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A Randomized, Double-blind, Parallel, Comparative Study to Evaluate the Efficacy and Safety of Ramosetron plus Dexamethasone Injection for the Prevention of Acute Chemotherapy-induced Nausea and Vomiting

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Objective: To evaluate the efficacy of intravenous ramosetron plus dexamethasone for the prevention of acute chemotherapy-induced nausea and vomiting.
Methods: Cancer patients scheduled to receive chemotherapy containing either of the four drugs (cisplatin, doxorubicin, epirubicin or oxaliplatin) were enrolled. They were randomized to receive intravenous ramosetron 0.3 mg plus dexamethasone 20 mg or granisetron 3 mg plus dexamethasone 20 mg 30 min before chemotherapy on day 1. The primary efficacy parameter is complete response rate, which was defined by the proportion of patients without vomiting and no requirement for rescue drugs within 24 h after chemotherapy.
Results: A total of 285 patients were enrolled. The primary efficacy analysis included 274 patients. The complete response rate was 77.37% in the ramosetron 0.3 mg plus dexamethasone 20 mg group (137 patients) and 81.75% in the granisetron 3 mg plus dexamethasone 20 mg group (137 patients) with a difference of −4.38% (95% confidence interval: −14.64, 5.89). Therefore, non-inferiority of ramosetron 0.3 mg plus dexamethasone 20 mg to granisetron 3 mg plus dexamethasone 20 mg was demonstrated with non-inferiority margin −15%. For patients treated with cisplatin, non-inferiority of ramosetron 0.3 mg plus dexamethasone 20 mg to granisetron 3 mg plus dexamethasone 20 mg could not be demonstrated. Only a few patients required rescue medications, 7.3% in the ramosetron 0.3 mg plus dexamethasone 20 mg group and 5.1% in the granisetron 3 mg plus dexamethasone 20 mg group ($P = 0.44$). All 285 patients were included for safety analysis; 36.11% (52/144) and 23.40% (33/141) experienced at least one adverse event within 24 h in the ramosetron 0.3 mg plus dexamethasone 20 mg and granisetron 3 mg plus dexamethasone 20 mg groups, respectively. Four ramosetron-related adverse events among 144 patients were observed including two moderate elevation of liver enzymes and one each of mild hiccup and moderate skin rash.
Conclusions: The combination of ramosetron plus dexamethasone was an effective treatment to prevent acute chemotherapy-induced nausea and vomiting.

Key words: chemotherapy – ramosetron – granisetron – vomiting

INTRODUCTION

Cancer patients requiring chemotherapy were constantly suffering from serious and sometimes intolerable adverse reactions such as nausea and vomiting could reduce the willingness of patients to receive long-term cancer treatment (1). Consequently, prevention and/or quick relief of chemotherapy-induced nausea and vomiting (CINV) had become an important issue to improve the quality of life (2).

A variety of receptors including 5-hydroxytryptamine$_3$ (5-HT$_3$), neurokinin-1 and cholecystokinin-1, located in the central nervous system and in the afferent vagus nerve endings of the gastrointestinal tract, stand very important roles in CINV (3,4). Chemotherapy could release 5-HT$_3$ from the enterochromaffin cells to induce CINV (5–7). Therefore, CINV could be reduced significantly by 5-HT$_3$ antagonists (4,8,9).

The 5-HT$_3$ antagonists included ondansetron, granisetron and tropisetron (10–14). Ramosetron is a new antiemetic drug to treat CINV via the pharmacological mechanism of persistent, strong and selective 5-HT$_3$ receptor blockade (15–17).

The efficacy between ramosetron and granisetron in CINV had been studied in previous small cohort receiving cisplatin and demonstrated that both drugs had similar efficacy (18–20). Therefore, in this larger, double-blind, randomized study, we tried to compare the efficacy and safety between ramosetron plus dexamethasone and granisetron plus dexamethasone in preventing CINV including high and moderate emetogenic antineoplastic agents (8,9).

PATIENTS AND METHODS

This study was approved by the Institutional Review Board of each institution and designed as a registration, double-blind, parallel, active control for ramosetron plus dexamethasone injection in the treatment of preventing CINV. After screening visit (-14 to 0 days), eligible patients were randomly assigned to receive intravenous injection of ramosetron 0.3 mg plus dexamethasone 20 mg (RD) or granisetron 3 mg plus dexamethasone 20 mg (GD) at 30 min before the start of chemotherapy infusion on day 1. Ondansetron 24 mg was used as rescue drug when subject experienced more than two vomiting episodes (three or above vomiting episodes) after the start of chemotherapy.

From January 2006 to December 2007, consecutive adult cancer patients who were scheduled to receive emetogenic chemotherapy were enrolled in the study. Cancer patients, age between 20 and 74 years old (inclusive) of either sex, were eligible for the study if they receive either of the following chemotherapeutic agents by IV infusion, alone in one single dose or combined with other chemotherapy regimens: cisplatin $\geq$50 mg/m^2, with infusion time 2 h $\pm$ 10 min; doxorubicin $\geq$50 mg/m^2, with infusion time $\leq$1 h; epirubicin $\geq$60 mg/m^2, with infusion time $\leq$1 h; and oxaliplatin $\geq$65 mg/m^2, with infusion time 2 h $\pm$ 10 min. Subjects should not have symptoms of vomiting for at least 1 week before dosing trial medication and Eastern Cooperative Oncology Group (ECOG) performance status scale no greater than 2 (ECOG $\leq$2). The study was approved by the ethics committee of each participating institution and all the patients' written informed consent forms were obtained. Patients were not eligible for the study if they met any of the following criteria: patients had received radiotherapy to the abdomen or pelvis within 4 weeks before entering this study; patients had received chemotherapy including either one of four regimens, namely cisplatin, doxorubicin, epirubicin or oxaliplatin, within 6 months before entering the study; patients had known heart failure or myocardial infarction or with laboratory abnormalities at screening including serum creatinine more than two times of upper limit of normal range, aspartate transferase (AST) and alanine transferase (ALT) more than three times of upper limit of normal range; patients had known concurrent diseases that may cause vomiting, such as gastrointestinal tract obstruction, epilepsy, brain metastases, brain tumor or intracranial hypertension; patients had taken medications that could influence the outcome of the study within 3 days before entering the study, such as anti-epilepsy drugs, anti-emetics, anti-psychotics or adrenocorticoids; patients with a history of allergy or intolerance to ramosetron, granisetron or dexamethasone; female subject who was pregnant or breastfeeding; patients with life expectancy $<$3 months; and patients participated other investigational drug trial within 1 month before entering this study.

The primary objective was to evaluate complete response (CR) rate which was defined by the proportion of patients without vomiting and no requirement for rescue drugs the 24 h period after the start of chemotherapy. The date and time of all vomiting episodes were recorded on the patient's daily record card during the 24 h evaluation period. Patients recorded date and time of each episode of vomiting (exclusion of stomach contents through the mouth) or retching (a non-productive attempt to vomit), with distinct episodes defined as those separated by at least 1 min. The secondary efficacy endpoints were to evaluate during the first, second, third and fourth 6 h duration and the total 24 h period after the start of chemotherapy which included: (i) the proportion of patients with vomiting; (ii) the nausea degree evaluated by patient's 10 cm visual analogue scale (VAS); (iii) total control rate with no vomiting plus nausea VAS $<$ 0.5 cm; and (iv) the proportion of subjects had received rescue drug(s).

Statistical Methods

The study enrolled 288 subjects to collect 262 evaluable subjects. On the basis of previous studies, we assumed that the CR rate of two treatment groups was the same 75%. We set $\alpha = 0.05$ and non-inferiority margin of -15% and it is necessary to complete 262 evaluable subjects to achieve 80% statistical power to detect the non-inferiority hypothesis based on binomial test. The full analysis set (FAS) cohort was defined as all randomized patients who ever received trial medication. The analysis based on the FAS cohort was performed for all demographic data, efficacy parameters and safety parameters. The per-protocol set (PPS) cohort was defined as primary efficacy measurement, fulfill all entry criteria, not taking any prohibited medication(s).

Table 1. Patients' characteristics (safety analysis set)

	All groups ($n = 285$)	Ramosetron + dexamethasone ($n = 144$)	Granisetron + dexamethasone ($n = 141$)	*P* value[a]
Sex, *n* (%)				
Male	110 (38.6)	54 (37.5)	56 (39.7)	0.42
Female	175 (61.4)	90 (62.5)	85 (60.3)	
Age (years)				
Median (range)	51 (22–74)	51 (29–73)	51 (22–74)	0.92
ECOG status, *n* (%)				
0	108 (37.9)	50 (34.7)	58 (41.1)	
1	161 (56.5)	87 (60.4)	74 (52.5)	0.51
2	16 (5.6)	7 (4.9)	9 (6.4)	
Chemotherapy, *n* (%)				
Cisplatin	132 (46.3)	68 (47.2)	64 (45.4)	
Doxorubicin	87 (30.5)	41 (28.5)	46 (32.6)	0.75
Epirubicin	44 (15.4)	25 (17.4)	19 (13.5)	
Oxaliplatin	22 (7.7)	10 (6.9)	12 (8.5)	
Primary cancer type, *n* (%)				
Breast	123 (43.2)	63 (43.8)	60 (42.6)	0.24
Lung	83 (29.1)	48 (33.3)	35 (24.8)	0.05
Nasopharynx	16 (5.6)	6 (4.2)	10 (7.1)	0.22
Mouth	13 (4.6)	6 (4.2)	7 (5.0)	0.71
Rectum	13 (17.5)	4 (13.8)	9 (20.5)	0.12
Liver	12 (4.2)	2 (1.4)	5 (3.5)	0.56
Bladder	9 (3.2)	2 (1.4)	7 (5.0)	0.07
Stomach	8 (2.8)	2 (1.4)	6 (4.3)	0.11
Esophagus	3 (1.1)	2 (1.4)	1 (0.7)	0.61
Testis	2 (0.7)	2 (1.4)	0 (0.0)	0.16
Brain	2 (0.7)	1 (0.7)	1 (0.0)	0.97
Others	1 (0.4)	1 (0.7)	0 (0.0)	0.32

ECOG, Eastern Cooperative Oncology Group.
[a]CMH test stratified by center and cisplatin status for categorical data. ANOVA model with center and cisplatin status as fixed effects for continuous data.

The margin of non-inferiority, say −15%, was decided by the assumption that the CR rate of placebo plus dexamethasone was not more than 30% for the moderately to high emetogenic potential chemotherapies which used in this study. The margin was reasonable and sufficiently conservative, since it was less than the half of the difference between placebo and active control. The CR rate was analyzed by using the method of confidence interval based on pooled data, regardless of chemotherapy regimen. RD group was declared as non-inferior if the lower limit of the 95% two-sided confidence interval (based on normal approximation with continuity correction to the binomial distribution) for the difference in CR rate between the two treatments (RD group minus GD group) was greater than −15%. Besides, the Cochran–Mantel–Haenszel (CMH) test stratified by center and cisplatin status was also used for comparing the difference in CR rate between the two treatment groups. All statistical tests were two-tailed with $\alpha = 0.05$.

Demographic characteristics including gender and age were summarized by descriptive statistics (Table 1). Frequency table was presented for gender including counts and percentage, whereas mean, standard deviation, maximum, minimum, median, inter-quartile range and 95% two-sided confidence interval were provided for continuous variables. Cancer history and general medical history were also provided with frequency tables including counts and percentage.

Secondary efficacy endpoints, including the proportion of patients with vomiting, total control rate and incidence of receiving rescue drug(s), were analyzed by the CMH test stratified by center and chemotherapeutic regimen to compare the difference among the two treatment arms. The

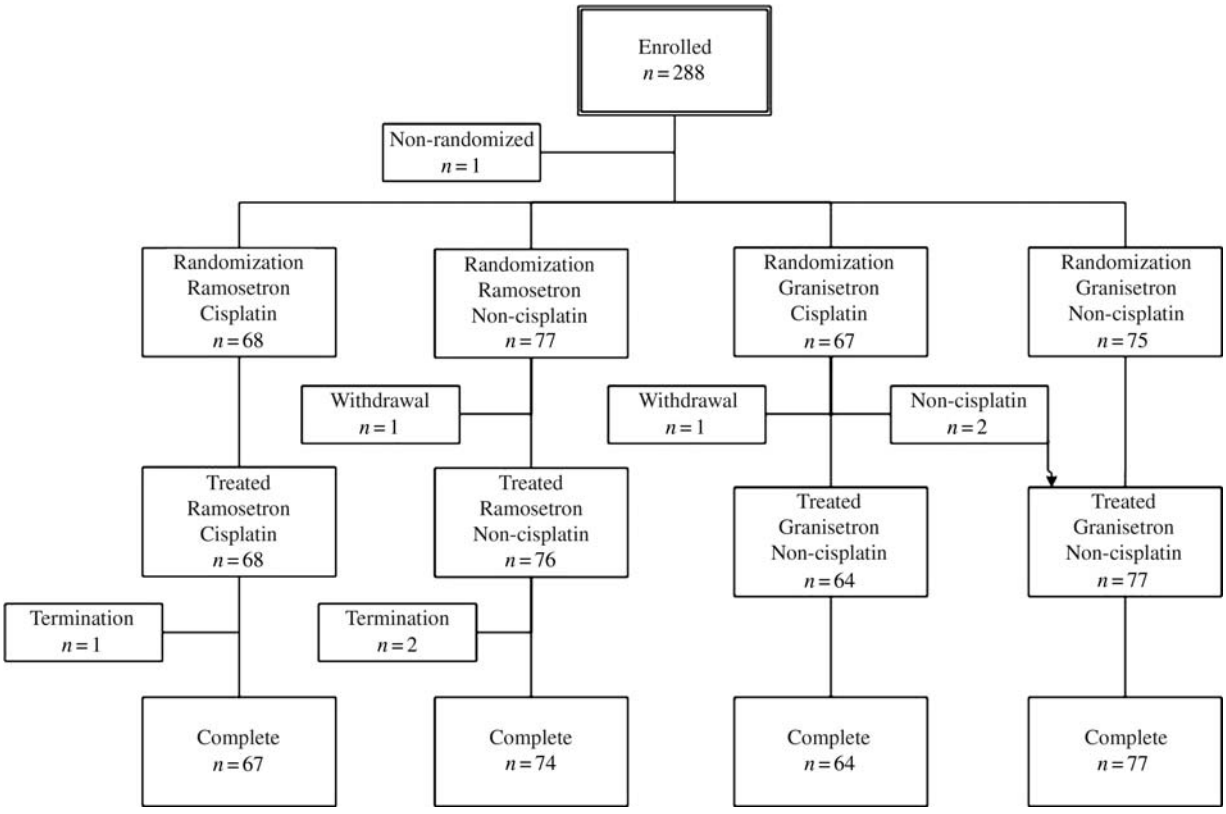

Figure 1. Description of patients' enrollment during the course of the study.

Table 2. Complete response rate during the first 24 h after chemotherapy (per-protocol set)

Patients group	RD ($n = 137$)	GD ($n = 137$)	Treatment difference	P value[a]
n (%) with CR	106 (77.37)	112 (81.75)	−4.38	0.33
95% CI	69.45, 84.08	74.25, 87.83	−14.64, 5.89	
Cisplatin group	$n = 62$	$n = 62$		
n (%) with CR	48 (77.42)	54 (87.10)	−9.68	0.13
95% CI	65.03, 87.07	76.15, 94.26	−24.63, 5.28	
Non-cisplatin group	$n = 75$	$n = 75$		
n (%) with CR	58 (77.33)	58 (77.33)	0.00	1.00
95% CI	66.21, 86.21	66.21, 86.21	−14.73, 14.73	

RD, ramosetron plus dexamethasone; GD, granisetron plus dexamethasone; CR, complete response; CI, confidence interval. 95% CI: exact method for response rate within each group, normal approximation with continuity correction to binomial distribution for treatment difference.
[a]CMH test stratified by center and cisplatin status, and Breslow-day test for homogeneity on per-protocol set.

number of vomiting and VAS of nausea were analyzed by using ANOVA with center and chemotherapeutic regimen as fixed effects for comparing the difference between two treatment groups. In the analysis of adverse events (AE), the Medical Dictionary for Regulatory Activities (MedDRA 10.0) AE dictionary was used to map verbatim AEs to preferred terms and system organ class. Descriptive statistics were provided for the incidence of AEs. Treatment groups were compared with respect to the proportion of subjects reporting treatment-emergent AEs both during the experimental period and within 7 days using Fisher's exact test. The severity (intensity) of each AE was rated mild as easily tolerated by the subject, causing minimal discomfort and not interfering with daily activities; moderate as sufficiently discomforting and was interfering with normal daily activities; and severe as preventing normal daily activities. A drug-related AE was defined as any event not present prior to exposure to study medication or any event already present, which worsened in either intensity or frequency following exposure to study medication. Since the study drug

Table 3. Analysis of proportion of patients with vomiting (per-protocol set)

	RD ($n = 137$)	GD ($n = 137$)	Treatment difference	P value[a]
First 6 h, *n* (%)	5 (3.65)	2 (1.46)	2.19	0.25
Second 6 h, *n* (%)	15 (10.95)	15 (10.95)	0.00	0.97
Third 6 h, *n* (%)	10 (7.30)	10 (7.30)	0.00	0.98
Fourth 6 h, *n* (%)	18 (13.14)	13 (9.49)	3.65	0.31
Total 24 h, *n* (%)	31 (22.63)	25 (18.25)	4.38	0.34
Cisplatin group	$n = 62$	$n = 62$		
First 6 h, *n* (%)	1 (1.61)	0 (0.00)	1.61	0.25
Second 6 h, *n* (%)	1 (1.61)	0 (0.00)	1.61	0.35
Third 6 h, *n* (%)	4 (6.45)	3 (4.84)	1.61	0.74
Fourth 6 h, *n* (%)	10 (16.13)	7 (11.29)	4.84	0.37
Total 24 h, *n* (%)	14 (22.58)	8 (12.90)	9.68	0.13
Non-cisplatin group	$n = 75$	$n = 75$		
First 6 h, *n* (%)	4 (5.33)	2 (2.67)	2.67	0.44
Second 6 h, *n* (%)	14 (18.67)	15 (20.00)	−1.33	0.81
Third 6 h, *n* (%)	6 (8.00)	7 (9.33)	−1.33	0.77
Fourth 6 h, *n* (%)	8 (10.67)	6 (8.00)	2.67	0.60
Total 24 h, *n* (%)	17 (22.67)	17 (22.67)	0.00	1.00

95% CI: exact method for response rate within each group, normal approximation with continuity correction to binomial distribution for treatment difference.
[a]CMH test stratified by center and cisplatin status.

Table 4. Analysis of the nausea visual analogue scale (centimeters) (per-protocol set)

	RD ($n = 137$)	GD ($n = 137$)	Treatment difference	P value[a]
0–6 h				
Mean	0.35	0.50	−0.15	0.21
95% CI	0.14, 0.57	0.29, 0.72	−0.38, 0.09	
Total 24 h				
Mean	0.90	0.87	0.03	0.91
95% CI	0.44, 1.36	0.42, 1.32	−0.47, 0.53	
Cisplatin group	$n = 62$	$n = 62$		
0–6 h				
Mean	0.02	0.13	−0.11	0.43
95% CI	−0.24, 0.29	−0.13, 0.39	−0.37, 0.16	
Total 24 h				
Mean	1.07	0.84	0.24	0.47
95% CI	0.43, 1.72	0.21, 1.46	−0.40, 0.88	
Non-cisplatin group	$n = 75$	$n = 75$		
0–6 h				
Mean	0.71	0.91	−0.20	0.34
95% CI	0.32, 1.10	0.51, 1.30	−0.61, 0.22	
Total 24 h				
Mean	0.85	0.98	−0.13	0.73
95% CI	0.14, 1.56	0.26, 1.69	−0.88, 0.62	

ANOVA model, dependent variable = center + (cisplatin status) + treatment group. Means are least square means based on ANOVA model.
[a]ANOVA model.

Table 5. Analysis of total control rate (per-protocol set)

	RD ($n = 137$)	GD ($n = 137$)	Treatment difference	P value[a]
Overall				
n (%) with TCR	76 (55.5)	79 (57.7)	−2.19	0.61
95% CI	46.75, 63.96	48.94, 66.05	−14.65, 10.28	
Cisplatin group	$n = 62$	$n = 62$		
n (%) with TCR	37 (59.7)	43 (69.4)	−9.68	0.20
95% CI	46.45, 71.95	56.35, 80.44	−28.05, 8.69	
Non-cisplatin group	$n = 75$	$n = 75$		
n (%) with TCR	39 (52.0)	36 (48.0)	4.00	0.65
95% CI	40.15, 63.69	36.31, 59.85	−13.32, 21.32	

TCR, total control rate. 95% CI: exact method for response rate within each group, normal approximation with continuity correction to binomial distribution for treatment difference.
[a]CMH test stratified by center and/or cisplatin status.

was used in combination with corticosteroids and all patients received chemotherapy subsequently, it was very difficult to differentiate the study drug-related AEs from other AEs. However, the side effects of both granisetron and ramosetron have been clearly delineated in previous studies (18–20). An AE considered to be drug-related was at the discretion of investigators by referring to the Investigator's Brochure.

RESULTS

Four centers enrolled a total of 288 patients in this study. One subject was not randomized to the study because his family refused to participate. The other 287 patients were eligible for the study and were randomized to one of the two treatment groups; 145 in the ramosetron group and 142 in the granisetron group. Among the 287 patients, 1 subject's ALT (131 U/l) was greater than three times of upper limit of normal range prior to the start of chemotherapy and was dropped out the study without administration of granisetron due to safety concern; the other one subject decided to withdraw her informed consent form before administration of ramosetron. These two patients were excluded from the FAS cohorts because of no study medication administered. Additionally, the clinical study was discontinued in three ramosetron-treated patients before completing 24 h evaluation period. However, these three patients were still included in FAS cohorts. In conclusion, a total of five patients prematurely discontinued the study (four in the RD group and one in the GD group). The comparison in discontinuation of the clinical study among treatment groups using Fisher's exact test revealed no bias among groups ($P = 0.3707$). Figure 1 demonstrates the disposition of patients.

Table 6. Summary of adverse events with incidence ≥1%

Events	Severity	Overall, $n = 285$ (%)	RD, $n = 144$ (%)	GD, $n = 141$ (%)	P value[a]
Upper abdominal pain	Mild	5 (1.75)	2 (1.39)	3 (2.13)	0.68
	Moderate	6 (2.11)	4 (2.78)	2 (1.42)	0.68
Constipation	Mild	21 (7.37)	6 (4.17)	15 (10.64)	0.04
	Moderate	24 (8.42)	14 (9.72)	10 (7.09)	0.52
Dyspnea	Mild	9 (3.16)	8 (5.56)	1 (0.71)	0.03
	Moderate	1 (0.35)	0 (0.00)	1 (0.71)	0.62
Hiccup	Mild	12 (4.21)	8 (5.56)	4 (2.84)	0.37
	Moderate	3 (1.05)	1 (0.69)	1 (0.71)	0.62
Anorexia	Mild	25 (8.77)	9 (6.25)	16 (11.35)	0.14
	Moderate	12 (4.21)	5 (3.47)	7 (4.96)	0.57
	Severe	1 (0.35)	1 (0.69)	0 (0.00)	1.00
Insomnia	Mild	17 (5.96)	8 (5.56)	9 (6.38)	0.81
	Moderate	10 (3.51)	8 (5.56)	2 (1.42)	0.10
Asthenia	Mild	11 (3.86)	4 (2.78)	7 (4.96)	0.37
	Moderate	4 (1.40)	1 (0.69)	3 (2.13)	0.37
Dizziness	Mild	11 (3.86)	5 (3.47)	6 (4.26)	0.77
	Moderate	4 (1.40)	2 (1.39)	2 (1.42)	1.00
Headache	Mild	11 (3.86)	4 (2.78)	7 (4.96)	0.37
	Moderate	5 (1.75)	3 (2.08)	2 (1.42)	1.00
ALT increased	Mild	6 (2.11)	3 (2.08)	3 (2.13)	1.00
	Moderate	2 (0.70)	3 (2.08)	1 (0.71)	1.00
AST increased	Mild	5 (1.75)	2 (1.39)	3 (2.13)	0.68
	Moderate	2 (0.70)	1 (0.69)	1 (0.71)	1.00
Anemia	Mild	2 (0.70)	1 (0.69)	1 (0.71)	1.00
	Moderate	5 (1.75)	4 (2.78)	1 (0.71)	0.37
Leukopenia	Mild	6 (2.11)	4 (2.78)	2 (1.42)	0.68
	Moderate	2 (0.70)	0 (0.00)	2 (1.42)	0.24
	Severe	4 (1.40)	4 (2.78)	0 (0.00)	0.12

ALT, alanine transferase; AST, aspartate transferase.
[a]Fisher's exact test.

During randomization procedure, two patients planned to receiving non-cisplatin chemotherapy were wrongly assigned to cisplatin stratum, and the randomization schedule in cisplatin stratum was used for treatment assignment. However, these two patients were included in the true strata, non-cisplatin chemotherapy, for data analysis. Of the total 285 treated patients, 11 patients (7 subjects in the RD group and 4 subjects in the GD group) were excluded from the PPS cohort because of protocol violations or deviations. After excluding the 11 subjects, the PPS cohort comprised a total of 274 subjects with 137 subjects in each of the two treatment groups.

The proportion of patients who achieved the CR during the 24 h period after chemotherapy is summarized in

Table 7. Summary of drug-related adverse events and laboratory changes (safety analysis set)

	Severity	Overall, $n = 285$ (%)	RD, $n = 144$ (%)	GD, $n = 141$ (%)	P value[a]
ALT elevation	Mild	1 (0.35)	0 (0.00)	1 (0.71)	1.00
	Moderate	1 (0.35)	1 (0.69)	0 (0.00)	
AST elevation	Mild	1 (0.35)	0 (0.00)	1 (0.71)	1.00
	Moderate	1 (0.35)	1 (0.69)	0 (0.00)	
Uric acid elevation	Mild	1 (0.35)	0 (0.00)	1 (0.71)	0.49
Constipation	Moderate	1 (0.35)	0 (0.00)	1 (0.71)	0.49
Hiccups	Mild	3 (1.05)	1 (0.69)	2 (1.42)	0.62
Skin rash	Moderate	1 (0.35)	1 (0.69)	0 (0.00)	1.00

[a]Fisher's exact test.

Table 2. The proportion of patients who achieve CR during the first 24 h after chemotherapy was 77.37% in the RD group and 81.75% in the GD group with the lower limit of the 95% confidence interval for the difference in CR rate being −14.64% which was above the pre-set non-inferiority margin, −15%. Thus, non-inferiority of RD to GD could be demonstrated for the prevention of CINV during the 24 h period after chemotherapy. For patients treated with cisplatin, non-inferiority of RD group to GD group with regard to CR was not demonstrated, and difference in CR rate between treatment groups was not statistically significant ($P = 0.13$), whereas in the non-cisplatin patients, the same CR rates were found among two treatment groups.

The proportion of patients with vomiting during the 6 and 24 h duration after the start of chemotherapy is summarized in Table 3. There were no significant differences in the proportion of patients with vomiting between the two groups. Table 4 summarizes the VAS of nausea scale of the two groups. The VAS of nausea scale at 6 h after chemotherapy was 0.35 and 0.50 cm for the RD and GD groups, respectively. After 24 h post-chemotherapy, the subjects reported 0.90 cm of the RD group and 0.87 cm of the GD group. At all the time period the nausea VAS evaluated, no statistically significant difference between the treatment groups was observed. Total control rate is given in Table 5. No difference between the two treatment groups could be found. In subgroup of non-cisplatin, the total control rate tended to be higher in the ramosetron group than in the granisetron group. The majority of patients did not take any rescue medication during the study period (RD vs. GD: 92.7 vs. 94.9%, $P = 0.44$).

AEs occurring in $\geq$1% of the patients in either treatment group are given in Table 6. During the study period, at least one AE was reported by 52 (36.11%) of the patients in the RD group and 33 (23.40%) of the patients in the GD group. Statistically significant difference between the two treatment groups was detected in the incidence of patients complaining of AEs. All drug-related AEs are summarized in Table 7. A total of seven (2.46%) patients experienced 10 drug-related AEs with three patients in the RD group and four patients in the GD group. Of the drug-related AEs, each one occurred within 24 h after administration of study medication. All the drug-related AEs were of mild or moderate severity. These included elevation of liver enzymes and uric acid, hiccup, skin rash and constipation. No statistical difference was detected among treatment groups. None of the subjects withdrew from the study prematurely due to the drug-related AEs.

DISCUSSION

Ramosetron is a recent member of the new class of selective 5-HT_3 receptor antagonists. It is a tetrahydrobenzimidazole derivative structurally independent of previously developed 5-HT_3 receptor antagonists (21). The structure of ramosetron results in more potent blocking of the 5-HT_3 receptor (15,16,18). In previous studies, the half-life of ramosetron was 5.78 ± 1.18 h, whereas that of granisetron was 3.14 ± 1.20 h. It might contribute that ramosetron has a longer duration of efficacy than does granisetron (18).

The proportion of patients achieving a CR was 77.37% of the RD group and 81.75% of the GD group. Non-inferiority of the RD group compared with the GD group was demonstrated. Subgroup analysis by chemotherapeutic regimen (cisplatin vs. non-cisplatin) showed that cisplatin patients tended to have higher CR rate than non-cisplatin patients. Non-inferiority of the RD to GD groups with regard to CR was also shown for non-cisplatin patients. Although, for cisplatin patients, non-inferiority of the RD to GD groups with regard to CR was not shown, difference in CR rate between treatment groups was not statistically significant ($P = 0.13$). Concerning the secondary efficacy parameters, the effects of the RD group were not significantly different from the GD group for nausea prevention and total control. Only a few patients required rescue medication during the 24 h period after the start of chemotherapy, 7.3% in the RD group and 5.1% in the GD group. In previous two studies which compared ramosetron and granisetron in the prevention of cisplatin-induced nausea and vomiting, the conclusions were that granisetron and ramosetron showed similar effectiveness for suppression of emesis (19,20). In our study, the effectiveness of ramosetron and granisetron was similar, not just in high emetogenic agent of cisplatin, but also in moderate emetogenic agents of non-cisplatin. Therefore, ramosetron could be used in all kinds of chemotherapeutic agents to get good control of CINV.

Both treatments were well tolerated, with no significant differences between groups. Most AEs were assessed as unlikely to be related to study medication and mild to moderate in intensity, but rather to the patient's underlying cancer or chemotherapeutic treatment. Constipation, anorexia, hiccups and insomnia were the AEs most frequently occurring in the two treatment groups. Although patients in the RD group

tended to experience little more AEs than patients in the GD group, incidence of adverse reactions (i.e. AEs considered to be treatment related) between the two groups was comparable. None of the deaths or serious AEs was assessed as related to the study medication.

In conclusion, the result of this study demonstrated that the RD group was non-inferior to the GD group in CR rate during the first 24 h after chemotherapy, especially in non-cisplatin patients, but not in cisplatin patients. Safety profile also showed a similar pattern in the treatment groups. It is thus recommended that in comparison to granisetron, a combination of ramosetron 0.3 mg plus dexamethasone 20 mg can be as an alternative given to prevent acute CINV.

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Conflict of interest statement

None declared.

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