

Intravenous Ondansetron plus Intravenous Dexamethasone with Different Ondansetron Dosing Schedules during Multiple Cycles of Cisplatin-based Chemotherapy

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Background: This study examined whether different ondansetron dosing schedules plus dexamethasone influenced antiemetic efficacy during multiple cycles of cisplatin-based chemotherapy (CT). Antiemetic activities between previous CT and subsequent cycles were compared.

Methods: The cross-over study involved 424 patients. Arm A, three doses of 8 mg ondansetron given intravenously (IV) at 4-hourly intervals plus dexamethasone 20 mg IV at the start of CT, followed by dexamethasone 5 mg IV every 12 hours. Arm B, as arm A but the three doses of 8 mg ondansetron were given at 24-hourly intervals. For those with complete protection from emesis in both arms, a single dose of 8 mg ondansetron (arm C) was tried during the following CT. Once complete protection of emesis could not be maintained, arm A regimens were administered in the subsequent cycles of CT.

Results: There were 384, 377 and 147 patients in arm A, arm B and arm C, respectively. Complete control of acute and delayed nausea/vomiting obtained in arm A were 91.4%/94.8% and 59.6%/70.1%, and in arm B were 90.4%/92.3% and 61.3% 72.7%. There was no significant difference in antiemetic efficacy between both arms. Decreased incidence of and delayed onset of nausea on day 2 were observed in arm B ($p = 0.002$). The emetic severity during previous CT correlated significantly with those of the subsequent CT. The complete control of nausea/vomiting was maintained in 81.6%/72.1% of arm C patients during the following 3rd-6th cycles of CT.

Conclusion: No difference in antiemetic efficacy was shown when a triple 8 mg dose of ondansetron was given at 4-hourly intervals or at 24-hourly intervals. However, the latter improved nausea on day 2. A single 8 mg dose of ondansetron can maintain antiemetic efficacy in the majority of complete responders in arm A and arm B.

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Key words: chemotherapy, cisplatin, emesis, 5-HT₃ antagonist, dexamethasone, ondansetron

The three-drug combination of a 5-hydroxytryptamine-3 (5-HT₃) receptor antagonist, dexametha-

sone and aprepitant is recommended before chemotherapy (CT) of high emetic risk. The three-

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drug combination of a 5-HT₃ receptor antagonist, dexamethasone and aprepitant is also recommended for patients receiving a combination of anthracycline and cyclophosphamide. For patients receiving other CT of moderate emetic risk, the two-drug combination of a 5-HT₃ receptor antagonist and dexamethasone is recommended. The complete protection rate for acute emesis is about 70%-90% after a cisplatin-based regimen.⁽¹⁻⁶⁾ Delayed emesis remains an unresolved problem and a challenge to oncologists. Despite the use of the most efficacious antiemetic therapy for cisplatin-treated patients, only about half of them achieve complete control of emesis.^(1,2,7-12)

Cancer patients usually receive multiple cycles of CT. However, data on maintained effectiveness of antiemetics in repeated consecutive cycles is lacking.⁽¹⁴⁻¹⁸⁾ Antiemetic efficacy seems to decrease with consecutive cycles of CT.⁽¹⁴⁻¹⁹⁾ Poor emetic control during previous CT has been correlated with nausea and vomiting during subsequent CT.^(16,18-20) However, these correlations are seldom addressed in the literature.⁽¹⁹⁾

We conducted this prospective study with different intravenous ondansetron dosing schedules for the control of cisplatin-induced emesis during multiple cycles of CT. Whether the different ondansetron dosing schedules significantly influenced antiemetic efficacy was examined.

METHODS

Patients

All patients in this study were scheduled to receive at least 50 mg/m² of cisplatin followed immediately by a continuous infusion of 5-fluorouracil (5-FU) with or without other chemotherapeutic agents (Table 1). Eligibility criteria included the following characteristics: age of at least 16 years, no prior experience of cisplatin-containing CT and an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. Exclusion criteria included any other concurrent severe illness, nausea or vomiting in the 24 hours before CT, other known causes of nausea or vomiting (e.g. central nervous system metastases, gastrointestinal obstruction, hypercalcemia), or concurrent therapy with corticosteroids or benzodiazepines (unless given for night sedation). All patients were hospitalized during CT administration.

Table 1. Characteristics of Patients

	Arm A (n = 384)	Arm B (n = 377)
Sex		
Male	249	243
Female	135	134
Age group		
15-49 years	129	125
50-64 years	133	128
65-82 years	122	124
Performance status		
0 or 1	361	351
2	23	26
Previous non-cisplatin chemotherapy		
No	356	349
Yes	28	28
Primary tumor		
Lung, mediastinum	30	27
Breast	28	28
Head and neck	60	60
Genitourinary	144	139
Gastrointestinal	98	98
Other	24	25
Chemotherapy regimen and daily dose (mg/ m ²)		
F1000 D1-4 or 5 / P 100 D1	19	18
F1000 D1-4 or 5 / P 75 D1	13	12
F1000 D1-3 / B 10 D2-3 / P 50 D1	40	42
F1000 D1-3 / M 6 D1 / P 50 D1	88	90
F500 D1-3 / L 30-35 D1-3 / P 50 D1	137	130
F500 D1-3 / L 30-35 D1-2 / Ep 30 / P 50 D1	35	39
F500 D1-3 / L 30-35 D1-2 / M 6 D1 / P 50 D1	28	23
F500 D1-3 / L 30-35 D1-2 / E 60 D1-2 / P 60 D1	24	23

Abbreviations: F: 5-Fluorouracil; P: Cisplatin; B: Bleomycin; M: Mitomycin; Ep: Epirubicin; E: Etoposide; L: Leucovorin; D: day.

Antiemetic therapy

This was a single institution study. A crossover design was conducted. The same CT drug was used during both courses using identical doses. Patients were assigned to one of two antiemetic treatments (arm A or arm B) according to their registration number (odd or even number) during the first cycle of CT. The antiemetic treatment for each patient crossed to the other form during the second cycle of CT.

Those who were registered as an odd number were scheduled to receive arm A first. Each CT cycle consisted of cisplatin 50 to 100 mg/m², dexamethasone 20 mg and 20% mannitol 100-150 ml administered in 500 ml of 5% dextrose in normal saline

(D₅S) for 3 hours. Ondansetron (Zofran; GlaxoWellcome Inc, Victoria, Australia) 8 mg in 100 ml dextrose was given as a 15 minute intravenous infusion starting 30 minutes before cisplatin administration, followed by ondansetron intravenous infusion every 4 hours for a total of three doses. In addition, all patients received 5 mg intravenous dexamethasone every 12 hours after cisplatin administration, and the drug was discontinued after the completion of CT.

Those who were registered as an even number were scheduled to receive arm B first. Dexamethasone was given as in Arm A. Ondansetron 8 mg in 100 ml dextrose was given as a 15 minute intravenous infusion starting 30 minutes prior to cisplatin, followed by ondansetron intravenous infusion 24 and 48 hours after cisplatin administration for a total of three doses.

We divided patients into 2 groups according to their antiemetic response, not complete responders and complete responders, after the completion of both treatment arms. Not complete responders defined those with either nausea or vomiting in arm A or arm B, and they were scheduled to receive arm A in the following cycle of CT. Complete responders defined those with neither nausea nor vomiting in both arms, and they were scheduled to receive arm C.

In arm C, dexamethasone was given as in arm A and arm B. Only a single dose of Ondansetron 8 mg in 100 ml dextrose was given as a 15 minute intravenous infusion starting 30 minutes prior to cisplatin. Those who failed to achieve complete prevention of nausea and vomiting in arm C were treated as in arm A in the following cycles of CT.

Intramuscular (IM) prochlorperazine was allowed to be given to patients for antiemetic rescue in both treatment arms. The rescue dose of prochlorperazine was 5 mg every 6 hours as needed.

Response assessment

Data concerning nausea and vomiting were recorded daily by the investigators (physicians and nurses) beginning when patients were admitted. Patients were requested to record their symptoms during the days after discharge. An emetic episode was defined as a vomit or a retch, or any number of continuous vomits or retches (not separated by at least 1 minute). Efficacy of therapy on vomiting was

defined as follows: complete response, no emetic episodes; major response, one to two emetic episodes; minor response, three to five emetic episodes; and failure, more than five emetic episodes. The patients assessed the severity of nausea with the following descriptions: (1) none; (2) mild, did not interfere with daily life; (3) moderate, interfered with daily life; and (4) severe, bedridden because of nausea. Analyses of nausea and vomiting were performed separately for day 1 (acute episodes) and days 2-6 (delayed episodes). The severity of delayed vomiting was based on the total number of emetic episodes recorded during the period. The intensity of delayed nausea was recorded as the worst nausea experienced during days 2-6.

Complete responders (arm C) were investigated for the maintenance of antiemetic efficacy in the following CT cycles according to the above definitions of response.

Statistical methods

Analyses of nausea and vomiting were done separately for day 1 (acute emesis) and days 2-6 (delayed emesis). The Chi-squared test was used to detect the significance of differences between the groups. A *p* value of less than 0.05 was considered to indicate statistical significance.

RESULTS

A total of 437 patients were enrolled from December 1995 through March 2001 at Chang Gung Memorial Hospital. During the first cycle of CT, 424 patients were evaluated for emesis. The causes of non-evaluation (*n* = 13) were as follows: previous cisplatin-containing CT (*n* = 6), intestinal obstruction (*n* = 2), hypercalcemia (*n* = 1), brain metastasis (*n* = 1), toxic death (*n* = 1) and concurrent therapy with corticosteroids (*n* = 1). The population consisted of 256 men and 144 women who ranged in age from 16 to 80 years (median, 58 years). During the second cycle of CT, 337 patients were evaluated for emesis. The causes of non-evaluation (*n* = 87; 40 in arm A and 47 in arm B) were as follows: progression or death due to neoplasm (*n* = 54), lost to follow-up (*n* = 15), different CT regimen (*n* = 7), refusal of CT due to side effects (*n* = 6), complication or death due to other illnesses (*n* = 2) and antiemetic treatment not given as scheduled (*n* = 3). There were 384 patients

in arm A and 377 patients in arm B. Detailed characteristics of the patients are listed in Table 1.

Efficacy

The antiemetic efficacy data for arm A and arm B are listed in Table 2. Complete protection from acute nausea/vomiting was obtained in 91.4%/94.8% of patients in arm A and in 90.4%/92.3% of patients in arm B. Complete plus major protection from acute nausea/vomiting was obtained in 95.6%/98.2% of patients in arm A and in 96.0%/97.9% of patients in arm B. Complete protection from delayed nausea/vomiting was obtained in 59.6%/70.1% of patients in arm A and in 61.3%/72.7% of patients in arm B. Complete plus major protection from delayed nausea/vomiting was obtained in 76.0%/80.8% of patients in arm A and in 77.5%/80.9% of patients in arm B. There were no differences in the control of both acute and delayed nausea/vomiting between the two arms of this study.

For patients who did not have complete protection of emesis, we evaluated onset and incidence of nausea/vomiting each day (Table 3). On day 2, the proportion of first occurrence of vomiting/nausea was lower in arm B compared to arm A ($p = 0.02$ and 0.002 , respectively). However, onset of vomiting on day 1 was marginally higher in arm B ($p = 0.08$). The delayed onset of nausea on day 2 to day 3 was

merely pronounced in arm B ($p = 0.009$). On day 2, the incidence of nausea was significantly lower in arm B compared with arm A ($p = 0.007$).

Adverse events

Adverse events tended to be minor. Hiccups and constipation were the most frequent adverse events, and occurred in 24.5% and 24.9% of patients in arm A and in 23.7% and 23.6% of patients in arm B, respectively. Dizziness, flushing, headache and diarrhea were reported by 5.2%, 4.4%, 3.6% and 1.6% of patients in arm A, and by 5.3%, 5.3%, 3.7% and 1.6% of patients in arm B, respectively.

Complete responders did not have antiemetic maintenance during subsequent cycles

A total of 174 patients were complete responders. Of these, 147 undergoing 3rd-6th cycles of identical CT were enrolled for investigation. Complete control rates for acute nausea/vomiting were maintained in 95.9%/97.3% of patients during the subsequent 3rd-6th cycles: 98.0%/98.6%, 97.2%/97.2%, 98.2%/100.0% and 100.0%/100.0% in the 3rd, 4th, 5th and 6th cycle, respectively. Complete control rates for delayed nausea/vomiting were maintained in 72.1%/81.6% of patients during the subsequent 3rd-6th cycles: 86.4%/92.5%, 89.7%/93.5%, 92.9%/ 95.2% and 95.7%/95.7% in the 3rd, 4th, 5th and 6th cycle,

Table 2. Response to Antiemetic

	Vomiting protection			Nausea protection	
	Arm A (n = 384)	Arm B (n = 377)		Arm A (n = 384)	Arm B (n = 377)
Day 1*					
Complete (0)	364 (94.8%)	348 (92.3%)	No	351 (91.4%)	341 (90.4%)
Major (1-2)	13 (3.4%)	21 (5.6%)	Mild	16 (4.2%)	21 (5.6%)
Minor (3-5)	3 (0.8%)	4 (1.1%)	Moderate	14 (3.6%)	11 (2.9%)
Failure (> 5)	4 (1.0%)	4 (1.1%)	Severe	3 (0.8%)	4 (1.1%)
Days 2-6†					
Complete (0)	269 (70.1%)	274 (72.7%)	No	229 (59.6%)	231 (61.3%)
Major (1-2)	41 (10.7%)	31 (8.2%)	Mild	63 (16.4%)	61 (16.2%)
Minor (3-5)	32 (8.3%)	37 (9.8%)	Moderate	70 (18.2%)	68 (18.08%)
Failure (> 5)	42 (10.9%)	35 (9.3%)	Severe	22 (5.7%)	17 (4.5%)
Days 1-6‡					
Complete (0)	265 (69%)	267 (70.8%)	No	225 (58.6)	226 (59.9%)

*: Vomiting protection- Complete, $p = 0.16$; Complete plus major, $p = 0.77$; Nausea- No, $p = 0.65$; No and mild, $p = 0.76$;

†: Vomiting protection- Complete, $p = 0.42$; Complete plus major, $p = 0.95$; Nausea- No, $p = 0.61$; No and mild, $p = 0.59$;

‡: Vomiting protection- Complete response, $p = 0.59$; Nausea- No nausea, $p = 0.70$.

Table 3. Onset and Incidence of Nausea and Vomiting in Not Complete Responders

	Vomiting		<i>p</i> value	Nausea		<i>p</i> value
	Arm A (n = 119)	Arm B (n = 110)		Arm A (n = 159)	Arm B (n = 151)	
Onset of emesis						
Day 1	20 (16.8%)	29 (26.4%)	0.08	33 (20.8%)	36 (23.8%)	0.51
Day 2	62 (52.1%)	41 (37.3%)	0.02	82 (51.6%)	52 (34.4%)	0.002
Day 3	29 (24.4%)	25 (22.7%)	0.77	30 (18.9%)	40 (26.5%)	0.11
Day 4	8 (6.7%)	13 (11.8%)	0.18	13 (8.2%)	19 (12.6%)	0.18
Days 5,6	0 (0%)	2 (1.8%)	0.14	1 (0.6%)	4 (2.6%)	0.16
First 2 days	82 (68.9%)	70 (63.6%)	0.39	115 (72.3%)	88 (58.3%)	0.009
First 3 days	111 (93.3%)	95 (85.6%)	0.08	145 (91.2%)	128 (84.8%)	0.08
First 4 days	119 (100.0%)	108 (98.2%)	0.14	158 (99.4%)	147 (97.4%)	0.16
Emesis incidence						
Day 1	20 (16.8%)	29 (26.4%)	0.08	33 (20.8%)	36 (23.8%)	0.51
Day 2	79 (66.4%)	62 (56.4%)	0.12	112 (70.4%)	84 (55.6%)	0.007
Day 3	82 (68.5%)	80 (72.7%)	0.53	123 (77.4%)	114 (75.5%)	0.70
Day 4	63 (52.9%)	65 (59.1%)	0.35	99 (62.3%)	100 (66.2%)	0.42
Days 5,6	35 (29.4%)	38 (34.5%)	0.35	54 (34%)	59 (39.1%)	0.35

respectively. Complete control rates for both acute and delayed nausea/vomiting through day 1 to day 6 were maintained in 72.1%/81.6% of patients during the subsequent 3rd-6th cycles: 86.4%/91.8%, 88.8%/92.5%, 92.9%/95.2% and 95.7%/95.7% in the 3rd, 4th, 5th and 6th cycle, respectively (Table 4).

Of these 147 patients enrolled in arm C for the prevention of cisplatin-induced emesis, 41 (27.9%) patients failed to maintain complete prevention of both nausea and vomiting in their 3rd cycles of CT. Thirty-eight patients were then substituted into arm A from arm C in the following 4th-6th cycles of CT. Thirty-two (84.2%) of them still experienced episodes of nausea and vomiting (Table 5): 44.7% had either vomiting or moderate to severe nausea in their subsequent cycles. Only 6 patients (15.8%) achieved complete protection from both nausea and vomiting. Of eleven patients with none or mild nausea but no vomiting, 9 (81.8%) experienced another episode of nausea with or without vomiting, and 2 (18.2%) progressed to vomiting \geq 3 with moderate nausea.

DISCUSSION

More than 90% of our patients achieved complete protection from acute nausea and vomiting. As

Table 4. Antiemesis Maintenance Rates of Complete Responders during Subsequent Cycles

Cycle of chemotherapy	No. of eligible patients	Complete responders for vomiting n (%)	Complete responders for nausea n (%)
3rd – 6th courses			
Days 1-6	147	120 (81.6%)	106 (72.1%)
Day 1		143 (97.3%)	141 (95.9%)
Days 2-6		120 (81.6%)	106 (72.1%)
3rd course			
Days 1-6	147	135 (91.8%)	127 (86.4%)
Day 1		145 (98.6%)	144 (98.0%)
Days 2-6		136 (92.5%)	127 (86.4%)
4th course			
Days 1-6	107	99 (92.5%)	95 (88.8%)
Day 1		104 (97.2%)	104 (97.2%)
Days 2-6		100 (93.5%)	96 (89.7%)
5th course			
Days 1-6	84	80 (95.2%)	78 (92.9%)
Day 1		84 (100.0%)	83 (98.8%)
Days 2-6		80 (95.2%)	78 (92.9%)
6th course			
Days 1-6	69	66 (95.7%)	66 (95.7%)
Day 1		69 (100.0%)	69 (100.0%)
Days 2-6		66 (95.7%)	66 (95.7%)

Table 5. Emesis Severity of Complete Responders with Failing Maintenance and Subsequent Cycles

	No.	Emesis severity of not complete responders in the 3 rd cycle							
		Nausea vomiting	Mild			Moderate			Severe
			None	Major	Minor	None	Major	Minor	Failure
Total	41		11	14	1	2	6	4	3
Evaluated patients	38		11	12	1	2	6	3	3
Antiemetic activity during subsequent 4 th -6 th cycles									
Nausea	Vomiting								
None	None	6	2	2	0	0	0	1	1
	Major	1	0	0	1	0	0	0	0
Mild	None	5	4	1	0	0	0	0	0
	Major	8	2	5	0	0	1	0	0
Moderate	None	1	1	0	0	0	0	0	0
	Major	6	0	2	0	0	4	0	0
	Minor	6	2	0	0	1	0	1	0
	Failure	2	0	0	0	1	0	1	0
Severe	Failure	3	0	0	0	0	1	0	2

in other trials, complete protection from delayed nausea and vomiting was obtained in approximately 60% and 70% of the patients, respectively. No difference was observed in the control of acute and delayed nausea/vomiting after the addition of dexamethasone to ondansetron, given as either a triple 8 mg dose at 4-hourly intervals or at 24-hourly intervals. However, the latter decreased the incidence of and delayed the onset of nausea on day 2.⁽²²⁾ In each cycle of CT, the 5-HT₃ receptor antagonist combination has proved to have higher antiemetic efficacy than a metoclopramide combination.^(16,20) With a 5-HT₃ receptor antagonist plus dexamethasone, the complete protection rate for acute and delayed emesis decreases in subsequent cycles.^(15,16,19,20)

Experiencing emesis in the prior cycle of CT has significant influence on emesis in the subsequent cycle.^(1,2,16,19) Delayed emesis is also significantly influenced by acute emesis, and delayed nausea seems to be more frequent than vomiting.^(1,2,18) The Italian Group for Antiemetic Research mentions that the incidence and intensity of delayed emesis remained similar during three subsequent cycles of CT.⁽¹⁸⁾ Bleiberg et al. also found that response rates were very similar for six CT courses.⁽¹³⁾ Dexamethasone alone may provide adequate protection against delayed emesis for patients who have not suffered from the acute form.⁽¹³⁾ We gave complete responders a single 8 mg dose of ondansetron plus dexamethasone for the prevention of emesis in the following

cycles of CT and only 4 patients (2.7%) experienced acute emesis. Antiemetic maintenance rates in their subsequent 3rd-6th cycles were 72.1%/81.6% for both acute and delayed nausea/vomiting; 97.5%/97.3% had no acute nausea/vomiting and 72.1%/81.6% had no delayed nausea/vomiting. Complete control rates for both acute and delayed nausea/vomiting in each cycle were maintained at 86.4%/91.8%, 88.8%/92.5%, 92.9%/95.2% and 95.7%/95.7% during the 3rd-6th cycles of therapy, respectively. The antiemetic maintenance rates were very similar, and these results are comparable to the 87.4% complete control of both delayed vomiting and moderate-to-severe nausea reported by the Italian Group for Antiemetic Research.⁽¹³⁾

Prior emesis influences antiemetic efficacy in subsequent cycles of CT. Once complete responders failed to be maintained by arm C, the arm A regimen was administered in the following cycles of CT. In this group, 84.2% of patients experienced other episodes of nausea and vomiting. Of the patients with mild nausea but no vomiting, about 81.8% of them had another emesis during subsequent cycles. Moreover, 18.2% patients had less antiemetic protection.

In our study, no difference in antiemetic efficacy was shown when a triple dose of 8 mg ondansetron was given either at 4-hourly intervals or at 24-hourly intervals. However, the latter regimen improved nausea on day 2. Emetic severity during previous CT

correlated with that of the subsequent CT. A single 8 mg dose of ondansetron, for cost savings, was feasible for the majority of those who had been complete responders to the triple doses of ondansetron in the previous CT. We hope that a new class of agents such as NK₁ receptor antagonists^(1,2,23) may have a potential role to treat these patients.

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不同給藥時程的 ondansetron 合併使用 dexamethasone 在 cisplatin 爲主的止吐效果

陳秉聰 廖宗琦

背景： 我們研究 ondansetron 依據不同的時程給藥，在合併使用 dexamethasone 時，對於以 cisplatin 爲主的化學治療處方所引起的嘔吐，在止吐效果上是否有所差異。

方法： 總共有 424 位病人參與這項研究。A 組接受 ondansetron 每次 8 毫克靜脈注射，共 3 次，間隔 4 小時，合併於化療前靜脈注射 dexamethasone 20 毫克及之後每 12 小時 5 毫克。B 組接受與 A 組病人相同給法的 dexamethasone，以及相同劑量的 ondansetron 3 次，但是給藥間隔變成 24 小時。A 組及 B 組病人於第二次化療時互相交換。病患如果接受 2 次治療後都沒有發生任何噁心或嘔吐，於下一次的化學治療時將只給一次 8 毫克的 ondansetron，並登記爲 C 組。C 組的病人一旦在後續的治療中發生嘔吐，之後將接受 A 組的給藥方法治療。

結果： A、B、C 3 組分別有 384、377 及 147 位病人次。在 A 組中，急性噁心 / 嘔吐得到完全控制的有 94.8% / 91.4%，延遲性噁心 / 嘔吐得到完全控制的有 70.1% / 59.6%。在 B 組中，急性噁心 / 嘔吐得到完全控制的有 92.3% / 90.4%，延遲性噁心 / 嘔吐得到完全控制的有 72.7% / 61.3%。在 B 組，延遲性噁心的發生率較低而且較晚發生。之前化療造成的嘔吐嚴重度，顯著的與之後化療的嘔吐有關。在 C 組接下來的第 3 次到第 6 次化療中，噁心 / 嘔吐的完全控制率可維持在 81.6% / 72.1%。

結論： Ondansetron 8 毫克每 4 小時或每 24 小時給 3 次，止吐效果並沒有差異。但後者改善了第二天發生噁心的機會。在 A 組及 B 組得到完全止吐效果的病患，單一次 8 毫克的 ondansetron 仍能維持多數病患的止吐效果。

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關鍵詞： 化學治療，cisplatin，嘔吐，5-HT3 antagonist，dexamethasone，ondansetron

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