Original article:

Chemotherapy induced nausea and vomiting in cancer patients

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Abstract:

Cancer is increasing at alarming rate globality. 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 he gut, serotonin acts on 5-HT3 receptors in the gut and brain stem and stimulate vagal afferents 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 and lead to unpredicted complications like aspiration pneumonia e.t.c. Anti cancer agents having highest morbidity in terms of nausea and vomiting. There is evidence that emesis control during chemotherapy acts on the quality and cost of treatment by allowing a better compliance to schedule 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] Present study is primarily to compare the efficiency, safety and cost of 5-HT3 receptor antagonists in cancer patients. Findings suggest that overall response for nausea and vomiting with Palonosetron was superior to Ondansetron and Granisetron, especially in high emetogenic chemotherapy regimens. Failure rate with Palonosetron was less when compared with Ondansetron and Granisetron for high emetogenic chemotherapy regimens. All the three drugs have almost similar side-effect profiles in prophylaxis of CINV secondary to moderately or highly emetogenic chemotherapy. The cost of Palonosetron is almost seven times that of Ondansetron and four times that of Granisetron for each chemotherapy cycle. Herapeutic option of choosing antiemetic by the treating physician has to focus on efficacy, safety and cost of the antiemetic to minimize the economic burden on the patient depending on economic status of the patient.

Introduction:

Cancer is increasing at alarming rate globality. 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 he gut, serotonin acts on 5-HT3 receptors in the gut and brain stem and stimulate vagal afferents 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 and lead to unpredicted complications like aspiration pneumonia e.t.c. Anti cancer agents having highest morbidity in terms of nausea and vomiting.There is evidence that emesis control during chemotherapy acts on the quality and cost of treatment by allowing a better compliance to schedule 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

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and treatment related expenditure.[2]5-HT3 receptor antagonists or serotonin antagonists suppress nausea and vomiting by inhibiting serotonin binding to the 5-HT3 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] 456 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 prospective study to compare the relative efficacies of ondanseiron, grannisetron and palonosetron for both acute and delayed onset emesis, in moderately and highly emetogenic chemotherapy against their respective prices in Indian market. Palonosetron is a 5-HT (3)-receptor antagonist (5-HT(3)-RA) that has been shown to be superior to other 5-HT(3)-RAs in phase III clinical trials for the prevention of acute, delayed, and overall chemotherapy-induced nausea and vomiting. The improved clinical efficacy of palonosetron may be due, in part, to its more potent binding and longer half-life. However, these attributes alone are not sufficient to explain the results with palonosetron. We sought to elucidate additional differences among 5-HT(3)- RAs that could help explain the observations in the clinic. To compare he safety, efficacy and pharmacoeconomic burden of antiemetic/prokinetic agents like Ondansetron, Granisetron and Palonosetron in prevention of chemotherapy induced nausea and vomiting in cancer patients undergoing chemotherapy were our objectives.

Materials and methods

The study was conducted on patients admitted to Swatantra Cancer Hospital, Rajahmundry, attached to G.S.L. Medical College, Rajahmundry from January 2012 to June 2013. This prospective study was carried out on various cancer patients who were receiving chemotherapy cycle from department of oncology Swatantra hospital.

Data collection: 90 cases were included in the study of which 30 received ondansetron 8 mg. 30 received i.v., Granisetron 3 mg i.v and 30 received palonosetron 0.75 mg i.v. 30 minutes before chemotherapy cycle. Proforma containing detailed information on each patient was prepared according to the protocol designed for the study.

Inclusion criteria

1) Cancer patients of more than 12 years age group.
2) Cancer patients of both sex male and female.
3) Cancer patients irrespective of duration of disease.

Exclusion criteria:

1) Pediatric age group.
2) Pregnant women
3) History of drug allergy to any of the stud medications.
4) Severe, uncontrolled, concurrent illness other than Neoplasia.
5) Asymptomatic metastases to the brain
6) Seizure disorder needling anticonvulsants unless clinically stable
7) Intestinal obstruction; concurrent of any other emetogenic drug radiotherapy
8) History of motion sickness.

Observation & results

Total 90 patients were included in the study, of whom 30 received Ondansetron 8 mg i.v. 30 received Granisetron 3mg i.v and 30 received palonosetron 0.75 mg i.v. 30 minutes prior to chemotherapy cycle.

Statistical methods:

ANOVA test have been used to find the significance of homogeneity of stud characteristics between three groups of patients.

$P < 0.05$; statistically significant.

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p>0.05 ; statistically insignificant

Statistical software:

The statistical software SPSSs 16 (Statistical package for Social sciences) versions was useds for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc. Figures are drawn by taking time on X-axis and percentage of patients on y-axis.

Table 1: Demographic characteristics of patients:

CHARACTERISTC	ONDONSETRON		GRANISETRON		PALONOSETRON	
	N	% of pt.s	N	% of pt.s	N	% of pt.s
Patient number	30		30		30	
Age(median, year)	48		49		47	33.3
Sex distribution:	12	33.3	13	33.3	14	
Male	18		17		16	
Female						

Table 2: Incident of nausea after treating with antiemetics in chemotherapy treated patients:

TIME		ONDANSETRON	GRANISETRON	PALONOSETRON	
				4(16.66%)	
No. Of Episodes Of nausea	0-24 Hrs	8(26.66%)	5(16.66%)		
	24-48 Hrs	5(16.66%)	4(13.33%)	3(10.00%)	
	48-72 Hrs	4(13.33%)	3(10.00%)	1(3.33%)	0.013
		17(56.66%)	12(40.00%)	8(26.66%)	

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P<0.05 considered statistically significant. Number in parenthesis represents percentage.

Table-3. Overall response to vomiting for each drug from day 1-3:

THERAPY RESPONSE	DAY	ONDANSETRON	GRANISETRON	PALONOSETRON	'P'Value
Complete Response	DAY1	22(73.3%)	23(76.6%)	25(83.3%)	0.04
	DAY2	17(56.6%)	19(63.3%)	20(66.6%)	
	DAY3	18(60.0%)	17(56.6%)	22(73.3%)	
Partial Response	DAY1	5(16.6%)	4(13.3%)	3(10.0%)	0.007
	DAY2	11(36.6%)	8(26.6%)	8(26.6%)	
	DAY3	10(33.3%)	3(10.0%)	7(23.3%)	
Failure	DAY1	3(10.0%)	3(10.0%)	2(6.6)%	0.142
	DAY2	2(6.6%)	5(16.6%)	2(6.6%)	
	DAY3	2(6.6%)		1(3.3%)	

P<0.05 CONSIDERED STATISTICALLY SIGNIFICANT. Number in parenthesis represents percentage

Table 4: Response for vomiting in High emetogenic chemotherapy regimen (HEC):

THERAPY RESPONSE	DAY	ONDAN SETRON	GRANI SETRON	PALONO SETRON	'P' Value
Completye Response	DAY1	11.(73.3%)	11(73.3%)	12(80%)	0.015
	DAY2	8(53.3%)	9(60.0%)	10(66.6%)	
	DAY3	10(66.6%)	10(66.6%)	12(80%)	
Partial Response	DAY1	3(20.0%)	2(13.3%)	2(13.3%)	0.017
	DAY2	5(33.3%)	4(26.6%)	4(26.6%)	
	DAY3	4(26.6%)	3(20.0%)	2((13.3%)	

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Failure	DAY1	1(6.6%)	2(13.3%)	1(6.6%)	0.049
	DAY2	2(13.3%)	2(13.3%)	1(6.6%)	
	DAY3	1(6.6%)	2(13.3%)	1(6.6%)	

P<0.05 considered statistically. Number in parenthesis represents percentage

Table 5: Response for vomiting in moderate emetogenic chemotherapy cycle (MEC):

THERAPY RESPONSE	DAY	ONDAN SETRON	GRANI SETRON	PALONO SETRON	'P' Value
COMPLETE RESPONSE	DAY1	11(73.3%)	12(80%)	13(86.6%)	0.132
	DAY2	9(60.0%)	10(66.6%)	10(66.6%	
	DAY3	8(53.3%)	7(46.6%)	1(6.6%)	
PARTIAL RESPONSE	DAY1	2(13.3%)	2(13.3%)	4(26.6%)	0.077
	DAY2	6(40.0%)	4(26.6%)	5(33.3%)	
	DAY3	6(40.0%)	5(33.3%)	1(6.6%)	
FAILURE	DAY1	2(13.2%)	1(6.6%)	1(6.6%)	0.548
	DAY2	0(0.0%)	1(6.6%)	1(6.6%)	
	DAY3	1(6.6%)	3(19.8%)	0(0.0%)	

P<0.05 considered satistically significant. Number in parenthesis represents percentage.

Discussion

Nausea and vomiting are still the major distressing health issue in patients undergoing chemotherapy. Although 5-HT_3-receptor antagonists along with a Corticosteroid are proved to be the key treatment regimen against CINV, [70, 72,73] the standard serotonin antagonist to be used in various chemotherapy regiments is yet to be known. There are some differences in metabolism and receptor specificities among the different serotonin antagonists.[74] Palonosetron is a highly potent, selective, second generation 5-HT_3 receptor antagonist (pKi 10.5 compared with 8.91 for Granisetron, 8.39 for Ondansetron).[75,76] Palonosetron shows a 40 h half life, [77,78] which is significantly longer

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than others in its class [Ondansetron, 4h;[79] Tropisetron 7.3h;[80] Dolasetron, 7.5h;[81] Granisetron, 8.9 h.[82] It shows both competitive binding and Allosteric interactions with he 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 palonosetros's dual action induces amplification of its inhibitory effect at the primary receptor binding site.[83] The incidence of nausea and emetic episodes were the primary efficacy variable in this study. In the present study patients treated with Palonosetron showed statistically significant lower episodes of nausea when compared with Granisetron and Palonosetron ('p' value 0.013). One study comparing palonosetron plus dexamethasone versus granisetron plus dexamethasone showed superiority of palonosetron in controlling delayed nauses in 1,114 participants (OR 1.63;95% CI1.27 to 2.10). The proportion of participants experiencing complete control of delayed nauses in the group with palonosetron was 210/555 (37.8%) versus 152/559 (27.2%) in the group with granisetron.[85] For high emetogenic chemotherapy (HEC) regimens like Cisplatin group of chemotherapy drugs there was statistical difference in vomiting between Ondansetron, Granisetron and Palonosetron for complete and partial response of the drug('p' values 0.015 and 0.017 respectively), and palonosetron exhibited statistically significant less failure rate of vomiting than the other two groups of drugs i.e Granisetron and Ondansetron. ('p'=0.049). In one study which 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.[83,84]. In moderately emetogenic regimens the superiority of palonosetron was clearly established in the acute phase (o-24 h), although apparent, much difference was not found in the subsequent hours (24-120 h).[86] In another study palonosetron plus dexamethasone and granisetron plus dexamethasone appeared similar and were not statistically different in complete response for acute nausea and vomiting in 1,114 participants (OR 1.11;95% CI 0.85 o 1.45).[85] In the present study for moderate emetogenic chemotherapy(MEC) regimens, Palonosetron did not exhibit statistically significant response to vomiting for complete and partial response when compared with Ondansetron and Granisetron. ('p' values 0.132 and 0.077 respectively), and the failure rate of vomiting for moderate emetogenic chemotherapy regimens was not statistically significant among Ondansetron, Granisetron and Palonoseron ('p' value 0.548). Palonosetron does seem to be highly effective for control of nausea and vomiting for moderate emetogenic chemotherapy regimens. Side effects which were monitored in the study are headache, gatro intestinal disturbance and dizziness. The percentage of patients showing headache was not statistically significant among Ondansetron, Granisetron and Palonosetron groups i.e., 16.66%, 16.66% and 13.33% respectively. Constipation was seen in 40% of the patients treated with Ondansetron, 43.33% of the patients treated with Granisetron and 50% of the patients treated with Palonosetron, which did not show statistical significant value. Similarly dizziness was seen in 13.33% patients of Ondansetron, 20% of patients of Granisetron and 16.66% patients of palonosetron group, which was almost similar in three groups. This side effect profile is similar and supportive with study conducted by Mitsue Saito et.al.[85] QT prolongation was seen in two patients of Ondansetron group which was an

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ECG finding and was clinically insignificant. Mild hypersensitivity reaction was seen in one patient of palonosetron group. 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 2012. In the present study, Ondansetron and Granisetron were given on Day 1 and 2, whereas Palonosetron was given only on Day 1. In relation to expenses Palonosetron was found to be the most expensive drug, followed by Granisetron, which was followed by Onansetron, and also the 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. Sample size is the major limitation for he present study. In this scenario further studies with large samples are needed to establish these particular aspects.

Conclusion:

Present study is primarily to compare the efficiency, safety and cost of 5-HT3 receptor antagonists in cancer patients. Findings suggest that overall response for nausea and vomiting with Palonosetron was superior to Ondansetron and Granisetron, especially in high emetogenic chemotherapy regimens. Failure rate with Palonosetron was less when compared with Ondansetron and Granisetron for high emetogenic chemotherapy regimens. All the three drugs have almost similar side-effect profiles in prophylaxis of CINV secondary to moderately or highly emetogenic chemotherapy. The cost of Palonosetron is almost seven times that of Ondansetron and four times that of Granisetron for each chemotherapy cycle. Herapeutic option of choosing antiemetic by the treating physician has to focus on efficacy, safety and cost of the antiemetic to minimize the economic burden on the patient depending on economic status of the patient.

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