Vol 10 | Issue 2 | 2020 | 20-28.

ge-ISSN 2248 – 9142
print-ISSN 2248 – 9134

International Journal of
Current Pharmaceutical & Clinical Research

www.ijcpcr.com

EFFICACY AND SAFETY OF ANTIEMETIC COMBINATIONS IN PATIENTS RECEIVING EMETOGENIC CHEMOTHERAPEUTIC AGENTS

Dr. Bharath Rangarajan[1]*, Dr. Anna Susan mathai[2]*, Dr. Sugumar subramanian[2]*, Dr. Mariya Thomas[2]*, Dr. Sherin Jacob Thomas[2]*, Dr.Sheenu Benoy[2]*

1*-MD (Internal Medicinre), DM (Medical Oncology), ECMO, PDCR, Consultant Medical Oncologist, Hemotologist And Stem Cell Transplant Physician.
2*- Pharm D (Doctor of Pharmacy), KMCH College of Pharmacy, Nehru Nagar, Klapatti, India.

ABSTRACT

Chemotherapy is a type of cancer treatment that uses one or more anti-cancer drugs (chemotherapeutic agents) as part of a standardized chemotherapy regimen. This means chemotherapy can kill cancer cells that have spread (metastasized) to parts of the body far away from the original (primary) tumor. Receptors for a number of neurotransmitters with potentially important roles in the emetic response are present in the dorsal vagal complex. These include the neurokinin-1, 5-HT3, and dopamine-2 receptors, which bind to substance P, 5-HT, and dopamine, respectively. 56 patients of the total number of 150 subjects underwent concurrent radiation therapy. Among the patients who received concurrent chemo-radiation, n=32(21.3%) were given OPD regimen, n=17(12.5%) were given APD regimen and n=7(4.7%) received APOD regimen. More number of patients with chemotherapy alone received complete response to anti-emetic regimen. Patients taking very highly emetogenic chemotherapy were n=11(7.3%) followed by highly emetogenic chemotherapy 101(67.3%) and moderately emetogenic chemotherapy 38(25.3%). In this observational study, no significant difference was observed between olanzapine and aprepitant in preventing nausea and emesis induced by highly and moderately emetogenic chemotherapy. Olanzapine can improve the complete response of acute and delayed, nausea and vomiting when compared with the standard therapy of anti-emesis. Thus Olanzapine has been shown to be safe and effective agent for the prevention of CINV, especially in delayed phase. It is also a highly cost effective drug compared with 5HT3 serotonin antagonist and NK1 antagonists. Thus we suggest olanzapine is a good choice for prophylactic treatment in chemotherapy.

Key words: CR, HEC, MEC, CINV.

INTRODUCTION

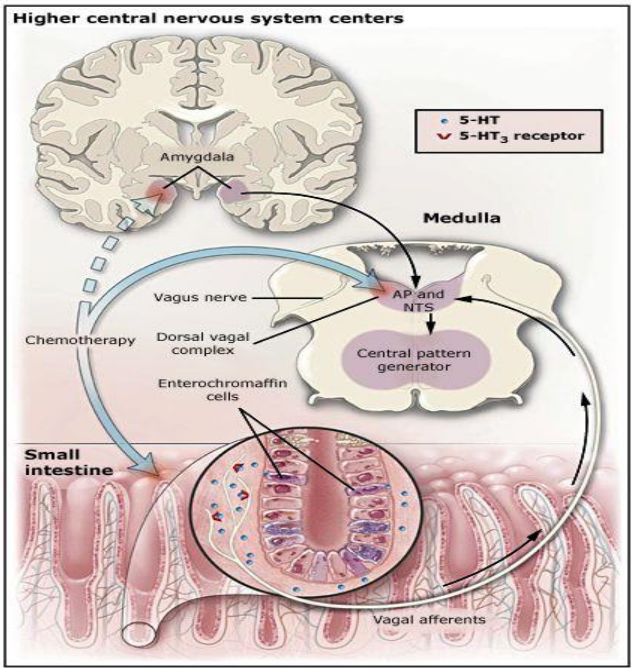
Cancer is a group of disease involving abnormal cell growth with the potential to invade or spread to other parts of the body. Cancer is often treated with radiation therapy, surgery, chemotherapy and targeted therapy alone or in combination. One of the common side effects of chemotherapy is chemotherapy induced nausea and vomiting (CINV). Chemotherapy is a type of cancer treatment that uses one or more anti-cancer drugs (chemotherapeutic agents) as part of a standardized chemotherapy regimen. This means chemotherapy can kill cancer cells that have spread (metastasized) to parts of the body far away from the original (primary) tumor [1].

Pathways of chemotherapeutic agents produce an emetic response

Chemotherapy causes emesis through effects at a number of sites. When antineoplastic agents are

Corresponding Author :- **Dr. Bharath Rangarajan** Email:- bharath37@gmail.com

administered, 5-hydroxytryptamine (5-HT) is released from the upper small intestine enterochromaffin cells, 5-HT activates 5-HT3 receptors on extrinsic intestinal vagal and spinal afferent nerves. These afferent fibers have projections to the nucleus tractus solitarius (NTS) and the area postrema (AP) [9], the two parts of the brain referred to collectively known as the dorsal vagal complex [2]. Receptors for a number of neurotransmitters with potentially important roles in the emetic response are present in the dorsal vagal complex. These include the neurokinin-1, 5-HT3, and dopamine-2 receptors, which bind to substance P, 5-HT, and dopamine, respectively. Receptors for other locally released mediators, such as cholecystokinin, and prostaglandins, are also present on the vagal afferent terminals [3]. However, the extent to which these mediators are involved at this peripheral site is unknown. Antineoplastic agents may also induce emesis through an interaction with the area postrema within the dorsal vagal complex [5].



Antiemetics

Antiemetic agents have been developed by identifying the receptors involved in emesis and nausea and creating agents that effectively block these receptors [6]. Complete response is defined as no emesis and no rescue therapy in cancer patients. Antiemetic therapy aims to minimize or eliminate CINV in an optimal manner in all cancer patients, so the methods of CINV control can be improved further. Recently, the Multinational Association of Supportive Care in Cancer (MASCC) and the European Society of Medical Oncology (ESMO) updated the guidelines for prevention of chemotherapy- and radiotherapy induced nausea and vomiting. Several large studies have shown that addition of aprepitant to a regimen containing granisetron or ondansetron and dexamethasone can significantly improve prevention of acute and delayed emesis for patients receiving highly emetogenic chemotherapy (HEC)[7].

According to the MASCC/ESMO guidelines, routine prophylaxis with an NK-1 receptor antagonist is not included for patients administered MEC. Conversely, the benefit of an aprepitant-containing triple antiemetic regimen for a broad range of MEC regimens has also been reported. The role of a NK-1 inhibitor with a second-generation 5-HT3 receptor antagonist as a prophylactic agent is also not clear. However, the efficacy of a regimen comprising palonosetron, an NK-1 inhibitor, and dexamethasone for MEC has not been investigated thoroughly [10].

General Principles of antiemetics used in CINV

- **Corticosteriods:** Dexamethasone one should be administered once daily (either orally or intravenously) for moderately and highly emetogenic chemotherapy and for 2 to 3 days after chemotherapy for regimens that are likely to cause significant delayed emesis.
- **Palonosetron:** A single intravenous palnosetron dose of 0.25 mg may be sufficient prior to the start of a 3-day chemotherapy regimen instead of multiple daily doses of another oral or intravenous serotonin antagonist. In terms of efficacy, the need for repeat dosing with palonosetron, either daily or less frequently. Palonosetron is believed to prevent emesis by blocking the binding of serotonin to 5-HT3 receptors located on the nerve terminals of the vagus in the gastrointestinal tract and centrally in the chemoreceptor trigger zone of the area postrema [11].
- **NK 1 Antagonists:** Aprepitant or fosaprepitant may be used for multiday chemotherapy regimen likely to be highly emetogenic and associated with significant risk for delayed nausea and emesis. It acts by selectively blocks the binding of substance P at the NK-1 receptor in the central nervous system.
- **Olanzapine:** Olanzapine is second generation atypical thienobenzodiazepine antipsychotic with a broad spectrum of neurotransmitter blockade including: Serotonin 5HT2a, 5HT2c, 5HT3, 5HT6 receptors, dopamine D1,D2,D3,D4 brain receptors, adrenergic receptors, acetylcholine muscarinic receptors, and H1 histamine receptors. This broad spectrum of action particularly of dopamine and serotonin receptors, has led to increasing interest in its use as an antiemetic as it is likely to act at the vomiting center and CTZ. It is used for treatment of chemotherapy related nausea and vomiting have suggested OLN to be an efficacious agent with relatively few side effects [12].

AIM

To evaluate the comparability of anti-emetic combinations in emetogenic chemotherapy regimens

OBJECTIVES

a) Primary Objectives: To evaluate the safety and efficacy of three different regimens (OPD, APD, APOD)

b) Secondary Objectives: To evaluate the toxicity of three different regimens (OPD, APD, APOD).

MATERIALS & METHODS

Study design:

A prospective comparative study in patients experiencing chemotherapy induced nausea and vomiting.

Study site:

Study was performed at Comprehensive Cancer Center, Kovai Medical Center and Hospital, Coimbatore, Tamil Nadu, India. The proposed protocol for the study was put forwarded to ethical committee in the study center and was approved. (Designated EC/AP/519/02/2017)

Study period

This study was conducted over a period of six months from February 2016 to July 2017

Inclusion criteria

- Patients having age of 15 years or above with confirmed malignant disease
- Both male and female patients.
- Patients receiving chemotherapy and radiation.
- Patients with a serum creatinine level of ≤ 2.0 mg/dl

Exclusion criteria

- Patients with history of CNS disease (brain metastases, seizure disorder)
- Patients on treatment with another antipsychotics for 30 days prior to or during the protocol therapy.
- Patients with hypersensitivity to olanzapine
- Patients having motion sickness.
- Pregnant Woman

Sources of data:

- Data Collection Form
- Patient Case Reports
- Medication/Treatment Chart
- CINV Diary
- Patient Interview

Study population

150 patients were observed in oncology department during study period.

Study protocol

Patients who met the inclusion criteria will be selected for the study. Demographic data, laboratory report and treatment chart will be collected. Further, patients will be categorized according to CINV grading. The data will be analyzed statistically to evaluate the efficacy and safety among the OPD, APD and APOD in patients receiving highly and moderately emetogenic potential agents and effective dosing of olanzapine in prevention of acute and delayed chemotherapy induced nausea and vomiting.

Statistical analysis

IBM SPSS (statistical package for the social science) version 24.0 was used for the statistical analysis. Pearson Chi Square Test was the statistical tool used to compare the safety and efficacy of antiemetic combinations. Significance of individual variables where found out using Chi Square Test. A value for $p<0.05$ was considered statistically significant.

RESULTS

This prospective interventional study was aimed to evaluate the safety and efficacy of OLN vs APR in patients receiving chemotherapy/ concurrent chemotherapy & radiation therapy. A total of 150 patients admitted to hospital were taken for study during the period from March 2017 to July 2017. Our study population was divided into 3 study arms based on the antiemetic regimen they received: APD, OPD, APOD.

Table 1. NCCN Levels of Emetogenicity [4]

Level 5	High Emetic Risk: 90% frequency of emesis
Level 3 or 4	Moderate Emetic Risk: 30-90% frequency of emesis
Level 2	Low Emetic Risk: 10-30% frequency of emesis
Level 1	Minimal Emetic Risk: <10% frequency of emesis

Table 2. Patient-related Risk Factors for Emesis Following Chemotherapy[8]

Major Factors	Minor Factors
Female	History of motion Sickness
Age <50 years	Emesis during past pregnancy
History of low prior chronic Alcohol intake (<1 ounce of alcohol/day)	
History of previous Chemotherapy-induced emesis	

Table 8: Number of Patients with and without vomiting in highly emetogenic regimen

Regimen	Without Vomiting	With Vomiting	Total
OPD	48	10	58
APD	30	4	34
APOD	16	4	20

Table 11: Effect of nausea in highly emetogenic chemotherapeutic agents

Antiemetic Regimen	Highly Emetogenic Regimen – Nausea					
	Acute Nausea		Delayed Nausea		Overall Nausea	
	CR	NO CR	CR	NO CR	CR	NO CR
OPD (n=58)	100.0% (n=58)	-	68.96% (n=40)	31.01% (n=18)	68.96% (n=40)	31.01% (n=18)
APD (n=34)	100.0% (n=34)	-	85.29% (n=29)	14.7% (n=5)	85.29% (n=29)	14.7% (n=5)
APOD (n=20)	100.0% (n=20)	-	75.0% (n=15)	25.0% (n=5)	75.0% (n=15)	25.0% (n=5)
Total	n=112	-	n=84	n=28	n=84	n=28

Table 12: Effect of vomiting in highly emetogenic chemotherapeutic agents in response to antiemetic combinations

Antiemetic Regimen	Moderate Emetogenic Regimen – Nausea					
	Acute Nausea		Delayed Nausea		Overall Nausea	
	CR	NO CR	CR	NO CR	CR	NO CR
OPD (n=9)	100.0% (n=9)	-	100.0% (n=9)	-	100.0% (n=9)	-
APD (n=27)	100.0% (n=27)	-	88.88% (n=24)	11.11% (n=3)	88.88% (n=24)	11.11% (n=3)
APOD (n=2)	100.0% (n=2)	-	100.0% (n=2)	-	100.0% (n=2)	-
Total	n=38	-	n=35	n=3	n=35	n=3

Table 13: Effect of nausea in moderate emetogenic chemotherapeutic agents in response to antiemetic combinations

Antiemetic Regimen	Moderate Emetogenic Regimen - Vomiting					
	Acute Nausea		Delayed Nausea		Overall Nausea	
	CR	NO CR	CR	NO CR	CR	NO CR
OPD (n=9)	100.0% (n=9)	-	100.0% (n=9)	-	100.0% (n=9)	-
APD (n=27)	100.0% (n=27)	-	96.29% (n=26)	3.70% (n=1)	96.29% (n=26)	3.70% (n=1)
APOD (n=2)	100.0% (n=2)	-	100.0% (n=2)	-	100.0% (n=2)	-
Total	n=38	-	n=37	n=1	n=37	n=1

Table 14: Effect of vomiting in moderate emetogenic chemotherapeutic agents in response to antiemetic combination

Antiemetic Regimen	Highly Emetogenic Regimen - Vomiting					
	Acute Nausea		Delayed Nausea		Overall Nausea	
	CR	NO CR	CR	NO CR	CR	NO CR
OPD (n=58)	100.0% (n=58)	-	82.75% (n=48)	17.24% (n=10)	82.75% (n=48)	17.24% (n=10)
APD (n=34)	100.0% (n=34)	-	88.23% (n=30)	11.76% (n=4)	88.23% (n=30)	11.76% (n=4)
APOD (n=20)	100.0% (n=20)	-	80.0% (n=16)	20.0% (n=4)	80.0% (n=16)	20.0% (n=4)
Total	n=112	-	n=94	n=18	n=94	n=18

Figure 1: Gender-Wise distribution among study population (n=150)

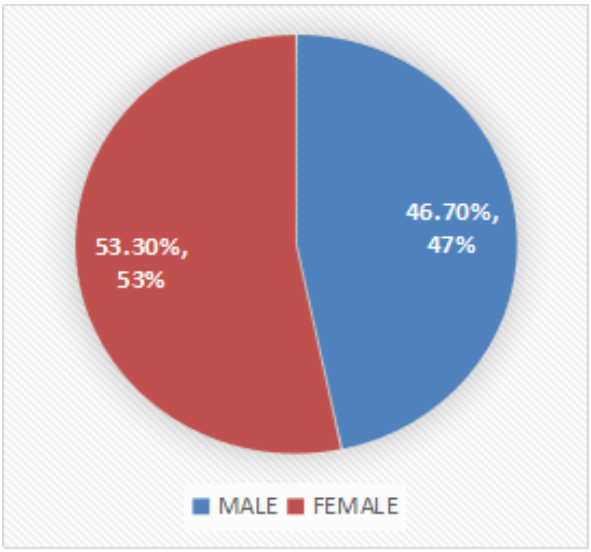


Figure 2: Age-Wise Distribution among the study population (n=150)

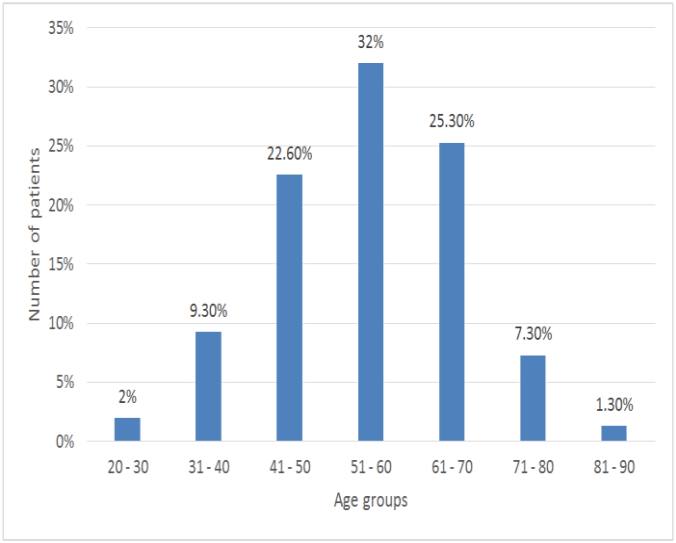


Figure 3: Distribution of Antiemetic regimen

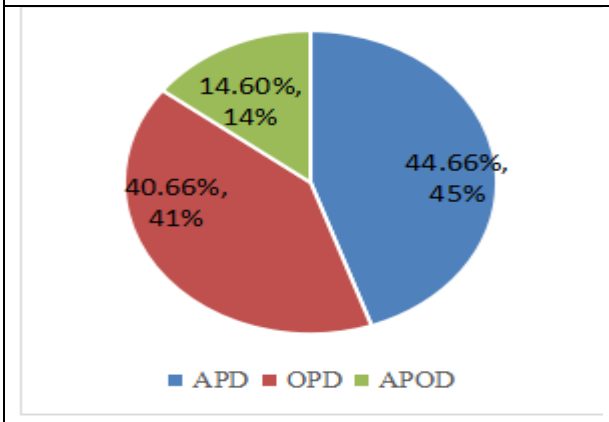


Table 4: Distribution of Antiemetic Regimen According to Type of Cancer

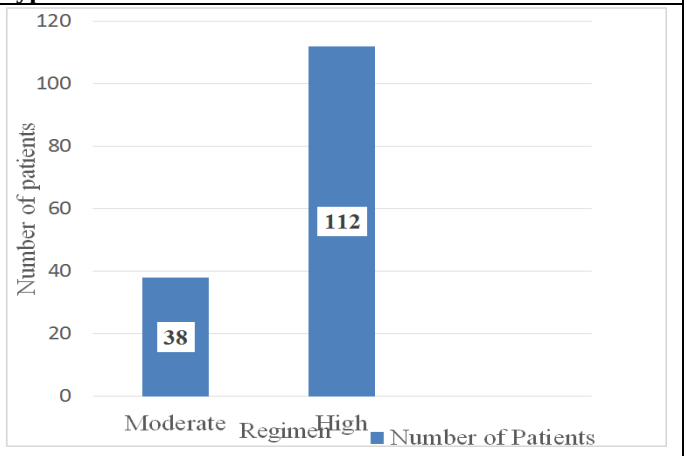
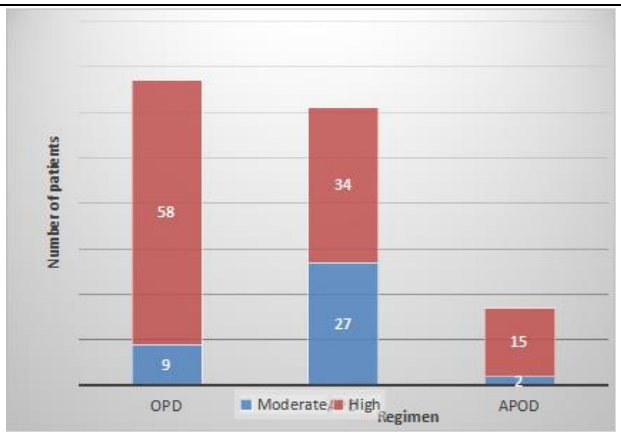


Figure 6: Number of Patients with and without nausea in highly emetogenic regimen



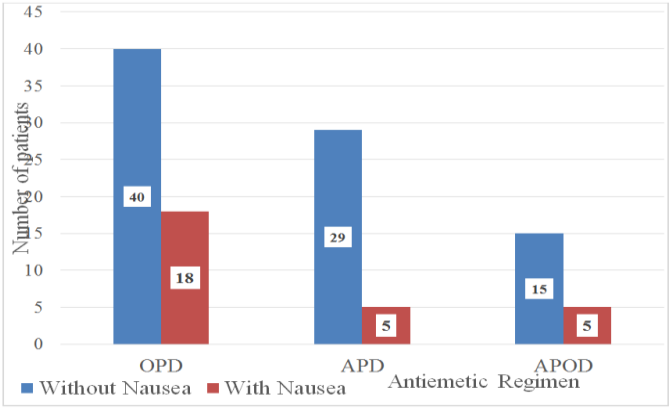


Figure 7: Number of Patients with and without vomiting in highly emetogenic regimen

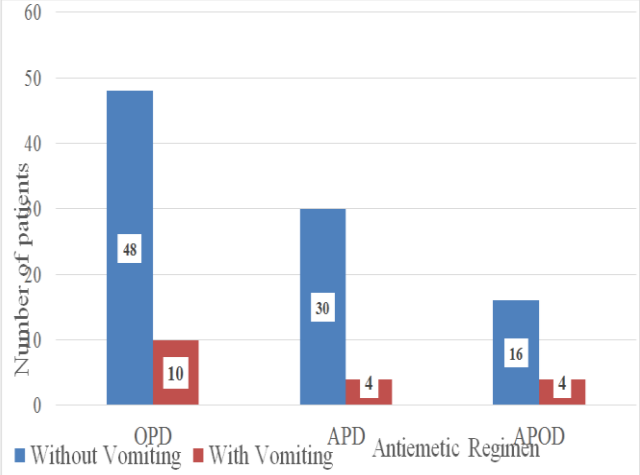


Figure 9: Number of Patients with and without vomiting in moderately emetogenic regimen

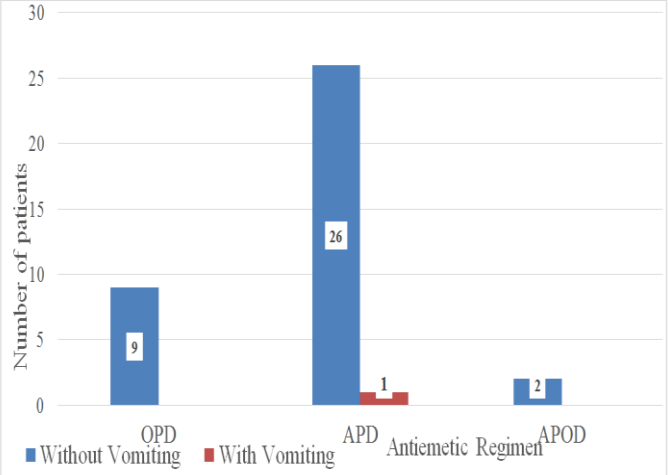
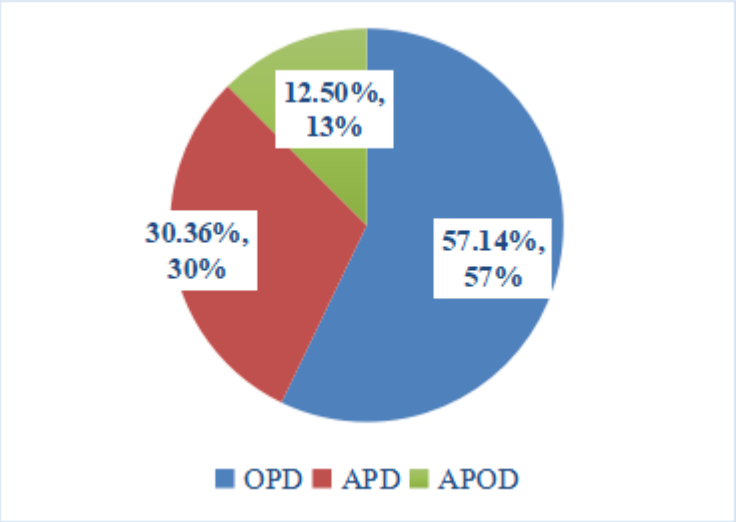


Figure 10: Number of Patients with Concurrent Radiation



Of the 150 patients who were prospectively observed, 70(47%) were males and 80(53%) were females. Out of 70 male patients, 45(30.0%) patients got a complete response (no emesis, no rescue). Among the 80 females enrolled, 67 (44.7%) got complete response. There is a significant difference observed in complete response in the enrolled male and female population ($p<0.01$).

Patients were classified into different age groups: highest frequency of patients was found at an interval of 51 – 60 yrs (32.0%) while the lowest frequency was found in 81 – 90 yrs (1.3%). Out of the 150 patients, 44.7% (n=67) patients were given OPD regimen, 40.7% (n=61) patients received APD regimen and 14.7% (n=22) recieved APOD regimen. Among the 67 patients who received OPD regimen, 31.3% (n=47) showed complete response, 34% (n=51) showed complete response in the APD group and 9.3% (n=14) in APOD group. There was no statistically significant difference in complete response between the three anti-emetic regimen groups ($p<0.01$).

56 patients of the total number of 150 subjects underwent concurrent radiation therapy. Among the patients who received concurrent chemo-radiation, n=32(21.3%) were given OPD regimen, n=17(12.5%) were given APD regimen and n=7(4.7%) received APOD regimen. There was a statistically significant difference in number of patients who had complete response in patients receiving chemotherapy alone as compared to patients receiving concurrent chemotherapy and radiation therapy ($p<0.05\%$). More number of patients with chemotherapy alone received complete response to anti-emetic regimen. Patients taking very highly emetogenic chemotherapy

were n=11(7.3%) followed by highly emetogenic chemotherapy 101(67.3%) and moderately emetogenic chemotherapy 38(25.3%). With increasing emetogenic potential of the chemotherapy, there was a decreasing trend in complete anti-emetic response with anti-emetic drug therapy. This were no statistical significant difference ($p<0.01\%$). By comparing the emetogenic potential of the drug with complete response, out of 101(67.3%) patients in high emetogenic, 72(48.0%) had complete response and 29(19.3%) had incomplete response. Among 11 (7.3%) patients taking very high emetogenic drugs, 6 (4.0%) had complete response and 5(3.3%) had incomplete response. In moderate emetogenic drugs, 34 (22.4%) patients were with complete response and 4(2.7%) were with incomplete response [13].

Patients were monitored for their acute phase (within 24 hours of initial exposure of chemotherapy), delayed phase (occurs more than 24 hours following chemotherapy and persist for 7 days), overall phase (prior to next chemotherapy). None of patients were not found to be nauseated in the acute phase. Grade A nausea was observed in Delayed phase in n=22(14.7%) and in n=28(18.7%) in overall phase [14].

OPD was comparable to APD vs APOD in the control of CINV. The difference between 3 arms were not significant with respect to control of nausea and vomiting in acute, delayed and overall periods ($p<0.01$).

DISCUSSION

According to the previous studies conducted, two anti-emetic regimens(APD, OPD) for chemotherapy induced nausea-vomiting were used. In our study, three antiemetic regimens (APD, OPD,APOD) were compared in terms of safety and efficacy. Olanzapine is an atypical antipsychotic that has antiemetic properties. It binds with high affinity to several receptors involved in the CINV pathways including dopamine D1–D5, 5HT2A, 5HT2C, 5HT3, 5HT6, muscarinic, alpha-adrenergic, and histamine H1 receptors. Olanzapine is cited in the NCCN and ESMO guidelines as a potential agent for breakthrough treatment of CINV.

Majority of participants in this study were female patients and showed significant difference with the antiemetic regimen when compared with CR. Studies conducted by [16] also demonstrated higher number of female patients but were not statistically significant. Emetogenic potential of chemotherapy drug showed significant difference with CR. In a randomized phase III trial of OLN versus APR for prevention of CINV conducted was controversial stating the CR rates were not significantly different from group of patients receiving HEC. The antiemetic regimens were comparable in the acute, delayed, and overall periods. In addition, the CR rates were similar to previous studies which used the same OLN antiemetic regimen and the standard therapy of APR regimen [15].

The CR in the acute period for patients receiving HEC observed in this study was most likely an important aspect in controlling delayed CINV. The studies carried out [17, 18] also showed highest level of CR in the acute period. In overall phase, the nausea control rate was found to be 82% in our study. According to the study conducted by [19] the control rate improved from 0% to 92%. Complete prevention of emesis and nausea after MEC has not yet been achieved, nor have symptoms completely resolved by the end of study collection period. This result was congruent with the study of Thomas [20].

CR and control of nausea in subsequent chemotherapy cycles were maintained for the antiemetic regimens. The results of this study demonstrate that in patients receiving HEC, the OPD regimen is equally beneficial to APD regimen in controlling emesis. There are also economic benefits of olanzapine. Cost per cycle of chemotherapy in Indian rupees(INR) was roughly 1300 for aprepitant and 50 for olanzapine tablets. Median of total cost of therapy per cycle was around 1500 INR and 270 INR for aprepitant and olanzapine group respectively. OLN not only elevated CR for CINV, specialy for acute, delayed nausea and vomiting but also improved the sleep, appetite of cancer patients when compared with standard anti emetic therapy. None of the patients developed any bothersome side effects due to olanzapine. Only a few patients (<5) complained about slightly increased sedation, which is an anticipated and acceptable effect of Olanzapine. All patients given Olanzapine containing antiemetic regimen are counselled by the oncology clinical pharmacist to avoid activities requiring alertness such as driving till their individual effect of medication is known to the patients. A limitation of our study is that we evaluated only one dose level of olanzapine (10mg) had been prescribed in our hospital. Lower or higher doses may have an effect on efficacy, toxic effects, or both. These issues should be considered in future clinical trials. Also study period is also limited.

Our study showed that olanzapine combined with an NK1-receptor antagonist, a 5-HT3–receptor antagonist, and dexamethasone is equally effective with these agents for the prevention of nausea and vomiting in patients who are receiving highly and moderately emetogenic chemotherapy[7]

Our study did not show any statistically significant difference in CR and cute phase and similar results were showed in other studies [20,21]. Olanzepine was found to be statistically and clinically superior to OTHER antiemetic regimen in the prophylaxis and recue of CINV in the breakthrough settings with no emesis. Apart from the meta analysis study conducted, found that OLN produced statisticaly significant superiority than other antiemetic regimens in our study.

CONCLUSION

In this observational study, no significant difference was observed between olanzapine and aprepitant in preventing nausea and emesis induced by highly and moderately emetogenic chemotherapy. Olanzapine can improve the complete response of acute and delayed, nausea and vomiting when compared with the standard therapy of anti-emesis. Thus Olanzapine has been shown to be safe and effective agent for the prevention of CINV, especially in delayed phase. It is also a highly cost effective drug compared with 5HT3 serotonin antagonist and NK1 antagonists. Thus we suggest olanzapine is a good choice for prophylactic treatment in chemotherapy.

ACKNOWLEDGEMENT:

First and foremost we bow in reverence to **The Lord Almighty** for the blessings which enabled us to accomplish this study successful.

REFERENCES

1. American Society of Cancer Oncology. Available from www.cancer.org/treatment/treatments-and-side-effects/treatment-types/chemotherapy.html
2. Jordan K, Sippel C, Schmoll HJ. Guidelines for Antiemetic Treatment of Chemotherapy-Induced Nausea and Vomiting: Past, Present, and Future Recommendations. *The Oncologist*, 12, 2007, 1143–1150.
3. Hesketh P.J. Defining the Emetogenicity of Cancer Chemotherapy Regimens: Relevance to Clinical Practice. *The Oncologist*, 4, 1999, 191-196.
4. Oncology Nursing Society. Emetogenic Risk of Chemotherapy and Biotherapy Agents. Available from https://www.ons.org/sites/default/files/emetogenicity_tool.pdf.
5. Miya T, Kobayashi K, Hino M et al., Efficacy of triple antiemetic therapy (palonosetron, dexamethasone, aprepitant) for chemotherapy induced nausea and vomiting in patients receiving carboplatin based, moderately emetogenic chemotherapy. *Springer Plus*, 5, 2016, 2080.
6. Tan M, Carides A, Rapoport B.L, et al. Aprepitant and Fosaprepitant: A 10-Year Review of Efficacy and Safety. *The Oncologist*, 20, 2015, 450–458.
7. Celio L, Nigar M, Ricchini, et al. Palonosetron in the prevention of chemotherapy induced nausea and vomiting: an evidence-based review of safety, efficacy, and place in therapy. *Core Evidence*, 10, 2015, 75–87.
8. Sutherland A, Naessens K, Plugge E, et al., Olanzapine for the prevention and treatment of cancer related nausea and vomiting in adults. Cochrane Database of Systematic Reviews 2017, (2). Art. No.: CD012555. DOI: 10.1002/14651858.CD012555.
9. American Society of Cancer Oncology. 2005-2017. Available from http://www.cancer.net/navigating-cancer-care/side-effects/nausea-and-vomiting
10. Rudolph M Navari, Sarah E. Gray et al. Olanzapine versus Aprepitant for the prevention of chemotherapy- induced nausea and vomiting: a randomized phase iii trial. *The Journal of Supportive Oncology*, 9(5), 2011, 188 – 195.
11. Kengo nagashima, satoru iwasa et al. a double blind randomized phase II study of olanzapine 10mg vs 5 mg for emesis induced by highly emetogenic chemotherapy. *Japanese journal of clinical oncology*, 45(2), 2015, 229 – 231.
12. Govind Babu, Smitha Carol Saldanha et al. The Efficacy, Safety, and Cost Benefit of Olanzapine versus Aprepitant in Highly Emetogenic Chemotherapy: A Pilot Study from South India. Chemotherapy Research and Practice December 2016, 1-5.
13. Celio L, Aapro M et al. Antipsychotics – Containing Regimen as an Alternative to Standard Delayed Nausea Induced By Highly Emetogenic Chemotherapy. *Journal of Clinical Oncology*, 47(2951), 2013, 1377- 1378.
14. Wang XF, Feng Y et al. A Meta-Analysis of Olanzapine for Prevention of Chemotherapy Induced Nausea and Vomiting. *Scientific Reports*, 4(4813), 2014, 1-6.
15. Tan L, Liu J, Chen J, et al. clinical research of olanzapine for prevention of chemotherapy induced nausea and vomiting. *Journal of experimental& Clinical Cancer Research*, (28), 2009, 1-7.GROTE
16. Aapro M.S, Abu S.M, Manikhas G.M et al., A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. *Annals of Oncology*, 17(9), 2016, 1441-1449.
17. Passik S.D, Kenneth L, Krish et al., A Retrospective Chart Review of the use of Olanzapine for the Prevention of Delayed Emesis in Cancer Patients. *Journal of Pain and Symptom Management*, 25(5), 2003, 485-489.
18. Navari RM. A Review of the Prevention of Nausea and Vomiting induced by Chemotherapy. European Oncology and Haematology, 9(1), 2013, 51-55.
19. Navari RM, Quin R, Ruddy KJ *et al.* Olanzapine for the prevention of chemotherapy-induced nausea and vomiting. *New England journal of medicine*, 375, 2016, 134-142.

20. Hirashima Y, Kasamatsu Y, Kado N *et al*. Efficacy and safety of olanzapine combined with aprepitant, palonosetron, and dexamethasone for preventing nausea and vomiting induced by cisplatin based chemotherapy in Gynecological cancer. *Support care cancer*, 24(2), 2016, 675-82.
21. Abe M, Kasamatsu Y, Kado N *et al*. Efficacy of olanzapine combined therapy for patients receiving highly emetogenic chemotherapy resistant to standard antiemetic therapy. *BioMed research International Journal*, 2015, ID956785, 1-6.