REVIEW

Recent advances in antiemetics: new formulations of 5HT$_3$-receptor antagonists

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Purpose: To discuss new therapeutic strategies for chemotherapy-induced nausea and vomiting (CINV) involving 5-hydroxytryptamine type 3 (5HT$_3$)-receptor antagonists (RAs).

Summary: CINV remains poorly controlled in patients receiving moderately emetogenic chemotherapy (MEC) or highly emetogenic chemotherapy (HEC); nausea and delayed-phase CINV (24–120 hours after chemotherapy) are the most difficult to control. National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) antiemesis-guideline recommendations for HEC include a four-drug regimen (5HT$_3$ RA, neurokinin 1 [NK$_1$] RA, dexamethasone, and olanzapine). For some MEC regimens, a three-drug regimen (5HT$_3$ RA, NK$_1$ RA, and dexamethasone) is recommended. While 5HT$_3$ RAs have dramatically improved CINV in the acute phase (0–24 hours after chemotherapy), their efficacy declines in the delayed phase. Newer formulations have been developed to extend 5HT$_3$-RA efficacy into the delayed phase. Granisetron extended-release subcutaneous (GERSC), the most recently approved 5HT$_3$ RA, provides slow, controlled release of therapeutic granisetron concentrations for ≥5 days. GERSC is included in the NCCN and ASCO guidelines for MEC and HEC, with NCCN-preferred status for MEC in the absence of an NK$_1$ RA. Efficacy and safety of 5HT$_3$ RAs in the context of guideline-recommended antiemetic therapy are reviewed.

Conclusion: Recent updates in antiemetic guidelines and the development of newer antiemetics should help mitigate CINV, this dreaded side effect of chemotherapy. GERSC, the most recently approved 5HT$_3$-RA formulation, is indicated for use with other antiemetics to prevent acute and delayed nausea and vomiting associated with initial and repeat courses of MEC and anthracycline–cyclophosphamide combination-chemotherapy regimens.

Keywords: chemotherapy-induced nausea and vomiting, serotonin-receptor antagonist, granisetron extended-release subcutaneous, granisetron extended-release injection, granisetron

Plain-language summary

This review article discusses different treatments that are used to prevent nausea and vomiting (NV) experienced by people with cancer who are being treated with chemotherapy: chemotherapy-induced NV (CINV). The article is about chemotherapy treatments that are the most likely to cause NV in people with cancer, called moderately emetogenic chemotherapy (MEC) and highly emetogenic chemotherapy (HEC). Guidelines from major medical organizations on how to prevent CINV are compared, and the problems in preventing CINV are discussed. Different types of drugs used to treat CINV and different combinations of these drugs are described. Even though several types of drugs are available to prevent CINV, many patients with cancer still suffer from NV. The advantages and disadvantages of drugs used to treat CINV are explained, and information about recently approved new drugs and new forms of existing drugs is provided. The article

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mainly describes a class of drugs called 5HT$_3$-receptor antagonists, which are often used to prevent nausea and vomiting. New drugs and new combinations of drugs may help control CINV in people with cancer who are treated with chemotherapy.

Introduction

Chemotherapy-induced nausea and vomiting (CINV) adversely affects patient health,[1,2] quality of life,[3,4] and chemotherapy compliance,[5] and is one of the most dreaded effects of chemotherapy.[6] This review focuses on current approaches and future directions involving 5-hydroxytryptamine type 3 (5HT$_3$)-receptor antagonists (RAs) for the management of CINV. Use of 5HT$_3$ RAs in the prevention of radiotherapy-induced and chemoradiation-induced NV is discussed briefly.

Chemotherapeutics differ in their emetogenicity. In the absence of antiemetic prophylaxis, agents associated with >90% risk of emesis are classified as highly emetogenic chemotherapy (HEC) and those associated with 30%–90% risk of emesis classified as moderately emetogenic chemotherapy (MEC).[7–9] Several oral targeted anticancer therapies, such as crizotinib, lenvatinib, olaparib, and panobinostat, are also recognized as being highly or moderately emetogenic.[7] The emetogenicity of combination regimens is determined by identifying the most emetogenic agent in the combination, then assessing the relative contribution of the other agents.[7,8] This review discusses treatment options for the prevention of CINV associated with MEC and HEC, as these are the most challenging settings; it does not discuss management of CINV associated with agents that have low-to-minimal emetogenicity.

In clinical trials, measurement of antiemetic efficacy covers a range of end points, involving emesis, nausea, and assessments of rescue medication use for breakthrough CINV (ie, CINV occurring despite the use of prophylactic antiemetics). A commonly used end point is complete response (CR; no emesis and no rescue medication use) during the acute phase (first 24 hours), delayed phase (>24–120 hours), and overall phase (0–120 hours) following chemotherapy administration. End points that also specifically involve nausea include complete control (CC; CR and only mild nausea), total response (CR and no nausea), and no nausea or no significant nausea (typically measured as <25 mm on a 100 mm visual analogue scale).

Despite considerable advances in antiemetics over the past 20 years, beginning with the introduction of the 5HT$_3$ RAs, prevention of CINV remains suboptimal. For example, one study in a community hospital setting found that chemotherapy-induced nausea and vomiting was reported in approximately 50% and up to a quarter of patients,

respectively, despite antiemetic prophylaxis.[10] Delayed CINV seems to be less well managed than acute CINV. In a US prospective study, 34% of patients reported experiencing acute CINV, whereas 58% of patients reported experiencing delayed CINV.[4] Both nausea and emesis appear to be more prevalent during the delayed phase than in the acute phase of CINV.[1] Lack of adequate CINV control has multiple adverse consequences. The negative effects of CINV on patient health and quality of life are well known, including reducing patient daily functioning, increasing patient anxiety and depression, and decreasing the patient's chemotherapy treatment adherence, leading to chemotherapy reductions or delays.[1,3,5,10–12] In addition, the costs of poorly controlled CINV are considerable. Analysis of data from 2018 working-age patients in a large US employment database with information from 45 large employers and more than 100 health-insurance payers (1997–2002) found that 28% of patients had uncontrolled CINV, and the associated monthly medical costs for these patients were approximately US$1,300 higher and indirect costs US$433 higher than for patients whose CINV was well controlled.[13] Using another database of more than 19,000 patients, 14% of patients had a CINV-associated hospital visit (inpatient, outpatient, or emergency room), and the mean cost per visit was US$4,043.[14] Therefore, prevention of CINV, especially delayed CINV, is critical in patients receiving chemotherapy, for both economic reasons and patient welfare.

Most 5HT$_3$-RA trials have focused on emesis control, using CR as a primary end point and nausea-control measures as secondary end points. Although emesis control has improved using new classes of antiemetics, the management of nausea, particularly in the delayed phase following HEC, is difficult. However, recent clinical trial focus has turned toward nausea control and the use of different classes of agents to prevent nausea. In a recent Phase III placebo-controlled trial of the antipsychotic olanzapine plus a three-drug antiemetic regimen (a neurokinin 1 [NK$_1$] RA plus a 5HT$_3$ RA plus dexamethasone) in patients receiving HEC, nausea prevention was the primary end point. The proportion of patients with no nausea was significantly higher with the addition of olanzapine across acute, delayed, and overall phases of CINV.[15]

Granisetron (Kytril; Roche Laboratories Inc., Nutley, NJ, USA [oral] and Genentech, San Francisco, CA, USA [intravenous]), ondansetron (Zofran; GlaxoSmithKline, Research Triangle, NC, USA), and palonosetron (Aloxi; Eisai, Woodcliff Lake, NJ, USA), are the most commonly used 5HT$_3$ RAs and the focus of this review. Dolasetron IV (Anzemet; Sanofi-Aventis, Bridgewater, NJ, USA) is no longer approved in the USA to prevent CINV, because of potential cardiac effects. Other first-generation 5HT$_3$ RAs

include azasetron, ramosetron, and tropisetron; however, they are not commercially available in the USA.[11,16] This review discusses new therapeutic strategies involving 5HT$_3$ RAs to improve management of delayed CINV following HEC and challenges associated with nausea prevention.

Antiemetic-guideline recommendations

The goal of CINV prophylaxis is to prevent NV following MEC or HEC across both acute and delayed phases. Because CINV is multifactorial, antiemetic prophylaxis often involves agents targeting neurotransmitters with complementary mechanisms of action, such as 5HT$_3$ RAs, NK$_1$ RAs, and the atypical antipsychotic olanzapine. Several antiemesis guidelines for clinical practice are available, based on clinical evidence and expert consensus, from the National Comprehensive Cancer Network (NCCN),[7] Multinational Association for Supportive Care in Cancer (MASCC) and European Society of Medical Oncology (ESMO),[17,18] and American Society of Clinical Oncology (ASCO; Table 1[7,17–19]).[19]

However, despite the availability of comprehensive CINV-prevention guidelines and a wide range of antiemetics, guideline adherence remains low. The INSPIRE study, involving 1,295 patients from US community practices, found that guideline-consistent CINV prophylaxis was administered in only 57% of patients.[20] Corticosteroids were commonly omitted in the delayed phase in patients receiving HEC, as were NK$_1$ RAs on day 1 in patients receiving MEC regimens, although NK$_1$ RAs are not uniformly recommended with MEC in antiemetic guidelines.[7,17–20] Data from the Pan European Emesis Registry of 991 patients found that guideline-consistent CINV prophylaxis during single-day chemotherapy was administered in only 55% of patients in the acute phase and 46% of patients in the delayed phase, and that guideline-consistent CINV prophylaxis significantly reduced the incidence of CINV compared with guideline-inconsistent prophylaxis.[21] More recently, in a retrospective analysis of a US claims database, of 1,059 patients receiving MEC or HEC, those who were given a guideline-recommended three-drug antiemetic regimen of an NK$_1$ RA plus a 5HT$_3$ RA plus dexamethasone had fewer CINV-related emergency-department visits (9%) than patients receiving a two-drug regimen of a 5HT$_3$ RA plus dexamethasone (15%) and had fewer CINV-related hospitalizations (4% vs 6%, respectively).[22] Poor patient adherence to antiemetic regimens, especially to prescribed oral antiemetics, may also be a barrier to effective CINV control, as reported in a multinational survey of 2,388 health-care providers.[5] Clearly, patients experiencing NV may be reluctant to take oral medications, even if they are prescribed to control CINV, and many patients undergoing chemotherapy have oral mucositis, which reduces their ability to swallow.[23]

Highly emetogenic chemotherapy

For the prevention of CINV associated with single-day HEC, the NCCN and MASCC/ESMO guidelines are in agreement in recommending a three-drug regimen of a 5HT$_3$ RA plus an NK$_1$ RA plus a steroid (typically dexamethasone) on day 1 of chemotherapy, followed by dexamethasone on the subsequent 2 or 3 days, with an oral NK$_1$ RA on days 2 and 3 only if an oral NK$_1$ RA is given on day 1 (Table 1). The 2017 ASCO and 2018 NCCN guidelines recommend a four-drug regimen that incorporates olanzapine on day 1, in addition to the three-drug regimen just mentioned above, followed by dexamethasone on days 2 and 3, and an oral NK$_1$ RA on days 2 and 3 only if an oral NK$_1$ RA is given on day 1; this is also an option in the NCCN guidelines.[7,19] The NCCN also recommends olanzapine plus palonosetron and dexamethasone as an alternative option on day 1,[7] and MASCC/ESMO guidelines recommend olanzapine plus a 5HT$_3$ RA plus dexamethasone for nausea control, but give a low-grade recommendation for this regimen.[7,17]

Since 2011, the high emetogenicity of the combination of an anthracycline and cyclophosphamide (AC) has been recognized by the NCCN, ASCO, and MASCC/ESMO. AC-based regimens were reclassified from MEC to HEC in the ASCO antiemesis guidelines, and AC-based chemotherapy for patients with breast cancer has a distinct recommendation for CINV prevention within the HEC category in the MASCC/ESMO guidelines.[7,17,19] Consequently, the ASCO-recommended antiemetic regimen for AC-based regimens is now the same as that recommended by NCCN guidelines for any HEC regimen: primarily a four-drug combination of a 5HT$_3$ RA, dexamethasone, an NK$_1$ RA, and olanzapine on day 1, with olanzapine on days 2–4 and dexamethasone on days 2–4 depending on the NK$_1$ RA administered on day 1.[7,19] The MASCC/ESMO guidelines recommend the three-drug regimen for AC-based chemotherapy on day 1 for acute CINV, with aprepitant (if aprepitant was given on day 1) or dexamethasone on days 2 and 3 to prevent delayed CINV. However, if any NK$_1$ RA was given other than aprepitant on day 1, MASCC/ESMO guidelines state that no other treatment is necessary on subsequent days.[17]

Carboplatin

Although carboplatin is classified as moderately emetogenic in MASCC/ESMO and ASCO guidelines,[17–19] NCCN guidelines

Table 1 Antiemesis-guideline recommendations for CINV prevention following HEC or MEC

HEC

Day 1	Days 2–4	Guideline
A, B, or C A: NK$_1$ RA (aprepitant PO or injectable emulsion[a]; fosaprepitant IV; netupitant/palonosetron PO[b]; rolapitant PO[c]) + 5-HT$_3$ RA[d,e] (dolasetron PO; granisetron SC[f], PO, IV, or GTDS; ondansetron PO or IV; or palonosetron IV) + steroid (dexamethasone[g] PO or IV)	A: Aprepitant PO daily on days 2 and 3 (if aprepitant PO used on day 1) + dexamethasone[g] PO/IV daily on days 2–4	NCCN v2.2018[7]
B: Olanzapine PO[h] + 5-HT$_3$ RA (palonosetron IV) + steroid (dexamethasone[g] PO or IV)	B: Olanzapine PO daily on days 2–4[h]	
C: NK$_1$ RA (aprepitant PO or injectable emulsion[a]; fosaprepitant IV; netupitant/palonosetron PO[b]; rolapitant PO[c]) + 5-HT$_3$ RA[d,e] (dolasetron PO; granisetron SC[f], PO, IV, or GTDS; ondansetron PO or IV; or palonosetron IV) + steroid (dexamethasone[g] PO or IV) + olanzapine PO[h,i,j]	C: Aprepitant PO daily on days 2 and 3 (if aprepitant PO used on day 1) + dexamethasone[g] PO/IV daily on days 2–4 + olanzapine PO daily on days 2–4[h]	
NK$_1$ RA (aprepitant PO, fosaprepitant IV, netupitant PO [as NEPA, including 5HT$_3$ RA palonosetron], or rolapitant PO) + 5HT$_3$ RA[k] (dolasetron PO; granisetron PO, IV, or GTDS; ondansetron PO or IV; palonosetron PO or IV; tropisetron PO) + steroid (dexamethasone PO or IV)	If aprepitant PO day 1, dexamethasone PO or IV days 2–4 + either aprepitant PO days 2 and 3 or metoclopramide days 2–4; otherwise, dexamethasone PO or IV days 2–4 For patients with breast cancer receiving AC-based HEC, if aprepitant day 1, aprepitant PO days 2 and 3 or dexamethasone days 2 and 3; otherwise, no further treatment if fosaprepitant, netupitant, or rolapitant used day 1	MASCC/ESMO 2016[17]
If nausea is an issue, olanzapine + 5HT$_3$ RA + dexamethasone		
NK$_1$ RA (aprepitant PO, fosaprepitant IV, NEPA, or rolapitant PO) + 5HT$_3$ RA[d] (granisetron SC, PO, IV, or GTDS; ondansetron PO or IV; palonosetron PO or IV; dolasetron PO; tropisetron PO or IV; ramosetron IV) + steroid (dexamethasone[l] PO) + olanzapine PO	If aprepitant PO day 1, aprepitant days 2 and 3 Dexamethasone[l] PO or IV days 2–4 (if aprepitant used); day 2, twice daily on days 3 and 4 (if fosaprepitant used); days 2–4 (if NEPA or rolapitant used) For AC-based HEC: if no NK$_1$ RA day 1, then dexamethasone PO or IV days 2–4 (if aprepitant, fosaprepitant, or NEPA used) + olanzapine PO days 2–4	ASCO 2017[19]

MEC

Day 1	Days 2 and 3	Guideline
D, E, or F D: 5HT$_3$ RA (dolasetron PO; granisetron SC[f] [preferred], PO, IV, or GTDS; ondansetron PO or IV; or palonosetron IV [preferred]) + steroid (dexamethasone[g] PO or IV)	D: Dexamethasone[g] PO/IV daily on days 2 and 3 or 5-HT$_3$ RA[m] (granisetron PO or IV, or ondansetron PO or IV or dolasetron PO)	NCCN v2.2018[7]
E: Olanzapine PO[h] + 5-HT$_3$ RA (palonosetron IV) + steroid (dexamethasone[g] PO or IV)	E: Olanzapine PO daily on days 2 and 3[h]	
F[n]: NK$_1$ RA (aprepitant PO or injectable emulsion[a]; fosaprepitant IV; netupitant/palonosetron PO[b]; rolapitant PO[c]) + 5-HT$_3$ RA[d,e] (dolasetron PO; granisetron SC[f], PO, IV, or GTDS; ondansetron PO or IV; or palonosetron IV) + steroid (dexamethasone[g] PO or IV)	F: Aprepitant PO daily on days 2 and 3 (if aprepitant PO used on day 1) ± dexamethasone[g] PO/IV daily on days 2 and 3	
5HT$_3$ RA + dexamethasone[o] (except for carboplatin regimens)	Dexamethasone days 2 and 3 (for patients treated with MEC, which has known potential for delayed emesis, eg, oxaliplatin, doxorubicin, or cyclophosphamide); no routine antiemetic prophylaxis for other chemotherapeutic agents	MASCC/ESMO 2016[18]
For carboplatin regimens: NK$_1$ RA + 5HT$_3$ RA + dexamethasone	If aprepitant day 1, aprepitant days 2 and 3 If other NK$_1$ RA day 1, no additional antiemetic prophylaxis	

(Continued)

Table 1 (*Continued*)

MEC		
Day 1	**Days 2 and 3**	**Guideline**
5HT$_3$ RA (dolasetron PO; granisetron SC, PO, IV, or GTDS; ondansetron IV or PO; or palonosetron IV or PO) + dexamethasone (IV or PO) (except for carboplatin regimens) For carboplatin regimens[p]: 5HT$_3$ RA + dexamethasone	Dexamethasone PO or IV days 2 and 3	ASCO 2017[19]

Notes: [a]Aprepitant injectable emulsion is a unique formulation of aprepitant and is not interchangeable with the intravenous formulation of fosaprepitant; [b]Available as a fixed combination product only; [c]Rolapitant has an extended half-life and should not be administered at less than 2-week intervals; [d]If netupitant/palonosetron fixed combination product used, no further 5-HT$_3$ RA is required; [e]When used in combination with an NK$_1$ antagonist, there is no preferred 5-HT$_3$ RA; [f]Granisetron extended-release injection is a unique formulation of granisetron using a polymer-based drug delivery system. This formulation is specifically intended for subcutaneous administration and is not interchangeable with the intravenous formulation. Granisetron extended-release injection has an extended half-life and should not be administered at less than 1-week intervals; [g]Emerging data in clinical practice suggest dexamethasone doses may be individualized. Higher doses may be considered, especially when an NK$_1$ RA is not given concomitantly. Lower doses, given for shorter durations, or even elimination of dexamethasone on subsequent days (for delayed nausea and emesis prevention) may be acceptable for non-cisplatin regimens based on patient characteristics; [h]Consider 5 mg dose for elderly or over-sedated patients; [i]Consider escalating to this option (C) when emesis induced by highly emetogenic cisplatin-based chemotherapy using an olanzapine regimen (B, E) or an NK$_1$ antagonist-containing regimen (A, B, D, or F); [j]Combination of olanzapine, aprepitant, or fosaprepitant, any 5-HT$_3$ RA, and dexamethasone was studied in patients receiving cisplatin or AC; [k]For patients receiving AC-based HEC, if NK$_1$ RA is not available, palonosetron is the preferred agent; [l]If NK$_1$ RA is not given day 1, higher dexamethasone dose is recommended days 1–4; [m]No further therapy required if palonosetron, granisetron extended-release injection, or granisetron transdermal patch given on day 1; [n]NK$_1$ RA should be added (to dexamethasone and a 5-HT$_3$ regimen for select patients with additional risk factors or previous treatment failure with a steroid + 5HT$_3$ RA alone; [o]Dexamethasone only in patients receiving MEC with a known potential for delayed emesis; [p]If carboplatin area under the concentration-time curve (AUC) is ≥4 mg/mL/min, add NK$_1$ RA.

Abbreviations: 5HT$_3$, 5-hydroxytryptamine type 3; AC, anthracycline–cyclophosphamide; ASCO, American Society of Clinical Oncology; CINV, chemotherapy-induced nausea and vomiting; ESMO, European Society of Medical Oncology; GTDS, granisetron transdermal system; HEC, highly emetogenic chemotherapy; IV, intravenously; MASCC, Multinational Association for Supportive Care in Cancer; MEC, moderately emetogenic chemotherapy; NCCN, National Comprehensive Cancer Network; NEPA, fixed-dose netupitant + palonosetron; NK$_1$, neurokinin 1; PO, per os (orally); RA, receptor antagonist; SC, subcutaneously.

note that carboplatin may be highly emetogenic in some patients, depending on dose (ie, if the carboplatin area under the concentration–time curve [AUC] is ≥4 mg/mL/min), and ASCO recommends an adjusted antiemetic regimen for patients receiving carboplatin with an area under the curve ≥4 mg/mL/min.[7,19] For patients receiving carboplatin, MASCC/ESMO guidelines recommend a three-drug antiemetic regimen of a 5HT$_3$ RA plus an NK$_1$ RA plus dexamethasone, similar to the regimen recommended for patients receiving HEC, with aprepitant on days 2 and 3 if given on day 1.[17] In a retrospective analysis of 1,059 patients in a US claims database, 73% of those treated with AC (classified as HEC) and 56% treated with cisplatin (HEC) received an antiemetic regimen containing an NK$_1$ RA compared with 23% treated with carboplatin. However, health-care-resource utilization (eg, emergency-room visits, hospitalization) was lower in patients whose antiemetic regimen included an NK$_1$ RA, suggesting that a three-drug antiemetic regimen may be more effective in preventing CINV in patients receiving carboplatin.[22]

Moderately emetogenic chemotherapy

For the prevention of CINV associated with single-day MEC, all three guidelines are in agreement in recommending a two-drug regimen of a 5HT$_3$ RA plus dexamethasone on day 1 and dexamethasone on days 2 and 3 (with some exceptions), although ASCO and MASCC/ESMO guidelines have separate recommendations for patients receiving carboplatin (Table 1).[7,17–19] The NCCN guidelines also recommend this two-drug

regimen plus an NK$_1$ RA on day 1 or a three-drug combination of olanzapine, palonosetron, and dexamethasone on day 1.[7] If the 5HT$_3$ RA palonosetron, extended-release (ER) granisetron transdermal delivery system (GTDS; Sancuso, ProStrakan, Bridgewater, NJ, USA), or granisetron ER subcutaneous (GERSC; Sustol, Heron Therapeutics, Redwood City, CA, USA) is given on day 1 with dexamethasone, NCCN guidelines state that no further antiemetic therapy is necessary on days 2 and 3.[7] Details of recommended prophylaxis on days 2 and 3 by all guidelines are shown in Table 1. For MEC, NCCN guidelines list palonosetron and GERSC as preferred 5HT$_3$ RAs in the absence of an NK$_1$ RA.[7]

Multiday chemotherapy

For multiday chemotherapy, treatment guidelines are less definitive, in part because there is a lack of evidence to support recommendations in this setting. ASCO guidelines suggest using an antiemetic agent appropriate for the emetogenic risk of the chemotherapeutic agent administered on each day and for 2 days after completion of the chemotherapy regimen, and suggest that the ER agents GTDS or GERSC may be preferable to a daily 5HT$_3$ RA. For patients receiving multiday cisplatin regimens, the three-drug combination of an NK$_1$ RA, 5HT$_3$ RA, and dexamethasone is recommended.[19] The NCCN guidelines propose taking several factors into account when determining the appropriate antiemetic regimen, including route of administration, duration of action, and dosage regimen of the antiemetic(s); administration in an inpatient or

outpatient setting; patient adherence to a regimen; and individual patient risk factors. Several general principles are proposed for each type of antiemetic agent. A $5HT_3$ RA should be used before each dose of MEC or HEC, and the need for subsequent doses should be based on the antiemetic agent and route of administration. Dexamethasone is recommended for each day of chemotherapy, continuing for 2–3 days afterward for HEC or MEC regimens known to have a higher risk of causing delayed emesis, but dexamethasone administration only on day 1 is an option for patients receiving MEC or noncisplatin HEC who have few CINV risk factors. An NK_1 RA may be used with MEC or HEC regimens that have a significant risk of causing delayed CINV, but there are limited data on the use of NK_1 RAs over multiple days.[7] The most recent updates to the MASCC/ESMO guidelines do not offer specific recommendations for antiemetics to prevent CINV associated with multiday HEC or MEC chemotherapy.[17,18]

Breakthrough CINV

For breakthrough CINV (ie, CINV occurring despite the use of guideline-recommended prophylactic antiemetics), ASCO and NCCN guidelines suggest adding an antiemetic agent with a different mechanism of action to that of the antiemetic(s) used during the previous chemotherapy cycle. Olanzapine may be added if it was not part of the initial antiemetic regimen, and other dopamine antagonists (eg, metoclopramide, phenothiazines) may also be considered.[7,19] Multiple concurrent antiemetics may be required and administered continuously, rather than as needed. If a combination of a $5HT_3$ RA and dexamethasone with or without an NK_1 RA has previously been used, other options of different classes include olanzapine, benzodiazepine, or metoclopramide.[7,19] The use of $5HT_3$ RAs in the breakthrough setting is based on their efficacy as prophylactic antiemetics, as there are no published data from prospective Phase III clinical trials on the use of $5HT_3$ RAs to treat breakthrough CINV. The most recent updates to the MASCC/ESMO guidelines have no specific recommendations for the prevention of breakthrough CINV associated with HEC or MEC.[17,18]

Benefits and limitations of $5HT_3$-RA formulations

The introduction of $5HT_3$ RAs dramatically improved the prevention of CINV, particularly in the acute phase.[24] Granisetron is a potent and highly selective $5HT_3$ RA with little or no affinity for other serotonin receptors or for dopaminergic, adrenergic, benzodiazepine, histaminic, or opioid receptors.[25] In contrast, in addition to binding with $5HT_3$

receptors, ondansetron binds with low affinity to $5HT_{1B}$, $5HT_{1C}$, α_1-adrenergic, and μ-opioid receptors.[26] Ondansetron is available for intravenous (IV) or oral administration only, whereas granisetron is available in a wide range of formulations (Table 2[25,27–37]). Dolasetron is only available in the oral formulation in the USA for CINV prevention (Table 2) due to the potential cardiac adverse events (AEs) observed with the IV formulation. Formulations of $5HT_3$ RAs may affect their utility. Injectable forms have an adherence advantage, whereas compliance with oral antiemetics may be suboptimal because of difficulty ingesting pills, especially for patients with head and neck cancer or those afraid to swallow pills for fear of inducing further emesis.[38,39]

Extending the efficacy of $5HT_3$ RAs into the delayed phase: palonosetron

Palonosetron, a potent and selective $5HT_3$ RA, is a second-generation agent with a half-life ($t_{1/2}$) that is longer (~40 hours)[40] than first-generation agents (Table 2). Additionally, in vitro research has suggested that palonosetron causes $5HT_3$-receptor internalization, leading to prolonged inhibition of $5HT_3$ RAs.[41] These properties ($t_{1/2}$, binding affinity, and receptor internalization) of palonosetron are believed to form the basis of its pharmacologic activity in the acute and delayed CINV phases.[26,41–43] However, direct evidence linking biochemical properties of palonosetron with its clinical efficacy is lacking. Notably, palonosetron IV is indicated for CINV prevention in both acute and delayed phases following MEC, but only in the acute phase following HEC.[34] In the USA, palonosetron is available only for IV administration.[34] At the time of its approval in the USA, palonosetron had not been investigated in combination with an NK_1 RA.

In 2014, the oral fixed-dose combination of the NK_1 RA netupitant 300 mg and palonosetron 0.5 mg (NEPA; Akynzeo, Helsinn Therapeutics Inc, Iselin, NJ, USA) became available for CINV prevention in both acute and delayed phases in patients treated with MEC or HEC.[36] Approval was based on three clinical trials in patients receiving HEC, MEC, and repeated cycles of chemotherapy.[37,44,45] In single-cycle trials in patients receiving MEC or HEC, NEPA plus dexamethasone was significantly superior to the comparator regimen across the delayed and overall CINV phases in terms of CR.[44,45] However, in these trials, NEPA plus dexamethasone was compared with a two-drug regimen of oral palonosetron plus dexamethasone, not the three-drug regimen recommended by all guidelines for patients receiving HEC and by some guidelines for patients receiving MEC.[7,17–19] Over multiple cycles, NEPA plus dexamethasone had similar CR rates to

Table 2 Characteristics of 5HT$_3$-RA formulations

Drug	Route of administration	Mean plasma $t_{1/2}$ (hours)	Approved adult dose and administration	Year of initial US approval; indication in adults for prevention of CINV
Dolasetron	PO[27]	7.3 ($t_{1/2}$ of hydrodolasetron, a dolasetron metabolite)	100 mg within 1 hour before chemotherapy	1997; associated with MEC, including initial and repeat course
Granisetron	IV[25]	9 (mean plasma $t_{1/2}$)	Single dose of 3 mg granisetron diluted in 20–50 mL infusion fluid given over 5 minutes, beginning within 30 minutes before chemotherapy start	1993; induced by cytotoxic chemotherapy
Granisetron	PO[28]	6.23 (terminal phase $t_{1/2}$, in healthy volunteers)	2 mg once daily (two 1 mg tablets or 10 mL oral solution) up to 1 hour before chemotherapy start or 1 mg twice daily, with first dose (1 mg tablet or 5 mL oral solution) given up to 1 hour before chemotherapy start and second dose (tablet or 5 mL oral solution) 12 hours after first dose	2001; associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin
Granisetron	Extended-release SC[29]	26.15 (750 mg), 28.8 (500 mg)[30]	Single SC injection in upper arm or abdomen at least 30 minutes before chemotherapy start	2016; acute and delayed NV associated with initial and repeat courses of cancer chemotherapy, including but not limited to HEC
Granisetron	TD[31]	NA	Patch is 52 cm² and contains 34.3 mg granisetron, delivered at 3.1 mg/24 hours; single transdermal patch applied to upper outer arm ≥24 hours (to maximum 48 hours) before chemotherapy; can wear patch up to 7 days, depending on chemotherapy duration	2008; in patients receiving MEC and/or HEC for up to 5 consecutive days
Ondansetron	IV[32]	3.5–5.5 (depending on age)	Three 0.15 mg/kg doses to maximum 16 mg/dose; first dose infused over 15 minutes, beginning 30 minutes before chemotherapy start; subsequent doses 4 and 8 hours after first dose	1991; associated with initial and repeat courses of emetogenic cancer chemotherapy
Ondansetron	PO[33]	3.1–6.2 (mean elimination $t_{1/2}$ for 8 mg dose; depending on age)	HEC: 24 mg as three 8 mg tablets 30 minutes before start of single-day HEC, including cisplatin ≥50 mg/m² MEC: one 8 mg tablet or 10 mL oral solution twice a day; first dose 30 minutes before chemotherapy; subsequent dose 8 hours after first dose; for 1–2 days after completion of chemotherapy, one 8 mg tablet or 10 mL oral solution twice a day (every 12 hours)	1992; associated with: • HEC, including cisplatin ≥50 mg/m² • Initial and repeat courses of MEC
Palonosetron	IV[34]	40[35]	0.25 mg once, infused over 30 seconds beginning ~30 minutes before chemotherapy start	2003; acute and delayed NV associated with initial and repeat MEC; acute NV associated with initial and repeat HEC
Palonosetron + netupitant (NEPA)	PO[36]	90[37]	One NEPA capsule (300 mg netupitant/0.5 mg palonosetron) ~1 hour before chemotherapy start, with or without food	2014; acute and delayed NV associated with initial and repeat cancer chemotherapy, including but not limited to HEC

Abbreviations: 5HT₃, 5-hydroxytryptamine type 3; CINV, chemotherapy-induced nausea and vomiting; HEC, highly emetogenic chemotherapy; IV, intravenously; MEC, moderately emetogenic chemotherapy; NA, not available; NEPA, fixed-dose netupitant + palonosetron; NV, nausea and vomiting; PO, per os (orally); SC, subcutaneously; RA, receptor antagonist; $t_{1/2}$, half-life; TD, transdermal.

a three-drug regimen of aprepitant, palonosetron, and dexamethasone, but a small numerical advantage in the delayed and overall phases.[37] In clinical trials, the NK$_1$ RA provided additional control of delayed CINV in combination with a 5HT$_3$ RA, suggesting that the NK$_1$ RA is providing the ben-

efit in the delayed phase.[46,47] In fact, the NEPA prescribing information states that palonosetron prevents CINV in the acute phase and netupitant prevents CINV in the acute and delayed phases.[36] Since NEPA provides an NK$_1$ RA and a 5HT$_3$ RA as a single oral dose, it has the potential to improve

the prevention of delayed CINV and improve adherence to guidelines for CINV prevention following HEC, which recommend combined use of NK_1 RA and $5HT_3$ RA plus a corticosteroid.[48] However, oral administration of NEPA may pose a challenge to some patients, as discussed earlier.

Palonosetron and its place in antiemetic treatment guidelines

Antiemesis guidelines recommend palonosetron as a preferred $5HT_3$ RA in some settings. In patients with breast cancer receiving AC-based chemotherapy (ie, a HEC regimen), a three-drug regimen of a $5HT_3$ RA, dexamethasone, and an NK_1 RA is recommended by the MASCC/ESMO guidelines, but palonosetron is stated as the preferred $5HT_3$ RA if an NK_1 RA is not available.[17] These recommendations were based on the results of Phase III trials of palonosetron in patients receiving HEC (Table 3[49–60]).[49,50] In patients receiving MEC or multiday chemotherapy, either palonosetron or GERSC is recommended in NCCN guidelines as a preferred $5HT_3$ RA in combination with dexamethasone for CINV prevention (ie, when no NK_1 RA is given).[7] In a recent trial in 341 patients with breast cancer receiving AC-based chemotherapy (reported as an abstract), palonosetron failed to show superiority over granisetron IV (CR 62.3% vs 60.4%, P=0.8) in the delayed phase, when each agent was combined with fosaprepitant and dexamethasone.[61] Recently, a double-blind, randomized study comparing a three-drug palonosetron regimen with a three-drug granisetron regimen in patients receiving AC-based HEC showed no significant difference between study arms in terms of delayed-phase CR, despite again using the 0.75 mg palonosetron dose.[62]

The NCCN guidelines considered two Phase III trials in the MEC setting to support palonosetron as a preferred $5HT_3$ RA in combination with dexamethasone to prevent CINV associated with MEC.[63,64] However, one study in patients receiving MEC reported that palonosetron IV was noninferior to dolasetron IV, which is no longer approved by the US Food and Drug Administration (FDA) for CINV prevention because of associated cardiac adverse effects (Table 4[45,59,60,63–73]).[63,74] The other study demonstrated superior CR in acute and delayed CINV phases of single-dose palonosetron 0.25 mg IV compared with single-dose ondansetron 32 mg IV in patients receiving MEC (Table 4).[64] However, this study did not use the recommended combination of ondansetron with dexamethasone. In a subsequent Phase III trial in patients receiving HEC, palonosetron 0.25 mg IV was noninferior to a first-generation $5HT_3$ RA (ondansetron 32 mg IV) in acute, delayed, and overall phases. Superiority of palonosetron to

ondansetron was shown only in a post hoc analysis, where CR with palonosetron was significantly higher in the delayed and overall phases compared with ondansetron when both agents were administered with dexamethasone.[49]

As such, the evidence to support the preference for palonosetron in CINV prevention in these settings has been questioned, and it has been suggested that there are insufficient data to support this designation.[75,76] Phase III trials evaluated single-dose palonosetron compared with single-dose dolasetron or ondansetron, both of which have shorter $t_{1/2}$ than palonosetron (Table 2), so would be expected to be less effective at controlling CINV beyond day 1 of chemotherapy. Meta-analyses of CINV trials have been used to support the choice of palonosetron as the preferred $5HT_3$ RA in CINV prevention.[77,78] However, such analyses may result in pooling data from trials with significant differences in study populations and dexamethasone usage, so their conclusions require validation in prospective, randomized trials.

Extending the efficacy of $5HT_3$ RAs into the delayed phase: granisetron

The short $t_{1/2}$ of the first-generation $5HT_3$ RAs (Table 2), such as granisetron, has limited their use in CINV prevention, especially for the delayed phase. Currently, two ER formulations of granisetron are available: GTDS and GERSC (previously APF530). The GTDS patch, which is 52 cm^2 in size, provides exposure similar to that of 2 mg oral granisetron. However, in contrast to oral granisetron, where maximum plasma concentration (C_{max}) is reached 2 hours after administration, drug exposure with GTDS is slower, with C_{max} reached 48 hours after patch application and granisetron exposure continuing over 5 days (Figure 1[29–31,79]).[79] Therefore, GTDS is a convenient option for CINV prevention, because it reduces pill burden for patients, particularly those who have difficulty in swallowing oral medication.[23] However, GTDS has potential drawbacks, including patch detachment,[80–82] which may result in a lack of antiemetic efficacy, and the need for patch application 24–48 hours prior to chemotherapy, which may result in unnecessary exposure to antiemetic if the patient does not proceed with their next round of chemotherapy.[83]

GERSC was developed as a long-acting formulation to provide prolonged $5HT_3$-RA action through sustained granisetron release, and was recently FDA-approved for use in adults in combination with other antiemetics for prevention of acute and delayed NV associated with initial and repeat courses of MEC or AC-combination chemotherapy regimens.[29] Extended granisetron release is achieved through Biochronomer technology (Figure 2) using a viscous,

Table 3 Results of Phase III clinical trials evaluating antiemetic efficacy in CINV prevention following HEC

Study	Antiemetic treatment and DEX dose	Patient demographics[a]	Primary end-point result	Secondary end-point result
Four-drug vs four-drug regimen				
Navari et al 2013[51]	(OLN vs metoclopramide [MTCP]) + (PALO + FOS + DEX) Day 1: PALO 0.25 mg IV + FOS 150 mg IV, DEX 12 mg IV Days 2–4: DEX 8 mg PO qd Days 2–5: OLN 10 mg PO qd or MTCP 10 mg PO tid	N=276 Median age 61–63 years, female 28%–30%, chemotherapy-naïve 100%	OLN vs MTCP Patients with no emesis in 72 hours after starting treatment 70% vs 31%, $P<0.01$	OLN vs MTCP Patients with no nausea in 72 hours after starting treatment 68% vs 23%, $P<0.01$
Three-drug vs three-drug regimen				
Grunberg et al 2011[52]	APR + OND + DEX vs FOS + OND + DEX <u>FOS regimen</u> Day 1: FOS 150 mg IV, OND 32 mg IV, DEX 12 mg PO Day 2: DEX 8 mg PO Days 3–4: DEX 8 mg bid <u>APR regimen</u> Day 1: APR 125 mg PO, OND 32 mg IV, DEX 12 mg PO Days 2–3: APR 80 mg PO, DEX 8 mg PO Day 4: DEX 8 mg PO	N=2,322 Median age 56–57 years, female 36%–37%	APR vs FOS CR overall phase: 71.9%, 95% CI 69.1%–74.5% vs 72.3%, 95% CI 69.6%–74.9%	APR vs FOS CR delayed phase: 74.3%, 95% CI 71.6%–76.9% vs 74.2%, 95% CI 71.6%–76.8% No emesis overall phase: 72.9%, 95% CI 70.2%–75.5% vs 74.6%, 95% CI 71.9%–77.1%
Navari et al 2011[53]	OLN + PALO + DEX vs APR + PALO + DEX Day 1: OLN 10 mg PO + PALO 0.25 mg IV + DEX 20 mg IV Days 2–4: OLN 10 mg/d PO (OPD) or Day 1: APR 125 mg PO + PALO 0.25 mg IV + DEX 12 mg IV Days 2–4: APR 80 mg PO + DEX 4 mg bid (APD)	N=247 Median age: 61–63 years, female 81%–83%, chemotherapy-naïve 100%	OLN vs APR CR overall phase: 77% vs 73%; $P>0.05$	OLN vs APR CR acute phase: 97% vs 87%, $P>0.05$ CR delayed phase: 77% vs 73%, $P>0.05$ No nausea Acute phase: 87% vs 87%, $P>0.05$ Delayed phase: 69% vs 38%;, $P\leq0.01$ Overall phase: 69% vs 38%, $P\leq0.01$
Schnadig et al 2016[54]	GERSC + FOS + DEX vs OND + FOS + DEX <u>Three-drug regimen</u> GERSC 10 mg SC (GRA 10 mg), OND placebo IV or OND 0.15 mg/kg IV, GERSC placebo SC, each with FOS 150 mg IV day 1 Day 1: DEX 12 mg IV Day 2: DEX 8 mg PO qd Days 3–4: DEX 8 mg PO bid	N=942 Mean age 56 years, female 80%–83%, white 82%, current alcohol use 37%–38%, smokers 16%	GERSC vs OND CR delayed phase: 64.7% vs 56.6%, $P=0.014$	GERSC vs OND CR overall phase: 58.4% vs 52.9%, $P=0.092$, $P=0.275$* CC delayed phase: 60.7% vs 53.1%, $P=0.088$, $P=0.088$* CC overall phase: 54.7% vs 49.6%, $P=0.123$, $P=0.247$* Rate of no emetic episodes: 82.2% vs 79.2%, $P=0.254$, $P=0.254$* *Hochberg-adjusted

(Continued)

Table 3 (*Continued*)

Study	Antiemetic treatment and DEX dose	Patient demographics[a]	Primary end-point result	Secondary end-point result
Three-drug vs two-drug regimen				
Hesketh et al 2003[55]	APR + OND + DEX vs placebo + OND + DEX <u>Standard-therapy group</u> Day 1: OND 32 mg IV + DEX 20 mg PO Days 2–4: DEX 8 mg bid <u>APR group</u> Day 1: APR 125 mg PO + OND 32 mg IV + DEX 12 mg PO Days 2–3: APR 80 mg PO + DEX 8 mg PO qd Days 2–4: DEX 8 mg PO qd	N=530 Mean age 58–59 years, female 14%, white 34%–35%, no alcoholic drinks/week 22%	CR overall (days 1–5 postcisplatin): APR vs placebo, 72.7% vs 52.3%, P<0.001	Secondary and exploratory end points CR acute phase: 89.2% vs 78.1%, P<0.001 CR delayed phase: 75.4% vs 55.8%, P<0.001 No emesis Acute phase: 90.0% vs 79.3%, P<0.01 Delayed phase: 80.8% vs 58.8%, P<0.01 Overall phase: 77.7% vs 55.0%, P<0.01 No nausea Acute phase: 72.3% vs 69.1% Delayed phase: 51.0% vs 47.7% Overall phase: 47.5% vs 44.2%
Poli-Bigelli et al 2003[56]	APR + OND + DEX vs placebo + OND + DEX APR, OND, DEX vs OND, DEX Day 1: OND 32 mg IV + DEX 20 mg Days 2–4: DEX 8 mg bid or Day 1: APR 125 mg PO + OND 32 mg IV + DEX 12 mg PO Days 2–3: APR 80 mg PO + DEX 8 mg PO qd D4: DEX 8 mg PO	N=569 Mean age 53–54 years, white 28%–31%, female 48%–49%, no alcohol per week 84%–87%	CR overall phase: APR vs placebo, 62.7% vs 43.3%, P<0.001	CR acute phase: 82.8% vs 68.4% CR delayed phase: 67.7% vs 46.8%
Saito et al 2013[57]	FOS + GRA + DEX vs placebo + GRA + DEX <u>FOS group</u> Day 1: FOS 150 mg, IV, GRA 40 µg/kg, IV, DEX 10 mg IV Day 2: DEX 4 mg IV Day 3: DEX 8 mg IV <u>Control group</u> Day 1: placebo, GRA 40 µg/kg, IV, DEX 20 mg IV Days 2–3: DEX 8 mg IV	N=347 Median age 62–63 years, female 26%, no alcohol intake 50%–64%	FOS vs placebo CR overall phase: 64.2% vs 47.3%, P=0.0015	FOS vs placebo CR acute phase: 93.6% vs 80.8%, P<0.005 CR delayed phase: 64.7% vs 48.6%, P<0.005
Hu et al 2014[58]	APR + GRA + DEX vs placebo + GRA + DEX <u>APR regimen</u> Day 1: APR 125 mg PO, GRA 3 mg IV, DEX 6 mg PO Days 2–3: APR 80 mg PO, DEX 3.75 mg PO Day 4: DEX 3.75 mg PO <u>Standard regimen</u> Day 1: placebo, GRA 3 mg IV, DEX 10.5 mg PO Days 2–4: DEX 7.5 mg PO	N=421 Mean age 53–54 years, female 34%, no alcohol use 84%–85%	APR vs placebo CR overall phase: 69.6% vs 57.0%, P=0.007	APR vs placebo CR acute phase: 79.4% vs 79.3%, P=0.9 CR delayed phase: 74.0% vs 59.4%, P<0.001

Two-drug vs two-drug regimen

Study	Regimen	Characteristics	Efficacy	
Aapro et al 2006[49]	PALO + DEX vs OND + DEX PALO 0.25 or 0.75 mg IV or OND 32 mg IV Day 1: single dose of DEX 20 mg IV allowed at physician discretion but not required, DEX prophylaxis in 67.3% of PALO, 66.5% of OND patients	N=673 Mean age, 51–53 years, female 51%–52%, white 51%–63%, no alcohol use 49%–52%, chemotherapy-naïve 58%–60%	PALO vs OND PALO 0.25 mg vs OND CR acute phase: 59.2% vs 57%, $P=0.701$ PALO 0.75 mg vs OND CR acute phase: 65.5% vs 57%, $P=0.079$	PALO vs OND PALO 0.25 mg vs OND CR delayed phase: 45.3% vs 38.9%, $P=0.180$ CR overall phase: 40.8% vs 33%, $P=0.095$ PALO 0.75 mg vs OND CR delayed phase: 48% vs 38.9%, $P=0.056$ CR overall phase: 42.2% vs 33%, $P=0.051$ Subgroup analysis of patients receiving study drug and prophylactic DEX during acute, delayed, and overall phases PALO 0.25 mg vs OND CR acute phase: 64.7% vs 55.8% CR delayed phase: 42.0% vs 28.6%, statistically significant CR overall phase: 40.7% vs 25.2%, statistically significant
Saito et al 2009[50]	PALO + DEX vs GRA + DEX PALO 0.75 mg IV or GRA 40 µg/kg IV Day 1: DEX 16 mg IV Days 2–3: DEX 8 mg IV for cisplatin-treated patients or 4 mg PO for AC-treated patients	N=1,143 Mean age 58 years, female 58%–59%, all patients from Japan, no alcohol use 42%–43%, chemotherapy-nonnaïve 7%–8%	PALO vs GRA CR acute phase: 75.3% vs 73.3%, $P=$ND CR delayed phase: 56.8% vs 44.5%, $P<0.0001$	PALO vs GRA CR overall phase: 51.5% vs 40.4%, $P=0.0001$ CC acute phase: 73.7% vs 72.1%, $P=$ND CC delayed phase: 53.0% vs 42.4%, $P=0.0003$ CC overall phase: 47.9% vs 38.1%, $P=0.0007$ • Number of emetic episodes, time to first emetic episode, and time to first use of rescue medication higher in PALO vs GRA • Time to treatment failure and percentage patients with severe nausea similar within 24 hours, lower in PALO vs GRA (5% vs 1.6%) at 96 hours • Statistically significantly higher number patients in PALO vs GRA with no nausea and no emetic episodes in delayed or overall phases

(Continued)

Table 3 (*Continued*)

Study	Antiemetic treatment and DEX dose	Patient demographics[a]	Primary end-point result	Secondary end-point result
Raftopoulos et al 2015[59]	GERSC + DEX vs PALO + DEX GERSC 5 mg or 10 mg SC, placebo IV or PALO 0.25 mg IV, placebo SC Day 1: DEX 20 mg IV Days 2–4: DEX 8 mg PO bid	N=1,428 Mean age, 57–58 years, female 63%–67%, white 58%–62%, chemotherapy-nonnaïve 56–59%	GERSC vs PALO in cycle 1 of HEC GERSC 5 mg SC vs PALO 0.25 mg IV CR acute phase: 77.7% vs 80.7%, P=0.49 CR delayed phase: 62.4% vs 64.3%, P=0.70 GERSC 10 mg SC vs PALO 0.25 mg IV CR acute phase: 81.3% vs 80.7%, P=0.91 CR delayed phase: 67.1% vs 64.3%, P=0.56	GERSC vs PALO CR overall phase, HEC GERSC 5 mg vs PALO 0.25 mg 57.6% vs 60.5%, 95% CI –11.8 to 6.1, P=NA GERSC 10 mg vs PALO 0.25 mg 63.3% vs 60.5%, 95% CI –5.9 to 11.6, P=NA
One-drug vs one-drug regimen				
Gebbia et al 1994[60]	OND vs GRA Day 1: OND 24 mg IV or GRA 3 mg IV Patients on fractionated chemotherapy Subsequent days: OND 8 mg PO bid or GRA 3 mg IV	N=182 Mean age, 59–60 years, female 31%–42%	OND vs GRA CR acute phase: 52% vs 49%, no significant difference CR delayed phase: 39% vs 36%, no significant difference	

Note: [a]NEPA, APR, and PALO administered 60 minutes prior to chemotherapy administration on day 1.

Abbreviations: AC, anthracycline-cyclophosphamide; APD, aprepitant; APR, aprepitant; bid, bis in die (twice daily); CC, complete control; CINV, chemotherapy-induced nausea and vomiting; CR, complete response; DEX, dexamethasone; FOS, fosaprepitant; GERSC, granisetron extended-release subcutaneously; GRA, granisetron; HEC, highly emetogenic chemotherapy; IV, intravenously; MTCP, metoclopramide; NA, not achieved; ND, not done; OLN, olanzapine; OND, ondansetron; OPD, olanzapine, palonosetron, dexamethasone; PALO, palonosetron; PO, per os (orally); qd, quaque die (once daily); SC, subcutaneously; tid, ter in die (three times daily).

Table 4 Results of Phase III clinical trials evaluating antiemetic efficacy in CINV prevention following MEC

Study	Antiemetic treatment and DEX dose	Patient demographics	Primary end-point results	Select secondary end-point results
Gebbia et al 1994[60]	OND vs GRA; day 1: OND 16 mg IV or GRA 3 mg IV	N=164; Mean age 54–57 years, female 78%–80%	OND vs GRA; CR acute phase: 69% vs 67%, P=NS	PALO vs OND; CR delayed phase: 45% vs 52%
Eisenberg et al 2003[63]	PALO (2 doses) vs DOLA, each + DEX or methylprednisolone; PALO (IV) 0.25 mg or 0.75 mg or DOLA 100 mg single DEX 20 mg IV or 20 mg PO or methylprednisolone 125 mg IV allowed	N=592; Age 53–55 years, female 82%–83%, white 30%–33%	PALO vs DOLA; CR acute phase: PALO 0.25 mg vs DOLA, 63% vs 52.9%, P=0.049; PALO 0.75 mg vs DOLA, 57.1% vs 52.9%, P=0.412	PALO vs DOLA; PALO 0.25 mg vs DOLA; CR delayed phase: 54% vs 38.7%, P=0.004; CR overall phase: 46% vs 34%, P=0.021; PALO 0.75 mg vs DOLA; CR delayed phase: 56.6% vs 38.7%, P<0.001; CR overall phase: 47.1% vs 34%, P=0.012
Gralla et al 2003[64]	PALO (2 doses) vs OND; PALO 0.25 or 0.75 mg IV or OND 32 mg IV; No DEX	N=570; Age ~55–56 years, female 71%–73%, white 98%–100%, nonsmoker 69%–70%, no alcohol use 42%–47%, chemotherapy-naïve 40%–42%	PALO vs OND; CR acute phase: PALO 0.25 mg vs OND, 81% vs 68.6%, P=0.0085; PALO 0.75 mg vs OND, 73.5% vs 68.6%, P=0.3067	PALO vs OND; PALO 0.25 mg vs OND; CR delayed phase: 74.1% vs 55.1%, P<0.001; Overall phase: 69.3% vs 50.3%, P<0.001; PALO 0.75 mg vs OND; CR delayed phase: 64.6% vs 55.1%, P=0.0730; Overall phase: 58.7% vs 50.3%, P=0.1192
Warr et al 2005[65]	OND + APR + DEX vs OND + DEX; Day 1: APR 125 mg PO or placebo, OND 8 mg PO before chemotherapy and 8 mg PO after first dose, DEX 12 mg PO; Days 2–3: APR 80 mg, placebo PO bid or Day 1: placebo, OND 8 mg PO before chemotherapy and 8 mg PO 8 hours after first dose, DEX 20 mg PO; Days 2–3: OND 8 mg PO bid, placebo PO	N=866; Mean age 52–53 years, female 100%, white 78%–80%	APR vs placebo; CR overall phase: APR vs placebo, 50.8% vs 42.5%, P=0.015	APR vs placebo; Proportion of patients with functional living index-emesis score >6 of 7; APR regimen vs control regimen; Total score: 63.5% vs 55.6%, P=0.019; Vomiting domain: 85.7% vs 71.8%, P<0.001; Nausea domain: 53.5% vs 50.5%
Grunberg et al 2009[66]	PALO + APR + DEX; PALO 0.25 mg IV + APR 285 mg PO + DEX 20 mg PO	N=41; Median age 51 years, female 98%, chemotherapy-naïve 100%	CR overall phase: 51%	No vomiting; Acute phase: 100%; Delayed phase: 95%; Overall phase: 95%; No significant nausea; Acute phase: 79%; Delayed phase: 59%; Overall phase: 56%; No nausea; Acute phase: 59%; Delayed phase: 41%; Overall phase: 32%

(Continued)

Table 4 (Continued)

Study	Antiemetic treatment and DEX dose	Patient demographics	Primary end-point results	Select secondary end-point results
Aapro et al 2010[67]	PALO with 1-day DEX vs PALO with 3-day DEX Day 1: PALO 0.25 mg IV and DEX 8 mg IV Days 2–3: placebo or DEX 8 mg PO	N=300 Mean age 52 years, female 100%	PALO + 1-day DEX vs PALO + 3-day DEX Noninferiority in CR over days 1–5: 53.6% vs 53.7%, P=0.487	PALO + 1-day DEX vs PALO + 3-day DEX CR acute phase: 69.5% vs 68.5%, P=0.573 CR delayed phase: 62.3% vs 65.8%, P=0.039 CC overall phase: 71.5% vs 72.5%, P=0.429 CC acute phase: 80.1% vs 79.2%, P=0.583 CC delayed phase: 78.8% vs 85.2%, P=0.077
Rapoport et al 2010[68]	APR + OND + DEX vs placebo + OND + DEX APR regimen Day 1: APR 125 mg PO, OND 8 mg PO prior to chemotherapy and 8 hours after first dose, DEX 12 mg PO Days 2–3: APR 80 mg PO, placebo PO bid Control regimen Day 1: placebo, OND 8 mg PO prior to chemotherapy and 8 hours after first dose, DEX 20 mg PO Days 2–3: OND 8 mg PO bid	N=848 Mean age 56–57 years, female 76%–78%	APR vs placebo No emesis overall phase: APR vs placebo, 76.2% vs 62.1%, P<0.001	APR vs placebo CR overall phase: 68.7% vs 56.3%, P<0.001
Celio et al 2011[69]	PALO with 1-day DEX vs PALO with 3-day DEX Day 1: PALO 0.25 mg IV and DEX 8 mg IV Days 2–3: No DEX or DEX 8 mg PO	N=334 Mean age 57 years, female 62%–68%, no alcohol consumption 60%–61%	PALO + 1 day DEX vs PALO + 3-day DEX CR overall phase: 67.5% vs 71.1% Treatment difference –3.6% (95% CI –13.5% to 6.3%), P=ND	PALO + 1 day DEX vs PALO + 3-day DEX CR acute phase: 88.6% vs 84.3%, P=0.262 CR delayed phase: 68.7% vs 77.7%, P=0.116 No nausea Acute phase: 78.5% vs 72.7%, 95% CI –3.5 to 15.2 Delayed phase: 57.1% vs 62.1%, 95% CI –15.7 to 5.6 Overall phase: 52.1% vs 56.5%, 95% CI –15.2 to 6.5
Boccia et al 2013[70]	PALO PO vs PALO IV PALO (0.25, 0.50, 0.75 mg) PO or PALO 0.25 mg IV, DEX 8 mg IV or placebo	N=651 Mean age 56–58 years, female 72%–74%, chemotherapy-naïve 57%–61%, no alcohol consumption 54%–65%	PALO PO vs IV CR acute phase 0.25 mg PO: 73.5% 0.50 mg PO: 76.3% 0.75 mg PO: 74.1% 0.25 mg IV: 70.4%	PALO PO vs IV CR delayed phase 0.25 mg PO: 59.4% 0.50 mg PO: 62.5% 0.75 mg PO: 60.1% 0.25 mg IV: 65.4% CR overall phase 0.25 mg PO: 53.5% 0.50 mg PO: 58.8% 0.75 mg PO: 53.2% 0.25 mg IV: 59.3%

Study	Regimen	Population	Primary efficacy	Outcomes
Aapro et al 2014[45]	NEPA + DEX vs PALO + DEX NEPA (netupitant 300 mg + PALO 0.50 mg) PO, or PALO 0.50 mg PO Day 1: DEX 12 mg PO with NEPA, or DEX 20 mg PO with PALO	N=1,455 Median age 54 years, female 98%, white 79%–80%, chemotherapy-naïve 100%	NEPA vs PALO CR delayed phase: 76.9% vs 69.5%, P=0.001	NEPA vs PALO No emesis Acute phase: 90.9% vs 87.3%, P=0.025 Delayed phase: 81.8% vs 75.6%, P=0.004 Overall phase: 79.8% vs 72.1%, P<0.001 No significant nausea Acute phase: 87.3% vs 87.9%, P=0.747 Delayed phase: 76.9% vs 71.3%, P=0.014 Overall phase: 74.6% vs 69.1%, P=0.020 Complete protection Acute phase: 82.3% vs 81.1%, P=0.528 Delayed phase: 67.3% vs 60.3%, P=0.005 Overall phase: 63.8% vs 57.9%, P=0.020
Schmitt et al 2014[71]	GRA + APR + DEX vs GRA + DEX APR 125 mg PO day 1, 80 mg PO days 2–4 + GRA 2 mg PO days 1–4 + DEX 4 mg day 1, 2 mg days 2–3 or Placebo + GRA 2 mg PO days 1–4 + DEX 8 mg day 1, 4 mg days 2–3	N=363 Median age 58 years, female 34%–39%	APR vs placebo CR overall phase: 58% vs 41%, P=0.0042	APR vs placebo CR acute phase: 97% vs 90%, P=0.022 CR delayed phase: 60% vs 46%, P=0.011 • No emesis within 120 hours: 78% vs 65%, P=0.0036 • No nausea within 120 hours: 85% vs 78%, P=0.106 • Rate of nausea and significant nausea • No impact on daily life: 74% vs 59%, P=0.004
Komatsu et al 2015[72]	PALO with 1-day DEX vs PALO with 3-day DEX PALO 0.75 mg IV + DEX 9.9 mg IV on day 1 Days 2–3: no DEX or DEX 8 mg IV or PO	N=308 Mean age, 64 years, female 43%–43.5%, no alcohol use within 180 days of enrollment 51%–52%	PALO with 1-day DEX vs PALO with 3-day DEX CR overall phase: 63.6% vs 66.2%, P=0.0004 for noninferiority test	PALO with 1-day DEX vs PALO with 3-day DEX CR acute phase: 92.2% vs 93.4% CR delayed phase: 64.9% vs 66.9% CC overall phase: 61.7% vs 64.9% CC acute phase: 92.2% vs 93.4% CC delayed phase: 63.0% vs 65.6%
Nishimura et al 2015[73]	5HT$_3$ RA + DEX vs 5HT$_3$ RA, + APR or FOS, + DEX Control Day 1: 5HT$_3$ RA IV + DEX 9.9 mg Days 2–3: DEX 4 mg bid APR Day 1: APR 125 mg PO, 5HT$_3$ RA IV + DEX 6.6 mg Days 2–3: APR 80 mg PO, DEX 2 mg bid For patients receiving FOS Day 1: FOS 150 mg IV, 5HT$_3$ RA IV, DEX 6.6 mg Day 2: DEX 2 mg bid PO Day 3: DEX 4 mg bid PO Second cycle: all patients received APR or FOS as above	N=413 Mean age, 64 years, female 80%–81%, chemotherapy-naïve 93%	Control vs APR No emesis, overall phase 83.6% vs 95.7%, P<0.0001	Control vs APR No nausea Acute phase: 90.2% vs 93.6%, P=0.23 Delayed phase: 61.8% vs 66.3%, P=0.36 Overall phase: 59.6% vs 65.2%, P=0.26

(Continued)

Table 4 (Continued)

Study	Antiemetic treatment and DEX dose	Patient demographics	Primary end-point results	Select secondary end-point results
Raftopoulos et al 2015[59]	GERSC + DEX vs PALO + DEX GERSC 5 mg or 10 mg SC or PALO (0.25 mg) IV Day 1: DEX 8 mg IV for MEC Days 2–4: DEX PO 8 mg twice daily	N=1,428 Mean age 55–58 years, female 63%–88%, white 56%–67%, chemotherapy-nonnaive 47%–59%	GERSC vs PALO In cycle 1, MEC GERSC 5 mg SC vs PALO 0.25 mg IV CR acute phase: 74.8% vs 75.0%, P=1.0 CR delayed phase: 51.4% vs 57.2%, P=0.24 GERSC 10 mg SC vs PALO 0.25 mg IV CR acute phase: 76.9% vs 75.0%, P=0.73 CR delayed phase: 58.5% vs 57.2%, P=0.84	GERSC vs PALO CR overall phase, MEC GERSC 5 mg SC vs PALO 0.25 mg IV: 48.6% vs 51.9%, 95% CI −2.9 to 6.2 GERSC 10 mg SC vs PALO 0.25 mg IV: 53.8% vs 51.9%, 95% CI −7.8 to 11.4

Note: NEPA, APR, and PALO administered 60 minutes prior to chemotherapy administration on day 1.
Abbreviations: 5HT₃, 5-hydroxytryptamine type 3; APR, aprepitant; bid, bis in die (twice daily); CC, complete control; CINV, chemotherapy-induced nausea and vomiting; CR, complete response; DEX, dexamethasone; DOLA, dolasetron; FOS, fosaprepitant; GRA, granisetron; GERSC, granisetron extended-release subcutaneously; IV, intravenously; MEC, moderately emetogenic chemotherapy; ND, not done; NEPA, fixed-dose netupitant + palonosetron; NS, not significant; OND, ondansetron; PALO, palonosetron; PO, per os (orally); RA, receptor antagonist; SC, subcutaneously.
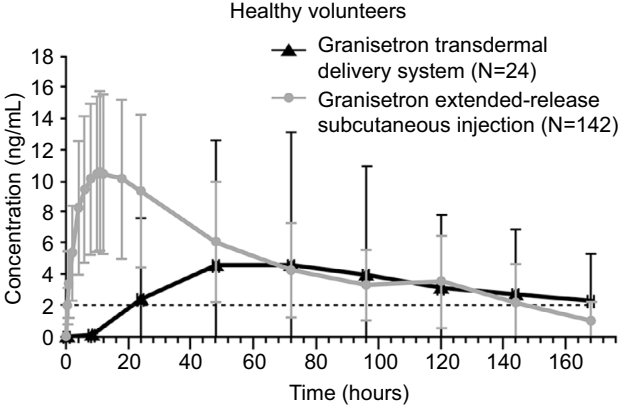

Figure 1 Extended-release formulations of granisetron: plasma granisetron concentrations following administration.
Notes: Data from these studies.[29–31,79] Dashed line indicates minimum therapeutic concentration of granisetron 2 ng/mL (data from patent application 20120258164 for granisetron transdermal delivery system).

bioerodible tri(ethylene glycol) poly(orthoester) (TEG-POE) polymer.[84] The POE polymer contains an orthoester linkage that is hydrolyzed to excreted fragments on exposure to an aqueous environment. The acid-labile nature of the TEG-POE polymer allows granisetron release by diffusion from the depot followed by controlled polymer hydrolysis, resulting in further release of granisetron.[85] In healthy subjects, granisetron is released from the polymer over an extended period (C_{max} occurring approximately 10 hours after administration) (Figure 1). The biphasic drug release from the polymer provides granisetron exposure into the delayed phase of CINV, with mean plasma concentration of 3.5 ng/mL (range 0–14 ng/mL) 5 days after a single 10 mg dose (Figure 2).[29] Following a single SC injection of GERSC to patients with cancer, time to C_{max} was reported as occurring approximately 24 hours postdose, and the $t_{1/2}$ of granisetron was 26–34 hours.[30] The difference in reported time to C_{max} in healthy subjects and patients with cancer may be an artifact of the small number of participants in these analyses and the timing of blood samples used to estimate these pharmacokinetic parameters. Overall, GERSC provides slow, controlled release of therapeutic granisetron concentrations for ≥5 days following a single SC injection.[30,84] The efficacy of GERSC in CINV prevention during acute and delayed phases following MEC or HEC has been shown in two large Phase III trials.[54,59,86] In contrast to GTDS, which is applied 24–48 hours prior to chemotherapy,[31] GERSC may be given shortly (≥30 minutes) before chemotherapy (Table 2). However, the GERSC single-dose syringe must be prepared at least 60 minutes prior to SC administration by warming the viscous liquid to room temperature, and the contents must be injected slowly by a health-care professional. A topical
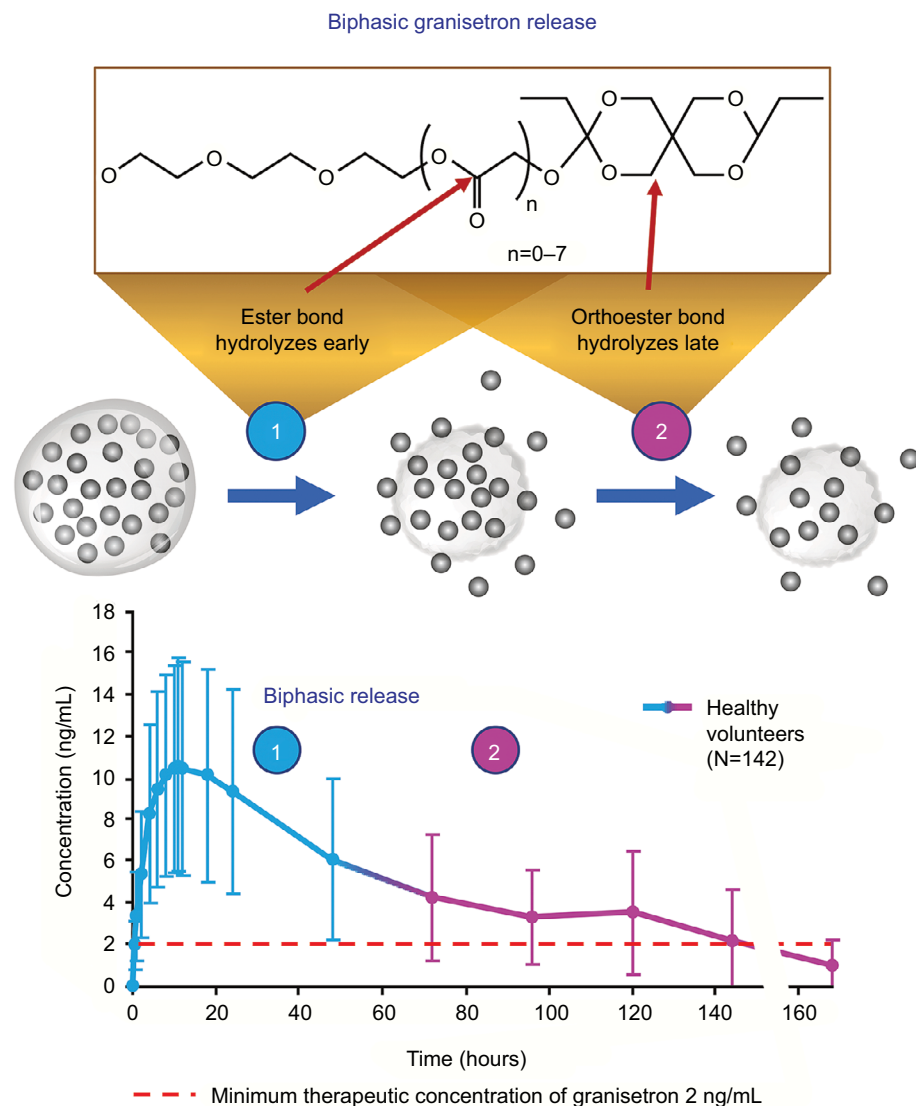
Figure 2 Biochronomer technology mechanism of action.

anesthetic may be applied to the injection site (IS) prior to administration.[29]

Clinical trial experience has established that 5HT$_3$ RAs effectively control emesis in the acute phase,[87–90] but their efficacy in the delayed phase is limited.[91,92] In Phase III trials, the addition of the NK$_1$ RA aprepitant to a regimen of a 5HT$_3$ RA plus dexamethasone improved CINV control over both acute and delayed phases following MEC or HEC (Tables 3 and 4).[55,56,68,93] In the Phase III MAGIC trial of GERSC versus ondansetron, each combined with an NK$_1$ RA and dexamethasone, the GERSC regimen provided superior delayed-phase CR in patients receiving HEC compared with the ondansetron regimen,[54] suggesting the involvement of 5HT$_3$ RAs in mitigating delayed as well as acute CINV.

Efficacy of combination therapies for CINV

The three-drug antiemetic regimen (5HT$_3$ RA + NK$_1$ RA + dexamethasone)

Currently, guidelines for CINV prevention following HEC recommend a three-drug regimen of a 5HT$_3$ RA, an NK$_1$ RA, and dexamethasone as an option, with NCCN and ASCO guidelines also proposing a four-drug regimen with the addition of olanzapine (Table 1). No 5HT$_3$ RA as a part of a three-drug regimen is preferred by any guideline for HEC.[7,17,19] Efficacy results from key Phase III trials in patients receiving HEC are summarized in Table 3. The MAGIC trial was the first Phase III registrational efficacy study to compare single doses of two 5HT$_3$ RAs – GERSC and

ondansetron – in a guideline-recommended three-drug versus three-drug regimen in 942 randomized patients receiving HEC[54] (Table 3). As expected from the ER design, compared with the ondansetron arm, the GERSC arm demonstrated a superior delayed-phase CR rate (64.7% vs 56.6%, P=0.014, absolute treatment difference 8.0%), challenging the view that 5HT$_3$ RAs have equal efficacy in delayed-phase CINV prevention following HEC.[11,94] Consistent with the primary end point of CR, the GERSC arm versus the ondansetron arm also showed benefit in reducing rescue medication use and nausea frequency in the delayed and overall CINV phases.[54] Additionally, patient-reported satisfaction with antiemetic therapy was significantly higher in the GERSC arm versus the ondansetron arm in the delayed phase.[54]

Because all patients in the MAGIC trial were from US community practices, these results are likely to be representative of outcomes in that practice setting. Importantly, the GERSC regimen demonstrated superiority to the ondansetron regimen in a population where the majority of patients were women (GERSC arm 79.6%, ondansetron arm 82.5%), a high-risk group for CINV.[54] Moreover, patients were stratified by planned use of cisplatin ($\geq$50 mg/m^2, yes/no), and the delayed-phase CR rate was higher in the GERSC arm (65.3%) versus the ondansetron arm (54.7%) in the 252 patients in the cisplatin stratum.[54] In a post hoc subgroup analysis of the 589 patients (65%) receiving AC-based HEC, at least 98% of whom were women, delayed-phase CR rates showed a trend favoring the GERSC arm (64%) over the ondansetron arm (56%).[95] A similar trend was found in the subgroup of 252 patients scheduled to receive cisplatin, where delayed-phase CR rates were numerically higher in the GERSC arm (65%) than in the ondansetron arm (55%).[96] These subgroup findings were consistent with the overall population, although the analyses were not powered to show a significant difference between groups.

The two-drug antiemetic regimen (5HT$_3$ RA + dexamethasone)

Guidelines for CINV prevention following MEC generally recommend a two-drug regimen of a 5HT$_3$ RA plus dexamethasone on day 1 (with or without an NK$_1$ RA) and dexamethasone on days 2 and 3, with NCCN guidelines proposing the addition of an NK$_1$ RA for patients with additional CINV risk factors or prior treatment failure.[7,18,19] Efficacy results from key Phase III trials in patients receiving MEC are summarized in Table 4. In the Phase III trial of GERSC compared with palonosetron, both in combination with dexamethasone, in patients receiving MEC (reanalyzed according to 2011

ASCO criteria[97]), both doses of GERSC (5 mg and 10 mg SC) were noninferior to palonosetron (0.25 mg IV) in preventing acute-phase CINV as determined by CR in cycle 1 of chemotherapy, and the 10 mg dose of GERSC was noninferior to palonosetron in preventing CINV in the delayed phase.[86]

Of interest, because of AEs associated with dexamethasone, such as insomnia, gastrointestinal symptoms, agitation, increased appetite, and weight gain,[98] several studies have investigated the efficacy of a dexamethasone-sparing palonosetron regimen involving 1-day versus 3-day dexamethasone in the MEC setting and reported the noninferiority of these regimens (Table 4).[67,69,72]

Nausea control

Significant advances have been made in emesis control following MEC or HEC with the use of newer agents, but nausea control following HEC remains suboptimal, especially in the delayed phase of CINV, with delayed nausea being reported by 68% of patients in one study.[10] A multinational survey of 2,388 health-care providers found delayed nausea to be most challenging to prevent,[5] and several patient-related factors, including younger age, type of cancer, and patient's perceived susceptibility to nausea, can contribute to increased incidence of chemotherapy-induced nausea.[99] Subjectivity in the measurement of nausea and its severity and a lack of understanding of underlying mechanisms pose barriers to optimal nausea control. In clinical trials, such end points as CC (CR with no more than mild nausea) and total response (CR with no nausea) provide some measure of nausea control, but rely on the patient's self-reporting of nausea frequency and severity.

In the MAGIC trial of GERSC, patients with CC in the delayed phase comprised 60.7% in the GERSC regimen and 53.1% in the ondansetron regimen, a treatment difference of 7.6% (95% CI 1.1%–14.0%, unadjusted P=0.022). Percentages of CC were also higher in the GERSC regimen than the ondansetron regimen in the overall phase, but the difference was not significant (54.7% vs 49.6%, respectively; unadjusted P=0.123). The proportions of patients with no nausea in the GERSC and ondansetron regimens were similar in the delayed (49.7% vs 44.2%, respectively; P=0.099) and overall phases (45.3% vs 40.5%, respectively; P=0.138).[54]

A recent Phase III trial of olanzapine versus placebo, each with a three-drug regimen of a 5HT$_3$ RA, an NK$_1$ RA, and dexamethasone, focused specifically on nausea control as the primary end point, and showed effective nausea control with the olanzapine regimen compared with the placebo regimen in patients receiving cisplatin or AC-based HEC. For patients in the olanzapine group compared with the placebo group,

the proportions of patients with no nausea (acute phase 74% vs 45%, respectively, P=0.002; delayed phase 42% vs 25%, P=0.002; overall phase 37% vs 22%, P=0.002) and with CR (acute phase 86% vs 65%, P<0.001; delayed phase 67% vs 52%, P=0.007; overall phase 64% vs 41%, P<0.001) were significantly higher across all CINV phases.[15]

Efficacy of 5HT$_3$ RAs in multicycle chemotherapy

In trials evaluating antiemetics in multicycle-chemotherapy settings, the efficacy of 5HT$_3$ RAs in CINV prevention was generally maintained over multiple cycles (Table 5[37,80,100–102]). Palonosetron at a dose of 0.75 mg, which is three times the approved dosage in the USA, was generally well tolerated in a Phase III trial in patients receiving cisplatin or AC-based HEC in Japan (Table 5).[100] CR rates were maintained across four cycles in the acute (range 72%–77%), delayed (range 56%–63%), and overall (range 52%–56%) phases.[100] A single-arm study in 156 patients receiving four to six cycles of cisplatin-based HEC evaluated CINV-prevention efficacy of palonosetron 0.25 mg IV in a three-drug regimen with oral aprepitant 125 mg and dexamethasone 20 mg IV on day 1. Overall-phase CR rates were maintained over six cycles, ranging from 74.4% to 82.0%. At least 90% of patients had no emesis, and at least 60% had no nausea across cycles.[103] The proportion of high-risk female patients in this study was 36%.

In a Phase III study of NEPA over multiple cycles, oral NEPA plus oral dexamethasone was compared with a control regimen of oral aprepitant plus oral palonosetron plus oral dexamethasone[37] (Table 5). Overall-phase CR rates were maintained over multiple cycles in patients receiving the NEPA regimen (HEC 79%–91%, MEC 80%–93%) or the control regimen (HEC 58–86%, MEC 82%–89%), and were slightly lower with the latter regimen. In the delayed phase, there was a small but consistent numerical advantage in CR of 2%–6% with the NEPA regimen compared with the control regimen. The proportion of patients with no significant nausea in the overall phase remained high in both groups. Around 50% of study patients were women, and overall-phase CR rates with the NEPA regimen were generally similar in men and women across cycles (data not shown).[37]

In a Phase III trial in patients receiving multiple cycles of MEC or HEC, sustainability of GERSC efficacy in CINV prevention was examined. Patients received GERSC 5 or 10 mg SC or palonosetron 0.25 mg IV in cycle 1. After cycle 1, no palonosetron was administered, and upon consent patients previously receiving palonosetron were rerandomized to receive GERSC 5 or 10 mg SC. CR rates were sustained over four cycles in patients receiving GERSC 10 mg once per cycle, with CR rates of 68.4% in patients in the acute phase of CINV, and 57.9% in the delayed phase following HEC; corresponding CR rates in patients receiving MEC were 56.5% and 41.3%, respectively. Emesis control was comparable to nausea control in patients receiving GERSC. Among patients in the MEC and HEC groups, respectively, 84%–88% and 63%–67% were women.[101] The higher proportion of women in the MEC group versus the HEC group and inclusion of AC-based regimens as MEC (as per guidelines at the time of the study design[8]) instead of HEC (as per current guidelines[7,17,19]) may have contributed to the lower CR rates in the MEC group compared with those in the HEC group. At the time of this study, the recommended antiemetic regimen for patients receiving multiple cycles of HEC did not include an NK$_1$ RA. The efficacy of GERSC as a part of a three-drug regimen remains to be investigated in the setting of multicycle MEC or HEC.

Efficacy of 5HT$_3$ RAs in multiday chemotherapy

There have been fewer trials evaluating the antiemetic efficacy of 5HT$_3$ RAs in patients receiving multiday chemotherapy than in those receiving single-day chemotherapy, and the NCCN guidelines recognize the lack of evidence to support recommendations in multiday-chemotherapy settings.[7] The efficacy of transdermal (GTDS) versus oral granisetron in preventing CINV was investigated in a Phase III study of 641 patients receiving their first cycle of a multiday MEC or HEC regimen (Table 5).[80] GTDS was noninferior to daily oral granisetron, and efficacy was maintained across the multiday-chemotherapy regimen (CC, GTDS 60%, oral granisetron 65%, 95% CI –13 to 3).[80] A small Phase III CINV-prevention study in 69 patients receiving 5-day cisplatin showed a significantly higher CR rate with a regimen of the NK$_1$ RA aprepitant plus a 5HT$_3$ RA (excluding palonosetron) plus dexamethasone versus a 5HT$_3$ RA plus dexamethasone (42% vs 13%, P<0.001) (Table 5).[102]

In a retrospective trial of palonosetron in comparison with ondansetron in patients receiving multiday cisplatin or carboplatin, palonosetron therapy was associated with a 63% lower risk of uncontrolled CINV (odds ratio 0.37, 95% CI 0.25–0.54; P<0.0001).[104] A pilot study involving administration of palonosetron 0.25 mg IV for 1, 2, or 3 days in patients receiving multiday high-dose melphalan and hematopoietic stem-cell transplantation suggested that multiple doses may be more effective than a single dose.[105] However, these results need confirmation in larger trials in combination with NK$_1$ RAs.

Table 5 Results of prospective Phase III clinical trials evaluating antiemetic efficacy in CINV prevention following multicycle or multiday chemotherapy

Study, treatment	Antiemetic treatment and DEX dose	Patient demographics	Primary end-point result	Select secondary end-point result
Multicycle chemotherapy				
Aogi et al 2012[100] Multiple cycles of cisplatin or AC	PALO + DEX PALO 0.75 mg IV Day 1: DEX 16 mg IV Days 2–3: DEX 8 mg IV (cisplatin-treated patients) or 4 mg PO for AC-treated patients	N=546 Mean age 58 years, female 57%, no alcohol consumption within 180 days of enrollment 44%	Treatment-related AEs: 44% of patients Serious AEs: 4% Study discontinuation due to treatment-related AEs: 1 No trend toward worsening AEs through successive cycles	PALO + DEX CR across cycles Acute phase: 77.0%–71.7% Delayed phase: 56.0%–62.6% Overall phase: 51.6%–56.1%
Gralla et al 2014[37] Multiple cycles of MEC or HEC	NEPA + DEX vs PALO + APR + DEX NEPA[a] (netupitant 300 mg + PALO 0.5 mg) PO + DEX or APR (125 mg PO day 1 80 mg days 2–3) + PALO 0.5 mg PO day 1 + DEX DEX PO for HEC Day 1: 12 mg Days 2–4: 8 mg DEX PO for MEC Day 1: 12 mg	N=413 Median age 57–59 years, female 49%–50%	Most frequent NEPA-related AEs: constipation (3.6%) and headache (1.0%); AEs did not increase over multiple chemotherapy cycles, most were mild–moderate; no cardiac safety concerns, no deaths related to study drug	NEPA + DEX vs APR + PALO + DEX CR overall phase Cycles 1: 81% vs 76% 2: 86% vs 81% 3: 91% vs 87% 4: 90% vs 88% 5: 92% vs 86% 6: 91% vs 86% CR overall phase for HEC across cycles NEPA: 79%–91% APR + PALO: 58%–86% CR overall phase for MEC across cycles NEPA: 80%–93% APR + PALO: 82%–89% No significant nausea Overall phase NEPA: 84%–92% APR, PALO: 81%–87%
Boccia et al 2015[101] Multiple cycles of MEC or HEC	GERSC + DEX vs PALO + DEX Cycle 1 GERSC 10 mg SC + placebo IV or GERSC 5 mg + placebo IV or PALO 0.25 mg IV + placebo SC No PALO after cycle 1: patients on PALO rerandomized 1:1 to GERSC 10 mg or 5 mg, upon consent DEX Day 1: 8 mg IV for MEC, 20 mg IV for HEC Days 2–4: 8 mg bid PO for HEC	N=1,428 Mean age 55–58 years, female 63%–88%, white 58%–68%	Post hoc analysis Across four cycles, per cycle GERSC 10 mg, HEC CR acute phase: 81.3%–87.8% CR delayed phase: 67.1%–83.1% Sustained CR over four cycles GERSC 10 mg, HEC CR acute phase: 68.4% CR delayed phase: 57.9% GERSC 10 mg, MEC CR acute phase: 56.5% CR delayed phase: 41.3% Cycle 1 PALO CR acute phase for MEC: 75% CR acute phase for HEC: 81%	

Multiday chemotherapy

Boccia et al 2011[80]	GTDS vs GRA PO	N=641	GTDS vs GRA PO	GTDS vs GRA PO
Multiday MEC or HEC	Granisetron transdermal delivery system (GTDS), one patch, 7 days or GRA PO	Mean age 54–55 years, female 16%–17%, white 25%–26%, never-smokers 17%–19%, no alcohol use 22%–23%, chemotherapy-naïve 22%–23%	First cycle of multiday chemotherapy (MEC or HEC)	CR (per protocol data set) 62% vs 68%, 95% CI –14.4 to 1.3
	2 mg/d, 3–5 days		CC (from first chemotherapy to 24 hours after last chemotherapy administration, per protocol data set): 60% vs 65%, 95% CI –12.9 to 3.1	Patch adhesion
	No DEX use information available			≥90% adhesion: 64% vs 78%
				≥75% adhesion: 90% vs 96%
				Complete detachment: 1% vs 1%
Albany et al 2012[102]	APR + 5HT$_3$ RA + DEX vs 5HT$_3$ RA + DEX + placebo (three-drug regimen, excluding PALO)	N=69	APR + 5HT$_3$ RA + DEX vs 5HT$_3$ RA + DEX + placebo	APR + 5HT$_3$ RA + DEX vs 5HT$_3$ RA + DEX + placebo
Two consecutive courses of 5 days cisplatin combination therapy	Days 1–2: DEX 20 mg PO qd	Median age 33 years, chemotherapy-naïve 83%	CR acute phase (days 1–5): 47% vs 15%, $P<0.001$	Emesis
	Days 1–5: 5HT$_3$ RA (excluding PALO)		CR delayed phase (days 6–8): 63% vs 35%, $P<0.001$	APR cycle vs control cycle: 16.2% vs 47.1%
	APR		CR overall phase (days 1–8): 42% vs 13%, $P<0.001$	Patient-preferred APR cycle vs placebo cycle: 55% vs 16%, $P<0.001$
	Day 3: APR 125 mg PO			
	Days 4–7: APR 80 mg			
	Days 6–7: DEX 4 mg bid			
	Day 8: DEX 4 mg bid			
	Placebo			
	Days 3–5: placebo			
	Days 6–7: placebo, DEX 8 mg bid			
	Day 8: DEX 4 mg bid			

Note: [a]NEPA, APR, and PALO administered 60 minutes prior to chemotherapy administration on day 1.
Abbreviations: 5HT$_3$, 5-hydroxytryptamine type 3; AC, anthracycline-cyclophosphamide; AE, adverse event; APR, aprepitant; bid, bis in die (twice daily); CC, complete control; CINV, chemotherapy-induced nausea and vomiting; CR, complete response; DEX, dexamethasone; GRA, granisetron; GERSC, granisetron extended-release subcutaneously; GTDS, granisetron transdermal system; HEC, highly emetogenic chemotherapy; IV, intravenously; MEC, moderately emetogenic chemotherapy; NEPA, fixed-dose netupitant + palonosetron; PALO, palonosetron; PO, per os (orally); qd, quaque die (once daily); RA, receptor antagonist; SC, subcutaneously.

Factors affecting the efficacy of 5HT$_3$ RAs in prevention of acute and delayed CINV

In addition to chemotherapy emetogenicity, patient-related risk factors influence CINV and may affect outcomes in clinical studies. These factors include female sex,[106] younger age,[99] history of low alcohol consumption,[107] history of motion sickness,[107] and history of previous chemotherapy-induced emesis.[11] As such, young female patients receiving HEC are at particularly high risk of experiencing CINV,[108] and differences in proportions of female patients in clinical studies may affect results. The development of predictive tools with a simple scoring system to identify patients at higher risk for CINV, based on a combination of patient- and chemotherapy-related risk factors, may assist in determining the most suitable antiemetic regimen for patients.[109]

Genetic variation in 5HT$_3$ receptors or molecules involved in their transport and metabolism may also lead to differences in antiemetic efficacy.[110,111] 5HT$_3$-RA metabolism is dependent on enzymes in the CYP450 family, with certain enzymes playing a dominant role in certain drugs.[112–114] For example, palonosetron and dolasetron are metabolized primarily by CYP2D6, whereas granisetron is metabolized primarily by CYP1A1;[110,115,116] there is no dominant CYP450 enzyme for metabolizing ondansetron.[110,112] CYP2D6 is also involved in the metabolism of a variety of drug classes, and genetic polymorphisms lead to alleles with different activities (defective, decreased, or increased), resulting in poor, intermediate, extensive, or ultrarapid metabolizers (UMs).[111,115] The frequency of UMs varies by race, and control of chemotherapy-induced vomiting using ondansetron or tropisetron is weakest in UM patients compared with poor or intermediate metabolizers.[117] A pharmacogenetically driven treatment pathway that accounts for CYP2D6 genotype has been proposed, suggesting that patients classed as CYP2D6 UMs receiving MEC or HEC should be given granisetron as the first-line 5HT$_3$ RA to circumvent the CYP2D6 pathway and reduce pharmacokinetic and pharmacodynamic variability.[115] It has been suggested that genetic polymorphisms of CYP3A4 among patients from different races influence granisetron exposure and thereby its efficacy.[114] Because the ER formulation of GERSC allows continuous exposure to granisetron, it may reduce interpatient variability in antiemetic efficacy resulting from differences in granisetron metabolism. Genetic variations in *5HT3R* may also exist, which may explain in part the decreased efficacy of 5HT$_3$ RAs in some patients.[115] Additional prospective studies investigating 5HT$_3$-receptor polymorphisms and drug transporters may further elucidate the role of genetics in antiemetic response.

Safety of 5HT$_3$ RAs
Most common AEs
The safety profile of 5HT$_3$ RAs is well documented, and these agents are typically well tolerated. The most commonly reported AEs associated with IV or PO 5HT$_3$ RAs are headache (0–24%, depending on the agent and formulation) and constipation (0–14%) (Table 6[25,27–29,31–33,36]).[25,28,29,31–34,36] Diarrhea, asthenia, and dyspepsia are other known AEs. The incidence of these AEs is generally similar across the 5HT$_3$ RAs[59,118,119] (Table 6), and they are generally mild and manageable. In IV and oral formulations of 5HT$_3$ RAs, headache is reported more frequently than constipation, but in the MAGIC trial of GERSC, this finding was reversed. In the Phase III MAGIC trial, constipation occurred in 22% of patients in the GERSC arm and 15% of patients in the ondansetron IV arm, while headache was less common (12% vs 18%, respectively).[54] Similar trends were observed with GTDS, which also provides ER granisetron: a higher proportion of GTDS-treated versus oral granisetron-treated patients (7% vs 3%) had constipation, whereas a lower proportion had headache (0.3% vs 2.5%).[80]

Hypersensitivity and injection-site reactions

Hypersensitivity reactions and IS reactions (ISRs) have been reported with all 5HT$_3$ RAs. Extremely rare instances (<1/10,000) of hypersensitivity, including anaphylaxis and ISRs, have been reported from postmarketing experience with palonosetron IV.[34] Rare and sometimes severe cases of hypersensitivity have been reported with IV granisetron (eg, anaphylaxis, hypotension, shortness of breath, and urticaria)[25] and ondansetron IV (eg, anaphylactic reactions, angioedema, bronchospasm, cardiopulmonary arrest, hypotension, laryngospasm, shock, shortness of breath, and stridor).[32] ISRs, including pain, redness, and burning, have also been reported with ondansetron IV.[32]

The Phase III trial of GERSC versus palonosetron IV in preventing CINV in patients receiving MEC or HEC showed that the safety profiles of these two agents were similar.[59] The most common treatment-related AEs were ISRs (GERSC 10 mg SC 38.9%, palonosetron 11.2%), constipation (GERSC 10 mg SC 4.5%, palonosetron 3.0%), and headache (GERSC 10 mg SC 2.8%, palonosetron 1.9%).[59]

In the Phase III MAGIC trial, GERSC was also generally well tolerated compared with ondansetron IV, and no

Table 6 Percentage of patients (≥2%) with AEs using 5HT₃ RA, based on drug-prescribing information

Drug, n	Headache, %	Constipation, %	Diarrhea, %	Asthenia, %	Fatigue, %	Dyspepsia, %	Dizziness, %	Pain, %	Other AEs, %
Dolasetron 100 mg PO n=227[27]	22.9	—	5.3	—	5.7	2.2	3.1	3.1	Bradycardia, 4.0 Tachycardia, 2.6 Chills, 2.2
Granisetron 40 μg/kg IV[a] n=1,268[25] —	14	3	4	5	—	—	—	—	Somnolence, 4
Granisetron 2 mg once daily PO[b] n=1,450[28]	20	14	9	18	—	6	5	4 (abdominal)	Dyspepsia, 6 Elevated (>2× normal values) levels AST (5) and ALT (6) Insomnia, 5 Fever, 5
GERSC SC, 10 mg granisetron[c] n=468, n=456[29]	9 (N=486) 13 (N=456)	14 (N=468) 22 (N=456)	8 (N=468) 9 (N=456)	4 (N=468) 2 (N=456)	11 (N=468) 21 (N=456)	3 (N=468) 6 (N=456)	3 (N=468) 5 (N=456)	7 (N=468) 7 (N=456), abdominal	Injection-site reactions, (including bruising, pain, erythema, mass or nodule, capillary bleeding), 37–62
GTDS transdermally[c] n=404[31]	—	5.4	—	—	—	—	—	—	—
Ondansetron IV (three 0.15 mg/ kg doses)[b] n=419[32]	16	11 (multiday ondansetron)	16	—	—	—	—	—	Fever, 8 Elevated (>2× normal values) levels AST and ALT, ~5
Ondansetron 24 mg once daily PO (HEC)[d] n=300[33]	11	—	4	—	—	—	—	—	—
Ondansetron 8 mg twice daily for 3 days, PO (MEC)[e] n=242[33]	24	9	6	—	13	—	5	—	—
Palonosetron 0.25 mg IV n=633[32]	9	5	—	—	—	—	—	—	—
Palonosetron + netupitant (NEPA), PO n=136 (HEC), c n=725 (AC)[36]	— (N=136) 9 (N=725)	3 (N=136) — (N=725)	—	— (N=136) 8 (N=725)	4 (N=136) 7 (N=725)	4 (N=136) — (N=725)	—	—	Erythema, 3 (N=136)

Notes: [a]AEs in >3% of patients; [b]AEs in >5% of patients; [c]AEs in ≥3% of patients; [d]AEs in ≥4% of patients; [e]AEs in ≥5% of patients.
Abbreviations: 5HT₃, 5-hydroxytryptamine type 3; AC, anthracycline–cyclophosphamide; AEs, adverse events; ALT, alanine transaminase; AST, aspartate transaminase; GERSC, granisetron extended-release subcutaneously; GTDS, granisetron transdermal system; HEC, highly emetogenic chemotherapy; IV, intravenously; MEC, moderately emetogenic chemotherapy; NEPA, fixed-dose netupitant 300 mg + palonosetron 0.5 mg; PO, per os (orally); RA, receptor antagonist; SC, subcutaneously.

unexpected safety findings were observed.[54] All ISRs were conservatively considered treatment-related, regardless of their time of occurrence following study-drug administration, and were graded by investigators on days 1 and 6 and at the final safety follow-up visit according to prespecified criteria representing only size differences, not functional impairment.[54] Additionally, patients were instructed to evaluate the IS on days 2 to 5 and record the ISR status in a provided diary. ISRs occurred in patients in both arms at a similar frequency (61.8% in the GERSC arm, 59.5% in the ondansetron arm), presumably because of the double-dummy design of the study, where both arms received SC and IV drug or vehicle placebo; most ISRs were mild–moderate and resolved over time.[54] No ISRs led to study discontinuation or death.[54]

Compared with the earlier Phase III trial, a greater proportion of patients receiving GERSC in the MAGIC trial reported ISRs.[54,59] Several factors may have contributed to this finding, including the assumption that all ISRs were treatment-related, grading only according to size and not functional impairment (which may have led investigators to pay greater attention to ISRs), and the instruction for patients to evaluate the site and record any signs of ISRs in patient diaries. Further, the MAGIC trial was conducted only in the USA, whereas the previous trial also included patients from Poland and India;[54,59] potential differences in ISR reporting across countries may have led to the observed ISR-reporting differences in the studies. The most common ISR in both trials was bruising, which was higher in the MAGIC trial (GERSC arm 41.9%, ondansetron arm 33.6%) than in the previous Phase III trial (GERSC 10 mg, related 15.6%, unrelated 4.3%; palonosetron 0.25 mg IV, related 6.5%, unrelated 2.6%).[54,59] However, if ISRs in the MAGIC trial were graded by National Cancer Institute Common Terminology Criteria for AEs instead of size, all instances of IS bruising of grades 2 and 3 would have been classified as grade 1. A Phase I crossover study demonstrated that GERSC may be administered to the abdomen or nondominant upper arm, but ISR incidence was higher in patients receiving abdominal (84.5%) versus upper-arm injections (69.2%).[120] Therefore, upper-arm administration may be preferable.

Serotonin syndrome

5HT$_3$ RAs have been associated with serious AEs, such as serotonin syndrome (involving symptoms of mental status changes), autonomic instability, neuromuscular symptoms, and seizures with or without gastrointestinal symptoms.[25,32–34,36] Serotonin syndrome results from increased serotonin signaling in the central nervous system.[121]

Occurrences of serotonin syndrome have generally been associated with concomitant use of serotonergic drugs and 5HT$_3$ RAs or with an overdose of 5HT$_3$ RAs.[33] Some fatalities resulting from serotonin syndrome have been reported with 5HT$_3$ RAs.[121] Patient monitoring for symptoms of serotonin syndrome and discontinuation of 5HT$_3$ RAs on their occurrence is recommended.

Cardiac effects

As a class, 5HT$_3$ RAs block cardiac hERG potassium channels with varying effectiveness,[83] so may be associated with abnormal cardiac electrical activity, such as a prolonged QT interval on electrocardiography (ECG). Dolasetron and ondansetron have lower clinical cardiac safety margins compared with granisetron and palonosetron.[83] In 2010, the FDA requested the withdrawal of the CINV indication for dolasetron IV, because of the possibility of life-threatening cardiac arrhythmias, such as QT-interval prolongation.[74] In 2012, the FDA restricted IV doses of ondansetron to three doses of 0.15 mg/kg administered every 4 hours to a maximum of 16 mg, given the risk of QT-interval prolongation.[122] Postmarketing reports of torsades de pointes have also been documented in patients using ondansetron.[32]

Other 5HT$_3$ RAs have demonstrated no clinically significant changes in QT interval. Palonosetron 0.25, 0.75, or 2.25 mg IV showed no significant effect on cardiac QT intervals in healthy volunteers.[123] Supratherapeutic doses of NEPA (netupitant 600 mg and palonosetron 1.5 mg) produced no significant change in QTc, PR, or QRS intervals in healthy volunteers.[124] In a thorough QT/QTc study in healthy volunteers, granisetron administered via GTDS achieved prolonged therapeutic plasma concentrations compared with granisetron IV, but this did not lead to significant or progressive QT prolongation.[125] In a similar study, GERSC 20 mg (twice the approved dose) elicited no clinically significant effect on QT interval compared with placebo.[126] Although ECG changes induced by 5HT$_3$ RAs can be asymptomatic and reversible, fatal cardiac arrhythmias can occur in certain cases.[127] NCCN guidelines recommend that patients at high risk of developing life-threatening cardiac arrhythmias, such as those with torsades de pointes, receive routine ECG monitoring during treatment with 5HT$_3$ RAs.[7]

Special populations

For ondansetron IV and PO and palonosetron IV, no dosage adjustment is recommended for patients with renal impairment or mild–moderate hepatic impairment.[32–34] In patients with severe hepatic impairment (Child–Pugh score ≥10), the

maximum total daily dose of ondansetron should not exceed 8 mg.[32,33] For NEPA, no dosage adjustment is necessary in patients with mild–moderate renal or hepatic impairment, but NEPA should be avoided in patients with severe hepatic or renal impairment or end-stage renal disease.[36] Total granisetron clearance is not affected in patients with severe renal failure receiving a single IV dose of granisetron, and no dosage adjustment is necessary in patients with hepatic impairment.[25] For granisetron PO, no dosage adjustment is recommended for patients with either renal or hepatic impairment.[28] No studies have investigated the pharmacokinetics of GTDS in patients with renal or hepatic impairment.[31] For GERSC, there are no pharmacokinetic data on the elimination of the TEG-POE polymer vehicle in patients with renal impairment, and the clinical significance of prolonged granisetron elimination in patients with cancer is unknown. Consequently, current recommendations are that GERSC should not be administered more than once every 14 days in patients with moderate renal impairment and should be avoided in patients with severe renal impairment.[29]

Clearance of ondansetron IV in pediatric patients aged 1–4 months is slower, and the $t_{1/2}$ is ~2.5-fold longer than in patients aged >4–24 months, so patients <4 months old receiving ondansetron IV should be closely monitored.[32] The safety and effectiveness of ondansetron PO have been established in pediatric patients ≥4 years of age receiving MEC, but not HEC.[33] The safety and effectiveness of palonosetron IV have been established in pediatric patients aged 1 month to <17 years. Pediatric patients require a higher IV dose of palonosetron than adults to prevent CINV, but the safety profile is consistent with that in adults.[34] For NEPA, safety and effectiveness in patients <18 years of age have not been established. For granisetron, the recommended IV dose in pediatric patients 2–16 years of age is 10 µg/kg. Benzyl alcohol, a component of granisetron 1 mg/mL IV, has been associated with serious adverse reactions and death, particularly in neonates.[25] The safety and effectiveness of granisetron PO, GTDS, and GERSC in pediatric patients have not been established.[28,29,31]

For ondansetron IV and PO, no overall differences in safety or effectiveness have been observed between elderly and younger patients, and no dosage adjustment is needed in patients >65 years of age. However, greater sensitivity of some older patients to ondansetron cannot be ruled out.[32,33] Population pharmacokinetic analyses of palonosetron IV have not revealed any differences between patients ≥65 years of age and younger adult patients.[34] For NEPA PO, the safety profiles in elderly and younger patients are similar.[36] For different formulations of granisetron, the safety and effec-

tiveness of granisetron IV and PO are similar in patients of various ages.[25,28] For GTDS and GERSC, clinical experience has not identified any differences in safety or effectiveness between elderly and younger patients.[29,31] In general, caution should be used when administering any of these agents to elderly patients, because of their increased likelihood of having decreased hepatic, renal, or cardiac function, concomitant diseases, and receiving other drug therapies.

Safety of 5HT$_3$ RAs in multicycle chemotherapy

5HT$_3$ RAs have generally been well tolerated in multicycle CINV-prevention trials. NEPA was generally safe when administered over multiple cycles to patients receiving MEC: the incidence of AEs did not increase across cycles.[37] Serious treatment-emergent AEs occurred in 16.2% of patients in the NEPA group (two were treatment-related) and 18.3% of patients in the aprepitant plus palonosetron group. GERSC was generally safe in patients receiving up to four cycles of MEC or HEC.[101] No treatment-related serious AEs were observed. Most ISRs were mild, and those of moderate severity occurred in less than 3% of patients. ISRs included bruising (GERSC 500 mg, 29.7%), nodules (GERSC 500 mg, 17.5%), erythema (GERSC 500 mg, 11.8%), pain (GERSC 500 mg, 7.2%), and bleeding (GERSC 500 mg, 6.6%).[101]

Safety of 5HT$_3$ RAs in multiday chemotherapy

In a Phase III trial of GTDS in patients receiving multiday chemotherapy, the most common AE was constipation, occurring in 7% of patients,[80] and no QTc prolongation occurred with GTDS. Multiple doses of palonosetron 0.25 mg IV administered with dexamethasone were well tolerated in patients with multiple myeloma receiving multiday melphalan and hematopoietic stem-cell transplantation, and no serious drug-related AEs were reported.[105] In patients receiving up to six cycles of cisplatin, a combination of palonosetron 0.25 mg IV, aprepitant 125 mg PO, and dexamethasone 20 mg IV on day 1 of chemotherapy was well tolerated.[103]

5HT$_3$ RAs for radiotherapy-induced NV and chemoradiation-induced NV

In addition to chemotherapy, other causes of NV include radiotherapy and concomitant chemotherapy and radiotherapy. Among patients receiving radiotherapy, 50%–80% may experience radiotherapy-induced NV (RINV), depending

on the site of irradiation, dose, fractionation schedule, and patient-related risk factors.[128] 5HT$_3$ RAs have been widely used for RINV prophylaxis,[128] and NCCN guidelines recommend pretreatment with oral granisetron or oral ondansetron, with or without oral dexamethasone, for each day of upper-abdomen, localized, or total-body irradiation.[7]

Despite widespread use of chemoradiation to treat gynecologic and other cancers, prophylactic antiemetic regimens for RINV and chemoradiation-induced NV (CRINV) are relatively underexplored.[129] The standard of care for women with cervical cancer involves weekly cisplatin-based HEC and concomitant fractionated radiotherapy, resulting in increased CINV risk in these patients, due to their young age, female sex, and the high emetogenicity of cisplatin.[129] In a Phase II study in 48 women receiving concomitant radiotherapy and cisplatin therapy for gynecologic cancers, prophylaxis with palonosetron 0.25 mg IV once on day 1 and prednisolone 100 mg once on day 1 followed by 50 mg twice on day 2, 25 mg twice on day 3, and 25 mg once on day 4 was insufficient for emesis control.[130] The primary end point, cumulative probability of patients completing five cycles of chemoradiation without emesis, was 57%.[130] A recent Phase III study in 246 women with cervical cancer receiving fractionated radiotherapy and weekly cisplatin for 5 weeks compared fosaprepitant 150 mg IV versus placebo, each combined with palonosetron 0.25 mg IV and dexamethasone 16 mg PO, for the control of CRINV.[131] All patients received dexamethasone 8 mg PO twice on day 2, 4 mg PO twice on day 3, and 4 mg once on day 4. This was the first study to investigate the efficacy of a three-drug regimen in CRINV prevention. A greater proportion of patients receiving the fosaprepitant three-drug regimen did not experience emesis at 5 weeks (65.7% vs 48.7%), with a lower cumulative risk of emesis in these patients (*P*=0.008). These results represent a significant advance in CRINV management.

Conclusion

With the recent addition of new formulations of 5HT$_3$ RAs, health-care providers have a variety of agents to choose from. However, these agents have important differences in efficacy and safety, and the appropriate antiemetic regimen must be selected carefully, considering both chemotherapy regimen and schedule and patient-related risk factors.

For patients receiving single-day HEC, a three-drug antiemetic regimen is recommended, and the 5HT$_3$ RA included in this regimen may influence the combination's efficacy in preventing CINV. Ideally, the 5HT$_3$ RA in combination with an NK$_1$ RA and a corticosteroid should prevent CINV across both acute and delayed phases following HEC. Based

on clinical experience, first-generation 5HT$_3$ RAs such as ondansetron, older formulations of granisetron, and dolasetron IV (no longer approved in the USA to prevent CINV, because of potential cardiac effects) are considered similar in efficacy for preventing acute CINV following MEC or HEC, but considered inadequate for preventing delayed CINV following HEC.[11] Recent results with GERSC, the ER polymer formulation of granisetron using novel Biochronomer technology, change this view.[54] Two large Phase III trials in 2,370 patients have demonstrated that a single dose of GERSC is effective in preventing CINV following MEC and HEC regimens.[54,59,86] GERSC was noninferior to the standard of care, palonosetron, in preventing CINV in the acute and delayed phases following MEC and in the acute phase following HEC, and numerically superior to palonosetron in preventing delayed CINV following HEC.[86] GERSC was also superior to ondansetron (when both agents were administered in the guideline-recommended three-drug regimen) in preventing delayed CINV following HEC.[54] In light of the need for better therapies to manage delayed CINV following HEC, GERSC provides a new and effective option. Furthermore, GERSC efficacy has been maintained over successive cycles of MEC or HEC.[101] Therefore, GERSC is a convenient and effective SC option for acute and delayed CINV prevention following MEC or HEC administered over single or multiple cycles. In the USA, GERSC is indicated for use in combination with other antiemetics for the prevention of acute and delayed NV associated with initial and repeat courses of MEC and AC combination-chemotherapy regimens.

Another recent formulation, NEPA (fixed-dose netupitant and palonosetron), in combination with dexamethasone, has shown superiority to palonosetron plus dexamethasone in controlling CINV following MEC in acute, delayed, and overall phases and was effective over multiple cycles of MEC or HEC.[37,45] As such, NEPA is an additional oral antiemetic option for patients receiving MEC or HEC.

Historically, CINV-prevention trials have typically used CR as the primary end point and focused on emesis control in both the acute and delayed phases of CINV, but delayed nausea, especially following HEC, continues to be inadequately controlled. The subjectivity in measuring nausea and the lack of understanding of its underlying pathophysiology have hindered the study of nausea control and the development of effective agents to prevent nausea. The use of a stringent no-nausea end point in clinical trials and a better understanding of the underlying pathophysiology are likely to lead to improved nausea control. Given the efficacy of olanzapine in nausea control, its addition to the existing three-drug regimen

may improve nausea management and may be the next step in CINV-prevention regimens. The continued occurrence of CINV, despite the availability of effective antiemetic regimens and comprehensive clinical practice guidelines, suggests the need for greater adherence to guidelines and better understanding of patient characteristics and genetic differences. Future research on 5HT$_3$-RA pharmacogenetics may improve the understanding of variability in patient response to antiemetics.[110,132]

Acknowledgments

Disclosure

JG has served as a member of a speaker bureau or advisory committee for Heron Therapeutics. LS has acted in a consultant/advisory role for Eisai, Helsinn, Merck, and Tesaro, received research funding from Helsinn, and served as a member of a speaker bureau or advisory committee for Helsinn and Merck. NG has served as a member of a speaker bureau or advisory committee for Eisai, Heron, and Tesaro. The authors report no other conflicts of interest in this work.

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