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REVIEW

Antiemetic therapy options for chemotherapy-induced nausea and vomiting in breast cancer patients

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Abstract: Chemotherapy-induced nausea and vomiting (CINV) continues to be one of the most distressing side effects of chemotherapy in breast cancer patients, which can result in poor compliance to therapy that may, in turn, affect overall survival. The extent of CINV is dependent on the emetogenic potential of the individual cytotoxic agents or regimens employed as well as certain patient factors. Advances in our understanding in the pathophysiology of CINV and the identification of risk factors have enabled the utilization of appropriate antiemetic regimens to improve the control of CINV. Most of the chemotherapy regimens used in this patient population are considered to be moderately emetogenic; 60%–90% of chemotherapeutic regimens used in breast cancer patients cause nausea and vomiting, amongst which regimens doxorubicin-cyclophosphamide (AC) combination is commonly regarded as of relatively higher emetogenicity. Currently, corticosteroids, 5-hydroxytryptamine 3 (5-HT3) receptor antagonists, and neurokinin 1 (NK-1) receptor antagonists are the three classes of antiemetic agents with the highest therapeutic index, which have been supported by data from large-scale randomized clinical trials. Treatment guidelines enable physicians to integrate the latest research data into their clinical practices. This review focuses on the three classes of antiemetic therapy options for CINV in breast cancer patients, as well as their safety and tolerability profiles. Recommendations from major guidelines/consensus including from the Multinational Association for Supportive Care in Cancer/European Society of Medical Oncology (MASCC/ESMO), the American Society of Clinical Oncology (ASCO), and the US National Comprehensive Cancer Network (NCCN), are also discussed. With the correct use of antiemetic regimens, chemotherapy-induced vomiting could be prevented in the majority of patients. However, chemotherapy-induced nausea remains an important symptom and a challenge for physicians to manage.

Keywords: cytotoxics, 5-HT3 antogonist, NK-1 antagonist

Introduction

Breast cancer is the most common cancer among women worldwide. Advances in the treatment armamentarium in the past two decades have improved prognosis and survival of breast cancer patients.

Treatment options for breast cancer rely on patient factors that include age, menopausal status, and comorbidities, as well as tumor factors which include histological features, stage of disease, biological factors, and history of prior chemotherapy. For patients with early breast cancer, adjuvant therapies that are considered include chemotherapy, targeted therapy, hormonal therapy as well as radiation therapy, all of which have been shown to improve long-term outcome of patients.

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Optimizing the quality of life during treatment is an important issue. From the patients' perceptive, chemotherapy-induced nausea and vomiting (CINV) is one of the most distressing adverse reactions of cancer therapy.[1] Since most of the chemotherapy regimens for breast cancer are of moderate emetogenic potential, optimization of an antiemetic regimen would significantly improve quality of life and potentially increase patients' acceptability and tolerability of chemotherapy, thereby allowing an increase in the completion rate of planned treatment, which has been shown to improve survival.

CINV may be classified into three categories: acute CINV starts within the first 24 hours after the initiation of chemotherapy. Delayed CINV occurs after the acute phase that peaks in 2–3 days and can last up to 1 week. Anticipatory nausea and vomiting occurs in subsequent cycles of chemotherapy secondary to a history of poor response to antiemetic agents in the previous cycle of chemotherapy that may in part be due to inadequate antiemetic prophylaxis; in these patients, emetic episodes are learned responses triggered by taste, odour, sight, thoughts, or anxiety.[1] An ideal antiemetic regimen should provide adequate antiemetic protection throughout the acute and delayed period of nausea and vomiting.

This article reviews the emetogenic risk factors and antiemetic therapy options for CINV in breast cancer patients as well as their safety and tolerability profiles.

Risk factors for CINV

The extent of chemotherapy-induced emesis depends on the emetogenic potential of the specific chemotherapeutic agent and regimen as well as patient-related factors.

Treatment-related factors

Treatment-related factors include the type of chemotherapy, dosage of the chemotherapeutic agents used, schedule, and route of administration. Standard regimens for breast cancer have often included combinations of agents, most commonly involving cyclophosphamide, anthracyclines such as doxorubicin and epirubicin, 5-fluorouracil (5-FU), methotrexate, taxanes including docetaxel and paclitaxel, and vinca alkaloids. These agents and combination regimens used are considered to be of different emetogenic potentials[5,6] (Table 1). Of note, one of the most common regimens that have been used in breast cancer patients is the doxorubicin-cyclophosphamide combination, commonly known as AC, which has been regarded to be of at least moderate emetogenic potential.[7–9]

Table 1 Relative emetogenic potential of chemotherapeutic agents in breast cancer patients (if no antiemetic prophylaxis is used)[a]

High (emetic risk ≥90%)	Intravenous agents
	Cisplatin
Moderate	Intravenous agents
(emetic risk 30%–90%)	Carboplatin
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin
	Epirubicin
	Combination of AC (doxorubicin and cyclophosphamide)[b]
	Oral agents
	Cyclophosphamide
	Vinorelbine
Low (emetic risk 10%–30%)	Intravenous agents
	Gemcitabine
	Liposomal doxorubicin
	Docetaxel
	Paclitaxel
	Methotrexate
	Flurouracil
	Trastuzumab
	Oral agents
	Capecitabine
Minimal (emetic risk <10%)	Intravenous agents
	Vinorelbine
	Bevacizumab

Notes: [a]With reference to MASCC/ESMO guidelines. Most of these drugs are similarly classified in the ASCO and NCCN guidelines. However, based on the experience and expertise of the panel members of each, variations exist between these guidelines; [b]AC combination represents a regimen of particularly great risk of nausea and vomiting.

Patient-related factors

In the general cancer patient population, the younger age group (<50 years) has been found to be more susceptible to CINV.[2] On the other hand, older age is associated with impaired metabolism of chemotherapy, which can lead to increased comorbidity. Further, older patients tend to suffer comorbidities and hence are often taking other medications, which may increase the risk of unwanted drug interactions and adverse effects. In addition, patients who have motion sickness and prior history of CINV are more susceptible to CINV. Conversely, patients with a history of high alcohol consumption have lower risk of CINV.[3,4]

A study of breast cancer patients has recently become available, and analysis in those receiving cyclophosphamide with doxorubicin or epirubicin combination chemotherapy confirmed that younger age (<55 years), no or low alcohol intake (0–4 drinks per week) and a history of pregnancy-related morning sickness are risk factors for CINV.[5] These findings were supported by another study based on other cancer patients who received cisplatin-based chemotherapy,[6] in which female gender was also identified as a risk factor.

Pathophysiology of nausea and vomiting

Nausea and vomiting are protective reflexes that rid the intestine and stomach of toxic substances. Multiple organs and various neurotransmitters are involved in the response to emetic triggers. Vomiting is triggered when afferent impulses from the cerebral cortex, chemoreceptor trigger zone, pharynx, and vagal afferent fibers of the gastrointestinal tract travel to the vomiting center, which is located in the medulla. Efferent impulses then travel from the vomiting center to the abdominal muscles, salivation center, cranial nerves, and respiratory center, thereby causing vomiting. The main neurotransmitter receptors involved in this signaling are serotonin (specifically 5-HT3), neurokinin-1 (NK-1), and dopamine receptors. During chemotherapy, serotonin is released and activates the 5-HT3 receptors which are present predominantly on the peripheral terminals of vagal afferents in the gastrointestinal tract and in the chemoreceptor trigger zone that lies in the area postrema outside of the blood–brain barrier. The chemoreceptor trigger zone signals to another area, the nucleus tractus solitarius, in the brain stem that also receives emetogenic stimuli from higher brain centers (eg, cortical and vestibular) as well as gastrointestinal vagal afferents, and is thought to orchestrate the patterns of central activity underlying CINV. Within the nucleus tractus solitarius, substance P acting at central NK-1 receptors is one of the final common mechanisms involved in activation and coordination of the vomiting reflex. Thus, antiemetic agents that target 5-HT3 receptors are effective in acute CINV, whereas agents that act on central NK-1 receptors, by way of blocking substance P, are effective for both acute and delayed CINV.

Other receptors that are involved include corticosteroid, histamine, cannabinoid, acetylcholine, GABA-containing, and opiate receptors.

Efficacy and safety of antiemetic agents

Advances in the understanding of the mechanisms of emesis have led to the development of more effective ways to minimize this distressing side effect.

In earlier studies, antiemetic agents were tested mostly on focused patients who were being treated with cisplatin, a cytotoxic which is regarded to be of high emetic risk. Most clinicians agree that an agent that reduces or prevents emesis following cisplatin will be at least as effective for other chemotherapeutic agents of high-to-moderate emetic potential. With the increase in data on antiemetics usage among cisplatin-treated patients, subsequent studies have focused on antiemetic cover for patients receiving anti-cancer treatment of moderately emetogenic potential, particularly regimens or agents for patients with breast cancer.

Combination chemotherapies that contain cyclophosphamide and an anthracycline, such as AC, are commonly used either in adjuvant or metastatic settings in breast cancer. Since the last decade, there has been growing awareness that women receiving AC or similar combination therapy are at high risk of emesis. As a result, AC or its similar counterpart has become the standard emetic stimulus in clinical trials that assess antiemetic agents among breast cancer patients.

Nowadays, antiemetic agents that are regarded as having the highest therapeutic index include NK-1 receptor antagonists, 5-HT3 receptor antagonists, and corticosteroids. Other classes of antiemetics that exist and are considered as part of the antiemetic regimens, include anticholinergics, dopamine antagonists, anxiolytics, antihistamines, and cannabinoids. In this review, the discussion will focus on data with regard to corticosteroids, 5-HT3 receptor antagonists, and NK-1 receptor antagonists.

Corticosteroids

Corticosteroids have a high therapeutic index in preventing chemotherapy-induced emesis. The mechanism of their action is not well known and could have been due to their anti-inflammatory effect. They are an integral part of antiemetic therapy for acute and delayed CINV.

Dexamethasone is recommended by all guidelines/consensus based on the fact that it is the corticosteroid most extensively studied and it is widely available. It is especially valuable when administered in combination with 5-HT3 receptor antagonists and NK-1 receptor antagonists in patients receiving chemotherapy of high or moderate emetic risk. In a recent meta-analysis, dexamethasone was revealed to be of particular value in preventing delayed CINV.[16]

Although a single dose of dexamethasone has been considered to be generally tolerable, it has been reported that hyperglycemia may occur even after one dose of 20 mg. Other common adverse effects are moderate-to-severe insomnia, epigastric discomfort, agitation, increased appetite, weight gain, and acne.[7]

5-HT3 receptor antagonists

The common 5-HT3 receptor antagonists that are currently available include ondansetron, granisetron, tropisetron, dolasetron, and palonosetron. Apart from polanosetron, these agents have been reported to have equivalent efficacy and safety profiles when given at equivalent doses and they can be used interchangeably for the prevention of acute CINV.[4,8] Single-dose

daily schedules have similar efficacy to multiple-dose daily schedules. Oral formulations are as effective as intravenous formulations.[8,9] These agents are well tolerated; the common adverse events include headache, transient elevation of hepatic aminotransferase levels, and constipation.[10] Apart from intravenous dolasetron which has been reported to be associated with an increased risk of potentially fatal torsade de pointes, there have been no reported clinical cardiovascular adverse events with the other 5-HT3 antagonists.[11] The cardiotoxicity associated with dolasetron has led to the US Food and Drug Administration (FDA) announcing that its injection formulation should no longer be used for the prevention of CINV in December 2010.

When combined with corticosteroids, 5-HT3 receptor antagonists are proven to be effective in controlling acute CINV in patients receiving highly emetogenic chemotherapy and moderately emetogenic chemotherapy especially in combination with corticosteroid.[12–15] The efficacy of this combination has been evaluated in numerous randomized clinical trials. For acute CINV, complete response rates can be achieved among 60%–70% and 80%–90% of patients who undergo high emetogenic and moderately emetogenic chemotherapy, respectively.[16–19] However, 5-HT3 receptor antagonists are not universally accepted as standard prophylactic therapy for delayed CINV.[1,14] In a meta-analysis by Geling et al, 5-HT3 receptor antagonists (excluding palonosetron) did not significantly improve control of delayed CINV.[10]

Palonosetron is the newest 5-HT3 receptor antagonist with a high binding affinity for the 5-HT3 receptor that is about 100-fold greater than that of ondansetron, granisetron, and dolasetron. In addition, it has a significantly longer half-life of around 40 hours.

There have been two noninferiority registration trials on the efficacy of palonosetron. In the first study,[20] 64% of patients received AC regimen, 17% patients received carboplatin-based regimen, and 7% patients received cyclophosphamide-based chemotherapy; palonosetron was found to be as effective as dolasetron for the prevention of acute emesis. In the second study, breast cancer patients accounted for 57% of the studied population;[21] intravenous palonosetron was proven to be superior to ondansetron in the prevention of acute emesis. In both of these trials, patients were also observed for delayed emesis in the absence of additional prophylactic antiemetics. For patients who received intravenous 0.25 mg palonosetron, complete response (no emetic episodes and no use of rescue medications) during 24–120 hours after chemotherapy was improved by 19% when compared to those who received ondansetron ($P = 0.001$), and by 15% when compared to those who received dolasetron ($P = 0.004$). Based on these studies, palonosetron was approved by the US FDA as the only 5-HT3 receptor antagonist with the indication for the prevention of both acute and delayed nausea and vomiting associated with initial and repeated courses of moderately emetogenic cancer chemotherapy.[22]

More recently, Saito et al have reported on a study in which half of the patients had breast cancer and were receiving anthracyline (doxorubicin or epirubicin) and cyclophosphamide combination chemotherapy. When compared to granisetron, palanosetron demonstrated a superior efficacy in preventing both the acute and delayed phase emesis.[23]

Further, in the study by Aapro et al,[24] the possibility of reducing the total dose of corticosteroids with the use of palonosetron was evaluated. The result showed that single-day palonosetron and dexamethasone can offer similar extents of protection to CINV when compared to that of multiple-day dexamethasone administration. Although the exact type of chemotherapeutic regimen was not stated in the studied population in the report by Aapro et al,[24] another study[25] confirmed that this single-day regimen of intravenous palonosetron plus dexamethasone was effective in the subgroup of patients who received AC.

An oral capsule formulation of palonosetron had been approved by the US FDA in 2008 for the prevention of acute nausea and vomiting after initial and repeated courses of moderately emetogenic chemotherapy.[26] The approval was based primarily on the data from a multicenter, randomized, double-blind, active-control clinical study which consisted of 635 patients.[27] During the acute-phase, oral palonosetron (0.5 mg) was noninferior to the 0.25 mg intravenous dose of palonosetron (76.3% vs 70.4%; 2-sided 98.3% confidence interval [CI]: −6.5%–18.2%). However, statistical noninferiority was not demonstrated during the delayed phase (62.5% vs 65.4%; 98.3% CI: 16.3%–10.5%).

In a recent meta-analysis assessing the efficacy of various 5-HT3 antagonists, palonosetron was shown to be more effective than other available 5-HT3 antagonists in preventing acute as well as delayed nausea and vomiting for both high and moderately emetogenic chemotherapy.[28]

Neurokinin-1 receptor antagonists

Aprepitant is the first approved NK-1 receptor antagonist[29] and is the only currently available agent in this class.

The initial published studies on aprepitant have been conducted in patients on high-dose cisplatin chemotherapy.[30] The efficacy of NK-1 receptor antagonists for chemotherapy other than cisplatin was postulated based on preclinical data[31]

and an unplanned subset analysis of the original studies, which assessed patients who received anthracycline or cyclophosphamide in addition to cisplatin.[32]

A subsequent study was conducted among patients who received moderately emetogenic chemotherapy, with 99% of 857 patients evaluated being on AC with or without other mildly emetogenic agents.[33] This double-blind randomized study assigned patients to either an aprepitant-containing regimen (triple combination of ondansetron, dexamethasone, and aprepitant in the first 24 hours, followed by aprepitant monotherapy for another 2 days), or a control regimen (combination of ondansetron and dexamethasone on day 1, followed by ondansetron for another 2 days). The aprepitant dosage consists of 125 mg on day 1 followed by 80 mg on days 2 and 3. The results showed that the proportion of patients who achieved complete response over 0–120 hours after the initiation of chemotherapy and the proportion with minimal or no impact on daily life according to the FILE questionnaire were significantly higher in favor of the aprepitant-containing regimen, 51% vs 42% ($P = 0.015$) and 64% vs 56% ($P = 0.019$), respectively. This has led to US FDA approval for aprepitant to be used in patients receiving moderately emetogenic chemotherapy in 2005. However, the study did not shown a benefit from aprepitant in terms of the endpoint of superiority in the prevention of nausea. Further safety and efficacy data were collected and reported for subsequent cycles of chemotherapy.[34] Aprepitant had sustained superiority over the control regimen; although both the aprepitant and control groups showed some reduction in efficacy over subsequent cycles, there was still an absolute improvement from 7% to 14.4% in complete response in the aprepitant groups.

A study with similar design to the above study was conducted by our group.[35] This study involved 120 Chinese breast cancer patients who uniformly received AC chemotherapy. The results revealed that patients receiving the aprepitant-based regimen had a significantly better quality of life in the vomiting domain regimen (mean score [SD] = 3.40 [13.18]) when compared with those who received the standard antiemetic (mean score [SD] = 23.99 [30.79]) ($P = 0.0002$). Further, the requirement for rescue medication appeared to be lower in patients treated with the aprepitant-based regimen than those given standard antiemetic regimen (11% vs 20%; $P = 0.06$).

The combination of aprepitant with palonosetron has been reported by Grunberg et al among 41 patients who received AC regimen.[36] This study evaluated a more convenient single-day three-drug antiemetic regimen for patients receiving moderately emetogenic chemotherapy. The dose of oral aprepitant was 285 mg given in combination with 0.25 mg intravenous palonosetron and 20 mg oral dexamethasone. Ninety-five percent of patients remained emesis-free over the 120-hour study period, without apparent safety concerns at this higher dose of aprepitant. However, palonosetron has not been studied with aprepitant in a double-blind, randomized fashion.

Fosaprepitant is the pro-drug for aprepitant which is administered intravenously. It is converted into aprepitant within 30 minutes after intravenous administration. Based on an equivalent study, 115 mg of fosaprepitant was the approved dose to be the substitute for the 125 mg orally administrated dose in the US. On the basis of publicly available data, oral aprepitant (125 mg) and intravenous fosaprepitant (115 mg) have similar mean plasma concentrations at 24 hours after dose and fosaprepitant up to 150 mg is generally well tolerated. There is no difference in the tolerability of the pro-drug from the active drug.[37] When fosaprepitant or ondansetron is given as monotherapy prior to cisplatin, fosaprepitant was shown to be active against cisplatin-induced emesis, particularly in the delayed phase.[38] In the acute period, the proportion of patients without emesis in the fosaprepitant group and ondansetron groups were 37% and 52%, respectively ($P > 0.05$). In the delayed period, the proportion of patients without emesis in the fosaprepitant and ondansetron treatment groups was significantly different at 72% and 30%, respectively ($P = 0.005$). On the other hand, the acceptable tolerability and efficacy of fosaprepitant with dexamethasone has also been reported in a Phase II study.[39] These early studies suggested that fosaprepitant could be used as an intravenous alternative to its oral counterpart, aprepitant.

Casopitant is a potent, selective, small-molecule, non-peptide competitive NK-1 receptor antagonist which can be administered orally or intravenously. In a large Phase III trial, patients were randomly assigned to one of the four arms: the control arm (placebo), a single oral dose casopitant arm (150 mg orally [PO] on day 1), a 3-day oral casopitant arm (150 mg PO on day 1, plus 50 mg PO on days 2–3), or a 3-day IV/oral casopitant arm (90 mg IV on day 1, plus 50 mg PO on days 2–3). All patients received dexamethasone 8 mg intravenously on day 1 and oral ondansetron 8 mg twice daily on days 1–3. Complete response (CR) rates for CINV were similar in all three treatment arms (73%–74%) and were superior to the control arm (59%, $P < 0.0001$).[40] This study demonstrates that a single-day intravenous casopitant was equally effective to the 3-day oral regimen, and the result of this study has paved the way for subsequent trials using neurokinin receptor-1 antagonist as a single-day intravenous regimen.

Thus, in the large Phase III EASE (evaluation of fosaprepitant in single-dose schedule) study, the efficacy of a single intravenous dose of fosaprepitant at 150 mg on day 1 was tested against the 3-day oral aprepitant regimen in patients receiving highly emetogenic chemotherapy. The result revealed that both arms had similar efficacy.[41]

However, due to the requirement of further safety assessment by the European Medicines Agency, the marketing of casopitant was withdrawn by the parent company in 2009, and further development of this agent has since been halted.

Both the single-day intravenous fosaprepitant and the 3-day oral aprepitant regimens are well tolerated. The most common adverse effects include headache, anorexia, fatigue, diarrhoea, hiccups, and mild transaminase elevation.[29,42–44] However, pain, erythema, or thrombophlebitis over the infusion site was more frequently reported among patients who received intravenous fosaprepitant (2.7% vs 0.3%, respectively). Thus, although single-dose intravenous regimen might improve patients' adherence and could simplify the schedules of antiemetic medication for patients and caregivers, the venous toxicities may deter wider acceptability of this agent.

Aprepitant is metabolized by cytochrome P450 (CYP3A4). It is a moderate inhibitor of CYP3A4 and mild inducer of CYP2C9; therefore, possible interactions between aprepitant and other drugs have been investigated. It has been reported that dexamethasone, a sensitive substrate of CYP3A4, has to have the dose reduced by 50% when given with aprepitant.[45–48]

Aprepitant has been reported to induce warfarin metabolism causing low international normalized ratio values as a result of its interaction with CYP2C9. Caution is therefore required when warfarin is administered together with aprepitant.[49] Other agents that may have potential interaction with aprepitant include phenytoin, itraconazole, and terfenadine.[45,48] Concern over the possible interaction of oral contraceptive medication with aprepitant has been reported but to our knowledge, there has been no report that directly addresses fosaprepitant in association with oral contraceptives. With the addition of aprepitant, reduction in AUC of ethinyl estradiol and norethindrone from baseline has been reported. Thus, it has been recommended that barrier contraception should be practiced during, and for 1 month following aprepitant treatment.[50]

Based on pharmacokinetic studies, aprepitant has been shown to have no significant toxicity when used together with 5-HT3 antagonists, including ondansetron, granisetron, and palanosetron,[50] as well as cytotoxic agents such as docetaxel,[51] vinorelbine,[50] and cyclophoshamide.[52] Importantly, based on the Phase III trial of moderately emetogenic chemotherapy, there were no significant differences in efficacy and chemotherapy-related toxicity between the aprepitant and control regimen.[33] Therefore, the clinical relevance of these potential interactions appears to be rather low after years of clinical experience.[50]

Prevention of CINV

The choice of antiemetic regimens for an individual patient is based largely on the risk of CINV. The approach of incorporating patient prognostic factors for CINV of individual patients into the emetic-risk assessment as a basis to modify the antiemetic regimen has been attempted. In the study by Warr et al,[5] older age, high ethanol use, and the absence of history of pregnancy-related morning sickness were identified as low-risk factors for CINV among breast cancer patients receiving anthracycline and cyclophosphamide combination chemotherapy. However, these factors were not considered to be clinically relevant for decision-making in antiemetic regimens, as only 3% of patients who were given an NK-1 receptor antagonist with 5-HT3 receptor antagonist and corticosteroids were considered to belong to the low-risk category. Hesketh et al[6] have also recently reported that although risk factors for emesis could be identified among patients receiving cisplatin-based chemotherapy, an appropriate antiemetic regimen with the inclusion of NK-1 receptor antagonist improved complete response to emesis, and this was irrespective of risk factors; further, optimal emetic regimens were found to eliminate the increased risk of CINV associated with the female gender. Thus, the chemotherapeutic agent or regimen to be administered remains to be the main determinant in assessing the emetogenic potential for CINV.

Adequate prophylactic antiemetic therapy should be given to all patients receiving anti-cancer treatments. Three main bodies have published antiemetic guidelines; these include the Multinational Association for Supportive Care in Cancer/European Society of Medical Oncology (MASCC/ESMO), the American Society of Clinical Oncology (ASCO), and the US National Comprehensive Cancer Network (NCCN).[9–11]

Based on these guidelines, individual chemotherapeutic agents or combinations are classified into four main emetic risk groups according to their emetogenic potential: high (>90% of patients having emetic episodes when no prophylactic antiemetic protection is provided), moderate (30%–90%), low (10%–30%), and minimal (<10%). Table 1 lists the emetogenic potential of various agents (including cytotoxics and biologics) that are commonly used in breast

cancer, based on MASCC/ESMO guidelines. The ASCO and NCCN have similar classifications in the respective guidelines, although slight variations exist, which are based on the experience and expertise of the individual panel members of each organization. It also has to be noted that whilst individual agents may be considered to be of moderate emetogenic potential, combinations of these agents may be regarded as having higher emetogenicity than the individual agents. For example, whilst doxorubicin and cyclophosphamide are individually considered to be of moderate emetogenic potential, the combination of these two agents as AC is considered to be a regimen of high emetogenic potential by NCCN, while according to ASCO and MASCC/ESMO, this is categorized as one regimen of moderate emetogenic potential but managed in a similar manner to that of high emetogenic potential.

Different levels of antiemetic prophylaxis for patients receiving different anti-cancer treatments used have been recommended according to the emetogenic potential of the agents (Table 2).

High emetogenic chemotherapy

Cisplatin is universally accepted to be of high emetogenic potential. AC has been put under this category according to NCCN guidelines.

Acute CINV

All three guidelines consistently recommend the triple combination of a 5-HT3 receptor antagonist, dexamethasone, and an NK-1 receptor antagonist (aprepitant/fosaprepitant) within the first 24 hours for acute CINV. In the MASCC/ESMO guidelines, fosaprepitant 115 mg is recommended on day 1 which can be considered with oral aprepitant on days 2–3. According to the NCCN guidelines, when a higher dose of fosaprepitant (150 mg) is used on day 1, oral aprepitant on days 2–3 could be omitted; however, the 150 mg dose is not an approved dose in countries including the US. For the dose of dexamethasone, all three guidelines recommend 20 mg prior to chemotherapy, although in the presence of NK-1 receptor antagonist, this dose can be reduced to 12 mg.

Delayed CINV

Adequate prophylaxis is indispensable as up to 90% of patients will experience delayed emesis when preventive antiemetics have not been administered. The guidelines suggest the combination of dexamethasone and an NK-1 receptor antagonist. The dose of dexamethasone recommended is 8 mg daily on days 2–4. The NCCN guidelines also suggest the addition of lorazepam in preventing both acute and delayed CINV.

Table 2 Antiemetic prophylaxis based on emesis risk as categorized by MASCC/ESMO, ASCO, and NCCN[8,12,58]

Guidelines/ consensus	Recommendation							
	High		Moderate		Low		Minimal	
	Acute CINV	Delayed CINV	Acute CINV	Delayed CINV	Acute CINV	Delayed CINV	Acute CINV	Delayed CINV
MASCC/ ESMO	5-HT3 RA + Dexa + Apr	Dexa + Apr	5-HT3 RA + Dexa *AC regimen*: 5-HT3 RA + Dexa + Apr	Dexa Apr	Dexa or 5-HT3 RA or DRA	a	a	a
ASCO	5-HT3 RA + Dexa + Apr	Dexa + Apr	5HT3 RA + Dexa *AC regimen*: Same as MASCC/ ESMO	Dexa or 5-HT3 RA	Dexa	a	a	a
NCCN	5-HT3 RA + Dexa + Apr ± Lora or 5-HT3 RA + Dexa + Fosapr *AC regimen*: Same	Dexa + Apr ± Lora or Dexa ± Apr Same	5-HT3 RA + Dexa ± Apr/Fosapr ± Lora (Palo D1 only)	5-HT3 RA or Dexa or Apr ± Dexa (if Apr used on D1) ± Lora	Dexa or prochlorperazine or metoclopramide ± Lora	a	a	a

Abbreviations: a, No routine prophylaxis; 5-HT3 RA, 5-HT3-receptor antagonist; AC, doxorubicin and cyclophosphamide; Apr, Aprepitant; ASCO, American Society of Clinical Oncology; Cosapr, cosaprepitant; CINV, chemotherapy-induced nausea and vomiting; Dexa, Dexamethasone; DRA, Dopamine Receptor Antagonist; ESMO, European School of Medical Oncology; Lora, lorazapam; MASCC, Multinational Association of Supportive Care in Cancer; NCCN, National Comprehensive Cancer Network; Palo, Palonosetron.

Moderately emetogenic chemotherapy

Intravenous carboplatin, cyclophosphamide, anthracyclines (doxorubicin and epirubicin), and oral cyclophosphamide and vinorelbine fall under this category. It has to be highlighted, however, that AC is placed under moderate emetogenic risk in the MASCC/ESMO and ASCO guidelines.

Acute CINV

All three guidelines recommend the combination of a 5-HT3 receptor antagonist plus dexamethasone. In addition, NCCN recommends the consideration of triple combination (with the addition of aprepitant or fosaprepitant), with or without lorazepam. According to the MASCC/ESMO and ASCO guidelines, the antiemetic prophylaxis for patients receiving AC is very much a regimen that is applied for patients receiving chemotherapy of high emetogenic potential. The MASCC/ESMO guidelines recommend that if an NK-1 receptor antagonist is not available for patients receiving AC chemotherapy, palonosetron would be the preferred 5-HT3 receptor antagonist as it is also effective in preventing delayed CINV.

With respect to the dose of dexamethasone, MASCC/ESMO recommends a single dose of 8 mg, while NCCN suggests 12 mg as a single dose.

Delayed CINV

Dexamethasone is recommended by all three guidelines as the agent of choice for delayed CINV, and the recommended dose of dexamethasone is either 4 mg twice a day or 8 mg daily on days 2–3. While ASCO and NCCN consider one of the 5-HT3 receptor antagonists as an alternative, data on their role in the delayed phase is rather limited.[13] The NCCN guidelines suggest that if aprepitant is used on day 1, then it can be combined with dexamethasone on days 2–3. This is in line with the recommendations of ASCO and MASCC/ESMO, which are mostly driven by the study of Warr et al.[33] In the study reported by Warr et al,[33] patients receiving moderately emetogenic chemotherapy were randomized to either aprepitant or ondansetron, given as monotherapy on days 2–3, for the prevention of delayed CINV. A complete response rate of 55% and 49%, respectively, was achieved in the delayed phase ($P = 0.064$). Based on these results, the combination of dexamethasone and aprepitant in the delayed phase has been suggested to have greater antiemetic efficacy.

If palonosetron is used, injection on day 1 is considered adequate without further requirements on days 2–3. Metoclopramide is not recommended.

Low emetogenic chemotherapy

Anti-cancer agents under this category include intravenous gemcitabine, liposomal doxorubicin, taxanes (docetaxel and paclitaxel), methotrexate, flurouracil, and trastuzumab, as well as oral capecitabine. Within the first 24 hours, all guidelines recommend dexamethasone as the antiemetic of choice, while dopamine receptor antagonist or 5-HT3 receptor antagonist have been recommended as alternatives to dexamethasone by MASCC/ESMO and NCCN guidelines. Prophylaxis beyond 24 hours has not been recommended.

Minimally emetogenic chemotherapy

Agents under this category include intravenous vinorelbine and bevacizumab. All three guidelines recommend that no antiemetic drug is routinely required for patients treated with agents of low emetic risk.

Conclusions

Breast cancer constitutes a significant proportion of the patient population in which chemotherapy is commonly indicated. The adjuvant chemotherapies for breast cancer usually involve moderately to highly emetogenic agents and regimens. Chemotherapy-induced nausea and vomiting can result in significant morbidity and impairment in quality of life, which may ultimately lead to poor compliance to anticancer treatment regimens that are potentially curative.

AC is one of the most common regimens used for breast cancer patients in the adjuvant setting. Although AC has been categorized by different guidelines as a regimen of highly or moderately emetogenic potential, all of them have consistently recommended this regimen to be managed as one of high emetogenicity, with antiemetic prophylaxis consisting of agents with the highest therapeutic index from three classes to be used, namely corticosteroid, 5-HT3, and NK-1 receptor antagonists.

Of interest, while these agents are currently considered to be targeting the prevention of CINV, it has been implicated that NK-1 receptor antagonists may have anti-tumor effects in addition to their antiemetic effect. Studies have shown that interaction exists between tachykinin peptides and neurokinin receptors, which has been correlated with breast cancer cell integration into the bone marrow microenvironment and breast cancer progression.[53] Investigations targeting neurokinin receptors may provide further insight into the additional role of this class of agents in cancer therapy.

While antiemetic regimen is being optimized with evidence-based antiemetic guidelines, it has to be mentioned that caregiver compliance has been reported to be disappointing in a number of studies.[54–57] There is, therefore, a great need to improve compliance to the recommended antiemetic guidelines among caregivers, as well as patients.[58]

Finally, clinicians have to acknowledge that despite the substantial progress in antiemetic therapy over the past two decades, symptoms of nausea remain a particularly challenging aspect of administering anticancer therapy. Nausea is not easily detectable unless specifically addressed during a medical assessment; however, it can lead to withdrawal of the patient and could impair the quality of life of an individual during chemotherapy. Further understanding of the underlying pathophysiology of CINV would allow the development of new drugs that could target specific neural signaling pathways involved in the triggering of nausea as well as vomiting.

Disclosure

The authors report no conflicts of interest in this work.

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