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Preventing chemotherapy-induced nausea and vomiting with netupitant/palonosetron, the first fixed combination antiemetic: current and future perspective

Matti Aapro^{*1}, Li Zhang², Sriram Yennu³, Thomas W LeBlanc⁴ & Lee Schwartzberg⁵

¹Genolier Cancer Centre, Clinique de Genolier, Genolier, Switzerland

²State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Department of Medical Oncology Sun Yat-sen University Cancer Center, Guangzhou, PR China

³Department of Palliative, Rehabilitation and Integrative Medicine, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

⁴Division of Hematologic Malignancies and Cellular Therapy, Duke University School of Medicine, Durham, NC 27705, USA

⁵Department of Hematology and Oncology, The West Clinic, Germantown, TN 38138, USA

*Author for correspondence: Tel.: +41 22 366 9136; maapro@genolier.net

Chemotherapy-induced nausea and vomiting (CINV) can be prevented in most patients receiving appropriate antiemetic treatment. However, inadequate uptake of current antiemetic guideline recommendations by physicians, and poor treatment adherence by patients, lead to suboptimal CINV control. There is an unmet need to optimize guideline-consistent use of antiemetics to improve CINV management and prevention. Herein, we provide an overview of CINV, then discuss oral and intravenous NEPA, the first fixed combination antiemetic, composed of netupitant/fosnetupitant and palonosetron. We describe the main pharmacologic and pharmacokinetic characteristics of NEPA, and review the clinical evidence supporting its use in the prevention of CINV.

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Chemotherapy-induced nausea and vomiting (CINV) is a common side effect, ranked by patients as one of the most distressing and feared consequences of chemotherapy [1,2]. Optimal CINV management is critical, as nausea and vomiting can negatively impact patients' quality of life (QoL) [3,4] and affect treatment completion [5,6]. Uncontrolled CINV can influence choice of chemotherapy by physicians, who report avoiding use of highly emetogenic chemotherapy (HEC) for patients with previous CINV [7]; similarly, uncontrolled CINV may influence patients to request modification or cancellation of their chemotherapy [7]. A recent study demonstrates that optimal management of chemotherapy-related symptoms, including nausea and vomiting, through integration of routine electronic patient-reported outcomes measurement is associated with improved QoL, longer duration of anticancer treatments, decreased utilization of emergency department care and increased overall survival [8,9].

Nausea and vomiting are part of the emetic reflex; however, both events can occur independently, suggesting a distinct pathophysiology that may be clinically relevant. This is reflected in the different efficacy of antiemetic drugs in the prevention of nausea and vomiting. While current antiemetics can greatly reduce the incidence of vomiting in most cancer patients, they show a modest effect on nausea control [10–12]. Hence, patients receiving antiemetic prophylaxis that is based on first-generation 5-hydroxytryptamine-3 (5-HT₃) receptor antagonists (RAs) often experience more nausea than vomiting, especially during the delayed phase (25–120 h) after moderately emetogenic chemotherapy (MEC) and HEC [13–15].

Vomiting is an objective reaction that is easily measured. On the other hand, the subjective nature of nausea renders its assessment and reporting a clinical challenge. Consequently, healthcare professionals often underestimate the incidence of nausea or minimize its impact on patients' overall wellbeing [13,16,17]. While clinicians' efforts have

traditionally been directed to the prevention of vomiting, the focus of clinical practice and of antiemetic research has shifted toward the control of nausea.

The pathophysiology of CINV

CINV is a complex multifactorial process that is mediated by multiple neurotransmitters, including serotonin, substance P and dopamine [18]. Chemotherapy induces the release of these neurotransmitters, which subsequently stimulate their cognate receptors on the terminals of afferent nerves in locations such as the GI tract, cerebral cortex, thalamus and vestibular region. These signals are then projected to the nucleus tractus solitarius (NTS), located in the dorsal brain stem [18,19], which coordinates autonomic processes involved in vomiting, and intestinal contraction and relaxation [19]. Neurotransmitters may also interact with receptors located in the chemoreceptor trigger zone in the area postrema of the brain, which in turn activate the NTS. CINV presents in the acute (0–24 h) and delayed phase after chemotherapy [10]. Acute CINV is predominantly mediated via the binding of serotonin to 5-HT₃ receptors in peripheral vagal afferents in the intestine [10], while activation of neurokinin-1 (NK₁) receptors by substance P occurs in central locations, mainly in the area postrema and NTS, and is the primary mechanism underlying delayed CINV [18,20]. These different pathophysiologies of acute and delayed CINV necessitate diverse pharmacologic approaches.

Antiemetic treatment landscape

The three drug classes with the highest therapeutic index achieving effective prophylaxis and management of CINV are 5-HT₃RA, NK₁RA and glucocorticoids (mainly dexamethasone) [10,21]. In addition, the atypical antipsychotic olanzapine, which antagonizes dopamine D₁ and D₂, and serotonin 5-HT_{2A} and 5-HT_{2C} receptors [22], has also been shown to provide protection in specific settings [23].

The first-generation 5-HT₃RA approved by the EMA and the US FDA include dolasetron, granisetron, ondansetron and tropisetron. Overall, the safety and efficacy [24,25] profiles are comparable, with their dosing schedule, route of administration and cost being the main differentiators. Depending on the dose and route of administration, first-generation 5-HT₃RA have been associated with increased risk of developing QT interval prolongation. The only second-generation 5-HT₃RA, palonosetron, differentiates from the first-generation agents by its higher potency, longer half-life and synergistic activity with the NK₁ receptor signaling pathway [26,27], which may explain its contribution to CINV prevention in both the acute and delayed phases. In a number of meta-analyses using pooled data from randomized studies, palonosetron has been shown to be more effective than first-generation 5-HT₃RA in preventing CINV in the acute [28–30], delayed [28–31] and overall (0–120 h) [29–31] phases in cancer patients receiving MEC and HEC. Regarding safety, despite the known class effect of 5-HT₃RA on QTc prolongation [32], palonosetron has not been associated with significant changes in duration of the QT interval adjusted for the patient's heart rate (QTc interval) [33]. This finding was confirmed in a meta-analysis showing statistically significantly lower mean QTc prolongation with palonosetron compared with first-generation 5-HT₃RA [29]. Additionally, palonosetron has been associated with statistically significantly lower incidence of dizziness compared with first-generation 5-HT₃RA [29,30], and Popovic *et al.* [29] showed statistical similarity between treatments in the frequency of constipation, headache and diarrhea. These differences may explain the better adherence to chemotherapeutic treatments described in patients receiving palonosetron in a real-world setting [34].

There are three approved oral NK₁RA: aprepitant, netupitant (fixed combination with palonosetron, as NEPA), and rolapitant. Each NK₁RA significantly improves CINV control when combined with 5-HT₃RA–dexamethasone over 5-HT₃RA–dexamethasone alone, with some differences being their activity in nausea control, the duration of their antiemetic activity and the administration schedule. Distinctions between NK₁RA are found in their level of success in preventing nausea, especially delayed nausea, which remains an important unmet need [11]. While oral NEPA showed a significant improvement in delayed and overall nausea control over oral palonosetron alone in patients receiving cisplatin or anthracycline-cyclophosphamide (AC) [35,36], there is no consistent evidence to suggest that the addition of aprepitant [37–40] or rolapitant [41,42] to 5-HT₃RA–dexamethasone improves protection against nausea. Aprepitant, combined with 5-HT₃RA–dexamethasone, and NEPA have both been shown to significantly reduce CINV during the acute, delayed and overall periods, as compared with the 5-HT₃RA plus dexamethasone combination alone, and rolapitant-based regimens have not shown significant antiemetic benefit in the acute phase [41,42]. The main differentiating aspects in oral dosing schedules between aprepitant, NEPA and rolapitant include: the half-life of the compound, which is longer for netupitant and rolapitant, allowing

Figure 1. Schedule of oral NK₁RA-based antiemetic regimens and administration timing of antiemetic agents for the prophylaxis of chemotherapy-induced nausea and vomiting associated with highly emetogenic chemotherapy (left) or moderately emetogenic chemotherapy (right). Blue circles indicate the number of doses. Highly emetogenic chemotherapy: the number of doses represented is based on the design of pivotal clinical trials of approved NK₁ RAs [35,37,38,41]. Moderately emetogenic chemotherapy: based on the design of pivotal clinical trials of approved NK₁ RAs [36,39,42,44,45]. In pivotal studies ondansetron was administered as a single 32-mg iv. dose. Currently, according to ondansetron summary of product characteristics, the 32-mg iv. dose should be split into three doses (16, 8 and 8 mg) on day 1 of chemotherapy, due to safety concerns related to QT prolongation. 5-HT₃RA: 5-Hydroxytryptamine-3 receptor antagonist; APR: Aprepitant; CINV: Chemotherapy-induced nausea and vomiting; DEX: Dexamethasone; GRAN: Granisetron; HEC: Highly emetogenic chemotherapy; iv.: Intravenous; MEC: Moderately emetogenic chemotherapy; NEPA: Netupitant/palonosetron; NK₁RA: Neurokinin-1 receptor antagonist; OND: Ondansetron; ROL: Rolapitant. Data taken from [43].

their administration only on the day of chemotherapy, whereas aprepitant is administered on days 1–3; whether it is a single or a combination agent, in NEPA, both the NK₁RA and 5-HT₃RA components are administered in a single dose, whereas in aprepitant- and rolapitant-based regimens the 5-HT₃RA is administered separately; interactions with CYP450 enzymes, since both aprepitant and netupitant are moderate inhibitors of CYP3A4, the dose of co-administered dexamethasone (CYP3A4 substrate) is reduced with aprepitant and NEPA. As a result, NEPA-based regimens offer the most convenient administration schedule, requiring the lowest number of doses (Figure 1) [35–39,41–45]. All three NK₁ RAs are now available in intravenous (iv.) form, which ensures complete adherence on day 1 [46–48]. Additionally, fosaprepitant, the iv. prodrug of aprepitant, has a longer half-life than oral aprepitant, and is administered only on the day of chemotherapy. Caution is advised when using iv. rolapitant due to the reported occurrence of anaphylaxis, anaphylactic shock and additional serious hypersensitivity reactions during or soon after its infusion [49].

Current antiemetic guidelines

Antiemetic guidelines have been developed by the Multinational Association of Supportive Care in Cancer (MASCC)/European Society for Medical Oncology (ESMO) [50], the American Society of Clinical Oncology (ASCO) [51] and the National Comprehensive Cancer Network (NCCN) [52]. For patients receiving HEC (including AC), the recommendation is either the triplet combination of an NK₁RA, a 5-HT₃RA and dexamethasone [50,52], or the quadruplet regimen of olanzapine, an NK₁RA, a 5-HT₃RA and dexamethasone [50,52]. For those receiving MEC, prophylaxis with a 5-HT₃RA plus dexamethasone on day 1 is generally advised [50–52]; if necessary, additional prophylaxis may be offered on days 2 and 3 of chemotherapy [50,52]. More recently, for patients receiving carboplatin (at any dose), MASCC/ESMO guidelines recommend prophylactic treatment with NK₁RA, 5-HT₃RA and dexamethasone [50], while both ASCO and NCCN guidelines suggest this triplet regimen only for patients receiving carboplatin administered at an area under the curve of ≥ 4 mg/ml/min [51,52].

Historically, the primary determinant of a patient developing CINV has been the fundamental emetogenicity of the chemotherapy. There are, however, a number of patient factors that increase risk, such as younger age,

female gender, low alcohol intake, anxiety, and a history of motion sickness or nausea during pregnancy [53,54]. Many clinicians do not take these individual factors into account when making treatment decisions. Several tools have been developed to determine a patient's cumulative emetic risk using these factors, and aid in the personalized selection of the antiemetic regimen. These include the validated MASCC Antiemesis Tool (MAT; available at: www.mascc.org) [55], composed of four questions concerning the intensity and frequency of nausea and/or vomiting after chemotherapy during the acute and delayed phases, and facilitating discussion between physicians and patients about CINV. Recently, in a study with data from 1198 patients receiving a total of 4197 chemotherapy cycles, Dranitsaris *et al.* [56] developed an algorithm to predict an individual patient's risk for CINV before each chemotherapy cycle. This model identified eight risk factors that were important predictors of grade ≥ 2 CINV during the 5 days following chemotherapy administration. These factors were: age < 60 years, anticipatory nausea and vomiting, history of morning sickness, < 7 h of sleep the night before chemotherapy, CINV in the prior cycle, the use of AC- or platinum-based chemotherapy, patient use of nonprescribed antiemetics at home, and the cycle of chemotherapy (with lower risk of CINV after the first cycle) [56]. On the basis of these factors, investigators developed a scoring algorithm to select the most appropriate antiemetic regimen. Prospective clinical validation of this prediction tool is pending.

If guideline recommendations are followed, CINV is preventable in most patients [57]. One large European observational study showed that patients who were treated in accordance with antiemetic guidelines had significantly better CINV control compared with those who did not receive guideline-consistent treatment (complete response [CR] rates of 60 vs 51%, respectively; $p = 0.008$) [58]. Similarly, observational studies in the UK [59], Asia [60] and the US oncology practices [61] also found an association between guideline adherence and effective CINV control.

Real-world evidence suggests that guidelines are not uniformly followed [56,58,61,62]. Guideline-inconsistent prescription of antiemetics is recognized both by physicians [7] and nurses [63,64], with the main discrepancies identified being the underutilization of NK₁RAs in the HEC setting [55,63–65], the use of agents that are not guideline recommended (such as metoclopramide, thalidomide, phenothiazine or benzodiazepine) [63,64,66], or the use of NK₁ RA monotherapy or NK₁ RA plus 5-HT₃ RA (no dexamethasone) in the HEC and MEC settings [7,65,67]. As a result, guideline-inconsistent antiemetic prophylaxis can reduce CINV control in both the HEC and MEC settings [56,58,60,62]. For example, prescription of NK₁RAs only in approximately 15% of patients receiving HEC or AC resulted in 61% of the patients having emesis, 47% acute nausea and 68% delayed nausea [56].

The main factors that contribute to the suboptimal adherence to guidelines include the underestimation of the incidence of CINV, especially in the delayed phase, by physicians [7,13,17,65], patients' under-reporting [16,64] and lack of routine screening for nausea. Other factors include 'physicians' preference' for particular antiemetic regimens and restrictions in access to specific antiemetics, both of which were identified as relevant barriers interfering with the implementation of guideline recommendations in two independent surveys with oncology nurses in the USA and Europe [63,64]. Finally, the complexity of some antiemetic regimens may result in poor patient adherence, and limit treatment completion as planned [63,64]. For example, depending on the NK₁ RA included in the regimen, patients sometimes must take a different number of doses of antiemetics both on the day of chemotherapy and on days 2–4 at home [50–52], (Figure 1) [35–39,41–45]. A survey of oncologists found that approximately one-third of patients miss or delay a dose during home administration of antiemetics [7]. Simplification of antiemetic regimens could improve adherence to guidelines by physicians and patients [7].

Netupitant/palonosetron

NEPA is the first fixed combination antiemetic, composed of the highly selective NK₁ RA netupitant (oral) or fosnetupitant (iv.), and the pharmacologically and clinically distinct second-generation 5-HT₃ RA palonosetron [10,27]. These two components show no relevant pharmacokinetic (PK) interactions in absorption, binding, metabolism or excretion. NEPA capsules are administered as a single oral dose, approximately 60 min prior to chemotherapy on day 1 of each cycle. However, recent PK/pharmacodynamic (PD) modeling studies suggest that shifting the timing of NEPA administration closer to the time of chemotherapy initiation, and possibly even co-administration with chemotherapy, may not affect its efficacy [68,69]. An iv. NEPA formulation has been developed to further improve convenience and was recently approved by the FDA [46].

NEPA: PD/PK properties of netupitant

Netupitant is a highly selective NK₁ RA that binds with high affinity to NK₁ receptors in the striatum (half-maximal response concentration = 10.2 ng/ml [coefficient of variation: 14.5%]) [70]. Per published literature, 90% NK₁

receptor occupancy (RO) in the striatum has been identified as the threshold that correlates with NK₁ RA antiemetic efficacy [71]. For netupitant, 92.5% of striatal NK₁ receptors were occupied at 6 h postadministration of 300 mg oral netupitant [70], and NK₁RO remained approximately 90% over 96 h in various brain regions [70]. PK/PD modeling has predicted that striatal 90% NK₁RO is achieved at a netupitant plasma concentration of 225 ng/ml, reached at 2.2 h after oral NEPA administration [68].

PK studies evaluating oral NEPA in healthy volunteers confirmed that the mean maximum plasma concentration (C_{max}) of netupitant of 595 ng/ml is achieved at approximately 5 h postdose [72]. Netupitant is rapidly absorbed and extensively metabolized by CYP3A4 into three main metabolites, M1 (N-demethylated netupitant), M2 (netupitant N-oxide) and M3 (monohydroxy netupitant). The plasma elimination half-life is approximately 100 h [72], with elimination predominantly via the hepatic/biliary route [70].

NEPA: PD/PK properties of palonosetron

Palonosetron, the only second-generation 5-HT₃RA [10,73], provides effective prophylaxis in the acute and delayed phases [74,75]. In addition to the higher binding affinity to 5-HT₃ receptors (pK_i = 10.45) [76] and a longer plasma half-life (40 h) compared with other 5-HT₃ RAs, palonosetron exhibits allosteric binding with positive cooperativity and prolonged inhibition of the 5-HT₃ receptor signaling pathway [27]. *In vitro*, the binding of palonosetron to 5-HT₃ receptors promotes internalization of both 5-HT₃ [77] and NK₁ receptors [77,78] and inhibits substance P-mediated effects through inhibition of 5-HT₃ and NK₁ receptor crosstalk [77]. Finally, netupitant and palonosetron exhibit synergy in the inhibition of NK₁ receptors [26]. These unique properties are exclusive to palonosetron and may explain its enhanced inhibition of the substance P response and efficacy in preventing delayed emesis [27].

PK/PD modeling has predicted that 90% 5-HT₃RO could be achieved with a palonosetron plasma concentration of 188 pg/ml, reached at 1.1 h after administration of oral NEPA [68]. A single oral dose of NEPA results in a mean C_{max} of 785 pg/ml, reached in 4.5 h [70]. Palonosetron is mainly metabolized by CYP2D6, and to a lesser degree by CYP3A4 and CYP1A2 with the primary metabolites being N-oxide palonosetron and 6-S-palonosetron, both with <1% of 5-HT₃RA activity of palonosetron. Palonosetron is predominantly eliminated via the urine and the feces [46,72].

Netupitant & palonosetron – complementary PK/PD profiles

Netupitant and palonosetron show no changes in their PK parameters on co-administration as compared with the single agents. Furthermore, both compounds show complementary PK profiles, supporting their combination in NEPA: netupitant and palonosetron present high absolute bioavailability of 63–87% and 97% [79], respectively, suggesting they do not experience clinically significant interactions with intestinal efflux transporters that might affect their absorption or excretion; palonosetron presents low binding affinity to plasma proteins, making it unlikely for palonosetron to displace protein-bound netupitant with potential clinical consequences; the metabolism of netupitant and palonosetron is mediated by different CYP450 enzymes, thus no clinically significant drug–drug interactions should be expected on co-administration. Additionally, their complementary PD properties, such as prolonged occupancy of their respective receptors, and their synergistic effects on NK₁ receptor pathway inhibition [26] provide further support for their combination.

NEPA drug–drug interactions

Netupitant is a substrate and moderate inhibitor of CYP3A4 [80]. Palonosetron, which is primarily metabolized by CYP2D6 [81], does not inhibit or induce activity of the CYP enzymes [82]. No relevant interactions have been demonstrated between netupitant and palonosetron at single doses up to 450 and 0.75 mg, respectively [82]. For netupitant, there is the potential for drug–drug interactions if it is co-administered with agents that are metabolized by CYP3A4 [80], such as erythromycin or midazolam, and dose adjustments may be required [80] (reviewed in Natale *et al.* [83]). In addition, as is the case with aprepitant, co-administration of NEPA with dexamethasone was shown to significantly increase dexamethasone exposure in a dose-dependent fashion [80], which led to the reduction in planned dose of dexamethasone in the pivotal NEPA clinical trials [35,36,44]. The same reduced dexamethasone dose has been used with the iv. NEPA formulation [84]. No interactions have been reported to date between NEPA and chemotherapeutic drugs that are metabolized by CYP3A4, and a safety analysis using pooled data from the pivotal studies showed lack of increased toxicity on co-administration of NEPA with cyclophosphamide, etoposide, or docetaxel [85,86]. However, caution should be taken when co-administering NEPA with chemotherapeutics that are metabolized predominantly by CYP3A4. Interestingly, no clinically relevant interactions between netupitant and

oral contraceptives have been described [82]. Netupitant is not an inducer or inhibitor of CYP2C9 and CYP2D6, and no dose adjustment is required when it is administered concomitantly with substrates of the P-glycoprotein transporter [87].

Efficacy of NEPA

The approval of NEPA in the USA and Europe was based on the efficacy of NEPA in preventing CINV in the HEC, AC and MEC settings, during the acute, delayed and overall phases in single and multiple cycles of chemotherapy (Table 1) [35,36,44,88] & (Table 2) [44,89].

A Phase II double-blind, randomized, dose-finding study of 694 patients receiving cisplatin-based HEC demonstrated the superiority of oral NEPA plus dexamethasone over oral palonosetron plus dexamethasone in terms of overall CR (no emesis, no rescue medication) rates at all doses of NEPA (100, 200 or 300 mg netupitant/0.50 mg palonosetron) tested ($p < 0.05$). NEPA (300 mg netupitant/0.50 mg palonosetron) had incremental benefits over the lower doses for each of the efficacy end points tested (CR, no emesis and no significant nausea [NSN] rates during the acute/delayed/overall phases) (Table 1) [35,36,44,88]. Consequently, the fixed combination of 300 mg netupitant and 0.50 mg palonosetron was identified as the optimal oral formulation for further clinical development of NEPA [35]. An aprepitant-ondansetron plus dexamethasone regimen was also included in the study as an exploratory arm for safety. While only qualitative comparisons can be made due to the nature of the study design, oral NEPA (300 mg netupitant/0.50 mg palonosetron) showed a consistent numeric advantage for all efficacy end points (CR, no emesis, NSN and complete protection across the acute/delayed/overall phases) over the oral aprepitant regimen.

The superiority of oral NEPA plus dexamethasone versus oral palonosetron plus dexamethasone was demonstrated in a double-blind, randomized Phase III study in 1455 patients receiving AC-based chemotherapy over multiple cycles [36]. CR rates were significantly higher for oral NEPA in the acute, delayed and overall phases (Table 1) [35,36,44,88]. The multiple-cycle extension stage of this trial showed that the benefit of oral NEPA was maintained over four cycles, with significantly higher overall CR rates observed in oral NEPA-treated patients versus oral palonosetron-treated patients for each cycle ($p \leq 0.001$), and cumulatively over the four cycles ($p < 0.0001$) [88] (Table 2) [44,89]. In addition, this study assessed the impact of NEPA on QoL, using the Functional Living Index Emesis questionnaire. A significantly greater proportion of oral NEPA-treated patients reported no impact on daily life in the nausea domain ($p = 0.015$), vomiting domain ($p = 0.001$) and overall combined domains ($p = 0.005$) [36], (Table 3) [36,88].

NEPA was also effective in the non-AC HEC and MEC settings. In a Phase III study designed to investigate the safety profile of NEPA over multiple cycles of chemotherapy, 413 patients were randomized 3:1 to receive oral NEPA plus dexamethasone or oral aprepitant-palonosetron plus dexamethasone (Table 1) [35,36,44,88] & (Table 2) [44,89]. High overall CR rates were observed in NEPA-treated patients in cycle 1 (81%, Table 1) and sustained across six chemotherapy cycles regardless of whether patients were receiving non-AC HEC or MEC (Table 2). Although the study objective was not powered for an efficacy comparison, and the aprepitant arm was included to provide context, oral NEPA showed a consistent numeric advantage over oral aprepitant-palonosetron in CR rates during the overall (between a 2 and 6% absolute difference in each cycle, Table 2) and delayed (between a 3 and 7% absolute difference in each cycle [44]) periods.

More recently, oral NEPA plus dexamethasone has been compared with oral aprepitant-granisetron plus dexamethasone in a randomized, Phase III trial of 829 patients receiving HEC conducted in Asia [88]. Importantly, this study shows the first head-to-head comparison of two regimens featuring the triplet combination of an NK₁ RA, a 5-HT₃RA and dexamethasone. The primary end point of demonstrating the noninferiority of a single dose of oral NEPA plus dexamethasone compared with the 3-day oral aprepitant-granisetron-dexamethasone regimen in terms of overall CR rates was met (73.8 vs 72.4%, respectively, with a noninferiority margin set at -10%). No-emesis and NSN rates numerically favored NEPA in the delayed and overall phases [88], while 'no rescue medication' rates were significantly higher for the NEPA arm during the delayed ($p < 0.05$) and overall ($p < 0.05$) phases. These results are in line with the numerically higher antiemetic efficacy reported for oral NEPA over oral aprepitant-containing regimens in the pivotal Phase II and III studies [35,44]. The oral NEPA treatment arm also exhibited significantly lower percentages of patients with breakthrough CINV (13.9 vs 8%; $p = 0.0063$), breakthrough emesis (7.3 vs 12.7%; $p = 0.009$) and breakthrough significant nausea (12.9 vs 18.5%; $p = 0.024$) on day 5 of chemotherapy [90]. Benefits in QoL were also reported, with a significantly higher proportion of NEPA-treated patients reporting no impact on daily life due to nausea during the delayed phase [88], (Table 3) [36,88].

Table 1. Summary of oral netupitant/palonosetron efficacy data in different settings: single cycle of chemotherapy.

Outcome, %	Cisplatin-based HEC ^{†,§§}		AC-based HEC ^{§§}		Non-AC-based HEC/MEC ^{§§}		Cisplatin-based HEC ^{§§}	
	NEPA ₃₀₀ + DEX (n = 135)	PALO + DEX (n = 136)	NEPA + DEX (n = 724)	PALO + DEX (n = 725)	NEPA + DEX (n = 309)	APR + PALO + DEX (n = 103)	NEPA + DEX (n = 412)	APR + GRAN + DEX (n = 416)
Complete response								
Acute	98.5 [†]	89.7	88.4 [¶]	85.0	92.9	94.2	84.5	87.0
Delayed	90.4 [§]	80.1	76.9 [#]	69.5	83.2	77.7	77.9	74.3
Overall	89.6 [‡]	76.5	74.3 [#]	66.6	80.6	75.7	73.8	72.4
No emesis								
Acute	98.5 [†]	89.7	90.9 [¶]	87.3	–	–	85.2	87.5
Delayed	91.9 [‡]	80.1	81.8 ^{††}	75.6	–	–	79.4	76.2
Overall	91.1 [‡]	76.5	79.8 [#]	72.1	–	–	75.0	74.0
No significant nausea								
Acute	98.5 [§]	93.4	87.3	87.9	90.6	93.2	89.8	87.3
Delayed	90.4 [‡]	80.9	76.9 [¶]	71.3	85.1	81.6	78.2	72.8
Overall	89.6 [§]	79.4	74.6 [¶]	69.1	84.1	80.6	75.7	70.4
Complete protection								
Acute	97.0 [‡]	87.5	82.3	81.1	–	–	–	–
Delayed	84.4 [§]	73.5	67.3 ^{††}	60.3	–	–	–	–
Overall	83.0 [‡]	69.9	63.8 [¶]	57.9	–	–	–	–
No rescue medication								
Acute	100	97.8	93.5	92.3	–	–	98.8	98.3
Delayed	98.5	97.1	85.8 ^{††}	80.6	–	–	97.6 ^{††}	94.7
Overall	98.5	95.6	84.0 [¶]	79.0	87.7	91.3	96.6 ^{††}	93.5

[†] Only the results of the NEPA₃₀₀ + DEX arm are shown (commercially approved dose).

[‡] $p \leq 0.01$ from logistic regression versus PALO + DEX.

[§] $p \leq 0.05$ from logistic regression versus PALO + DEX.

[¶] $p \leq 0.05$ versus PALO + DEX using a two-sided Cochran–Mantel–Haenszel test stratified by treatment, age group and region.

[#] $p \leq 0.001$ versus PALO + DEX using a two-sided Cochran–Mantel–Haenszel test stratified by treatment, age group and region.

^{††} $p \leq 0.01$ versus PALO + DEX using a two-sided Cochran–Mantel–Haenszel test stratified by treatment, age group and region.

^{‡‡} $p < 0.05$ versus APR + GRAN + DEX based on the Cochran–Mantel–Haenszel test with gender as a stratifying variable.

^{§§} From left to right: Cisplatin-based HEC [35]; AC-based HEC [36]; Non-AC-based HEC/MEC [44]; Cisplatin-based HEC [88].

AC: Anthracycline and cyclophosphamide; APR: Aprepitant; DEX: Dexamethasone; GRAN: Granisetron; HEC: Highly emetogenic chemotherapy; MEC: Moderately emetogenic chemotherapy; NEPA: Netupitant/palonosetron; PALO: Palonosetron.

Table 2. Summary of oral netupitant/palonosetron efficacy in the overall phase (0–120 h) – multiple cycles of chemotherapy.

Outcome, %	AC-based HEC ^{††} cycles: 1/2/3/4		Non-AC-based HEC/MEC ^{††} cycles: 1/2/3/4/5/6	
	NEPA + DEX (n = 724/635/598/551)	PALO + DEX (n = 725/651/606/560)	NEPA + DEX (n = 309/280/259/233/156/124)	APR + PALO + DEX (n = 103/96/90/81/57/44)
Complete response				
Cycle 1	74.3 [‡]	66.6	80.6	75.7
Cycle 2	80.3 [§]	66.7	86.1	81.3
Cycle 3	83.8 [§]	70.3	90.7	86.7
Cycle 4	83.8 [§]	74.6	90.1	87.7
Cycle 5	–	–	91.7	86.0
Cycle 6	–	–	91.1	86.4
No emesis[†]				
Cycle 1	79.8 [¶]	72.1	–	–
Cycle 2	85.5 [§]	73.7	–	–
Cycle 3	88.3 [§]	77.2	–	–
Cycle 4	87.3 [¶]	79.5	–	–
No significant nausea[†]				
Cycle 1	74.6 [#]	69.1	84.1	80.6
Cycle 2	77.3 [#]	71.6	86.8	86.5
Cycle 3	78.4 [#]	73.3	89.6	83.3
Cycle 4	80.2 [#]	75.2	91.8	86.4
Cycle 5	–	–	92.3	82.5
Cycle 6	–	–	90.3	84.1

[†]Prespecified for cycle 1, using a two-sided Cochran–Mantel–Haenszel test stratified by treatment, age group and region. *Post hoc* analysis for cycles 2–4. Not adjusted for multiple comparisons.

[‡]p = 0.001.

[§]p < 0.0001.

[¶]p < 0.001.

[#]p < 0.05.

^{††}AC-based HEC [89]; Non-AC-based HEC/MEC [44].

AC: Anthracycline and cyclophosphamide; APR: Aprepitant; DEX: Dexamethasone; HEC: Highly emetogenic chemotherapy; MEC: Moderately emetogenic chemotherapy; NEPA: Netupitant/palonosetron; PALO: Palonosetron.

Table 3. Summary of oral netupitant/palonosetron quality-of-life data in different settings – single cycle of chemotherapy.

No impact on daily life, %	AC-based HEC [#]		Cisplatin-based HEC [#]	
	NEPA + DEX (n = 724)	PALO + DEX (n = 725)	NEPA + DEX (n = 412)	APR + GRAN + DEX (n = 416)
Nausea domain				
Acute	–	–	81.8	80.0
Delayed	–	–	71.1 [¶]	65.1
Overall	71.5 [†]	65.8	–	–
Vomiting domain				
Acute	–	–	87.9	86.8
Delayed	–	–	81.3	77.4
Overall	90.1 [‡]	84.4	–	–
Combined domain				
Acute	–	–	86.2	83.2
Delayed	–	–	76.0	70.7
Overall	78.5 [§]	72.1	–	–

[†]p ≤ 0.05 versus PALO + DEX using a two-sided Cochran–Mantel–Haenszel test stratified by treatment, age group and region.

[‡]p ≤ 0.001 versus PALO + DEX using a two-sided Cochran–Mantel–Haenszel test stratified by treatment, age group and region.

[§]p ≤ 0.01 versus PALO + DEX using a two-sided Cochran–Mantel–Haenszel test stratified by treatment, age group and region.

[¶]Statistically significant difference versus APR + GRAN + DEX using a two-sided Cochran–Mantel–Haenszel test stratified by gender.

[#]AC-based HEC [36]; Cisplatin-based HEC [88].

AC: Anthracycline and cyclophosphamide; APR: Aprepitant; DEX: Dexamethasone; GRAN: Granisetron; HEC: Highly emetogenic chemotherapy; NEPA: Netupitant/palonosetron; PALO: Palonosetron.

With the advent of newer antiemetics during the last few decades, the incidence of CINV has greatly decreased, with the prevention of vomiting possible in most patients [10,57]. However, nausea remains a significant unmet need, with control generally being suboptimal, especially for delayed nausea. Each of the pivotal NEPA studies provides evidence indicating that NEPA offers a promising strategy for better control of nausea. Oral NEPA was

superior to oral palonosetron in controlling nausea in patients receiving cisplatin- or AC-based HEC in single and multiple cycles [35,36]. Significantly lower rates of NSN were reported in the oral NEPA treatment arm compared with the oral palonosetron arm in patients receiving cisplatin-based chemotherapy in the acute ($p \leq 0.05$), delayed ($p \leq 0.01$) and overall ($p \leq 0.05$) phases [35]. Meanwhile, in patients receiving AC-based HEC, oral NEPA induced a significant reduction of NSN in the delayed ($p = 0.014$) and overall ($p = 0.020$) phases compared with oral palonosetron [36]; this control was sustained over four cycles, and overall NSN rates ranged from 75 to 80% with oral NEPA versus 69 to 75% with oral palonosetron [89]. The effect of NEPA on prevention of nausea was also determined over multiple cycles of non-AC HEC or MEC [44]. NEPA was efficacious, with overall NSN rates of 84–92%, which were maintained over six cycles [91]. In the head-to-head Phase III trial against oral aprepitant-granisetron plus dexamethasone, NSN rates were numerically higher in the oral NEPA arm compared with the aprepitant arm in the delayed (78 vs 73%) and overall (76 vs 70%) phases [88]. This numeric advantage in the oral NEPA arm was more apparent in the subset of patients receiving cisplatin $\geq 70\text{-mg/m}^2$ dose during all phases (acute: 88 vs 84%; delayed: 76 vs 68%; overall: 74 vs 66%) [92].

Safety of NEPA

Overall, oral NEPA has been well tolerated in published studies, with a favorable safety profile. No unexpected safety signals were observed and the adverse event (AE) profile was similar to that reported for oral palonosetron- and aprepitant-based regimens. The overall incidence, type, frequency and intensity of treatment-emergent AEs (TEAEs), as well as treatment-related AEs (TRAEs) were consistent with the population of patients undergoing antineoplastic therapy and the toxic effects of chemotherapy [93], (Table 4) [35,36,44,83,88]. Most AEs were mild or moderate in intensity. The most frequently observed TRAEs were hiccups [35,88], constipation and headache [36,44], AEs that are associated with the class effects of 5-HT₃RA (headache and constipation) [31], NK₁RA and high-dose steroids (hiccups) [94,95].

Several studies demonstrated the tolerability of NEPA over multiple cycles of chemotherapy. In patients receiving at least six cycles of non-AC HEC or MEC [44], oral NEPA was not associated with any increase in TEAEs over multiple cycles and had a comparable safety profile with the exploratory oral aprepitant-palonosetron arm. A low proportion of TRAEs was observed in patients receiving NEPA across cycles 1–6 (10.1%), with the most frequently reported being constipation (3.6%) and headache (1%), which were the same as reported during cycle 1 of the same study. Similar proportions of patients experienced serious TEAEs in both arms (oral NEPA: 16.2%; oral aprepitant-palonosetron: 18.3%), two of which were in the NEPA treatment arm and deemed related to study drug (ventricular extrasystoles in cycle 6 and acute psychosis in cycle 1). No deaths were attributed to NEPA [44], (Table 4) [35,36,44,84,88]. Similar results were observed in the AC-based HEC setting [36]. There was no increase in the incidence of TEAEs or TRAEs across the multiple-cycle extension period (between four and six cycles). The safety profile was comparable between the oral NEPA plus dexamethasone and oral palonosetron plus dexamethasone treatment arms, with most events being mild to moderate in intensity. Similarly, the most frequently reported TRAEs were headache (oral NEPA: 3.5%; oral palonosetron: 2.8%) and constipation (oral NEPA: 2.0%; oral palonosetron: 2.2%). No TRAEs led to discontinuation, and there were no deaths during the multiple-cycle extension period in the oral NEPA group [89].

QTc prolongation has been identified as a potential safety issue associated with 5-HT₃RA. Consequently, a thorough QT trial [96] was conducted, to determine the effect of NEPA on cardiac repolarization [97]. Overall, 196 healthy subjects were enrolled in one of the following treatment groups: placebo; 200 mg netupitant plus 0.50 mg palonosetron; 600 mg netupitant plus 1.5 mg palonosetron; or 400 mg moxifloxacin (control). No significant effects were observed on the individually heart rate-corrected QT interval after treatment with NEPA even at supratherapeutic doses. Similarly, no significant changes were observed on the heart rate, PR interval duration, QRS interval duration or cardiac morphology compared with placebo. In conclusion, NEPA was not associated with cardiotoxicity or untoward cardiac safety signals [97].

One publication [98] pooled the safety data from >3200 patients enrolled in the Phase II/III trials included in the clinical program of NEPA [35,36,44], in addition to a Phase II study comparing oral and iv. palonosetron [99]. The frequency of TEAEs and TRAEs was similar between patients treated with oral NEPA plus dexamethasone, oral palonosetron plus dexamethasone, and aprepitant-ondansetron/palonosetron plus dexamethasone. TEAEs were mostly of mild intensity and primarily included hematologic toxicity, alopecia and general weakness, which are common chemotherapy and disease-related AEs. In accordance with the individual studies, the most frequently reported TRAEs (in $\geq 2\%$ of patients) were headache and constipation. No significant cardiac effects were reported.

Table 4. Summary of netupitant/palonosetron safety data.

Type of AE and number of patients (%)	Oral NEPA						iv. NEPA							
	Cisplatin-based HEC ^{§,††}			Non-AC-based HEC and MEC ^{††}			Cisplatin-based HEC ^{††}			HEC regimen ^{††}				
	Single cycle			Entire period [#]			Single cycle			Entire period (cycles 1-4)				
	NEPA + PALO + DEX (n = 135)			NEPA + PALO + DEX (n = 104)			NEPA + PALO + DEX (n = 413)			iv. NEPA + DEX (n = 203)				
	NEPA + PALO + DEX (n = 136)			NEPA + PALO + DEX (n = 308)			NEPA + PALO + DEX (n = 416)			iv. NEPA + DEX (n = 201)				
Any TEAE	68 (50.0)	67 (49.3)	551 (76.0)	507 (69.9)	199 (64.6)	64 (61.5)	265 (86.0)	95 (91.3)	240 (58.1)	239 (57.5)	120 (59.1)	135 (67.2)	169 (83.3)	174 (86.6)
Serious AE	0	3 (2.2)	13 (1.8)	12 (1.7)	18 (5.8)	4 (3.8)	50 (16.2)	19 (18.3)	20 (4.8)	19 (4.6)	29 (14.3)	21 (10.4)	41 (20.2)	43 (21.4)
Any TRAE [†]	21 (15.4)	17 (12.5)	59 (8.1)	52 (7.2)	16 (5.2)	3 (2.9)	31 (10.1)	6 (5.8)	76 (18.4)	60 (14.4)	18 (8.9)	19 (9.5)	26 (12.8)	23 (11.4)
Severe TRAE [†]	0	2 (1.5)	5 (0.7)	0	1 (0.3)	0	1 (0.3)	0	NA	NA	1 (0.5)	2 (1.0)	2 (1.0)	3 (1.5)
Serious TRAE [†]	0	0	0	0	1 (0.3)	0	2 (0.6)	0	2 (0.5)	2 (0.5)	0	0	0	0
Most common TRAE [†] (≥2%):														
Constipation	–	–	15 (2.1)	15 (2.1)	7 (2.3)	0	11 (3.6)	1 (1.0)	33 (8.0)	26 (6.3)	10 (4.9)	11 (5.5)	13 (6.4)	12 (6.0)
Headache	–	–	24 (3.3)	22 (3.0)	–	–	–	–	–	–	–	–	–	–
Hiccups	7 (5.1)	5 (3.7)	–	–	–	–	–	–	11 (2.7)	6 (1.4)	–	–	–	–
Increased ALT	–	–	–	–	–	–	–	–	–	–	–	–	4 (2.0)	4 (2.0)
TRAE [†] leading to discontinuation	0	0	0	2 (0.3)	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.5)	0	2 (1.0)	1 (0.5)
Total deaths	0	0	0	1 (0.1)	7 (2.3) [¶]	0	16 (5.2) [¶]	1 (1.0) [¶]	0	4 (1.0) [¶]	7 (3.4) [¶]	6 (3.0) [¶]	10 (4.9) [¶]	14 (7.0) [¶]
† Considered by the investigator to be possibly, probably or definitely related to study drug (from [36]).														
‡ By Medical Dictionary for Regulatory Activities (MedDRA) version 14.0 preferred term.														
§ Only the results of the NEPA ₃₀₀ + DEX arm are shown (commercially approved dose).														
¶ All events were judged unrelated to study drug.														
* Includes cycle 1 through all cycles.														
†† From left to right: Cisplatin-based HEC [35]; AC-based HEC [36]; Non-AC-based HEC and MEC [44]; Cisplatin-based HEC [88]; HEC regimen [84].														
AC: Anthracycline and cyclophosphamide; AE: Adverse event; ALT: Alanine aminotransferase; APR: Aprepitant; DEX: Dexamethasone; GRAN: Granisetron; HEC: Highly emetogenic chemotherapy; iv.: Intravenous; MEC: Moderately emetogenic chemotherapy; NA: Not available; NEPA: Netupitant/palonosetron; PALO: Palonosetron; TEAE: Treatment-emergent adverse event; TRAE: Treatment-related adverse event.														

Intravenous NEPA

The new iv. NEPA formulation was approved in April 2018 by the FDA for the prevention of CINV in patients receiving HEC, with a limitation of use in the AC setting [46]. This formulation consists of fosnetupitant (235 mg) plus palonosetron (0.25 mg). Intravenous NEPA is administered as a 30-min infusion of a 50-ml solution, 30 min prior to chemotherapy.

Fosnetupitant is a water-soluble phosphorylated prodrug of netupitant that is rapidly converted to netupitant following iv. administration [100]. In a Phase I study in 147 healthy volunteers, administration of iv. fosnetupitant hydrochloride at doses ranging from 20 to 390 mg was found to be well tolerated and with a safety profile similar to that of oral NEPA (Helsinn, data on file). Moreover, the 235-mg iv. dose of free-base fosnetupitant (corresponding to a 260-mg dose of fosnetupitant chloride hydrochloride) was bioequivalent, in terms of exposure (area under the curve) to the netupitant dose (300 mg) used in the approved oral NEPA formulation [46]. Finally, since fosnetupitant does not require surfactants, emulsifiers or solubility enhancers to achieve a clear injectable solution, the risk for unexpected allergic reactions is very low [84].

The dose of palonosetron used in iv. NEPA, 0.25 mg, corresponds with the dose in the approved palonosetron iv. formulation. A Phase III study in 440 patients with solid tumors receiving HEC [100] has demonstrated noninferiority of palonosetron 0.25 mg administered as a 30-min iv. infusion compared with the approved 30-s iv. bolus, in terms of CR in the acute phase, with the frequencies of no emetic episodes and no rescue medication in the acute, delayed and overall phases also similar between the two treatment groups. Both arms showed comparable safety profiles.

In a recent study in cancer patients receiving HEC, fosnetupitant conversion occurred rapidly and netupitant C_{max} was reached at the end of the 30-min iv. NEPA infusion period, with plateau plasma concentrations maintained for 3–6 h [101]. Netupitant showed a long plasma elimination half-life of 144 h and systemic exposure of 15,588 h·ng/ml, both in line with those observed for oral NEPA. Palonosetron C_{max} was also reached at the end of the infusion, and other than the expected differences in C_{max} , the PK profile of palonosetron as a component of the iv. NEPA formulation and the approved 30-s iv. bolus were comparable [32,102,103].

In addition to the bioequivalence study required for approval of the iv. formulation, the clinical program of iv. NEPA included a Phase III safety study evaluating the new iv. NEPA formulation administered with dexamethasone over initial and multiple cycles of HEC [84], which provides clinicians with valuable safety information. In total, 404 patients received iv. NEPA plus dexamethasone (N = 203) or oral NEPA plus dexamethasone (N = 201) prior to HEC (up to four cycles; mainly high-dose cisplatin) on day 1. The overall incidence and intensity of TEAEs were comparable between the two treatment groups, with 59 and 83% of patients receiving iv. NEPA versus 67 and 87% of patients receiving oral NEPA experiencing greater than or equal to TEAE during cycle 1 and throughout the entire study, respectively [84]. The most common TEAEs in both arms were neutropenia (iv. NEPA: 30%; oral NEPA: 29%) and anemia (iv. NEPA: 16%; oral NEPA: 19%), consistent with those expected for cancer patients receiving cisplatin-based chemotherapy. TRAEs were reported in 13% of patients receiving iv. NEPA versus 11% receiving oral NEPA; the most common (in $\geq 2\%$ of patients) was constipation (iv. NEPA: 6%; oral NEPA: 6%). No serious TRAEs or deaths were reported; one iv. NEPA patient experienced a possible TRAE (increased hepatic enzymes), which led to discontinuation. Importantly, no infusion site reactions related to iv. NEPA administration were reported. Overall, there was no increase in incidence rates of total or individual AEs across cycles 1–4, whether treatment related or not. There was no indication of increased cardiac safety concerns with iv. or oral NEPA after the first or subsequent cycles of HEC [84]. Even though the Schwartzberg 2018 study was not designed or powered to compare efficacy between the two formulations, both iv. and oral NEPA demonstrated efficacy at preventing CINV. Overall CR rates for cycle 1 were 77 and 84%, and no-emesis rates were 84 and 89% for iv. and oral NEPA, respectively. Similar efficacy between the NEPA formulations in the non-AC HEC setting was also established in a *post hoc* analysis comparing efficacy data from the iv. NEPA safety Phase III study (N = 203) and pooled data from three oral NEPA pivotal trials (N = 823) showing an overall CR rate of 77 versus 80%, respectively [104]. The safety of iv. NEPA is currently being evaluated in a Phase IIIb study in patients receiving AC-based chemotherapy.

Conclusion

Advances in antiemetic research over the last decade have led to substantial improvements, especially for the prevention of vomiting in most patients. In recent years, clinicians' focus has shifted toward better control of nausea and enhancing the well being and QoL of their patients receiving chemotherapy. Evidence points to a link between improved nausea and vomiting control, and a benefit in QoL and overall survival of cancer patients [8,9]. Suboptimal

CINV control can be multifactorial, but likely occurs as a consequence of inadequate adherence by physicians to current antiemetic guideline recommendations, and to the prescribed antiemetic regimens by patients; therefore, strategies that improve clinicians' and patients' adherence may prove valuable at increasing CINV control and ultimately improving the QoL and clinical outcomes of cancer patients.

NEPA is the first and only oral combination antiemetic that, by targeting two critical emetic pathways in a single capsule, offers easy and convenient CINV prophylaxis; it is now also available in an iv. form. NEPA offers effective 5-day long-lasting CINV control, particularly of nausea, which has proved elusive with other antiemetics.

The compatibility between the PK profiles of the two components, netupitant and palonosetron, as the oral fixed combination NEPA, provides an administration convenience that may reduce potential dosing mistakes by patients and increase antiemetic treatment adherence. This has the potential to facilitate completion of chemotherapy as planned, which could ultimately improve the overall survival of cancer patients.

The administration convenience of oral NEPA may also be enhanced on the day of dosing. Currently administered as a convenient single dose, approximately 60 min prior to chemotherapy on day 1, recent PK/PD modeling studies suggest it may be possible to administer NEPA closer to the time of chemotherapy initiation without negatively affecting antiemetic efficacy [68,69]. Clinical validation of this point is still needed.

The available data suggest that NEPA in its new iv. formulation has a safety profile comparable with that of oral NEPA. This iv. formulation could further improve the convenience of NEPA by offering an additional mode of administration for healthcare professionals that ensures patient adherence, provide an alternative to cancer patients who are unable to swallow oral medications, and facilitate access to antiemetics on the basis of individual health plan variations.

In conclusion, selection of the most convenient antiemetic regimen that facilitates adherence to guideline recommendations is a valuable tool to improve CINV prophylaxis, and especially nausea control. NEPA, as an oral or iv. formulation, offers a simplified prophylactic antiemetic alternative that provides long-lasting effective control of nausea and vomiting, in addition to freedom of choice in route of administration for patients able or unable to tolerate an oral or iv. medication. Ultimately, antiemetic prophylaxis with NEPA may lead to QoL benefits to cancer patients undergoing emetogenic chemotherapy treatment.

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Executive summary

Chemotherapy-induced nausea & vomiting treatment landscape

- Despite recent advances in the development of new prophylactic antiemetics, chemotherapy-induced nausea & vomiting (CINV), and mostly nausea, is still not controlled in all patients, particularly in the delayed phase. Nonadherence to antiemetic guideline recommendations is, in part, responsible for suboptimal CINV control.
- Three main drug classes constitute the antiemetic armamentarium: neurokinin-1 receptor antagonists (NK₁RAs), 5-hydroxytryptamine-3 (5-HT₃)RAs and steroids (mainly dexamethasone [DEX]).

Antiemetic guidelines

- Evidence-based antiemetic guidelines recommend a three-drug regimen with an NK₁RA, a 5-HT₃RA and DEX for prophylaxis of CINV associated with highly emetogenic chemotherapy (HEC; including anthracycline-cyclophosphamide) and carboplatin-based regimens, and for selected patients receiving moderately emetogenic chemotherapy (MEC).

Netupitant/palonosetron

- NEPA is the first and only fixed combination antiemetic, composed of the NK₁RA netupitant and the 5-HT₃RA palonosetron. Thus, NEPA targets two critical pathways associated with CINV in a single dose administered 60 (oral NEPA) or 30 min (intravenous [iv.] NEPA) before chemotherapy.
- Oral NEPA (netupitant 300 mg/palonosetron 0.50 mg) is approved in combination with DEX for the prevention of acute and delayed CINV associated with HEC and MEC.
- Intravenous NEPA (fosnetupitant 235 mg/palonosetron 0.25 mg) is approved in combination with DEX for the prevention of acute and delayed CINV associated with HEC.

NEPA pharmacokinetics/pharmacodynamics

- Netupitant is a highly selective NK₁RA that binds with high affinity to the NK₁ receptors in the striatum, with a long half-life of approximately 100 h. Palonosetron is a pharmacologically and clinically distinct second-generation 5-HT₃RA with a long half-life of approximately 40 h.
- Netupitant and palonosetron show complementary pharmacokinetic profiles, supporting their combination in NEPA. The dose of DEX is reduced when co-administered with NEPA.
- Fosnetupitant is rapidly converted to netupitant. In iv. NEPA, netupitant and palonosetron pharmacokinetic profiles are similar to those observed for oral NEPA.

NEPA: antiemetic efficacy

- Oral NEPA plus DEX provides superior CINV control compared with oral palonosetron plus DEX during the acute and delayed phases following single and multiple cycles of HEC and MEC, and significantly improves nausea control and quality of life of patients.
- Oral NEPA plus DEX administered only on the day of chemotherapy is noninferior to 3-day oral aprepitant-granisetron plus DEX in CINV control following HEC.

NEPA: safety

- NEPA is well tolerated, with a safety profile consistent with that expected for NK₁ and 5-HT₃RAs.
- Intravenous NEPA is well tolerated, with a safety profile similar to that of oral NEPA, and with no injection site reactions associated with iv. NEPA.

NEPA: convenience of dosing

- NEPA offers simple and convenient antiemetic prophylaxis by: reducing the number of doses of antiemetics; reducing the frequency of dosing; being administered immediately before chemotherapy, either orally or as an iv. infusion.
- In conclusion, NEPA is a valuable option to improve adherence to antiemetic guidelines by clinicians and patients for ultimate CINV control.

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