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Comparing Different Antiemetic Regimens for Chemotherapy Induced Nausea and Vomiting

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Abstract

Background: Chemotherapy Induced Nausea and Vomiting (CINV) is a major problem for all cancer patients. 5-hydroxytryptamine 3 (5-HT3)-receptor antagonists or serotonin antagonists used along with dexamethasone is the most widely used antiemetic regimen in chemotherapy. But the best drug of the different serotonin antagonists, which is both efficacious and economic, remains a matter of debate.

Aims & Objectives: To compare the relative efficacies and safeties of ondansetron, granisetron and palonosetron, when used along with equal dose of dexamethasone, in moderately to highly emetogenic chemotherapy by a double blind, randomized controlled trial in order to obtain the most potent and cost effective drug.

Methods: 1213 adult patients, 487 on highly and 726 on moderately emetogenic chemotherapy, admitted in various departments of a teaching hospital in India from November 05, 2007 to September 30, 2009 were included in the study. Patients were randomly assigned to receive ondansetron 8 mg or granisetron 3mg or palonosetron 0.75 mg (single dose), 30 min before receiving chemotherapy, along with 16 mg of intravenous dexamethasone on Day 1 and 4mg on Day 2 and 3. The observation period started with the initiation of chemotherapy (0 h) and continued for 24 h after completion of the chemotherapy for acute emesis and up to Day 5 for delayed nausea and vomiting.

Results: For highly emetogenic regimens, 52 of 64 patients (81.2%) had complete response during the acute phase in palonosetron group compared with 181 of 237 patients (76.4%) in the ondansetron group and 130 of 186 patients (69.9%) in granisetron group. During the delayed phase, 41 patients (64%) had complete response in the palonosetron group compared with 133 patients (56.1%) in the ondansetron group and 114 patients (61.2%) in granisetron group**.** For moderately emetogenic regimens, 86 of 93 patients (92.5%) had complete response during the acute phase in palonosetron group compared with 291 of 379 patients (76.8%) in the ondansetron group and 210 of 254 patients (82.6%) in granisetron group. During the delayed phase, 63 patients (67.7%) had complete response in the palonosetron group compared with 216 patients (57%) in the ondansetron group and 162 patients (63.8%) in granisetron group**.** Main treatment related side effects were constipation and elevation of liver enzymes which was comparable for all the 3 drugs.

Conclusion: When administered with dexamethasone before chemotherapy, although palonosetron is found to be more efficacious, cost wise ondansetron may be preferred in highly emetogenic regimens, although palonosetron requires only a single dosing. However in moderately emetogenic regimens, granisetron outshines ondansetron and is further outshined by palonosetron in both acute and delayed emesis and thus the decision should be taken as per patient profile.

Study Limitations: The study has fewer numbers of patients taking palonosetron due to financial limitations of the patients, which is present in any developing country. Although we have compared the cost and availability of the 3 drugs, a detailed cost analysis could not be done due to paucity of resources.

Keywords: Chemotherapy induced nausea and vomiting, 5-HT3 receptor antagonist, dexamethasone, ondansetron, granisetron, palonosetron

Introduction

Cancer is increasing at an alarming rate globally. Chemotherapy is the primary treatment for cancer and in some cases the only resort. Most of the chemotherapeutic drugs have been found to cause release of large amounts of serotonin from enterochromaffin cells in the gut [1], serotonin acts on 5-HT_3 receptors in the gut and brain stem and stimulate vagal affarents to initiate the vomiting reflex. Chemotherapy induced nausea and vomiting (CINV) remains a significant problem for cancer patients, having a long lasting effect on their quality of life.

There is evidence that emesis control during chemotherapy acts on the quality and cost of treatment by allowing a better compliance to scheduled drug dose. It improves the quality of life of patients by reducing the intensity and number of side effects and thereby reducing the length of hospitalization and treatment related expenditure [2].

5-HT_3 receptor antagonists or serotonin antagonists suppress nausea and vomiting by inhibiting serotonin binding to the 5-HT_3 receptors. Serotonin antagonists are found to be very effective in controlling CINV and are used along with dexamethasone as a potent antiemetic regimen in chemotherapy [3-6].

Nowadays the stores in India are flooded with many options of serotonin antagonists coming at different prices. So comparison of their relative efficacies and safeties in Indian patients against their prices is needed before prescribing them indiscriminately. Hence we have performed a double blind, randomized controlled trial to compare the relative efficacies of ondansetron, granisetron and palonosetron for both acute and delayed onset emesis, in moderately and highly emetogenic chemotherapy against their respective prices in Indian market.

Patients and methods

Eligible patients for this double blind, randomized controlled trial were men and women

aged 15 years or above with confirmed malignant disease and admitted to any department of Bankura Sammilani Medical College and Hospital, India from November 05, 2007 to September 30, 2009 for the purpose of receiving either one day of moderately or highly emetogenic chemotherapy or moderately or highly emetogenic chemotherapy for Day 1 and lower emetogenic drugs on the subsequent days. Emetogenic levels of common chemotherapy and biotherapy agents are given in Figure 1 [7-9].

Exclusion criteria included: severe, uncontrolled, concurrent illness other than neoplasia; asymptomatic metastases to the brain; seizure disorder needing anticonvulsants unless clinically stable; intestinal obstruction; concurrent intake of any other emetogenic drug or radiotherapy or a known hypersensitivity to 5-HT_3-receptor antagonists or dexamethasone.

1213 patients were found to be eligible for the study, among them 487 were on highly emetogenic and 726 were on moderately emetogenic chemotherapy. The study was approved by the ethical board of institute and all patients provided written informed consent before enrolment. Patients were randomly assigned to receive ondansetron or granisetron or palonosetron. All study personnel and patients were blinded to the treatment assignment for the duration of the study and the nursing staffs injecting the drugs were prohibited from divulging any information on drug assignment even to the doctors giving the chemotherapeutic drugs.

Ondansetron 8 mg or granisetron 3 mg were given on Day 1 and Day 2 or palonosetron 0.75 mg was given on Day 1, intravenously, 30 min before chemotherapy, along with 16 mg of intravenous dexamethasone on Day 1 and 4 mg on Day 2 and Day 3. Patients were followed for 5 days for the efficacy endpoints and 8 days for the safety endpoints.

The primary efficacy endpoints of this study were the proportion of patients with a complete response during the acute phase (0–24 hours post chemotherapy). Secondary efficacy endpoints included complete response during successive 24 h time periods (i.e., 24–48 h, 48–72 h, 72–96 h, and 96–120 h) and for the overall chronic phase (24-120 hours post chemotherapy).

Complete response was defined as no emetic episodes, no rescue medication use, and no more than mild nausea. People having 0–1 vomits and/or moderate nausea for a maximum of 4 hours were termed as partial response. Failure delineated ≥ 2 vomits, or severe nausea or nausea lasting more than 4 hours.

Statistical Analysis

All data were analyzed using SAS software, version 9.1. Chi-square test or Fisher's exact test was used to compare the proportions. A both sided p value of ≤ 0.05 was considered statistically significant.

Results

In the group receiving highly emetogenic chemotherapy, 287 (58.9%) were females and 200 (41.1%) were males and in the group receiving moderately emetogenic chemotherapy, 370 (50.9%) were females and 356 (49.1%) were males. Overall, previous history of chemotherapy was present in 916 patients (75.5%), while 297 (24.5%) were chemotherapy-naive. Highly emetogenic regimens chiefly had cisplatin (96.3%), and as a part of antiemetic therapy 237 patients were prescribed ondansetron, 186 granisetron and 64 palonosetron. While the moderately emetogenic regimens consisted of lower dose (<1500 mg/m²) cyclophosphamide (85.8%) and doxorubicin (12.8%) and for combating the emesis 379 patients were put on ondansetron, 254 on granisetron and 93 on palonosetron**.** Baseline and demographic characteristics of the patients are given in Table 1.

The doses of the serotonin antagonists were administered as per previous research data regarding their optimal dose related efficacy. Ondansetron 8 mg is found to be equally efficacious to ondansetron 32 mg for both highly and moderately emetogenic chemotherapy [10-11]. Although United States Food and Drug Administration deemed that the 10 µg/kg dose for granisetron was fully effective, results suggest that there is some benefit to the higher 40 µg/kg (3mg) dose in certain patient groups [12], hence the higher dose was used. A clear dose–response relation was noted over a 120 h study period when 0.075 mg, 0.25 mg, and 0.75 mg doses of palonosetron were given with dexamethasone to prevent CINV associated with highly emetogenic chemotherapy, indicating a significant difference in response with the 0.075 mg dose compared with the two higher doses [13]. Also another study with moderately emetogenic regimen revealed dose-dependent increases in complete response with more than a 10% difference in the highest complete response recorded in the 0.75 mg dose group compared with the 0.25 mg, in both delayed and overall phases [14]. Three doses of palonosetron were well-tolerated and did not show any increase in adverse effects related to dose. The better efficacy with the 0.75 mg dose than with the lower doses and the similar safety profile suggested that palonosetron 0.75 mg be the recommended dose for use in this trial.

Overall, irrespective of the emetogenicity of the regimens, palonosetron is found to be the best acting drug followed by granisetron, although the difference in the efficacies of the drugs was not huge. 472 patients (76.6%) in ondansetron group, 340 (77.27%) in granisetron group and 138 (87.8%) in palonosetron group showed complete response in the acute phase (0-24 hours) (p value = 0.021); compared to 350 patients (56.8%) in ondansetron group, 279 (63.4%) in granisetron group and 106 (67.5%) in palonosetron group in chronic phase (24-120 hours) (p value= 0.013). Complete

responses obtained for each drug on daily basis is illustrated in Figure 2. All the responses obtained for each drug from Day 1 to 5 have been given in Table 2.

For highly emetogenic regimens it was postulated that palonosetron is superior to ondansetron, which was found to be false, as p values were > 0.05. 52 patients (81.2%) had complete response during the acute phase (0-24 hours) in palonosetron group compared with 181 patients (76.4%) in the ondansetron group and 130 patients (69.9%) in granisetron group (p value = 0.246). During the overall chronic phase (24-120 hours), 41 patients (64%) had complete response in the palonosetron group compared with 133 patients (56.1%) in the ondansetron group and 114 patients (61.2%) in granisetron group (p value = 0.461). Complete responses obtained for each drug on a 24 hourly basis is illustrated in Figure 3. Responses of each drug in the highly emetogenic regimen, from Day 1 to 5 have been given in Table 3.

For moderately emetogenic regimens it was postulated that palonosetron is superior to granisetron which was superior to ondansetron, which was found to be true, as p values were ≤ 0.05. 86 patients (92.5%) had complete response during the acute phase (0-24 hours) in palonosetron group compared with 291 patients (76.8%) in the ondansetron group and 210 patients (82.6%) in granisetron group (p value = 0.01). During the delayed phase (24-120 hours), 63 patients (67.7%) had complete response in the palonosetron group compared with 216 patients (57%) in the ondansetron group and 162 patients (63.8%) in granisetron group (p value = 0.05)**.** Complete responses obtained for each drug on a 24 hourly basis is illustrated in Figure 4. Responses of each drug in the moderately emetogenic regimen, from Day 1 to 5 have been given in Table 4.

There were no clinically relevant differences between groups with regard to overall incidence of side effects (p value = 0.99998). As was expected, headache and constipation were the most common side effects (6) occurring in 11 (1.8%) and 26 (4.2%) patients respectively among ondansetron users; while it was 8 (1.8%) and 19 (4.3%) for granisetron users and 3 (1.9%) and 8 (5.1%) for palonosetron users. Hypokalemia occurred in 9 (1.5%) ondansetron users, 7 (1.6%) granisetron users and 2 (1.3%) palonosetron users. Elevation of liver enzymes alanine transaminase (ALT) and aspartate transaminase (AST) was also noted, although none of the patients reported increase in serum bilirubin. Table 5 has details of the treatment related side effects.

Discussion

Nausea and vomiting are still the major distressing health issues in patients undergoing chemotherapy. Although 5-HT_3-receptor antagonists along with a corticosteroid are proved to be the key treatment regimen against CINV (3-6), the standard serotonin antagonist to be used in various chemotherapy regimens is yet to be known.

There are some differences in metabolism and receptor specificities among the

different serotonin antagonists [15]. Palonosetron is a highly potent, selective, second-generation 5-HT_3 receptor antagonist with a receptor binding affinity higher than other 5-HT_3 receptor antagonists (pKi 10.5 compared with 8.91 for granisetron, 8.39 for ondansetron) [16-17]. Palonosetron shows a 40 h half life [18-19] which is significantly longer than others in its class [ondansetron, 4 h [20]; tropisetron, 7.3 h [21]; dolasetron, 7.5 h [22]; granisetron, 8.9 h [23]]. It shows both competitive binding and allosteric interactions with the 5-HT_3-receptor and requires only a single dosing contrary to ondansetron and granisetron, which show strictly competitive antagonism. As the allosteric interactions can induce changes in the receptor conformation; it is speculated that palonosetron's dual action induces amplification of its inhibitory effect at the primary receptor binding site [24].

In our study when considered irrespective of the emetogenicity of the regimens, palonosetron is found to be the best acting drug followed by granisetron more so from Day 2 onwards, i.e. the period after the initial 24 hours. But in highly emetogenic regimens no momentous difference was found between the efficacies of the drugs, contrary to previous studies [25, 26]. In moderately emetogenic regimens the superiority of palonosetron was clearly established in the acute phase (0-24 h) [27], although apparent, much difference was not found in the subsequent hours (24-120 h).

All the patients were observed till Day 8 for the occurrence of any side effects. Side effect profiles of the drugs were found to be similar [26] (p value = 0.99998), with no life threatening adverse effects occurring (see Figure 5). 39 (6.3%) patients in ondansetron group, 28 (6.4%) in granisetron group and 17 (10.8%) in palonosetron group were found to be having at least one antiemetic drug related side effect (p value= 0.118). The incidence of prolongation of the heart-rate-corrected QT interval (QTc) was found in 5 (0.8%) patients on ondansetron, although caused no further complications. 3 patients on ondansetron and 2 patients on granisetron died within Day 5-8 of chemotherapy initiation, although the cause of the deaths were found to be due to the malignant processes itself and unrelated to the antiemetic treatment.

There are several brand names for a given 5HT_3 receptor antagonists in India. The cost of drug expenditure was based on the mean price of all parenteral combinations available in Indian market as in December 2009. In our study, ondansetron and granisetron were given on Day 1 and 2, whereas palonosetron was given only on Day 1. Calculations of expenses for each drug/cycle are given in Table 6. Palonosetron was found to be the most expensive drug, followed by granisetron, also supply of palonosetron in the medicine shops is inadequate in lieu of its cost. The cost of dexamethasone was not included in analysis, since it is the same for the 3 arms of treatment. Information available was not sufficient for a detailed cost analysis and hence there should be further research regarding the detailed cost analysis of the drugs.

Conclusion

Our study is the first one to compare the efficiency and cost of 5-HT_3 receptor

antagonists in Indian patients. It suggests that ondansetron, granisetron and palonosetron have similar efficacy and side-effect profiles in prophylaxis of CINV secondary to moderately or highly emetogenic chemotherapy. Preference among them must be based on other parameters such as cost, ease of administration, patient preferences, co morbid illnesses and drug interactions.

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Tables

Table 1: Demographic characteristics of patients

Characteristics	Ondasetron		Granisetron		Palonosetron	
	n	%	n	%	n	%
Patient number	616	50.8	440	36.3	157	12.9
Age (median, year)	48		49		47	
Sex distribution						
Male	275	44.6	210	47.7	71	45.2
Female	341	55.4	230	52.3	86	54.8
Prior chemotherapy	459	74.5	337	76.6	120	76.4

Table 2: Overall responses of each drug from Day 1 to 5

DAY	THERAPY RESPONSE	ONDANSETRON	GRANISETRON	PALONOSETRON	P value
Day 1	Complete Response	472 (76.63%)	340 (77.27%)	138 (87.89%)	0.02
	Partial Response	104 (16.88%)	65 (14.77%)	14 (8.92%)	
	Failure	40 (6.49%)	35 (7.96%)	5 (3.19%)	
Day 2	Complete Response	355 (57.63%)	284 (64.55%)	108 (68.78%)	0.04
	Partial Response	209 (33.92%)	121 (27.49%)	38 (24.21%)	
	Failure	52 (8.45%)	35 (7.96%)	11 (7.01%)	
Day 3	Complete Response	355 (57.63%)	269 (61.13%)	107 (68.15%)	0.0002
	Partial Response	218 (35.39%)	116 (26.36%)	35 (22.29%)	
	Failure	43 (6.98%)	55 (12.51%)	15 (9.56%)	
Day 4	Complete Response	344(55.85%)	282 (64.01%)	103 (65.60%)	0.013
	Partial Response	218 (35.39%)	115 (26.27%)	42 (26.76%)	
	Failure	54 (8.76%)	43 (9.72%)	12 (7.64%)	
Day 5	Complete Response	347 (56.33%)	281 (63.87%)	106 (67.52%)	0.006
	Partial Response	217 (35.23%)	116 (26.36%)	43 (27.39%)	
	Failure	52 (8.44%)	43 (9.77%)	8 (5.09%)	

Table 3: Overall responses of each drug for highly emetogenic chemotherapy from Day 1 to 5

DAY	THERAPY RESPONSE	ONDANSETRON	GRANISETRON	PALONOSETRON	P value
Day 1	Complete Response	181 (76.35%)	130 (69.89%)	52 (81.26%)	0.24
	Partial Response	40 (16.89%)	35 (18.82%)	9(14.06%)	
	Failure	16 (6.76%)	21 (11.29%)	3 (4.68%)	
Day 2	Complete Response	138 (58.23%)	118 (63.45%)	44 (68.76%)	0.42
	Partial Response	75 (31.65%)	55 (29.57%)	17 (26.56%)	
	Failure	24 (10.12%)	13 (6.98%)	3 (4.68%)	
Day 3	Complete Response	135 (56.97%)	109 (58.61%)	43 (67.19%)	0.0014
	Partial Response	88 (37.13%)	47 (25.27%)	15 (23.44%)	
	Failure	14 (5.90%)	30 (16.12%)	6 (9.37%)	
Day 4	Complete Response	130 (54.86%)	120 (64.52%)	38 (59.38%)	0.15
	Partial Response	85 (35.86%)	45 (24.19%)	20 (31.25%)	
	Failure	22 (9.28%)	21 (11.29%)	6 (9.37%)	
Day 5	Complete Response	132 (55.69%)	117 (62.90%)	39 (60.93%)	0.63
	Partial Response	79 (33.34%)	53 (28.49%)	18 (28.13%)	
	Failure	26 (10.97%)	16 (8.61%)	7 (10.94%)	

Table 4: Overall responses of each drug for moderately emetogenic chemotherapy from Day 1 to 5

DAY	THERAPY RESPONSE	ONDANSETRON	GRANISETRON	PALONOSETRON	P value
Day 1	Complete Response	291 (76.78%)	210 (82.67%)	86 (92.47%)	0.01
	Partial Response	64 (16.88%)	30 (11.81%)	5(5.37%)	
	Failure	24 (6.34%)	14 (5.52%)	2 (2.16%)	
Day 2	Complete Response	217 (57.25%)	166 (65.35%)	64 (68.81%)	0.05
	Partial Response	134 (35.36%)	66 (25.98%)	21 (22.58%)	
	Failure	28 (7.39%)	22 (8.67%)	8 (8.61%)	
Day 3	Complete Response	220 (58.04%)	160 (63.00%)	64 (68.81%)	0.09
	Partial	130 (34.30%)	69 (27.16%)	20 (21.51%)	

	Response				
	Failure	29 (7.66%)	25 (9.84%)	9 (9.68%)	
Day 4	Complete Response	214 (56.46%)	162 (63.77%)	65 (69.89%)	0.09
	Partial Response	133 (35.09%)	70 (27.56%)	22 (23.65%)	
	Failure	32 (8.45%)	22 (8.67%)	6 (6.46%)	
Day 5	Complete Response	215 (56.72%)	164 (64.56%)	67 (72.04%)	0.0006
	Partial Response	138 (36.41%)	63 (24.81%)	25 (26.88%)	
	Failure	26 (6.87%)	27 (10.63%)	1 (1.08%)	

Table 5: Details of the treatment related side effects

DRUG	**Headache**	**Constipation**	**Hypokalemia**	**Elevation of ALT**	**Elevation of AST**
ONDANSETRON	11 (1.8%)	26 (4.2%)	9 (1.5%)	10 (1.6%)	8 (1.3%)
GRANISETRON	8 (1.8%)	19 (4.3%)	7 (1.6%)	8 (1.8%)	5 (1.1%)
PALONOSETRON	3 (1.9%)	8 (5.1%)	2 (1.3%)	3 (1.9%)	2 (1.3%)

Table 6: Calculations of expenses for each 5HT3 receptor antagonists used for one cycle (costs of the drugs given are mean costs of all the brands available in Indian market)

Drug	**Required Dose**	**Cost** (**INR=** Indian Rupee**)**	**Number of doses required/cycle**	**Total Cost** (**INR=** Indian Rupee**)**
ONDANSETRON	8 mg	32 INR	2	64 INR
GRANISETRON	3 mg	57 INR	2	114 INR
PALONOSETRON	0.75 mg	430 INR	1	430 INR

Figures

Figure 1: List of chemotherapeutic agents according to their emetogenicity [7-9]

High (> 90% frequency of emesis)	**Low (10%–30% frequency of emesis)**
Cetuximab	Carmustine > 250 mg/ m^2
Cisplatin > 50 mg/ m^2	Cytarabine 100–200 mg/ m^2
Cyclophosphamide > 1,500 mg/ m^2	Docetaxel
Dacarbazine	Etoposide
Mechlorethamine	5-fluorouracil
Procarbazine (oral)	Gemcitabine
Streptozocin	Methotrexate > 50 mg/ m^2
	Mitomycin
	Mitoxantrone
	Paclitaxel
Moderate (30%–90% frequency of emesis)	**Minimal (< 10% frequency of emesis)**
Carboplatin	Bevacizumab
Cyclophosphamide < 1,500 mg/ m^2	Bleomycin
Cyclophosphamide (oral)	Bortezomib
Cytarabine > 1 g/ m^2	Busulfan
Daunorubicin	Fludarabine
Doxorubicin	Gefitinib
Epirubicin	Hydroxyurea (oral)
Etoposide (oral)	Rituximab
Idarubicin	Trastuzumab
Ifosfamide	2-chlorodeoxyadenosine
Imatinib (oral)	Vinblastine
Irinotecan	Vincristine
Oxaliplatin > 75 mg/ m^2	Vinorelbine
Temozolomide (oral)	
Vinorelbine (oral)	

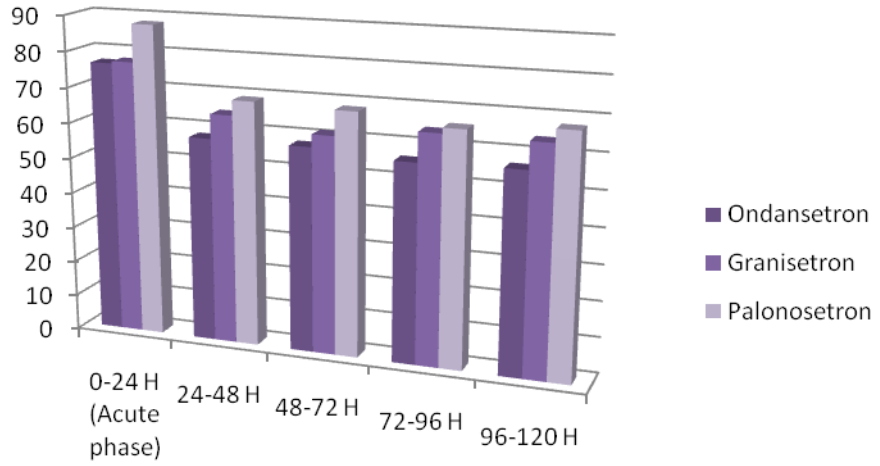

Figure 2: Time course of complete response, % by 24 hour period

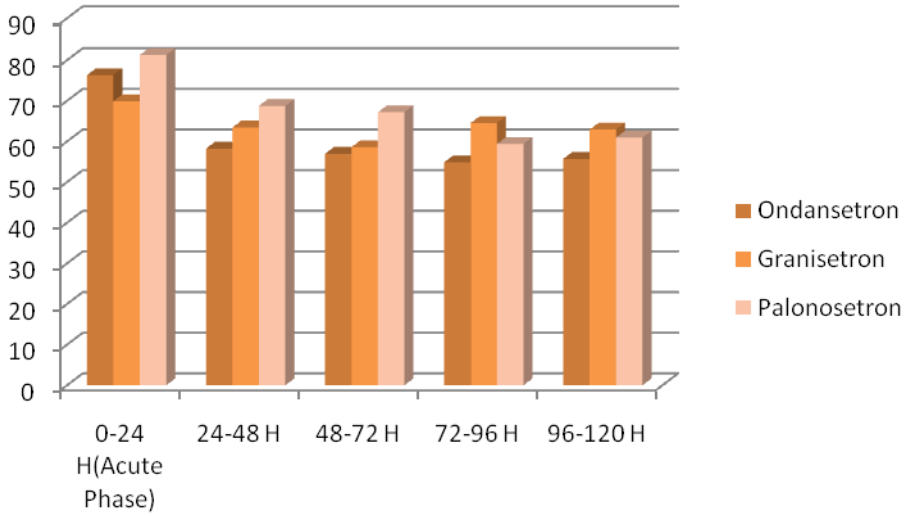

Figure 3: Time course of complete response, % by 24 hour period in highly emetogenic chemotherapy regimen

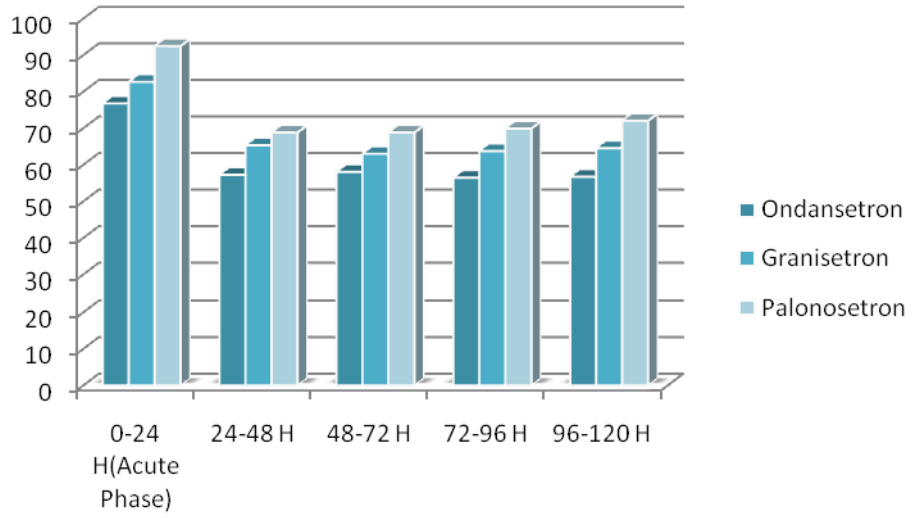

Figure 4: Time course of complete response, % by 24 hour period in moderately emetogenic chemotherapy regimen

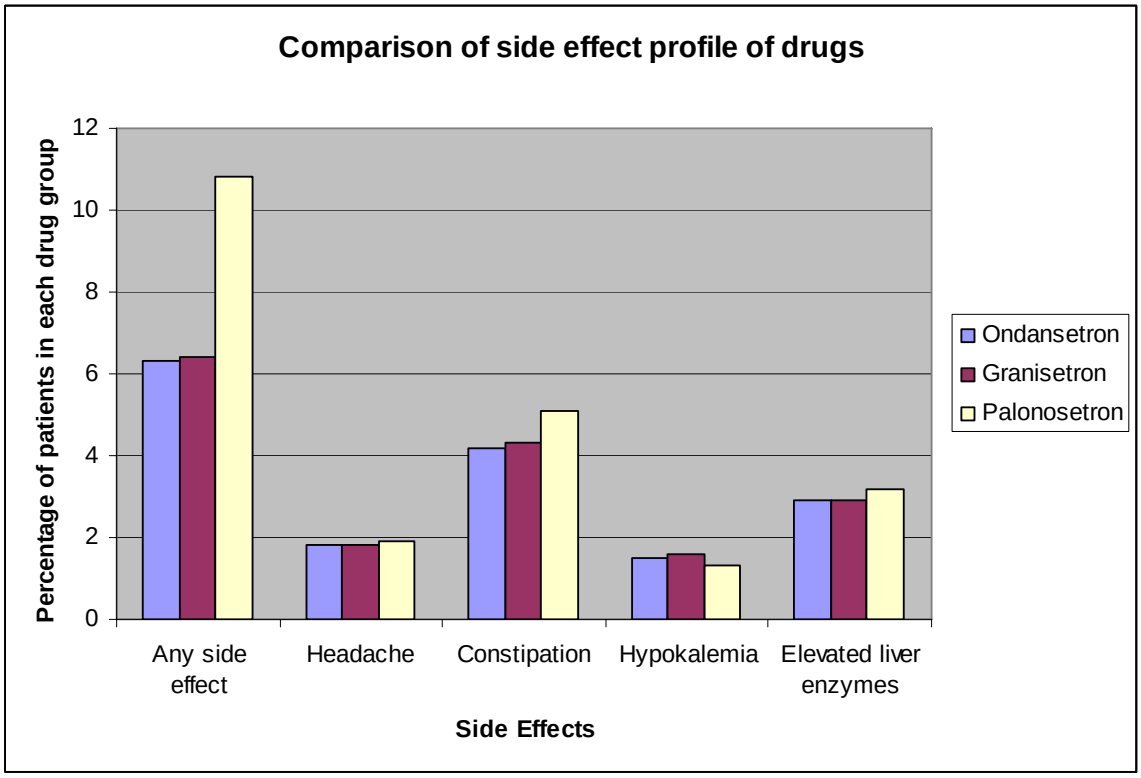

Figure 5: Comparison of the side effect profile of the drugs