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REVIEW ARTICLE

Prevention of chemotherapy-induced nausea: the role of neurokinin-1 (NK_1) receptor antagonists

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Abstract Chemotherapy-induced nausea (CIN) has a significant negative impact on the quality of life of cancer patients. The use of 5-hydroxytryptamine-3 ($5\text{-}HT_3$) receptor antagonists (RAs) has reduced the risk of vomiting, but (except for palonosetron) their effect on nausea, especially delayed nausea, is limited. This article reviews the role of NK_1RAs when combined with $5\text{-}HT_3$RA–dexamethasone in CIN prophylaxis. Aprepitant has not shown consistent superiority over a two-drug (ondansetron–dexamethasone) combination in nausea control after cisplatin– or anthracycline–cyclophosphamide (AC)-based highly emetogenic chemotherapy (HEC). Recently, dexamethasone and dexamethasone–metoclopramide were demonstrated to be non-inferior to aprepitant and aprepitant–dexamethasone, respectively, for the control of delayed nausea after HEC (AC/cisplatin), and are now recognized in the guidelines. The potential impact of the new NK_1RAs rolapitant and netupitant (oral fixed combination with palonosetron, as NEPA) in CIN prophylaxis is discussed. While the clinical significance of the effect on nausea of the rolapitant–granisetron–dexamethasone combination after cisplatin is not conclusive, rolapitant addition showed no improvement in nausea prophylaxis after AC or moderately emetogenic chemotherapy (MEC). NEPA was superior to palonosetron in the control of nausea after HEC (AC/cisplatin). Moreover, the efficacy of NEPA in nausea control was maintained over multiple cycles of HEC/MEC. Recently, NK_1RAs have been challenged by olanzapine, with olanzapine showing superior efficacy in nausea prevention after HEC. Fixed antiemetic combinations (such as NEPA) or new antiemetics with a long half-life that may be given once per chemotherapy cycle (rolapitant or NEPA) may improve patient compliance with antiemetic treatment.

Keywords NK_1 receptor antagonist · Chemotherapy-induced nausea (CIN) · Chemotherapy-induced nausea and vomiting (CINV) · Antiemetic guidelines

Introduction

Chemotherapy-induced nausea and vomiting (CINV) remains a critical clinical challenge, with important deleterious effects on patients' quality of life (QoL). Uncontrolled CINV can lead to anorexia, malnutrition, dehydration, and metabolic imbalances. Moreover, poor CINV control in previous cycles may result in anticipatory CINV. Potential consequences of uncontrolled CINV are poor treatment compliance and even discontinuation of potentially beneficial chemotherapy [1–5]. Advances in antiemetic therapies have greatly reduced CINV incidence, and vomiting can be prevented in the majority of cancer patients [6, 7]. While improvements have also occurred in the prevention of nausea, this control is markedly less than with vomiting and can be particularly prominent in delayed nausea during the course of chemotherapy [1, 8–13]. Prevention of nausea has become a top priority in antiemetic clinical research, and many have considered that this should be the primary endpoint in clinical trials.

Antiemetic guidelines categorize chemotherapeutic agents based on the frequency with which patients experience acute emesis (0–24 h after chemotherapy) in the absence of

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antiemetic prophylaxis into four CINV risk levels: highly emetogenic chemotherapy (HEC: by non-anthracycline–cyclophosphamide (non-AC) and AC–HEC), moderately emetogenic chemotherapy (MEC; carboplatin and others), low emetogenic chemotherapy, and minimally emetogenic chemotherapy. Antiemetics with highest therapeutic index are 5-hydroxytryptamine-3 (5-HT_3) receptor antagonists (RAs), NK_1RAs, and corticosteroids, especially dexamethasone [6, 11, 14].

The NK_1RA family of antiemetics acts by blocking substance P activity at NK_1 receptors in the brain, offering a mechanism of action distinct from and complementary to 5-HT_3RAs. NK_1RAs were rapidly incorporated into international antiemetic guidelines and are currently recommended for prevention of CINV induced by non-AC– and AC–HEC [1, 10, 15–21] or carboplatin-based MEC [21]. The two newest members of this class, netupitant (in a fixed combination with palonosetron as NEPA) and rolapitant have recently become available [22–24] and are also included in antiemetic guidelines [1, 10, 21].

This review focuses on prevention of CIN and the role of NK_1RAs in its management.

Neuropharmacology of nausea

Nausea is defined as an epigastric discomfort or unpleasant awareness of being on the verge of vomiting. Vomiting is the retrograde expulsion of gastric contents through the mouth [25].

Nausea and vomiting often are clinically associated; however, nausea can occur alone or with other symptoms such as dyspepsia. Nausea is a subjective sensation, while vomiting is an objective reflex that can be easily measured [26].

The neuropharmacology of nausea and vomiting is also distinct and, particularly in the case of nausea, not well understood. In contrast to vomiting, nausea has been shown to require conscious awareness and cortical function [27]. Additionally, some studies have demonstrated that nausea is accompanied by an increase in vasopressin and oxytocin levels [28]. Elevations in plasma cortisol, β-endorphin, epinephrine, and norepinephrine concentrations and alterations in gastric myoelectric activity also occurred in subjects who developed nausea in motion sickness models [29, 30].

The aprepitant–ondansetron–dexamethasone regimen, although significantly superior in the control of chemotherapy-induced vomiting, was not superior in the control of overall nausea when compared to ondansetron–dexamethasone [15, 17]. This observation suggests that nausea and vomiting may occur through distinct, although shared, pharmacologic mechanisms, and that better protection against nausea likely requires targeting receptors other than 5-HT_3 and NK_1 [31]. Muscarinic, histaminic, and adrenergic receptors, involved in the mechanism of vomiting and nausea unrelated to chemotherapy [32], are potential candidates. Identification and characterization of brain mechanisms leading to nausea await further research.

Methodology and data gaps in nausea assessment in clinical trials

Assessment of nausea is challenging because of its subjective nature, and methods for its clinical evaluation have not evolved substantially over the past 30 years [33]. Until recently, nausea has not been the primary efficacy endpoint in antiemetic clinical studies. Instead, nausea has been evaluated as part of the composite term "complete response" (CR) (no emesis and no rescue medication), where "no need for rescue" serves as a surrogate marker for no nausea or only mild nausea. Nausea has also been assessed as a secondary efficacy endpoint in most studies, where nausea duration and intensity are commonly reported as "no nausea" (visual analog scale (VAS) <5 mm) and/or "no significant nausea" (NSN; VAS <25 mm), measured daily and overall 0–120 h from the start of chemotherapy, and for different periods of the day. Additionally, the Functional Living Index-Emesis (FLIE) questionnaire collects patient-reported information on different aspects of nausea and vomiting that might impact patients' daily life. Because of the subjective nature of nausea, the design of clinical studies with matching identical placebo medication in the control arm is of special importance.

Correctly reporting the onset of nausea (as acute, delayed, or overall) is also of great relevance. Of special concern is the management of delayed nausea, which has a higher incidence [34–37] and greater severity than acute nausea, and is less responsive to treatment [36, 38]. The subjective nature of nausea and communication barriers between healthcare professionals and patients may result in nausea underreporting by patients and in underestimation of its incidence, especially during the delayed phase, by healthcare professionals [37, 39, 40]. Subjective toxicities are more likely to be underreported by physicians in oncology clinical trials [41]. For nausea, an underreporting of 40.7% has been described in this large pooled database (N = 1090) of three randomized trials [41].

NK_1RAs in nausea prevention

NK_1RAs bring significant improvement in CINV control [6, 7, 32, 42]; however, their role in nausea prophylaxis is less established. Here, we review clinical data on nausea-related outcomes from selected NK_1RA trials in which nausea was evaluated either as part of CR or as a secondary endpoint (Table 1) [15–18, 43–52].

Table 1 Summary of studies for the prevention of CIN in patients treated with NK_1RAs in phase III clinical trials[a]

Reference	Patients randomized	Chemotherapy regimen	Antiemetic prophylaxis	Proportion of patients with no significant nausea (%)		
				Acute	Delayed	Overall
Aprepitant						
Warr [17]	866	AC-HEC	APR + OND + DEX vs. PBO + OND + DEX	NA	NA	61 vs. 56 *No nausea* (%) 33 vs. 33
Rapoport [18]	848	AC-HEC/MEC	APR + OND + DEX vs. PBO + OND + DEX	NA	NA	73.6 vs. 66.4*
Hesketh [15]	530	HEC	APR + OND + DEX vs. PBO + OND + DEX	90.6 vs. 86.5	75.3 vs. 68.5	73.2 vs. 66.0
Poli-Bigelli [16]	569	HEC	APR + OND + DEX vs. PBO + OND + DEX	NA	73 vs. 65 *No nausea* (%) 52.7 vs. 39.9**	71 vs. 64 *No nausea* (%) 48.8 vs. 38.8*
Schmoll [45]	489	HEC	APR + OND + DEX vs. PBO + OND + DEX	92.1 vs. 89.5	75.9 vs. 72.1	73.1 vs. 69.7
Fosaprepitant						
Grunberg [46]	2322	HEC	FOS + OND + DEX vs. APR + OND + DEX	NA	NA	70.1 vs. 70.4 *No nausea* (%) 53.0 vs. 50.9
Weinstein [47]	1015	MEC	FOS + OND + DEX (D1) vs. PBO + OND + DEX (D1) followed by OND (D2–3)			83.1 vs. 78.3* *No nausea* (%) 65.3 vs. 61.6
Aprepitant/fosaprepitant in delayed nausea						
Roila [48]	580	AC-HEC	Both arms APR + PAL + DEX (D1) followed by APR once-daily (D2–3) + PBO once daily (evenings) vs. DEX twice daily (D2–3)	36.3 vs. 32.6 *No nausea* (%) 53.6 vs. 52.0	56.8 vs. 63.7 *No nausea* (%) 43.9 vs. 49.1	NA
Roila [49]	284	HEC	Both arms APR + PAL + DEX (D1) followed by APR (D2–3) + DEX (D2–4) vs. MTC (D2–4) + DEX (D2–4)	87.8 vs. 89.8 *No nausea* (%) 80.3 vs. 86.9	77.6 vs. 81.0 *No nausea* (%) 71.4 vs. 73	NA
Rolapitant						
Schwartzberg [44]	1369	AC–HEC/MEC	D1: ROL + GRAN + DEX vs. PBO + GRAN + DEX D2–3: GRAN	82 vs. 85 *No nausea* (%) 65 vs. 66	73 vs. 69 *No nausea* (%) 48 vs. 45	71 vs. 67 *No nausea* (%) 45 vs. 42
Rapoport [43]	532 (Study 1)	HEC	D1: ROL + GRAN + DEX vs. PBO + GRAN + DEX D2–4: DEX	86 vs. 79* *No nausea* (%) 68 vs. 61	73 vs. 65* *No nausea* (%) 53 vs. 42**	72 vs. 63* *No nausea* (%) 50 vs. 39*
Rapoport [43]	555 (Study 2)	HEC	D1: ROL + GRAN + DEX vs. PBO + GRAN + DEX D2–4: DEX	90 vs. 86 *No nausea* (%) 73 vs. 68	75 vs. 69 *No nausea* (%) 58 vs. 47**	73 vs. 68 *No nausea* (%) 55 vs. 44**
NEPA						
Aapro [50]	1455	AC-HEC	NEPA + DEX (D1) vs. PAL + DEX (D1)	87.3 vs. 87.9	76.9 vs. 71.3*	74.6 vs. 69.1*
Gralla[b] [51]	413	HEC/MEC	NEPA + DEX[c] + PBO vs. APR + PAL + DEX[c]	NA	NA	84.1–92.3 vs. 80.8–86.5 cycles (1–6)
Hesketh[d] [52]	694	HEC	$NEPA_{300}$ ($NETU_{300}$ + PAL) + DEX (D1–4) (N = 143) vs. PAL + DEX (D1–4) + PBO (N = 136)	98.5 vs. 93.4*	90.4 vs. 80.9*	89.6 vs. 79.4*

AC anthracycline plus cyclophosphamide, *APR* aprepitant, *CIN* chemotherapy-induced nausea, *D* day, *DEX* dexamethasone, *FOS* fosaprepitant, *GRAN* granisetron, *HEC* highly emetogenic chemotherapy, *MEC* moderately emetogenic chemotherapy, *MTC* metoclopramide, *NA* not available, *NEPA* netupitant (300 mg) plus palonosetron (0.5 mg), *NETU* netupitant, NK_1 neurokinin-1, *OND* ondansetron, *PAL* palonosetron, *PBO* placebo, *RA* receptor antagonist, *ROL* rolapitant

[a] Nausea was not the primary endpoint of these phase III trials

[b] No formal testing was performed for between-group comparisons

[c] Dexamethasone was administered on days 1–4 in patients receiving HEC and on day 1 in patients receiving MEC

[d] Phase II pivotal study. $NEPA_{100}$/$NEPA_{200}$/$NEPA_{300}$ + DEX doses were analyzed. Only data from $NEPA_{300}$ + DEX vs. PAL + DEX are presented

*$p \leq 0.05$;**$p \leq 0.01$

Aprepitant/fosaprepitant

The addition of aprepitant/fosaprepitant to 5-HT$_3$RA and dexamethasone Aprepitant was the first NK$_1$RA approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA), in 2003. Next, fosaprepitant, an intravenous water-soluble phosphoryl prodrug of aprepitant, was approved in 2008. Fosaprepitant is rapidly converted to the active form (aprepitant) and has demonstrated bioequivalence and non-inferiority to aprepitant [46, 53].

Three phase III trials have compared the aprepitant–ondansetron–dexamethasone combination with ondansetron–dexamethasone alone in cisplatin-based HEC-treated patients [15, 16, 45]. No significant differences were observed in frequency of NSN in the overall period or in the acute and delayed periods (where reported) in these studies.

The contribution of aprepitant to the standard ondansetron–dexamethasone regimen was also analyzed in breast cancer patients treated with AC–HEC [17]. In this study, no significant differences were observed between the aprepitant and standard-treatment arms in percentage of patients reporting overall "no nausea" and NSN. Finally, a study by Rapoport et al. explored use of the aprepitant regimen in patients receiving AC and various MEC regimens. The percentage of patients reporting NSN during the overall period was significantly higher in the aprepitant than in the control group ($p < 0.05$) [18]. No separate analyses were performed for acute and delayed nausea in these studies [17, 18].

Recently, fosaprepitant was evaluated in a phase III trial that compared a single-day, fosaprepitant-containing antiemetic triplet regimen to a standard 3-day 5-HT$_3$RA–dexamethasone regimen in patients treated with MEC [47]. Randomized patients received single-dose (1) fosaprepitant in combination with ondansetron–dexamethasone or (2) ondansetron–dexamethasone on day 1. On days 2 and 3, ondansetron was administered only to patients in the control group. Overall, the proportion of patients with NSN was greater in the fosaprepitant group ($p = 0.026$), but no significant differences were observed in the rates of no nausea ($p = 0.156$).

Finally, aprepitant/fosaprepitant have been evaluated in a phase III study in oxaliplatin-treated patients with colorectal cancer. Women treated with aprepitant/fosaprepitant achieved significantly higher rates of no nausea and complete protection, compared to women in the control group, suggesting a specific benefit of aprepitant treatment in the female gender [54].

In conclusion, no consistent superiority in the control of nausea after HEC or MEC was observed with the addition of aprepitant over the ondansetron–dexamethasone combination. This finding prodded antiemetic research to focus on nausea control.

Aprepitant/fosaprepitant compared with other agents The efficacy between aprepitant and prochlorperazine treatment was compared in patients receiving anthracyclines and/or platinum agents. Treatment with aprepitant was as effective as prochlorperazine, both in combination with palonosetron–dexamethasone, in delayed nausea control ($p = 0.557$) [55].

Olanzapine, an atypical antipsychotic, is a potent dopaminergic and serotonergic RA, and it also binds to adrenergic, histaminergic, and muscarinic receptors [56]. A phase III randomized trial compared aprepitant to olanzapine (10 mg orally, on day 1 pre-chemotherapy, and days 2–4 post-chemotherapy) both combined with palonosetron–dexamethasone, in patients receiving cisplatin or AC [57]. The percentage of patients without nausea (no nausea = 0, scale 0–10, MD Anderson Symptom Inventory) was greater in the olanzapine group than in the aprepitant group during the delayed and overall periods. Recently, a randomized, double-blind phase III study compared the efficacy of olanzapine (same dosing regimen) and fosaprepitant, both in combination with palonosetron–dexamethasone, in patients receiving concurrent local radiation and cisplatin-based HEC. Nausea control was one of the main outcome measures. No nausea (0, scale 0–10, VAS) rates were significantly higher in patients receiving olanzapine compared to fosaprepitant during the delayed and overall periods ($p < 0.01$) [58]. The superiority of olanzapine may provide new insight into the pathophysiology of CIN. It is possible that receptors other than 5-HT$_3$ and NK$_1$ may be important for nausea control [32, 59]. The action of olanzapine on dopaminergic, histaminic, and muscarinic receptors provides a potential explanation for its activity in the control of nausea, especially delayed nausea. Olanzapine is also an effective antiemetic for treatment of chronic chemotherapy-unrelated nausea in palliative care [60]. The efficacy of olanzapine on CIN was recently recognized by the Multinational Association of Supportive Care in Cancer and European Society for Medical Oncology (MASCC/ESMO) and the National Comprehensive Cancer Network (NCCN) guidelines [1, 21].

A summary of the above mentioned studies is presented in Table 2 [55, 57, 58].

Aprepitant in delayed nausea prevention Aprepitant was compared to dexamethasone for prevention of delayed emesis in 580 breast cancer patients receiving AC [48]. All patients were treated with an aprepitant–palonosetron–dexamethasone regimen before chemotherapy, and then randomized to receive oral dexamethasone or aprepitant on days 2–3. During the delayed phase, no significant differences were observed in rates of no nausea ($p = 0.24$) and NSN ($p = 0.10$) between aprepitant and dexamethasone treatment, respectively (Table 1) [15–18, 43–52]. Maximum nausea severity and nausea duration were also comparable between the two groups [48]. Non-inferiority of dexamethasone was recently

Table 2 Summary of studies for the prevention of CIN with antiemetic regimens based on aprepitant/fosaprepitant compared to other agents

Reference	Patients randomized	Chemotherapy regimen	Antiemetic prophylaxis	Proportion of patients with no nausea (%)		
				Acute	Delayed	Overall
Navari [57]	251	HEC (AC/non-AC)	APR + PAL + DEX vs. OLZ + PAL + DEX	87 vs. 87	38 vs. 69*	38 vs. 69*
Navari [58]	109	HEC (+ radiotherapy)	FOS + PAL + DEX vs. OLZ + PAL + DEX	77 vs. 86	41 vs. 71	41 vs. 71
Roscoe [55]	513	HEC/MEC	Both arms PAL + DEX (D1) followed by DEX (D2–3), and: APR once daily (D2–3) + PBO twice daily vs. PROC three times daily (D2–3)	NA	No significant difference	NA

AC anthracycline plus cyclophosphamide, *APR* aprepitant, *CIN* chemotherapy-induced nausea, *DEX* dexamethasone, *FOS* fosaprepitant, *HEC* highly emetogenic chemotherapy, *MEC* moderately emetogenic chemotherapy, *NA* not available, *OLZ* olanzapine, *PAL* palonosetron, *PROC* prochlorperazine

*$p < 0.01$

recognized by MASCC/ESMO guidelines following AC–HEC [21].

In another study, 284 evaluable patients receiving cisplatin-based HEC were treated with aprepitant–palonosetron–dexamethasone before cisplatin-based chemotherapy [49]. Patients were then randomly assigned to treatment with aprepitant on days 2–3 or metoclopramide on days 2–4 (plus dexamethasone on days 2–4 in both groups). The proportion of patients with no nausea ($p = 0.80$) and NSN ($p = 0.56$) in the delayed phase was similar in both arms, and no significant differences regarding maximum severity of nausea or nausea duration were observed. Non-inferiority of metoclopramide–dexamethasone was recently recognized by MASCC/ESMO guidelines following non-AC–HEC [21].

Rolapitant

The novel NK_1RA rolapitant received FDA approval in 2015 for delayed CINV prevention [24]. Rolapitant has a long half-life (approximately 180 h) and, consistent with its pharmacokinetic profile, has been shown to provide CINV protection for the overall risk period after chemotherapy [43, 44]. The benefit of adding rolapitant to a 5-HT_3RA–dexamethasone regimen was evaluated in patients receiving MEC and HEC. In a phase III trial, 1369 patients received (1) rolapitant in combination with granisetron–dexamethasone or (2) placebo in combination with granisetron–dexamethasone, before AC–HEC or MEC [44]. Granisetron was continued on days 2–3 in both arms, not in line with current guidelines' recommendations. The two groups presented a similar percentage of patients with NSN during the acute ($p = 0.1927$), delayed ($p = 0.1944$), and overall ($p = 0.1182$) phases. Likewise, there were no significant differences in the no nausea rates between the two groups in all treatment phases: acute ($p = 0.6932$), delayed ($p = 0.2013$), or overall ($p = 0.2193$). In conclusion, in patients receiving AC–HEC or MEC, the addition of rolapitant did not offer improvement in nausea control over granisetron–dexamethasone.

A similar rolapitant-based regimen was assessed in two phase III trials (HEC-1 and HEC-2) in a total of 1087 patients receiving cisplatin-based HEC [43]. Patients in both studies received (1) rolapitant plus granisetron–dexamethasone or (2) placebo in combination with granisetron–dexamethasone before HEC and daily dexamethasone on days 2–4 in both groups. In the analysis of the individual studies, only study HEC-1 showed significantly higher NSN rates in all phases for the rolapitant group. Additionally, rates of no nausea in the acute phase were not significantly different between rolapitant and the control group in either study [43] (Table 1) [15–18, 43–52]. In the pooled analysis of both studies, rolapitant treatment resulted in significantly superior rates of NSN compared to control during the acute (88 vs. 83%; $p = 0.0090$), delayed (74 vs. 67%; $p = 0.0108$), and overall (72 vs. 65%; $p = 0.0174$) periods. Also, in the pooled study analysis, a significantly greater proportion of patients in the rolapitant group had no nausea in the acute (70 vs. 64%; $p = 0.0304$), delayed (56 vs. 44%, $p = 0.0002$), and overall (52 vs. 42%, $p = 0.0004$) phases. Due to discrepancies between the studies, no clear conclusions can be drawn regarding the clinical significance of rolapitant on nausea induced by HEC.

NEPA: the first oral combination antiemetic

NEPA is a single, oral, fixed-combination capsule composed of the novel NK_1RA netupitant (300 mg) plus the second-generation 5-HT_3RA palonosetron (0.5 mg). Netupitant has a half-life of 90 h and high binding affinity for the NK_1 receptor. Palonosetron presents 5-HT_3 receptor allosteric binding with positive cooperativity, can trigger 5-HT_3 receptor internalization, and can inhibit 5-HT_3/NK_1 receptor cross-talk [61]. Therefore, NEPA is the combination of two highly effective antiemetic agents that antagonizes two key

neurotransmitters involved in the pathophysiology of CINV (substance P and serotonin). The efficacy and safety of NEPA were demonstrated in three pivotal trials [50–52].

In the randomized phase II pivotal study of 694 patients receiving cisplatin-based HEC, three different doses of NEPA (netupitant 100, 200, or 300 mg, each with palonosetron 0.50 mg) were compared with palonosetron alone; all patients also received dexamethasone [52]. Significantly lower rates of NSN were reported in the NEPA (300 mg) group compared with the group that received oral palonosetron for the acute ($p \leq 0.05$), delayed ($p \leq 0.01$), and overall ($p \leq 0.05$) phases [52, 62] (Fig. 1a) [62]. The efficacy of NEPA plus dexamethasone on day 1 was compared with oral palonosetron and dexamethasone in a phase III trial with 1455 patients receiving AC [50]. Treatment with NEPA was associated with a significant reduction in the rate of NSN in the delayed and overall phases ($p = 0.014$ and $p = 0.020$) compared with oral palonosetron [50] (Fig. 1b) [62]. Superiority of NEPA–dexamethasone in nausea control was maintained over 4 cycles of AC chemotherapy, with overall NSN rates ranging from 75 to 80% (Fig. 1c) [62]. Therefore, in patients receiving cisplatin- or AC-based HEC, the NEPA–dexamethasone regimen offers significant improvement in nausea control over palonosetron–dexamethasone.

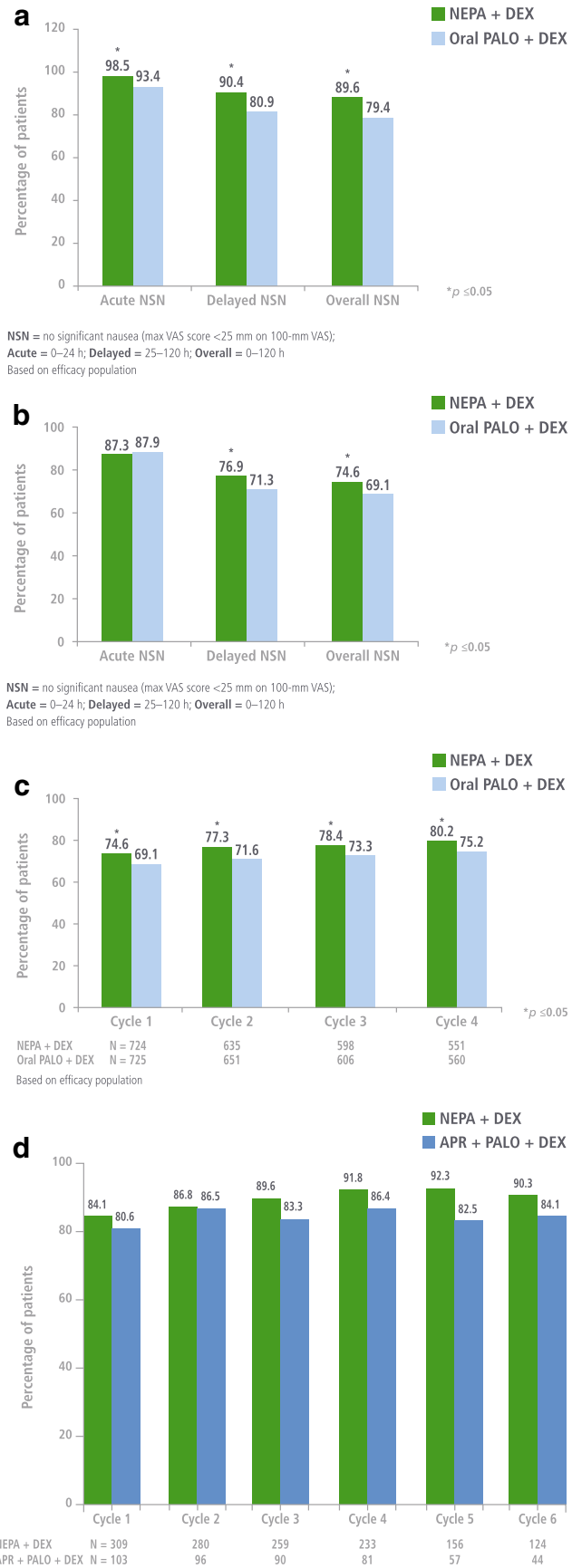
A phase III trial was conducted in 413 patients to evaluate the safety of NEPA, and also to determine NEPA efficacy over multiple cycles of HEC (non-AC) or MEC treatment [51]. Patients were randomized (3:1) to either NEPA–dexamethasone or aprepitant–palonosetron–dexamethasone. The aprepitant regimen was included to help interpret any unexpected safety finding that might have emerged in the NEPA group. Efficacy of NEPA–dexamethasone on nausea control was maintained over 6 cycles, with overall NSN rates between 84 and 92% (Fig. 1d) [62].

Finally, in population subanalyses on gynecologic ($n = 130$) or lung ($n = 231$) cancer patients, NEPA treatment achieved high NSN rates after cisplatin- or carboplatin-based chemotherapy [63, 64]. In breast cancer patients ($n = 1460$), NEPA–dexamethasone was significantly superior to palonosetron–dexamethasone in overall NSN and across four chemotherapy cycles [65]. Of note, gynecologic and female breast cancer patients represent high-risk populations for CINV, since female gender is a well-known risk factor.

Additional factors to consider when selecting NK_1RA for CIN control

The safety of NK_1RAs

Generally, NK_1RAs present favorable tolerability with a safety profile similar to non–NK_1RA-based regimens and mostly with mild and infrequent adverse events (AEs). A meta-analysis reported hiccups and fatigue/asthenia as the most



◀ **Fig. 1** **a** No significant nausea after cycle 1 in patients receiving HEC; **b** no significant nausea after cycle 1 in patients receiving AC; **c** no significant nausea rates (overall 0–120 h) over cycles 1–4 in patients receiving AC; **d** no significant nausea rates (overall 0–120 h) over cycles 1–6 in patients receiving HEC or non-AC MEC. *5-HT$_3$* 5-hydroxytryptamine-3, *AC* anthracycline and cyclophosphamide, *APR* aprepitant, *DEX* dexamethasone, *HEC* highly emetogenic chemotherapy, *MEC* moderately emetogenic chemotherapy, *NEPA* netupitant (300 mg) plus palonosetron (0.5 mg), *NK$_1$* neurokinin-1, *PALO* palonosetron, *RA* receptor antagonist, *VAS* visual analog scale [Bošnjak S, Schwartzberg LS, Rizzi G, Borroni ME (2014) Evaluation of nausea control with NEPA, a novel oral combination antiemetic. J Clin Oncol 32(Suppl): abstract 169]

common AEs associated with aprepitant/fosaprepitant, as well as increased incidence of severe infections [19]. Fosaprepitant administration has also been associated with infusion-site reactions [66]. For rolapitant, the most frequent AEs include fatigue, constipation, headache, hiccups, and dyspepsia, with neutropenia the most common grade 3–4 AE [43, 44]. NEPA has shown a similar safety profile to palonosetron, with headache and constipation as the most frequent AEs, and no evidence for cardiac safety concerns [51, 67]. The most frequent toxicities associated with metoclopramide comprise sedation, diarrhea, and extrapyramidal reactions [68]. Recently, the EMA has recommended a restriction on the dose and duration of metoclopramide use, to minimize the risk of potentially serious neurologic AEs [69].

Potential interactions between NK$_1$RAs and other chemotherapy agents should also be considered. Both aprepitant and netupitant can inhibit cytochrome P-450 isoenzyme 3A4 (CYP3A4), and a reduced dose of dexamethasone (CYP3A4 substrate) should be administered with aprepitant and NEPA. Additionally, aprepitant is a CYP3A4 inducer and has the potential to increase ifosfamide-mediated neurotoxicity [70]. No increased toxicities have been reported to date related to NEPA interaction with chemotherapeutic agents [71, 72]. Rolapitant does not affect CYP3A4, and dexamethasone dose adjustments are not required when they are coadministered [24]. However, rolapitant is a CYP2D6 inhibitor and should not be used concomitantly with CYP2D6 substrates with a narrow therapeutic index [24]. Of note, CYP2D6 participates in the metabolism of all 5-HT$_3$RAs except granisetron [73, 74], which may limit the choice of partner 5-HT$_3$RA.

Schedule and convenience of administration of different NK$_1$RAs and implications for patient compliance

The use of oral antiemetics with increased half-life, such as NEPA and rolapitant, which can be administered orally once per chemotherapy cycle, may be especially beneficial, whereas aprepitant follows a 3-day schedule [15, 43, 44, 50–52]. Additionally, NEPA as a combination agent includes the NK$_1$RA and 5-HT$_3$RA in a single capsule, while both aprepitant- and rolapitant-based regimens require additional administration of the 5-HT$_3$RA separately. Adopting strategies that simplify antiemetic treatment may potentially ensure both antiemetic and chemotherapy compliance by patients.

The choice of 5-HT$_3$RA

The potential role of palonosetron, and its contribution to CIN prevention, when combined with an NK$_1$RA requires further consideration. A pooled analysis showed that in patients receiving intravenous palonosetron prophylaxis before HEC or MEC, no nausea rates were numerically higher compared with first-generation 5-HT$_3$RAs in the delayed and overall phases, and that patients experienced significantly less-severe nausea (delayed, $p = 0.0002$; overall, $p = 0.011$) [12]. These effects may be explained by the pharmacologically and clinically distinct properties of palonosetron as compared to first-generation 5-HT$_3$RAs [75]. During its clinical development, NEPA was superior to palonosetron in the control of overall and delayed nausea (measured by NSN) [50, 52].

International guidelines recommendations

Recommendations for CINV prophylaxis have been defined in the MASCC/ESMO [21], American Society of Clinical Oncology (ASCO) [10], and NCCN [1] guidelines. These recommendations are based on evidence from clinical studies in which the primary efficacy endpoint was most commonly CR and not a nausea-related outcome. CINV prophylaxis with the NK$_1$RA–5-HT$_3$RA–dexamethasone triplet combination is recommended for patients receiving AC and non-AC HEC by all three guidelines and for patients receiving carboplatin-based chemotherapy by MASCC/ESMO guidelines [21]. In MEC-treated patients, the NK$_1$RA–5-HT$_3$RA–dexamethasone combination is also recommended for selected patients in accordance with clinician's decision by ASCO guidelines [10], and by NCCN guidelines in patients with further high-risk factors, or if previous 5-HT$_3$RA–dexamethasone treatment has failed [1].

Regarding the choice of NK$_1$RA, all four NK$_1$RAs were gradually incorporated into international guidelines in a timely manner following their approval in the respective geographic regions. Currently, aprepitant/fosaprepitant and NEPA are recommended by all three guidelines [1, 10, 21], and rolapitant is included in recommendations by MASCC/ESMO and NCCN [1, 21].

Future directions

Nausea control has become the top priority of current antiemetic research, to reach the final goal of "no nausea/no vomiting" after anticancer treatment. Progress in understanding the pathophysiology of nausea, and the design of clinical trials with nausea as primary efficacy endpoint should help

determine the most effective antiemetic combination for nausea prevention.

The accurate measurement of nausea, both in clinical trials and in daily practice, remains a priority. While VAS and categorical scales (as documented in the MASCC antiemesis tool (MAT) [25]) may provide reproducible and useful measurements, results are often documented inconsistently, and NSN or no nausea are not reported at times. We would advise that the VAS actual scores be reported and analyzed, rather than be categorized. These additional measures should improve the consistency of the data and could assist in statistical review. Reporting exact VAS scores for nausea and for individual items on the nausea domain of the FLIE questionnaire in all patients (including those for whom treatment has failed) would also aid in understanding the effect of antiemetics on patients' QoL as suggested by Andrews [76]. Furthermore, strategies to improve patient-healthcare professional communication and use of tools that incorporate patient-reported outcomes to evaluate toxicity in cancer clinical trials may help prevent underreporting of nausea [41].

The benefit of adding olanzapine to a triplet aprepitant/fosaprepitant–5-HT_3RA–dexamethasone regimen for the control of nausea has been evaluated in a phase III study in 380 patients receiving cisplatin- or AC-based HEC [77]. Nausea prophylaxis was the primary endpoint. The proportion of patients with no nausea (0, scale 0–10, VAS) was significantly greater in the olanzapine group during the acute (74 vs. 45%; $p = 0.002$), delayed (42 vs. 25%; $p = 0.002$), and overall (37 vs. 22%; $p = 0.002$) periods. Olanzapine (10 mg daily for 4 days) was associated with transient but significantly increased sedation [77]. No grade 3–4 olanzapine-related AEs have been reported in CINV clinical trials [32, 59, 77]. The addition of olanzapine to aprepitant-/fosaprepitant-containing antiemetic regimens can improve CINV control without substantial added costs [78]. In addition, the effectiveness of olanzapine was comparable to aprepitant for the prevention of CINV [57] and provides a more cost-effective alternative to aprepitant-based regimens.

Further efforts should be made to better define the overall potential for CIN in a given patient, including anticancer drug-, patient-, and disease-related factors [79, 80]. Moreover, the efficacy of guideline-recommended antiemetics in real-life situations (outside of controlled conditions of clinical trials, in patients receiving medications or interventions known to induce nausea, for example, opioids) should be analyzed. Currently, a need to improve guideline adherence by clinicians and compliance with antiemetic regimens by patients exists. Simplification of antiemetic regimens with agents that are administered orally once per chemotherapy cycle, such as rolapitant (as single-agent NK_1RA) or NEPA (as a fixed combination of an NK_1RA and a 5-HT_3RA) may contribute to this improvement. While the addition of olanzapine to the triple combination has proven to improve CINV prophylaxis [77], compliance with this complex four-drug antiemetic regimen and its feasibility outside of clinical trials needs to be evaluated.

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Compliance with ethical standards

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References

1. National Comprehensive Cancer Network (2016) NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Antiemesis. Version 2.2016. https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf. Accessed 12 August 2016
2. Ballatori E, Roila F, Ruggeri B, Betti M, Sarti S, Soru G, Cruciani G, Di Maio M, Andrea B, Deuson RR (2007) The impact of chemotherapy-induced nausea and vomiting on health-related quality of life. Support Care Cancer 15:179–185
3. Bloechl-Daum B, Deuson RR, Mavros P, Hansen M, Herrstedt J (2006) Delayed nausea and vomiting continue to reduce patients' quality of life after highly and moderately emetogenic chemotherapy despite antiemetic treatment. J Clin Oncol 24:4472–4478
4. Cohen L, de Moor CA, Eisenberg P, Ming EE, Hu H (2007) Chemotherapy-induced nausea and vomiting: incidence and impact on patient quality of life at community oncology settings. Support Care Cancer 15:497–503
5. Glaus A, Knipping C, Morant R, Böhme C, Lebert B, Beldermann F, Glawogger B, Ortega PF, Hüsler A, Deuson R (2004) Chemotherapy-induced nausea and vomiting in routine practice: a European perspective. Support Care Cancer 12:708–715
6. Jordan K, Jahn F, Aapro M (2015) Recent developments in the prevention of chemotherapy-induced nausea and vomiting (CINV): a comprehensive review. Ann Oncol 26:1081–1090
7. Navari RM, Aapro M (2016) Antiemetic prophylaxis for chemotherapy-induced nausea and vomiting. N Engl J Med 374:1356–1367
8. Dibble SL, Isreal J, Nussey B, Casey K, Luce J (2003) Delayed chemotherapy-induced nausea in women treated for breast cancer. Oncol Nurs Forum 30:E40–E47
9. Roila F, Herrstedt J, Aapro M, Gralla RJ, Einhorn LH, Ballatori E, Bria E, Clark-Snow RA, Espersen BT, Feyer P, Grunberg SM, Hesketh PJ, Jordan K, Kris MG, Maranzano E, Molassiotis A, Morrow G, Olver I, Rapoport BL, Rittenberg C, Saito M, Tonato

M, Warr D, ESMO/MASCC Guidelines Working Group (2010) Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Ann Oncol 21(Suppl 5): v232–v243

10. Hesketh PJ, Bohlke K, Lyman GH, Basch E, Chesney M, Clark-Snow RA, Danso MA, Jordan K, Somerfield MR, Kris MG, American Society of Clinical Oncology (2016) Antiemetics: American Society of Clinical Oncology focused guideline update. J Clin Oncol 34:381–386
11. Jordan K, Gralla R, Jahn F, Molassiotis A (2014) International antiemetic guidelines on chemotherapy induced nausea and vomiting (CINV): content and implementation in daily routine practice. Eur J Pharmacol 722:197–202
12. Schwartzberg L, Barbour SY, Morrow GR, Ballinari G, Thorn MD, Cox D (2014) Pooled analysis of phase III clinical studies of palonosetron versus ondansetron, dolasetron, and granisetron in the prevention of chemotherapy-induced nausea and vomiting (CINV). Support Care Cancer 22:469–477
13. Aapro MS, Molassiotis A, Olver I (2005) Anticipatory nausea and vomiting. Support Care Cancer 13:117–121
14. Hesketh PJ (2008) Chemotherapy-induced nausea and vomiting. N Engl J Med 358:2482–2494
15. Hesketh PJ, Grunberg SM, Gralla RJ, Warr DG, Roila F, de Wit R, Chawla SP, Carides AD, Ianus J, Elmer ME, Evans JK, Beck K, Reines S, Horgan KJ, Aprepitant Protocol 052 Study Group (2003) The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin—the Aprepitant Protocol 052 Study Group. J Clin Oncol 21:4112–4119
16. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, Julie Ma G, Eldridge K, Hipple A, Evans JK, Horgan KJ, Lawson F, Aprepitant Protocol 054 Study Group (2003) Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. Cancer 97:3090–3098
17. Warr DG, Hesketh PJ, Gralla RJ, Muss HB, Herrstedt J, Eisenberg PD, Raftopoulos H, Grunberg SM, Gabriel M, Rodgers A, Bohidar N, Klinger G, Hustad CM, Horgan KJ, Skobieranda F (2005) Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. J Clin Oncol 23: 2822–2830
18. Rapoport BL, Jordan K, Boice JA, Taylor A, Brown C, Hardwick JS, Carides A, Webb T, Schmoll HJ (2010) Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study. Support Care Cancer 18:423–431
19. dos Santos LV, Souza FH, Brunetto AT, Sasse AD, da Silveira Noqueira Lima JP (2012) Neurokinin-1 receptor antagonists for chemotherapy-induced nausea and vomiting: a systematic review. J Natl Cancer Inst 104:1280–1292
20. Miura S, Watanabe S, Sato K, Makino M, Kobayashi O, Miyao H, Iwashima A, Okajima M, Tanaka J, Tanaka H, Kagamu H, Yokoyama A, Narita I, Yoshizawa H (2013) The efficacy of triplet antiemetic therapy with 0.75 mg of palonosetron for chemotherapy-induced nausea and vomiting in lung cancer patients receiving highly emetogenic chemotherapy. Support Care Cancer 21:2575–2581
21. Roila F, Molassiotis A, Herrstedt J, Aapro M, Gralla RJ, Bruera E, Clark-Snow RA, Dupuis LL, Einhorn LH, Feyer P, Hesketh PJ, Jordan K, Olver I, Rapoport BL, Roscoe J, Ruhlmann CH, Walsh D, Warr D, van der Wetering M, on behalf of the participants of the MASCC/ESMO Consensus Conference Copenhagen 2015 (2016) 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol 27(suppl 5):v119–v133
22. US Food and Drug Administration (2014) FDA approves Akynzeo for nausea and vomiting associated with cancer chemotherapy. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm418375.htm. Accessed 12 August 2016
23. European Medicines Agency (2015) Akynzeo http://www.ema.europa.eu/ema/index.jsp?curl = pages/medicines/human/medicines/003728/smops/Positive/human_smop_000801.jsp&mid = WC0b01ac058001d127. Accessed 12 August 2016
24. Varubi (rolapitant) [prescribing information] (2015) Waltham, MA: TESARO, Inc. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206500s000lbl.pdf. Accessed 12 August 2016
25. Molassiotis A, Coventry PA, Stricker CT, Clements C, Eaby B, Velders L, Rittenberg C, Gralla RJ (2007) Validation and psychometric assessment of a short clinical scale to measure chemotherapy-induced nausea and vomiting: the MASCC antiemesis tool. J Pain Symptom Manage 34:148–159
26. Muth ER, Stern RM, Thayer JF, Koch KL (1996) Assessment of the multiple dimensions of nausea: the nausea profile (NP). J Psychosom Res 40:511–520
27. Napadow V, Sheehan JD, Kim J, Lacount LT, Park K, Kaptchuk TJ, Rosen BR, Kuo B (2013) The brain circuitry underlying the temporal evolution of nausea in humans. Cereb Cortex 23:806–813
28. Hornby PJ (2001) Central neurocircuitry associated with emesis. Am J Med 111(Suppl 8A):106S–112S
29. Carpenter DO (1990) Neural mechanisms of emesis. Can J Physiol Pharmacol 68:230–236
30. Xu LH, Koch KL, Summy-Long J, Stern RM, Seaton JF, Harrison TS, Demers LM, Bingaman S (1993) Hypothalamic and gastric myoelectrical responses during vection-induced nausea in healthy Chinese subjects. Am J Physiol 265:E578–E584
31. Sanger GJ, Andrews PL (2006) Treatment of nausea and vomiting: gaps in our knowledge. Auton Neurosci 129:3–16
32. Navari RM (2013) Management of chemotherapy-induced nausea and vomiting: focus on newer agents and new uses for older agents. Drugs 73:249–262
33. Morrow GR (1992) Methodology and assessment in clinical antiemetic research: a meta-analysis of outcome parameters. Br J Cancer 66:S38–S41
34. O'Brien BJ, Rusthoven J, Rocchi A, Latreille J, Fine S, Vandenberg T, Laberge F (1993) Impact of chemotherapy-associated nausea and vomiting on patients' functional status and on costs: survey of five Canadian centres. CMAJ 149:296–302
35. Griffin AM, Butow PN, Coates AS, Childs AM, Ellis PM, Dunn SM, Tattersall MH (1996) On the receiving end. V: patient perceptions of the side effects of cancer chemotherapy in 1993. Ann Oncol 7:189–195
36. Perez EA, Hesketh P, Sandbach J, Reeves J, Chawla S, Markman M, Hainsworth J, Bushnell W, Friedman C (1998) Comparison of single-dose oral granisetron versus intravenous ondansetron in the prevention of nausea and vomiting induced by moderately emetogenic chemotherapy: a multicenter, double-blind, randomized parallel study. J Clin Oncol 16:754–760
37. Grunberg SM, Deuson RR, Mavros P, Geling O, Hansen M, Cruciani G, Daniele B, De Pouvourville G, Rubenstein EB, Daugaard G (2004) Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. Cancer 100:2261–2268
38. Hickok JT, Roscoe JA, Morrow GR, Bole CW, Zhao H, Hoelzer KL, Dakhil SR, Moore T, Fitch TR (2005) 5-Hydroxytryptamine-receptor antagonists versus prochlorperazine for control of delayed nausea caused by doxorubicin: a URCC CCOP randomised controlled trial. Lancet Oncol 6:765–772

39. Salsman JM, Grunberg SM, Beaumont JL, Rogers M, Paul D, Clayman ML, Cella D (2012) Communicating about chemotherapy-induced nausea and vomiting: a comparison of patient and provider perspectives. J Natl Compr Canc Netw 10:149–157
40. Majem M, Moreno MA, Calvo N, Feliu A, Perez J, Mangues MA, Barnadas A (2011) Perception of healthcare providers versus patient reported incidence of chemotherapy-induced nausea and vomiting after the addition of NK-1 receptor antagonists. Support Care Cancer 19:1983–1990
41. Di Maio M, Gallo C, Leighl NB, Piccirillo MC, Daniele G, Nuzzo F, Gridelli C, Gebbia V, Ciardiello F, De Placido S, Ceribelli A, Favaretto AG, de Matteis A, Feld R, Butts C, Bryce J, Signoriello S, Morabito A, Rocco G, Perrone F (2015) Symptomatic toxicities experienced during anticancer treatment: agreement between patient and physician reporting in three randomized trials. J Clin Oncol 33:910–915
42. Rojas C, Slusher BS (2015) Mechanisms and latest clinical studies of new NK1 receptor antagonists for chemotherapy-induced nausea and vomiting: Rolapitant and NEPA (netupitant/palonosetron). Cancer Treat Rev 41:904–913
43. Rapoport BL, Chasen MR, Gridelli C, Urban L, Modiano MR, Schnadig ID, Poma A, Arora S, Kansra V, Schwartzberg LS, Navari RM (2015) Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of cisplatin-based highly emetogenic chemotherapy in patients with cancer: two randomised, active-controlled, double-blind, phase 3 trials. Lancet Oncol 16:1079–1089
44. Schwartzberg LS, Modiano MR, Rapoport BL, Chasen MR, Gridelli C, Urban L, Poma A, Arora S, Navari RM, Schnadig ID (2015) Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of moderately emetogenic chemotherapy or anthracycline and cyclophosphamide regimens in patients with cancer: a randomised, active-controlled, double-blind, phase 3 trial. Lancet Oncol 16: 1071–1078
45. Schmoll HJ, Aapro MS, Poli-Bigelli S, Kim HK, Park K, Jordan K, von Pawel J, Giezek H, Ahmed T, Chan CY (2006) Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for antiemetic efficacy in high-dose cisplatin treatment. Ann Oncol 17:1000–1006
46. Grunberg S, Chua D, Maru A, Dinis J, DeVandry S, Boice JA, Hardwick JS, Beckford E, Taylor A, Carides A, Roila F, Herrstedt J (2011) Single-dose fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with cisplatin therapy: randomized, double-blind study protocol–EASE. J Clin Oncol 29:1495–1501
47. Weinstein C, Jordan K, Green SA, Camacho E, Khanani S, Beckford-Brathwaite E, Vallejos W, Liang LW, Noga SJ, Rapoport BL (2016) Single-dose fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy: results of a randomized, double-blind phase III trial. Ann Oncol 27:172–178
48. Roila F, Ruggeri B, Ballatori E, Del Favero A, Tonato M (2014) Aprepitant versus dexamethasone for preventing chemotherapy-induced delayed emesis in patients with breast cancer: a randomized double-blind study. J Clin Oncol 32:101–106
49. Roila F, Ruggeri B, Ballatori E, Fatigoni S, Caserta C, Licitra L, Mirabile A, Ionta MT, Massidda B, Cavanna L, Palladino MA, Tocci A, Fava S, Colantonio I, Angelelli L, Ciuffreda L, Fasola G, Zerilli F, Italian Group for Antiemetic Research (2015) Aprepitant versus metoclopramide, both combined with dexamethasone, for the prevention of cisplatin-induced delayed emesis: a randomized, double-blind study. Ann Oncol 26:1248–1253
50. Aapro M, Rugo H, Rossi G, Rizzi G, Borroni ME, Bondarenko I, Sarosiek T, Oprean C, Cardona-Huerta S, Lorusso V, Karthaus M, Schwartzberg L, Grunberg S (2014) A randomized phase III study evaluating the efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy. Ann Oncol 25:1328–1333
51. Gralla RJ, Bosnjak SM, Hontsa A, Balser C, Rizzi G, Rossi G, Borroni ME, Jordan K (2014) A phase III study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting over repeated cycles of chemotherapy. Ann Oncol 25:1333–1339
52. Hesketh PJ, Rossi G, Rizzi G, Palmas M, Alyasova A, Bondarenko I, Lisyanskaya A, Gralla RJ (2014) Efficacy and safety of NEPA, an oral combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy: a randomized dose-ranging pivotal study. Ann Oncol 25:1340–1346
53. Lasseter KC, Gambale J, Jin B, Bergman A, Constanzer M, Dru J, Han TH, Majumdar A, Evans JK, Murphy MG (2007) Tolerability of fosaprepitant and bioequivalency to aprepitant in healthy subjects. J Clin Pharmacol 47:834–840
54. Nishimura J, Satoh T, Fukunaga M, Takemoto H, Nakata K, Ide Y, Fukuzaki T, Kudo T, Miyake Y, Yasui M, Morita S, Sakai D, Uemura M, Hata T, Takemasa I, Mizushima T, Ohno Y, Yamamoto H, Sekimoto M (2015) A phase III trial of aprepitant in colorectal cancer patients receiving oxaliplatin-based chemotherapy (SENRI Trial). Ann Oncol 26(Suppl 4):iv108. Abstract O-001
55. Roscoe JA, Heckler CE, Morrow GR, Mohile SG, Dakhil SR, Wade JL, Kuebler JP (2012) Prevention of delayed nausea: a University of Rochester Cancer Center Community Clinical Oncology Program study of patients receiving chemotherapy. J Clin Oncol 30:3389–3395
56. Brafford MV, Glode A (2014) Olanzapine: an antiemetic option for chemotherapy-induced nausea and vomiting. J Adv Pract Oncol 5: 24–29
57. Navari RM, Gray SE, Kerr AC (2011) Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial. J Support Oncol 9:188–195
58. Navari RM, Nagy CK (2015) Olanzapine versus fosaprepitant for the prevention of nausea and vomiting in patients receiving concurrent chemoradiation treatment. J Clin Oncol 33(Suppl): abstract 9502
59. Navari RM (2014) Olanzapine for the prevention and treatment of chronic nausea and chemotherapy-induced nausea and vomiting. Eur J Pharmacol 722:180–186
60. Davis MP, Hallerberg G, Palliative Medicine Study Group of the Multinational Association of Supportive Care in Cancer (2010) A systematic review of the treatment of nausea and/or vomiting in cancer unrelated to chemotherapy or radiation. J Pain Symptom Manage 39:756–767
61. Rojas C, Raje M, Tsukamoto T, Slusher BS (2014) Molecular mechanisms of 5-HT(3) and NK(1) receptor antagonists in prevention of emesis. Eur J Pharmacol 722:26–37
62. Bošnjak S, Schwartzberg LS, Rizzi G, Borroni ME (2014) Evaluation of nausea control with NEPA, a novel oral combination antiemetic. J Clin Oncol 32(Suppl): abstract 169
63. Bošnjak S, Stamatovic L, Jordan K, Rizzi G (2015) Prevention of chemotherapy-induced nausea and vomiting (CINV) with NEPA, the first oral combination antiemetic, in patients with gynecological cancers receiving platinum-based chemotherapy. European Society of Gynaecological Oncology Congress; 24–27 October 2015; Nice, France. Abstract ESGO-0356
64. Carreras EM (2015) Efficacy of the antiemetic combination agent, NEPA, in patients with lung cancer receiving platinum chemotherapy. 16th World Conference on Lung Cancer. MASCC-IASLC

Joint Session: Palliative and Supportive Care; 6–9 September; Denver, Colorado. Oral presentation 29.03

65. Rugo HS, Aapro M, Rizzi G (2015) Nausea control and quality-of-life benefit with NEPA, the first combination agent, in patients with breast cancer receiving anthracycline/cyclophosphamide (AC) chemotherapy. San Antonio Breast Cancer Symposium; 8–12 December 2015; San Antonio, Texas. Abstract P1-10-06
66. Langford P, Chrisp P (2010) Fosaprepitant and aprepitant: an update of the evidence for their place in the prevention of chemotherapy-induced nausea and vomiting. Core Evid 5:77–90
67. Lorusso V, Karthaus M, Aapro M (2015) Review of oral fixed-dose combination netupitant and palonosetron (NEPA) for the treatment of chemotherapy-induced nausea and vomiting. Future Oncol 11: 565–577
68. Gralla RJ (1983) Metoclopramide. A review of antiemetic trials. Drugs 25(Suppl 1):63–73
69. European Medicines Agency (2013) Metoclopramide-containing medicines. http://www.ema.europa.eu/ema/index.jsp?curl = pages/medicines/human/referrals/Metoclopramide-containing_medicines/human_referral_000349.jsp&mid = WC0b01ac05805c516f. Accessed 12 August 2016
70. Séjourné A, Noal S, Boone M, Bihan C, Sassier M, Andrejak M, Chauffert B (2014) Two cases of fatal encephalopathy related to ifosfamide: an adverse role of aprepitant? Case Rep Oncol 7:669–672
71. Schwartzberg L, Oprean C, Cardona-Huerta S, Rizzi G, Rossi G, Palmas M, Karthaus M, Aapro M (2013) No evidence of increased cyclophosphamide toxicity associated with the antiemetic agent NEPA, a fixed-dose combination of netupitant and palonosetron. 55th American Society of Hematology Annual Meeting and Exposition; 7–10 December 2013; New Orleans, Louisiana. Abstract 2949
72. Aapro M, Jordan K, Palmas M, Clerici G, Rizzi G, Giorgino R (2016) No signals of increased toxicity after concomitant administration of NEPA with etoposide or docetaxel: pooled safety data analysis from 4 pivotal studies. MASCC/ISOO Annual Meeting on Supportive Care in Cancer; 23–25 June 2016; Adelaide, Australia. Abstract MASCC-0565
73. Blower PR (2003) Granisetron: relating pharmacology to clinical efficacy. Support Care Cancer 11:93–100
74. Gridelli C, Aapro M (2004) Factors influencing the choice of 5-HT3-receptor antagonist antiemetics: focus on elderly cancer patients. Support Care Cancer 12:487–496
75. Rojas C, Slusher BS (2012) Pharmacological mechanisms of 5-HT_3 and tachykinin NK_1 receptor antagonism to prevent chemotherapy-induced nausea and vomiting. Eur J Pharmacol 684:1–7
76. Andrews PL (2014) Netupitant and palonosetron (NEPA): a winning team in the race for the optimal treatment of chemotherapy-induced nausea and vomiting? Ann Oncol 25:1258–1259
77. Navari RM, Qin R, Ruddy KJ, Liu H, Powell SF, Bajaj M, Dietrich L, Biggs D, Lafky JM, Loprinzi CL (2016) Olanzapine for the prevention of chemotherapy-induced nausea and vomiting. N Engl J Med 375:134–142
78. Bosnjak SM, Dimitrijevic J, Djordjevic F (2016) Cancer and chemotherapy-induced nausea and vomiting: a focus on olanzapine. Curr Opin Support Palliat Care 10(2):180–188
79. Dranitsaris G, Molasiotis A, Clemons M, Roeland E, Schwartzberg L, Warr D, Jordan K, Dielenseger P, Aapro M (2016) Development of a prediction tool for identifying patients at high risk for chemotherapy-induced nausea and vomiting (CINV). MASCC/ISOO Annual Meeting on Supportive Care in Cancer; 23–25 June 2016; Adelaide, Australia. Abstract MASCC-0602
80. Di Mattei VE, Carnelli L, Carrara L, Bernardi M, Rancoita PM, Bergamini A, Ritella C, Rabaiotti E, Mangili G, Sarno L, Candiani M (2016) Chemotherapy-induced nausea and vomiting in gynecological cancer patients: "treatment-related" and "patient-related" risk factors. MASCC/ISOO Annual Meeting on Supportive Care in Cancer; 23–25 June 2016; Adelaide, Australia. Abstract MASCC-0419