A STUDY COMPARING THE EFFICACY OF ONDANSETRON, PALENOSETRON AND APREPITANT IN THE PREVENTION OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING IN BREAST CANCER PATIENTS RECEIVING MODERATELY EMETOGENIC CHEMOTHERAPY

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CERTIFICATE

This is to certify that this dissertation on "A STUDY COMPARING THE EFFICACY OF ONDANSETRON, PALENOSETRON AND APREPITANT IN THE PREVENTION OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING IN BREAST CANCER PATIENTS RECEIVING MODERATELY EMETOGENIC CHEMOTHERAPY " is a bonafide work done by Dr Shashidhar V Karpurmath, in the department of Medical oncology, College of Oncological sciences, Adyar, Chennai, under my overall supervision and guidance, to my satisfaction.

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"Oh his lovable and selfless attitude
On his preliminary and priceless contribution
Emerge in my heart the tears of joy and gratitude
And I am indebted to HIM forever "

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CONTENTS

INTRODUCTION

Nausea and vomiting are the most feared complications of chemotherapy experienced by the patients.[1,2.] Almost 70-80% of all cancer patients will be having chemotherapy induced nausea and vomiting.[3,4] The prevention of chemotherapy induced nausea and vomiting (CINV) is very much important and necessary because it has huge implications on both patient's and clinician's perspective. As it is the most common problem faced by patients and as it can be prevented or controlled to a certain extent with the judicious and careful use of anti emetics sums up the significance of the need to select an appropriate anti emetic regimen for a particular class of chemotherapy.

Prevention is always better than cure ,which is an old age saying holds very true in the perspective of CINV also because it is always important to prevent CINV rather than treat CINV as damage would have already occurred in the form of poor oral intake, affection of quality of life , anxiety in the minds of patients ,creating doubts about their ability to tolerate further chemotherapy thus leading to anticipatory vomiting in the subsequent cycles or loss of compliance leading to inadequate treatment of the disease and last but not the least the financial burden on the individual and the family for supportive care, hospital admission and the rescue medications .[5]

Treatment of breast cancer also has undergone considerable improvement in the recent times leading to increased chance of cure .Hence it becomes extremely important to provide the cure with least toxicities and side effects of treatment. The chemotherapy used in breast cancer patients falls under moderately emetogenic chemotherapy type (MEC) [6] . The choice of anti emetic regimen in patients treated for highly emetogenic chemotherapy is clear and non controversial. The same cannot be told about the anti emetic regimen in patients receiving

MEC.[7]The development of newer anti emetic agents like palonosetron, aprepitant, fosaprepitant and casopitant has led to tremendous opportunities and improved patient care. Conventionally ondansetron was the anti emetic of choice for patients receiving MEC but now with the advent of aprepitant it is becoming the new standard of care as an antiemetic regimen of choice in patients receiving MEC especially those receiving a combination of anthracycline and an alkylating agent.[7] There are only a few trials and studies using aprepitant in patients receiving MEC and in fact there are no studies till date comparing palonosetron with aprepitant in the prevention of CINV in MEC. Hence our study is a sincere effort in that regard trying to compare palonosetron and aprepitant to ondansetron. And we also have compared palonosetron with aprepitant with respect to their efficacies in the prevention of CINV .This will be of great help to a limited resource country like ours, where a cheaper alternative can be of great relief to the patient herself/himself and also to the treating centres and also will have great financial implications If a cheaper alternative is obtained.

AIM

PRIMARY OUTCOME

- To compare the Complete response rates in the ondansetron, palonosetron and aprepitant based antiemetic prophylaxis regimen in patients of breast cancer patients receiving moderately emetogenic chemotherapy

SECONDARY OUTCOMES

- To determine the complete response during the acute phase after initiation of chemotherapy
- To determine the complete response during the delayed phase after initiation of chemotherapy
- To determine the impact of CINV on quality of life using the Functional living Index-Emesis(FLIE) scores in each of the 3 arms
- To determine the effect of antiemetic agents on the reduction of usage of rescue medications

REVIEW OF LITERATURE

"*No greater opportunity or obligation can fall the lot of a human being than to be a physician .In the care of the suffering he needs technical skill, scientific knowledge, and human understanding. He who uses these with courage, humility, and wisdom will provide a unique service for his fellow man and will build an enduring edifice of character within himself. The physician should ask of his destiny no more than this, and he should be content with no less."*

Thus every physician has an important role to play in the holistic approach of treatment of patients enabling them to lead a better life. Both disease related as well as treatment related toxicities have to be tackled in order to improve the quality of life of patients.

Chemotherapy induced nausea and vomiting being the most common complication needs to be treated adequately. Better understanding of the pathophysiology of CINV helps in a more efficient control of the same.

Inadequately controlled emesis impairs functional activity and quality of life for patients, increases the use of health care resources, and may occasionally compromise adherence to treatment.[5,6,7,8] Chemotherapy plays an important role in the treatment of various cancers and its role remains unquestioned though it comes with its side effects. New insights into the pathophysiology of chemotherapy-induced nausea and vomiting, a better understanding of the risk factors for these effects, and the availability of new antiemetic agents have all contributed to substantial improvements in emetic control.

Pathophysiology of Chemotherapy induced nausea and Vomiting –

Vomiting can be defined as the oral expulsion of the gastrointestinal contents resulting from contractions of the gut and thoracoabdominal wall musculature. Nausea is defined as a subjective

unpleasant wave like feeling in the back of the throat and/or stomach that signals imminent vomiting [9,10].The vomiting reflex is present in many animal species, ranging from fish to higher mammals, and has been viewed from an evolutionary perspective as a protective mechanism against ingested toxins.[11,12,13]

The central nervous system plays a critical role in the physiology of nausea and vomiting, serving as the primary site that receives and processes a variety of emetic stimuli. The central nervous system also plays a primary role in generating efferent signals which are sent to a number of organs and tissues in a process that eventually results in vomiting.[13,14]

Pioneering studies conducted by Wang and Borison nearly 60 years ago proposed the concept of a central site (vomiting center) located in the medulla that serves as a final common pathway for processing all afferent impulses that can initiate emesis.[15] It has been mentioned that the vomiting centre does not exist as an anatomically distinct site[16] but is a collection of loosely arranged neuronal tissue in the medulla which coordinates the emetic reflex. [13,17] These neurons which coordinate the complex events of emesis have been designated as complex pattern regulator.[18] ,[19]

Antineoplastic agents cause emesis through effects at a number of sites. After the administration of chemotherapy, free radicals are generated, leading to localized exocytotic release of 5-hydroxytryptamine(5-HT) ,substance P and cholecystokinin from the enterochromaffin cells. These mediators act on the respective receptors which are located on the terminal ends of the vagal afferents. Vagal afferent fibers project to the dorsal brain stem, primarily to the nucleus tractus solitarius(NTS), and, to a lesser extent, the area postrema(AP), the two parts of the brain referred to collectively as the dorsal vagal complex. 5HT3, neurokinin and dopaminergic receptors are also present on the dorsal vagal complex. Efferent fibers project

from the dorsal vagal complex to the final effector of the emetic reflex, the central pattern generator,which is located more ventrally in the brainstem.[7] Antineoplastic agents can also induce emesis through direct interaction with the area postrema within the dorsal vagal complex. The area postrema which is also called as chemoreceptor trigger zone is a circumventricular organ located at the caudal end of the floor of the fourth ventricle, which is accessible to blood and cerebrospinal fluid–borne emetic stimuli. [20,21,22]Other potential sources of efferent input that result in emesis after chemotherapy include a number of structures in the temporal lobe, such as the amygdala.[23,24] Evidence for this pathway is less well established than for other proposed sites of chemotherapeutic action.

Fig 1- Various neurotransmitters in the pathophysiology of CINV

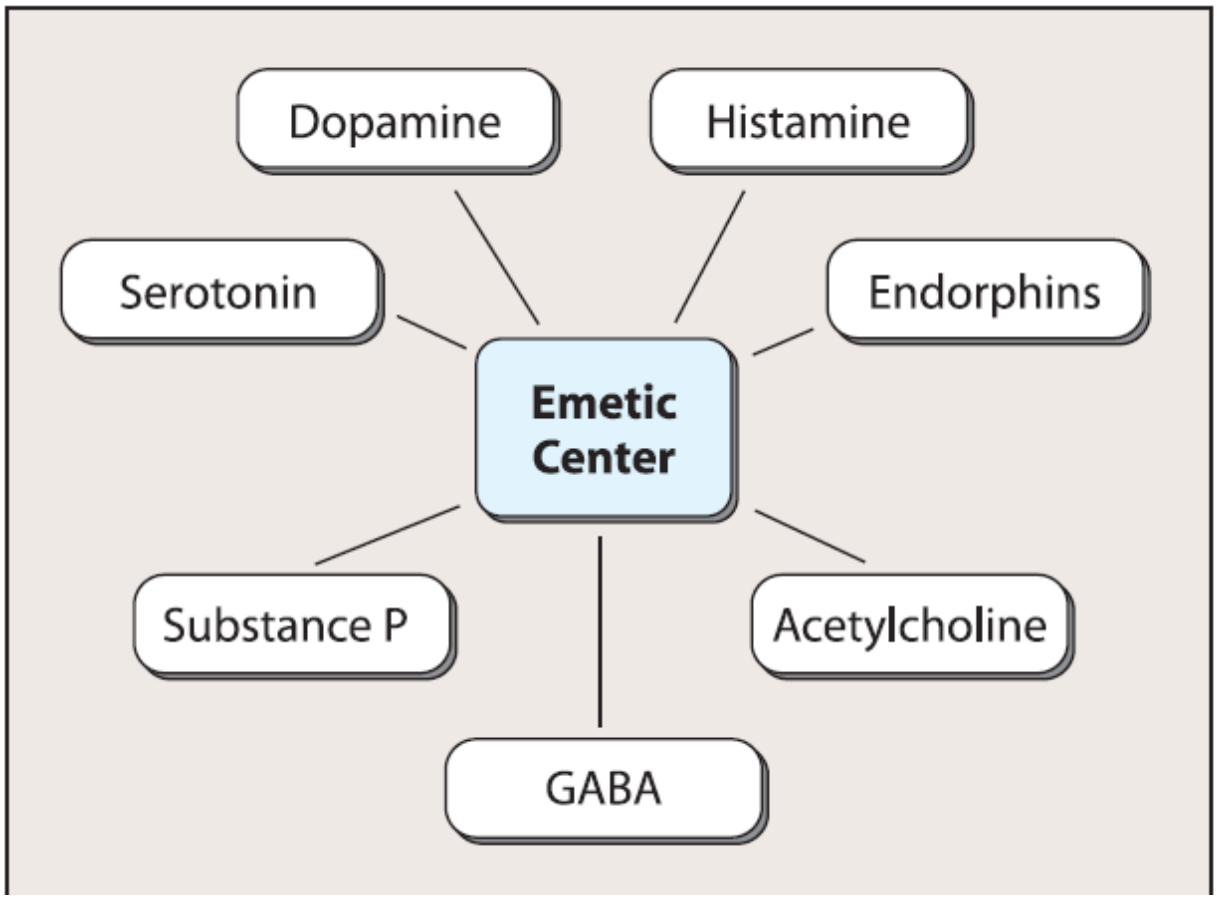
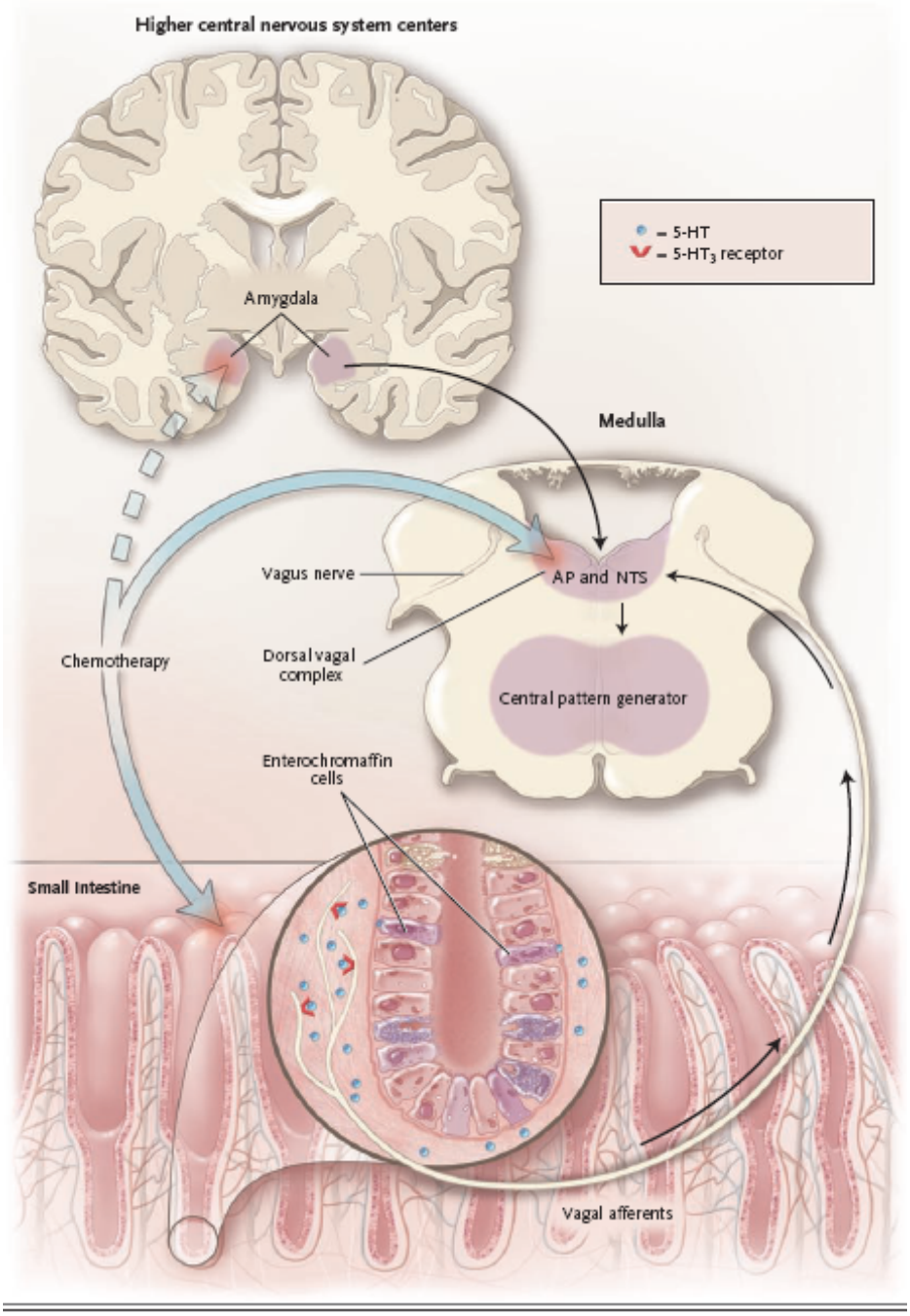


Fig 2 – Patho physiology of CINV



Appreciation of the fact that CINV can be divided into distinct emetic clinical syndromes was crucial and an important milestone in the rational evolution of anti emetic therapy. This was first identified with use of the agent cisplatin. Most important in this regard was the concept of acute as compared with delayed emesis, In the absence of effective antiemetic prophylaxis, virtually all patients receiving cisplatin will have nausea and vomiting 1 to 2 hours after receiving chemotherapy.[25] At approximately 18 to 24 hours, the emesis typically subsides, only to recur and reach a second peak at approximately 48 to 72 hours after administration of the agent.[26]

Thus CINV is differentiated into three categories: acute onset (mostly serotonin related), occurring within 24 hours of initial administration of chemotherapy; delayed onset (in part substance P related), occurring 24 hours to several days after initial treatment; and anticipatory, observed in patients whose emetic episodes are triggered by taste, odor, sight, thoughts, or anxiety secondary to a history of poor response to antiemetic agents or inadequate antiemetic prophylaxis in the previous cycle of chemotherapy. Anticipatory vomiting usually starts one to four hours before chemotherapy but sometimes can occur few days before the administration of chemotherapy. [27,28]

Factors affecting CINV-

Factors determining the occurrence of CINV can be divided into patient related and treatment related. Patient related factors are age ,sex, alcohol intake, prior history of hyperemesis gravidarum during pregnancy, prior history of motion sickness, type of personality with CINV being more common in the younger individuals, females ,non alcoholics , anxious personalities and females with past history of hyper emesis gravidarum. The treatment related factors being the emetogenicity of chemotherapy and the dose of the chemotherapeutic agent. [29,30] Chemotherapy agents were classified into 5 groups based on their intrinsic

emetogenicity.[31] In 2004 it was modified and they were reclassified into four groups namely highly emetogenic, moderately emetogenic, low emetogenic and minimal emetogenic.

Hesketh's classification of level of emetogenicity of chemotherapeutic agents [7]

Level 1 (minimal risk, <10%)	Level 2 (low risk, 10–30%)	Level 3 (moderate risk, 31–90%)	Level 4 (high risk, >90%)
Bevacizumab	Bortezomib	Carboplatin	Carmustine
Bleomycin	Cetuximab	Cyclophosphamide (≤1.5 g/m²)	Cisplatin
Busulfan	Cytarabine (≤100 mg/m² of body-surface area)	Cytarabine (>1 g/m²)	Cyclophosphamide (>1.5 g/m²)
Cladribine	Docetaxel	Daunorubicin	Dacarbazine
Fludarabine	Etoposide	Doxorubicin	Mechlorethamine
Vinblastine	Fluorouracil	Epirubicin	Streptozocin
Vincristine	Gemcitabine	Idarubicin	
Vinorelbine	Ixabepilone	Ifosfamide	
	Lapatinib	Irinotecan	
	Methotrexate	Oxaliplatin	
	Mitomycin		
	Mitoxantrone		
	Paclitaxel		
	Pemetrexed		
	Temsirolimus		
	Topotecan		
	Trastuzumab		

Anti emetic agents

The history of anti emetic therapy dates back to 1960s when some antiemetic efficacy on the part of phenothiazines was reported .The introduction of high-dose metoclopramide and combination treatment with corticosteroids in the 1980s were significant developments and then came the introduction of serotonin (5-hydroxytryptamine3 [5-HT3]) receptor antagonists into clinical practice in the 1990s which was a milestone in the development of anti emetic therapy. Currently introduction of a new class of antiemetics neurokinin-1 antagonists and the introduction of newer generation of 5HT3 receptor antagonists has revolutionized the anti emetic treatment. The available pharmacologic agents for treatment of CINV currently consist of

corticosteroids, dopamine antagonists, 5-HT3 receptor antagonists, and NK-1 receptor antagonists.

First-generation 5-HT3 receptor antagonists— dolasetron , ondansetron and granisetron have been a standard in preventive treatment of CINV for several years. Recent guidelines indicate that these agents are therapeutically equivalent, based on the highest level of evidence, and that oral and intravenous (IV) doses are equally effective. The introduction of the second-generation 5-HT3 antagonist palonosetron and the NK-1 antagonist aprepitant in 2003 marks what appears to be a significant advance in the management of CINV as mentioned already.[32,33]

Newer agents like fosaprepitant, casopitant and others are being evaluated .

Dopamine receptor antagonists

Three classes of dopamine receptor antagonists may be used in patients with nausea or vomiting: Phenothiazines ,Butyrophenones and Benzamides.

Phenothiazines — The phenothiazines were the first group of drugs to demonstrate substantial activity in the prevention of chemotherapy-induced nausea and vomiting.[34] They act predominantly by antagonizing D2-dopamine receptors in the area postrema of the midbrain, but also have M1-muscarinic and H1-histamine blocking effects.

Prochlorperazine is the most commonly used antiemetic in this class; it is moderately effective for nausea caused by various gastrointestinal disorders and mild to moderate but not highly emetogenic chemotherapy .[35,36] However, careful clinical studies of the efficacy of this agent are not available, and a placebo effect may occur in nearly 80 percent of patients.[35,37] Typical dose regimens are 5 to 10 mg PO every six to eight hours, 5 to 10 mg IM or 2.5 to 10 mg IV every three to four hours, or 25 mg by rectal suppository every 12 hours.

Chlorpromazine is used less often than prochlorperazine; the dose of this drug is 10 to 25 mg PO every four to six hours, 25 mg IV every three to four hours, or 100 mg rectally every six to eight hours. Thiethylperazine is another drug of this class of antiemetics which is given at a dose of 10 mg PO or 2 mg IM every 8 to 24 hours. The main adverse effects of the phenothiazines are extrapyramidal reactions such as dystonia and, with prolonged use, tardive dyskinesia. Acute dystonia can be treated with diphenhydramine (Benadryl) 25 to 50 mg IM. Hypotension can also occur, particularly in the elderly or with intravenous infusion.

Butyrophenones — Butyrophenones are major tranquilizers that potentiate the actions of opioids and have an antiemetic effect when used alone. They are primarily used as a preanesthetic agent or for procedural sedation, but are also effective for postoperative nausea and vomiting. Butyrophenones have also been used for the treatment of nausea and vomiting in other settings. Droperidol , a short-acting drug, is usually given in a dose of 1.25 to 5 mg IM.Haloperidol also can be used but the main disadvantage is its long half life of about 18 hours which limits its use.

The side effect profile and antiemetic efficacy of the butyrophenones appear to be similar to those of the phenothiazines. Prior to the advent of the 5-HT receptor antagonists, these agents at higher doses were a reasonable alternative to high-dose metoclopramide .[38] However, in recent years, the need for this class of agents and their utilization have declined.

Benzamides — Metoclopramide causes central and peripheral dopamine D2 antagonism at low doses, and weak 5-HT3 blockade at the higher doses used for emesis caused by cytotoxic drug therapy .[36] It also stimulates cholinergic receptors on gastric smooth muscle cells and enhances acetylcholine release at the neuromuscular junction.

At standard doses, metoclopramide has a modest antiemetic effect .[39] It also speeds gastric emptying in patients with gastroparesis and increases tone in the lower esophageal sphincter.

High-dose intravenous metoclopramide combined with dexamethasone and diphenhydramine (to counteract the dopaminergic toxicity of metoclopramide) was formerly the antiemetic regimen of choice with highly emetogenic chemotherapy.[36,40,41] However, it has largely been replaced by the 5-HT3 receptor antagonists due to their superior efficacy and safety. One problem is that metoclopramide crosses the blood-brain barrier. Thus, it commonly causes neurologic side effects such as akathisia, dystonia, and tardive dyskinesia, especially in the elderly and at high doses.[13,42] Metoclopramide is primarily used at present as an adjunctive agent for the prevention of cisplatin-induced delayed emesis and with emesis failing first-line treatment.

Two other benzamides are trimethobenzamide and domperidone. Trimethobenzamide can be given at doses of 250 mg PO every six to eight hours or 200 mg IM or by suppository every six to eight hours. However, this agent was no better than placebo in one study of patients with a variety of illnesses [5], and was only mildly effective in patients receiving chemotherapy in other reports .[34,43] Prochlorperazine was more effective .[34,35]

Domperidone is a D2-blocker with selective peripheral activity in the upper gastrointestinal tract. The major advantage of this drug is that it does not cross the blood-brain barrier and therefore lacks the neurologic side effects of metoclopramide.

5-HT3 Antagonists

The introduction of selective 5-HT3–receptor antagonists in the early 1990s revolutionized the management of chemotherapy-induced nausea and vomiting. Currently five 5-HT3 antagonists are widely available namely ondansetron, granisetron , dolasetron , tropisetron and a more recently introduced palonosetron . These drugs form the cornerstone of

prophylactic therapy for chemotherapy with moderate to high emetic potential. Multiple prospective randomized trials have demonstrated the therapeutic equivalence of the four older 5-HT3 antagonists, which is also supported by a number of meta analyses.[44,45] As a class, these agents have few adverse effects of their own and no limiting toxicity at typical doses. The most common adverse events are mild headache, transient elevation of hepatic aminotransferase levels, and constipation. Once daily schedules are similar in efficacy to multiple dose daily schedules, and at the approved doses, the oral formulation is therapeutically equivalent to the intravenous route of administration.[46,47] Clinical trials with the older 5-HT3 antagonists (e.g., granisetron, ondansetron), have shown much lower efficacy for the delayed type of chemotherapy-induced nausea and vomiting as compared with the acute type. These agents appear to have little activity when used to prevent delayed emesis induced by cisplatin and only modest activity when used to prevent delayed emesis induced by moderately emetogenic chemotherapy.[7]

The recommended prophylactic regimen for the most emetogenic chemotherapy consists of granisetron (2 mg PO), ondansetron (16 to 24 mg PO per day) or dolasetron (100 mg PO), or palonosetron (0.25 mg IV) combined with dexamethasone (12 mg PO) and aprepitant (125 mg PO)

Another advantage with the 5-HT3 receptor antagonists is a favorable toxicity profile. They are generally well tolerated, with mild headache the most frequent adverse event, occurring in approximately 15 to 20 percent of patients. Asthenia and constipation occur in 5 to 10 percent, and dizziness occurs in approximately 10 percent of patients treated intravenously and in 5

percent of those receiving the oral formulation .[48] There are no cognitive, psychomotor, or affective disturbances .[49]

Palonosetron-Palonosetron HCl is an isoquinolone hydrochloride with an empirical formula of C19H24N2O HCl and a molecular weight of 332.87. It is freely soluble in water, soluble in propylene glycol, and slightly soluble in ethanol and 2-propanol. Palonosetron injection is a sterile, clear, colorless, nonpyrogenic, isotonic, buffered solution for intravenous administration. It is a second generation 5HT3 receptor antagonist. It differs from the previous generation 5HT3 receptor in its higher affinity and longer plasma half life. Palonosetron is a highly potent, selective, 5-HT3 receptor antagonist with a 5-HT3 receptor binding affinity that is 100-fold higher than other 5-HT3 receptor antagonists (p*K*i 10.5 compared with 8.91 for granisetron, 8.81 for tropisetron, 8.39 for ondansetron, 7.6 for dolasetron) [50,51,52] Palonosetron also has an extended plasma elimination half-life of 40 h [53] significantly longer than others in its class (ondansetron, 4 h [54] tropisetron, 7.3 h [55] dolasetron, 7.5 h [56]granisetron, 8.9 h [57]

After intravenous dosing of palonosetron in healthy subjects and cancer patients, an initial decline in plasma concentration is followed by a slow elimination from the body. Mean maximum plasma concentration and area under the concentration – time curves are generally dose-proportional over the dose range of 0.3 to 90 μg/kg in healthy subjects and in cancer patients.[58] Palonosetron has a volume of distribution of approximately 8.3 ± 2.5 L/kg and is 62% bound to plasma proteins. Palonosetron is eliminated from the body through renal excretion and metabolic pathways. After a single intravenous dose of 10 μg/kg 14C palonosetron, approximately 80% of the dose was recovered within 144 hours in the urine with palonosetron representing approximately 40% of the administered dose. The mean terminal elimination half-life is approximately 40 hours .

Approximately 50% of palonosetron is metabolized to form two primary metabolites. Each of these metabolites has less than 1% of the 5-HT3 receptor antagonist activity of palonosetron. The metabolic pathways are mediated via multiple CYP enzymes, including CYP2D6, and to a lesser extent, CYP3A and CYP1A2. Clinical pharmacokinetic parameters are not significantly different between poor and extensive CYP2D6 metabolizers. The potential for clinically significant drug interactions with palonosetron appears to be low.[58,59,60] In controlled clinical trials, palonosetron has been safely administered with corticosteroids, analgesics, anti-emetics, antispasmodics, and anticholinergic agents. Palonosetron did not inhibit the antitumor activity of five chemotherapeutic agents (cisplatin, cyclophosphamide, cytarabine, doxorubicin, and mitomycin C) in murine tumor models.[60]

Population pharmacokinetic analysis did not reveal any differences between cancer patients more than 65 years of age and younger patients. Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetics and hepatic impairment does not significantly affect total body clearance of palonosetron compared to healthy patients. Therefore, dosage adjustment is not necessary for patients with renal or hepatic impairment.[59,61]

Palonosetron is a relatively safe drug and this has been proved in many phase II and phase III trials. Results from the phase II dose-ranging study and phase III comparative studies in patients receiving MEC and HEC were the basis for approval of palonosetron by the FDA.[62,63,58,64,65] In these studies, patients were exposed to a wide range of palonosetron doses, up to 25 times the approved palonosetron dose of 0.25 mg. The adverse reactions reported were the most common reactions reported for the 5-HT3 receptor antagonist class, headache, and constipation. All other reactions occurred at an incidence of less than1% in patients treated with 0.25 mg of palonosetron.[59,66] There were no clinically relevant differences seen among

palonosetron, ondansetron, or dolasetron in laboratory, electrocardiographic, or vital sign changes.[59] A clinical study in male and female volunteers showed that the cardiac profile of palonosetron is the same as placebo. There were no electrocardiographic or dose response effects, including QTc prolongation, of palonosetron up to a 2.25 mg iv dose, a 9-fold safety margin.[67] In phase III studies, palonosetron was safely administered in 192 patients with pre-existing cardiac impairment.[59] The safety of palonosetron administered over repeated cycles of MEC or HEC was demonstrated in an open-label multinational phase III study [65,68] Palonosetron at 3 times the approved dose was well tolerated over repeated cycles with no unexpected adverse events. There were no clinically relevant differences among cycles, and the number of adverse reactions did not increase from cycle one to cycle three.

Corticosteroids

Corticosteroids were first shown to be effective antiemetic agents more than 25 years ago.[69] They can be effective when administered as a single agent in patients receiving chemotherapy of low emetic potential. They are the mainstay in the prevention of both acute and delayed chemotherapy induced nausea and vomiting .They were the most commonly used agents in the prevention of CINV as compared to other anti emetics in a large meta analysis which had more than 5000 patients.[70] Corticosteroids are most beneficial, however, when used in combination with other antiemetic agents. This has been well demonstrated when corticosteroids have been used in combination with the 5-HT3–receptor antagonists. [71,72,73] Corticosteroids are effective for both acute and delayed emesis.[73] Relatively little is known about the site or mechanism of action of corticosteroids as compared with the 5-HT3 antagonists and neurokinin-1 antagonists. In delayed emesis role of corticosteroids has been very important. Chemotherapy induced enhanced cell lysis resulting in release of break down products and various neurotransmitters leads to

inflammation and emesis, so this is counteracted by the administration of corticosteroids and this is the basis of efficacy of corticosteroids in delayed emesis.[74]

Many types of corticosteroids have been used as antiemetic agents. The widest experience has been reported with dexamethasone and methylprednisolone. Optimal pre chemotherapy dose of dexamethasone with highly and moderately emetogenic chemotherapy in prevention of acute emesis is well studied [75,76] but optimal dose-ranging data for delayed emesis are lacking. When corticosteroids are administered with the moderate cytochrome P-450 3A4 inhibitor aprepitant, doses should be reduced by approximately 50% . The only exception would be cases in which corticosteroids constitute part of the antineoplastic regimen. In those instances, therapeutic corticosteroid doses should not be attenuated.

Neurokinin-1 receptor antagonists-

Aprepitant is the new antiemetic agent which has dramatically affected the control of CINV . Aprepitant is the most widely studied and the most commonly used drug of all the NK1 receptor antagonists[77]. Aprepitant has been shown to inhibit both the acute and delayed emesis induced by cytotoxic chemotherapeutic such as cisplatin by blocking substance P landing on receptors in the neurons. It was first approved by the FDA in 2003 as an oral antiemetic drug. Aprepitant has an average bioavailability of 60-65% when consumed orally, with 95% of the drug being bound to plasma proteins. Its peak plasma concentration is achieved about 4 hours after administration and is mainly eliminated from body by phase I metabolism. Invitro studies using human liver microsomes indicate that aprepitant is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. The half-life ranged from approximately 9 to 13 hours. No dose adjustment is needed in renal disease or mild to moderate hepatic insufficiency (Child-Pugh score 5-9)[77.]

Aprepitant is available commercially as capsules in bottles or blister pack. It is given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist. The recommended dose of Aprepitant is 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg once daily in the morning on Days 2 and 3. Capsules can be stored at 20-25°C. Most of the aprepitant studies have been conducted in adult patients(10-15). A pilot, single-institution, randomized, double-blind, placebo-controlled trial by Herrington, *et al*.[78] found that in patients who were receiving palonosetron, aprepitant, and dexamethasone for highly emetogenic chemotherapy, a single dose of aprepitant displayed similar effectiveness compared with 3-day aprepitant. Only a few adolescent studies are available. A clinical regimen tried effectively in adolescents by Gore, *et al*.[79] is one of the studies which was done to clarify the efficacy and safety of aprepitant in adolescents. Pediatric studies are required to establish the role of this drug in management of CINV. The main reported side effects of aprepitant are constipation, fatigue and diarrhea. In view of its induction ofvarious enzymes, there is a possibility of drug interactions..

Fosaprepitant

It is an intravenous alternative to the current oral formulation for aprepitant.It will be mainly useful in patients who cannot tolerate orally administered medications due to active mucositis, difficulty in swallowing, or poor function of the GI tract may require intravenous antiemetics prior to chemotherapy.[80] Intravenous dexamethasone and intravenous 5-HT3 receptor antagonists are available, but only an oral form of aprepitant was available till now. Fosaprepitant would allow more convenient dosing in some clinical settings while maintaining efficacy and overall therapeutic margins.

Fosaprepitant dimeglumine (MK-0517 or L- 758,298), a prodrug of aprepitant, was developed to

provide a parenteral alternative to the orally administered aprepitant [81,82] Fosaprepitant is rapidly converted to aprepitant via the action of ubiquitous phosphatases. Based on equivalence studies, 115 mg fosaprepitant seems to be the substitute for 125 mg orally administrated aprepitant. Tolerability of the prodrug is no different from the active drug. In phase I and II trials, fosaprepitant shows efficacy, but most of the large randomized efficacy studies have utilized aprepitant. Fosaprepitant has recently been approved by FDA and EMEA as an intravenous substitute for oral aprepitant on day 1 of the standard 3-day CINV prevention regimen, which also includes dexamethasone and a 5-HT3 antagonist. Side effects are similar to aprepitant with the addition of mild venous irritation and headache.

The tolerability of fosaprepitant has been evaluated in clinical trials with approximately 150 patients [83,84]. In these studies, fosaprepitant was given as a single intravenous dose (0.2 – 200 mg), infused over 15 – 30 min, reconstituted in saline or polysorbate 80 to concentrations ranging from 1 to 25 mg/ml. Fosaprepitant has also been administered in single daily doses (25 – 100 mg) on four consecutive days. The studies showed acceptable venous tolerability at 1 mg/ml, infused over 15 – 30 min, but a concentration of 25 mg/ml at doses of 50 mg and 100 mg, infused over 30 sec, was associated with venous irritation. Based on these studies, the incidence of venous irritation depends on the total dose, the concentration, and the rate of infusion [85].

During the development of aprepitant, certain studies that assessed the tolerability of fosaprepitant also evaluated its efficacy in patients receiving chemotherapy. In a comparison of fosaprepitant versus ondansetron, each given as monotherapy prior to cisplatin, fosaprepitant was active against cisplatin-induced emesis, in particular in the delayed phase [83] Moreover, an additional trial demonstrated the tolerability and efficacy of fosaprepitant as part of combination therapy with dexamethasone [84]. The clinical profile of fosaprepitant in these early studies

suggested that fosaprepitant could be appropriate as an intravenous alternative to the aprepitant oral capsule.

In a study in healthy subjects, fosaprepitant was well tolerated up to 150 mg (1 mg/ml), and fosaprepitant 115 mg was AUC bioequivalent to aprepitant 125 mg [85]. Fosaprepitant in the intravenous dose of 115 mg has been recently approved (February, 2008) by the FDA and the European Union (January, 2008) as an alternative to oral aprepitant 125 mg on day 1 of a 3-day regimen, with oral aprepitant 80 mg administered on days 2 and 3. Further studies are in progress to determine the efficacy, safety, and tolerability of a single dose of intravenous fosaprepitant necessary to replace the three-day oral regimen [86].

Casopitant

Casopitant is a novel substituted piperazine derivative, which has potential for the treatment of conditions mediated by tachykinins, including substance P and other neurokinins. Casopitant competitively binds to the NK-1 receptor, thereby inhibiting NK-1 receptor binding of substance P and blocking the activity of the receptor [87]. Casopitant and its mesylate salt are being developed for the potential treatment of CINV, postoperative nausea and vomiting (PONV), anxiety, depression, and insomnia. Phase II and Phase III clinical trials have been completed for CINV [88,89.90,91] and Post operative nausea and vomiting [92], Two Phase III clinical trials with intravenous and oral casopitant have been completed. The first was designed to demonstrate that casopitant, when used in addition to dexamethasone plus ondansetron, is more effective in the prevention of vomiting than dexamethasone and ondansetron alone in patients with solid malignant tumors receiving cisplatin- based highly emetogenic chemotherapy [91]. In the first 120 hours of the first treatment cycle, complete responses were observed in 86% of patients in the oral casopitant (150 mg) group, compared with 66% for controls ($p < 0.0001$) and, in the first 24

hours complete response rates were 95% and 88% for the 150 mg oral casopitant and control groups, respectively ($p = 0.0044$). No vomiting occurred in 89% of patients and no significant nausea (NSN), as defined by the study, occurred in 78% of patients in the 150 mg oral casopitant group, compared with 68% ($p < 0.0001$) and 69% ($p = 0.0272$) for the control group, respectively. In treatment cycles two to six, the complete response rates were 94, 92, 93, 91 and 100%, respectively, in the casopitant treatment group, compared with 77, 78, 74, 97 and 56%, respectively, for the control group.

The second of these Phase III clinical trials was designed to establish whether casopitant, when used in addition to dexamethasone plus ondansetron, is more effective in the prevention of vomiting than dexamethasone and ondansetron alone in patients receiving non-cisplatin-based moderately emetogenic chemotherapy [90]. The enrollment was 1933 patients with solid malignant tumors, mostly breast cancer (96%) with the primary endpoint again being complete response in the first 120 h post chemotherapy. Patients received oral casopitant in a schedule of oral casopitant (150 mg on day 1 and 50 mg/day on days 2 and 3); intravenous casopitant (90 mg) on day 1, followed by 2 days of oral casopitant (50 mg/day); or oral casopitant (150 mg) on day 1. Treatment was continued for up to four cycles. Patients also received oral ondansetron (8 mg BID on days 1 – 3) and intravenous dexamethasone (8 mg on day 1). In the first 120 h of the first treatment cycle for the intravenous/oral casopitant dose group, the complete response rate was 74% compared with 59% for controls ($p < 0.0001$). In the first 24 h, the complete response rate was 86% compared with 85% for controls ($p = 0.585$). There was no vomiting over 120 h in 78 and 63% of patients for the casopitant and control groups, respectively ($p < 0.0001$). In treatment cycles two to four, complete responses were achieved in 81, 80, and 84% of patients in the intravenous/oral casopitant dose group compared with 63, 67, and 69% in the control group,

respectively. In the single oral casopitant dose group and the three oral casopitant dose groups, complete responses were observed in 73 and 73% of patients ($p < 0.0001$), respectively, over the first 120 h of the first treatment cycle, and in 88% ($p = 0.1586$) and 89% ($p = 0.0545$) of patients in the first 24 h. No vomiting occurred in 80 and 81% of patients ($p < 0.0001$) in these two dose groups, respectively. In treatment cycles two to four, complete responses were achieved in 80, 79, and 82% of patients in the single oral casopitant dose group and in 81, 80, and 84% of patients in the three oral casopitant dose group, respectively.

A third Phase III clinical trial has been initiated to establish the efficacy of a single intravenous dose of casopitant, administered in combination with ondansetron and dexamethasone, in preventing CINV in 700 patients with colorectal cancer receiving the moderately emetogenic chemotherapy oxaliplatin. The primary endpoint of this trial is the measurement of vomiting and the use of rescue medication during cycle 1 .[93]

Olanzapine

Olanzapine is an FDA-approved antipsychotic that blocks multiple neurotransmitters: dopamine at D1, D2, D3, D4 brain receptors, serotonin at 5-HT2a, 5-HT2c, 5-HT3, 5-HT6 receptors, catecholamines at alpha1 adrenergic receptors, acetylcholine at muscarinic receptors, and histamine at H1 receptors [94,95]. Common side effects are sedation and weight gain [96,97], as well as an association with the onset of diabetes mellitus [98]. Olanzapine's activity at multiple receptors, particularly at the D2 and 5-HT3 receptors, which appear to be involved in nausea and emesis, suggests that it may have significant anti-emetic properties.

A Phase I study demonstrated that olanzapine could be safely used for the prevention of delayed emesis in cancer patients receiving their first cycle of chemotherapy consisting

of cyclophosphamide, doxorubicin, cisplatin and/or irinotecan [99]. Using the maximum tolerated dose of olanzapine in the Phase I trial, a Phase II trial was performed for the prevention of CINV in patients receiving their first course of either highly emetogenic or moderately emetogenic chemotherapy. When olanzapine was added to granisetron and dexamethasone in the acute period, and added to dexamethasone in the delayed period, there was a very high complete response (no emesis, no rescue) and excellent control of nausea. The study concluded that olanzapine is safe and highly effective in controlling acute and delayed CINV in patients receiving highly emetogenic and moderately emetogenic chemotherapy [100].

An additional Phase II study was performed to determine the control of acute and delayed CINV in patients receiving moderately emetogenic chemotherapy and highly emetogenic chemotherapy with the combined use of palonosetron and olanzapine, and dexamethasone with the dexamethasone given on day one only. On day 1 of chemotherapy, 40 chemotherapy-naïve patients received an anti-emetic regimen consisting of dexamethasone, palonosetron, and olanzapine. Patients continued olanzapine for days 2 – 4 following chemotherapy administration. Patients recorded daily episodes of emesis, utilizing the MD Anderson Symptom Inventory, and the utilization of rescue therapy. For the first cycle of chemotherapy, the complete response (no emesis, no rescue) for the acute period (24 h postchemotherapy) was 100%, the delayed period (days 2 – 5 postchemotherapy) 75%, and the overall period (0 – 120 h postchemotherapy) 75% in 8 patients receiving highly emetogenic chemotherapy and was 97%, 75%, and 72% in 32 patients receiving moderately emetogenic chemotherapy. No nausea for patients in the acute period was 100%, the delayed period 50%, and the overall period 50% in 8 patients receiving highly emetogenic chemotherapy and was 100%, 78%, and 78% in 32 patients receiving moderately emetogenic chemotherapy. The complete response and control of nausea in

subsequent cycles of chemotherapy were not significantly different from cycle one. Olanzapine combined with a single dose of dexamethasone and a single dose of palonosetron was very effective in controlling acute and delayed CINV in patients receiving both highly and moderately emetogenic chemotherapy [101].

Gabapentin

A recent report by Guttuso et al. [102] in a small number of patients receiving adjuvant chemotherapy (doxorubicin, cyclophosphamide) for breast cancer suggested that the anticonvulsant gabapentin might reduce delayed nausea. Further studies will be necessary to determine the efficacy of this agent.

Cannabinoids

Two oral formulations of cannabinoids, dronabinol and nabilone, have been approved by the FDA for use in CINV refractory to conventional antiemetic therapy [103] The National Comprehensive Cancer Network has suggested the use of cannabinoids for breakthrough treatment [104]. Cannabinoid receptors of the CB1 type are present in the area postrema, NTS, and dorsal motor nucleus which are key sites within the brainstem for emetogenic control [105]. Recent evidence suggests that cannabinoid CB2 receptors are present on brainstem neurons and may have a role in mediating the cannabinoids effects on emesis [105,106].

There have been no comparative studies of dronabinol and nabilone with the 5-HT3 receptor antagonists and the NK-1 receptor antagonists in the prevention of CINV. The role of the cannabinoids in the prevention of CINV remains to be established [103].

Anti-emetic prophylaxis –

Chemotherapy used in the treatment of most nonhematologic and some hematologic cancers is most frequently administered intravenously over the course of a single day. This is also the

setting in which clinical data on the use of antiemetic agents are most abundant. The fundamental principle that should guide decisions about antiemetic treatment is that complete prevention of nausea and vomiting is the ultimate objective, and it is best accomplished with the use of appropriate, evidence-based preventive treatment. The choice of regimen is guided by two considerations: the emetogenic potential of the chemotherapy and whether there is a substantial risk of delayed nausea and vomiting.

Anti-emetic prophylaxis in highly emetogenic chemotherapy(HEC) – The anti-emetic regimen of choice in this setting is a combination of aprepitant, 5HT3 receptor antagonist and dexamethasone. Abundant clinical data support this combination for patients receiving cisplatin-based chemotherapy. Hesketh et al showed in their study that compared with standard dual therapy , addition of aprepitant was generally well tolerated and provided consistently superior protection against CINV in patients receiving highly emetogenic chemotherapy.[107].Warr et al showed in their study that aprepitant arm in comparison to the standard dual therapy arm had a statistically significant less nausea, better control of acute and delayed emesis and also lower frequency of the intake of rescue medications .[108].Similarly Poli-Bigelli study which was a latin American study showed that addition of aprepitant to the standard anti-emetic therapy significantly improves the control of CINV.[109].Chawla et al in their study also confirmed the superiority of the addition of aprepitant to the standard antiemetic arm.[110].Thus based on the available data addition of aprepitant to the standard antiemetic regimen results in significant improvement in the control of acute emesis, delayed emesis, nausea and also has a better quality of life .

Palonosetron has also been approved for the prevention of acute CINV in patients receiving either moderately or highly emetogenic chemotherapy and for the prevention of delayed CINV

in patients receiving moderately emetogenic chemotherapy. In recent studies, compared to the first-generation 5-HT3 receptor antagonists, palonosetron in combination with dexamethasone demonstrated better control of delayed CINV in patients receiving highly emetogenic chemotherapy.

Grunberg et al in their study of 667 patients receiving highly emetogenic Chemotherapy (HEC) (cisplatin, 60 mg/m2) compared one of two doses of palonosetron (0.25 mg or 0.75 mg) or ondansetron (32 mg) pre-chemotherapy. Sixty-seven percent of the patients in all three study arms also received dexamethasone. Single-dose palonosetron was as effective as ondansetron in preventing acute CINV and with dexamethasone pretreatment, its effectiveness was significantly increased over ondansetron throughout the 5-day post chemotherapy period.[64].

Hajdenberg et al[111] reported the results of another multicenter, open-label study evaluating the use of palonosetron (0.25 mg) and dexamethasone (8 mg) prior to patients receiving moderately to highly emetogenic chemotherapy .A CR was observed in 84% of patients in the first 24 hours post-chemotherapy (acute), 59% of patients during days 2 to 5 (delayed), and 59% days 1 to 5 (overall period). No nausea was observed in 78% of patients in the acute period, and 50% in the overall period. No significant adverse events were reported in the study. Saito et al[112] conducted a double-blind, double-dummy, randomized, comparative phase III trial in 1143 patients receiving HEC (cisplatin or the combination of an anthracycline and cyclophosphamide). Of 555 patients in the palonosetron group, 418 (75.3%) had a complete response during the first 24 hours (acute period) compared with 410 of 559 patients (73.3%) in the granisetron group. During the delayed period, 315 of 555 patients (56.8%) had a complete response in the palonosetron group compared with 249 of 559 patients (44.5%) in the granisetron group ($P < 0.0001$). When administered with dexamethasone, palonosetron prevented CINV which was non-inferior to

granisetron in the acute period and better than granisetron in the delayed period, with a comparable safety profile for the two treatments. Thus palonosetron is effective in the control of CINV both acute and delayed and also has a modest improvement in the quality of life of patients receiving highly emetogenic chemotherapy. Even though palonosetron is proved superior to other first generation 5HT3 receptor antagonists , the guidelines do not mention the use of any particular 5HT3receptor antagonist in combining with dexamethasone and aprepitant.

Anti- emetic prophylaxis in Moderately emetogenic chemotherapy-

As compared to the scenario in the HEC group ,the choice of use of anti-emetic prophylaxis in the MEC group is relatively controversial. Conventionally dexamethasone and 5HT3receptor antagonists in combination were the agents of choice .The role of aprepitant in the control of emesis in the MEC is becoming more clear and strong .A study by Warr et al was one of the first studies to define the role of the aprepitant in the control of emesis in patients receiving moderately emetogenic chemotherapy. This study showed that aprepitant arm had a better control of CINV as compared to the standard arm.[113] A Chinese study also was done which compared addition of aprepitant to the standard anti emetic regimen and showed that addition of aprepitant is beneficial.[114].

Various studies for palonosetron are reported which have showed efficacy of palonosetron over other first generation 5HT3receptor antagonists. Gralla et al [63] showed that a single intravenous dose of palonosetron 0.25 mg was significantly superior to intravenous ondansetron 32 mg in the prevention of acute and delayed CINV in patients receiving MEC116. Eisenberg et al [62] in their study showed that single dose of palonosetron was superior to granisetron in patients receiving MEC . Thus based on the above mentioned studies and many

more phase II studies , palonosetron has been found to be superior to first generation 5HT3receptor antagonists in the management of patients receiving MEC.

According to the update on antiemetic guidelines in 2007 by Karin Jordan [115] which included the Multinational Association of Supportive Care in Cancer (MASCC) antiemetic guidelines , NCCN guidelines for anti emetics and ASCO guidelines recommended the combination of a 5-HT3RA plus dexamethasone with or without aprepitant for acute CINV with moderately emetogenic chemotherapy. However, the key question in this setting is whether aprepitant should be part of the antiemetic prophylaxis. The ASCO and MASCC guidelines recommend the triple combination (a 5-HT3RA, dexamethasone, and aprepitant) for patients receiving the combination of an anthracycline and cyclophosphamide– based regimen. The NCCN guidelines, however, broaden the spectrum of the use of aprepitant in this setting and advise use in selected patients receiving other chemotherapies of moderately emetogenic risk (e.g., carboplatin, epirubicin, ifosfamide, irinotecan). Dexamethasone is the preferred agent to use for delayedCINV with moderately emetogenic chemotherapy. Nonetheless, when aprepitant is used for the prevention of acute CINV then it should also be used for the prophylaxis of delayed CINV as monotherapy, as stated by the MASCC and ASCO guidelines. As discussed before, the NCCN guidelines suggest aprepitant with or without dexamethasone in this situation. A 5-HT3RA can be used as an alternative, although their therapeutic role in the delayed phase is rather limited [116]. In contrast to all three previously published guidelines, metoclopramide is not reflected in the new guidelines as an alternative option.

Low Emetogenic Chemotherapy

The MASCC and ASCO guidelines unanimously recommend the use of a steroid alone in the first 24 hours and no prophylaxis beyond 24 hours for acute CINV with low emetogenic

chemotherapy. The NCCN guidelines recommend prochlorperazine or metoclopramide as well, as alternative drugs to dexamethasone.

Minimally Emetogenic Chemotherapy

All three guidelines suggest that, for patients treated with agents of low emetic risk, no antiemetic drug should be routinely administered before chemotherapy.

MANAGEMENT OF BREAKTHROUGH AND REFRACTORY CINV

Breakthrough CINV is defined as an event that happens in spite of optimal preventive treatment. Refractory CINV is CINV that recurs in subsequent cycles of therapy when all previous preventive and rescue treatments fail. If optimal treatment has been given as prophylaxis, repeated dosing of the same agents is unlikely to be successful the addition of dopamine-receptor antagonists (metoclopramide) might be useful, or adding other
agents such as benzodiazepines or neuroleptics. Olanzapine, an atypical neuroleptic, could also be considered, as suggested by the MASCC and NCCN guidelines.

Various antiemetic guidelines [115]

	High		Moderate		Low		Minimal	
Group	Acute CINV	Delayed CINV	Acute CINV	Delayed CINV	Acute CINV	Delayed CINV	Acute CINV	Delayed CINV
MASCC	5-HT_3RA + dexamethasone + aprepitant	Dexamethasone + aprepitant	1. Anthracycline/ cyclophosphamide 5-HT_3RA + dexamethasone + aprepitant	Aprepitant or dexamethasone	Dexamethasone	[a]	[a]	[a]
			2. Other than anthracycline/ cyclophosphamide 5-HT_3RA + dexamethasone	Dexamethasone, 5-HT_3RA may be used as an alternative				
ASCO	5-HT_3RA + dexamethasone + aprepitant	Dexamethasone + aprepitant	1. Anthracycline/ cyclophosphamide 5-HT_3RA + dexamethasone + aprepitant	Aprepitant	Dexamethasone	[a]	[a]	[a]
			2. Other than anthracycline/ cyclophosphamide 5-HT_3RA + dexamethasone	Dexamethasone or a 5-HT_3RA				
NCCN	5-HT_3RA + dexamethasone + aprepitant ± lorazepam	Dexamethasone + aprepitant ± lorazepam	1. Anthracycline/ cyclophosphamide or in selected patients 5-HT_3RA + dexamethasone + aprepitant ± lorazepam	Aprepitant ± dexamethasone ± lorazepam	Dexamethasone ± Lorazepam or Prochlorperazine ± lorazepam or metoclopramide ± lorazepam or	[a]	[a]	[a]
			2. Other than anthracycline/ cyclophosphamide 5-HT_3RA + dexamethasone ± lorazepam	Dexamethasone or 5-HT_3RA, both ± lorazepam				

[a]No routine prophylaxis.
Abbreviations: 5-HT_3RA, 5-HT_3-receptor antagonist; ASCO, American Society of Clinical Oncology; CINV, chemotherapy-induced nausea and vomiting; MASCC, Multinational Association of Supportive Care in Cancer; NCCN, National Comprehensive Cancer Network.

METHODS AND MATERIALS

Newly diagnosed patients of breast carcinoma receiving the first cycle of moderately emetogenic chemotherapy were included in the study.

Inclusion criteria-

- Patients with carcinoma breast confirmed histopathologically /cytologically
- Age more than 18 years
- Patients receiving their first cycle of chemotherapy
- Patients should be receiving moderately emetogenic chemotherapy as per the Hesketh's classification – combination of anthracycline and cyclophosphamide, anthracyclines alone, Cyclophosphamide alone with a dose of 750mg/m2 to 1.5 gm/m2, any combination containing anthracyclines and cyclophosphamide (dose of less than 1.5 gm/m2)
- Patients with predicted life expectancy of more than or equal to 4 months
- Patients with karnofsky score of more than or equal to 60

Exclusion criteria-

- Patients with CNS metastases
- Patients who had vomited in the 24 hours before the expected date of chemotherapy
- Patients taking corticosteroids (any dose) for any other causes like bronchial asthma etc
- Patients who have received radiation to abdomen or pelvis in the week before the chemotherapy date

- Patients having active infection, a systemic fungal infection
- Patients with abnormal renal function (> 1.5 times the normal value)
- Patients with abnormal LFT (Total bilirubin->1.5 times the normal)
- Patients with elevated liver enzymes (>1.5 times the normal)
- Patients with abnormal hemogram(WBC count<3000),Absolute neutrophil cont <1500, platelet count <1lakh
- Patients who have taken any anti emetic within 48 hrs prior to chemotherapy

The 150 patients who were eligible to be included in the study, after taking informed consent were randomly assorted to one of the three arms of prophylactic anti emetic therapy.

Ondansetron arm -Patients received 8mg of intravenous ondansetron and 8mg of intravenous dexamethasone prior to chemotherapy followed by 8mg of oral ondansetron 8 hrs after chemotherapy followed by 8mg of oral ondansetron twice daily on day2 and day3.

Palonosetron arm -Patients received 0.25mg of intravenous palonosetron 30 minutes prior to chemotherapy.8 mg of intravenous dexamethasone to be administered as premedication prior to chemotherapy. No drugs on day2 and day3.

Aprepitant arm –Patients on day1 received 125 mg of oral aprepitant 1 hour prior to chemotherapy followed by 8mg of intravenous ondansetron and 4mg of intravenous dexamethasone prior to chemotherapy followed by 8 mg of oral ondansetron 8 hrs after chemotherapy. Patients received 80 mg of aprepitant on days 2 and 3.

Patients were allowed rescue medications during any time in the study period if they had emesis or severe nausea even in the absence of emesis. Domperidone, ondansetron, phenothiazines, butryophenones and benzodiazepines were allowed as rescue medication.

Patients were given a printed sheet of paper which had 5 columns for the 5 days after chemotherapy and patients were also given the FLIE questionnaire in their local language on Day 1 and were explained clearly in their local language that they will be required to fill the questionnaire on day 6. Patients also were clearly instructed to note down the emetic episodes if at all they had emesis. They were asked to note the date of emesis, time of emesis, number of emetic episodes and rescue medication details like what rescue medication and for how many days they have taken the same. On Day 6 patients were again assessed and were asked to fill the FLIE questionnaire.

FLIE questionnaire has 2 domains – nausea domain and vomiting domain. Each domain has 9 questions. Patient has to mark her/his responses on a visual analogue scale which is marked from 1 to 7 dividing the scale into 6 equal parts. If the nausea/vomiting has affected the individual to the maximum then they have to mark 1 and If they are not at all affected by nausea or vomiting then they have to mark 7 and in between markings denote the intensity of affection as per the score. So score of 6 and above for a question is taken as the patient has not been affected by nausea/vomiting. 9 questions are there in each domain and a score of >54 in that domain means that the patient is having excellent quality of life and is not affected by CINV. FLIE scores are taken individually for domains and then added with a score of >108 suggesting excellent quality of life

Complete response (CR) was defined as no emesis or no intake of rescue medications during a period of 120 hours after the initiation of chemotherapy.

Acute CR was defined as no vomiting episodes and no intake of rescue medications during the first 24 hours after chemotherapy.

Delayed CR was defined as no vomiting episodes and no intake of rescue medications after 24 hours after chemotherapy up to 120 hours.

Moderately emetogenic chemotherapy was defined as per the Hesketh's classification of chemotherapeutic agents. It was defined as risk of emesis of 31-90% following the administration of chemotherapy in the absence of antiemetic prophylaxis. combination of anthracycline and cyclophosphamide, anthracyclines alone, Cyclophosphamide alone with a dose of 750mg/m2 to 1.5 gm/m2, any combination containing anthracyclines and cyclophosphamide (dose of less than 1.5 gm/m2).

Chi-square test, Mantel-haenszel and Yates corrected were the statistical methods which were used to calculate the significance of the results.

Institute protocol for the treatment of breast cancer-

Early breast cancer – upfront surgery followed by adjuvant chemotherapy with or without radiotherapy followed by hormonal manipulation in appropriate settings

Locally advanced breast cancer – neo- adjuvant chemotherapy 2-3 cycles of 600mg/m2 5fluorouracil+ 60mg/m2 of epirubicin + 600 mg/m2 of cyclophoshamide or 175 mg/m2 paclitaxel + 60 mg/m2 of epirubicin with 40 Gy radiotherapy to breast, axilla with or without supra clavicular area followed by modified radical mastectomy followed by completion of chemotherapy and then hormonal manipulation appropriately. Radiotherapy to internal mammary region also is given to appropriate patients.

Metastatic breast carcinoma – Chemotherapy , bisphoponates whenever indicated, palliative radiotherapy wherever indicated.

RESULTS

DEMOGRAPHIC PROFILE

150 patients of breast cancer receiving moderately emetogenic chemotherapy were included in the study with 50 each receiving ondansetron or palonosetron or aprepitant as the antiemetic prophylaxis.

Age distribution – The median age in the ondansetron arm was 46, in the palonosetron arm was 45 and 51 in the aprepitant arm.

Tab-1 – age distribution

	Median age	Min age	Max age
Ondansetron	46	27	65
palonosetron	45	34	61
Aprepitant	51	33	65

Breast cancer patients in neo-adjuvant, adjuvant and metastatic settings were all included with the patients being equally distributed in all the three arms .Ondansetron arm had 60% of patients in neoadjuvant setting with 78% in palonosetron arm and 70% in aprepitant arm. 30% of patients in ondansetron arm were in adjuvant setting with palonosetron having 14% and aprepitant having 18% in adjuvant setting. Patients with metastatic breast cancer were also equally distributed in each arm with 10%, 8% and 12% respectively in ondansetron, palonosetron and aprepitant arms.

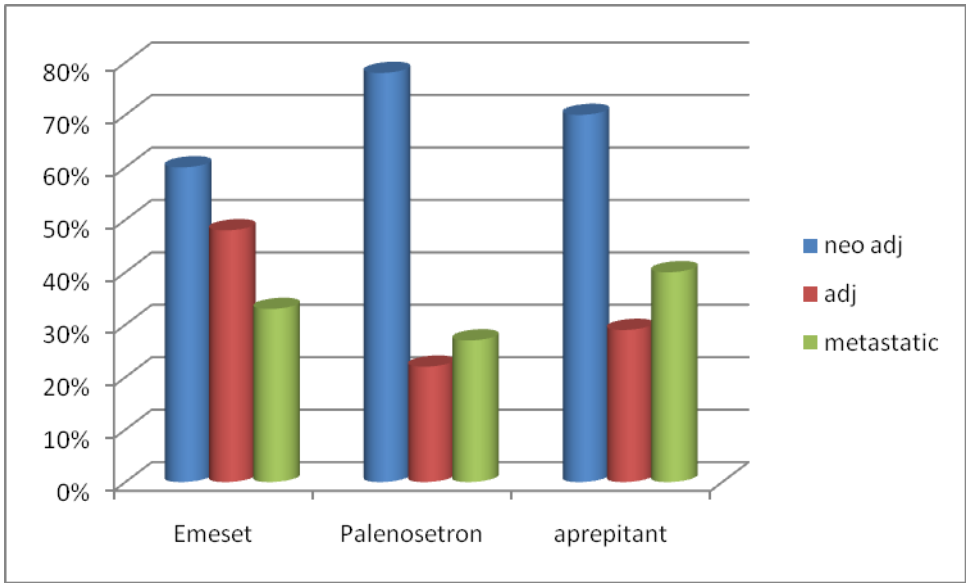


Fig – 3 – distribution of the patients in various settings in the three arms

Number of patients in each arm receiving radiation to the chest wall was almost similar with 32% in ondansetron arm, 34% in palonosetron arm and 33% in aprepitant arm respectively.

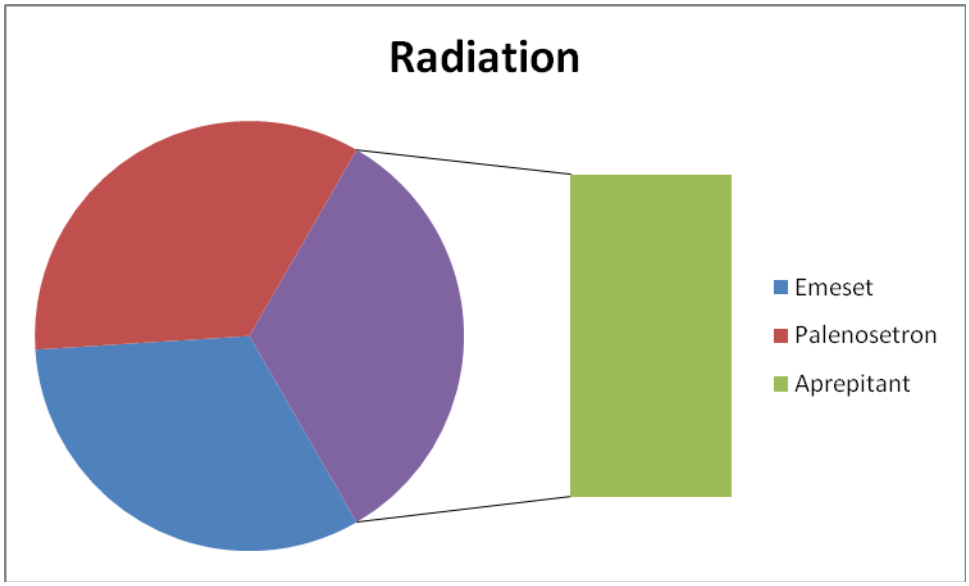


Fig 4- distribution of patients in each arm receiving radiation

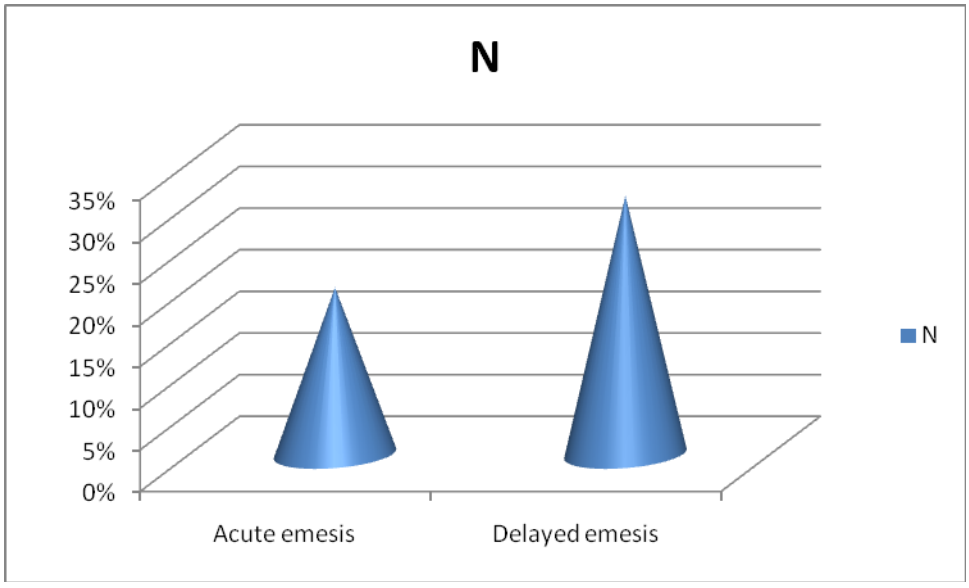
Patients in all three arms were fairly matched with respect to the other variables like co morbid conditions, ER, PR and HER-2 neu receptor status.

Tab 2- Variables in the three arms

	Ondansetron	Palonosetron	Aprepitant	P- value
Hypertension	27%	35%	37%	0.6272
Diabetes Mel	32	25	43	0.04
IHD	2	2	0	0.6024
ER	31	31	36	0.4205
PR	33	34	33	0.9733
HER 2neu	31	36	32	0.8029

Outcomes-Responses in each of the arms were anlysed and complete response in acute phase, delayed phase and for a total duration of 120 hours after chemotherapy were obtained. Throughout the study population 20% had acute emesis and 31% had delayed emesis.

Fig-5- Acute and delayed emesis percentages across the study population



So 36%, 18% and 06% in the ondansetron, palonosetron and aprepitant arms respectively had acute emesis. 62%, 24% and 08% of patients in ondansetron, palonosetron and aprepitant arms respectively had delayed emesis.

Fig 6- Acute emesis and delayed emesis in each arm

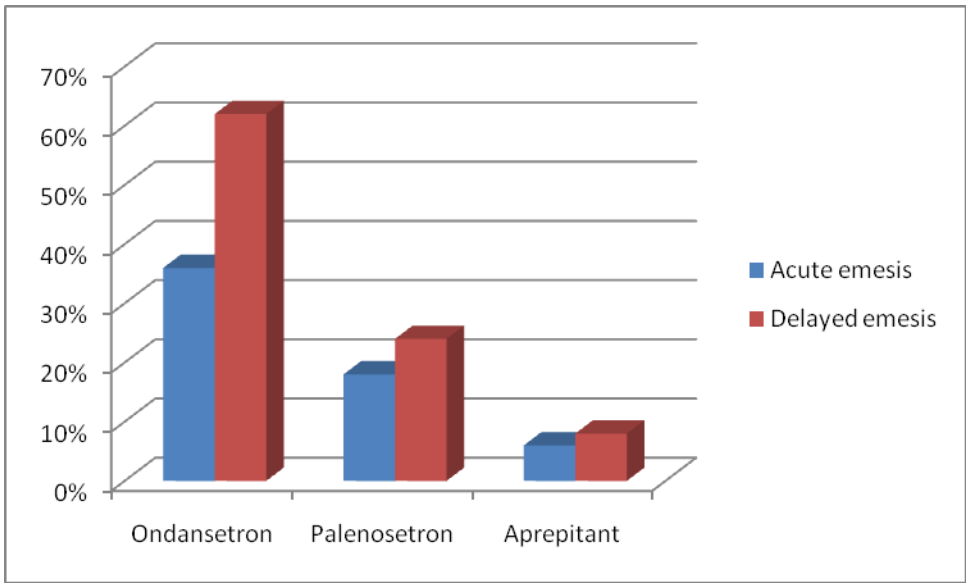
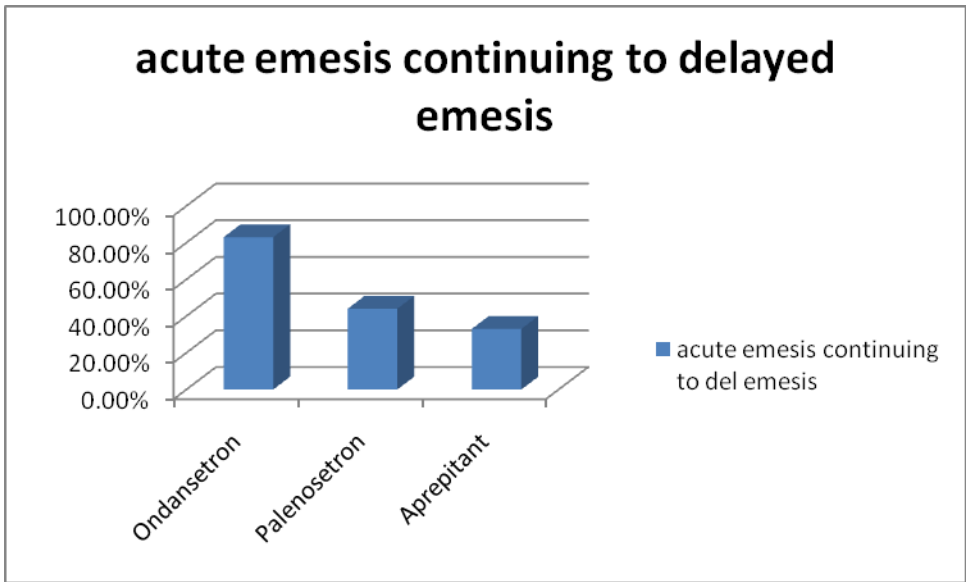
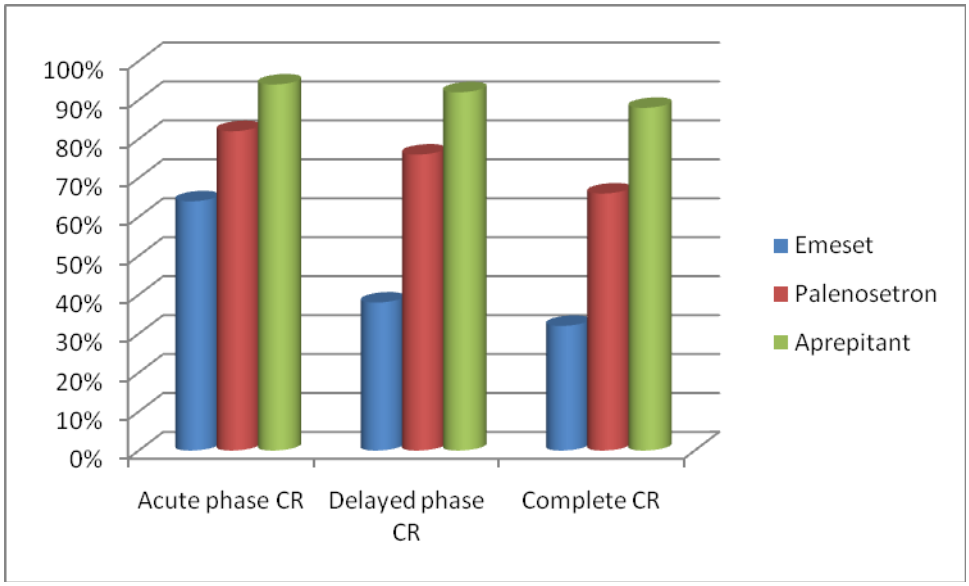


Fig7- Acute emesis progressing to delayed emesis



83.3% in the ondansetron arm, 44.4% in the palonosetron arm and 33.3% in the aprepitant arm with acute emesis continued to have delayed emesis.

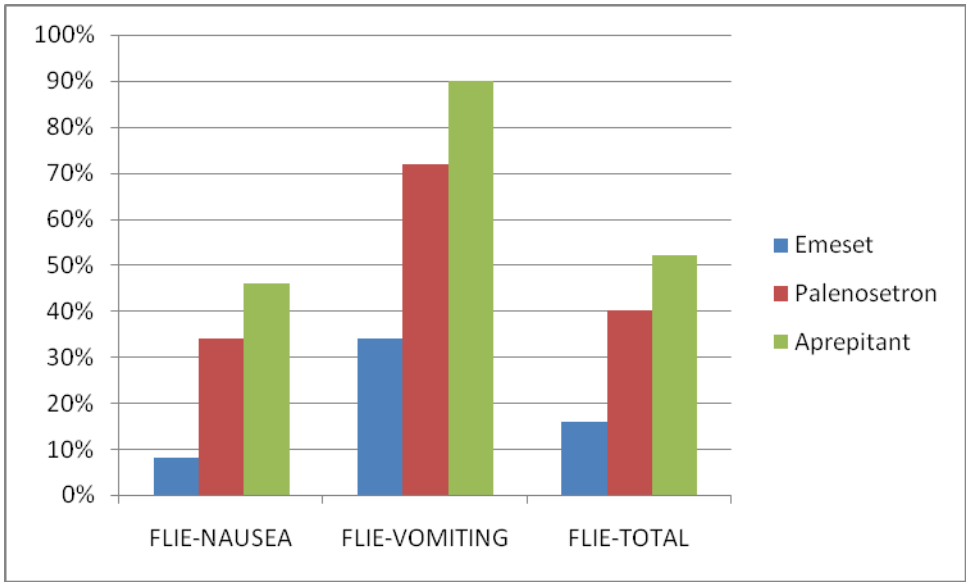
Fig 8- Complete response rates in acute, delayed and total phase



Complete responses were much better in the aprepitant and palonosetron arms as compared to the control ondansetron arm 64%, 82% and 94% were the acute phase CR rates in ondansetron, palonosetron and aprepitant arms which were statistically significant (p-0.0008).

Similarly delayed phase CR rates of 38%, 76%, 92% and total CR rates of 32%, 66% and 88% were obtained in ondansetron, palonosetron and aprepitant arms respectively

Fig 9- Functional living index – emesis score rates



As seen in the Figure 7 and table3 the functional living index- emesis (FLIE) scores were better in the aprepitant and palonosetron arms as compared to the ondansetron arms.

Table 3-FLIE scores among the three arms

	FLIE-NAUSEA Score>54	FLIE- VOMITING Score>54	FLIE-TOTAL Score>108
Ondansetron	8%	34%	16%
Palonosetron	34%	72%	40%
Aprepitant	46%	90%	52%

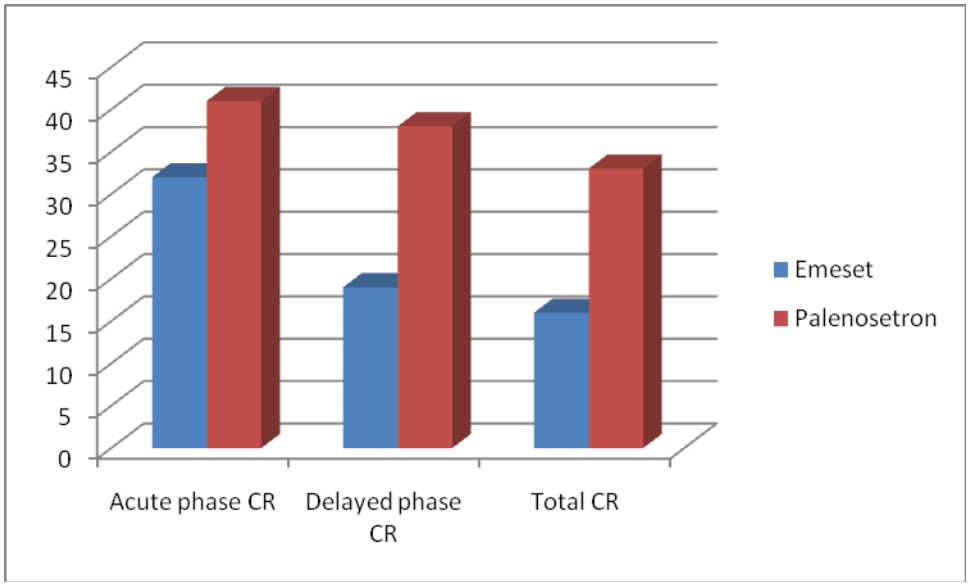
Number of patients taking rescue medications was also less in the palonosetron and aprepitant arms 64% and 86% respectively.

Table – 4 Comparison of the three drugs with respect to the use of rescue medications

	Number of patients taking rescue medications
Ondansetron	68%
Palonosetron	36%
Aprepitant	14%

Palonosetron when compared to ondansetron had a significantly favourable outcome with respect to the control of CINV.

Fig10- Comparison of CR rates in ondansetron and palonosetron arms

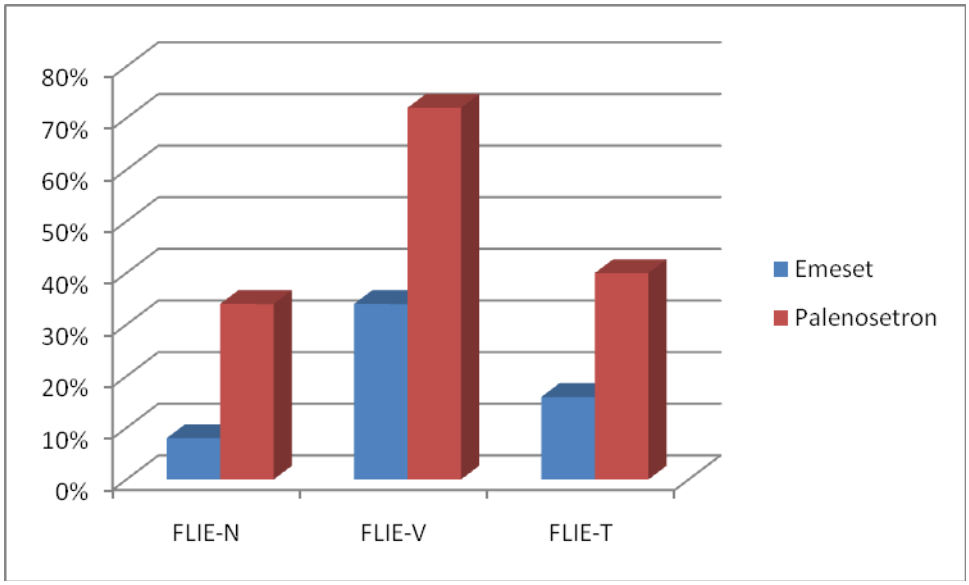


The acute phase CR rate in ondansetron arm was 64% as compared to 82% in the palonosetron arm which was statistically significant (p- 0.04 as per the Mantel-Haenszel method).

The difference between the two arms was much more evident in delayed phase CR rates of 38% in ondansetron arm as compared to the 76% in the palonosetron arm with a p value of 0.0001(Yates corrected method and mantel- Haenszel methods).

The CR rates over the total period of 120 hours which was the total CR rate was also significantly high in palonosetron arm with a value of 66% as compare to 32% in the ondansetron arm (p- 0.001-Yates corrected method)

Fig 11- comparison of FLIE scores between the ondansetron and palonosetron arms

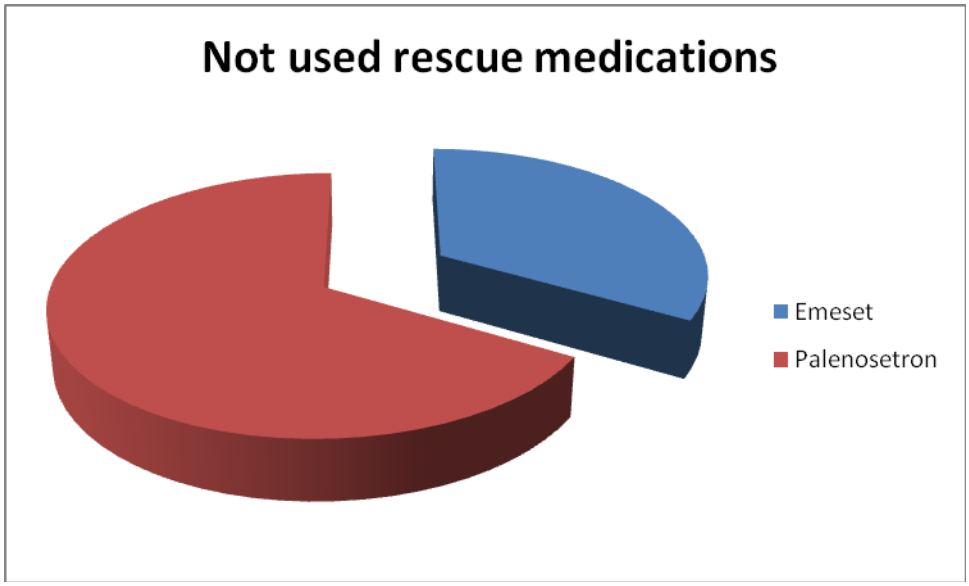


Palonosetron also was significantly better with respect to the FLIE scores for nausea , vomiting and the total FLIE score .8% in ondansetron arm had FLIE nausea score of >54 as compared to 34% in the palonosetron arm. The scores in FLIE vomiting domain were 34% and 72% respectively for ondansetron and palonosetron arms with a statistically significant p value of

0.003 (Yates corrected method. The total FLIE score of >108 was seen in 16% in ondansetron arm as compared to 40% in palonosetron arm (p-0.014 by Yates corrected method)

32% of patients in ondansetron arm did not use rescue medication as compared to 64% in the palonosetron arm which again was a statistically significant difference (p- 0.002 by Yates corrected method)

Fig 12- Comparison of the Rescue medication usage between ondansetron and palonosetron arms

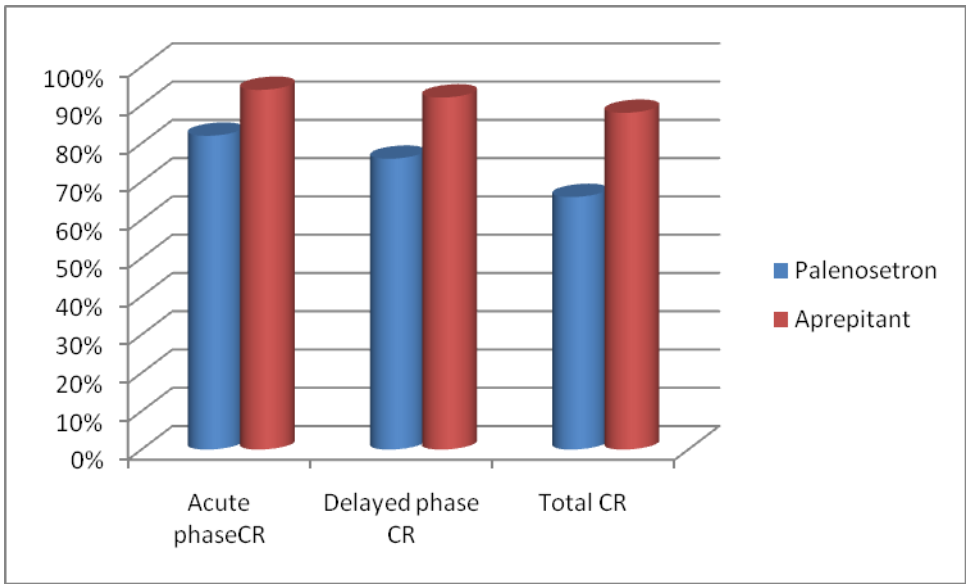


Thus palonosetron in comparison to the conventional anti- emetic ondansetron fared better with respect to the control of emesis in acute phase, delayed phase and combined acute and delayed phases. Palonosetron also had significantly favourable outcome with respect to FLIE scores in both nausea and vomiting domains and also the total FLIE score.

Palonosetron was then compared to aprepitant and the acute phase CR rates 82% in palonosetron arm as compared to 94% in aprepitant arm which was not statistically significant (p- 0.12 Yates corrected method).Aprepitant fared better than palonosetron in delayed phase control, total CR,

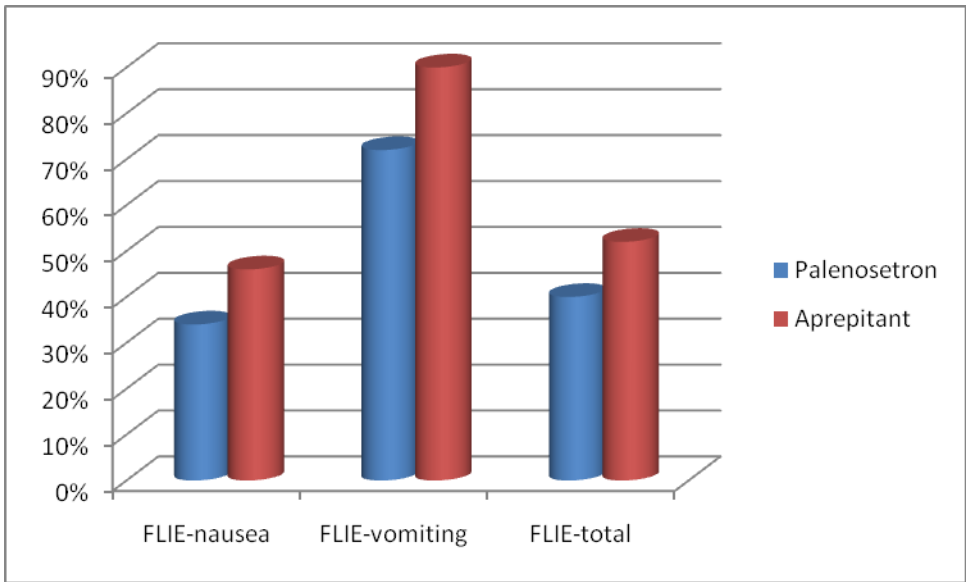
FLIE score in vomiting domain and with respect to rescue medication usage .76% achieved delayed phase CR in palonosetron arm as compared to 92% in aprepitant arm which was statistically significant with a p value 0.02.Total CR was achieved in 66% of patients in the palonosetron arm as compared to 88% in aprepitant arm which was statistically significant , p-0.01 as per the Yates corrected method.

Fig 13 – Comparison of Aprepitant and Palonosetron



34% in Palonosetron arm achieved a FLIE score of >54 in nausea domain as compared to 46% in aprepitant arm which was not statistically significant, p- 0.30

Fig14- comparison of Aprepitant and Palonosetron for FLIE scores



In vomiting domain aprepitant arm had significantly better results with 90% achieving a score of >54 as compared to 72% in palonosetron arm (p-0.04).FLIE total score of >108 was achieved by 40% in palonosetron arm as compared to 52% in aprepitant arm, p-0.31.In aprepitant arm 86% did not use rescue medications as compared to the 64% in the palonosetron arm, p- 0.02. Aprepitant was much superior to ondansetron in all the parameters with CR rates of 94% in acute phase, 92% for delayed phase, 88% both acute and delayed phase combined as compared to 64%, 38% and 32% respectively in the ondansetron arm.

Table-5 Comparison of Ondansetron and Aprepitant

	Acute CR	Delayed CR	Total CR	FLIE-N >54	FLIE-V >54	FLIE-T >108	Rescue med used
Aprepitant	94%	92%	88%	46%	90%	52%	68%
Ondansetron	64%	38%	32%	08%	34%	16%	14%

As shown in the above table aprepitant fared much better than ondansetron arm with FLIE scores of 46% in nausea domain, 90% in vomiting domain and 52% in the combined domain as compared to the respective scores of 08%, 34% and 16% in the ondansetron arm.68% in the aprepitant arm did not use rescue medications as compared to 14% in the ondansetron arm .All the values were statistically significant.

Aprepitant fared much better than the conventional ondansetron and also palonosetron. Subset analysis comparing the efficacy of palonosetron and aprepitant in patients less than 50 years and more than 50 years was done.

Table 6- Comparison of Palonosetron and Aprepitant in age <50 years

	Acute CR	Del CR	Total CR	FLIE-N Score>54	FLIE-V Score>54	FLIE-T Score>108	Res med not taken
Aprepitant	90%	95%	90%	55%	95%	55%	90%
Palonosetron	86%	72.2%	63.8%	33.3%	69.4%	38.8%	61.1%
P value	0.67 NS	0.03	0.03	0.19 NS	0.02	0.37 NS	0.04

So as can be observed from the above table, in patients less than 50 years, aprepitant fared better than palonosetron in all the comparable response parameters with statistically significant difference noted in delayed CR, total CR and FLIE-score in the vomiting domain with values of 95%,90% and 95% respectively in aprepitant arm as compared to 72.2%, 63.8% and 69.4% for the palonosetron arm.90% of the patients in aprepitant arm did not take rescue medications as compared to 61.1% in the palonosetron arm.

Table 7- Comparison of Palonosetron and Aprepitant in age >50 years

	Acute CR	Del CR	Total CR	FLIE-N Score>54	FLIE-V Score>54	FLIE-T Score>108	Res med not taken
Aprepitant	96%	90%	86.6%	40%	86.6%	50%	83.3%
Palonosetron	71%	85.5%	71.4%	35.7%	78.5%	44.4%	71.4%
P value	0.02 Sig	0.67	0.24	0.95	0.66	0.90	0.29

Interestingly in the patients >50 years the difference between aprepitant and palonosetron is negligible with only statistically significant outcome in the acute phase CR rates of 96% in aprepitant arm as compared to 71% in the palonosetron arm. Delayed phase and Total CR rates were 90% and 86.6% respectively in aprepitant arms as compared to 85.5% and 71.4% in the palonosetron arm. The favourable FLIE scores in the nausea domain, vomiting domain and combined were seen in 35.7%, 78.5% and 38.8% respectively in palonosetron arm as compared to 40%, 86.6% and 44.4% in the aprepitant arm.61.1% in the palonosetron arm did not take rescue medications as compared to 71.4% in the aprepitant arm which was not statistically significant.

DISCUSSION

Anti emetic prophylaxis in patients receiving Highly emetogenic chemotherapy (HEC) is well standardized and clear but unfortunately very few studies are available in the literature evaluating the role of newer anti emetics in the prevention of CINV in patients receiving Moderately emetogenic chemotherapy (MEC).The scenario of anti emetic prophylaxis is also less clear regarding the optimum anti emetic prophylaxis in MEC. The role of Aprepitant and Palonosetron to a certain extent is not yet clearly determined in MEC. Patients with breast cancer receiving a combination of anthracyclines and Cyclophosphamide have a peculiar problem. Female gender is a risk factor for development of CINV and coupled with the combination of drugs like anthracyclines with Cyclophosphamide the patients are more likely to develop CINV as compared to the subsets receiving other MEC. Hence a more potent anti-emetic regimen is likely required for these patients instead of the currently existing conventional anti emetics.

In our study we have compared the anti-emetic efficacies of the two newer drugs palonosetron and aprepitant to the conventional and a more time tested ondansetron. We have also compared palonosetron and aprepitant with respect to their ability to control acute emesis, delayed emesis, impact on the quality of life issues by the reduction of of nausea and vomiting and their ability to reduce the intake of rescue medications post chemotherapy.

The primary end point of our study was to assess the ability of the three anti emetic agents to achieve complete response defined as absence of vomiting and no intake of the rescue medications during a period of 120 hours post chemotherapy.

Fig 15- CR rates in Warr et al study

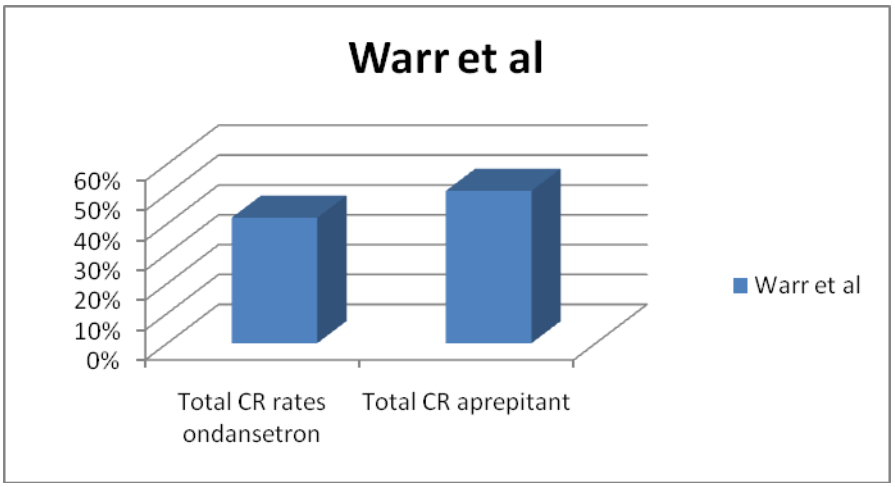
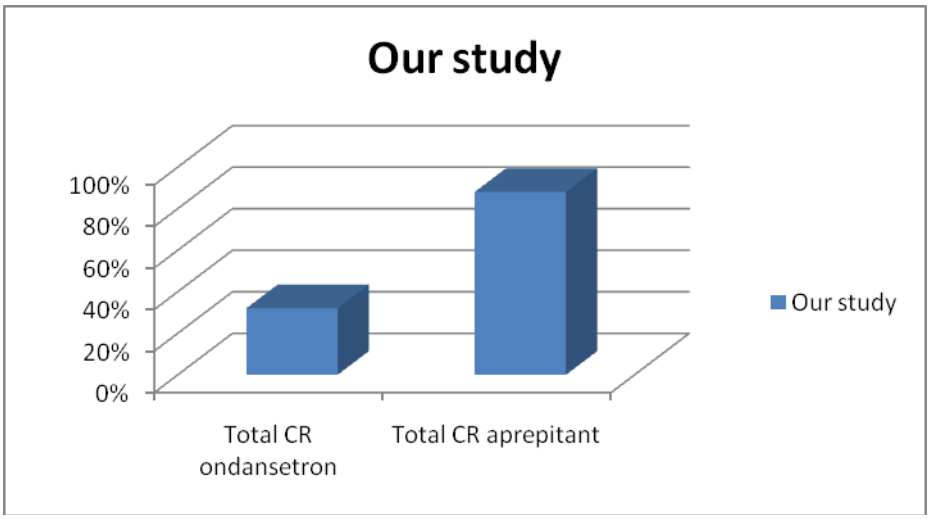


Fig 16- CR rates in our study



The total complete response rates were 32%, 66% and 88% for ondansetron, palonosetron and aprepitant arms respectively. Palonosetron had statistically significant total CR rates as compared to ondansetron (p-0.001) and in turn aprepitant had better total CR rates than palonosetron which was statistically significant in patients less than 50 yrs .David G Warr[113] et al in their study of efficacy of aprepitant in patients with breast cancer receiving MEC showed that aprepitant arm had significant improvement in total CR rates 51% in aprepitant arm and 42% in the ondansetron

arm. Winnie Yeo et al [114] comparing the effect of addition of aprepitant to the standard antiemetic regimen in patients with breast cancer receiving MEC however failed to show any benefit for aprepitant in the CR rates of acute and delayed phases. The possible explanation may be that it had a small number (127patients) and a second point may be the difference in the ethnicity of the study populations between their study and study of Warr et al and ours. Gralla et al [63] comparing the efficacy of palonosetron to ondansetron in prevention of CINV in patients receiving MEC had a total CR rate of 69.3% which was comparable to our study.Eisenberg [62]et al also showed that palonosetron was better than ondansetron in patients receiving MEC.

Secondary end points in our study were to find out the efficacy of the three drugs in achieving CR in acute phase, CR in delayed phase, impact on quality of life based on the FLIE scores, in reducing the intake of rescue medications .94% in the aprepitant arm as compared to the 64% in ondansetron arm achieved CR in acute phase which was statistically significant and Warr et al[113] in their study also had improved CR rates in acute phase with 76% in aprepitant arm versus 69% in ondansetron arm. Acute phase CR rates with palonosetron arm was 82% which was almost similar to the Gralla et al [63]study where the acute phase CR rate for palonosetron was 81%.

Fig 17-Warr et al study

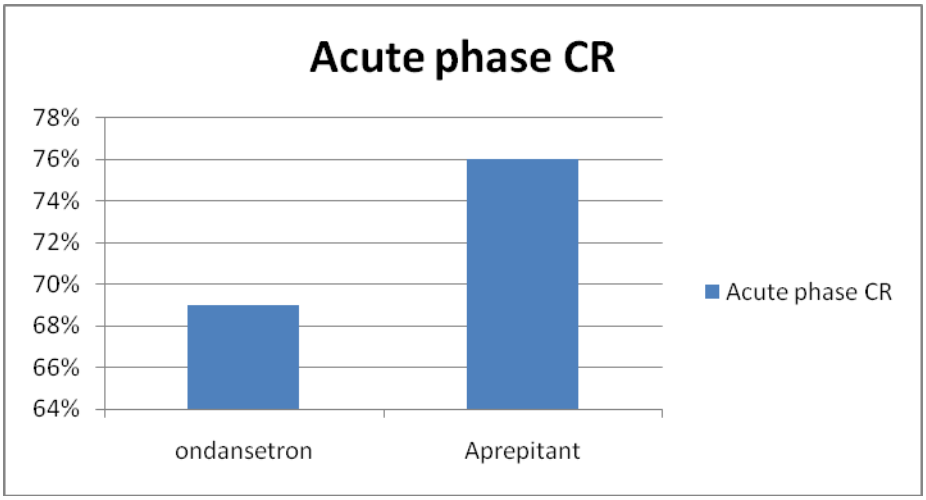
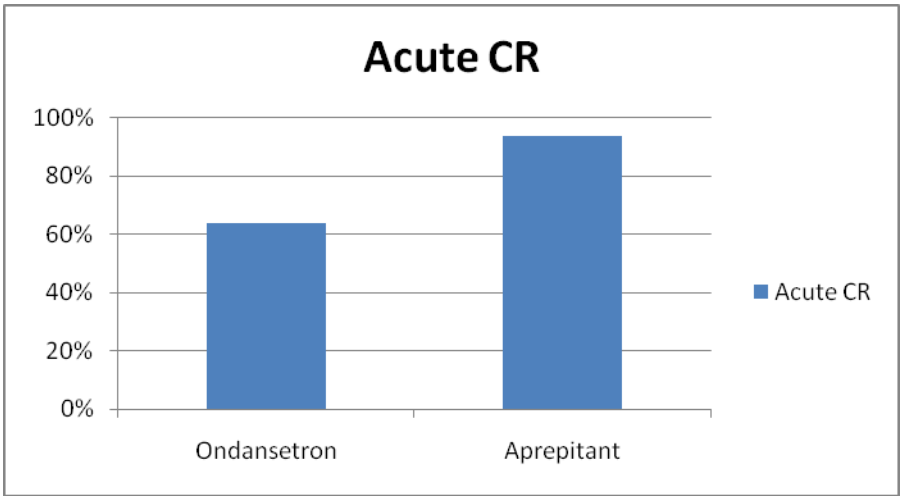


Fig 18- Our study



In our study 20% of the total study population had acute emesis and delayed emesis was seen in 31% which was almost correlating with the Warr et [113] al study in which they studied the efficacy of aprepitant in patients receiving HEC, with acute emesis occurring in 20% and delayed emesis in 35% of the entire study population .In our study 83.3% of patients with acute

emesis continued to have delayed emesis in ondansetron arm compared to 44.4% in palonosetron arm and 33.3% in aprepitant arm. Emesis in acute phase is known to be associated with greater likelihood of emesis in the delayed phase which was again consistent in our study. The percentage of patients with acute emesis progressing to delayed emesis was significantly lower in the aprepitant arm as compared to other two arms with palonosetron faring better than ondansetron as mentioned above. However regardless of whether patients had acute emesis or not , the incidence of delayed emesis was consistently lower in the aprepitant arm 92% as compared to 78% in palonosetron arm and 38% in the ondansetron arm thus signifying the greater efficacy of aprepitant. In the warr [113] et al study the corresponding delayed phase CR rates were 55% in aprepitant arm and 49% in ondansetron arm.

In our study the delayed phase CR rate was 76% in the palonosetron arm which was again consistent with the delayed phase CR rate of 74.1% in the Gralla et al study.

The other secondary end points in our study were to determine the impact of the anti-emetic regimen on the quality of life based on the FLIE questionnaire .90% of patients in aprepitant arm had FLIE score of >54 in vomiting domain as compared to 72% in palonosetron arm and 34% in ondansetron arm. Warr [113] et al in their study had almost similar values for aprepitant arm which was 85.7% but the ondansetron arm also had a 71.8% with score of >54 which was higher than the ondansetron arm in our study which possibly could be explained by the increased number of patients in ondansetron arm achieving CR as compared to our ondansetron group.46% in the aprepitant arm could manage a FLIE score of >54 in nausea domain as compared to 34% in palonosetron and 08% in ondansetron arms which was inferior to the values of 53.5% and 50.5% for the aprepitant and ondansetron arms respectively in the Warr et al[113]study denoting that possibly patients in our study group had more nausea which can be most probably attributed to

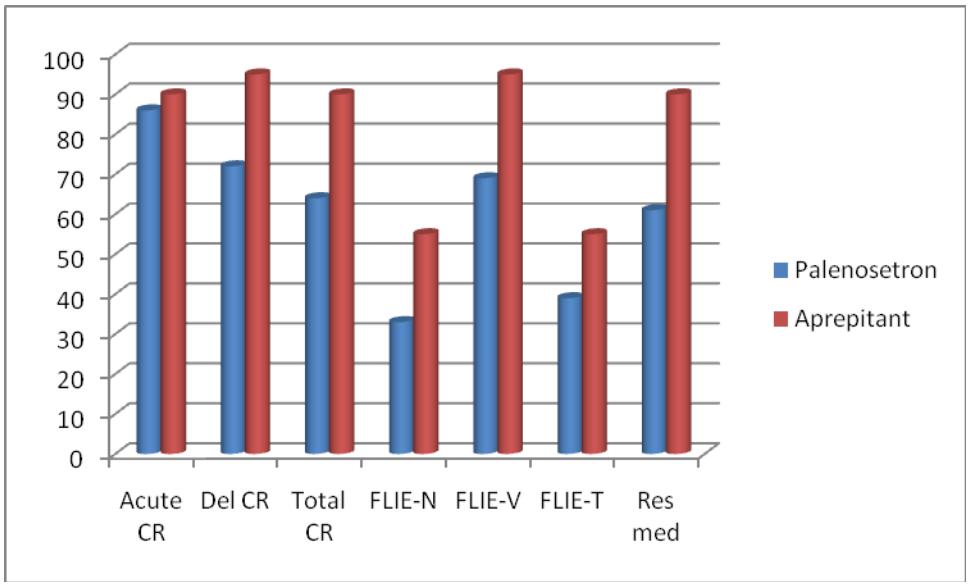
the poor nutrition and social status of majority of our patients.FLIE total scores of >108 was obtained by 52% of patients in aprepitant arm compared to 40% and 16% in palonosetron and ondansetron arms respectively which again was inferior to values of 63.5% and 55.6% in aprepitant and ondansetron arms of Warr et al study.

In patients receiving aprepitant 86% of patients did not take rescue medications as compared as compared to 64% in the palonosetron arm and 14% in the ondansetron arm .Winnie Yeo et al[114] in their study also showed that patients taking aprepitant had lesser incidence of intake of rescue medications.

Hence the primary and secondary outcomes denote that Aprepitant and Palonosetron are significantly better than ondansetron in the control of CINV in patients receiving MEC .The impact on quality of life in nausea domain is not affected by any of the three drugs but in the vomiting domain again palonosetron and aprepitant fare better than ondansetron.

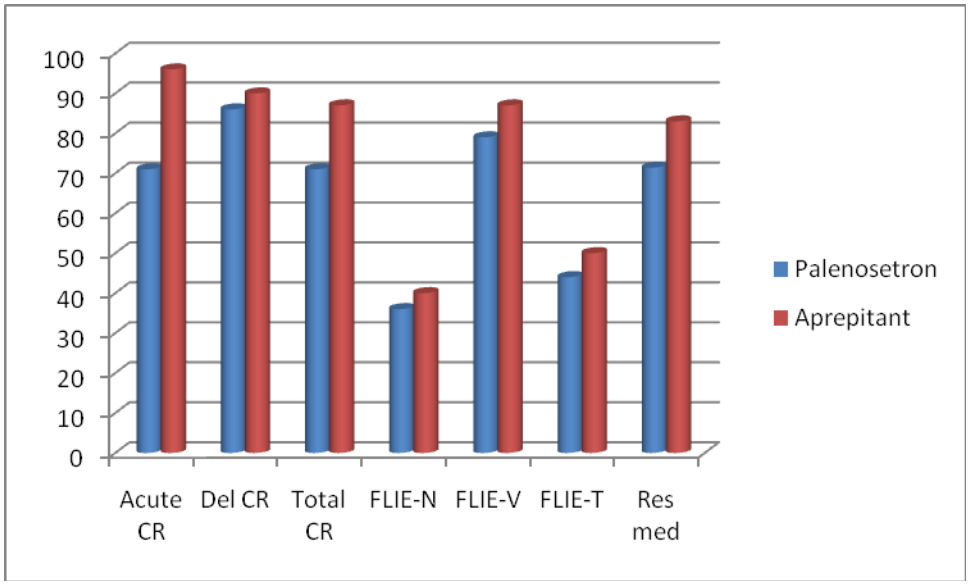
There are no studies which have compared palonosetron head to head with aprepitant in patients receiving either HEC or MEC .Our study is notable and in fact is more relevant in a limited resource country like ours as majority of the patients will not be able to afford most of the medicines. So whether palonosetron is inferior to aprepitant or equal in efficacy to aprepitant will be an interesting question to answer. In our study even though on preliminary analysis aprepitant was superior to palonosetron but on subset analysis with the study population stratified into > 50 years and < 50 years , palonosetron fared almost non inferior to aprepitant in the more than 50 years age group.

Fig 19 – In patients < 50 years, comparison of aprepitant with palonosetron



Aprepitant was superior to palonosetron in most of the parameters in patients aged < 50 years. Interestingly aprepitant was found to be almost similar in efficacy to palonosetron in patients aged > 50 years.

Fig 20- In >50 years comparison of palonosetron and aprepitant



One possible explanation is younger females are at increased risk of CINV as compared to the older population , Hence whether palonosetron became non inferior to aprepitant in the elderly population because their overall risk of developing CINV itself is low needs to be proved further. As the number of patients in our study group was small further studies with large numbers are required to prove or disprove the above mentioned observation.

In comparison to ondansetron, both palonosetron and aprepitant have statistically significant Antiemetic action in patients receiving MEC with better control of CINV in both acute and delayed phases and with significant impact on the improvement of quality of life in vomiting domain in FLIE as compared to nausea domain. Aprepitant based antiemetic regimen is better than palonosetron regimen in patients receiving MEC with age less than 50 years but interestingly palonosetron is non inferior to aprepitant based regimen in patients aged more than 50 years.

CONCLUSIONS

1. Ondansetron based anti-emetic prophylaxis even in patients receiving moderately emetogenic chemotherapy is sub optimal
2. Palonosetron is superior to ondansetron in the prevention of CINV in patients receiving moderately emetogenic chemotherapy
3. Aprepitant is superior to both ondansetron and palonosetron in the prevention of CINV in patients receiving moderately emetogenic chemotherapy
4. In patients less than 50 years the superiority of aprepitant over palonosetron is more evident
5. In patients more than 50 years palonosetron is non inferior to aprepitant.
6. Nausea continues to be a persistent problem in spite of adequate control of emesis, as shown in the FLIE indices for nausea domain
7. Administration of aprepitant or palonosetron leads to decrease in the use of rescue medications
8. In places with limited resources palonosetron is an useful option as a substitute for aprepitant especially in patients aged > 50 years

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