

It has to be noted that, while the ASCO guidelines consider AC regimens, commonly used in patients with breast

cancer, as highly emetogenic, they remain classified as MEC regimens by the MASCC/ESMO guidelines. This discordance in the classification is simply due to differing approaches for recognizing that the patient-related risk factors contribute to the emetic risk for this population. Therefore, consistent with the HEC recommendations, the ASCO guidelines suggest delayed prophylaxis with both a NK₁ RA and DEX, while the MASCC/ESMO guidelines limit their delayed recommendation exclusively to the use of aprepitant.

Moderately Emetogenic Chemotherapy

For acute CINV, patients should be given a combination of palonosetron and DEX. If palonosetron is unavailable, another 5-HT₃ RA can be substituted. The MASCC/ESMO guidelines limit their recommendation to this combination, whereas the ASCO guidelines suggest that the addition of aprepitant can be considered in selected patients. Although this is not clearly defined, the implication is that if clinicians feel that a patient presents at a higher risk (perhaps due to patient-related risk factors), the addition of the NK₁ RA can be considered.

For delayed CINV, DEX alone is the preferred agent. However, if an aprepitant regimen was used for the prevention of acute CINV, aprepitant ± DEX should be used. 5-HT₃ RAs may be used as an alternative agent to DEX, but not in the situation when palonosetron was the initial 5-HT₃ RA of choice.

Low Emetogenic Chemotherapy

The application of a single agent, e.g. a low dose of DEX, is sufficient for the prevention of both acute and delayed CINV. Although the routine use of 5-HT₃ RAs has been observed in clinical practice, it is considered an over-treatment and should, therefore, be avoided in patients without additional risk factors.

Minimally Emetogenic Chemotherapy

All guideline suggest that most patients receiving minimally emetogenic chemotherapy do not require antiemetic prophylaxis and, therefore, nothing should be administered routinely.

Management of Breakthrough and Refractory CINV

‘Breakthrough CINV’ is defined as CINV that occurs despite optimal preventative treatment. ‘Refractory CINV’ is defined as the recurrence of CINV in subsequent cycles of chemotherapy when all previous preventive and rescue treatments failed. If the best possible treatment has already been given as prophylaxis, repeated dosing of the same agents is unlikely to be successful. In this setting, olanzapine may be the best option. Indeed, recent trials demonstrated its effectiveness in treating breakthrough CINV [28]. Further options are either the addition of dopamine receptor antagonists (e.g. metoclopramide) or other agents such as benzodiazepines or

other neuroleptics. The use of cannabinoids can also be considered in patients with refractory CINV.

Management of Radiation-Induced Nausea and Vomiting

Since radiation therapy (RT) is part of the treatment plan of most breast cancer patients, the prevention and treatment of radiation-induced nausea and vomiting (RINV) also plays an important role in the overall care plan of these patients [29]. The recent guidelines from both MASCC/ESMO and ASCO divide the risk of emesis due to RT into 4 categories [1, 30]. Most breast cancer patients receiving adjuvant radiation to the breast are at minimal risk of developing RINV, and, therefore, no prophylactic antiemetic treatment is necessary. Yet due to the generally elevated risk of nausea and emesis in young female patients, a rescue agent such as 5-HT₃ RAs or dopamine receptor antagonists may be used. In the low and moderate risk setting, prophylaxis with a 5-HT₃ RA is recommended, possibly adjusted by adding DEX in the moderate risk setting. Although a high risk of developing RINV is not common in breast cancer treatment, prophylaxis with both 5-HT₃ RAs and DEX is recommended for such patients. No randomized studies are available with regard to the potential value of an NK₁ RA in this setting.

Conclusion

While the introduction of the 5-HT₃ RA class transformed CINV prevention for patients 20 years ago, the pathophysiology of CINV itself has been elucidated during the last decade of research. Antiemetic combinations targeting multiple molecular pathways have been identified, and the NK₁ RA class has been introduced into the antiemetic armamentarium, essentially optimizing CINV control for the majority of patients. However, this control can only be achieved if appropriate antiemetic prophylaxis is administered to patients. Despite some differences between the guidelines, they all provide reliable, up-to-date and reasonably consistent recommendations to guide clinicians on the ideal use of antiemetics. Unfortunately, adherence to antiemetic guidelines is suboptimal, despite research suggesting that guideline conformity improves CINV control [31]. In a large observational study performed recently in nearly 1000 patients in 8 European countries, Aapro and

colleagues [31] showed guideline adherence in only 29% of patients. They also showed better CINV control and less utilization of health care resources in those patients receiving guideline-consistent CINV prophylaxis. Clearly, a need exists for greater adherence to the guideline recommendations to improve the quality of care for cancer patients. While studies are needed to identify specific barriers to guideline use within individual clinics and hospitals, measures that can be taken to enhance adherence include efficient education, monitoring and training of all staff, use of standardized antiemetic protocols included in chemotherapy order forms, providing feedback to clinicians on patient CINV outcomes and clinical interventions by pharmacists in the event of insufficient antiemetic orders.

As females with breast cancer represent a particularly challenging population in terms of emesis control, it is especially crucial that antiemetic recommendations are followed to allow these patients to maintain their quality of life and continue their cancer treatment plan. Further research is warranted to explore the underlying pathophysiology of nausea so that new treatments can be developed to optimize nausea prevention, to evaluate opportunities to reinforce and encourage guideline implementation in clinical practice, and to see if novel guideline-based antiemetic combinations (such as netupitant/palonosetron) will improve CINV control for patients.

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