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Generic Netupitant Plus Palonosetron and Dexamethasone for Prophylaxis of Chemotherapy-Induced Nausea and Vomiting (CINV) in Cancer Patients Receiving Highly or Moderately Emetogenic Chemotherapy: A Retrospective Study

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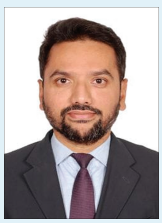
Abstract



Krishna Chaitanya Puligundla

Chemotherapy-induced nausea and vomiting (CINV) is a challenging adverse effect that is associated with deteriorating quality of life. Inhibiting neurokinin 1 and 5-hydroxytryptamine type 3 receptors involved in the major emesis pathways has significantly prevented CINV and is recommended as standard treatment in international antiemetic guidelines. This retrospective study was conducted to explore the efficacy of formulated netupitant (NE; 300 mg) and palonosetron (PA; 0.50mg) tablets with dexamethasone in patients receiving high and moderate emetogenic chemotherapy. A single dose of NE, PA, and dexamethasone was given 1 hour prior to the chemotherapy for 4 days. The key end-points were to assess complete response (CR), complete protection (CP), and complete control (CC) with no emesis, no nausea, and no use of rescue medication during acute (0–24 hours) and delayed phase (24–120 hours) of CINV. This study conducted on 212 patients showed overall rates of CR, CP, and CC as 97.5, 91.1, and 92.19%, respectively, in the acute phase and 95.09, 88.06, and 87.74% in a delayed phase. These patients underwent 1,387 cycles of chemotherapy involving both high emetogenic chemotherapy and moderate emetogenic chemotherapy regimens. A decrease in the rate of CR, CP, and CC from 93.47, 76.20, and 73.90% (acute phase) to 86.95, 69.67, and 67.37% (delayed phase) with highly emetogenic chemotherapy was observed, while the combination treatment achieved 100 CR, CP, and CC in both the acute and delayed phase with the moderately emetogenic chemotherapy regimen. Our study demonstrated the promising efficacy of the triple treatment with formulated NE and PA tablets in combination with dexamethasone in preventing and managing CINV in real-world settings.

Keywords

- chemotherapy-induced nausea and vomiting
- emetogenic chemotherapy
- NK 1 receptor antagonist
- 5-HT3 receptor antagonists
- NEPA

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a complex condition that can have a detrimental effect on a patient's health, causing electrolyte imbalance, dehydration, and malnutrition that can result in challenges with adherence to therapy, ultimately leading to suboptimal cancer treatment.[1,2] Based on the occurrence of the emesis, CINV is categorized into acute and delayed phases. Acute CINV triggers within 24 hours of the commencement of chemotherapy predominantly by serotonin release from enterochromaffin cells within the gastrointestinal tract. The serotonin release activates the 5- hydroxytryptamine type 3 (5-HT3) receptors in the intestines, which transmit the signals to the brain to initiate the emetic reflex. However, delayed CINV usually occurs after 24 hours of administration of chemotherapeutic agents through the release of substance P and activation of neurokinin 1 (NK_1) receptors. This activation signals the abdominal muscles, diaphragm, and stomach to trigger emesis via stimulating the dorsal vagal complex comprising the vomiting center.[2,3] Therefore, inhibiting both 5HT-3 and NK_1 receptors simultaneously can effectively reduce both acute and delayed CINV. International guideline committees also recommend the use of a combination of antiemetic drugs that target various molecular pathways linked to emesis as the established standard of care for preventing CINV.[4] The use of a combination of netupitant (NE), an NK1 receptor antagonist, and palonosetron (PA), which acts as a 5HT-3 receptor antagonist, has proven to be effective in managing and preventing CINV by blocking two predominant emetic pathways.[5]

Netupitant-palonosetron (NEPA), a fixed dose combination of two antiemetic drugs, is the first commercially available single dose to prevent CINV.[6] The extended duration of action of both the antiemetic agents (NE: 90 hours; PA: 40 hours) ultimately prolongs the half-life of the combination, making single oral administration sufficient for managing acute as well as delayed CINV.[1,7] NEPA has also proven the sustained efficacy and tolerance in multiple cycles of emetogenic chemotherapy during different phases of trials.

Though the safety and efficacy of commercially available NEPA capsules have been evaluated across the globe in various clinical trials, adherence to the guidelines regarding the use of NEPA in clinical practice is suboptimal.[2] It has also been reported that results from these clinical trials of antiemetic drugs may not represent actual real-world data. Therefore, a retrospective study is required to evaluate the practical effectiveness of the recommended anti-emetic regimen for CINV.[8] Notwithstanding the fact that in today's market, convenience in dosing and administration alone is insufficient as a product differentiator; it must be integrated into the overall product formulation strategy like improving solubility, bioavailability, reducing side effect, and taste masking to enhance efficacy. Drug reformulation plays a crucial role in meeting patient and prescriber needs, boosting patient acceptance, and ensuring adherence to prescribed regimens.[9]

Therefore, this retrospective study was conducted to evaluate the practical effectiveness of the formulated NE (300mg) and PA (0.5mg) tablets along with dexamethasone (with varying doses) in patients receiving highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC) in real-world settings.

Materials and Methods

Study Design

This was a retrospective study conducted at Soumya Multispecialty Hospital, Secunderabad, Telangana. This study got an ethics committee approval from the institutional ethics committee due to its retrospective nature. This study was conducted in accordance with the Helsinki Declaration as revised in 2013.

Patients' Disposition

Naïve and non-naïve patients to chemotherapy having more than or equal to 18 years of age, either male or female, were enrolled in the study. Both in and outpatients receiving MEC and HEC regimens were included. MEC regimen comprises either bendamustine or carboplatin (area under the curve [AUC] <4) or dactinomycin or epirubicin ($\leq 90\ mg/m^2$) or ifosfamide ($<2\ g/m^2$ per dose) or methotrexate ($\geq$ 250 mg/m^2) or oxaliplatin, while HEC regimen involved treatment with either AC or carboplatin (AUC ≥ 4) or cisplatin or dacarbazine or fam-trastuzumab deruxtecan or melphalan ($\geq 140\ mg/m^2$). Patients who were pregnant, breastfeeding, having pre-existing nausea or vomiting, and hypersensitivity to the excipients of NEPA were excluded from the study.

Treatment

A triple combination of NE (300mg), PA (0.5mg), and dexamethasone was given orally 1 hour prior to the chemotherapy for 4 days. The dose of NE and PA was kept constant, while dexamethasone treatment typically involved an initial 12 mg on the day of chemotherapy, followed by 8mg on the second, third, and fourth day for patients receiving both HEC and MEC regimens. The absence of nausea and emesis was recorded as a response to the treatment during the acute (0–24 hours) and delayed (24–120 hours) phase.

End-Points

The objective of the study was to assess the efficacy of formulated NE, PA tablets, and dexamethasone in multiple cycles of MEC and HEC regimens during the acute and delayed phases of CINV. The key end-points during this study were no nausea, no emesis, and no use of rescue medication during acute as well as delayed phases in both the MEC and HEC regimens after the triple-treatment administration. Any patient was said to have significant nausea if the symptoms were more severe and lasted longer, more disabling, and felt worse than normal nausea. The following terminologies were used during the analysis of results:

Complete response (CR): No emesis and no use of rescue medication.

Complete protection (CP): No emesis, no significant nausea, and no use of rescue medication

Complete control (CC): No emesis, no nausea, and no use of rescue medication.

Data

The data collected were consolidated in a Microsoft Excel spreadsheet, and the percentage was calculated by keeping the total number of subjects as the denominator and the number of subjects with a specific response in the numerator.

Results

A total of 212 patients were enrolled in the study. Of these, 68 (32.08%) were males and 144 (67.92%) were females. The most common primary tumor site was the ovary (57), followed by the breast (52), the colo-rectum (43), and head and neck (29). All the patients entered in multiple chemotherapy cycles of either HEC or MEC regimen. The demographic data and chemotherapy regimen of 212 patients are reported in ►Table 1.

After the administration of combination treatment involving NE, PA, and dexamethasone, the overall rates of CR, CP, and CC in the acute phase were 97.5, 91.1, and 92.19%, respectively. In contrast, the response was slightly lower, with 95.09, 88.06, and 87.74% for CR, CP, and CC in the delayed phase (►Fig. 1).

The enrolled cancer patients received a total of 1,387 cycles of both HEC and MEC regimens. Among patients who underwent 521 cycles of HEC regimen, CR, CP, and CC were achieved in 93.47, 76.20, and 73.90% during the acute phase, while it decreased to 86.95, 69.67, and 67.37 in the delayed phase, respectively (►Fig. 2).

During the administration of 866 cycles of the MEC regimen, the combination treatment with NE, PA, and dexamethasone successfully achieved 100% CR, CP, and CC in both acute and delayed phases of CINV (►Fig. 3).

Discussion

CINV is a common and troublesome side effect of chemotherapy that can impact the quality of life and also delay the treatment.[3] International oncology associations like the Multinational Association of Supportive Care in Cancer, the European Society for Medical Oncology,[10] and the American Society of Clinical Oncology[11] recommend the use of 5HT-3 receptor antagonists and NK1 receptor antagonists for

Table 1 Baseline demographic data and chemotherapy regimen

Parameters		Values
Total patients **Male (*n*, %)** **Female (*n*, %)**		212 68 (32.08%) 144 (67.92%)
Primary tumor site	Ovary	57
	Breast	52
	Colo-rectum	43
	Head and neck	29
	Others	31
Chemotherapy		Cycles
High emetic risk chemotherapy	AC (4 cycles)	168
	Carboplatin AUC ≥4 (6–8 cycles)	180
	Cisplatin (8 cycles)	152
	Dacarbazine	18
	Melphalan ≥140 mg/m^2	3
Total HEC cycles		521
Moderate emetic risk chemotherapy	Bendamustine	80
	Carboplatin AUC <4 (weekly 10–12 cycles)	620
	Dactinomycin	12
	Epirubicin ≤90 mg/m^2	40
	Ifosfamide <2 g/m^2 per dose	52
	Methotrexate ≥250 mg/m^2	4
	Oxaliplatin	58
Total MEC cycles		866
Total cycles		1,387

Abbreviations: AUC, area under the curve; HEC, high emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy.

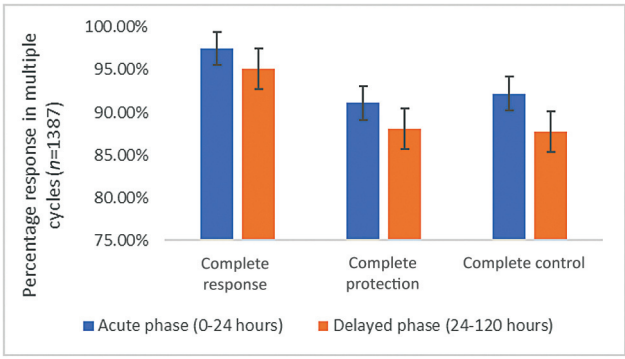

Fig. 1 The histogram showing the overall complete response, complete protection, and complete control after the administration of triple treatment during the acute and delayed phase.

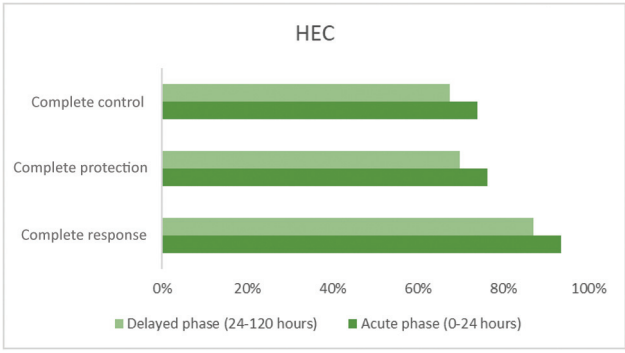

Fig. 2 Efficacy results for patients treated with NE, PA, and dexamethasone receiving HEC ($n = 521$). HEC, high emetogenic chemotherapy; NE, netupitant; PA, palonosetron.

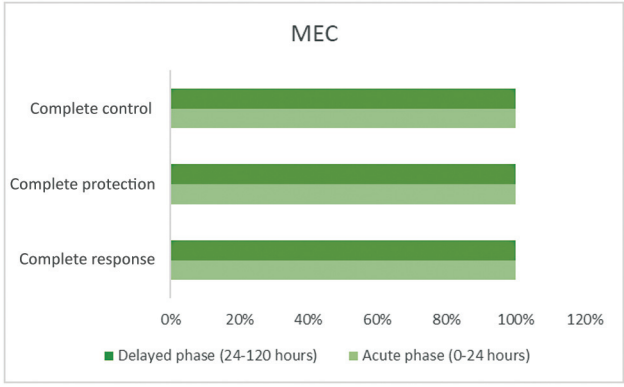

Fig. 3 Efficacy results for patients treated with NE, PA, and dexamethasone receiving MEC ($n = 866$). MEC, moderately emetogenic chemotherapy; NE, netupitant; PA, palonosetron.

managing CINV. Numerous in vitro studies have established the synergistic effect of NK_1 and 5HT-3 receptor antagonists in improving acute as well as delayed CINV.[12] The combination treatment, along with corticosteroids like dexamethasone, is followed as a standard protocol for prophylaxis of CINV in both MEC and HEC regimens.[13] NEPA is the first antiemetic combination of NK_1 and 5HT-3 receptor antagonists available as a suitable prophylactic approach to manage nausea and vomiting induced by emetogenic chemotherapy.[4]

In this retrospective study, 212 patients were administered a triple combination of NE, PA, and dexamethasone in a single dose 1 hour prior to the commencement of chemotherapy. The overall CR, CP, and CC were evaluated as the endpoints to demonstrate the efficacy of the formulated NE, PA tablets in the real-world setting. The response of our study was in line with the previously reported clinical trials conducted by Hesketh et al 2014[14] and Zhang et al 2018,[15] where the rates of achieving CR were slightly greater in the acute phase (97.5%) compared to delayed phase (95.09%) of CINV. Hesketh et al reported 98.5% of CR in the acute phase and 90.4% in the delayed phase,[14] whereas Zhang et al conducted a study on Chinese patients where 84.5% of CR was observed in the acute phase and 77.9% in delayed phase after the treatment with NEPA and dexamethasone.[15] Similar results were reported in the real-world study conducted by Conter et al.[16] Thus, the overall range of CR in the above studies was between 67 and 98.5%.

Since the commonly prescribed emetogenic chemotherapy in our study was carboplatin with different doses in both HEC and MEC regimens, the treatment with NE, PA, and dexamethasone had overall good control in acute as well as delayed phases. Though there was a decrease in the rate of CR, CP, and CC from 93.47, 76.20, and 73.90% (acute phase) to 86.95, 69.67, and 67.37% (delayed phase) with HEC, the combination treatment achieved an impressive 100% CR, CP, and CC in both the acute and delayed phase with the MEC regimen.

In oncology settings, effectively managing CINV necessitates careful consideration of antiemetic agents due to their potential toxicities. Studies have shown antiemetics associated with extrapyramidal symptoms such as tardive dyskinesia, akathisia, and dystonia. Additionally, serotonin antagonists, while effective in controlling CINV, have been linked to QTc interval prolongation, increasing the risk of arrhythmias like Torsades de Pointes.[17,18] In our study, the CC of CINV, defined as the complete absence of nausea, emesis, and no use of rescue medication, was notably high. Specifically, the CC was 92.19% in the acute phase and 87.74% in the delayed phase. This performance surpasses that reported Aapro et al.[7]

In line with our study's positive findings, another multicentric research led by Vaswani et al looked at how well NEPA works in real-world situations in India. They found that out of the 329 patients undergoing MEC or HEC, 93% had a good response during the first phase, and 85.71% during the delayed phase.[6] This may be attributed to the additive efficacy of receptor internalization, the synergistic actions of PA and NE in inhibiting the crosstalk phenomena, and the extended and enhanced receptor occupancy attained by NE.[6]

These outcomes highlight the exceptional effectiveness of the NE, PA-formulated tablets compared to the results of the studies conducted on commercially available NEPA capsules in preventing and managing CINV in both phases of chemotherapy. In summary, the triple treatment with NE, PA, and dexamethasone to prevent and manage CINV offers promising efficacy that may favor an antiemetic guideline consistent with prophylaxis in real-world settings. While this study

provides valuable insights into the efficacy and safety of the NE, PA-formulated tablets, it is important to note that direct comparisons with other chemotherapy agents were not conducted. Future studies incorporating comparative analyses between different chemotherapy agents may offer further clarity on optimal treatment strategies.

Conclusion

CINV is a significant challenge for cancer patients, affecting their quality of life and potentially delaying treatment. This retrospective study demonstrates the efficacy of formulated NE and PA tablets in preventing and managing CINV in real-world settings. The results of our study demonstrated the promising efficacy of the triple treatment with formulated NE and PA tablets in combination with dexamethasone in preventing and managing CINV in real-world settings.

Authors' Contribution

All the authors contributed equally to the conception and design of the study, acquisition of data, drafting of the article or revising it critically for important intellectual content, and final approval of the version to be submitted.

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None.

Conflict of Interest

None declared.

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