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ABOUT COVER

Editorial board member of *World Journal of Clinical Oncology*, Dr. Takura is a Project Professor in the Department of Healthcare Economics and Health Policy, Graduate School of Medicine, University of Tokyo, Japan. He is part-time Research Fellow of the Cabinet Office and Chairman of the Specialized Agency of Cost-effectiveness Evaluation, Ministry of Health, Labour and Welfare. Dr. Takura also serves as a Guest Professor at Osaka University Graduate School of Medicine. Dr. Takura's research has focused on socioeconomic evaluation of cancer treatments and renal transplantation, and cost effectiveness analysis of revascularization for ischemic heart disease. His current approach to this work involves integrating big data from various sources. (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Oncology* (*WJCO*, *World J Clin Oncol*) is to provide scholars and readers from various fields of oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJCO mainly publishes articles reporting research results and findings obtained in the field of oncology and covering a wide range of topics including art of oncology, biology of neoplasia, breast cancer, cancer prevention and control, cancer-related complications, diagnosis in oncology, gastrointestinal cancer, genetic testing for cancer, gynecologic cancer, head and neck cancer, hematologic malignancy, lung cancer, melanoma, molecular oncology, neurooncology, palliative and supportive care, pediatric oncology, surgical oncology, translational oncology, and urologic oncology.

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ORIGINAL ARTICLE

Retrospective Study

Effectiveness of a novel, fixed dose combination of netupitant and palonosetron in prevention of chemotherapy induced nausea and vomiting: A real-life study from India

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Abstract

BACKGROUND

A new, oral fixed dose combination of highly selective neurokinin-1 receptor antagonist, netupitant with 5HT3 receptor antagonist, netupitant and palonosetron (NEPA) was approved in India for prevention of chemotherapy induced nausea and vomiting (CINV).

AIM

To assess effectiveness of NEPA in real-world scenario.

METHODS

We retrospectively assessed the medical records and patient dairies of adult patients who received highly emetogenic or moderately emetogenic chemotherapy (HEC/MEC) and treated with NEPA (Netupitant 300 mg + Palanosetron 0.50 mg) for prevention of CINV. Complete response (CR) was defined as no emesis or no requirement of rescue medication in overall phase (0 to 5 d), acute phase (0-24 h) and delayed phase (2 to 5 d).

RESULTS

In 403 patients included in the analysis, mean age was 56.24 ± 11.11 years and 55.09% were females. Breast cancer (25.06%) was most common malignancy encountered. HEC and MEC were administered in 54.6% and 45.4% patients respectively. CR in overall phase was 93.79% whereas it was 98.01% in acute CINV and 93.79% in delayed CINV. Overall CR in HEC and MEC groups was 93.63% and 93.98% respectively. CR was more than 90% in different chemotherapy cycles except in group of patients of cycle 4 where CR was 88.88%.

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CONCLUSION
NEPA is a novel combination that is effective in preventing CINV in up to 93% cases treated with highly emetogenic or moderately emetogenic chemotherapy. This study brings the first real-life evidence of its effectiveness in India population.

Key words: Chemotherapy induced nausea vomiting; Netupitant; Palonosetron; Cancer; Chemotherapy

Core tip: A fixed-dose combination of Netupitant (300 mg) and Palonosetron (0.50 mg) indicated for the prevention of acute and delayed phase of nausea-vomiting in patients on highly and moderately emetogenic chemotherapeutic regimen was recently approved in India. There was no data on the effectiveness of this fixed dose combination in Indian patients in real world setting,the pervious data available was part of regulatory trial conducted in controlled environment, which may not give the real picture of the usage of the molecule in clinical setting. So to look for the effectiveness of the molecule in real world setting this study was conducted among.

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INTRODUCTION

Chemotherapy induced nausea and vomiting (CINV) is one of the most feared adverse events in various cancer chemotherapy regimens[1]. Evidence suggests that the incidence of acute CINV varies from 30% to 90% and that of delayed CINV is reported to be 28%-50%[2-4]. Rates of nausea (28.8% to 53.5%) and vomiting (9.4% to 19.2%) in the overall phase reported from Asia Paicifc region after first cycle of chemotherapy were varied[5]. A study from North India observed the CINV prevalence of 25.5%[6]. These data suggest that CINV may affect upto half of all the patients receiving highly-emetogenic or moderately-emetogenic chemotherapies (HEC/MEC).

Pathomechanistically, serotonin and substance P are major neurotransmitters involved in acute and delayed CINV. Serotonin binds to 5HT3 receptor present mainly in the gastrointestinal tract and Substance P binds with neurokinin-1 (NK1) receptors in the nucleus tractus solitarius and induces vomiting. Therefore, targeting serotonergic and neurokinin pathways are helpful in prevention of CINV[7]. The European Society of Medical Oncology and the Multinational Association of Supportive Care in Cancer guidelines recommend 5HT3 receptor antagonist, dexamethasone and NK1 receptor antagonist in acute CINV, whereas later two are advised in delayed CINV[8]. Recently, a new, oral fixed dose combination (FDC) of netupitant (highly selective NK1 receptor antagonist, 300 mg) with Netupitant and palonosetron (5HT3 receptor antagonist, 0.5 mg) (NEPA) was approved in India[9]. NEPA + DEX has been found to be clinically superior to monotherapy of palonosetron + DEX in preventing both acute and delayed CINV[10,11]. Being a recent and novel FDC antiemetic with limited evidence in Indian setting, there is need to further understand its efficacy and safety. Hence, we planned this observational study to determine efficacy of NEPA in prevention of CINV.

MATERIALS AND METHODS

Study design

This single-centre, retrospective study was conducted in patients treated with HEC/MEC.

Ethics

Study was initiated after the approval from independent ethics committee and was conducted according to good clinical practice and applicable regulatory guidelines.

Setting

This study was conducted in tertiary care centre in Hyderabad, India. This centre provides super-specialty services in management of various malignancies. It caters to the urban, semi urban and rural population.

Participants

Adults aged > 18 years of either sex who were treated with HEC/MEC and prescribed NEPA irrespective of the number of chemotherapy cycles from June 2019 to December 2019 were identified from the patient database at our centre. Any patient treated with low-emetogenic chemotherapy or those who received chemotherapy with minimal emetogenic potential were excluded.

Treatment schedule in participants

After identifying the patients from the database, their demographic and baseline data mentioned in medical records was captured in structured case record form. Demographic data included age, gender, and clinical data on type of chemotherapy, current number of cycles, *etc*. were noted. As a standard practice, the given treatment schedule was followed in all patients for prevention of CINV.

Before initiating chemotherapy, all patients were treated with a single oral capsule of netupitant 300 mg and palonosetron hydrochloride 0.5 mg. After 60 min, chemotherapy was initiated. Dexamethasone (12 mg intravenous once) was concomitantly administered intravenously in all patients. Data on nausea and vomiting was captured by patients in patient diaries which were available with their medical records. From these diaries, events of nausea and vomiting were identified during first 24 h and over day 1 to day 5. Events that occurred within first 24 h were considered as acute CINV and those between day 2 and day 5 were considered as delayed CINV (Figure 1).

Outcome measurement

The main outcome assessed was complete repose (CR) to NEPA. CR was defined as no emesis or no requirement of rescue medication. CR was determined in acute phase (0-24 h), delayed phase (24-120 h) and in overall phase (0-120 h). Overall CR was primary outcome measure. Effect of study drug was also evaluated by emetogenicity of chemotherapy as high and moderate as well as in by the cycle of chemotherapy.

RESULTS

Baseline characteristics

In total, 403 patients were identified and analysed. Baseline characteristics of the study patients are shown in (Table 1). Mean age of the participants was 56.24 ± 11.11 years with majority being in age group of 51 to 65 years (51.36%). Proportion of females was slightly higher than males (55.09% *vs* 44.91% respectively). Among study participants, most common malignancy was of breast (25.06%) followed by colon (15.63%), oral cavity (10.66%) and others as shown in (Table 1). 54.6% patients had received HEC whereas remaining were treated with MEC. Also, patients were in different cycles of chemotherapy regimens as shown in (Table 1).

Outcome assessment

CR in overall population: For overall phase, the CR in our study was 93.79%. CR in acute and delayed phase CINV was 98.01% and 93.79% respectively (Table 2).

CR as per emetogenic potential of chemotherapy: We further analysed the CR according the chemotherapy regimen. In participants who received HEC (n = 220), overall CR was observed in 93.63% whereas 97.27% had CR in acute phase, and 93.63% had CR in delayed phase. Similarly, in patients receiving MEC (n = 183), overall response was seen in 93.98% whereas CR in acute and delayed CINV was 98.90% and 93.98% respectively.

CR as per number of chemotherapy cycles: All the enrolled participants were on

Table 1 Baseline characteristics of enrolled patients

Characteristics	Observations
Age (yr)	
mean ± SD	56.24 ± 11.11
Age groups	
≤ 35	16 (3.97)
36-50	97 (24.06)
51-65	207 (51.36)
66-80	75 (18.61)
Gender	
Male	181 (44. 91)
Female	222 (55.09)
Type of cancer	
Breast	101 (25.06)
Colon	63 (15.63)
Oral	43 (10.66)
Lung	29 (7.19)
Gall bladder	24 (5.95)
Epiglottis	13 (3.2)
Cervix	12 (2.97)
Rectum	12 (2.97)
Others[1]	106 (26.03)
Chemotherapy	
Highly emetogenic	220 (54.6)
Moderately emetogenic	183 (45.4)
Chemotherapy cycles	
1	75 (18.61)
2	89 (22.08)
3	30 (7.44)
4	90 (22.33)
5	52 (12.90)
> 5	67 (16.62)

Data presented as mean±standard deviation or frequency (%); Baseline demographic characteristics of patients enrolled in the study, distribution of there age (mean ± standard deviation), gender, type of cancer, type of chemotherapy and the chemotherapy cycle.
[1]Others- Includes following cancers-Endometrial; Larynx, Stomach; B cell lymphoma; Ewing's Sarcoma; Tonsil; Osteoblastoma; Mediastinal lymphadenopathy; Peri ampullary; Testis; Pyloric antrum; Pyriform fossa; Oropharynx; Ovary; Pancreas.

various cycles of chemotherapy (Tables 1 and 3). Overall CR was 90% or more in all groups of chemotherapy cycles except in the group of patients with 4 cycles in whom overall CR was 83%. Similarly, the CR in acute CINV was over 90% in all chemotherapy cycle groups except patients who had 4 chemotherapy cycles in whom CR in acute CINV was 88.88%. Acute CINV CR was 100% in patients who had 5 chemotherapy cycles. CR in the delayed CINV phase was similar to overall CR in all chemotherapy cycle groups.

Table 2 Outcome assessments

Population	Number of participants	Acute phase, Number of participants (%)	Delayed phase, Number of participants (%)	Overall phase, Number of participants (%)
Overall	403	397 (98.01)	378 (93.79)	378 (93.79)
Highly emetogenic chemotherapy	220	214 (97.27)	206 (93.63)	206 (93.63)
Moderately emetogenic chemotherapy	183	181 (98.90)	172 (93.98)	172 (93.98)

Complete response rate in acute delayed and overall phase among patients on highly and moderately emetogenic chemotherapy regimen.

Table 3 Complete response rate among enroled patients

Chemothrapy cycle	Number of participants	Acute phase-number of participants (%)	Delayed phase-number of participants (%)	Overall phase-number of participants (%)
1	75	73 (97.33)	68 (90.66)	68 (90.66)
2	89	88 (98.87)	86 (96.22)	86 (96.22)
3	30	28 (93.33)	27 (90.00)	27 (90.00)
4	90	80 (88.88)	75 (83.00)	75 (83.00)
5	52	52 (100.00)	51 (98.07)	51 (98.07)
> 5	67	65 (97.01)	63 (94.02)	63 (94.02)

Complete response rate in acute, delayed and overall phase among patients enrolled in various cycles of chemotherapy.

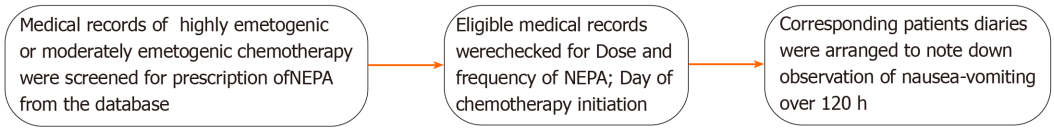

Figure 1 Study flow chart. Study flow: Medical records and patient dairies were evaluated for incidence and severity of nausea-vomiting, time period was form the time chemotherapy was administered to 120 h (day 1 to day 5) to look for complete response in acute, delayed and overall phase. NEPA: Netupitant and palonosetron.

DISCUSSION

Combination of netupitant and palonosetron is first of its own kind FDC for prevention of CINV. In this study, we demonstrated that NEPA was effective in preventing CINV as shown by CR of 93.79% in overall and delayed phase with CR of 98.01% in acute phase. Compared to the finding of Hesketh *et al*[10] who observed CR in 89.6% patients, CR in our study was substantially higher. This is probably attributable to the differences in participants in two studies as Hesketh *et al*[10] included patients receiving HEC only. Badalamenti *et al*[12] (2019) also reported overall CR in first chemotherapy cycle to be 88.9%[12]. This indicates overall excellent efficacy of NEPA in preventing acute and delayed phase CINV. The combination has also been found to be more effective than monotherapy with palonosetron. In randomized, double-blind, study involving patients on MEC, Aapro *et al*[13] demonstrated that the CR in overall phase, acute phase and delayed phase was 74.3%, 88.4% and 76.9% in NEPA group and 66.6%, 85.0% and 69.5% with palonosetron monotherapy. Dexamethasone was co-administered in both treatment groups[13]. Hesketh *et al*[10] also reported NEPA was superior to palonosetron in preventing CINV in patients receiving HEC[10]. This suggest that NEPA is highly effective in preventing CINV in any level of emetogenic chemotherapy. Further, CINV due to chemotherapy can lead to reduced quality of life, impairment in home and occupational activities, may add to increased cost and cause organ damage in the long run, preventing CINV is one of the primary goals of therapy[14-17]. Therefore, single oral dose of NEPA can contribute the improved quality

of life of patients receiving chemotherapeutic regimens.

We observed persistent CR in patients from different number of chemotherapy cycles suggesting that effectiveness of NEPA is not affected in repeated administration or initiating at any chemotherapy cycle. The overall CR in first cycle was similar to those who had more than five chemotherapy cycles. Similar finding was observed by Gralla *et al*[18] in evaluation of patients receiving HEC or MEC. They found consistent overall CR which was 81%, 86%, 91%, 90%, 92% and 91% in cycles 1, 2, 3, 4, 5, and 6 of chemotherapy[18]. Combined with our observation, the evidence is clear that NEPA is highly effective in preventing CINV over multiple cycles of HEC/MEC. This has important clinical implications as single dose is effective and there is no need of repeat administration or rescue medications. With improved patient education, compliance to chemotherapy regimens can be improved substantially with appropriate intake of antiemetics[19].

We observe certain strengths and limitations in our study. Study has inherent limitations of retrospective design. We assessed the response acute and delayed phase but its efficacy in anticipatory, breakthrough, and refractory CINV in Indian population require further assessment. Although efficacy in low emetogenic chemotherapy was not assessed, NEPA is expected to be efficacious in these group of patients as it had proved its efficacy in HEC/MEC. Further, age and gender difference in efficacy as well as efficacy in different tumours can be assessed to identify population that can get most benefited with use of NEPA. Also, we did not compare the efficacy with existing therapies which would have provided more insights in understanding the benefits with NEPA. Nonetheless, our initial experience with NEPA suggests its effective utility in preventing CINV in HEC/MEC.

A novel FDC of netupitant and palonosetron has been approved for prevention of CINV. We observed that this FDC is effective in preventing CINV in patients receiving HEC/MEC with complete response rate of 93.79% with near complete response in acute phase of CINV. Also, the response was maintained irrespective of HEC or MEC administration as well as repose was consistent across number of chemotherapy cycles. Thus, in real-world setting, we find that NEPA is effective for preventing CINV over multiple cycles of highly or moderately emetogenic potential chemotherapy regimens. These finding need to be further confirmed in larger, randomized, comparative studies.

ARTICLE HIGHLIGHTS

Research background

Chemotherapy induced nausea and vomiting (CINV) is one of the most feared adverse events with patient receving chemotherapy regimens. Pathomechanistically, serotonin and substance P are major neurotransmitters involved in acute and delayed CINV, targeting both optimizes CINV control. NEPA, an oral fixed dose combination Netupitant (300 mg) and Palonosetron (0.50 mg), was recently approved in India for the management of CINV. Hence there was a need to evaluate the effectiveness of NEPA in Indian setting in real world scenario.

Research motivation

To analyse the effectiveness of NEPA in prevention of CINV among Indian patients who have received highly and moderately emetogenic chemotherapy regimen.

Research objectives

To elucidate the clinical effectiveness of NEPA, in terms of the complete response in acute-delayed and overall phase of nausea-vomiting irrespective of the chemotherapy cycle. Thereby, we hope to generate the real world evidnce on the usefulness of NEPA in the management of CINV patients in India.

Research methods

Medical records and patient diaries of adults cancer patients who were treated with highly emetogenic or moderately emetogenic chemotherapy and received NEPA irrespective of the number of chemotherapy cycles from June 2019 to December 2019 were retrieved. Relevant clinical variables such as presence or absence of nausea-vomiting and if present, the severity of nausea on visual analog scale and cycle wise distribution of the data were captured.

Research results

The study demonstrated that complete response in overall phase was 93.79% whereas it was 98.01% in acute CINV and 93.79% in delayed CINV. Overall complete response in highly emetogenic chemotherapy group of patients was 93.63% and in moderately emetogenic group of patients was 93.98%.

Research conclusions

We found that the oral fixed dose combination of netupitant 300 mg and palonosetron hydrochloride 0.5 mg is effective in preventing CINV in patients receiving highly or moderately emetogenic chemotherapy regimen in the real world setting. Also, the response was consistent across number of chemotherapy cycles.

Research perspectives

This study demonstrated the clinical effectiveness of NEPA among Indian patients in managing CINV, and serves as an impetus for future research.

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