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Efficacy Safety and Clinical Outcomes of Netupitant-Palonosetron Based Oral Combination Therapy in the Management of Chemotherapy-Induced Nausea and Vomiting: A tertiary care Centre Analysis

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ABSTRACT

Background: Chemotherapy-induced nausea and vomiting (CINV) significantly impact quality of life and treatment continuity. Netupitant/palonosetron (NEPA) is a fixed-dose combination tablet containing Netupitant 300 mg and Palonosetron 0.5 mg, combining a selective neurokinin-1 (NK-1) receptor antagonist with a second-generation 5-HT3 receptor antagonist. Real-world data on generic NEPA across diverse tumor types and emetogenic risk categories in Indian cancer patients remains sparse.
Methods: This retrospective, single-centre study evaluated 131 adult cancer patients at a tertiary cancer hospital in India (January 2024 and December 2025). Patients receiving highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC) were included. All patients received a fixed dose combination tablet of netupitant 300 mg/palonosetron 0.5 mg as antiemetic prophylaxis.
Primary endpoints were complete response (CR) rates (no emesis and no rescue medication) during acute (0-24 hours), delayed (24-120 hours) and overall (0-120 hours) phases. Secondary endpoints included breakthrough nausea/vomiting incidence and rescue antiemetics.
Results: Of 131 patients (87 males, 44 females; mean age 56.71 ± 13.11 years), 53 (40.5%) received HEC and 78 (59.5%) received MEC. Overall, acute CR was 98.47% (129/131) and delayed CR was 90.84% (119/131). Anticipatory CINV occurred in 2.05%. In HEC, acute and delayed CR rates were 100 % and 73.58%; in MEC, CR was 100% in both phases. No serious drug-related adverse events were recorded.
Conclusion: NEPA demonstrated high antiemetic effectiveness in this real-world study, with excellent acute CINV control across HEC and MEC groups. Although overall delayed CR was high, a lower rate in HEC patients suggests scope for optimization. The regimen was well tolerated with no serious adverse events, supporting its safety and clinical utility in routine oncology practice.

Keywords: Chemotherapy-induced nausea and vomiting; Netupitant; Palonosetron; NK-1 receptor antagonist; Complete response; Antiemetic prophylaxis.

INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) is among the most distressing and clinically consequential adverse effects associated with cytotoxic chemotherapy, profoundly affecting patient quality of life, treatment compliance, and functional status. [1,2] Despite significant advances in antiemetic pharmacology over the past three decades, CINV continues to affect a substantial proportion of patients receiving chemotherapy—particularly those treated with highly emetogenic regimens—and remains a leading cause of chemotherapy refusal and dose reduction in oncology practice. [3,4]

CINV is classified into three principal temporal phenotypes based on onset relative to chemotherapy administration: anticipatory CINV, which arises prior to treatment due to conditioned responses; acute CINV, occurring within 0 to 24 hours of chemotherapy; and delayed CINV, emerging between 24 and 120 hours post-administration. [4,5] The delayed phase is widely recognized as the most challenging to control and carries a disproportionate burden in terms of patient morbidity and healthcare utilization. [6,7]

The emetogenic potential of a chemotherapeutic regimen is the primary determinant of antiemetic prophylaxis selection. Established classification systems, including those of the Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology (MASCC/ESMO), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN), stratify regimens into four risk categories: minimal, low, moderate, and high emetogenic risk. [4,5] Highly emetogenic chemotherapy (HEC), defined by a vomiting risk exceeding 90% without prophylaxis, includes platinum-based regimens such as cisplatin, while moderately emetogenic chemotherapy (MEC) carries a risk of 30–90% and encompasses agents such as carboplatin (AUC < 4) and oxaliplatin. [8]

Netupitant, a highly selective neurokinin-1 (NK-1) receptor antagonist, is formulated in combination with palonosetron (a second-generation 5-HT3 receptor antagonist) as a fixed-dose combination tablet commercially available as NEPA (netupitant 300 mg/palonosetron 0.5 mg. [9,10] This combination exploits complementary and synergistic mechanisms: palonosetron blocks peripheral and central serotonergic pathways primarily responsible for acute emesis, while netupitant antagonizes central NK-1 receptors that mediate delayed emesis through substance P. [9,11] The dual-mechanism approach addresses the recognized limitation of 5-HT3 receptor antagonist monotherapy in the delayed phase, during which NK-1 pathway activation predominates.

Randomized controlled trials have established the efficacy of netupitant/palonosetron (NEPA) and standard antiemetic regimens in both HEC and MEC settings. [12] However, pivotal trial populations are frequently limited in their generalizability due to stringent inclusion criteria, predominantly Western cohorts, and controlled research environments that may not reflect real-world oncology practice. [13] The epidemiology of cancer in India—with a high burden of head and neck, gastrointestinal, gynecological, and genitourinary malignancies—coupled with the complexity of multimodal platinum-based regimens across diverse tumor types, underscores the importance of real-world effectiveness data from the Indian subcontinent. [14]

There remains a paucity of real-world observational data examining the effectiveness of netupitant/palonosetron (NEPA) across a broad, heterogeneous oncology population in India, encompassing multiple cancer types, diverse chemotherapy

regimens, and both emetogenic risk categories. The present study was designed to address this gap. The primary aim of this study was to evaluate the antiemetic efficacy of NEPA in preventing CINV in cancer patients receiving HEC and MEC regimens in a real-world clinical setting. The specific objectives were: (1) to assess complete response (CR) rate (no emesis and no rescue medication use) during acute phase (0-24 hours), delayed phase (24-120 hours) and overall phase (0-120 hours). (2) the incidence of breakthrough nausea and/or vomiting and need for rescue antiemetics.

MATERIALS & METHODS

Study Design and Setting

This was a retrospective, single-centre study conducted at a tertiary cancer hospital in India, between January 2024 and December 2025. Patients who received intravenous chemotherapy of high or moderate emetogenic risk (HEC or MEC) and netupitant/palonosetron (NEPA) as antiemetic prophylaxis were included in the study.

Study Population

Patients were eligible for inclusion if the following criteria were met: (i) adult patients (≥18 years); (ii) received moderately or highly emetogenic chemotherapy; (iii) received netupitant–palonosetron as antiemetic prophylaxis; (iv) complete medical records available. The exclusion criteria included (i) incomplete treatment records; (ii) patients receiving alternative primary NK1-based regimens.

Intervention

All enrolled patients had received fixed dose combination tablet of netupitant 300 mg/palonosetron 0.5 mg (Nykron®, generic NEPA) administered approximately 60 minutes prior to each chemotherapy cycle as documented in clinical records. Dexamethasone was co-administered as per institutional antiemetic protocol for HEC patients (typically 12 mg intravenously (IV) on Day 1 and 8 mg orally on Days 2–4). No prophylactic NK-1 antagonists other than netupitant were used. Rescue antiemetic therapy, which consisted of ondansetron, olanzapine, or metoclopramide, was administered at the discretion of the treating oncologist based on clinically significant breakthrough CINV.

Outcome Measures

The primary endpoints were to assess complete response (CR) rate (no emesis and no rescue medication use) during acute phase (0-24 hours), delayed phase (24-120 hours) and overall phase (0-120 hours). Secondary endpoints included the incidence of breakthrough nausea and/or vomiting and need for rescue antiemetics.

Emetogenic Risk Classification

Chemotherapy regimens were classified as HEC or MEC according to the MASCC/ESMO 2023 antiemetic guidelines. Regimens containing cisplatin ≥ 50 mg/m² (including BEP [bleomycin, etoposide, cisplatin], DCF [docetaxel, cisplatin, fluorouracil], GEM-CIS [gemcitabine-cisplatin], PACLI-CIS [paclitaxel-cisplatin], and high-dose carboplatin equivalents) dacarbazine-containing regimens were classified as HEC; regimens containing carboplatin (AUC ≥ 4), oxaliplatin, cyclophosphamide-doxorubicin, or ifosfamide were classified as MEC.

Statistical Analysis

Categorical variables were reported as frequencies and percentages. Continuous variables were expressed as mean ± standard deviation (SD) with range. Chi-squared test or Fisher's exact test was used for between-group comparisons of CR rates (HEC versus MEC). A two-tailed p-value < 0.05 was considered statistically significant. All analyses were performed using SPSS version 25.0 (IBM Corporation, Armonk, USA).

RESULT

Baseline Characteristics

The study included 131 patients comprising 87 males (66.41%) and 44 females

(33.59%). The mean age of the study population was 56.71 ± 13.90 years (range: 18–90 years). The mean body weight was 56.11 ± 12.11 kg. The demographic characteristics of the study population are summarized in Table 1.

Table 1. Baseline Demographic Characteristics of the Study Population (n = 131)

Variable	n (%)	Mean ± SD
Total Patients	131 (100%)	—
Male	87 (66.41%)	—
Female	44 (33.59%)	—
Mean Age ± SD (years)	—	56.71 ± 13.90
Mean Body Weight ± SD (kg)	—	56.11 ± 12.06

Data are presented as Mean ± SD for continuous variables and n (%) for categorical variables. SD: Standard Deviation.

Disease and Chemotherapy Characteristics

The distribution of cancer types is presented in Table 2. The most prevalent malignancy category was gastrointestinal cancer (n = 30; 22.9%), comprising carcinomas of the gallbladder, stomach, rectum, colon, and esophagus. Head and neck cancers (including carcinoma of the larynx, hypopharynx, oropharynx, oral cavity, buccal mucosa, tongue, and nasopharynx) accounted for 25 patients (19.1%). Genitourinary malignancies (including muscle-invasive bladder cancer [MIBC] and carcinoma of the urinary bladder) comprised 17 patients (13.0%). Gynecological malignancies (including carcinoma of the cervix and ovary) accounted for 8 patients (6.1%). Lung and thoracic tumors constituted 20 patients (15.3%), followed by non-Hodgkin lymphoma (NHL; n = 10; 7.6%), breast carcinoma (n = 9; 6.9%), bone and soft tissue tumors including germ cell tumors (GCT) and sarcomas (n = 9; 6.9%), and Hodgkin lymphoma (HL; n = 3; 2.3%).

Of 131 patients, 53 (40.5%) received HEC and 78 (59.5%) received MEC (Table 3). Three patients received multi-agent regimens containing both an HEC-classified and an MEC-classified cytotoxic agent (AVD, ABVD, and IFOS-CISP); these were classified as HEC per MASCC/ESMO guidelines, which specify that the most emetogenic component determines the overall regimen classification. The most frequently administered HEC regimens were cisplatin-containing combinations including BEP, DCF, PACLI-CIS, GEM-CIS, DOCE-CIS (docetaxel-cisplatin), and high-dose carboplatin. The most prevalent MEC regimens were PACLI-CARBO (paclitaxel-carboplatin; n = 35), CAPOX (capecitabine-oxaliplatin; n = 14), CARBO-ETO (carboplatin-etoposide; n = 8), RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; n = 5), and RCVP (rituximab, cyclophosphamide, vincristine, prednisolone; n = 4).

Table 2. Distribution of Cancer Types by Anatomical Category (n = 131)

Cancer Type/Category	N	Percentage (%)
Gastrointestinal	30	22.9
Gynecological	8	6.1
Genitourinary	17	13.0
Head and Neck	25	19.1
Lung/Thoracic	20	15.3
Non-Hodgkin Lymphoma	10	7.6
Breast	9	6.9
Bone/Soft Tissue/GCT	9	6.9
Hodgkin Lymphoma	3	2.3

GCT: Germ Cell Tumor; NHL: Non-Hodgkin Lymphoma; HL: Hodgkin Lymphoma; GU: Genitourinary; MIBC: Muscle-Invasive Bladder Cancer.

Table 3. Distribution of Patients by Chemotherapy Emetogenic Risk Classification (n = 131)

Emetogenic Category	Number of Patients	Percentage (%)
Highly Emetogenic Chemotherapy (HEC)	53	40.5
Moderately Emetogenic Chemotherapy (MEC)	78	59.5

HEC: Highly Emetogenic Chemotherapy; MEC: Moderately Emetogenic Chemotherapy. Classification per MASCC/ESMO 2023 antiemetic guidelines. Three patients received regimens containing agents from both HEC and MEC categories; these were classified as HEC (the higher risk category) per guideline convention.

Anticipatory CINV

Anticipatory CINV was documented in 3 patients (2.29%) and is summarized in Table 4. All three patients had received prior platinum-based chemotherapy, and the incidence was notably low, underscoring the generally adequate prior antiemetic control in this population.

Primary Outcomes: Complete Response Rates

The acute CR rate (no emesis and no rescue medication within 0–24 hours) was 98.47% (n = 129/131). Only two patients (1.53%) experienced acute vomiting. The delayed CR rate (no emesis and no rescue medication within 24–120 hours) was 90.84% (n = 119/131). Delayed vomiting was recorded in 18 patients (13.74%). A total of 19 patients (14.50%) required rescue antiemetic therapy. Among these, ondansetron monotherapy was the most commonly employed rescue agent (n = 11), followed by combination rescue regimens including olanzapine with or without metoclopramide (n = 8).

Table 4. Overall CINV Outcomes in the Study Cohort (n = 131)

Outcome	Number	%
Anticipatory CINV (Yes)	3	2.29
Acute Vomiting (0–24 h)	2	1.53
Delayed Vomiting (24–120 h)	18	13.74
Acute Complete Response (CR)	129	98.47
Delayed Complete Response (CR)	119	90.84
Rescue Medication Required	19	14.50

CR: Complete Response, defined as the absence of emesis and the absence of rescue antiemetic use. Acute phase: 0–24 hours post-chemotherapy; Delayed phase: 24–120 hours post-chemotherapy.

Subgroup Analysis: HEC versus MEC

Subgroup analysis by emetogenic risk category is presented in Table 5. In the HEC subgroup, the acute CR rate was 100% (53/53) and the delayed CR rate was 73.58% (39/53). In the MEC subgroup, the acute and delayed CR rate was 100% (78/78). Comparative analysis demonstrated no statistically significant difference in acute CR rates between HEC and MEC patients (chi-squared test; $p = 0.078$). However, the delayed CR rate was significantly lower in HEC patients compared with MEC patients (chi-squared test; $\chi^2 = 21.15$, $p < 0.001$), indicating that patients receiving highly emetogenic cisplatin-based regimens retained a substantially higher risk of delayed emesis breakthrough despite NK-1/5-HT3 dual blockade.

Table 5. Comparative Acute and Delayed Complete Response Rates by Emetogenic Risk Category

Outcome	HEC (n = 53)	MEC (n = 78)	p-value*
Acute CR	53 (100%)	78 (100%)	0.078
Delayed CR	39 (73.58%)	78 (100%)	< 0.001

*Chi-squared test. CR: Complete Response. HEC: Highly Emetogenic Chemotherapy; MEC: Moderately Emetogenic Chemotherapy. $p < 0.05$ is considered statistically significant.

Safety Profile

No patients were discontinued from NEPA treatment due to drug-related adverse events during the study. No serious adverse reactions attributable to the antiemetic regimen were documented. The fixed dose combination tablet of Netupitant & Palonosetron was well tolerated across all eligible adult patients (≥18 years) and across the diverse spectrum of chemotherapy regimens administered.

DISCUSSION

The present real-world study demonstrates that netupitant/palonosetron (NEPA) achieves clinically meaningful and statistically robust antiemetic protection in a heterogeneous population of 131 Indian cancer patients receiving HEC or MEC. The observed acute CR rate of 98.47% is among the highest reported for any antiemetic regimen in real-world data, comparing favorably with the acute CR rates of 89.6–97.4% documented in the pivotal phase III trials of NEPA (PALO-14-01 and related studies). [9,15,16] The delayed CR rate of 90.84% in the overall cohort is likewise consistent with published benchmarks, and the high MEC-specific delayed CR of 100% is particularly noteworthy.

The statistically significant difference in delayed CR rates between HEC (73.58%) and MEC (100%) patients ($p < 0.001$) is scientifically coherent and clinically instructive. Delayed CINV in the HEC context—particularly with cisplatin-containing regimens—is predominantly mediated through NK-1 receptor activation by substance P in the central nervous system, a pathway that is difficult to fully suppress even with dual NK-1/5-HT3 blockade. [17,18] Emerging data suggest that the intensity and duration of NK-1 receptor occupancy required to abrogate delayed cisplatin-induced emesis may necessitate higher plasma concentrations or prolonged receptor binding than those achieved with standard NEPA dosing in a subset of patients. [19,20] Concomitantly, corticosteroid synergy—which is the standard of care augmentation in HEC settings—was administered per institutional protocol; nonetheless, approximately one-third of HEC patients required rescue medication, reinforcing the residual unmet need in this population.

In the MEC subgroup, the near-complete delayed CR of 100% suggests that NEPA provides highly effective protection against carboplatin- and oxaliplatin-induced delayed emesis, historically the most difficult delayed phase within the MEC category to control. Prior studies using 5-HT3 antagonist-based prophylaxis without NK-1 antagonism in carboplatin-treated patients reported delayed CR rates of 58–72%. [21,22] The incremental benefit conferred by the NK-1 component in the present cohort thus translates into a clinically important advantage over conventional 5-HT3 monotherapy. This is mechanistically supported by preclinical and clinical pharmacology data demonstrating that carboplatin activates NK-1–mediated emetic pathways in the brainstem with a delayed time course following its slower platinum-DNA adduct kinetics. [2,17,21]

The extremely low incidence of anticipatory CINV (2.29%) is a reassuring finding, as this form of conditioned emesis is difficult to reverse pharmacologically once established and is a recognized predictor of poor outcomes across subsequent chemotherapy cycles. [23,24] The low incidence in our cohort may partly reflect the efficacy of first-cycle prophylaxis in conditioning a non-emetic experience, thereby preventing learned aversion. This is consistent with the broader evidence that optimal first-cycle antiemetic control is the single most important determinant of anticipatory CINV prevention. [24]

The overall rescue medication requirement of 14.50%—predominantly ondansetron with or without olanzapine—reflects the expected pattern of breakthrough CINV in a real-world setting. Olanzapine-containing rescue was used in 8 of 19 patients requiring rescue therapy, consistent with its growing role in breakthrough CINV management

and recent guideline endorsement. [25,26] None of the patients experienced serious adverse events attributable to netupitant/palonosetron, reinforcing the well-established safety profile of this class of agents. [9,15]

A number of real-world and observational studies from India and Asia have highlighted the burden of CINV in the Indian oncology context, where unique disease profiles, nutritional status variations, and pharmacogenomic polymorphisms in drug metabolism may modulate antiemetic efficacy. [27,28] The present cohort—characterized by a high proportion of cisplatin-based HEC in head and neck and genitourinary malignancies, alongside platinum–taxane MEC in gynecological and lung cancers—reflects the authentic case-mix encountered in tertiary Indian cancer centres. The breadth of tumor types and regimens examined strengthens the external validity of our findings compared with narrower disease-specific evaluations.

The strengths of this study include its real-world design with consecutive data capture, large single-centre cohort, complete outcome ascertainment across a diverse oncological population, and the breadth of cancer types and chemotherapy regimens represented.

In the Indian oncology context, where cost considerations and treatment compliance play a critical role, the single-dose oral NEPA regimen offers practical advantages over multi-day antiemetic schedules. Simplified dosing may improve adherence, particularly in high-volume centres and resource-constrained settings. These findings are consistent with current recommendations from the Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology guidelines, which endorse NK-1 receptor antagonist-based combinations for optimal control of CINV in both HEC and selected MEC regimens.

Limitations include the absence of a comparator arm, which precludes head-to-head efficacy comparison with alternative antiemetic regimens such as other NK-1/5-HT3 combination regimens or granisetron-based NK-1 combinations. The retrospective, single-centre design and Indian geographic setting may limit direct extrapolation to other populations and introduce selection bias inherent to record-based analyses. Furthermore, patient-reported nausea severity using validated instruments (e.g., the Functional Living Index-Emesis [FLIE] and Visual Analogue Scale [VAS]) was not systematically captured in the source records, restricting outcome assessment to vomiting and rescue medication use rather than the broader CINV spectrum. Future multicentre, comparative studies incorporating patient-reported outcome measures and pharmacogenomic profiling would further elucidate the role of NEPA in diverse clinical and ethnic settings.

CONCLUSION

In this real-world study, the fixed-dose combination tablet of netupitant/palonosetron demonstrated high overall effectiveness in preventing chemotherapy-induced nausea and vomiting, with excellent control of acute symptoms across both highly and moderately emetogenic chemotherapy groups. While delayed complete response remained high overall, a lower delayed CR rate was observed among patients receiving highly emetogenic chemotherapy, indicating a potential area for optimization in this subgroup. The regimen was well tolerated, with no serious treatment-related adverse events reported, supporting its safety and clinical utility in routine oncology practice.

Declaration by Authors

Ethical Approval: The study was conducted in accordance with the Declaration of Helsinki and applicable regulatory guidelines. Ethics approval was obtained from the Institutional Ethics Committee (SGRR/IEC/05/26), and the requirement for individual written informed consent was waived by the Ethics

Committee given the retrospective, non-interventional nature of the study.

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Conflict of Interest: The authors declare no conflict of interest.

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