Jpn J Clin Oncol 2005;35(12)695–699
doi:10.1093/jjco/hyi192

Original Articles

Comparison of Ramosetron and Granisetron for the Prevention of Acute and Delayed Emesis in Cisplatin-Based Chemotherapy: a Randomized Controlled Trial

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Received November 16, 2004; accepted October 2, 2005; published online November 30, 2005

Objective: A clinical study of ramosetron was carried out to evaluate its efficacy in preventing both acute and delayed emesis in cisplatin-based chemotherapy by using a double-blind method with granisetron as the comparative drug.
Methods: Cisplatin at a dose of $\geqslant$70 mg/m^2 was administered as a single intravenous (i.v.) infusion over 4 h. Patients were randomly assigned to receive either ramosetron (0.3 mg i.v. bolus 30 min before cisplatin on Day 1 and a 0.1 mg tablet in the morning for Days 2 to 5 after completion of chemotherapy; n = 36) or granisetron (3 mg i.v. infusion 30 min before cisplatin on Day 1 and a 1 mg tablet in the morning for Days 2 to 5 after completion of chemotherapy; n = 37). 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 on Days 2 to 5 for delayed nausea and vomiting.
Results: A total of 73 patients were eligible for evaluation, with 36 patients in the ramosetron group and 37 in the granisetron group. The efficacy of both drugs was analyzed in terms of the degree of achievement in each day of treatment. Ramosetron was as effective as granisetron in preventing nausea and vomiting (both acute and delayed emesis). The two drugs had a similar safety profile and adverse events were generally mild and transient.
Conclusions: Ramosetron is effective and safe for the control of acute and delayed emesis induced by cisplatin.

Key words: cisplatin – chemotherapy – nausea and vomiting – ramosetron – granisetron

INTRODUCTION

Chemotherapy-induced nausea and vomiting are the symptoms that cause most nuisance to patients receiving chemotherapy. In particular, in the guidelines issued by the American Society of Clinical Oncology (1), cisplatin is described as having a high risk of acute and delayed emesis. Uncontrolled nausea and vomiting may significantly affect the patient's well being. Patients can develop dehydration, electrolyte imbalances and malnutrition which may eventually force them to discontinue therapy because of their highly negative impact on quality of life. Therefore, effective antiemetic therapy should be established in order to completely prevent nausea and vomiting.

The discovery that serotonin (5-HT$_3$) receptors play a pivotal role in chemotherapy-induced emesis led to the development of specific 5-HT$_3$ serotonin receptor antagonists that enable physicians to effectively control cisplatin-induced nausea and vomiting (1). Ramosetron hydrochloride is a novel, highly selective 5-HT$_3$ receptor antagonist developed by Yamanouchi Pharmaceutical Co., Ltd. (Japan) (2–4). Studies in a ferret model show that ramosetron activity has a duration 10 times that of granisetron, and thus is considered to be a long-acting serotonin antagonist agent (5,6). Results of a Phase III clinical study in Japan suggested that ramosetron (0.3 mg) injection is significantly more effective and has a better control of nausea and vomiting than does granisetron (40 μg/kg) given intravenously (i.v) (7).

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Thus, this study was conducted to evaluate the efficacy and safety of ramosetron compared with granisetron for the prevention of acute and delayed nausea and vomiting induced by cisplatin in Thai patients receiving chemotherapy.

PATIENTS AND METHODS

This was a double-blind comparative study conducted at the Thanyaburi Cancer Center, Patumthani, Thailand. In this study patients were randomized into one of two groups. Patients were assigned to receive either ramosetron or granisetron by i.v. injection as a single dose 30 min before administration of cisplatin. The patients then took oral preparations of the same drugs for Days 2 to 5 for the prevention of delayed emesis.

PATIENTS

The physician in charge of the study obtained informed consent from the patients and confirmed that patients were appropriate to participate in the study based on the inclusion and exclusion criteria. The study was approved by the institution review board at the Mahavajiralongkorn Cancer Center, Thanyaburi, Patumthani, Thailand. The case registration center then received information from each doctor, registered the identification codes of the patients and scheduled administration of the test drugs.

A total of 73 patients with cancer were enrolled into the study who were aged between 20 and 80 years and were scheduled to receive their first course of cisplatin (CDDP) chemotherapy $\geqslant$70 mg/m^2 with single or multiple dose regimen (Days 1, 2, 3, 4 and 5) at the Mahavajiralongkorn Cancer Center, between February 2003 and August 2003. Among them 36 and 37 patients were randomized to receive ramosetron or granisetron, respectively. Treatment with steroids in these patients was allowed if such drugs were part of the chemotherapy regimen. In fact, all patients received dexamethasone i.v. 20 mg before administration of cisplatin. Exclusion criteria were as follows: any disorders causing nausea, brain tumor, brain metastasis and epilepsy; concomitant diseases that may cause vomiting (for example, active peptic ulcer, gastric outlet obstruction or intestinal obstruction); complications with severe disorders of the heart, kidney and liver; and being pregnant or possibly being pregnant. In addition, patients were excluded if they took drugs that may affect the gastrointestinal tract or central nervous system within 24 h before starting the study (for example, other antiemetics or psychotropic drugs) or who had experienced vomiting in the previous 24 h.

Patient characteristics including age, height, body weight, body mass index, performance status, diagnosis, underlying disease and complications were recorded at enrollment. Details of the surgical procedures/radiotherapy instituted, previous treatment conducted before initiation of the study and status of CDDP and study drugs administered were recorded.

DRUG ADMINISTRATION

Cisplatin at a dose of $\geqslant$70 mg/m^2 was administered as a single i.v. infusion over 4 h. A total of 73 patients were randomly allocated into two groups to receive an i.v. injection of either ramosetron (0.3 mg bolus) or granisetron (3 mg infusion) 30 min before administration of cisplatin on Day 1 and then to take oral preparations of the same drug (ramosetron, 0.1 mg tablet; granisetron, 1 mg tablet) in the morning or 1 h before receiving cisplatin for Days 2 to 5. All patients received dexamethasone i.v. 20 mg before cisplatin administration.

Before opening the study, a registration center was established. The center was responsible for drug allocation, patient registration and study blindness. After confirming that the patients met all criteria, one nurse prepared for the study drug using identical syringes. The study drug was then sent to another nurse confirming that the study drug was stable and identical in appearance. Then a syringe containing the study drug was handed directly to the investigator. The study drug code was sealed and not opened until all evaluations had been finalized after the completion of treatment.

ASSESSMENT

The observation period started concomitantly with the start of chemotherapy. The assigned nurse recorded the study drug number in a roll, the number of episodes of retching or vomiting, the degree of nausea and adverse events. Patients were evaluated for 24 h after the start of cisplatin infusion for acute emesis and from Days 2 to 5 for the occurrence of delayed nausea and vomiting. The time and number of nausea and vomiting episodes were recorded every 6 h.

The response rate of the study drugs after 0–24 h after administration was evaluated by applying the grade of nausea and the total number of vomiting incidents to the following table:

No. of vomiting	Grade of nausea		
	A	B	C
0	Highly effective	Highly effective	Moderately effective
1–2	Highly effective	Moderately effective	Slightly effective
3–4	Moderately effective	Slightly effective	Not effective
$\geqslant$5	Not effective	Not effective	Not effective

PRIMARY OUTCOME

INHIBITION OF ACUTE AND DELAYED NAUSEA

The severity of nausea was evaluated according to the following 4-grade scale every 6 h after administration of the study drug: none (no nausea); mild (slight nausea but no disruption to daily activities); moderate (nausea and some disruption to

daily activities); and severe (extreme nausea and severe disruption to daily activities).

Inhibition of Acute and Delayed Vomiting

The time points for vomiting (including retching) were observed for 24 h after administration of the study drug and recorded. The frequency of vomiting was recorded every 6 h after administration. Emetic episodes are, by definition, separated by the absence of vomiting or retching for at least 1 min. The emetic response rate was tabulated for patients using the following criteria: complete (no emetic episode); major (1 to 2 episodes); minor (3 to 5 episodes); and failure (>5 episodes).

Response Rate

The response rate of the study drugs was evaluated by the following 4-grade scale based on the condition of nausea and vomiting (highly effective, moderately effective, slightly effective and not effective) according to the criteria for evaluation of response rate in the period of 0–24 h after administration.

Adverse Events

When an adverse drug reaction occurred, the nature, date of onset (duration), severity (mild, moderate and severe), clinical course and measures taken were recorded. Laboratory examinations included the following: liver function test, kidney function test, hematological test, measurement of blood levels of lipid, electrolytes and glucose in the fasting state; urinalysis; and physical examination including body temperature, blood pressure and pulse rate. All laboratory and physical examinations were measured before administration of the study drug and at the completion of the study.

Statistical Analysis

Sample Size Calculation

Sample size was calculated by the following formula:

$$N = 2\{Z(\alpha) + Z(2\beta)\}^2\pi(1 - \pi)/\delta^2 + 2/\delta$$

Level of significance: $\alpha = 0.05$
Power of test: $1 - \beta = 0.8$
Calculation formula: $N = 2\{Z(\alpha) + Z(2\beta)\}^2\,\pi(1 - \pi)/\delta^2 + 2/\delta$
π = (Response rate of control drug + Response rate of test drug)/2
$\delta = 0.1 -$ (Response rate of control drug − Response rate of test drug)
$Z(\alpha) = Z(0.05) = 1.645$
$Z(2\beta) = Z(2 \times 0.2) = 0.842$

The planned sample size was 40, 20 patients per arm. This sample size was designed to provide the study with 80% power to detect improvement in response rate of 45% in the granisetron arm and 79% in the ramosetron arm at the 0.05 alpha error level.

The previous comparative study in Japan by Noda et al. (7) demonstrated that the response rates of ramosetron and granisetron were 79.3 versus 45.2%, respectively, 24 h after administration ($P < 0.01$).

Statistical analysis was performed using Statistical Package for the Social Science (SPSS) version 11. Comparison of clinical characteristics, safety and antiemetic efficacy between the two groups was made using the Chi-square test, *P*-value of <0.05 was considered to indicate statistical significance.

RESULTS

Of the 73 participants enrolled, 36 and 37 were randomized to receive ramosetron or granisetron, respectively. Patient characteristics are given in Table 1. The age of the patients, performance status, body mass index and primary tumor site were similar in both groups.

Prevention of Acute and Delayed Nausea

There was no nausea reported in the first 24 h after the start of cisplatin infusion in 66.7 and 59.5% of patients in the

Table 1. Patient characteristics ($n = 73$)

Characteristics	Group R ($n = 36$)	Group G ($n = 37$)
Age (years)		
Mean ± SD	54.53 ± 10.16	53.97 ± 10.50
Range	40–80	37–72
Sex		
Female	18	19
Male	18	18
Performance status		
0	5	7
1	24	27
2	7	3
Body mass index (mean ± SD)		
Mean ± SD	1.47 ± 0.13	1.52 ± 0.18
Range	1.25–1.86	1.20–2.10
Diagnosis		
Head and neck	16	11
Cervix	11	15
Lung	5	2
Ovary	1	2
Stomach–esophagus	2	1
Urinary bladder	1	–
Testis	–	1
Other	–	5
Chemotherapy		
CDDP	25	26
CDDP + 5-FU	5	8
CDDP + VP-16	5	2
CDDP + other 1	1	1

R, ramosetron; G, granisetron.

Table 2. Effects of ramosetron (R) and granisetron (G) on nausea

Time after chemotherapy (days)	Group	Number (%) of patients with nausea				Total
		None	Mild	Moderate	Severe	
1	R	24 (66.7)	10 (27.8)	1 (2.8)	1 (2.8)	36 (100)
	G	22 (59.5)	12 (32.4)	2 (5.4)	1 (2.7)	37 (100)
2	R	19 (52.8)	14 (38.9)	1 (2.8)	2 (5.6)	36 (100)
	G	19 (51.4)	14 (37.8)	3 (8.1)	1 (2.7)	37 (100)
3	R	12 (33.3)	16 (44.4)	7 (19.4)	1 (2.8)	36 (100)
	G	11 (29.7)	19 (51.4)	7 (18.9)	0 (0)	37 (100)
4	R	10 (27.8)	17 (47.2)	9 (25.0)	0 (0)	36 (100)
	G	8 (21.6)	21 (56.8)	7 (18.9)	1 (2.7)	37 (100)
5	R	11 (30.6)	18 (50.0)	6 (16.7)	1 (2.8)	36 (100)
	G	14 (37.8)	16 (43.2)	6 (16.2)	1 (2.7)	37 (100)

All table entries have *P*-value of >0.05.

Table 3. Effect of ramosetron (R) and granisetron (G) on vomiting

Time after chemotherapy (days)	Group	Number (%) of patients with vomiting				Total
		Complete	Major	Minor	Failure	
1	R	27 (75.0)	6 (16.7)	2 (5.6)	1 (2.8)	36 (100)
	G	26 (70.3)	9 (24.3)	1 (2.7)	1 (2.7)	37 (100)
2	R	20 (55.6)	12 (33.3)	2 (5.6)	2 (5.6)	36 (100)
	G	23 (62.2)	10 (27.0)	3 (8.1)	1 (2.7)	37 (100)
3	R	16 (44.4)	12 (33.3)	7 (19.4)	1 (2.8)	36 (100)
	G	19 (51.4)	13 (35.1)	4 (10.8)	1 (2.7)	37 (100)
4	R	19 (52.8)	10 (27.8)	6 (16.7)	1 (2.8)	36 (100)
	G	16 (43.2)	15 (40.5)	4 (10.8)	2 (5.4)	37 (100)
5	R	21 (58.3)	9 (25.0)	5 (13.9)	1 (2.8)	36 (100)
	G	20 (54.0)	12 (32.4)	3 (8.1)	2 (5.4)	37 (100)

All table entries have a *P*-value of >0.05.

ramosetron and granisetron groups, respectively. Mild nausea occurred in 27.8 and 32.4% of patients receiving ramosetron and granisetron, respectively. Only one patient in both groups had severe nausea. No delayed nausea on Days 2, 3, 4 and 5 was observed in 52.8, 33.3, 27.8 and 30.6% of the ramosetron group, and in 51.4, 29.7, 21.6 and 37.8% of the granisetron group. The difference between the two groups was not significant (Table 2).

Prevention of Acute and Delayed Vomiting

The effectiveness of ramosetron and granisetron in prevention of vomiting did not significantly differ in both acute and delayed control. In the first 24 h after the start of cisplatin infusion, 75.0 and 70.3% of patients in the ramosetron and granisetron groups, respectively, had complete control. The incidences of major and minor control in both groups were similar. Only one case in both groups had failure of control. For the prevention of delayed vomiting from Days 2 to 5, complete control was reported for 55.6, 44.4, 52.8 and 58.3% in the ramosetron group and for 62.2, 51.4, 43.2 and 54.0% in the granisetron group (Table 3).

Response Rates

The response rates of ramosetron and granisetron in prevention of nausea and vomiting in both acute and delayed emesis are shown in Table 4. In the acute phase, the response rates of ramosetron and granisetron were 75 and 70.3% (highly effective), respectively. The response rates of both drugs decreased for the prevention of delayed emesis during Days 2 to 5; highly effective were 55.6, 50, 55.5 and 58.3% in the ramosetron group and 59.5, 45.9, 43.2 and 54% in granisetron group.

Table 4. Response rate of ramosetron (R) and granisetron (G) on vomiting

Time after chemotherapy (days)	Group	Number (%) of patients with vomiting				Total
		Highly effective	Moderate effective	Slightly effective	Not effective	
1	R	27 (75.0)	7 (19.4)	0 (0.0)	2 (5.6)	36 (100)
	G	26 (70.3)	8 (21.6)	1 (2.7)	2 (5.4)	37 (100)
2	R	20 (55.6)	12 (33.3)	2 (5.6)	2 (5.6)	36 (100)
	G	22 (59.5)	10 (27.0)	2 (5.4)	3 (8.1)	37 (100)
3	R	18 (50.0)	12 (33.3)	5 (13.9)	1 (2.8)	36 (100)
	G	17 (45.9)	13 (35.1)	6 (16.2)	1 (2.7)	37 (100)
4	R	20 (55.5)	10 (27.8)	5 (13.9)	1 (2.8)	36 (100)
	G	16 (43.2)	15 (40.5)	4 (10.8)	2 (5.4)	37 (100)
5	R	21 (58.3)	9 (25.0)	5 (13.9)	1 (2.8)	36 (100)
	G	20 (54.0)	12 (32.4)	3 (8.1)	2 (5.4)	37 (100)

All table entries have a *P*-value of >0.05.

Adverse Events

Table 5 shows the adverse events that occurred in patients receiving ramosetron and granisetron. No serious side effects were found in either group. All adverse events were mild and transient. The most common adverse events in the ramosetron group were headache (11.1%), dizziness (8.3%) and flushing (5.5%). The most common side effects in the granisetron group were dizziness (24.3%), fever (8.1%), headache (5.4%), hiccups (5.4%) and flushing (5.4%). Patients receiving granisetron appeared to experience a higher incidence of dizziness than those receiving ramosetron, but this difference was not significant. The incidence of adverse events was not significantly different in either group.

Table 5. Adverse events of ramosetron (R) and granisetron (G)

Adverse events	R (n = 36)	G (n = 37)
Dizziness	3 (8.3)	9 (24.3)
Dyspepsia	1 (2.8)	1 (2.7)
Diarrhea	0	1 (2.7)
Constipation	1 (2.8)	0
Stomachache	1 (2.8)	0
Headache	4 (11.1)	2 (5.4)
Hiccups	1 (2.8)	2 (5.4)
Flushing	2 (5.5)	2 (5.4)
Fever	1 (2.8)	3 (8.1)
Weak	0	1 (2.7)
Chest pain	0	1 (2.7)

Table entries are numbers of patients (%). All entries have a P-value of >0.05.

DISCUSSION

The efficacy of ramosetron has been reported by several clinical trials performed in Japan (7,8). Noda et al. (7) conducted a Phase III clinical trial and found that ramosetron and granisetron were similarly effective in preventing acute nausea and vomiting. In this randomized, controlled, double-blind trial, the efficacy and safety of ramosetron were compared with those of granisetron in controlling acute and delayed emesis in patients receiving high doses ($\geqslant$70 mg/m^2) of highly emetogenic cisplatin chemotherapy. This study showed that ramosetron substantially improved the control of emesis 24 h after the completion of chemotherapy. Its efficacy and safety were similar to those of granisetron with respect to the number of emetic episodes over the 5 day study period. Each dose of the study drugs (ramosetron i.v. 0.3 mg and granisetron i.v. 3 mg) are at the same level as have been shown to be effective in Japanese patients (7). This result was in accordance with the study of Koizumi et al. (9) in which ramosetron and granisetron were found to have similar effectiveness for the suppression of emesis.

Cisplatin is regarded as a highly potent emetogenic agent causing a high incidence of both acute and delayed nausea and vomiting (1). In this study, the rate of prevention of acute emesis, or complete response, for ramosetron was 66.7% compared with 59.5% for granisetron. In contrast to findings for acute emesis, management of delayed emesis remains problematic, thus, in this study only about 52.8, 33.3, 27.8 and 30.6% of patients achieved control of nausea symptoms for Days 2 to 5 in the ramosetron group. The granisetron group had a complete response rate of 51.4, 29.7, 21.6 and 37.8% for control of delayed nausea for Days 2 to 5, similar to ramosetron. The same results were reported in the control of vomiting in both groups.

The main adverse events after administration of ramosetron and granisetron were dizziness, headache and flushing. All adverse events were mild and transient. The rate of side effects was similar in the two groups, except for dizziness, which appeared to have a higher incidence in the granisetron group.

CONCLUSION

The efficacy and safety profiles of ramosetron were similar to those of granisetron for the prevention of acute and delayed emesis in patients receiving cisplatin chemotherapy. However, this study fails to demonstrate the superiority of ramosetron to granisetron in response rate of acute and delayed emesis.

Acknowledgments

This study was supported by Yamanouchi (Thailand).

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