Role of aprepitant in chemotherapy induced nausea and vomiting

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Abstract

Background: Nausea and vomiting is the most common adverse effect of most of the chemotherapeutic agents. Large range of antiemetics has been used since ages. Aprepitant is an NK-1 receptor antagonist which blocks the emetic effects of substance P. The present study is to determine the effectiveness of aprepitant in preventing nausea and vomiting in patients receiving chemotherapy when combined with standard regimen.

Methods: In this is an institutional based single arm randomized study patients received aprepitant 125 mg per oral, dexamethasone 8mg intravenous, palonosetron 0.25 mg intravenous 30 min before chemotherapy on scheduled D1 followed by aprepitant 80 mg on Day2 and Day3.The primary end point was the proportion of patients with no emetic episodes and no rescue medication [complete response (CR)] during the 24 h after chemotherapy administration (acute period).

Results: Out of 83 patients observed males were 49 and females were 34 and with performance status 0, total of 47.56 (68%) achieved complete response in overall period. This includes 62 patients (74%) in acute period and 49 patients (59%) in delayed period.

Conclusion: Aprepitant along with palonosetron and dexamethasone effectively and significantly prevents chemotherapy induced nausea and vomiting.

Keywords: Aprepitant, nausea and vomiting, palonosetron.

Introduction

Chemotherapy induced nausea and vomiting (CINV) is the most common and predictable adverse effect of the cytotoxic drugs. Antiemetic agents are the most common intervention in the management of treatment-related nausea and vomiting (N&V). The basis for antiemetic therapy is the neurochemical control of vomiting. Although the exact mechanism is not well understood, peripheral neuroreceptors and the chemoreceptor trigger zone (CTZ) are known to contain receptors for serotonin, histamine (H1 and H2), dopamine, acetylcholine, opioids, and numerous other endogenous neurotransmitters[1,2]. Many antiemetics act by competitively blocking receptors for these substances, thereby inhibiting stimulation of peripheral nerves at the CTZ and possibly at the vomiting centre. The most significant predicting factor of CINV is cytotoxic drug itself. They exhibit different emetic potential and cause emesis by different mechanisms[3].

The most common mechanism of nausea and vomiting is acute emesis which starts within few hours of beginning of chemotherapy lasting up to 24 hours. Delayed emesis commences from day one lasting at least for five days[4]. Patients with poor control of post chemotherapy emesis have significant morbidity and dramatic impact on quality of life[5]. Increased risk of CINV is associated with factors like age less than 50, female gender, vomiting during previous chemotherapy, anxiety. CINV causes electrolyte imbalance, weakness, weight loss, anorexia, dehydration and decline in behavioral and mental status. The introduction of serotonin antagonists and their widespread adoption in the early to mid1990's led to significant improvement in the ability to control chemotherapy induced nausea and vomiting and it's potential negative impact on patient's quality of life (QOL). Palonosetron is a 5-HT3 receptor antagonist (second generation) that has antiemetic activity at both central and GI sites. In comparison to the older 5-HT3 receptor antagonists, it has a higher binding affinity to the 5-HT3 receptors, a higher potency, a significantly longer half-life (approximately 40 hours, four to five times longer than that of dolasetron, granisetron, or ondansetron), and an excellent safety profile[8].

Aprepitant is an NK-1 receptor antagonist which blocks theemetic effects of substance P. When combined with standard regimen of dexamethasone and 5HT[3] antagonist, aprepitant is effective in preventing CINV in patients receiving highly emetogenic chemotherapy[9].

Materials and Methods

This was an Institutional based randomized study. This study included 100 patients who were scheduled to receive emetogenic chemotherapy at Regional cancer centre, Indira Gandhi Institute of Medical Sciences, Patna during the year 2014.

Inclusion criteria:

1. Age≥ 18 years and ≤69 years.
2. Histologically confirmed malignant diseases.

3. Eastern Cooperative Oncology Group performance status of 0 to 2.
4. Patients who were naive to chemotherapy
5. Adequate renal hematological hepatic parameters.
6. Females with negative urine beta HCG test.
7. Patients who were not on any other drugs inducing emesis.

Exclusion criteria:

1. Age≤ 18 and ≥ 70 years.
2. Evidence of CNS disease or psychiatric illness causing vomiting
3. Altered renal, hematological, hepatic parameters.
4. Patient with primary or secondary CNS malignancies
5. Patients with other cause of vomiting (like bowel obstruction) not related to chemotherapy
6. Patients with nausea and vomiting before the chemotherapy
7. Patients with contraindication to use corticosteroids (any active infection)
8. Patients with prior chemotherapy.

Treatment

Patients who were enrolled in this study received aprepitant 125 mg per oral, dexamethasone 8mg intravenous, palonosetron 0.25 mg intravenous 30 min before chemotherapy on scheduled D1 followed by aprepitant 80 mg on Day2 and Day3. Study dairy have been maintained to enroll the patients before the start of study and followed up to 5 days post chemotherapy. The frequencies of nausea, vomiting and rescue medication are all recorded daily. Patients were reviewed twice daily during the 5day study period to record the events.

Endpoint

Complete response (no emesis and no rescue therapy) during the five days of study period in patients receiving first cycle chemotherapy.

Response and analysis

Common Terminology Criteria for Adverse Events (CTCAE) Version4.0 was used to analyze the response to study drugs.

Results

Demographics: A total 100 patients were screened according to protocol for enrollment in to the study. Out of them 17 were concluded ineligible based on preformed criteria. The rest 83 patients were enrolled into study and given protocol antiemetic therapy. Among them 49 were males and 34 were females with median age group of 49years. Out of 83 patients 56 (68%) achieved complete response in overall period. This includes 62 patients (74%) in acute period and 49 patients (59%) in delayed period.

Additional endpoints were also evaluated. No emesis was seen in 65(78%) for overall period, including 69(84%) in acute period and 51(62%) in delayed period.

Table 1:

Gender	
Male	49
Female	34
Performance status	
0	47
1	25
2	11
Tumor type	
Breast	15
Cervix	20
Lung	18
Head & neck	21
Ovary	9
Chemotherapy drug/regimen	
Cisplatin	23
Cyclophosphamide	15
Epirubicin	15
5-flourouracil	19
Docetaxel	13
Previous chemotherapy	
Yes	9
No	83

Ecog Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Common Terminology Criteria for Adverse Events (CTCAE) Version4.0

Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death

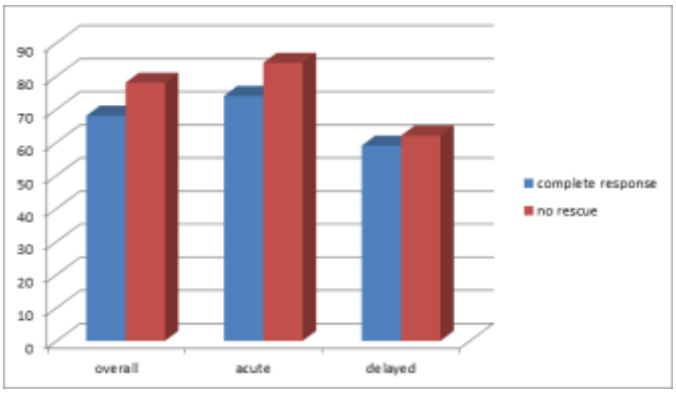


Fig. 1

Emesis free and no rescue patients (n=83)

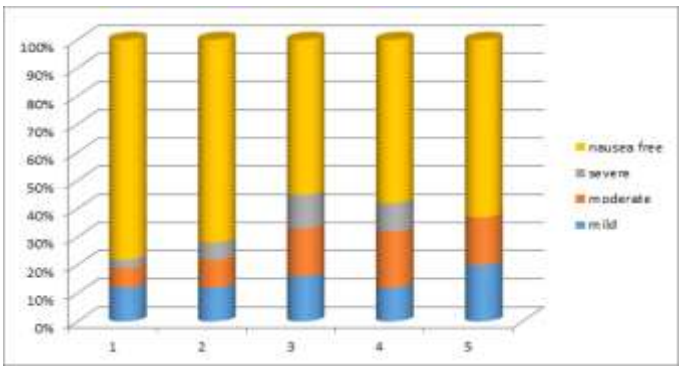


Fig. 2

Nausea severity (n=83)

Discussion

Emesis after chemotherapy is one of the most challenging task in supportive oncology to be taken care of. Anticipation is the key point in mitigating the maximum post chemotherapy nausea and emesis effects. Selection of the drugs to prevent CINV has been a challenge since ages because there are many pre-requisites to be met. Even though there are wide range of drugs significant incidence has been noted in patients. In this study, among the 5HT3 antagonists palonosetron has been chosen over ondansetron due to its efficacy in protecting patients from emesis and decreasing interference with functioning[10]. The chemotherapy induced nausea and emesis is the most underestimated event by many health professionals especially delayed vomiting[12,13]. The incidence of this problem continues exist even with the most effective drug hence combination therapy has been studied along with aprepitant and dexamethasone[11]. Incidence of this problem is more in delayed phase than early phase where there is a need of new strategy always. The complete response rates for antiemetics are always behind that of early phase which has to be improved[14].

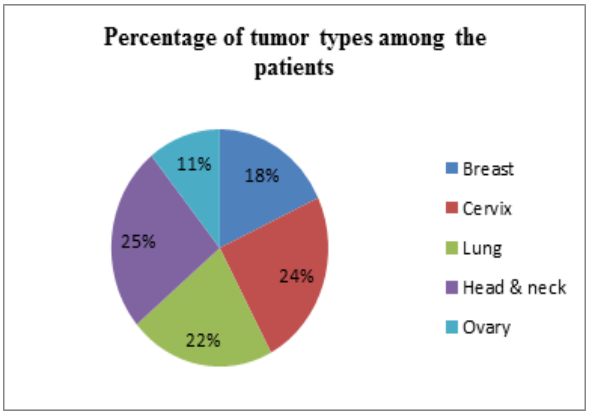
The metabolism of the 5HT3 antagonists is not interfered by NK1 antagonists significantly[15,16]. Adherenceof physician and compliance of patients are two key issues in supportive oncology. The treating physicians are with curative intent follow the therapeutic guidelines than the supportive guidelines which aborts the toxicities of chemotherapeutic drugs[17]. Compliance of patients depends on many factors like socioeconomic status, patient physician relationship[18].

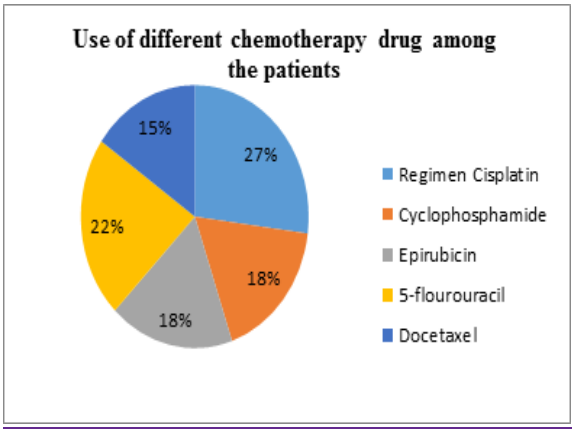
Usually ondansetron is given in three doses 2hours apart but because of its safety profile even single dose prevent emesis during acute period[19]. With the development of higher efficacy drug like palonosetron whose half-life is 40 hrs gave a drug effect of multiple days even with single dose[20,21]. The emesis during delayed period is covered by a drug like palonosetron which has extended life or giving drug just before the anticipated time of emesis. There are many studies showing that 5 day course of treatment is no more effective than the short course therapy. In this present study aprepitant was selected due to its higher efficacy and safety profile even with single dose.

Triplet therapy with palonosetron/ aprepitant/ dexamethasone has been studied by many groups. Grote[22] studied combination of 3 day aprepitant, 4day dexamethasone and single dose palonosetron which showed 88% during the acute (0–24 hours) interval,78% during the delayed (> 24–120 hours) interval, and 78% during the overall (0–120 hours post chemotherapy) interval. Herrington[23] compared 1 and 3 day course of aprepitant, 4 day dexamethasone and palonosetron single dose shows better results with aprepitant. Steven M et al studied the three drug regimen which showed the similar results like that of the present study[24]. The response rates in this present study reveals that combination therapy using aprepitant gives higher prevention rates of emesis in patients taking chemotherapy. A randomized, open-label, crossover, pharmacokinetic/safety study of a single IV dose of palonosetron (0.25 mg) with or without aprepitant in healthy subjects demonstrated that palonosetron can be safely coadministered with aprepitant, with no dosage adjustment necessary[25]. In this study aprepitant has no significant interaction of pharmacokinetics with serotonin inhibitors.

Conclusion

1. The triplet therapy is safe and highly effective in preventing chemotherapy induced nausea and vomiting.
2. The only disadvantage is the cost of regimen.





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