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Original Article

Effectiveness of Prophylactic Antiemetic Regimen to Anthracycline Chemotherapy

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ABSTRACT

Objectives: The availability of efficacy and safety profile of prophylactic antiemetic medications in various high emetogenic chemotherapy protocols will make it a valuable therapeutic option for healthcare provider. Hence this research aimed to assess the comparative safety and efficacy of prophylactic antiemetic regimen during anthracycline chemotherapy and their impact on Quality of Life (QoL). **Materials and Methods:** This is a prospective, observational study that included 55 patients with anthracycline Chemotherapy. The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was used to grade cases of nausea and vomiting. We assessed the percentage of complete response and complete control of CINV and health-related quality of life was assessed using the Functional Living Index-Emesis (FLIE), a 5-day recall tool. Statistical analysis: The Statistical Package for the Social Sciences (SPSS) Statistics for Windows, Version 16.0 (IBM Corp, Armonk, NY) was used to conduct the statistical analysis. A P-value of less than 0.05 was deemed to indicate statistical significance. **Results:** The complete response rates for NEPD/APD and NEOPD/AOPD were 91.66% and 89.47%, respectively, whereas the complete control rates were 55.55% and 52.63%. In the CTCAE version 5.0 studies, only 3.6% of nausea and 1.8% of vomiting cases were classified as Grade 3, with no cases classified as Grade 4 or 5. The FLIE score was greater than 54 in the vomiting domain and less than 54 in the nausea domain, indicating that CINV had a minimal impact on daily life. **Conclusion:** This observational study showed that both NEPD/APD and NEOPD/AOPD regimens had similar efficacy and safety profiles in managing nausea and vomiting during anthracycline-based chemotherapy, with minimal impact on QoL and mild adverse events.

Keywords: Anthracyclines, Antiemetics, Prophylactics, Quality of Life, Chemotherapy.

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INTRODUCTION

Chemotherapy Induced Nausea and Vomiting (CINV) is a significant contributor to the rise in morbidity and healthcare costs. It is considered the most feared adverse effect of cancer therapy, affecting up to 40% of patients and impacting various aspects such as treatment adherence, Quality of Life (QoL) and overall outcomes.[1,2] Patients undergoing chemotherapy who experience severe and poorly managed CINV have reported life-threatening situations.[3]

There exist five distinct categories of clinical syndromes related to CINV, namely acute, delayed, anticipatory, breakthrough and refractory. Acute CINV, occurring within 24 hr, is triggered by the activation of type 3 serotonin receptors in the gastrointestinal tract, while delayed CINV (24-120 hr) has multiple causative factors. The prevalence of acute CINV in moderate- to high-risk chemotherapy settings ranges from 30% to 90%.[4,5]

Diverse treatment approaches are employed for acute and delayed CINV phases due to variations in underlying mechanisms and pharmacological pathways.[6] Both patient-specific and treatment-related factors play crucial roles as risk determinants for CINV development. Patient-related factors encompass age, gender (female), history of motion sickness, alcohol use and previous emesis post-treatment, while treatment-specific risk factors involve emetogenicity of the chemotherapeutic agent, dosage, treatment schedule and chemotherapy combinations.[7,8]

Chemotherapeutic agents are classified based on their emetogenic potential into minor (<10%), low (10-30%), moderate (30-90%) and high (>90%) categories. Among these agents, anthracyclines are prominent for treating various cancers such as Acute lymphocytic leukemia, Hodgkin's lymphoma, Breast cancer, Bladder cancer and many more.[9,10] Despite their efficacy, anthracyclines are associated with a wide range of adverse events,

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with acute phase nausea and vomiting being the most common side effects.[11,12]

The management of CINV typically involves the use of antiemetic medications with diverse mechanisms of action.[4] The rationale behind antiemetic therapy lies in the neurochemical regulation of vomiting, although the exact mechanisms remain unclear. Drugs like 5-HT3 antagonists, corticosteroids, NK-1 receptor antagonists, olanzapine and dopamine receptor antagonists exhibit antiemetic and anti-nausea properties.[13,14]

Current clinical guidelines advise prophylactic management of CINV based on the emetogenic potential of the selected chemotherapeutic agents. For patients undergoing regimens with high emetogenicity, a combination of a 5-HT3 receptor antagonist, NK-1 receptor antagonist, dexamethasone, with or without olanzapine, is recommended prior to chemotherapy administration.[15,16]

Netupitant plus Palonosetron signifies a notable progression in the management of CINV in patients undergoing High Emetogenic Chemotherapy (HEC). Its distinctive dual-mode of action, directed towards both the acute and delayed phases of CINV, offers comprehensive symptom management and enhances the quality of life for patients.[17]

The consistent effectiveness and advantageous safety profile of prophylactic antiemetic medications across various cancer types and chemotherapy protocols will make it as a valuable therapeutic choice for healthcare providers. This research emerges from the necessity to assess comparative effectiveness and safety of prophylactic antiemetic drugs in addressing CINV, particularly among patients receiving anthracyclines chemotherapeutic agents across various chemotherapy protocols, with the aim of establishing treatment preferences that are clinically significant based on efficacy and safety considerations.

MATERIALS AND METHODS

This prospective observational study, conducted in the Department of Medical Oncology at Kovai Medical Center and Hospitals in Coimbatore, South India, adhered to a non-interventional approach. The institutional ethical committee approved the study with the reference number EC/AP/949/07/2022. Written informed consent was obtained from all study participants.

The calculated sample size was determined to be 52 by utilizing the following equation, incorporating a 95% confidence interval, a 5% margin of error, a 0.5 population proportion, a Z-score of 1.96 and a total population size of 60.

$$\text{Sample Size} = \frac{Z^2P(1-P)/e^2}{1 + (Z^2P(1-P)/e^2N)}$$

N: Population size, P: Population Proportion, Z: Z-Score, e: Margin of error.

Encompassing 55 patients, this research focused on individuals undergoing prophylactic antiemetic treatment for anthracycline-based chemotherapeutics across various chemotherapy protocols. Two antiemetic regimens were included in this study: Netupitant/Aprepitant, Palonosetron, Dexamethasone (NEPD/APD) and Netupitant/Aprepitant, Olanzapine, Palonosetron, Dexamethasone (NEOPD/AOPD). There were no post-chemotherapy Dexamethasone prescriptions in our study, resulting in Dexamethasone sparing.

Inclusion Criteria

Individuals aged eighteen years and older, of any gender, with an Eastern Cooperative Oncology Group (ECOG)[18] performance status ranging from 0 to 2 and who were administered the first-line anthracyclines chemotherapy regimen, were encompassed within the scope of our investigation.

Exclusion Criteria

Patients with hepatic failure, renal disorders, acute leukemia, cerebral metastases, psychiatric conditions impacting daily functioning, pregnant or nursing females and individuals experiencing emesis within 24 hr before chemotherapy initiation were all omitted from participation in this research investigation.

Study Methodology

As per the inclusion and exclusion criteria mentioned, participants were recruited for the present investigation. The baseline characteristics of the participants were obtained through the patient data collection form. The analysis focused on the overall rates of complete response and complete control in the combined acute (less than 24 hr) and delayed (24-120 hr) phases of CINV over three consecutive cycles. A complete response denoted the absence of emesis or the necessity for rescue medication. Complete control was defined as the absence of emesis, use of rescue medication and significant nausea. QoL among subjects undergoing chemotherapy with CINV prophylaxis was evaluated using the Functional Living Index Emesis (FLIE) questionnaire, a validated patient-reported outcome tool designed for assessing nausea and vomiting.[19] The FLIE questionnaire comprises two domains, each with nine identical items. Patients were asked to recall their experience over 5 days. The average score for each domain was calculated, with scores exceeding 54 indicating no impact of CINV on daily activities. The severity of nausea and vomiting and other adverse events were graded (Grade 1: Mild, Grade 2: Moderate, Grade 3: Severe, Grade 4: Life-threatening consequences, Grade 5: Death)

based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[20]

Statistical Analysis

The statistical software known as the Statistical Package for the Social Sciences (SPSS) Statistics for Windows, Version 16.0 (IBM Corp, Armonk, NY) was employed to conduct the statistical analysis. The descriptive analysis assessed study parameters to estimate mean (±SD), percentage and frequency. Pearson's Chi-square test was utilized to examine the significance of the distribution of study parameters among the various categories. A *p*-value of less than 0.05 was deemed to indicate statistical significance.

RESULTS

This study, conducted in a prospective observational manner, encompassed 61 individuals. Six patients were excluded from the analysis due to inadequate data and 55 patients were taken for evaluation in the present investigation. The characteristics and demographic details of the study population at baseline are presented in Table 1. The mean age of the participants was 58 years, with the majority being female (82%). Within our study sample, NEPD/APD was prescribed with greater frequency (65%) compared to NEOPD/AOPD. The most commonly prescribed chemotherapy protocol in our study population was Doxorubicin/Cyclophosphamide (25%).

The comparative efficacy of NEPD/APD and NEOPD/AOPD in Anthracycline Chemotherapy protocols is depicted in Table

Table 1: Baseline Demographic and Clinical Characteristics.

Variables	Frequency (*n*=55)	Percentage (%)
Gender		
Male	10	18
Female	45	82
Age Distribution (years)		
18-30	1	2
31-40	8	15
41-50	12	22
51-60	19	32
61-70	15	27
71-80	1	2
Antiemetic regimen		
NEPD/APD	36	65
NEOPD/AOPD	19	35
Chemotherapy Protocol		
Epirubicin/Cyclophosphamide (EC)	11	20
Rituximab/Cyclophosphamide/Doxorubicin/Vincristine/ Prednisolone (R-CHOP)	9	16
Doxorubicin/Cyclophosphamide	14	25
Fluorouracil/Epirubicin/Hydrochloride/Cyclophosphamide (FEC)	9	16
Etoposide phosphate/Prednisone/Vincristine sulfate (Oncovin)/Cyclophosphamide/Doxorubicin hydrochloride (hydroxydaunorubicin)/Rituximab (DA-EPOCH-R)	1	2
Doxorubicin/Cisplatin	1	2
Ifosfamide/Doxorubicin	2	4
Pegylated Liposomal Doxorubicin/ Carboplatin	2	4
Pegylated Liposomal Doxorubicin	1	2
Epirubicin/Oxaliplatin/Capecitabine	3	5
Etoposide/Carboplatin/Doxorubicin	1	2
Vincristine sulfate/Dactinomycin (Actinomycin-D)/ Cyclophosphamide (VAC)	1	2

2. The complete response rates for NEPD/APD and NEOPD/AOPD were 91.66% and 89.47%, while the complete control rates were 55.55% and 52.63% respectively. Statistical analysis revealed no significant differences between NEPD/APD and NEOPD/AOPD in terms of both complete response and complete control outcomes.

Table 3 exhibits the evaluation of Nausea and vomiting utilizing CTCAE-Version 5.0 on prophylactic antiemetic protocols. A mere 3.6% of instances within the Nausea category and 1.8% in the vomiting category were assessed as Grade 3, with none being documented as Grades 4 and 5, thus highlighting the safety of the examined prophylactic antiemetic protocols.

Table 4 exhibits the results of the CTCAE -Version 5.0 concerning adverse events. The observed adverse effects included Somnolence, Constipation and Headache. Among the cases where headache was present, the highest percentage of 7.3% were classified as Grade 2, while no instances were categorized as Grades 3, 4, or 5, signifying the efficacy of prophylactic antiemetic treatments.

Table 5 presents the combined domain scores of the patients across three chemotherapy cycles derived from the FLIE, which is employed for evaluating their QoL. Throughout the three cycles, the combined domain score of NEPD/APD exhibited a slight superiority compared to NEOPD/AOPD.

Table 6 presents the combined and specific nausea and vomiting domain scores of the patients obtained from the FLIE, which was employed for the evaluation of their Quality of Life. The prophylactic NEPD/APD and NEOPD/AOPD for CINV were determined to have no impact on the patient's daily activities for vomiting, as the vomiting domain score exceeded 54. Nevertheless, the score in the nausea domain falls below 54.

DISCUSSION

One of the most serious concerns about anticancer therapy is CINV, which causes physical and psychological suffering and lowers patient's QOL. Anthracycline chemotherapy has a significant emetogenic rate. As a result, for optimal treatment of the accompanying CINV, international authorities prescribe combination antiemetic regimens including 5HT3-RA, corticosteroids, NK1-RA and/or olanzapine.[21]

The safety and effectiveness of two antiemetic regimens were compared in our study: NEOPD/AOPD-Netupitant/Aprepitant, Olanzapine, Palonosetron and dexamethasone and NEPD/

Table 2: The comparison of prophylactic antiemetic regimen effectiveness in Anthracycline Chemotherapy regimen.

Antiemetic regimen	Effectiveness	No. of Patents (*n* (%))	*p* value	
			Complete Response	Complete Control
NEPD/APD (*n*=36)	Complete Response	33 (91.66)	1.000	0.587
	Complete Control	20 (55.55)		
NEOPD/AOPD (*n*=19)	Complete Response	17 (89.47)		
	Complete Control	10 (52.63)		

Table 3: Assessment of Nausea and vomiting using Common Terminology Criteria for Adverse Events (CTCAE-Version 5.0) on prophylactic antiemetic regimen.

CTCAE Grade	Nausea (*n* (%))	Vomiting (*n* (%))
Grade 1	10 (18.2)	3 (5.5)
Grade 2	11 (20.2)	1 (1.8)
Grade 3	2 (3.6)	1 (1.8)
Grade 4	None	None
Grade 5	None	None

Table 4: Assessment of Adverse Events using Common Terminology Criteria for Adverse Events (CTCAE -Version 5.0) on prophylactic antiemetic regimen.

Grade	Somnolence	Constipation	Headache
Grade 1	1 (1.8)	None	1 (1.8)
Grade 2	1 (1.8)	3 (5.5)	4 (7.3)
Grade 3	None	None	None
Grade 4	None	None	None
Grade 5	None	None	None

Table 5: Comparison of patient's Quality of Life assessment using the Functional Living Index-Emesis (FLIE) on prophylactic antiemetic regimen among anthracycline cycles.

Antiemetic Regimen	5-Day Recall FLIE Score combined domain		
	Cycle I	Cycle II	Cycle III
NEPD/APD	109.40	111.52	109.48
NEOPD/AOPD	106.13	106.06	106.25

Table 6: Comparison of patient's Quality of Life assessment using the Functional Living Index-Emesis (FLIE) on prophylactic antiemetic regimen.

Antiemetic Regimen	5-Day Recall FLIE Score		
	Combined Domain	Nausea Domain	Vomiting Domain
NEPD/APD	107.75	52.15	55.55
NEOPD/AOPD	106.82	51.01	55.57

APD-Netupitant/Aprepitant, Palonosetron and dexamethasone. 55 patients were included in this study for assessment. The participants' average age was 58 years old and 82% of them were female. Because of its high efficacy, anthracycline chemotherapy is still a mainstay in the treatment of various malignancies; including breast cancer.[22] Females dominated our study for this reason. At the time of diagnosis, half of the women with breast cancer were 62 years of age or younger.[23] Our mean participants' age is consistent with this. In general, individualized and efficient patient care depends on understanding the effects of age, gender, cancer type and treatment outcomes.

NEPD/APD was administered more frequently (65%) in our study group than NEOPD/AOPD. The most commonly prescribed chemotherapy treatment in our study population was doxorubicin/cyclophosphamide (25%). For NEPD/APD and NEOPD/AOPD, the complete response rates were 91.66% and 89.47%, respectively, whereas the complete control rates were 55.55% and 52.63%. Both complete response and complete control results did not significantly differ between NEPD/APD and NEOPD/AOPD, according to statistical analysis.

The same results were observed in our previous study, where antiemetic regimens such as OPD (olanzapine, palonosetron and dexamethasone), APD (aprepitant, palonosetron and dexamethasone) and APOD (aprepitant, palonosetron, olanzapine and dexamethasone) were compared and no significant difference in efficacy was obtained.[24] In this investigation, Netupitant was added to the study regimens and compared and the results were consistent with our earlier findings.

According to the study, olanzapine may mitigate anorexia, fatigue and vomiting when added to the steroid-sparing tri-drug combination; however, the full response rate remained unchanged.[25] This is consistent with our findings.

According to CTCAE-Version 5.0, only 3.6% of nausea and 1.8% of vomiting cases were classified as Grade 3 in our study, showing the efficacy of the tested preventive antiemetic treatments. The side effects that were noted included headache, constipation and somnolence. Not a single case with adverse events was classified as Grade 3, 4, or 5, indicating that prophylactic antiemetic medications are safe. In this investigation, adverse effects were not dosage-related and were similar between groups.

Similar findings from previous research were reported, indicating that headache and constipation were the most frequently encountered treatment-related side effects in NEPD/PD regimens and that somnolence is one of the most frequently occurring adverse events associated with olanzapine.[25,26] These adverse effects highlight the necessity of customized treatment plans based on the risk assessment and preferences of the patient.

In terms of QoL, the FLIE combined domain score of NEPD/APD showed a marginal advantage over NEOPD/AOPD over the course of the three cycles under study. Since the vomiting domain score was higher than 54, our study found that the prophylactic NEPD/APD and NEOPD/AOPD for CINV had no effect on the patient's daily activities for vomiting. However, the nausea domain score is lower than 54.

Prophylactic antiemetics are essential in enhancing the QoL in patients undergoing highly emetogenic chemotherapy regimens. Recent antiemetic protocols such as netupitant-palonosetron or aprepitant/olanzapine have exhibited superior QoL outcomes in patients treated with doxorubicin-cyclophosphamide.[27] Furthermore, the utilization of NEPA prophylaxis has demonstrated positive impacts on QoL and high rates of complete response among breast cancer patients undergoing anthracycline-based chemotherapy.[28] These outcomes validate our research findings.

The implementation of evidence-based international antiemetic guidelines, which advocate against single-agent therapies and recommend the use of multi-agent approaches comprising 5HT3-RA, corticosteroids, NK1-RA and/or olanzapine, is crucial for further improving the QoL of individuals receiving Highly Emetogenic Chemotherapy. Additionally, the supplementation of olanzapine to a regimen that spares steroids for antiemetic purposes has proven effective in reducing vomiting, anorexia and

fatigue, thereby contributing significantly to the enhanced QoL of breast cancer patients undergoing anthracycline chemotherapy.[29]

In this observational study, both NEPD/APD and NEOPD/AOPD regimens exhibited comparable efficacy and were considered safer for the management of nausea and vomiting in patients receiving anthracycline-based chemotherapy. The patients demonstrated favorable tolerance to all chemotherapy protocols and antiemetic regimens, resulting in minimal impact on their Quality of Life and only mild adverse events observed without any fatalities.

Consequently, our results provide valuable insights for healthcare professionals regarding prophylactic antiemetic prescriptions and the optimal use of dexamethasone to uphold the effectiveness of antiemetic therapy throughout the designated cycles of anthracycline-based chemotherapy, especially in individuals with increased vulnerability to corticosteroid-related adverse reactions. This study further underscores the importance of adhering to current guidelines for prophylactic CINV management in HEC in order to attain comprehensive CINV control and guarantee optimal chemotherapy outcomes and patient satisfaction.

LIMITATIONS

The subsequent limitations of the present study are duly acknowledged: it was carried out at a singular institution, encompassed a limited sample size, focused solely on three rounds of chemotherapy and lacked a control cohort. While prospective investigations are highly advantageous, their findings may be influenced by potential confounders and intrinsic biases. Individuals with potential confounders or contraindications to the experimental treatment were excluded to ensure the robustness of the study results. Notwithstanding these constraints, our research offers valuable insights into the field and contributes to the advancement of knowledge in this domain.

CONCLUSION

Both the NEPD/APD and NEOPD/AOPD regimens proved to be equally effective and safer in controlling symptoms of nausea and vomiting in patients receiving chemotherapy based on anthracycline in this observational study. The patients exhibited good tolerance to all chemotherapy protocols and antiemetic regimens, with very less impact on their Quality of Life and only mild adverse events noted. As a result, our findings offer valuable guidance to clinicians on prophylactic antiemetic prescriptions and optimizing the utilization of dexamethasone to maintain the efficacy of antiemetic treatment across the prescribed cycles of anthracycline-based chemotherapy, particularly in patients with heightened susceptibility to corticosteroid-related adverse effects. An in-depth analysis of effective dosage, potential drug interactions and long-term safety data is crucial for enhancing prophylactic antiemetic regimens, aiming to enhance the management of CINV and overall patient satisfaction.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

CINV: Chemotherapy Induced Nausea and Vomiting; **QoL:** Quality of Life; **5HT3-RA:** 5-hydroxytryptamine 3 receptor antagonist; **NK1-RA:** Neurokinin-1; **HEC:** High Emetogenic Chemotherapy; **NEPD:** Netupitant, Palonosetron and Dexamethasone; **APD:** Aprepitant, Palonosetron and Dexamethasone; **NEOPD:** Netupitant, Olanzapine, Palonosetron and Dexamethasone; **AOPD:** Aprepitant, Olanzapine, Palonosetron and Dexamethasone; **ECOG:** Eastern Cooperative Oncology Group; **FLIE:** Functional Living Index Emesis; **CTCAE:** Common Terminology Criteria for Adverse Events; **SPSS:** Statistical Package for the Social Sciences; **SD:** Standard Deviation.

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