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Symptom Management and Supportive Care

A Pragmatic Study Evaluating NEPA Versus Aprepitant for Prevention of Chemotherapy-Induced Nausea and Vomiting in Patients Receiving Moderately Emetogenic Chemotherapy

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Chemotherapy-induced nausea and vomiting • Netupitant • Palonosetron • Aprepitant • NEPA

Abstract

Background. Neurokinin (NK) 1 receptor antagonists (RAs), administered in combination with a 5-hydroxytryptamine-3 (5-HT_3) RA and dexamethasone (DEX), have demonstrated clear improvements in chemotherapy-induced nausea and vomiting (CINV) prevention over a 5-HT_3RA plus DEX. However, studies comparing the NK_1RAs in the class are lacking. A fixed combination of a highly selective NK_1RA, netupitant, and the 5-HT_3RA, palonosetron (NEPA), simultaneously targets two critical antiemetic pathways, thereby offering a simple convenient antiemetic with long-lasting protection from CINV. This study is the first head-to-head NK_1RA comparative study in patients receiving anthracycline cyclophosphamide (AC) and non-AC moderately emetogenic chemotherapy (MEC).

Materials and Methods. This was a pragmatic, multicenter, randomized, single-cycle, open-label, prospective study designed to demonstrate noninferiority of single-dose NEPA to a 3-day aprepitant regimen in preventing CINV in chemotherapy-naive patients receiving AC/non-AC MEC in a real-life setting. The primary efficacy endpoint was complete response (no emesis/no rescue) during the overall (0–120 hour) phase. Noninferiority was achieved if the lower limit of the 95% confidence interval (CI) of the difference between NEPA and the aprepitant group was greater than the noninferiority margin set at −10%.

Results. Noninferiority of NEPA versus aprepitant was demonstrated (risk difference 9.2%; 95% CI, −2.3% to 20.7%); the overall complete response rate was numerically higher for NEPA (64.9%) than aprepitant (54.1%). Secondary endpoints also revealed numerically higher rates for NEPA than aprepitant.

Conclusion. This pragmatic study in patients with cancer receiving AC and non-AC MEC revealed that a single dose of oral NEPA plus DEX was at least as effective as a 3-day aprepitant regimen, with indication of a potential efficacy benefit for NEPA. ***The Oncologist*** 2021;26:e1870–e1879

Implications for Practice: In the absence of comparative neurokinin 1 (NK_1) receptor antagonist (RA) studies, guideline committees and clinicians consider NK_1RA agents to be interchangeable and equivalent. This is the first head-to-head study comparing one NK_1RA (oral netupitant/palonosetron [NEPA]) versus another (aprepitant) in patients receiving anthracycline cyclophosphamide (AC) and non-AC moderately emetogenic chemotherapy. Noninferiority of NEPA versus the aprepitant regimen was demonstrated; the overall complete response (no emesis and no rescue use) rate was numerically higher for NEPA (65%) than aprepitant (54%). As a single-dose combination antiemetic, NEPA not only simplifies dosing but may offer a potential efficacy benefit over the current standard-of-care.

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Introduction

Use of combinations of antiemetic agents has revolutionized supportive care for cancer patients by dramatically improving prevention of chemotherapy-induced nausea and vomiting (CINV) for patients undergoing emetogenic chemotherapy [1]. CINV, and in particular emesis, can now be prevented in the majority of patients when guideline-recommended antiemetic prophylaxis is administered [2, 3]. Consequently, the quality-of-life of patients with cancer is improved and patients are able to continue their chemotherapy without dose reductions or disruption [1].

Evidence-based antiemetic guidelines, whether international (i.e., American Society of Clinical Oncology [4] or Multinational Association of Supportive Care in Cancer [MASCC]/European Society for Medical Oncology [ESMO]) [5] or national (e.g., National Comprehensive Cancer Network [NCCN]) [6], all consistently recommend coadministration of a combination regimen consisting of a neurokinin-1 (NK_1) receptor antagonist (RA), 5-hydroxytryptamine-3 ($5\text{-}HT_3$) RA and a corticosteroid, such as dexamethasone (DEX) ($\pm$ olanzapine) for patients receiving highly emetogenic chemotherapy (HEC), including anthracycline/cyclophosphamide (AC)-based regimens. NCCN guidelines also recommend this "triple" combination in the moderately emetogenic chemotherapy (MEC) setting for patients at higher emetic risk or for whom previous $5\text{-}HT_3$ RA plus DEX treatment has failed.

Aprepitant was the first NK_1 RA approved, with numerous studies establishing superior efficacy when used in conjunction with a $5\text{-}HT_3$ RA plus DEX over the "double" combination of a 5-HT $_3$ RA plus DEX in the cisplatin-based HEC [7–9] and AC [10] settings. Subsequent alternative formulations (i.e., fosaprepitant, intravenous [IV] aprepitant/HTX-019) or agents (i.e., rolapitant) were approved based on demonstrating pharmacokinetic bioequivalence [11] or noninferiority [12] to the oral formulation or by similarly demostrating an incremental benefit of the NK_1 RA triple regimen over a $5\text{-}HT_3$ RA plus dexamethasone [13]. As was the case with aprepitant, these registration studies occurred primarily in the HEC settings [12–14], with comparative studies evaluating one NK_1 RA regimen versus another lacking.

Netupitant/palonosetron (NEPA) is the only oral fixed combination antiemetic agent developed and uniquely comprises a highly selective NK_1 RA, netupitant (300 mg) and the clinically [15] and pharmacologically [16] distinct $5\text{-}HT_3$ RA, palonosetron (0.5 mg). The simultaneous targeting of two critical antiemetic pathways, in unison with the single-dose administration, offers a simpler convenient antiemetic with long-lasting protection from CINV. Consistent with the development of other NK_1 RAs, pivotal registration studies for the U.S. and Europe demonstrated superiority of NEPA plus DEX over palonosetron plus DEX in preventing CINV following both cisplatin- [17] and AC-based chemotherapy [18]. NEPA also showed sustained efficacy over multiple cycles in both HEC and MEC settings [19, 20].

For approval in China, a regulatory requirement mandated a comparison of NEPA + DEX to an aprepitant triple regimen. The first head-to-head trial comparing one NK_1 RA to another was conducted in patients receiving cisplatin-based HEC [21]. This study demonstrated noninferiority of NEPA to an aprepitant (APR)/granisetron regimen for the primary endpoint of overall (0–120 hours) complete response (no emesis and no rescue use), with outcomes for secondary efficacy endpoints favoring NEPA.

A follow-up head-to-head comparative study (NCT03831633) was subsequently conducted in France, expanding on the existing data set for NEPA by exploring NEPA versus an aprepitant standard-of-care (SoC) regimen in the AC/non-AC MEC setting in real-world clinical practice. The Association Francophone des Soins Oncologiques de Support (AFSOS) antiemetic guidance [22] in France suggests that an NK_1 RA regimen be administered prophylactically in both the HEC and MEC settings. Herein are described the results of this first head-to-head NK_1 RA comparative study in the AC/non-AC MEC setting, designed as a pragmatic study with an objective to demonstrate noninferiority of single-dose NEPA to a 3-day aprepitant SoC regimen in preventing CINV in patients receiving AC/non-AC MEC in a real-life setting.

Materials and Methods

Study Design

This was a pragmatic, multicenter, randomized, single-cycle, open-label, parallel group prospective study, conducted at 30 enrolling sites in France between November 2018 and October 2019. The trial protocol was approved by an independent ethics committee and all patients provided written informed consent prior to initiation of any study treatment. The study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice and the Declaration of Helsinki. This trial was registered with ClinicalTrials.gov with identifier NCT03831633.

Patients

Eligible patients were male or female, ≥18 years, naive to chemotherapy, and scheduled to receive their first course of AC-based chemotherapy or MEC for treatment of a histologically or cytologically confirmed solid malignant tumor. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0–2. Patients were eligible if they were scheduled to receive prevention of CINV with either NEPA or aprepitant (the SoC in France). Patients were ineligible if they were pregnant or breastfeeding or if they had any hypersensitivity to active substances, excipients, or other ingredients of NEPA or aprepitant.

Treatment

Patients who met the inclusion and exclusion criteria were randomly assigned (1:1) to receive either NEPA or aprepitant treatment, both in conjunction with DEX prior to chemotherapy on day 1. Randomization was stratified by chemotherapy (AC and non-AC MEC).

NEPA was administered as a single oral capsule approximately 1 hour prior to chemotherapy on day 1 only, whereas oral aprepitant 125 mg was administered approximately 1 hour prior to chemotherapy and also once daily (80 mg) on days 2 and 3. Per protocol intravenous ondansetron 8 mg was the 5-HT_3 RA to be administered in conjunction with aprepitant prior to chemotherapy on day 1. Dexamethasone (8 mg daily) was to be continued on days 2–4 in both groups. Randomization used an interactive web response system; treatment was initiated on the day of randomization.

Assessments

From the start of chemotherapy on day 1 until day 6, each patient completed a diary, capturing information pertaining to emetic episodes, severity of nausea, and concomitant medications taken. An emetic episode was defined as any episode of vomiting or retching or combined vomiting and retching. Severity of nausea was evaluated on a daily basis using a 100-mm horizontal visual analog scale (VAS). The left end of the scale (0 mm) was labeled as "no nausea," and the right end of the scale (100 mm) was labeled as "extremely strong nausea."

The primary efficacy endpoint was complete response (no emesis and no rescue medication) during the overall (0–120 hours) phase following initiation of chemotherapy.

Key secondary efficacy endpoints were complete response during the acute (0–24 hours) and delayed (>24–120 hours) phases. Additional secondary endpoints included no emesis and no rescue use rates and proportion of patients with no significant nausea (VAS score <25 mm) during the acute, delayed and overall phases. Safety was assessed primarily through collection of treatment-emergent adverse events.

Statistical Analysis

The full analysis set (FAS) population was defined as all randomized patients who received at least one dose of antiemetic treatment and chemotherapy and had a record of any data post randomization. Following the intent-to-treat principle, patients were assigned in the analyses to the group they were initially randomized. The as treated (AS) population included patients from the FAS population but they were assigned to the treatment group according to the study treatment they actually received. Although not permitted by study protocol, one patient received both study treatments; for the statistical analyses of the AS population, the patient was considered as receiving the SoC (aprepitant regimen). Patients in the AS population were reassigned to the correct stratum (AC or non-AC MEC) according to the chemotherapy that they actually received. The AS population was defined as the primary population for the primary efficacy endpoint (overall complete response); as a sensitivity analysis, complete response was also evaluated in the FAS population. The FAS population was the population analyzed for the secondary efficacy endpoints.

For the primary endpoint of overall complete response, the noninferiority of NEPA and the aprepitant regimen was demonstrated if the lower limit of the confidence interval (CI; two-sided 95% CI significance level) of the difference between NEPA and the aprepitant group in the proportion of patients with overall complete response was greater than −10%. In addition, the odds ratio estimates and associated 95% CIs were analyzed using a logistic regression model with stratification factor, age, and sex as covariates and no interaction. The 95% CI was obtained by applying the delta method for the computation of the SE of the difference in percentage. The probability of complete response to treatment was modeled using the logit link function.

It was planned in the protocol to test the noninferiority of NEPA in each of the AC and non-AC MEC subgroups by a sequential procedure (all patients → AC → non-AC). If noninferiority was demonstrated for overall complete response in the overall study population, then the AC population was to be evaluated; if noninferiority was demonstrated for AC, then the non-AC subgroup would have been tested as well. Based on this sequential procedure, the statistical testing was to stop if noninferiority was not demonstrated; however, post hoc analyses of noninferiority were performed to have a comprehensive picture of the results.

For the key and additional secondary efficacy endpoints, statistical analyses were carried out using the same methods described for the primary endpoint. The sample size in the study was based on the assumption of an overall complete response rate of approximately 78% in both treatment groups. The noninferiority margin was set at −10%. For a one-sided test of difference using a type I error of 0.025, a sample size of 426 total patients was needed to ensure 80% power; sample sizes of 168 patients in the AC and 258 patients in the non-AC MEC groups were predefined.

The number and proportion of patients who experienced treatment-emergent adverse events and treatment-related adverse events were listed and descriptively summarized by treatment group.

Results

Patient Population

A total of 430 patients were randomized ($n = 215$ to each treatment group). Seven patients were screened but not randomized because they did not meet inclusion criteria (Fig. 1). The FAS and AS populations had almost identical numbers of patients ($n = 187/188$ patients in the NEPA arm and $n = 186/185$ in the aprepitant arm, respectively). The main reasons for exclusion from the randomization groups were no administration of antiemetic treatment and lack of data after randomization.

Baseline characteristics were generally similar between the two treatment groups for all patients and also for the AC and non-AC MEC subsets (Table 1). The patient population included predominantly women with breast cancer in the AC subset and predominantly men in the non-AC MEC subset; gastric and lung cancer were the most common cancer types in the non-AC MEC group and oxaliplatin and carboplatin were the most commonly administered chemotherapy.

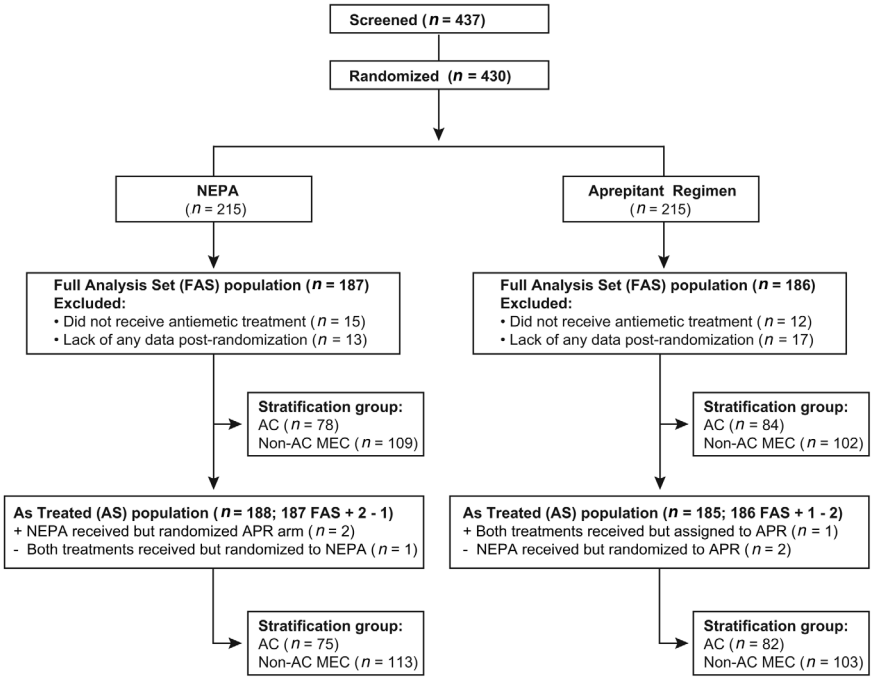

Figure 1. Consort diagram.
Abbreviations: AC, anthracycline cyclophosphamide; APR, aprepitant; MEC, moderately emetogenic chemotherapy; NEPA, netupitant/palonosetron.

Compliance to the NEPA regimen was 100%, whereas only 89% patients in the aprepitant arm received all three aprepitant doses (days 1–3). The majority of patients (91% in both groups) received a corticosteroid on day 1; however, only approximately half of patients took a corticosteroid on days 2 and 3 and approximately a third on day 4. Methylprednisolone was the most commonly used corticosteroid. Corticosteroid use was balanced between groups for the overall population as well as in the AC and non-AC MEC subsets. Table 2 presents an overview of the actual use antiemetics making up both treatment groups.

Efficacy

Complete Response, No Emesis, No Rescue Use, and No Significant Nausea in the Overall Study Population

The primary endpoint, defined as complete response (no emetic episode and no rescue medication) during the overall phase in the AS population, was numerically higher for NEPA (64.9%) compared with the aprepitant regimen (54.1%). Noninferiority was established with the lower limit of the 95% CI of the difference between NEPA and aprepitant at −2.3%, above the noninferiority margin of −10%; the risk difference of NEPA minus aprepitant was 9.2% (Fig. 2).

In the FAS population, noninferiority of NEPA and aprepitant was also reached with overall complete response rates of 65.2% and 53.8%, respectively, a difference of 9.7% and 95% CI (−1.6 to 21.0). The complete response rates during the acute and delayed phases (key secondary endpoints) were also numerically higher for NEPA (74.5% and 90.4%, respectively) than for the aprepitant regimen (68.1% and 85.9%, respectively); noninferiority between NEPA and aprepitant was established.

The secondary endpoint analyses of proportions of patients with no emesis, no rescue use, and no significant nausea in the FAS population revealed consistently numerically higher rates for NEPA than the aprepitant regimen, with the greatest difference (6%) seen during the overall phase for no rescue use and no significant nausea (Table 3).

Complete Response, No Emesis, No Rescue Use, and No Significant Nausea in the AC/Non-AC MEC Subsets

The results for the prespecified secondary endpoint analyses in the subsets of patients receiving AC or non-AC MEC are as follows.

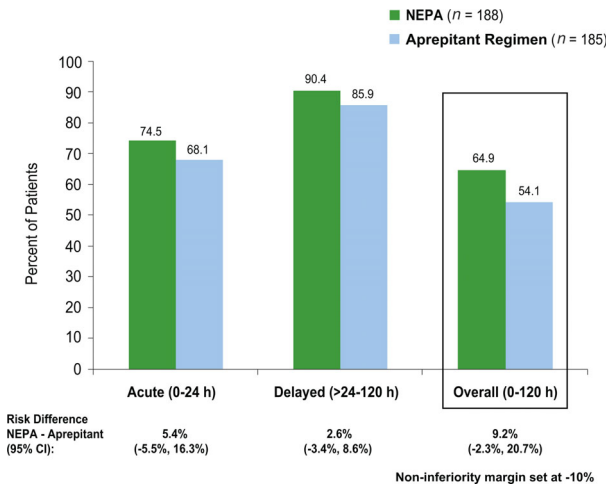

Figure 2. Complete response rates (overall study population, as treated population).
Abbreviations: CI, confidence interval; NEPA, netupitant/palonosetron.

Table 1. Patient baseline and disease characteristics (full analysis set population)

Characteristic	NEPA			Aprepitant regimen		
	AC ($n = 78$)	Non-AC MEC ($n = 109$)	Overall ($n = 187$)	AC ($n = 84$)	Non-AC MEC ($n = 102$)	Overall ($n = 186$)
Gender, *n* (%)						
Male	2 (2.6)	65 (59.6)	67 (35.8)	4 (4.8)	48 (47.1)	52 (28.0)
Female	76 (97.4)	44 (40.4)	120 (64.2)	80 (95.2)	54 (52.9)	134 (72.0)
Age, mean (SD), yr	56 (11)	66 (11)	62 (12)	54 (12)	64 (10)	59 (12)
<60, *n* (%)	46 (59.0)	30 (27.5)	76 (40.6)	53 (63.1)	36 (35.3)	89 (47.8)
≥60, *n* (%	32 (41.0)	79 (72.5)	111 (59.4)	31 (36.9)	66 (64.7)	97 (52.2)
Most common (≥5%) cancer types, *n* (%)						
Breast	73 (93.6)	4 (3.7)	77 (41.2)	81 (96.4)	5 (4.9)	86 (46.2)
Gastric	0	33 (30.3)	33 (17.6)	1 (1.2)	35 (34.3)	36 (19.4)
Lung	0	19 (17.4)	19 (10.2)	0	12 (11.8)	12 (6.5)
Most common AC/non-AC MEC, *n* (%)						
Cyclophosphamide	75 (96.2)	3 (2.8)	78 (41.7)	81 (96.4)	5 (4.9)	86 (46.2)
Epirubicin	66 (84.6)	0	66 (35.3)	74 (88.1)	2 (2.0)	76 (40.9)
Doxorubicin	10 (12.8)	0	10 (5.3)	7 (8.3)	1 (1.0)	8 (4.3)
Oxaliplatin	1 (1.3)	56 (51.4)	57 (30.5)	1 (1.2)	57 (55.9)	58 (31.2)
Carboplatin	1 (1.3)	46 (42.2)	47 (25.1)	1 (1.2)	35 (34.3)	36 (19.4)
Irinotecan	1 (1.3)	15 (13.8)	16 (8.6)	0	19 (18.6)	19 (10.2)

Abbreviations: AC, anthracycline cyclophosphamide; MEC, moderately emetogenic chemotherapy; NEPA, netupitant/palonosetron.

Table 2. Actual administration of study treatments (full analysis set population)

Characteristic	NEPA			Aprepitant regimen		
	AC ($n = 78$)	Non-AC MEC ($n = 109$)	Overall ($n = 187$)	AC ($n = 84$)	Non-AC MEC ($n = 102$)	Overall ($n = 186$)
NEPA received on day 1	78 (100)	109 (100)	187 (100)	NA	NA	NA
Aprepitant taken on:						
Day 1	NA	NA	NA	83 (98.8)	101 (99.0)	184 (98.9)
Day 2	NA	NA	NA	74 (88.1)	94 (92.2)	168 (90.3)
Day 3	NA	NA	NA	73 (86.9)	92 (90.2)	165 (88.7)
Type of 5-HT_3 RA used with aprepitant						
Ondansetron	NA	NA	NA	74 (88.1)	79 (77.5)	153 (82.3)
Granisetron	NA	NA	NA	5 (6.3)	8 (7.8)	13 (7.0)
Palonosetron	NA	NA	NA	1 (1.2)	7 (6.9)	8 (4.3)
None	NA	NA	NA	4 (4.8)	8 (7.8)	12 (6.5)
Corticosteroid taken on:						
Day 1	72 (92.3)	98 (89.9)	170 (90.9)	78 (92.9)	92 (90.2)	170 (91.4)
Day 2	46 (59.0)	47 (43.1)	93 (49.7)	51 (60.7)	46 (45.1)	97 (52.2)
Day 3	46 (59.0)	45 (41.3)	91 (48.7)	50 (59.5)	41 (40.2)	91 (48.9)
Day 4	30 (38.5)	34 (31.3)	64 (34.2)	30 (35.7)	29 (28.4)	59 (31.7)

Data are presented as *n* (%).
Abbreviations: 5-HT_3, 5-hydroxytryptamine-3; AC, anthracycline cyclophosphamide; MEC, moderately emetogenic chemotherapy; NA, not applicable; NEPA, netupitant/palonosetron; RA, receptor antagonist.

In the AC subset, noninferiority of NEPA and the aprepitant regimen was established for complete response during the delayed phase but not during the acute and overall phases. However, slightly higher complete response rates were seen for NEPA than aprepitant during all phases post-chemotherapy (Fig. 3). For the secondary efficacy endpoints, the most notable finding was a 13% difference favoring NEPA for rates of no significant nausea during both delayed and overall phases (Table 4).

Table 3. Secondary efficacy endpoints (all patients, full analysis set population)

Endpoint, *n* (%)	NEPA ($n = 187$)	Aprepitant regimen ($n = 186$)	Risk difference (95% CI)
No emesis			
Acute	152 (81.3)	145 (78.0)	1.9 (−7.4 to 11.3)
Delayed	169 (90.4)	164 (88.2)	1.0 (−5.1 to 7.2)
Overall	134 (71.7)	123 (66.1)	3.4 (−7.4 to 14.3)
No rescue use			
Acute	160 (85.6)	153 (82.3)	2.6 (−5.7 to 11.0)
Delayed	171 (91.4)	162 (87.1)	2.9 (−3.3 to 9.0)
Overall	144 (77.0)	129 (69.4)	6.2 (−3.6 to 16.0)
NSN			
Acute	139 (77.2)	136 (74.3)	1.8 (−8.5 to 12.2)
Delayed	127 (70.9)	115 (63.9)	4.8 (−5.9 to 15.5)
Overall	116 (64.8)	102 (56.4)	6.3 (−5.1 to 17.7)

Abbreviations: CI, confidence interval; NEPA, netupitant/palonosetron; NSN, no significant nausea.

In the non-AC MEC subset, noninferiority between treatment groups was established for complete response during the delayed phase as a preplanned analysis and during the acute and overall phases, as post hoc analyses. Numerically higher rates were seen for NEPA during all phases. Most notably, a difference of 12% was seen favoring NEPA during the overall phase (Fig. 3). For secondary efficacy endpoints, the most notable finding was an 8% difference favoring NEPA for no emesis rates during the overall phase (Table 4).

Safety

Overall, the proportion of patients with at least one treatment-emergent adverse event (AE) was comparable between the two treatment groups (supplemental online Table 1). The majority of AEs were grade 1 and 2; the serious AEs reported were consistent with those observed in patients with cancer undergoing chemotherapy. Consistent with the expected adverse events for these products, the most common treatment-related adverse events were constipation, headache, and hiccups. All treatment-related events in the NEPA arm were grade 1, whereas one event in the aprepitant arm was grade 1 and the other event was grade 2.

Discussion

There are currently multiple options of oral and IV NK_1 RAs for clinicians to choose from. Most clinical studies evaluating the efficacy of the NK_1 RAs have been conducted in the cisplatin HEC setting [7–9, 12, 13, 17, 23], with just a few studies in the AC [10, 18, 24] non-AC MEC [25], or combined AC/non-AC MEC settings [26, 27]. Consistent with the earlier results in the cisplatin-based HEC settings, a clear benefit of the NK_1 RA-containing triplet over the 5-HT_3 RA/DEX doublet was established in both the AC and non-AC MEC settings. Despite this there is no consensus across guidelines for use of NK_1 RAs in the non-AC MEC setting. All international and national guidelines are aligned with the recommendation of prophylactic administration of an NK_1 RA-containing regimen for patients receiving HEC or AC. However, similar alignment is not seen in the non-AC MEC setting, where only national guidelines (e.g., NCCN [6]) or guidances (e.g., AFSOS [22]) recommend an NK_1 RA.

Interestingly, ESMO (who traditionally partners with MASCC on antiemetic guidelines) recently issued a guidance regarding supportive care strategies during the Covid-19 pandemic [28]. In an effort to minimize urgent care/emergency department visits during this time, they recommended administration of a "generous antiemetic prophylactic regimen" including an NK_1 RA. They also suggested consideration of palonosetron as the 5-HT_3 RA because of its potential better efficacy in the delayed phase. This aligns with a recent large, retrospective study evaluating U.S. health records of 17,609 patients undergoing a variety of HEC and MEC. In this study, a substantial proportion of the avoidable acute care visits involved CINV [29].

In the absence of comparative studies, guideline committees and clinicians consider the NK_1 RA agents to be interchangeable and equivalent. This study is first head-to-head study comparing one NK_1 RA versus another in the AC/non-AC MEC setting.

For the primary endpoint of overall complete response, NEPA demonstrated noninferiority to the aprepitant SoC regimen. It is noteworthy that the overall complete response rate for NEPA (65%) exceeded that for aprepitant (54%) by >10%, a difference considered to be clinically significant and guideline-changing according to published information [5, 30]. Consistent with the results for the primary endpoint, noninferiority was also seen for complete response during the acute and delayed phases, with numerically higher rates shown for NEPA. These numerically higher rates for NEPA-treated patients in the overall study population were also consistently seen for the secondary efficacy endpoints, particularly during the overall phase post-chemotherapy.

For the stratification factors AC and non-AC MEC, only exploratory subgroup analyses were performed. However, it was reassuring that noninferiority was seen for treatment groups for complete response in the delayed phase and the

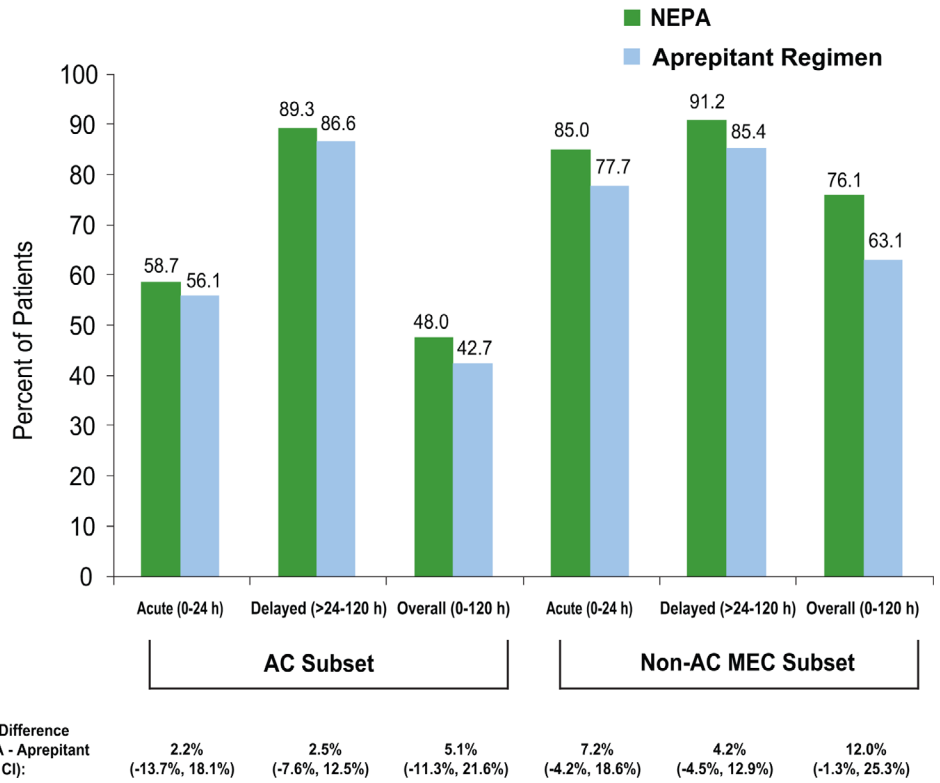

Figure 3. Complete response rates (AC and non-AC MEC subsets, full analysis set population).
Abbreviations: AC, anthracycline cyclophosphamide; CI, confidence interval; MEC, moderately emetogenic chemotherapy; NEPA, netupitant/palonosetron.

Table 4. Efficacy results for AC and non-AC MEC subsets (full analysis set population)

	AC			Non-AC MEC)		
Endpoint, *n* (%)	**NEPA (*n* = 78)**	**Aprepitant (*n* = 84)**	**Risk difference (95% CI)**	**NEPA (*n* = 109)**	**Aprepitant (*n* = 102)**	**Risk difference (95% CI)**
No emesis						
Acute	50 (64.1)	57 (67.9)	−4.5 (−19.3 to 10.3)	102 (93.6)	88 (86.3)	7.6 (−1.1 to 16.2)
Delayed	69 (88.5)	72 (85.7)	2.6 (−7.8 to 12.9)	100 (91.7)	92 (90.2)	0.1 (−8.3 to 8.4)
Overall	41 (52.6)	45 (53.6)	−2.0 (−17.9 to 13.9)	93 (85.3)	78 (76.5)	7.8 (−3.7 to 19.4)
No rescue use						
Acute	63 (80.8)	62 (73.8)	6.6 (−6.3 to 19.5)	97 (89.0)	91 (89.2)	−0.6 (−9.7 to 8.6)
Delayed	69 (88.5)	73 (86.9)	1.5 (−8.7 to 11.6)	102 (93.6)	89 (87.3)	5.1 (−3.1 to 13.3)
Overall	54 (69.2)	51 (60.7)	8.1 (−6.7 to 22.9)	90 (82.6)	78 (76.5)	5.0 (−6.7 to 16.8)
NSN						
Acute	46 (61.3)	51 (62.2)	−1.6 (−17.2 to 14.0)	93 (88.6)	85 (84.2)	5.0 (−4.9 to 14.9)
Delayed	51 (68.9)	45 (54.9)	13.2 (−2.4 to 28.9)	76 (72.4)	70 (71.4)	−1.3 (−14.8 to 12.2)
Overall	43 (58.1)	37 (45.1)	12.8 (−3.7 to 29.2)	73 (69.5)	65 (65.7)	1.7 (−12.4 to 15.7)

Abbreviations: AC, anthracycline cyclophosphamide; CI, confidence interval; MEC, moderately emetogenic chemotherapy; NEPA, netupitant/palonosetron; NSN, no significant nausea.

response rates for NEPA were slightly higher than those for aprepitant in the acute and overall phases. For secondary endpoints in the AC subset, NEPA showed the most substantial benefit controlling nausea during the delayed and overall phases (in which a 13% difference was seen).

Per the original sequential noninferiority analysis plan, the absence of noninferiority in the AC subset halted evaluation of noninferiority in the non-AC MEC group. The between-treatment comparisons in this non-AC subset for acute and overall complete response were ultimately explored as post hoc analyses. In this subset of patients receiving non-AC MEC, NEPA was noninferior to the aprepitant SoC regimen for complete response during the acute, delayed and overall phases, showing a substantial incremental benefit >12% in the overall

phase. Consistent with this, among the secondary endpoints assessed, NEPA showed the most sizeable benefit over the aprepitant regimen in emesis control in which an 8% difference was seen during the overall phase.

In addition to being the first study to evaluate two NK_1 RA regimens in the less well-studied AC/non-AC MEC setting, this study also expands on the NEPA data set by exploring its effectiveness outside the constraints of a rigorous controlled registration trial in a diverse population with cancer in a real-world setting. Pragmatic clinical trials are welcomed as a valuable means to obtaining the type of high-quality scientific evidence that has the potential to directly enhance health care decision-making [31].

It was impressive to note that the effectiveness of NEPA was in line with that seen for aprepitant [26] and rolapitant [27] triple regimens in randomized double-blind phase III trials in a similar mixed AC/non-AC MEC population. The overall complete response rate in the current pragmatic trial was 65% for NEPA, in contrast to 69% for both aprepitant and rolapitant regimens in each of the two historical controlled and blinded trials. The lower response rate (54%) for the aprepitant regimen in the current study is not entirely unexpected, as it is generally believed that randomized controlled clinical trials conducted with experienced investigators and highly selected patients may reveal benefits exceeding those expected in a real-world setting [32]. In addition, as might be predicted in clinical practice, there was not complete adherence to the multi-agent antiemetic regimen. Some patients (7%) in the aprepitant group did not receive a 5-HT_3 RA and approximately 10% did not take the prescribed follow-up doses of aprepitant on days 2 and 3. In addition, most patients in both groups only received a corticosteroid on day 1. This highlights the value of a simplified antiemetic regimen in a real-world setting.

Another example of reduced effectiveness in a real-world setting was shown in a recent prospective, observational trial exploring the effectiveness of aprepitant/fosaprepitant in a heterogenous population receiving predominantly cisplatin-based HEC or AC; an overall complete response rate of just 34% was seen in the AC subset [33]. A prior NEPA real-life noninterventional study was conducted in a large heterogenous population of 2,173 patients with various tumor types receiving a variety of HEC and MEC [34]. Reassuringly, the response rates seen in that study were consistent with those shown in the pivotal NEPA studies.

The safety profile of NEPA in the current study was in line with that reported in the NEPA pivotal trials and the product label and also consistent with that seen for the aprepitant regimen and in general the profile of adverse events in the NK_1 RA and 5-HT_3 RA classes.

Limitations of this study include that it was only a single-cycle study and an open-label design, which, although common in pragmatic trials, is susceptible to bias. As discussed previously, another limitation was the low power that was ultimately seen for detecting noninferiority in the AC subset. This led to the decision to run post hoc noninferiority testing that would have been done in a sequential manner had the AC group been better powered. Given the small number of patients in each of the AC and non-AC MEC subgroups the results for these subgroups should be interpreted with caution. Another potential limitation of this study was that there was a greater proportion (13%) of women receiving the aprepitant regimen than NEPA in the non-AC MEC subset. As female gender is a risk factor for CINV, this may have potentially put this subset at a greater risk for CINV.

It is important to note that the 5-HT_3 RAs were different in each of the treatment arms. Palonosetron is a fixed component of the NEPA formulation and ondansetron was selected as the 5-HT_3 RA in the aprepitant SoC regimen as it reflects the most commonly used 5-HT_3 RA in combination with aprepitant in France. As a pragmatic study, it was important that the NK_1 RA comparator regimen reflect what is standardly administered. Although these 5-HT_3 RAs differed, there is some evidence to suggest a potential benefit exists for NEPA versus aprepitant, even when administered with palonosetron. In the Gralla et al. NEPA registration trial [19], an aprepitant plus palonosetron arm was included as a safety reference; efficacy was assessed as a secondary endpoint. Although the study randomized patients at a 3:1 (NEPA:APR) ratio, the cycle 1 overall complete response rates were 80.6% (249/309) for NEPA versus 75.7% (78/103) for aprepitant/palonosetron.

Although the efficacy endpoints in this study mimicked those in NEPA and APR registration trials in the AC and non-AC MEC settings [10, 18, 26], future trials should include endpoints assessing complete control of nausea, as this remains the greatest unmet need for patients receiving emetogenic chemotherapy. Although NCCN antiemetic guidelines have acknowledged NEPA and rolapitant as effective agents for decreasing nausea, they also report that the addition of olanzapine is especially effective for reducing nausea [6]. Future trials should also explore the benefit of adding olanzapine to the NEPA and aprepitant regimens in order to optimize control of nausea, particularly in patients receiving AC chemotherapy, in whom control of delayed nausea is especially challenging.

NEPA, as a fixed combination antiemetic, simplifies dosing and eliminates the complexity of administering multiple agents and over multiple days (such as is the case with aprepitant SoC), thereby minimizing the potential for non-compliance with treatment. NEPA also uniquely targets two antiemetic pathways by combining an NK_1 RA (netupitant) with the pharmacologically/clinically distinct 5-HT_3 RA palonosetron, aligning it pertinently with the recent ESMO Covid-19 guidance.

Conclusion

This pragmatic real-world study in a heterogenous population of patients with cancer receiving AC and non-AC MEC revealed that a single dose of oral NEPA plus DEX was at least as effective as a 3-day aprepitant SoC regimen with evidence of a potential efficacy benefit, particularly in patients receiving non-AC MEC. As studies have shown that CINV risk can be increased by as much as 6-fold in subsequent cycles if poorly controlled in cycle one [35, 36], optimal prophylaxis prior to initiation of chemotherapy is critical.

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Disclosures

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