Individual Patient Data Meta-analysis of NEPA versus Aprepitant Antiemetic Regimens in the Prevention of Chemotherapy-induced Nausea and Vomiting (CINV)

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BACKGROUND

- While the unequivocal antiemetic benefits of adding an NK_1 receptor antagonist (RA) to a 5-HT_3 RA and dexamethasone (DEX) have been reported in numerous individual trials and confirmed in several systematic reviews and meta-analyses[1-3], only a few studies have been designed to compare the individual NK_1 RA agents.
- In the absence of conclusive data showing the superiority of one NK_1RA over another, antiemetic guidelines consider all NK_1 RAs equivalent and interchangeable.[4-7]

OBJECTIVE

- This individual patient data (IPD) analysis aimed to assess the efficacy of netupitant/fosnetupitant versus aprepitant/fosaprepitant-based regimens in preventing CINV in adult cancer patients undergoing highly (HEC) or moderately emetogenic chemotherapy (MEC) utilizing published comparative clinical trials.

METHODS

Search Strategy and Eligibility

- This research followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) and PRISMA-IPD guidelines.
- The Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE databases were searched for articles published between 2003, the year of aprepitant's approval, to April 1, 2022.
- Published randomized controlled trials (RCTs) that compared netupitant/fosnetupitant (NEPA) (in combination with palonosetron and DEX) with aprepitant/fosaprepitant (in combination with any 5-HT_3 RA agent and DEX) given as CINV prophylaxis to patients with cancer receiving HEC or MEC were included.

Data Analysis

- Patients treated with aprepitant and fosaprepitant with any 5-HT_3 RA were pooled (referred to as "aprepitant"-based regimens) and patients treated with oral and IV NEPA were combined ("NEPA"-based regimens).
- Efficacy analyses compared antiemetic treatments from cycle 1 in the intent-to-treat (ITT) total population for all emetogenic categories combined.
- A secondary analysis was conducted on a subpopulation of patients for whom an NK_1 RA regimen is indicated as primary antiemetic prophylaxis according to the most recent 2023 MASCC/ESMO antiemetic guidelines.[6,7] This subset included only patients receiving HEC (anthracycline cyclophosphamide (AC) and non-AC), carboplatin, or females < 50 years old receiving oxaliplatin (referred to as "guideline-based subset").
- Data was combined for assessment of complete response (no emesis and no use of rescue medication) and no significant nausea (defined as either a score of <25 mm on a 100 mm visual analog scale or no more than mild nausea on a likert scale) during the acute (0-24h), delayed (>24-120h), and overall (0-120h) phases post-chemotherapy. Daily rates of breakthrough CINV (i.e., inverse of complete response) were also compared.
- A two-step approach consisting of analysis of each single trial (1st step) followed by the combination of individual study estimates (2nd step) resorting to a weighted average method implemented using SAS Mixed Procedure was used.[8] Risk ratios (RR) and the random effect model was used to combine outcomes across studies. Two-tailed 95% confidence intervals (95% CI) with associated 2-sided p-values were calculated for RR on the pooled ITT population. Whenever feasible, missing data was imputed in the SAS ADaM datasets using Missing Value Treated as Failure techniques (MVTF).

RESULTS

Included Studies

- A total of 204 articles were identified from the database search. After duplicate removal and removal for other reasons (such as abstracts/incomplete manuscripts), 61 articles were screened and assessed for eligibility. Of these, 54 were excluded for various reasons (eg, not RCTs, not head-to-head comparisons of aprepitant and NEPA), ultimately leaving six studies (with seven publications) in this IPD meta-analysis.[9-15]
- All six studies were high-quality randomized studies, five of which were blinded[9-14] and one of which was an open-label pragmatic study at 30 centers in France[15]. Four studies included patients receiving non-AC HEC[9-12], two studies included AC[14,15] and two studies included MEC[10,15].

Patient Demographics

- A total of 2,767 patients were included in this IPD meta-analysis.
- The majority of patients were male and the mean age was 58. Most (81%) patients received HEC and about two-thirds (68%) received the oral formulations of NEPA and aprepitant (**Table 1**).

Table 1. Patient Demographics and Chemotherapy (All Patients)

	NEPA (n=1486)	Aprepitant (n=1281)	All Patients (N = 2767)
Age (mean ± SD, years)	**58.5** (±10.7)	**58.3** (±11.0)	**58.4** (±10.9)
Sex			
Female	**596** (40.1%)	**503** (39.3%)	**1099** (39.7%)
Male	**890** (59.9%)	**778** (60.7%)	**1668** (60.3%)
Most Common Chemotherapy Agents			
Highly Emetogenic	**1142** (76.9%)	**1012** (86.0%)	**2244** (81.1%)
Cisplatin	**1011** (68.0%)	**966** (75.4%)	**1977** (71.4%)
Anthracycline Cyclophosphamide	**129** (8.7%)	**133** (10.4%)	**262** (9.5%)
Moderately Emetogenic*	**344** (23.1%)	**179** (14.0%)	**523** (18.9%)
Carboplatin	**191** (12.6%)	**86** (6.7%)	**277** (10.0%)
Oxaliplatin	**103** (6.9%)	**77** (6.0%)	**180** (6.5%)
Irinotecan	**22** (1.5%)	**20** (1.6%)	**42** (1.5%)
Doxorubicin	**33** (2.2%)	**7** (0.5%)	**40** (1.4%)
Chemotherapy Naïve	**1481** (99.7%)	**1281** (100%)	**2762** (99.8%)
Chemotherapy Non-naïve	**5** (0.3%)	**0**	**5** (0.2%)
Most Common Cancer Types			
Lung	**734** (49.4%)	**620** (48.4%)	**1354** (48.9%)
Breast	**176** (11.8%)	**153** (11.9%)	**329** (12.0%)
Head & Neck	**168** (11.3%)	**142** (11.1%)	**310** (11.2%)
Ovarian	**63** (4.2%)	**51** (4.0%)	**114** (4.1%)
Colon/Colorectal	**66** (4.4%)	**38** (3.0%)	**104** (3.8%)
Other	**279** (18.8%)	**277** (21.6%)	**556** (20.1%)
Antiemetic Regimen			
IV NEPA	**443** (29.8%)	**0**	**443** (16.1%)
Oral NEPA	**1043** (70.2%)	0	**1043** (37.7%)
Fosaprepitant (IV)	**0**	**442** (34.5%)	**442** (16.0%)
Aprepitant (oral)	**0**	**839** (65.5%)	**839** (30.3%)

*Patients who received more than one MEC agent are included with each agent

Efficacy Outcomes

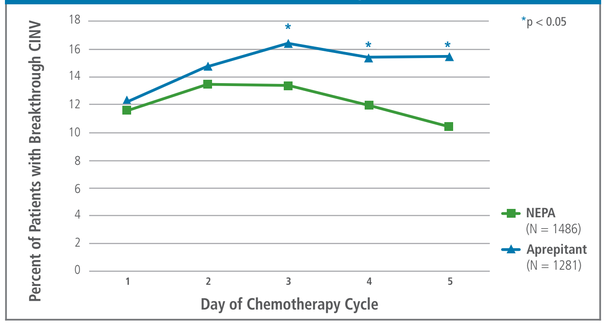
All Patients

- A significantly higher proportion of patients treated with NEPA than those who received aprepitant experienced complete response during the delayed and overall phases following chemotherapy (**Table 2**). This significant difference was also seen in daily rates of breakthrough CINV on Days 3, 4 and 5 where NEPA-treated patients experienced significantly less breakthrough symptoms than aprepitant-treated patients (**Table 2 and Figure 1**).
- Similar results were seen for the endpoint of no significant nausea, where significantly higher rates were also seen for NEPA over aprepitant during the delayed and overall phases as well as on individual Days 3, 4 and 5 (**Table 2**).

Table 2. Proportions of Patients Experiencing Complete Response and No Significant Nausea (All Patients in the ITT Population)

Time Point	NEPA (n=1486)	Aprepitant (n=1281)	Risk Ratio	Two-Tailed 95% CI	P-value
Complete Response					
Acute (Day 1)	1314 (88.4%)	1124 (87.7%)	1.008	(0.985, 1.031)	0.4865
Day 2 (25-48 h)	1285 (86.5%)	1091 (85.2%)	1.006	(0.979, 1.035)	0.6560
Day 3 (49-72 h)	1287 (86.6%)	1069 (83.5%)	1.029	(1.001, 1.058)	**0.0408**
Day 4 (73-96 h)	1307 (88%)	1083 (84.5%)	1.037	(1.010, 1.065)	**0.0072**
Day 5 (97-120 h)	1331 (89.6%)	1083 (84.5%)	1.057	(1.028, 1.087)	**0.0001**
Delayed (25-120 h)	1159 (78%)	931 (72.7%)	1.054	(1.011, 1.098)	**0.0125**
Overall (0-120 h)	1114 (75%)	900 (70.3%)	1.050	(1.005, 1.097)	**0.0300**
No Significant Nausea					
Acute (Day 1)	1332 (89.6%)	1139 (88.9%)	1.007	(0.978, 1.036)	0.6551
Day 2 (25-48 h)	1301 (87.6%)	1102 (86%)	1.013	(0.986, 1.040)	0.3590
Day 3 (49-72 h)	1306 (87.9%)	1074 (83.8%)	1.039	(1.010, 1.069)	**0.0074**
Day 4 (73-96 h)	1327 (89.3%)	1098 (85.7%)	1.044	(1.017, 1.072)	**0.0015**
Day 5 (97-120 h)	1326 (89.2%)	1096 (85.6%)	1.037	(1.008, 1.066)	**0.0118**
Delayed (25-120 h)	1198 (80.6%)	973 (76%)	1.046	(1.008, 1.086)	**0.0189**
Overall (0-120 h)	1160 (78.1%)	939 (73.3%)	1.047	(1.006, 1.090)	**0.0240**

Figure 1. Daily Incidence of Breakthrough Emesis and/or Use of Rescue Medication (All Patients in the ITT Population)



Guideline-based Subset

Patients Receiving non-AC and AC HEC, Carboplatin and Oxaliplatin/Female/<50 years

- There were 2,532 patients in the subset for whom an NK_1 RA is recommended as primary prophylaxis by guidelines[6,7]
- Consistent with the results seen in all patients, significantly higher complete response and no significant nausea rates were seen for NEPA than for aprepitant during the delayed and overall phases and on individual Days 3, 4 and 5 (**Table 3**).

Table 3. Proportions of Patients Experiencing Complete Response and No Significant Nausea (Guideline-based Subset)

Time Point	NEPA (n=1339)	Aprepitant (n=1193)	Risk Ratio	Two-Tailed 95% CI	P-value
Complete Response					
Acute (Day 1)	1185 (88.5%)	1053 (88.3%)	1.011	(0.987, 1.035)	0.3875
Day 2 (25-48 h)	1151 (86.0%)	1015 (85.1%)	1.006	(0.977, 1.035)	0.7081
Day 3 (49-72 h)	1160 (86.6%)	998 (83.7%)	1.030	(1.001, 1.060)	**0.0418**
Day 4 (73-96 h)	1182 (88.3%)	1013 (84.9%)	1.037	(1.009, 1.065)	**0.0090**
Day 5 (97-120 h)	1205 (90.0%)	1006 (84.3%)	1.063	(1.033, 1.094)	**<.0001**
Delayed (25-120 h)	1039 (77.6%)	870 (72.9%)	1.051	(1.007, 1.096)	**0.0220**
Overall (0-120 h)	998 (74.5%)	842 (70.6%)	1.047	(1.001, 1.096)	**0.0469**
No Significant Nausea					
Acute (Day 1)	1199 (89.5%)	1066 (89.4%)	1.007	(0.978, 1.037)	0.6490
Day 2 (25-48 h)	1171 (87.5%)	1025 (85.9%)	1.017	(0.989, 1.045)	0.2422
Day 3 (49-72 h)	1180 (88.1%)	1000 (83.8%)	1.043	(1.013, 1.074)	**0.0050**
Day 4 (73-96 h)	1198 (89.5%)	1021 (85.6%)	1.047	(1.019, 1.076)	**0.0010**
Day 5 (97-120 h)	1193 (89.1%)	1019 (85.4%)	1.039	(1.009, 1.069)	**0.0114**
Delayed (25-120 h)	1080 (80.7%)	906 (75.9%)	1.050	(1.009, 1.091)	**0.0155**
Overall (0-120 h)	1045 (78.0%)	878 (73.6%)	1.049	(1.006, 1.094)	**0.0245**

CONCLUSION

- These IPD meta-analysis findings indicate that NEPA-based regimens offer greater protection from CINV than aprepitant regimens, especially on Days 3-5 (days established as risk factors for CINV beyond 120h).

CONSIDERATIONS & IMPLICATIONS FOR PRACTICE

- These findings are aligned with a pooled analysis of three NEPA registration trials which showed that oral NEPA was more effective than the 3-day oral aprepitant regimen in preventing CINV during the delayed phase and on Days 3-5 post-cisplatin.[16]
- This large IPD analysis includes three additional studies and encompasses a more expansive population of patients including those receiving AC-based HEC and various MEC, including carboplatin and oxaliplatin which guidelines suggest warrant an NK_1 RA regimen.
- Interestingly, in both analyses the greatest incremental difference in efficacy was seen on Day 5 suggesting NEPA's benefit may continue beyond the delayed phase. In fact, two of the studies included in this IPD meta-analysis explored the efficacy out to 144h[15] and 168h[12] and showed netupitant[15]/fosnetupitant[12] (NEPA) regimens to be more effective at CINV prevention for this extended duration than aprepitant/fosaprepitant regimens.
- This differentiation could be due to pharmacological differences between NEPA and aprepitant including a longer elimination half-life[17,18] and extended receptor occupancy for NEPA.[19,20]
- These findings suggest that NEPA-based regimens may be particularly promising for managing the extended duration of CINV associated with emerging anticancer targeted therapies, such as antibody drug conjugates (ADCs).

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DISCLOSURE STATEMENT: Dr. Rudoph Navari reports no conflicts of interest.

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