Comparison of Ondansetron-Dexamethasone-Lorazepam *versus* Metoclopramide-Dexamethasone-Lorazepam in the Control of Cisplatin Induced Emesis

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Abstract

The antiemetic effect of ondansetron-dexamethasone-lorazepam *versus* those of metoclopramide-dexamethasone-lorazepam were evaluated in 30 ovarian cancer patients undergoing treatment with the same chemotherapeutic regimen (cisplatin 60 mg/m^2 and cyclophosphamide 700 mg/m^2). Patients were randomly selected to receive either the ondansetron arm or the metoclopramide arm in their first cycle of chemotherapy, but were given an alternative combination in the second cycle. In the ondansetron arm, ondansetron was given 8 mg intravenously (IV) plus dexamethasone 20 mg IV and lorazepam 0.5 mg oral. For the metoclopramide arm, metoclopramide 10 mg was given IV plus dexamethasone 20 mg IV and lorazepam 0.5 mg oral. All antiemetics were given twice ; 30 minutes before and 6 hours after chemotherapy. In the metoclopramide arm, metoclopramide 40 mg continuous infusion was also administered. During the acute phase, the ondansetron combination was significantly superior to the metoclopramide combination for all evaluation parameters. Complete control of emesis was 90 per cent *vs* 36.7 per cent, complete protection from nausea was 80 per cent *vs* 43.3 per cent, and complete protection from both nausea and vomiting was 73.3 per cent *vs* 30.0 per cent. Forty per cent of patients in the ondansetron arm did not complain of any adverse reaction compared to 13.4 per cent in the metoclopramide arm. It can be concluded, therefore, that a combination of ondansetron, dexamethasone and lorazepam appears to provide a significantly better emetic control with less adverse reaction than the metoclopramide combination in the acute nausea-vomiting phase after receiving cisplatin.

Key word : Cisplatin, Emesis, Ondansetron, Metoclopramide

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Nausea and vomiting are distressing side effects of chemotherapy. These associated side effects affect the quality of life and willingness to continue with the treatment. Cisplatin is one of the most commonly used chemotherapies and has a highly emetogenic effect. All patients vomited during 24 hours after the administration of high dose cisplatin unless antiemetic agents were given[1]. With the best conventional antiemetic treatment such as a combination of metoclopramide, dexamethasone and benzodiazepine, cisplatin induced emesis was controlled in only 60 per cent of the patients[2]. Moreover, a high dose of metoclopramide causes a distressing extrapyramidal reaction[2,3]. Ondansetron, a highly selective 5-HT3 receptor antagonist, has shown promise as an effective antiemitic agent in patients receiving both cisplatin and non-cisplatin chemotherapy[4-6]. The antiemetic effect of ondansetron appears to be enhancing and more comfortable with the addition of dexamethasone[7-9] and lorazepam[9].

Many studies have evaluated the efficacy of ondansetron in comparison with metoclopramide in patients receiving cisplatin[10-17]. However, nearly all of these studies compared the antiemetic effect in patients receiving different doses and schedules of cisplatin. They usually controlled only the dose in wide ranges of cisplatin such as 50-100 mg/m^2 or $\geq$ 50 mg/m^2, etc, and cisplatin could be given either as a single agent or combined with other cytotoxic drugs. As we know, the emetogenic effect of chemotherapy and its control depend on many factors including those inherent to the patients (such as age, gender, history of chemotherapy and alcohol use) and those related to the chemotherapeutic regimen (such as agent, dose, route and schedule of chemotherapy)[18]. Hence ; to know the exact efficacy of an ondansetron combination regimen in comparison to a metoclopramide combination regimen, we conducted a randomized crossover study comparing these 2 antiemetic regimens in chemotherapy-naived ovarian cancer patients receiving the same dose and schedule of cisplatin and cyclophosphamide.

PATIENTS AND METHOD

Thirty patients with newly diagnosed common epithelial ovarian cancer after operation who were chemotherapy-naived were included in this study. These patients were scheduled to receive the same dose of cisplatin 60 mg/m^2 and cyclophosphamide 700 mg/m^2 every 4 weeks for at least 2 cycles. To meet the criteria for inclusion, no patients could have a severe illness other than ovarian cancer, other causes of vomiting such as central nervous system metastasis or gut obstruction, concurrent use of corticosteroid, benzodiazepine or other antiemetics.

These patients were randomized to receive either 8 mg of intravenous ondansetron or 10 mg of metoclopramide 30 minutes before and 6 hours after chemotherapy in the first cycle. In the metoclopramide arm, patients also received 40 mg of metoclopramide continuous infusion for 4 hours starting at the same time as cisplatin chemotherapy. At the second cycle of chemotherapy, administered at the same dose and schedule, patients were crossed to receive the alternative antiemetic regimen. Both antiemetic regimens were given together with 20 mg of intravenous dexamethasone and 0.5 mg oral lorazepam 30 minutes before and 6 hours after chemotherapy. All patients were monitored for nausea and vomiting in the hospital for 24 hours.

The efficacy of the antiemetic treatment was assessed during the 24 hours after chemotherapy and was based on the number of emetic episodes, the time to first emesis, and the intensity of nausea. A single emetic episode was defined as any vomiting that produced liquid or 1-5 retches within 5 minutes. Emetic episodes were separated from each other by the absence of vomiting or retching for at least 5 minutes. The absence of emesis was defined as complete control ; 1 or 2 episodes as major control ; 3-5 as partial control ; more than 5 as no control. The time to first emesis was calculated as the time between the beginning of cisplatin infusion and the first emetic episode. Nausea was recorded according to a grading scale : 0 none; 1 mild (did not interfere with normal daily life) ; 2 moderate (interfered with normal daily life) ; 3 severe (bedridden because of nausea). Complete protection of nausea and vomiting was defined as absence of both emesis and nausea.

Side effects were assessed by general questioning of the patients. Following the second cycle of chemotherapy the patients were asked to indicate their preference for one or the other of the antiemetic treatments.

Chi-squares or Fisher's exact test where applicable were used to analyze patients' characte-

ristics, the result of antiemetic treatment and side effects of the treatment. All tests were two tailed and $p \leq 0.05$ was considered significant.

RESULTS

All 30 patients completed two cycles of chemotherapy at the same dose and schedule. Fourteen patients were randomized to receive the ondansetron combination regimen while 16 received the metoclopramide combination regimen in their first cycle. Their characteristics and histology of ovarian cancer are reported in Table 1, which were balanced between the two groups.

The ondansetron combination regimen was significantly superior to the metoclopramide combination regimen for all evaluation parameters. Complete control of emesis was obtained in 90 per cent in the ondansetron arm and 36.7 per cent in the metoclopramide arm. Moreover, 100 per cent of those in the ondansetron arm achieved complete or major control of emesis compared to 70 per cent in the metoclopramide arm (Table 2). The median time to first emesis was 14 hours (range 5-15.3 hours) in the ondansetron arm and 5.5 hours (range 0.5-13 hours) in the metoclopramide arm. This difference was statistically significant (p=0.004).

Table 1. Patient characteristics and histology of ovarian cancer.

Patient characteristics	Ondansetron arm first		Metoclopramide arm first		P-value
Number of patients	14		16		
Age (years)					
Median (Range)	50 (40-63)		48 (26-69)		0.5
		%		%	
21-30	-		1	6.3	0.5
31-40	1	7.1	4	25.0	
41-50	6	42.9	4	25.0	
51-60	4	28.6	4	25.0	
61-70	3	21.4	3	18.7	
History of alcohol use					
No history of alcohol use	14	100	15	93.7	0.5
History of occasional drinking	-		1	6.3	
Histology of ovarian cancer					
Serous cystadenocarcinoma	4	28.6	7	43.7	0.7
Mucinous cystadenocarcinoma	6	42.9	5	31.3	
Endometrioid carcinoma	2	14.3	3	18.7	
Clear cell carcinoma	1	7.1	1	6.3	
Mixed epithelial carcinoma	1	7.1	-		

Table 2. Efficacy of treatment.

	Ondansetron arm		Metoclopramide arm	
	Number	%	Number	%
Control of emesis (p value < 0.0001)				
Complete control	27	90.0	11	36.7
Major control	3	10.0	10	33.3
Partial control	-	-	8	26.7
No control	-	-	1	3.3
Intensity of nausea (p value = 0.003)				
None	24	80.0	13	43.3
Mild (do not interfere with normal daily life)	4	13.3	6	20.0
Moderate (interfere with normal daily life)	2	6.7	6	20.0
Severe (bed ridden because of nausea)	-	-	5	16.7
Protection of nausea and vomiting (p value = 0.0007)				
Complete protection	22	73.3	9	30.0
Incomplete protection	8	26.7	21	70.0
Number of patients	30	100	30	100

Complete protection from nausea was 80 per cent in the ondansetron arm compared to 43.3 per cent in the metoclopramide arm. Complete protection from both nausea and vomiting was also significantly greater in patients treated with the ondansetron combination (73.3%) than in those receiving the metoclopramide combination (30%).

Table 3 shows the distribution of complete protection from both nausea and vomiting by the sequence of treatment. This table shows that 9 of 14 patients who received the ondansetron combination in their first cycle achieved complete control. Of these 9; 3 also obtained complete control from the metoclopramide combination. Regarding 16 patients who received the metoclopramide combination in their first cycle, only 5 had complete control and 4 of these 5 also obtained complete protection from the ondansetron combination in the next cycle. Interestingly, 9 of 11 patients who did not achieve complete control from metoclopramide in their first course achieved complete control in their second cycle with the ondansetron combination regimen.

At the end of the study; all but one expressed a treatment preference. Twenty-eight chose the ondansetron combination regimen while only one preferred the metoclopramide combination. This difference was statistically significant.

The side effects considered to be related to antiemetic treatment are shown in Table 4. Forty per cent of those taking the ondansetron arm had no side effects compared to 13.4 per cent in the metoclopramide arm. The common side effects were sedation and headache in both regimens which was not much different. However, 1 patient in the metoclopramide arm experienced acute dystonia and another one had diarrhea during treatment. These two side effects were not found in the ondansetron arm.

DISCUSSION

Ondansetron, as a single agent, has proved to be more effective than single agent metoclopramide for acute phase nausea and vomiting from cisplatin[10-13]. Dexamethasone enhanced the antiemeitc effect of both ondansetron[7-9] and metoclopramide[19-21]. Lorazepam, in addition to both ondansetron[9] and metoclopramide[22], also helped the patients to be more comfortable and less restless. Hence, it is curious whether ondansetron combined with other agents has more efficacy than the metoclopramide combination.

Table 3. Complete protection from both nausea and vomiting by sequence of treatment.

Sequence of treatment	C -> C	C -> I	I -> C	I -> I
Ondansetron arm -> Metoclopramide arm	3	6	1	4
Metoclopramide arm -> Ondansetron arm	4	1	9	2

C = Complete protection from both nausea and vomiting
I = Incomplete protection from both nausea and vomiting

Table 4. Side effects.

Antiemetic regimen	Ondansetron combination (n=30)		Metoclopramide combination (n=30)		P-value
Side effect	Number	%	Number	%	
No adverse effect	12	40.0	4	13.4	0.019*
Sedation	17	56.7	19	63.4	1.000
Headache	7	23.4	7	23.4	0.60
Constipation	3	10.0	2	6.7	0.64
Diarrhea	-	-	1	3.3	0.31
Acute dystonia	-	-	1	3.3	0.31

* Some patients had more than 1 side effect

A randomized Italian study[14,15] in patients receiving cisplatin (as a single agent or in combination with other agents) at dose of $\geq$ 50 mg/m^2 demonstrated that ondansetron and dexamethasone regimen was more effective and better tolerated than metoclopramide - dexamethasone - diphenhydramine combination, complete protection against emesis was achieved in 78.7 per cent in the ondansetron arm compared to 59.5 per cent in the metoclopramide arm ($p < 0.002$).

Navari's study[16] compared ondansetron-dexamethasone-lorazepam with metoclopramide-dexamethasone-diphenhydramine-lorazepam in patients receiving 70-100 mg/m^2 cisplatin (as a single agent or in combination with other agents). Complete control of emesis was achieved in 37 of 40 patients receiving the ondansetron arm compared to 36 of 40 in the metoclopramide arm which was not significantly different. However, considering the major control of emesis (0-1 episode); the ondansetron arm was more effective since another 3 patients of the ondansetron arm had only 1 episode of nausea/vomiting, while 4 patients in the metoclopramide arm had more than 1 episode.

In contrast to these two studies, Fanning[17] could not demonstrate the superiority of the ondansetron regimen. Forty per cent of the metoclopramide arm (metoclopramide-diphenhydramine-proclorperazine-lorazepam) developed severe vomiting (> 5 episodes) compared to 65 per cent in the ondansetron arm (ondansetron-dexamethasone-proclorperazine-lorazepam) in patients receiving cisplatin 70 mg/m^2 in combination with carboplatin 100 mg/m^2 ($p = 0.5$).

However, our study proved that ondansetron in combination with dexamethasone and lorazepam has significantly more efficacy in the protection of acute nausea and vomiting from cisplatin than metoclopramide-dexamethasone-lorazepam. In those who vomited, patients receiving the ondansetron regimen had a significantly later onset of vomiting which is concordant with other studies [10,14].

Our study tried to control the factors that affect the emetogenic effect of chemotherapy such as sex, history of chemotherapy use, dose and schedule of chemotherapy. All of our patients were female patients with ovarian cancer who were chemotherapy-naived and receiving the same dose of cisplatin 60 mg/m^2 and cyclophosphamide 700 mg/m^2. Furthermore, we used a crossover design to avoid interpatient variability in other factors such as age and history of alcohol use. Moreover, patients' treatment preference could thus be expressed and nearly all of our patients chose the ondansetron combination. In a crossover study, the carry-over effect may interfere, however, such an effect was not seen in our study.

Considering the adverse effects, the ondansetron combination had a significantly less adverse effect than the metoclopramide combination. Some studies have claimed that headache was an ondansetron-related side effect[10,16] and occurred more commonly in patients receiving ondansetron[10]. Our study, like others[11,14], showed that the incidence of headache was not significantly different between ondansetron- or metoclopramide- treated patients. No patient in the ondansetron arm had an extrapyramidal side effect or diarrhea.

In conclusion, ondansetron-dexamethasone-lorazepam is more efficacious than metoclopramide-dexamethasone-lorazepam in preventing the acute phase of both nausea and emesis from cisplatin with less adverse effect.

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ประสิทธิภาพของ Ondansetron–dexamethasone–lorazepam เปรียบเทียบกับ Metoclopramide–dexamethasone–lorazepam ในการป้องกันอาการคลื่นไส้อาเจียนจาก Cisplatin

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การศึกษานี้ได้เปรียบเทียบประสิทธิภาพในการป้องกันอาการคลื่นไส้ อาเจียน ของ ondansetron–dexamethasone–lorazepam กับ metoclopramide–dexamethasone–lorazepam ในผู้ป่วยมะเร็งรังไข่ 30 ราย ที่ได้รับเคมีบำบัดชนิดและปริมาณเท่ากันคือ cisplatin 60 มก/ม^2 และ cyclophosphamide 700 มก/ม^2 ผู้ป่วยจะได้รับการสุ่มเลือกว่า ในครั้งแรกของการให้เคมีบำบัดจะได้รับ ondansetron arm หรือ metoclopramide arm และจะได้ยาต้านอาเจียนอีกชนิดหนึ่งในการให้เคมีบำบัดครั้งต่อไป การให้ ondansetron combination จะให้ ondansetron 8 มก และ dexamethasone 20 มก ทางเส้นเลือดดำ ร่วมกับรับประทาน lorazepam 0.5 มก การให้ metoclopramide combination จะให้ metoclopramide 10 มก และ dexamethasone 20 มก ทางเส้นเลือดดำ ร่วมกับรับประทาน lorazepam 0.5 มก ยาต้านอาเจียนทุกชนิดจะให้ 2 ครั้ง คือ 30 นาทีก่อน และ 6 ชั่วโมงหลังการให้เคมีบำบัด ในรายที่ให้ metoclopramide combination จะให้ metoclopramide 40 มก ทางเส้นเลือดดำช้า ๆ ด้วย การศึกษานี้พบว่า ondansetron combination มีประสิทธิภาพดีกว่า metoclopramide combination ทั้งการป้องกันไม่ให้เกิดการอาเจียน 90% *vs* 36.7% การป้องกันไม่ให้มีอาการคลื่นไส้ 80% *vs* 43.3% การป้องกันไม่ให้มีทั้งอาการคลื่นไส้และอาเจียน 73.3% *vs* 30.0% ผู้ป่วยที่ได้รับ ondansetron combination ไม่มีอาการข้างเคียง 40% เทียบกับ 13.4% ในรายที่ได้รับ metoclopramide combination โดยสรุปพบว่า ondansetron–dexamethasone–lorazepam มีประสิทธิภาพในการป้องกันอาการคลื่นไส้อาเจียนจาก cisplatin ในช่วง 24 ชั่วโมงแรก ดีกว่า metoclopramide–dexamethasone–lorazepam อย่างมีนัยสำคัญทางสถิติ และมีอาการข้างเคียงน้อยกว่า

คำสำคัญ : Cisplatin, อาการคลื่นไส้–อาเจียน, Ondansetron, Metoclopramide

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