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Original research article

A comparative study of aprepitant and olanzapine in prevention of chemotherapy induced nausea and vomiting in carcinoma breast patients

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Abstract

Background: Nausea and vomiting the most common side effect of chemotherapy is perceived as a major adverse effect of the treatment. Chemotherapy-induced nausea and vomiting (CINV) is associated with a significant deterioration in quality of life, causing severe clinical conditions, such as electrolyte imbalances, dehydration, malnutrition and leading to treatment discontinuation. Fortunately, improvements in treatments for nausea and vomiting have been able to mitigate these adverse effects in most patients. This study aims to compare Olanzapine with Aprepitant in the prevention of CINV.

Methods and Materials: The study was conducted in breast cancer patients attending the department of oncology at KR hospital. The patients who met inclusion criteria were randomized to one of these two antiemetic regimens.

Group A: Aprepitant group

Group B: Olanzapine group Protocol therapy was continued with each chemotherapy cycle until discontinuation of the same regimen of chemotherapy. Patients were permitted to take rescue therapy of the treating investigator's choice for nausea and/or vomiting based on clinical circumstances. Patients were asked to record daily episodes of vomiting (number and time) and the utilization of rescue therapy. Patients were contacted telephonically to remind them to complete the forms.

Results: CR for vomiting in the acute period was 91.8% and 90.4% (p=0.730); for the delayed period 67.2% and 83.3% (p=0.040); for the overall period 62.3% and 81.7% (p=0.018) for the Olanzapine and Aprepitant arm respectively.

Conclusion: This study shows that Olanzapine is better than Aprepitant in terms of prevention of nausea. While Aprepitant is good in the prevention of vomiting. Hence combination of both Olanzapine and Aprepitant would mitigate both nausea and vomiting in a better way. Combination of these two agents needs to be studied in future studies.

Keywords: Nausea, vomiting, aprepitant, olanzapine.

Introduction

The most common malignancy in women is Breast cancer. Chemotherapy is a common modality for treatment of Carcinoma Breast. Chemotherapy Induced Nausea and Vomiting (CINV) the most common side effect of chemotherapy [1], is associated with a significant deterioration in quality of life [2] and is perceived as a major adverse effect by patients. Regardless of the fact that chemotherapy improves survival, it has its own toxicity and side effects of which nausea and vomiting being significant can affect patient compliance. To avoid the clinical consequences of CINV like dehydration, electrolyte imbalance, malnutrition, anorexia, stress and anxiety, it is imperative to provide prophylaxis and treatment for CINV [3]. The principal neurotransmitters that drive CINV in all forms are serotonin, dopamine, acetylcholine, and substance P [4, 5]. The use of 5- hydroxytryptamine3 (5-HT3) receptor antagonist plus dexamethasone has significantly improved the control of acute CINV [6]. Recent studies have demonstrated additional improvement in the control of acute CINV and delayed CINV with the use of newer agents: Palonosetron, a second generation 5-HT3 receptor antagonist [7]. Aprepitant, the first agent available in the drug class of neurokinin-1 (NK1)-receptor antagonists [8, 9] and Olanzapine, an antipsychotic which is used in the treatment of psychotic symptom [10], blocks multiple neurotransmitters in the central nervous system [11]. These newer drugs incorporated in prophylactic regimens for CINV have resulted in significantly reduced rates of this feared complication of cytotoxic chemotherapy. A recent randomized trial evidence has suggested that Olanzapine may have a role in both the prevention and treatment of CINV [12, 13].

Aprepitant is an oral Neurokinin-1 (NK-1) receptor antagonist which has antiemetic properties that are

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mediated through central blockade in the area postrema [8, 9]. It is a highly selective NK1-receptor antagonist that crosses the blood-brain barrier and occupies brain NK1 receptors. It has no affinity for serotonin, dopamine or corticosteroid receptors. Aprepitant is used in combination with 5-HT3- receptor antagonists and corticosteroids for prevention of acute and delayed nausea and vomiting from highly emetogenic chemotherapeutic regimens. Combined therapy with Aprepitant, Palonosetron and dexamethasone prevents acute emesis in 80-90% of patients compared to less than 70% treated without Aprepitant. Prevention of delayed emesis occurs in more than 70% of patients receiving combined therapy to 30-50% treated without Aprepitant. 14 Olanzapine has been investigated for use as an antiemetic, particularly for the control of chemotherapy Induced Nausea and Vomiting (CINV) [12, 13]. A 2007 study demonstrated its successful potential for this use, achieving a complete response in the acute prevention of nausea and vomiting in patients treated with moderately and high emetogenic chemotherapy [15].

Materials and Methods

Patients diagnosed with Carcinoma Breast receiving Doxorubicin 60 mg/m2 and Cyclophosphamide 600 mg/m2 from Krishna Rajendra Hospital, Mysore were recruited, after obtaining ethics approval. This randomized prospective study was conducted between February 2016 to February 2017.

The objective of the study was to i) compare the efficacy of Aprepitant and Olanzapine in the prevention of chemotherapy induced nausea, ii) compare the efficacy of Aprepitant and Olanzapine in the prevention of acute and delayed emesis due to moderately emetogenic agents. Protocol therapy was continued with each chemotherapy cycle until discontinuation of the same regimen of chemotherapy. Patients were permitted to take rescue therapy of the treating investigator's choice for nausea and/or vomiting based on clinical circumstances. In this study acute period is defined as 0–24 hours post chemotherapy, delayed period as day 2-5 post chemotherapy and overall period as day 1–5 post chemotherapy. The primary end point of the study is complete response (CR) for nausea that is no nausea in the acute, delayed and overall periods. Secondary endpoint is CR for vomiting and no use of rescue drugs in acute, delayed and overall period. Beginning with the first day of chemotherapy (day1) and daily through day 5, patients were asked to record daily episodes of nausea using a visual analogue scale from 0 to 10, with 0 indicating no nausea and 10 indicating a maximal level of nausea. They were asked to record daily episodes of vomiting (number and time) and the utilization of rescue therapy. Patients were contacted telephonically to remind them to complete the forms. The study included female subjects with histologically confirmed breast cancer scheduled for chemotherapy (naïve), aged > 18 years not complaining of nausea in the past 24 hours prior to initiation of chemotherapy. The patients must have Renal and liver function tests within the following limits- Serum Creatinine ≤ 1.4 mg/dL, Serum Bilirubin ≤ 1.2 mg/dL, Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvic Transaminase (SGPT) less than or equal to three times the upper limits of normal. The Total Leukocyte Count > 2000 cells/mm3. Females of child bearing potential had to have a negative urine pregnancy test. Patients with history of seizure disorder, Brain Metastasis, treatment with another antipsychotic agent such as risperidone, quetiapine, clozapine, phenothiazine or butyrophenone for 30 days prior to or during protocol therapy, Hypersensitivity to olanzapine, History of cardiac arrhythmia, Uncontrolled congestive cardiac failure or acute myocardial infarction in the previous 6 months or History of diabetes mellitus were excluded from the study. Randomization was done using computer generated numbers.122 patients were randomly divided into two groups with 61 patients in each. After obtaining informed consent, subjects were randomized to either groups.

Group A patients received the following treatment- Day 1 - Inj. Palonosetron 0.25 mg, Inj. Dexamethasone 8 mg, Tab. Aprepitant 125 mg: Day 2

- Tab. Aprepitant 80 mg; Day 3 - Tab. Aprepitant 80 mg.
- Group B patients received the following treatment- Day 1 - Inj. Palonosetron 0.25 mg, Inj. Dexamethasone 8 mg, Tab. Olanzapine 10 mg; Day 2 Tab. Olanzapine 10 mg; Day 3 – Tab. Olanzapine 10 mg.

The sample size for the study was determined using estimation technique, and was calculated based on one year prevalence rate of 0.189 for Carcinoma Breast (p = 87/460),with an alpha of5%, and absolute allowable error 10%as61 in each group. Protocol therapy continued with each chemotherapy cycle until discontinuation of the same regimen of chemotherapy. Patients were permitted to take rescue therapy of the treating doctor's choice for nausea and/or vomiting based on clinical circumstances. The data obtained were analyzed for statistical significance (P) with appropriate statistical tests using R software. Starting first day of chemotherapy (Day 1), through Day 5 patients were asked to record daily episodes of nausea using a visual analogue scale from 0 to 10, with 0 indicating no nausea and 10 indicating a maximal level of nausea and any utilization of rescue drugs. They were also asked to record daily episodes of vomiting (number and time), the daily intensity of symptoms and the utilization of rescue therapy. The primary end point in the study was assessment of Complete Response (CR) for nausea, that is to see whether no nausea and no use of rescue drugs in the acute, delayed and overall periods.

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Secondary end point is the Complete Response (CR) for Vomiting in acute, delayed and overall period. Acute Period was defined as 0-24 hours post chemotherapy, delayed period was day 2-5 post chemotherapy and overall period was day 1-5 post chemotherapy.

Results

Table 1: Response rates

Complete response	Olanzapine group (patients number)	Aprepitant group (patients number)	p Value
Acute nausea	85.2% (52/61)	65% (39/60)	0.010
Delayed nausea	55.7% (34/61)	50% (30/60)	0.527
Overall nausea	54.1% (29/61)	48.3% (33/60)	0.526
Acute vomiting	91.8% (56/61)	90% (54/60)	0.730
Delayed vomiting	67.2% (41/61)	83.3% (50/60)	0.040
Overall vomiting	62.3% (38/61)	81.7% (49/60)	0.018

A total of 121 chemotherapy naïve breast cancer patients were enrolled in the study from December 2015 to December 2016. Olanzapine group had 61 patients and Aprepitant group had 60 patients. Median age of the study population was 47 years; range 29-80, Eastern Cooperative Oncology Group (ECOG) performance status was 0 and 1. Cure rate for nausea in the acute period was 85.2% and 65% (p=0.010); for the delayed periodit was 55.7% and 50% (p=0.527); and for the overall period 54.1% and 48.3% (p=0.526) for the Olanzapine, and Aprepitant arm respectively. CR for vomiting in the acute period was 91.8% and 90.4% (p=0.730); for the delayed period 67.2% and 83.3% (p=0.040); for the overall period 62.3% and 81.7% (p=0.018) for the Olanzapine and Aprepitant arm respectively. There was no Grade 3 or 4 toxicities in both the arms.

Discussion

A Randomized, Double-Blind, placebo- controlled trail by Naomi Mizukami *et al.* in Japan on 44 patients scheduled to receive highly or moderately emetogenic chemotherapy yielded similar results as our study. All patients received a 5-HT3 receptor antagonist, steroid and neurokinin-1 receptor antagonist. Patients were randomly assigned to take 5mg/day of oral Olanzapine or placebo daily from day before chemotherapy (Day 0) to Day 5. The rate of patients achieving total control was significantly higher in the group receiving Olanzapine than in the control group. Furthermore, the Olanzapine group experienced better Quality of Life than the control group [17].

A Phase III trial was performed from the Indiana University School of Medicine and University of Norte Dame by Rudolph M. Navari on 241 chemotherapy patients receiving cisplatin or cyclophosphamide and doxorubicin, comparing Olanzapine and Aprepitant in combination with palonosetron and dexamethasone. The study concluded by stating that Olanzapine was comparable to Aprepitant in the control of CINV and nausea was better controlled by Olanzapine [16].

A retrospective study was performed by Flank *et al.*, Department of Pharmacy at The Hospital for Sick Children, Toronto, Canada where sixty children below the age of 18 with poorly tolerated CINV were started on Olanzapine at 0.1 mg/kg/dose. Most of the children experienced complete CIV control throughout the acute phase and the effects of Olanzapine was also monitored throughout the entire course of chemotherapy. The study concluded by stating that Olanzapine may be an important option to improve chemotherapy Induced Vomiting in children [19]. In a study conducted by Hocking CM *et al.* at Flinders Centre for Innovation in Cancer, Bedford Park, South Australia with 488 patients from three trials of CINV prophylaxis and 323 patients of three trials of breakthrough CINV, regimens with Olanzapine were associated with significant improvements in CINV prevention with both Moderately Emetogenic Chemotherapy (MEC) and Highly Emetogenic Chemotherapy (HEC). Data from the Randomized Controlled Trials support the use of an Olanzapine containing combination regimen as an option for CINV prophylaxis and single agent Olanzapine for the treatment of breakthrough CINV. In the included trials, the short duration of Olanzapine appears safe and well tolerated [19].

Conclusion

This study shows that Olanzapine is better than Aprepitant in terms of prevention of nausea. Whereas Aprepitant is good in the prevention of vomiting. Hence combination of both Olanzapine and Aprepitant would mitigate both nausea and vomiting in a better way. Combination of these two agents needs to be studied in future studies.

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