EFFICACY OF OLANZAPINE CONTAINING REGIMEN IN PREVENTION OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING IN PATIENTS OF BREAST CANCER RECEIVING HIGHLY EMETOGENIC CHEMOTHERAPY

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ABSTRACT

Objective: To investigate the efficacy of Olanzapine containing regimen as prophylaxis of Chemotherapy Induced Nausea/Vomiting (CINV) in patients with breast cancer, receiving Highly Ematogenic Chemotherapy (HEC).
Study Design: Quasi experimental study.
Place and Duration of Study: This study was carried out at department of Medical Oncology, CMH Rawalpindi, from Aug 2015 till Feb 2017.
Methodology: After meeting the inclusion/exclusion criteria, 44 patient of breast cancer receiving Doxorubicin and Cyclophosphamide chemotherapy, were equally divided in group A and B. Group A received conventional ondansetron IV (8mg), dexamethasone IV (8mg) and Zantac IV (50mg) on day 0 (30 min before chemotherapy) with ondansetron PO (8mg) BD on day 1 and 2, while group B received olanzapine PO (10mg), dexamethasone IV (8mg) and ondansetron IV (8mg) on day 0 with olanzapine PO (10mg) OD on day 1 and 2. Nausea / vomiting scores were calculated in each patient from Day 0 till Day 6. Any episode of rescue medication was also recorded for control of breakthrough nausea/vomiting. The primary efficacy point was to compare complete response between 2 groups, where complete response was defined as Nausea score <2, Vomiting score 0 and no use of rescue medications.
Results: Twenty out of 22 patients (90.9%) showed a complete response in group B, whereas only 8 (36.4%) out of 22 (36.4%) patients showed complete response in group A.
Conclusion: Olanzapine containing regimen has shown better efficacy than conventional CINV prophylaxis regimen for patients receiving HEC in breast cancer.

Keywords: Chemotherapy Induced Nausea/Vomiting, Highly Ematogenic Chemotherapy, Olanzapine.

INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) is a well-documented adverse effect for patients undergoing chemotherapy treatment[1]. This is often the most feared side effect experienced by cancer patients and apart from causing significant discomfort to the patient, this can even lead to metabolic disturbances, anorexia and negatively impact the quality of life of a morbidly ill patient[2]. The severity of chemotherapy induced nausea and vomiting depends not only on the specific agent prescribed but also on the dose used. Some chemotherapeutic drugs are therefore particularly notorious for causing CINV and are referred to as 'highly emetogenic', often leading to failure in compliance, economic burden on both patient and healthcare system via increased hospital visits[3]. Furthermore, increased 'first experience' severe nausea and vomiting often leads to 'anticipatory' emesis in later cycles as well[4].

Breast cancer is one of the most common malignancies worldwide[5]. Pakistani females have one of the highest incidence rates in the world[6]. Current practice in Pakistan includes the use of Anthracyclinand Cyclophosphamide (AC) chemotherapy followed by taxanes. This AC chemotherapy regimen has been classified by the American Society of Clinical Oncology (ASCO) as highly emetogenicchemotherapy (HEC)[7]. Further agents like 5 Fluouracil are also commonly added

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to this regimen which may increase the efficacy but aggravates the emetogenic effect[8].

Several guidelines exist to prevent CINV in patients receiving HEC, catering for both acute phase and the delayed phase of CINV[9]. Most recommend the use of 5- hydroxytryptamine type 3 (5-HT3) receptor antagonist along with intravenous dexamethasone and a neurokinin 1 (NK1) antagonist for prevention of CINV in HEC and similar combinations of moderately ematogenic chemotherapy (MEC)[10]. NK 1 antagonist (Aprepitant) containing regimens are although effective but very expensive, on the contrary olanzapine containing regimens are cheaper but still are not frequently in useacross Pakistan. The conventional CINV prophylaxis for HEC in Pakistan usually consists of dexamethasone, ondansetron and Ranitidine.

Olanzapine is primarily used as an antipsychotic medication[11]. The mechanism of action of this compound involves blocking most of neuro-transmittors like dopamine at D1, D2, D3 and D4 brain receptors, serotonin at 5-HT_{2a}, 5-HT_{2c}, 5-HT_3, and 5-HT_6receptors, catecholamines at alpha-1 adrenergic receptors, acetylcholine at muscarinic receptors, and histamine at H1 receptors[12].

Several studies in published literature have studied the efficacy of olanzapine in the prophylaxis as well as treatment of CINV and also for breakthrough CINV[13]. Limited research was found that investigated the efficacy of this medication in the control of CINV in Pakistani population. We were interested in its efficacy in patient with breast cancer receiving HEC in Pakistan.

The objective of this study was to investigate the efficacy of olanzapine containing regimen as prophylaxis for CINV in patients with breast cancer receiving HEC.

METHODOLOGY

This was a Quasi experimental study conducted at the Combined Military Hospital, Rawalpindi (Department of Medical Oncology) from Aug 2015 till Feb 2017.

Inclusion criteria was patients of breast cancer receiving AC (Doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2) chemotherapy, Chemonaive patients, predicted life expectancy >6 months, performance status (Eastern coopera-tive oncology group) 0-1 andage between 30 and 60 years. Exclusion was criteriaany associated intracranial or liver metastatic disease, vomiting within 48 hrs before the day of chemotherapy, active ongoing infection. Severe concurrent illness, already receiving systemic steroids. ANC <1.5, PLT <100,000, ALT >1.5 times ULN, Creatinine >1.5 times ULN and Baseline ECG showing long QTc interval.

After taking ethical approval from the hospitals ethical committee, 44 patients of breast cancer meeting the inclusion criteria were randomly assigned to group A and B (22 in each). Non probability consecutive sampling was done and randomization was done through random number tables. Both groups were well matched for age and staging parameters. Nausea/vomiting prevention regimen in both the groups (table-I).

All patients were given diaries to monitor efficacy of nausea/vomiting prevention from initiation of chemo infusion (0 hrs) until morning of day 6 (120 hrs). In their diaries, each patient documented daily average nausea score by Visual Analog Score: 0 means no nausea and 10 means severe nausea. Vomiting score was also similarly documented daily by Visual Analog Score: 0 means no vomiting and 10 means severe vomiting and use of rescue medications to control breakthrough nausea/vomiting was also recorded if required. Patients were allowed to take rescue medication e.g dexamethasone, domperidone or ondansetrone to control breakthrough nausea/vomiting.

The primary efficacy point was to compare complete response between 2 groups, where complete response is defined as Nausea score <2, Vomiting score 0 and no use of rescue medications.

Data was analyzed in SPSS version 21. Mean ± SD were calculated for quantitative variables. Frequency and percentages were calculates for quantitative variables Mann-Whitney U-test was uesd for comparison. A *p*-value ≤0.05 considered as significant value.

RESULTS

A total of 44 patients were enrolled (22 in each group A and B).

The demographic details are described in table-II. The antiemetic regimens (including dosages) for each group has already been described above.

Table-I: CINV prophylaxis regimen given to both study groups.

Days	Regimen A	Regimen B
Day 0 (before chemotherapy)	Ondansetron 8mg IV Dexamethasone 8mg IV Ranitidine 50mg IV	Olanzapine 10mg PO Ondansetron 8mg IV Dexamethasone 8mg IV
Day 1	Ondansetron (PO) 8mg x BD	Olanzapine (PO) 10mg x OD
Day 2	Ondansetron (PO) 8mg x BD	Olanzapine (PO) 10mg x OD

Table-II: Patient demographics and baseline characteristics.

	n	Minimum	Maximum	Mean±S.D
Age of Patient	44	36	58	47.75 ± 6.217
Gender		**Frequency**		**Percentage**
Male		3		6.8
Female		41		93.2

Table-III: Nausea score in groups receiving each prophylactic regimen.

	Group	n	Median (IQR)	Mean Rank	*p*-value
Nausea Score	A	22	4 (4.50)	30.86	<0.001
	B	22	2 (1.50)	14.14	

Table-IV: Emesis score in groups receiving each prophylactic regimen.

	Group	N	Median (IQR)	Mean Rank	*p*-value
Emesis Score	A	22	3 (2.00)	29.14	<0.001
	B	22	2 (3)	15.86	

The mean age of the study population was 47.75 years and both groups were well matched for age and gender.

The average nausea and emesis score reported by patients in each group was described in table-III.

Sixteen patients (72.7%) in group A required breakthrough medication whereas only 3 patients (13.6%) required breakthrough medication in group B. Twenty out of 22 patients (90.9%) therefore showed a complete response in group B, whereas only 8 out of 22 patients (36.4%) showed complete response in group A (p<0.001) (table-IV).

DISCUSSION

Adequate control of nausea and vomiting is of paramount importance to improve compliance to any regimen of chemotherapy and to improve the overall quality of life of patients with cancer.

The VAS score for nausea and emesis has proved practical, accurate and reproducible in a large number of clinical trials and therefore this method was adapted in the present study. We further observed that increased communication between patient and health care professional allowed our patients to use such tools to objectively report toxicity of the treatment and prevented under reporting of nausea.

Olanzapine was originally introduced as an anti-psychotic agent, but its high affinity to bind to several receptors in the CNS including dopamine, histamine, muscurinic and alpha adrenergic receptors has also proven it effective against CINV[14]. Various studies have investigated its efficacy to control symptoms of nausea and vomiting in both MEC and HEC in several types of cancers, both in the young[15]and the old[16].

Olanzapine has also been recommended by the NCCN and ESMO as a useful drug for breakthrough CINV[17]. Furthermore its efficacy has been studied in the prevention of both acute and delayed phases of CINV[18].

A single phase III study showed that olanzapine was comparable in efficacy to aprepitant when combined with dexamethasone and palonsetron when use as prophylaxis of CINV in HEC[19]. Our findings have also demonstrated an increased efficacy of olanzapine containing regimen compared to conventional prophylaxis treatment of CINV offered routinely to our patients. Although we have not compared olanzapine with aprepitant containing antiemetic regimen in this study (which is standard of care in international oncology centers), but we intended to do this comparison study in near future.

Assessment of side effects of olanzapine was not part of our study but the most frequently observed adverse effect of olanzapine containing regimen was drowsiness and dizziness. This was observed in less than 16% of our patients and was comparable to the frequency of similar symptoms in the other group. Other symptoms reported included asthenia and fatigue (8%) and constipation (5%). However, this agent was generally well tolerated by the majority of our cohort. Other studies have also exhibited good tolerance to this medication in cancer patients[20]. Although olanzapine in notorious to cause hyperglycemia, but in our study we have not observed severe abnormalities in blood glucose profiles in patients who received olanzapine.

Worthy to note here was the pharma-coeconomics of this drug (expressed as cost: benefit in terms of monetary value, efficacy and enhanced quality of life). In a developing country like Pakistan the positive efficacy and tolerability profile, as demonstrated by our study, favors this drug when considering optimal healthcare resource allocation in a very heavily burdened health budget. Although aprepitant containing antiemetic regimen remains standard of care in HEC, but considering high cost of this drug in Pakistan, it is difficult to prescribe it uniformly to all HEC regimens. Considering relatively small sample size of our study population, we do recommend further trials on larger populations to support our results.

CONCLUSION

Olanzapine containing regimen has shown better efficacy as compared to conventional CINV prophylaxis regimen for patients receiving HEC in breast cancer.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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