

Ramosetron hydrochloride for the prevention of cancer chemotherapy induced nausea and vomiting: The Indian experience

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Abstract

Background: Despite the advent of 5-HT₃ antagonists, control of delayed gastrointestinal adverse events with cancer chemotherapy is still not optimal. This open label, active controlled, multicentric clinical trial was undertaken to assess the comparative efficacy and safety of ramosetron with ondansetron for the prevention of acute and delayed nausea and vomiting associated with emetogenic cancer chemotherapy in adult patients in India. **Materials and Methods:** Enrolled patients received treatment with ramosetron hydrochloride 0.1 mg or ondansetron hydrochloride 4 mg tablets once daily in the morning for 5 days starting 1 h before the start of chemotherapy. Severity grades of nausea and vomiting were recorded on a daily basis for a period of 5 days and complete response rate (CRR) and effective rate (ER) were calculated. Clinical adverse events were recorded and hematological and biochemical investigations were performed for safety assessment. **Results:** A total of 114 patients in ramosetron group and 100 patients in ondansetron group completed the study and were eligible for efficacy and safety analysis. CRR and ERs show that while ramosetron is non-inferior to ondansetron in the control of early nausea and vomiting (occurring during the first 24 h) after the treatment with emetogenic chemotherapy, it is superior to ondansetron in the control of delayed nausea and vomiting (occurring after the first 24 h). The proportion of patients achieving a cumulative complete response (for the entire study period) is significantly greater in ramosetron group as compared to ondansetron group (27.2% vs. 7.0%; $P < 0.001$). Ramosetron was well tolerated by all the study participants. **Conclusions:** Ramosetron is significantly more effective than ondansetron for the control of delayed nausea and vomiting induced by emetogenic cancer chemotherapy.

Key words: Chemotherapy induced nausea and vomiting, India, ondansetron, ramosetron

Introduction

Gastrointestinal adverse events like nausea and vomiting are the common adverse events significantly affecting the quality of life of patients receiving chemotherapy. Patients often develop dehydration, electrolyte imbalances and malnutrition which affect the compliance to therapy, compromising the dosage and thus the efficacy of the regimen. Control of nausea and vomiting have significantly improved after the advent of 5-HT₃ antagonists, leading to a remarkably better quality of life of the cancer patients.^[1] However, improved gastrointestinal tolerance with cancer chemotherapy is still incomplete and control of “delayed nausea and vomiting” in particular, remains an area of unmet therapeutic need. The ability of the currently available 5-HT₃ antagonists such as ondansetron, granisetron and tropisetron to control these

symptoms, which appear beyond 24 h of administration of chemotherapy is considered to be limited.^[2,3] Further, in the control of acute nausea/vomiting also, some of the patients do not respond to a given 5-HT₃ antagonist. However, these patients are still benefited by changeover to another agent and there is no complete “cross-resistance” between the different agents despite structural similarities.^[4]

Ramosetron, a new member in the class of selective 5-HT₃ receptor antagonists, is a tetrahydrobenzimidazole derivative structurally independent of the previously developed 5-HT₃ receptor antagonists such as ondansetron, granisetron and tropisetron. It is more potent and has longer-lasting effects than the older agents because of a slower rate of dissociation from the target receptor and higher binding affinity. The safety and efficacy of ramosetron in the management and prevention of nausea and vomiting associated with emetogenic cancer chemotherapy as well as in post-operative setting is well-established.^[5] Ramosetron has a flexible administration schedule with 0.1 mg oral tablet for the prevention and 0.3 mg/2 ml intravenous injection for the treatment of nausea and vomiting.^[6,7] Comparative clinical trials have shown that the treatment efficacy with ramosetron in early post-dose period is similar to or higher than that of granisetron or ondansetron, but it is significantly better in the late phases due to its longer duration of action.^[5] Ramosetron has also been shown to be effective and is approved internationally for the treatment of diarrhea-predominant irritable bowel syndrome in males as 2.5 µg and 5 µg tablets.^[8]

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Although the efficacy and safety of ramosetron is established internationally, there is no data on the efficacy and safety of this drug in the Indian population. This phase III study was conducted to evaluate the comparative efficacy and safety of ramosetron hydrochloride 0.1 mg tablets with ondansetron hydrochloride 4 mg tablets for the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy in adult patients of Indian origin.

Materials and Methods

This prospective, open label, active controlled multicentric, phase III non-inferiority clinical trial was conducted at four different centers in India. The study was approved by the licensing authority (Drugs Controller General of India) and the institutional/independent ethics committees of each of the participating centers before start of the study. It was conducted in compliance with the good clinical practice guidelines issued by the international conference on harmonization of technical requirements for registration of pharmaceuticals for human use and the ethical principles of the declaration of Helsinki. Informed consent was obtained from all the patients before the start of any screening procedure.

Patients

Patients of either sex, 18-75 years of age, receiving emetogenic cancer chemotherapy were included in the study. Patients suffering from concomitant diseases that may cause vomiting (for example, active peptic ulcer, gastric outlet obstruction or intestinal obstruction, brain tumor, brain metastasis and epilepsy) and those who had experienced vomiting in the past 24 h prior to enrolment into the study due to any reason were excluded from the study. Patients taking medications that can affect the gastrointestinal tract or central nervous system (for example, other antiemetics or antipsychotics) or with a history of hypersensitivity to ondansetron or any other 5-HT₃ antagonists were not eligible for enrolment. Patients having clinically significant concomitant illnesses such as cardiac, renal or hepatic disease, those with anticipated survival of <3 months or those who had participated in another clinical trial in the past 3 months or patients having a continuing history of alcohol and/or drug abuse were also excluded from the study. Female patients with pregnancy or lactation were not included in the study.

Drug administration

Patients enrolled in the study were randomized to receive either one tablet of ramosetron hydrochloride 0.1 mg (Group R) or one tablet of ondansetron hydrochloride 4 mg (Group O) once a day in the morning for 5 consecutive days starting 1 h before the start of chemotherapy on the 1st day of the study.

Concomitant medications which could possibly influence the outcome of the trial such as other antiemetics, antipsychotics or sedatives were not permitted during the study. In the event of severe nausea and/or vomiting in any of the

enrolled patients, a rescue anti-emetic could be used at the discretion of the investigator in the best interest of the patient and details of such rescue medication usage were recorded. Treatment with corticosteroids in the enrolled patients was allowed only if such drugs were a part of the chemotherapy regimen. Medications for other concomitant illnesses, if present, were permitted as deemed necessary by the investigator and recorded in the case record form.

Assessments

Efficacy assessments were based on the severity of nausea and vomiting in the patients enrolled in the two study groups after administration of emetogenic cancer chemotherapy during the follow-up period. Severity of nausea and vomiting during the 24 h after each dose of the study medication was recorded according to a 4 point response criteria adapted from the “national cancer institute common toxicity criteria”.^[9] Efficacy assessments also included a intergroup comparison of the complete response rate (CRR), defined as the “Number of patients reporting Grade 0 (no incidence) of nausea or vomiting” and; the effective rate (ER), defined as the “Number of patients reporting Grade 0 (no nausea) or Grade 1 nausea only and Grade 0 vomiting (no vomiting)” as calculated on a daily basis and cumulatively for the entire study period. Investigators’ global assessment of efficacy on a 4-point rating scale of excellent, good, fair and poor at the end of the study was also analyzed.

Adverse events were documented by the investigators on a daily basis, including date of onset and end (duration), intensity (mild, moderate or severe), treatment required and outcome. The relationship of the study medication to adverse event was determined by assigning one of the four criteria (definite, probable, possible or remote) to each adverse event. Standard laboratory tests including hematology, blood biochemistries and urine analysis were performed before administration of the study drug and at the end of treatment for the assessment of safety of the study medications. Clinically significant abnormalities in the laboratory investigations were documented as adverse events.

Statistical analysis

On the basis of previous studies, 68% and 63% CRR were assumed for patients treated with ramosetron and ondansetron at day 1, respectively. Setting α at 0.05, power at 80% and assuming a non-inferiority margin of 15%, a sample size of minimum of 200 patients was calculated including 10% dropouts. The non-inferiority margin was less than half the difference between the placebo and the active control.^[10] The data collected during the study was analyzed for demographics, efficacy and safety. Data are presented as mean \pm standard deviation or number (proportions). Per-protocol data set including all the patients without deviations and fulfilling all the entry criteria was considered for the analysis. Ramosetron was considered to be non-inferior to ondansetron for the prevention of chemotherapy induced nausea and vomiting (CINV) if the lower limit of the 95% two sided

confidence interval (CI) for the difference in day 1 CRR between the two treatments (Group R minus Group O) was greater than -15% . Ramosetron was considered to be superior to ondansetron if the lower limit of the 95% two sided CI for the difference in the results of two groups was more than zero. Unpaired Student's *t*-test and Chi-square (χ^2) test were used for analysis where applicable and $P < 0.05$ were considered to be statistically significant.

Results

Patients' characteristics

A total of 214 patients receiving emetogenic cancer chemotherapy were enrolled in this clinical trial - 114 patients in Group R and 100 patients in Group O. All the 214 patients completed the study as per the protocol and hence qualified for efficacy as well as tolerability analysis at the end of the study.

Majority of the patients enrolled in the study were known cancer patients suffering from various malignancies and were already being treated with emetogenic cancer chemotherapy before screening. The emetogenic potential of the chemotherapy regimens received by these patients was evaluated as per the American Society of Clinical Oncology guidelines.^[11,12] There was no significant difference in the emetogenic potential of the chemotherapy received by the patients enrolled in each group. Both groups were similar in terms of the demographic and baseline characteristics as shown in Table 1. 7 (6.1%) and 5 (4.4%) patients had received dexamethasone and prednisolone, respectively in Group R as a part of their chemotherapeutic regimen; while, 14 (14.0%) and 7 (7.0%) patients had received the same in Group O.

Efficacy analysis

Both ramosetron and ondansetron were highly effective in preventing acute nausea and vomiting and none of the patients reported Grade 3 severity of nausea or vomiting in either of the study group on day 1 of the study. There was no significant difference (nausea: $P = 0.29$; vomiting: $P = 0.51$) between the various severity grades of nausea and vomiting in Group R and Group O on day 1 [Figures 1 and 2]. The proportion of patients achieving complete response at day 1 after chemotherapy was 64.0% in the Group R and 60.0% in the Group O with the lower limit of 95% CI for the difference in CRR being -8.8% which was above the pre-set non-inferiority margin of -15% . Thus, ramosetron was found to be non-inferior to ondansetron in the prevention of acute nausea and vomiting after chemotherapy [Table 2]. The ER in the patients in Group R (78.6%) was also non-inferior (lower limit of 95% CI for the difference was -7.3%) to that achieved by the patients in the Group O (75.0%) [Table 2].

Ramosetron demonstrated a better therapeutic efficacy in preventing the delayed nausea and vomiting (after 24 h of chemotherapy) with a lesser number of patients in Group R reporting "mild", "moderate" or "severe" nausea/vomiting during the entire study period as compared to the patients

Table 1: Demographic characteristics of the patients

Characteristics	Group R (n=114)	Group O (n=100)	P value
Age (years)	47.3±12.6	44.7±13.1	0.15
Sex, n			
Female	77 (67.5)	64 (64.0)	0.59
Male	37 (32.5)	36 (36.0)	
BMI (kg/m ²)	23.2±4.4	22.3±4.6	0.18
Duration of illness (months)	8.8±10.8	8.1±6.8	0.54
Diagnosis			
Breast	56 (49.1)	49 (49.0)	0.75
Head and neck	17 (14.9)	8 (8.0)	
Ovary	12 (10.5)	11 (11.0)	
Lung and bronchus	6 (5.2)	4 (4.0)	
Gastrointestinal tract	5 (4.3)	6 (6.0)	
Hematopoietic system	5 (4.3)	4 (4.0)	
Musculoskeletal system	4 (3.6)	5 (5.0)	
Others	9 (8.0)	13 (13.0)	
Emetogenic potential*			
High (emesis risk >90% without antiemetics)	41 (36.0)	24 (24.0)	0.14
Moderate (emesis risk 30-90% without antiemetics)	69 (60.5)	70 (70.0)	
Low (emesis risk 10-30% without antiemetics)	4 (3.5)	6 (6.0)	

Data expressed as mean±SD or n (%). *As per American society of clinical oncology guidelines. SD=Standard deviation, BMI=Body mass index

Table 2: CPR and ER at day 1 in the patients [% (95% CI)]

Parameter	Group R (%)	Group O (%)	Treatment difference (%)	P value
Complete response rate	64.0 (72.5, 54.9)	60.0 (69.1, 50.2)	4 (16.8, -8.8)	0.64
Effective rate	78.9 (85.4, 70.6)	75.0 (82.5, 65.7)	3.9 (15.3, -7.3)	0.60

CI=Confidence interval, CPR=Complete response rate, ER=Effective rate

in Group O. The differences in severity grades reported in the patients for nausea was statistically significant at all the time-points after the 1st day of study; while statistical significance was not reached on all the time-points for vomiting [Figures 1 and 2]. Moreover, patients in the Group R achieved a significantly higher CRR and ER on all the time points after day 1 as compared to the patients in Group O [Figure 3]. The proportion of patients achieving a cumulative complete response for the entire study period was also significantly greater in Group R as compared to Group O (27.2% [95% CI: 35.4%, 19.0%] vs. 7.0% [95% CI: 12%, 2%]; difference 20.2% [95% CI: 29.7%, 10.2%]; $P < 0.001$). The cumulative ER for the entire study period was also significantly higher in Group R as compared to Group O (52.6% [95% CI: 61.8%, 43.5%] vs. 24.0% [95% CI: 32.4%, 15.6%]; difference 28.6 [95% CI: 40.2%, 15.7%]; $P < 0.001$).

Further, the requirement of any rescue-antiemetic in the patients enrolled in either study group was also recorded. A total of 13 patients (11.4% [95% CI: 17.2%, 5.6%])

received other antiemetics in Group R, of which the most common were domperidone (6.1%) and ondansetron (4.4%); while 20 patients (20.0% [95% CI: 27.8%, 12.2%]) received such rescue antiemetics in Group O, of which also the most common medications were domperidone (8.0%) and additional doses of ondansetron (5.0%). However, this difference in the requirement of the rescue anti-emetics in each group was not statistically significant ($P = 0.08$).

At the end of the study, the investigators gave their overall assessment of efficacy to both the study drugs, as shown in Figure 4. According to this comparative assessment based on global impression for the prevention of CINV, ramosetron was considered to have a significantly better efficacy when compared to ondansetron ($P < 0.001$).

Safety analysis

Both the study drugs were well tolerated by all the patients in the study. During the study period, 8 (7.0% [95% CI: 2.3-11.7%]) adverse events were reported in Group R and 5 (5.0% [95% CI: 0.7-9.3%]) adverse events were reported in Group O. The details of these adverse events along with their severity are

shown in Table 3. All these 13 adverse events were rated by the investigators to have a “unlikely” association with the respective study medication. They resolved completely, either spontaneously or by symptomatic treatment during the course of the study. No serious adverse event was reported by any of the patients enrolled in the study. None of the patients discontinued the study medication due to adverse event during the entire course of the study. Moreover, there was no clinically significant alteration in any of the routine hematological and biochemical parameters at the end of therapy with the study drugs as compared to the baseline in any of the patients in this study.

Discussion

This is the first Indian study carried out to compare the efficacy and safety of ramosetron hydrochloride 0.1 mg tablets with ondansetron hydrochloride 4 mg tablets for the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy in adult patients. The results of this study indicate that ramosetron is non-inferior to ondansetron in the control of early nausea and vomiting (occurring during the first 24 h) and is superior to ondansetron in the control of delayed nausea

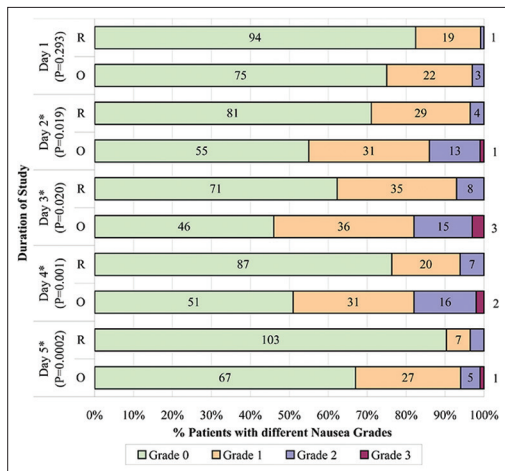


Figure 1: The difference in the severity grades of nausea with significance levels (Group R, n = 114 and Group O, n = 100) *Statistically significant P values

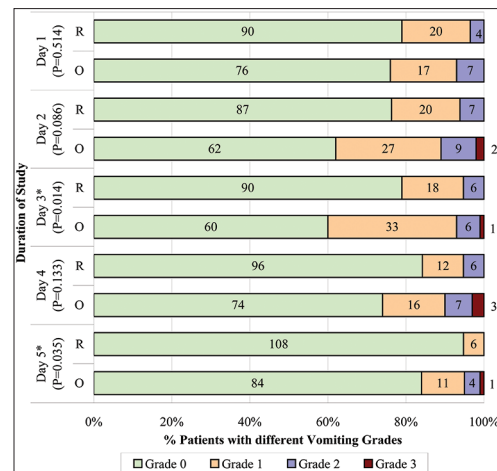


Figure 2: The difference in the severity grades of vomiting with significance levels (Group R, n = 114 and Group O, n = 100) *Statistically significant P values

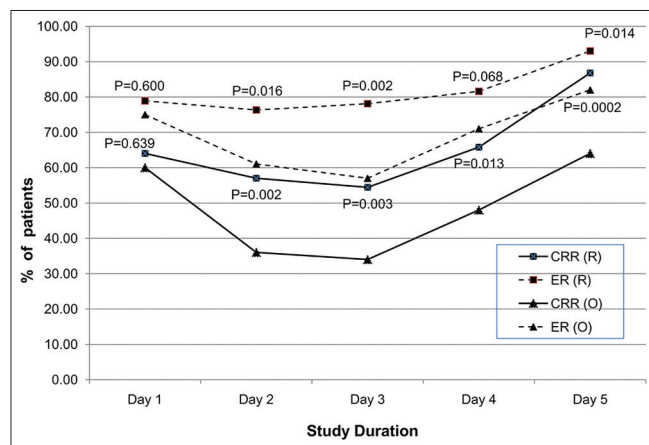


Figure 3: Complete response rate and effective rate at different time points during the study (Group R, n = 114 and Group O, n = 100)

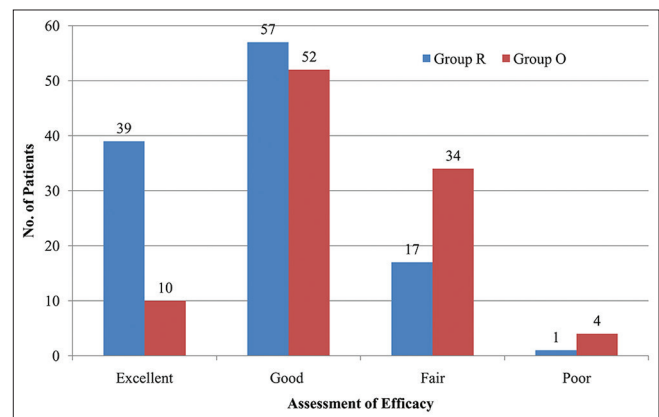


Figure 4: Investigators’ opinion on global assessment of efficacy (Group R, n = 114 and Group O, n = 100)

Table 3: List of adverse events (no. (%))

Nature	Severity	Group R (n=114)	Group O (n=100)
Body ache	Mild	2 (1.7)	1 (1.0)
	Moderate	1 (0.9)	-
Weakness	Severe	-	2 (2.0)
Fever	Mild	1 (0.9)	1 (1.0)
Mouth ulcer	Mild	-	1 (1.0)
	Moderate	1 (0.9)	-
Diarrhea	Mild	1 (0.9)	-
Giddiness	Moderate	1 (0.9)	-
Neutropenia	Mild	1 (0.9)	-
Total		8 (7.0)	5 (5.0)

and vomiting (occurring after the first 24 h) after treatment with emetogenic chemotherapy. It is a very well-tolerated drug in cancer patients.

It was seen in our study that the intensity of nausea and vomiting progressively increases from day 2 onwards, in spite of prophylactic treatment, as reported by the severity grades of these symptoms in patients during the course of study. In fact, delayed nausea and vomiting beyond 24 h of chemotherapy administration is reported to be incompletely assuaged by existing 5-HT₃ antagonists.^[2,3] In our study, we observed that ramosetron was significantly better than ondansetron for the prevention of delayed symptoms at all time-points beyond 24 h with consistently higher treatment response rates reported. This effect could be attributed to the longer half-life of the drug and the active metabolite of ramosetron which maintains high receptor occupancy and thus prolongs the action of the drug providing a good therapeutic effect.^[13] However, it is to be noted that the emesis control was still not complete.

Several studies comparing the efficacy of ramosetron (oral or intravenous) with ondansetron,^[13,14] granisetron^[10,15-18] and tropisetron^[5] for the prevention of chemotherapy induced gastrointestinal adverse effects are published internationally. However, the severity grades used as efficacy parameters, emetogenic potential of the chemotherapy regimens and the time-points of assessment are very diverse; therefore accurate efficacy comparisons of the findings of our study with these studies are difficult. Overall, these studies have shown that ramosetron is non-inferior to other 5-HT₃ antagonists for the prevention of acute nausea and vomiting; while it is generally better for the control of symptoms beyond 24 h of treatment. Ramosetron is also shown to be effective in the patients receiving chemo-radiotherapy who did not sufficiently respond to ondansetron in the previous therapy cycles.^[19] The efficacy findings of our study are also consistent with the results of these previous studies. Future studies should be done to optimize the use of ramosetron in combination with corticosteroids and/or neurokinin antagonists; as is currently recommended for other 5-HT₃ antagonists, in order to attain complete emesis control.

Most of the studies evaluating ramosetron for the prevention of CINV until date, had enrolled patients on

chemotherapeutic agents with high emetogenic potential, especially those using Cisplatin based chemotherapy regimens.^[13-15] Although restricting the patient enrolment to a particular regimen helps in reducing the variance in the study population, the compatibility and efficacy of the study drug with various other chemotherapeutic agents having different emetogenic potentials is not established. Our study has evaluated the overall therapeutic efficacy and safety of ramosetron and ondansetron in all the chemotherapy induced emetogenic risk categories. The emetogenic categories were fairly comparable in both groups, with the majority of the patients in both groups having received chemotherapy of moderate to high emetogenic potential. The results of our study suggest that ramosetron can be used along with all kinds of chemotherapeutic agents with varying emetogenic potential that are likely to be seen in any real time clinical setting to attain good control of CINV.

Both the treatments were well-tolerated, with no significant differences between the two groups. Further, since the patients enrolled in the study were being treated with cytotoxic chemotherapeutic agents, the causal association of the reported adverse events to either of the study medication needed to be critically evaluated, given the known potential of the chemotherapeutic agents to cause adverse events. Thus, on causality assessment, adverse events reported in the study were unlikely to be attributable to either of the study medications with any degree of certainty. Moreover, previous published clinical trials have reported the incidence of adverse events during treatment with ramosetron ranging from 2.1% to 76.7%;^[10,13-15,17,18] however, causal association is rated to be uncertain for majority of them. The adverse events rate reported in the present study is 7% and is in line with the previous studies.

Our study demonstrates the efficacy and safety of ramosetron in cancer patient population in India. The open label design of the study is likely to be influenced by the investigator bias. However, comparability of both the study groups is verifiable from the similar baseline characteristics of the patients enrolled in each treatment arm. Further, use of an active comparator and patient reported objective outcomes as efficacy parameters ensure the validity of the results of study. The efficacy results could be less than optimal in ondansetron group at the dose studied; still an earlier comparative study had used this dose of ondansetron,^[14] and other studies^[5,13-18] comparing different doses and oral/parenteral formulations of other 5-HT₃ antagonists and ramosetron have shown efficacy results similar to those reported in the present study.

Conclusion

The results of our above comparative, multicentric, clinical trial clearly indicate that ramosetron hydrochloride 0.1 mg tablet given once a day is non-inferior to ondansetron 4 mg tablet given once a day in the control of early nausea and vomiting (occurring during the first 24 h)

after the treatment with emetogenic chemotherapy and is superior to ondansetron 4 mg tablet given once a day in the control of delayed nausea and vomiting (occurring after the first 24 h). Further, ramosetron tablets are very well tolerated. Ramosetron thus appears to be a suitable first-line therapeutic alternative for the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy in Indian patients.

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