Phase II Trial of Ramosetron Plus Dexamethasone in the Prevention of Cisplatin-Induced Nausea and Vomiting

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Objective: *To evaluate the clinical efficacy of ramosetron hydrochloride in the combination with dexamethasone for the prevention of nausea and vomiting induced by cisplatin.*
Material and Method: *Thirty in-patients with malignant tumor being treated with cisplatin at a dose of 70 mg/m2 or more for a total of 94 cycles were scheduled to receive ramosetron 0.3 mg IV given 30 minutes before chemotherapy and dexamthasone 20 mg IV on day 1 for the prevention of acute emesis and continued with ramosetron tablet 0.1 mg one tablet orally one hour before chemotherapy or in the morning in case of no chemotherapy scheduled and dexamethasone capsule 5 mg 2 capsules twice daily on day 2 to day 5 for the prevention of delayed emesis. The evaluation period started concomitantly with the start of chemotherapy (hour 0) and continued until 24 hours after completion of chemotherapy. The antiemetic efficacy of ramosetron plus dexamethasone was analyzed according to the occurrence of nausea and vomiting within 24 hours of treatment cycle. The study emphasized both on acute and delayed emesis control.*
Assessment: *The degree of severity of nausea was determined according to the following criteria: 0: None: nausea does not occur, 1: Mild: slight nausea but no disruption to daily acitivites, 2: Moderate: nausea and some disruption to daily activities, 3: Severe: extreme nausea and severe disruption to daily activities. The control of vomiting episodes was determined according to the frequency of vomiting (including retching) as the following criteria: Complete: 0 emesis episode, Major: 1-2 emesis episodes, Minor: 3-5 emesis episodes, Failure: > 5 emesis episodes.*
Results: *The result of all 94 cycles of the first day of treatment on acute emesis (0-24 hours) were none 80.9%, mild 18.1%, and moderate 1.1% for nausea episode. For the vomiting control were complete 81.9%, major 16%, minor 1.1% and failure 1.1% respectively. The efficacy of the prevention of delayed emesis (day 2 to day 5) for nausea episode were 67%, 66%, 70.2%, and 75.5% no nausea respectively. For the vomiting control were 75.5%, 74.5%, 86.2%, and 88.3% complete control on day 2 to day 5. No serious adverse events occurred. Hiccups, constipation, and dull headache were reported as the common side effects of ramosetron.*
Conclusion: *Ramosetron combined with dexamethasone is effective for the prevention of both acute and delayed emesis associated with cisplatin. The prevention of acute emesis seems to be more effective than the prevention of delayed emesis. Adverse events were mild. No serious side effects occurred in the present study.*

Keywords: *Ramosetron, Dexamethasone, Cisplatin-induced emesis*

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Chemotherapy-induced nausea and vomiting are unpleasant side effects that cause the most concern to patients receiving chemotherapy. These symptoms vary from slight nausea to protracted vomiting with physiological complications including dehydration electrolyte imbalance, which can significantly affect a patient's well being. Therefore, the goal of antiemetic therapy is to prevent emesis completely.

Over the last 20 years, substantial improvement in the control of chemotherapy induced nausea and vomiting has been demonstrated in many clinical

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trials. 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 receptor antagonists for use as an antiemetic agents. Several studies have shown the superiority of these agents to other antiemetics for prophylaxis of cisplatin-induced nausea and vomiting[1].

Ramosetron hydrochloride is a novel anti-emetic 5-HT_3 antagonist developed by Yamanouchi Pharmaceutical LTD. Ramosetron demonstrates potent and persistent prophylaxis of nausea and vomiting associated with emetogenic chemotherapy and appears to be at least as effective as ondansetron, the leading serotonin-3 antagonist in the group. Studies in a ferret model demonstrated that ramosetron has the duration of action ten times more than the action of granisetron and, therefore, is considered to be the long acting serotonin-3 antagonist. Initial studies suggested that the efficacy and safety of ramosetron was not dose-dependent above a dose of 0.6 mg[2]. It is widely used for the prevention of nausea and vomiting due to chemotherapy in Japan, Korea, the Republic of China and the Philippines. In the phase-III clinical comparative study in Japan, ramosetron (0.3 mg) injection was significantly more effective and had a better control of nausea and vomiting compared with Granisetron (50 mcg/kg)[3].

The present study was conducted to evaluate the clinical efficacy and safety profile of ramosetron 0.3 mg given intravenously combined with dexamethasone IV 20 mg before cisplatin on day 1 and ramosetron tablet 0.1 mg in the morning with dexamethasone capsule 5 mg two capsules given orally twice a day on days 2-5 in the prevention of acute and delayed nausea and vomiting induced by chemotherapy containing cisplatin regimen in Thai subjects.

Objective

To evaluate the clinical efficacy of ramosetron in the combination with dexamethasone for the prevention of nausea and vomiting associated with cisplatin.

Material and Method

Subjects

From February, 2003 to August, 2004 cancer patients being treated with cisplatin $\geq$ 70 mg/m^2 were scheduled to receive ramosetron 0.3 mg IV and dexamethasone 20 mg IV on day one given before cisplatin for the prevention of acute emesis. Cisplatin was administered only on the first day of cycle, either alone or in combination with other chemotherapeutic agents. On day 2-5, patients with no chemotherapy or only low emetic potential agents received oral ramosetron 0.1 mg daily in the morning and dexamethasone capsule (5 mg) 2 capsules twice daily.

Inclusion Criteria

1. Patients who agreed to participate in the present study and submitted written consent forms prior to the study.

2. Patients aged 20-70 years old with malignant disease.

3. Patients who received highly emetogenic antineoplastic agents (e.g. cisplatin $\geq$ 70 mg/m^2) either alone or in combination with other chemotherapy.

Exclusion criteria

1. Patients with cerebral edema, primary or secondary brain neoplasm with signs and symptoms of increased ICP and/or brain metastases.

2. Patients with concomitant disease, which may cause nausea and vomiting e.g. active peptic ulcer disease, gastric outlet obstruction, intestinal obstruction.

3. Patients with co-morbid illness including cardiac, renal, or hepatic diseases.

4. Patients receiving concomitant radiotherapy to any abdominal field within 24 hours before or 24 hours after anti-emetic treatment.

5. Pregnant patients and lactating patients (A pregnancy test must be performed on each female patient within two weeks of initiation of therapy and be negative).

6. Concomitant administration of other antiemetics or drugs with antiemetic activity (e.g. benzodiazepines).

7. Patients with anticipatory nausea and vomiting related to prior chemotherapy.

8. Patients with known hypersensitivity to any 5HT3-receptor antagonist.

Parameters of Observation

Definition of terms

♦ Vomiting - defined as expulsion of stomach contents.

♦ Retching - defined as an effort to vomit without expulsion of stomach contents.

♦ Acute emesis - defined as emesis occuring within 24 hours after receiving chemotherapy.

♦ Delayed emesis - defined as emesis takes place 24 to 48 hours after giving chemotherapy.

♦ Each will be considered emetic episodes. Emetic episode is separated by an interval of less than 5 minutes will be counted as a single episode.

♦ Vomiting and Nausea will be graded according to the NCI grading of toxicity. The time of occurrence of the first episode of vomiting/retching will also be noted.

Evaluation of Outcome Parameters

The evaluation period will start concomitantly with the start of the chemotherapy (hour 0), and it will continue until 24 hours after completion of the chemotherapy. Patients will be observed for the occurrence of nausea and vomiting within 24 hours after administration of the antiemetic and the chemotherapy regimen.

Clinical and Laboratory Assessment

Laboratory testing

Before the start of treatment in each cycle a full blood count, liver and kidney function tests were analyzed.

Parameters of observation

The subjective assessments should be made according to the following guidelines:

(1) Nausea

The degree of nausea for the 24-hour observation period is determined according to the following criteria.

0 None (Nausea does not occur)
1 Mild (slight nausea but no disruption of daily activities)
2 Moderate (nausea and some disruption of daily activities)
3 Severe (extreme nausea and severe disruption of daily activities)

(2) Vomiting/Retching

The frequency of vomiting (including retching) was recorded for 24 hours after the end of chemotherapy. The time of the occurrence of the first episode was also noted. A single vomiting episode was equivalent to a single retching episode. Vomiting and/or retching separated by less than a 5 minute interval was counted as a single episode.

Determine the frequency of vomiting (including retching) every 6 hours after administration of the study drugs (0-6, 6-12, 12-18, and 18-24 hours), and calculate the number of vomiting incidents 0-6 hours and 0-24 hours after administration.

Complete response 0 emetic episode
Major response 1-2 emetic episodes
Minor response 3-5 emetic episodes
Failure > 5 emetic episodes

Adverse events

All adverse events observed by the investigators or reported by the patients were recorded.

Statistical analysis

The pair t-test was used to compare pre and post treatment laboratory results. The antiemetic efficacy was expressed in number and percentage.

Results

Thirty patients were given 94 cycles of treatment. There were 19 males and 11 females with a mean age of 55.1 $\pm$ 10.16 years (23-69). Four patients received 6 cycles, 5 received 5, 5 received 4, 3 received 3, 2 received 2, and the remaining patients received only one cycle. The most common malignancy in the present study was lung cancer (63.3%), followed by liver cancer (13.3%) (Table 1).

Treatment Efficacy

A total of 30 patients were included in the present study. Response rate was evaluated for up to six cycles of treatment. The antiemetic efficacy of this antiemetic regimen was analysed according to degree of achievement in each day of treatment cycle. The authors emphasized on both acute and delayed emetic control. To evaluate the persistence of antiemetic efficacy the authors evaluated the results in every cycle of treatment for each patient.

For all 94 cycles of treatment, there were 80.9 percent complete control, 18.1 percent major control, and 1.1 percent moderate control for nausea episodes on the first day of cycle. For the vomiting control on the first day, there was 81.9 percent complete control, 16.0 percent major control, and 1.1 percent for both minor control and failure. On the second day of cycle, the percentage of complete control was 67.0 percent for nausea episode and 75.5 percent for vomiting episode. The percentage of major control was 28.7 percent for nausea episode and 21.3 percent for vomiting episode. There was 2.1 percent minor control for both nausea and vomiting episode. The failure rate was 2.1 percent for nausea episode and 1.1 percent for vomiting episode. After the second day, the percentage of complete control increased day by day for both nausea and vomiting episode.

Table 1. Patient characteristics

Total 30 patients	Number (percent)
Sex	
Male	19 (63.3%)
Female	11 (36.7%)
ECOG performance status	
0	15 (50.0%)
1	12 (40.0%)
2	3 (10.0%)
3	0
4	0
Primary tumor site	
Lung	19 (63.3%)
Liver	4 (13.3%)
Ovary	1 (3.3%)
Cervix	1 (3.3%)
Tongue	1 (3.3%)
Colon	1 (3.3%)
Breast	1 (3.3%)
Unknown	2 (6.7%)
Previous chemotherapy	9 (30.0%)
Previous radiotherapy	1 (3.3%)
Cisplatin dosage regimen	
80 mg	1 (3.3%)
90 mg	1 (3.3%)
100 mg	9 (30.0%)
110 mg	2 (6.7%)
120 mg	7 (23.3%)
130 mg	4 (13.3%)
140 mg	3 (10.0%)
150 mg	2 (6.7%)
160 mg	0
170 mg	1 (3.3%)

For acute emesis, there was only one case of failure for nausea control and no failure for vomiting. There was less antiemetic efficacy for delayed control as shown in Table 4-5. A few patients stopped the trial before completing the regimen; three cases failed to control both acute and delayed emesis, three patients had adverse drug reactions mostly from hiccups, three patients had progressive diseases and two patients died from the disease.

Acute Emesis

Table 2. Efficacy on the control of nausea on acute emesis

Grade of nausea	0-24 hours (n = 94)
0	76 (80.8%)
1	17 (18.1%)
2	1 (1.1%)
3	0

Table 3. Efficacy on the control of vomiting on acute emesis

Vomiting	0-24 hours (n = 94)
Complete control	77 (81.9%)
Major control	15 (16.0%)
Minor control	1 (1.1%)
Fail control	1 (1.1%)

Delayed emesis

Table 4. Efficacy on the control of nausea on delayed emesis according to treatment day

Grade of nausea	Day 2 (n = 94)	Day 3 (n = 94)	Day 4 (n = 94)	Day 5 (n = 94)
0	63 (67.0%)	62 (66.0%)	66 (70.2%)	71 (75.5%)
1	27 (28.7%)	27 (28.7%)	24 (25.5%)	22 (23.4%)
2	2 (2.1%)	2 (2.1%)	1 (1.1%)	0
3	2 (2.1%)	3 (3.3%)	3 (3.3%)	1 (1.1%)

Table 5. Efficacy on the control of vomiting on delayed emesis according to treatment day

Vomiting	Day 2 (n = 94)	Day 3 (n = 94)	Day 4 (n = 94)	Day 5 (n = 94)
Complete control	71 (75.5%)	70 (74.5%)	81 (86.2%)	83 (88.3%)
Major control	20 (21.3%)	21 (22.3%)	11 (11.7%)	9 (9.6%)
Minor control	2 (2.1%)	1 (1.1%)	0	0
Fail control	1 (1.1%)	2 (2.1%)	2 (2.1%)	2 (2.1%)

Table 6. Adverse events

Adverse event	No. of adverse events
1. Itching	2 (6.7%)
2. Dull headache	4 (13.3%)
3. Dyspepsia	2 (6.6%)
4. Edematous both legs	1 (3.3%)
5. Hypoglycemia	1 (3.3%)
6. Thrombocytosis	1 (3.3 %)
7. Hiccup	4 (13.3%)
8. Constipation	4 (13.3%)
9. Numbness of both hands	1 (3.3%)
10. Flushing	1 (3.3%)
11. Blurred vision	1 (3.3%)
12. Dizziness	3 (10.0%)

Adverse Events

No serious adverse events related to ramosetron occurred. Hiccups, constipation, and dull headache were reported in 4 patients and spontaneously recovered by the end of the cycle.

Discussion

The result of this open label study demonstrated that the combination of ramosetron and dexamethasone was effective for prevention of nausea and vomiting after the administration of cisplatin in doses greater than 70 mg/m^2, especially in the acute phase. In this present trial, there were 80.9 percent complete control for nausea episode and 81.9 percent complete control for vomiting episode on the first day of chemotherapy. This result showed that the response rate of ramosetron was enhanced by the addition of dexamethasone similar to other studies which stated that corticosteroids such as dexamethasone enhance the antiemetic efficacy of granisetron, ondansetron, and tropisetron[4-8]. For the continuing regimen, oral ramosetron and oral dexamethasone lead to a significant enhancement of efficacy in delayed emesis. In the present study, the percentage of complete control was 67 percent and major control was 28.7 percent for nausea episode. Simultaneously the percentage of vomiting control was 75.5 percent complete control and 21.3 percent major control. These results are in agreement with those of other studies of cisplatin-induced delayed emesis, which have shown combination treatment with intravenous ramosetron plus dexamethasone substantially enhanced control of emesis in the 24 hour period after the administration of cisplatin ($\geq$ 50 mg/m^2), and this improved response was still evident up to 72 hours after cisplatin adminstration with continued ramosetron plus dexamethasone therapy given orally on days 2 and 3[9].

The adverse effects of ramosetron in the present study were mild and transient. The common events included headache, dizziness, and constipation. The only probable drug-related side effect in the present study was hiccups in four patients. It persisted for 1-2 days and disappeared without any treatment. One patient reported thrombocytosis, hypoglycemia, and edematous of both legs. However, these side effects seem to be not related to the study drug.

In conclusion, the combination of ramosetron and dexamethasone was effective and safe for the prevention of both acute and delayed cisplatin-induced emesis.

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การศึกษาระยะที่ 2 แบบเปิดของยา ramosetron hydrochloride ร่วมกับ dexamethasone ในการป้องกันอาการคลื่นไส้และอาเจียนที่เกิดจาก cisplatin

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วัตถุประสงค์: เพื่อประเมินประสิทธิภาพ และความปลอดภัยของยา ramosetron hydrochloride ร่วมกับยา dexamethasone ในการป้องกันอาการคลื่นไส้และอาเจียนที่เกิดจาก cisplatin

สถานที่ทำการศึกษา: หน่วยมะเร็งวิทยา ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

รูปแบบการวิจัย: ศึกษาแบบเปิด

วัสดุและวิธีการ: ผู้ป่วยมะเร็งที่ได้รับยาเคมีบำบัด cisplatin ขนาดที่มากกว่า 70 มก./พื้นที่ผิว (ตารางเมตร)

วิธีการ: ผู้ป่วยมะเร็งจำนวน 30 ราย ได้รับยา ramosetron hydrochloride ขนาด 0.3 มก.ทางหลอดเลือดดำ 30 นาที ก่อนให้เคมีบำบัด cisplatin ร่วมกับ dexamethasone – ขนาด 20 มก. ทางหลอดเลือดดำ ในวันแรกของการให้ยาเคมีบำบัด เพื่อป้องกันอาการคลื่นไส้และอาเจียนชนิดเฉียบพลัน (acute emesis) หลังจากนั้นในวันที่ 2 ถึงวันที่ 5 ของการรับยาเคมีบำบัด คนไข้จะได้รับยา ramosetron ขนาด 0.1 มก. ชนิดรับประทาน 1 ชั่วโมงก่อนให้เคมีบำบัดหรือก่อนรับประทานอาหารเช้าในวันที่ไม่มีการรับยาเคมีบำบัด ร่วมกับยา dexamethasone ชนิดรับประทาน ขนาด 5 มก. 2 แคปซูล วันละ 2 ครั้ง เช้า-เย็น เพื่อป้องกันอาการคลื่นไส้และอาเจียน ชนิดต่อเนื่องยาวนาน (delayed emesis) การประเมินผลของยาจะบันทึกอาการคลื่นไส้และอาเจียนของคนไข้เป็นเวลา 24 ชั่วโมงทุกวัน โดยเริ่มบันทึกอาการเมื่อเริ่มให้ยาเคมีบำบัด การประเมินประสิทธิภาพของยาจะดูจากอาการคลื่นไส้ และอาเจียนที่เกิดขึ้นในระยะเวลา 24 ชั่วโมงของการรักษา

ผลการศึกษา: ผู้ป่วยจำนวน 30 ราย ได้รับยาเคมีบำบัดทั้งสิ้น 94 cycle เป็นผู้ชายจำนวน 19 ราย และผู้หญิงจำนวน 11 ราย อายุระหว่าง 23-69 ปี ชนิดของมะเร็งส่วนใหญ่เป็นมะเร็งปอด ร้อยละ 63.3 และมะเร็งตับ ร้อยละ 13.3 พบว่ายาสามารถป้องกันผู้ป่วยจากอาการคลื่นไส้ได้ร้อยละ 80.9 และป้องกันอาการอาเจียนชนิดเฉียบพลันอย่างสมบูรณ์ (complete response) ได้ร้อยละ 81.9 ป้องกันอาการคลื่นไส้ชนิดต่อเนื่องยาวนานได้อย่างสมบูรณ์ (complete response) ร้อยละ 67, 66, 70.2, และ 75.5 ในวันที่ 2 ถึงวันที่ 5 ตามลำดับ และป้องกันอาการอาเจียนชนิดต่อเนื่องยาวนาน ได้ผลอย่างสมบูรณ์ (complete response) ร้อยละ 75.5, 74.5, 86.2 และ 88.3 ในวันที่ 2 ถึงวันที่ 5 ตามลำดับ ไม่พบอาการไม่พึงประสงค์ที่รุนแรง คนไข้ทนต่อยาได้ดี อาการไม่พึงประสงค์ที่พบ คือ สะอึก ปวดศีรษะแบบตื้อ ๆ และท้องผูก

สรุป: ยา ramosetron ร่วมกับ dexamethasone มีประสิทธิภาพในการป้องกันอาการคลื่นไส้และอาเจียนที่เกิดจากเคมีบำบัด cisplatin ทั้งชนิดเฉียบพลันและชนิดต่อเนื่องยาวนาน คนไข้ทนต่อยาได้ดี ไม่พบอาการ ข้างเคียงที่รุนแรง