ORIGINAL RESEARCH PAPER

Oncology/Radiotherapy

ROLE OF APRIPITANT IN TREATMENT OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING

KEY WORDS:

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ABSTRACT

Introduction: Nausea and vomiting associated with chemotherapy agents are most common and can lead to serious side effects, which can cause marked reduction in quality of life (1 – 3). Severity and incidence of CINV depend on the type of anti-cancer drug emetogenically. Emetogenicity of a drug can be divided into three categories—high, moderate, and low or mild. Aprepitant is a neurokinin 1 (NK-1) which has different action mechanism to control or prevent CINV. (13). Aprepitant can block selectively and binding of substance P at NK2 receptor in central nervous system area causes control of acute and delayed CINV. (8,9) **Material and Method:** All the enrolled patients received tablet aprepitant 125 mg per oral, dexamethasone 8mg intravenous push or in load normal saline 30 minutes prior to chemotherapy on D1, followed by 80mg per oral on D2 and D3. **Results:** Total 270 Patients were included in this study. 116 were females, 144 were males common age group was 40 to 50 year in females. While 50 to 60 year of age was commonest group among males. Commonest site of malignancy was Carcinoma breast, 2nd commonest was Carcinoma gall bladder and 3rd commonest was carcinoma cervix among females.

INTRODUCTION

Nausea and vomiting associated with chemotherapy agents are most common and can lead to serious side effects, which can cause marked reduction in quality of life (1 – 3). Severity and incidence of CINV depend on the type of anticancer drug emetogenically. Emetogenicity of a drug can be divided into three categories—high, moderate and low and mild, according to emetogenic property in absence of antiemetic prophylaxis (4)

1. Highly emetogenic drugs which has the capacity to cause symptoms in >90% of patients, without any antiemetic treatment.
2. Moderate emetogenic drugs which can cause symptoms in80- 90% of patients.
3. Low emetogenic drugs are which can cause symptoms in10- 30% of patients. (5)

Some of the patient related risk factors are also responsible such as females and younger age groups. Mechanism which is involved to cause emesis by stimulation in the neuron –anatomical center (6)

1. Emetic center
2. Chemoreceptor trigger zone center
3. The vagal nerve afferent stimulators (7)

CTZ center is sensitive for chemical stimulation and it is the main action site of antiemetic drugs (8). CTZ center closely related to blood brain barrier permeability which allows circulation of mediators as direct action of emetic center. Important transmitters which moderate the emetic process are Dopamine, Serotonin and substance P. Various receptors 5 HTA, 2A, 2C, 3A, 3B, 4 receptors CBC and Adrenergic are involved in emesis mechanism (9). Opioid receptors are also shown to act as a mediator anti-emetic (10) effect in humans (11).

After absorption of cytotoxic drugs into blood stream gastro-intestinal tract can cause damage of enterochromaffin cells. This damage leads to subsequent release of 5HT3 and stimulation of CTZ center occurs via 5HT3 receptors. As a resultant contraction of abdominal muscle, diaphragm, stomach and esophagus and an emetic response (12). Now a days effective clinically prophylactics or drugs are available for prevention or treatment of CINV including 5 hydroxy tryptamine type 3 receptor antagonist with dexamethasone, neurokinin, and receptor antagonist (nki, RA), benzodiapenes and some anti-psychotic drugs.

Aprepitant is a neurokinin 1 & (NK-1) RA which has different action mechanism to control or prevent CINV. (13). Aprepitant can block selectively and binding of substance P at NK2 receptor in central nervous system areas which causes control of acute and delayed CINV. (8,9)

Minimally emetogenic drugs are which can cause symptoms in <10% of patients.

Sl. No	Emetogenic capacity	Cytotoxic drugs
1	High	Cisplatin Cyclophosphamide Dacarbazine Carmustine
2	Moderate	Cyclophosphamide Carboplatin Irinotecan Doxorubicin Cytarabine Oxaliplatin Ifosfamide Daunorubicin Epirubicin
3	Low	Paclitaxel Docetaxel Etoposide Pemetrexed Gemcitabine 5-Fluorouracil Bortezomib Trastuzumab
4	Minimal	Bleomycin Vinblastine Vincristine Bevacizumab

Aprepitant is an effective, orally bio available selective NK-1 receptor inhibitor affect significatively antagonizes substance P by erasing blood brain barrier providing dramatic response in prevention of CINV(17). After adding with 5HT3 antagonist dexamethasone it can provide significant improvement in prevention of highly emetogenetic chemotherapy induced Nausea and vomiting.

An update by Anti-emetics American Society of clinical oncology guideline suggested that no evidence shows that Cortico-steroids should be avoided with anti-emetic therapy when chemotherapy is added with checkpoint inhibitors (16).

MATERIAL & METHOD

Inclusion Criteria	Exclusion Criteria
1. Age >18 and < 20 Year 2. Histologically Proven cancer patients 3. ECOG status between 0-2	1. Patients with brain tumour, brain metastases 2. Compromised renal and hepatic function

4. Patients who were received chemotherapy. 5. Patients not receiving any kind of antiemetic drugs. 6. Normal Liver function renal function test.	3. Patients with psychiatric illness. 4. Patients of Carcinoma esophagus, Carcinoma stomach, Intestinal obstruction. 5. Patients with brain chemotherapy.

Treatment Method

All the enrolled patients received tablet aprepitant 125 mg per oral, dexamethasone 8mg intravenous push or in load normal saline 30 minutes prior to chemotherapy on D1, followed by 80 mg per oral on D2 and D3.

Evaluation

Done by frequency of vomiting and Nausea were recorded twice daily for real. 5 day to record the event for 5 weeks.

(a) End Point

Complete response

---- no emesis, no further treatment required

(b) No Response

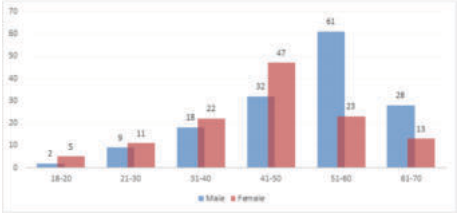
----- Treatment required after 5 days of therapy

RESULTS

Total 270 Patients were included in this study. 116 were females, 144 were males common age group was 40 to 50 year in females. While 50 to 60 year of age was commonest group among males.

Table:1 AgeWise Distribution Of Male And Female.

Age Distribution	Male	Female
18-20	2	5
21-30	9	11
31-40	18	22
41-50	32	47
51-60	61	23
61-70	28	13
Total	144	166



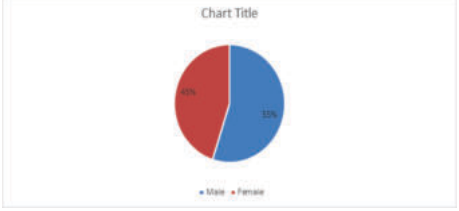
Graph. 1: AgeWise Distribution Of Male And Female

Commonest site of malignancy was ca breast, 2nd commonest was ca gall bladder and 3rd commonest was carcinoma cervix among females.

Demographic Profile

Table:2 Male And Female Ratio As Per Total Number Of Disease.

Male	144
Female	116
Total	260

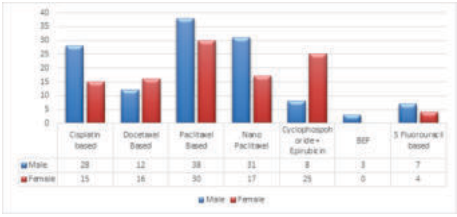


Graph.2 Male And Female Ratio

Head and neck carcinoma was commonest, 2nd commonest was gastrointestinal, 3rd commonest was ca lung. Commonest chemotherapeutic agents were used are describe in table:-

Table:3male And Female Distribution Of The Medication Administered.

Medication Administered	Male	Female
Cisplatin based	28	15
Docetaxel Based	12	16
Paclitaxel Based	38	30
Nano Paclitaxel	31	17
Cyclophospohoride + Epirubicin	8	25
BEP	3	0
5 Fluorouracil based	7	4
Total	127	107

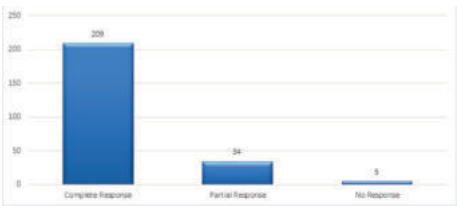


Graph:3 Distribution Of Medication Administered, Male And Female Distribution.

Commonly used agents were platinum and taxane based. 248 patients were evaluated and 12 patients excluded during treatment due to low performance status. 139 male patients and 109 female patients were evaluated out of 248 patients 209 patients were shown complete response, in which 120 were males, 88 were females. 76% patients achieved completed response in acute period and 53% achieved in delayed period.

Table-4 Response

Particular	No. of Patients
Complete Response	209
Partial Response	34
No Response	5
Total	270



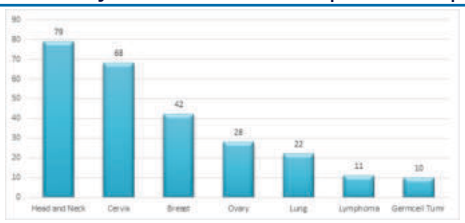
Graph-4 Response

No emesis was observed in 83% for acute period. Incidence of nausea was gradually decreasing as period increasing.

Most common age group was 41-50 years in females and 51-60years in males. The most common site of disease in males was Ca Head and Neck. Second most common was gastro-intestinal (including Liver, Stomach & Gallbladder). In females, the most common cancer site was Carcinoma Breast followed by Gall Bladder. Third most common was Head and Neck

Table:5 Distribution Of Patients According To Disease

Head and Neck	79
Cervix	68
Breast	42
Ovary	28
Lung	22
Lymphoma	11
Germcell Tumr	10
Total	260



Graph:5 Distribution Of Patients According To Disease

DISCUSSION

Nausea and vomiting are commonest adverse effect due to chemotherapy (17). Acute nausea and vomiting (occur with in 24 hours) Delay. (a day after chemotherapy received) anticipatory (Before starting chemotherapy) 2/3 (18, 19) severely and intensity of nausea and vomiting varies from patients to patients, regimes, Chemotherapeutic agents, cancer related factors, inadequate Control lead to malnutrition, dehydration and other complication

A number of clinical trial have shown the effectiveness of aprepitant for prevention of nausea and vomiting included by moderately and highly emetogenic chemotherapy. (20-23) Three randomised controlled trials evaluated 857 patients with various carcinoma (24) and 127 patients of breast cancer (25)

Evaluation done by assessing effectiveness with cisplatin Patient who had vomiting 16% showed improvement, 17 % shown improvement in acute vomiting with ondansetron can prevent vomiting during acute phase with three doses every 2 hours in single dose because of its safety protocol, (26) Palonosetron is highly effective during with long half life 40 hours. It usually prescribed in single dose and can be continues for further (27, 28) There is need to control vomiting in delayed period many studies shown that 5 days therapy is not affective than short course therapy.

Present study uses aprepitant which had higher effective with good safety profile even in single dose, grota (22) studies show that 3 drug combination aprepitant, dexamethasone and palonosetron for 3 days and dexamethasone with palonosetron on Day 4 can control vomiting in 88% of patients in acute phase (0-24hr) and 78% in delayed phase (>24- 120 hr). (29) compared aprepitant on D1 and 3 day, 4th day single dose of palonosetron and Dexamethasone shown better results. Similar result shown by steven M (30). Our study shown response rate similar with these studies.

A randomized open level study shown Pharmacokinetic safety of a use of 0.25mg palonosetron with aprepitant (31) No significant interaction of pharmacokinetics with serotonin inhibitors found.

CONCLUSION

The Study shown good antiemetic effect by using three drug therapy with palonosetron, dexamethasone and aprepitant in medium emetogenic chemotherapy and highly emetogenic chemotherapy induced nausea and vomiting with triplet drug therapy is well tolerated by all age group of patients.

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