Comparison of Granisetron, Ondansetron, and Tropisetron in the Prophylaxis of Acute Nausea and Vomiting Induced by Cisplatin for the Treatment of Head and Neck Cancer: A Randomized Controlled Trial

Giovanni Mantovani, M.D.
Antonio Macciò, M.D.
Alessandro Bianchi, M.D.
Luigi Curreli, M.D.
Massimo Ghiani, M.D.
Ernesto Proto, M.D.
Maria C. Santona, M.D.

Department of Medical Oncology, University of Cagliari, 09124 Cagliari, Italy.

The authors thank Prof. Paolo Contu, Dept. of Hygiene and Public Health, University of Cagliari, for his helpful advice in the statistical evaluation of the results.

Address for reprints: Prof. Giovanni Mantovani, M.D., Department of Medical Oncology, Institute of Internal Medicine, University of Cagliari, Via S. Giorgio 12, 09124 Cagliari, Italy.

Received January 5, 1995; revision received April 18, 1995 and July 14, 1995; accepted July 14, 1995.

BACKGROUND. A single-institution, prospective, randomized, open controlled trial was carried out on head and neck cancer patients to compare granisetron (GRA), ondansetron (OND), and tropisetron (TRO) in the prevention of cisplatin-induced acute nausea and vomiting. All patients were chemotherapy-naïve and treated with cisplatin on Day 1 (80 to 100 mg/m^2).

METHODS. One hundred seventeen patients were treated for a total of 463 cycles of cisplatin-based chemotherapy and randomized to receive 24 mg of OND intravenously (i.v.), 3 mg of GRA i.v., or 5 mg of TRO i.v. for the control of acute nausea and emesis.

RESULTS. In the GRA group, complete response (CR) was obtained in 119 of 165 cycles (72.1%), major response (MR) in 32 cycles (19.4%), minor response (MiR) in 5 cycles (3%), and a failure (F) in 9 cycles (5.5%). In the OND group, CR was obtained in 110 of 150 cycles (73.3%), MR in 31 cycles (20.7%), MiR in 2 cycles (1.3%), and F in 7 cycles (4.7%). In the TRO group, CR was obtained in 100 of 148 cycles (67.6%), MR in 26 cycles (17.6%), MiR in 15 cycles (10.1%), and F in 7 cycles (4.7%). Major efficacy (CR + MR) was obtained in 151 of 165 cycles (91.5%) for GRA, in 141 of 150 cycles (94.0%) for OND, and in 126 of 148 cycles (85.2%) for TRO. The difference in major efficacy between OND and TRO was statistically significant. When comparing MiR, both GRA and OND were more effective than TRO. No other significant differences were observed among the three antiemetic agents.

CONCLUSIONS. Although our results were achieved in an open trial, they show that GRA and OND are equally effective antiemetic agents in the prevention of cisplatin-induced acute nausea and vomiting. TRO provides almost the same protection but is not as effective as OND for major efficacy. All three antiemetics can be administered safely to patients undergoing chemotherapy with cisplatin at doses of 80 mg/m^2 or more. *Cancer* **1996; 77:941–8.** © *1996 American Cancer Society.*

KEYWORDS: acute nausea, vomiting, cisplatin, granisetron (GRA), ondansetron (OND), tropisetron (TRO), head and neck cancer patients, 5-HT$_3$ receptor antagonists.

Severe nausea and vomiting are common and distressing side effects associated with cisplatin chemotherapy for malignant diseases.[1] Cisplatin-induced vomiting is mediated by serotonin, which is stored and released by the enterochromaffin cells of the small intestine. The released serotonin may contribute to the development of emesis by binding to 5-HT$_3$ receptors on vagal and splanchnic fibers endowed in the small intestine wall. The subsequent afferent stimuli to specific areas of the

TABLE 1
Clinical Characteristics of Patients Treated with Cisplatin (80 to 100 mg/m^2)

No. of patients	117
Males/females	113/4
Mean age: years (M ± SD)	58.2 ± 9.9
Age range	31–78
No. of cycles	
Granisetron	165
Ondansetron	150
Tropisetron	148
Performance status (ECOG)	
0	70 pts
1	36 pts
2	9 pts
3	2 pts
Cancer stage	
Stage II	6 pts
Stage III	29 pts
Stage IV	82 pts
Site of primary tumor	
Oral cavity	32 pts
Oropharynx	28 pts
Hypopharynx	10 pts
Larynx	43 pts
Maxillary sinus	2 pts
Upper oesophagus	2 pts
Previous chemotherapy	
Yes	—
No	117 pts
Chemotherapy	
Al-Sarraf's regimen (CDDP 100 mg/m^2 + 5-FU 1000 mg/m^2)	40 pts
Our regimen (CDDP 80 mg/m^2 + 5-FU 600 mg/m^2 + VNR 20 mg/m^2)	77 pts
Crossed over once	19 pts
Crossed over twice	2 pts
Mean No. of chemotherapy cycles/patient	3.9

CDDP: cisplatin; 5-FU: 5-fluorouracil; VNR: vinorelbine.

TABLE 2
Response Criteria Over the Initial 24-h Period Following Chemotherapy

Complete response	no nausea or vomiting or only mild nausea in the 24 hrs after starting cytostatic therapy
Major response	single vomiting episode in the 24 hrs after starting cytostatic therapy or no vomiting, but moderate to severe nausea
Minor response	2–4 vomiting episodes in the 24 hrs after starting chemotherapy
Failures	>4 vomiting episodes in the 24 hrs after starting chemotherapy
Major efficacy	complete and major response

Soukop, 1990; Smith, 1990.

central nervous system, such as the chemoreceptor trigger zone, can trigger emesis.

The antiemetic efficacy of highly selective antagonists of 5–HT_3 receptors in preventing cisplatin-induced emesis has been clearly demonstrated in preclinical studies and has provided a strong rationale for the introduction of these agents into clinical practice.[2,3] Among a large number of selective 5–HT_3 receptor antagonists evaluated, three agents, namely granisetron (Gra), ondansetron (Ond), and tropisetron (Tro), were approved for clinical use in most European countries (Tro has not yet been approved for use in the United States).

As stressed by Tonato et al.,[4] "in the past there has been only speculation based on efficacy rates from the literature as to which agent (Ond or Gra) is more effective for the control of cisplatin-induced emesis."[5] To our knowledge, only two studies, one by Jantunen et al.[6] and the other by our group,[7] have compared the effectiveness of all three agents (Gra, Ond, and Tro) for the control of acute vomiting induced by cisplatin-based chemotherapy. A third study comparing the three antiserotonin agents,[8] involved moderately emetogenic chemotherapy agents and not cisplatin. All other studies have compared one of the 5–HT_3 receptor antagonists (± dexamethasone) with a "standard" highdose metoclopramide combination,[9,10] or one antagonist with another, either Ond versus Gra,[5,11–13] or Ond versus Tro.[14]

Hence, additional comparative clinical studies are required to establish the eventual differences among 5–HT_3 receptor antagonists.

AIM OF THE STUDY

With this purpose we carried out a single-institution, prospective, randomized, open controlled trial to compare Gra, Ond, and Tro in the prevention of cisplatin-induced acute nausea and vomiting.

A total of 117 patients treated with 80 mg/m^2 or more of cisplatin for advanced head and neck cancer (mainly Stage III or IV) were enrolled in the study. The main clinical features of the patients are reported in Table 1.

The main characteristics of our study were:

1. Patients had similar tumor sites (head and neck cancer).
2. Forty patients were treated with Al-Sarraf's classical chemotherapeutic regimen: 100 mg/m^2 of cisplatin diluted in 500 cc of normal saline over 2 hours using a standard pre- and post-hydration protocol with forced diuresis by 250 cc of 18% mannitol on Day 1 plus 1000 mg/m^2 of 5–fluorouracil (5-FU) intravenously (i.v.), continuous infusion for 120 hours on Days 1 to 5. Seventy-seven patients were treated with a regimen used in our institute: 80 mg/m^2 of cisplatin diluted in 500 cc of normal saline over 2 hours according to a standard pre- and post-hydration protocol with forced di-

TABLE 3
Characteristics of Patients According to Treatment Groups

	Granisetron		Ondansetron		Tropisetron	
No. of patients	38		39		40	
Mean age: years (range)	58.0	(31–75)	59.3	(31–74)	56.4	(40–78)
	No.	(%)	No.	(%)	No.	(%)
Performance status (ECOG)						
0	25	(65.79)	27	(69.23)	19	(47.50)[a]
1	10	(26.32)	10	(25.64)	16	(40.00)
2	2	(5.26)	2	(5.13)	4	(10.00)
3	1	(2.63)	—	—	1	(2.50)
Cancer stage						
Stage II	2	(5.26)	4	(10.26)	—	—
Stage III	11	(28.95)	11	(28.21)	10	(25.00)
Stage IV	25	(65.79)	24	(61.54)	30	(75.00)

[a] Chi-square test.
All differences are not statistically significant.

uresis by 250 cc of 18% mannitol on Day 1; 600 mg/m^2 of 5-FU diluted in 500 cc of normal saline infused during a period of 4 hours on Days 2 to 5; and 20 mg/m^2 of vinorelbine diluted in 250 cc of normal saline during a period of 20 minutes on Days 2 and 8.

3. All patients were chemotherapy-naïve.

MATERIALS AND METHODS

Study Design

After obtaining approval from the ethical committee of our institute and written informed consent from the patients, a single-institution, prospective, randomized, open controlled trial was carried out to compare Gra, Ond, and Tro in the control of acute nausea and emesis due to cisplatin.

Sample size was calculated on the assumption that almost all of the patients receiving 70 mg/m^2 or more of cisplatin vomit without any antiemetic therapy and that complete protection rates were 72% for Gra,[7] from 44%[15] to 65%[7] for Ond, and from 44% to 53% for Tro.[7,16]

Thus, 130 cycles had to be administered to demonstrate a 20% advantage for Gra at the significance level of $\alpha = 0.05$ with a power of $\beta = 0.9$. In addition, all patients received a single dose of cisplatin on Day 1.

The following inclusion criteria were applied to our study: no previous chemotherapy; Karnofsky performance status (KPS) of 60 or more; absence of clinically detectable brain metastasis; absence of neoplastic involvement of the stomach and bowel that could lead to partial obstruction; no history of non-neoplastic severe gastric or bowel diseases; no concomitant treatment with other antiemetic drugs, including steroids; no anticipatory emesis; no concomitant severe neurologic, hepatic, or renal diseases, and no drug abuse or long-term use of psychotropic drugs. It must also be stressed that all of the patients were on study drugs for multiple courses of chemotherapy.

Before starting chemotherapy, the patients were randomly assigned to one of three antiemetic treatment groups. The same antiemetic coverage was maintained during the following chemotherapy cycles unless failure was experienced; in this case the patient was randomly assigned to one of the other two drugs. In our study, 19 patients were crossed-over to a second group. Two of these patients again failed to respond to treatment and were subsequently crossed-over to a third group.

Antiemetic Schedule

The antiemetic schedule consisted of 24 mg of Ond diluted in 250 ml of normal saline given i.v. during a period of 30 minutes before starting chemotherapy, and 3 mg of Gra or 5 mg of Tro, both diluted in 100 ml of normal saline given i.v. during a period of 15 minutes before chemotherapy. No other antiemetics were administered within the first 24 hours of chemotherapy.

Nausea and vomiting during the first 24 hours were evaluated according to Soukop's and Smith's Scale[17,18] and are reported in Table 2.

Antiemetic treatment was continued to control nausea and vomiting from Day 2 onward, but response is not reported because the purpose of this paper is to evaluate only acute nausea and vomiting. Delayed nausea and vomiting are probably a different phenomenon, requiring a different study approach.

TABLE 4
Effect of Granisetron, Ondansetron, and Tropisetron on the Frequency of Cisplatin-Induced Acute Nausea and Vomiting

	Granisetron		Ondansetron		Tropisetron	
Total cycles	165		150		148	
Response	**No. of cycles**	**%**	**No. of cycles**	**%**	**No. of cycles**	**%**
Complete response (CR)	119	72.1	110	73.3	100	67.6*
Major response (MR)	32	19.4	31	20.7	26	17.6
Major efficacy (CR + MR)	151	91.5	141	94.0	126	85.2
Minor response (MiR)	5	3.0	2	1.3	15	10.1
Failures (F)	9	5.5	7	4.7	7	4.7

* chi-square test		*P* value
Granisetron vs. Ondansetron	CR	0.909
Granisetron vs. Tropisetron	CR	0.451
Ondansetron vs. Tropisetron	CR	0.335
Granisetron vs. Ondansetron	MR	0.888
Granisetron vs. Tropisetron	MR	0.788
Ondansetron vs. Tropisetron	MR	0.594
Granisetron vs. Ondansetron	CR + MR	0.529
Granisetron vs. Tropisetron	CR + MR	0.112
Ondansetron vs. Tropisetron	CR + MR	0.021
Granisetron vs. Ondansetron	MiR	0.524
Granisetron vs. Tropisetron	MiR	0.020
Ondansetron vs. Tropisetron	MiR	0.002
Granisetron vs. Ondansetron	F	0.951
Granisetron vs. Tropisetron	F	0.973
Ondansetron vs. Tropisetron	F	0.804

The treatment groups were well-matched for age, sex (almost all patients were males), performance status, and disease Stage (Table 3).

Statistical Analysis

Data were reported as relative frequency (%). The chi-square test and a confidence interval of 95% were used.

RESULTS

A total of 463 chemotherapy cycles were evaluated. The data reported only concerned the evaluation of acute nausea and emesis.

Acute Nausea and Emesis

Table 4 shows the effect of Gra, Ond, and Tro on acute nausea and vomiting for the first 24 hours after cisplatin administration.

In the Gra group, complete response (CR) was obtained in 119 out of 165 cycles (72.1%), major response (MR) in 32 cycles (19.4%), minor response (MiR) in 5 cycles (3.%), and failure (F) in 9 cycles (5.5%).

In the Ond group, CR was achieved in 110 out of 150 cycles (73.3%), MR in 31 cycles (20.7%), MiR in 2 cycles (1.3%), and F in 7 cycles (4.7%).

In the Tro group, patients yielded a CR in 100 out of 148 cycles (67.6%), MR in 26 cycles (17.6%), MiR in 15 cycles (10.1%), and F in 7 cycles (4.7%).

Major efficacy (CR + MR) was achieved in 151 out of 165 cycles (91.5%) for Gra, in 141 out of 150 cycles (94.0%) for Ond, and in 126 out of 148 cycles (85.2%) for Tro.

The difference in CR + MR between Ond and Tro was statistically significant. As far as MiR was concerned, both Gra and Ond were more effective than Tro. No other comparisons among the three drugs yielded significant differences.

Additionally, we assessed the response rates to the three drugs at the beginning of the second, third, and subsequent chemotherapy cycles to determine if the antiemetic effect achieved at the start of the first cycle was maintained. Only minor changes were observed in comparisons with the first chemotherapy cycle, and the differences did not reach statistical significance (Table 5).

The patients who failed to respond (more than 4

TABLE 5
Response Rates to Three Antiemetics at the Start of the First Chemotherapy Cycle Compared With the Second, Third, and Subsequent Chemotherapy Cycles

	Granisetron							
	1st cycle		2nd cycle		3rd cycle		Subsequent cycles	
Response	No.	%	No.	%	No.	%	No.	%
Complete response (CR)	32	84.2	22	66.7	20	74.1	45	67.2
Major response (MR)	4	10.5	9	27.3	6	22.2	13	19.4
Major efficacy (CR + MR)	36	94.7	31	93.9	26	96.3	58	86.6
Minor response (MiR)	1	2.6	—	—	—	—	4	6.0
Failures (F)	1	2.6	2	6.1	1	3.7	5	7.4
Total	38		33		27		67	
	Ondansetron							
	1st cycle		2nd cycle		3rd cycle		Subsequent cycles	
Response	No.	%	No.	%	No.	%	No.	%
Complete response (CR)	32	82.1	28	80.0	19	61.3	31	68.9
Major response (MR)	7	17.9	7	20.0	8	25.8	9	20.0
Major efficacy (CR + MR)	39	100.0	35	100.0	27	87.1	40	88.9
Minor responses (MiR)	—	—	—	—	1	3.2	1	2.2
Failures (F)	—	—	—	—	3	9.7	4	8.9
Total	39		35		31		45	
	Tropisetron							
	1st cycle		2nd cycle		3rd cycle		Subsequent cycles	
Response	No.	%	No.	%	No.	%	No.	%
Complete response (CR)	29	72.5	24	66.7	19	65.5	28	65.1
Major response (MR)	6	15.0	7	19.4	5	17.2	8	18.6
Major efficacy (CR + MR)	35	87.5	31	86.1	24	82.8	36	83.7
Minor response (MiR)	3	7.5	4	11.1	4	13.8	4	9.3
Failures (F)	2	5.0	1	2.8	1	3.4	3	7.0
Total	40		36		29		43	

[1] Chi-square test.
No statistically significant differences in response rates to antiemetic treatment in comparisons between the first and subsequent chemotherapy cycles.

vomiting episodes: 9 in the Gra group, 7 in the Ond group, and 7 in the Tro group) were treated with 1 or 2 additional i.v. doses of the same antiemetic drug previously administered, that is, 8 mg to 16 mg for Ond, 3 mg to 6 mg for Gra, 5 mg to 10 mg for Tro. Five of these patients also had to be treated with 30 mg of Metoclopramide i.v. plus 16 mg of Dexamethasone i.v. No further treatment failure was recorded.

The response data of the "crossover" patients are reported in Table 6. In general, the 19 patients who crossed-over to a second group responded well to treatment, regardless of the first antiemetic used. However, one of the two patients who crossed-over failed three times to respond to treatment.

Safety

Gra, Ond, and Tro were all well tolerated and no severe side effects were observed during treatment. The incidence of headache, a common complaint among patients receiving 5-HT_3 antagonists, was less than 10% and not significantly different in any of the three treatment arms. No other relevant side effects were observed in any of the patients during treatment. None of the patients had to interrupt chemotherapy for lack of emesis control.

DISCUSSION

It must first of all be emphasized that the CR rates obtained for the three antiemetics in our study are better than those previously reported for these drugs.[12-14] This

TABLE 6
Response Data of the "Crossover" Patients

19 patients crossed-over once:			
1st antiemetic	2nd antiemetic	Response	Further chemotherapy
Gra	Ond	F	No
Gra	Ond	MiR	
Gra	Ond	MiR	
Gra	Ond	MR	
Gra	Ond	CR	
Gra	Tro	MR	
Gra	Tro	MR	
Ond	Gra	CR	
Ond	Gra	F	No
Ond	Tro	MiR	
Ond	Tro	MiR	
Ond	Tro	F	No
Ond	Tro	F	No
Tro	Gra	MR	
Tro	Gra	MR	
Tro	Gra	MiR	
Tro	Gra	MiR	
Tro	Ond	MR	
Tro	Ond	MiR	

Two patients crossed over twice:				
1st antiemetic	2nd antiemetic	3rd antiemetic	Response	Further chemotherapy
Ond	Gra	Tro	MR	
Gra	Ond	Tro	F	No

CR: complete response; MR: major response; MiR: minor response; F: failures.

may possibly be explained by the careful selection of the patients and the chemotherapeutic schedule. In fact, since the clinical introduction of 5-HT_3 antagonists for the prophylaxis of chemotherapy-induced emesis, this is to our knowledge the first study that compares the antiemetic efficacy of the three most largely used drugs in cisplatin-induced acute nausea and vomiting in a very homogeneous patient population. (All patients were well matched for cancer types and sites and for the most important clinical characteristics. They were all chemotherapy-naïve and treated with two very similar chemotherapeutic schedules: either cisplatin 100 mg/m^2 + 5-FU 1000 mg/m^2, or cisplatin 80 mg/m^2 + 5-FU 600 mg/m^2 + vinorelbine 20 mg/m^2.)

The only previous study to compare the three 5-HT_3 antagonists was a three-way, randomized cross-over carried out on a rather heterogeneous patient population, non-naïve to chemotherapy, receiving "moderately" emetogenic (cyclophosphamide containing) chemotherapy.[6] This study found a better complete control of emesis and fewer failures with Gra than with Ond.

Different from our previously reported data,[7] the results of the present study show a substantially equivalent activity of the three 5-HT_3 antagonists in the complete control of acute nausea and vomiting. This is probably due to the inadequate size of the former patient sampling. Our study confirms the previously reported equal effectiveness of Gra and Ond in controlling cisplatin-induced nausea and emesis,[19,20] while Tro was found to be slightly less effective than Ond. Moreover, both Gra and Ond had better MiR rates than Tro. No significant differences were found in comparisons with subsequent chemotherapy cycles.

Of the two major trial designs used in antiemetic studies, ours was basically parallel. Crossing-over was restricted to patients who failed to respond to the randomly assigned treatment. Conversely, the possibility of assessing preference between treatments was not a major goal of our study.[21]

Like the above cited study,[6] ours was an open, randomized trial. Despite the opinion of some authors,[21] we believe that our study may nevertheless fulfil the requirements of a sound methodology in showing differences among different antiemetic treatments for the following reasons: (1) A blind study requires one or more companies to support it which is not the case concerning our

trial because it was independently aimed at assessing the comparative effectiveness of the three 5-HT_3 receptor antagonists. (2) All three drugs compared were currently on the market and, therefore, a blind study was not feasible without the drug supply and support of the producers. (3) The study was blind as far as the patients were concerned, in fact, the patients did not know to which of the three antiemetics they had been assigned. Furthermore, it must be noted that all treatments were administered by nursing personnel at our institute on an inpatient basis (all patients were hospitalized) and, finally, our evaluation system was based on Soukop's and Smith's Scale (Table 2), which is one of the most widely used tools for assessing nausea and vomiting in this type of study.[17,18]

From a general point of view, of the several methodological problems that arise in clinical antiemetic studies[21-24]: (1) variables related to the patient population[25,26]; (2) variables related to emetic stimulus[27]; (3) variables related to the antiemetic drug[28,29]; (4) variables related to the study design[30]; (5) variables related to the evaluation system,[27] our study was able to overcome at least the first two inconveniences. Our patient population was, in fact, very homogeneous and the emetic stimulus was always the same, i.e., cisplatin. Almost all of our patients (113 out of 117) were males with head and neck cancer which could hypothetically mean that our results may not be generalized. However, no studies are known of single agents showing differences in efficacy related to sex or cancer site. As for the antiemetic drugs, they are all three of the same class (i.e., the new 5-HT_3 receptor antagonists) and were employed according to the route, schedule of administration, and doses currently recommended in Europe, that is, 24 mg for Ond, 3 mg for Gra, and 5 mg for Tro. Gra is used in Europe in a larger dose than that recommended in the United States which must be considered when comparing studies carried out in the two different countries.

The large majority of previous studies are not comparable to ours because they do not involve cisplatin-treated patients,[31] which is the only condition in which the 5-HT_3 receptor antagonists are the drugs of choice.[32] Moreover, the patient and treatment characteristics in other studies were generally very heterogeneous.[33]

In our trial, the three antiemetic drugs were well tolerated and no severe side effects were observed in any of the three treatment arms.

Although not directly connected with our study, the difference in cost between the three drugs must also be considered. For one hospitalized patient/one day treatment with Gra is approximately 50% of the cost of Ond ($20.75 and $41.72, respectively) and 75% of the cost for Tro ($20.75 and $26.15, respectively), with a clear estimated budgetary impact in favor of Gra. However, as the dose currently recommended by the producer of Ond is 8 mg, the costs ratio between the drugs may now be different.

The approach to problems such as anticipatory vomiting or delayed emesis have been deliberately omitted in our study.

In conclusion, although our results were achieved in an open trial, they show that Gra and Ond are equally effective in the prevention of acute nausea and vomiting while Tro is slightly less effective when compared with Ond for CR + MR. All three antiemetics can be administered safely to patients undergoing cisplatin-based chemotherapy at doses greater than or equal to 80 mg/m^2.

Although our study substantially confirms the statement of Gralla[34] that the antiemetic effectiveness of Gra, Ond, and Tro is similar, further studies on large patient samplings are required to show small differences, such as those reported in this study. These trials, aimed at proving the clinical significance of these small differences among the 5-HT_3 receptor antagonists, may require a very large number of enrolled patients; some of these studies are already underway.[4]

REFERENCES

1. Whitehead VM. Cancer treatment needs better antiemetics. *N Engl J Med* 1975;293:199-200.
2. Andrews PLR, Rareport WG, Sanger GJ. Neuropharmacology of emesis induced by anti-cancer therapy. *Trends Pharmacol Sci* 1988;9:334-41.
3. Hesketh PJ. Treatment of chemotherapy-induced emesis in the 1990s: impact of the 5-HT_3 receptor antagonists. *Support Care Cancer* 1994;2:286-92.
4. Tonato M, Roila F, Del Favero A. Are there differences among the serotonin antagonists? *Support Care Cancer* 1994;2:293-6.
5. Dilly SG. Are granisetron and ondansetron equivalent in the clinic? *Eur J Cancer* 1992;28A Suppl 1:32S-35S.
6. Jantunen JT, Muhonen TT, Kataja VV, Elander MK, Teerenhovi L. 5-HT_3 receptor antagonists in the prophylaxis of acute vomiting induced by moderately emetogenic chemotherapy—A randomised study. *Eur J Cancer* 1993;29A:1669-72.
7. Mantovani G, Macciò A, Curreli I., Bianchi A, Gebbia V, Testa A. Comparison of the effectiveness of three 5-HT_3 receptor antagonists in the prophylaxis of acute vomiting induced by highly emetogenic chemotherapy (high-dose cisplatin) for the treatment of primary head and neck cancer. *Proc Am Soc Clin Oncol* 1994;13:428.
8. Massidda B, Laconi S, Foddi MR, Salamah K, Ionta MT. Prevention of non-cisplatin induced emesis: Role of the antagonists of 5-HT_3 Receptors. *Ann Oncol* 1994;5 Suppl 8:204.
9. Italian Group for Antiemetic Research. Ondansetron + dexamethasone vs metoclopramide + dexamethasone + diphenhydramine in prevention of cisplatin-induced emesis. *Lancet* 1992;340:96-9.
10. Chevallier B on the behalf of the Granisetron Study Group. Efficacy and safety of granisetron compared with high-dose metoclopramide plus dexamethasone in patients receiving high-dose cisplatin in single-blind study. *Eur J Cancer* 1990;26 Suppl 1:33-6.

11. de Boer M, de Wit R, Stoter G, Verweij J. Are 5-HT_3 antagonists fully cross resistant? A pilot experience. *Eur J Cancer* 1993;29A Suppl 6:265S.
12. Martoni A, Angelelli B, Guaraldi M, Strocchi E, Pannuti F. Granisetron (Gra) vs Ondansetron (Ond) in the prevention of cis-platinum-induced emesis. An open randomized cross-over study. *Proc Am Soc Clin Oncol* 1994;13:431.
13. Pellier P, Dilly SG, Friedman C, Yocom K. Crossover analysis of efficacy and side effects of granisetron and ondansetron. *Proc Am Soc Clin Oncol* 1994;13:441.
14. Riess H, Drechsler S, Evers C, Faerber L. Tropisetron (Tro) vs. Ondansetron (Ond) in prophylaxis of chemotherapy-induced emesis (CE). *Eur J Cancer* 1993;29A Suppl 6:211S.
15. Seynaeve C, Schuller J, Buser K, Porteder H, Van Belle S, Selved P, et al. Comparison of the anti-emetic efficacy of different doses of ondansetron, given as either a continuous infusion or a single intravenous dose, in acute cisplatin-induced emesis. A multicentre, double-blind, randomised, parallel group study. *Br J Cancer* 1992;66:192–7.
16. Dogliotti L, Antonacci RA, Pazè E, Ortega C, Berruti A, Faggiuolo R. Three years' experience with tropisetron in the control of nausea and vomiting in cisplatin-treated patients. *Drug* 1992;43 Suppl 3:6–10.
17. Soukop M on the behalf of the Granisetron Study Group. A comparison of two dose levels of granisetron in patients receiving high-dose cisplatin. *Eur J Cancer* 1990;26:15S–19S.
18. Smith IE on the behalf of the Granisetron Study Group. A comparison of two dose levels of granisetron in patients receiving moderately emetogenic cytostatic chemotherapy. *Eur J Cancer* 1990;26:19S–23S.
19. Ruff P, Paska W, Goedhals L, Puillard P, Riviere A, Vorobiof D, et al. Ondansetron compared with granisetron in the prophylaxis of cisplatin-induced acute emesis: a multicentre double blind, randomized, parallel-group study. *Oncology* 1994;51:113–8.
20. Gebbia V, Cannata G, Testa A, Curto G, Valenza R, Cipolla C, et al. Ondansetron versus granisetron in the prevention of chemotherapy-induced nausea and vomiting. *Cancer* 1994;74:1945–52.
21. Tonato M, Roila F, Del Favero A. Methodology of antiemetic trials. A review. *Ann Oncol* 1991;2:107–14.
22. Joss RA, Brand BC, Buser KS, Cerny T. The symptomatic control of cytostatic drug-induced emesis. A recent history and review. *Eur J Cancer* 1990;26 Suppl 1:2S–8S.
23. Olver IN, Simon RM, Aisner J. Antiemetic studies: a methodological discussion. *Cancer Treat Rep* 1986;70:555–63.
24. Pater JL, Willan AR. Methodologic issues in trials of antiemetics. *J Clin Oncol* 1984;2:484–7.
25. D'Acquisto RW, Tyson LB, Gralla RJ, Clark RA, Kris MG, von Witte DM, et al. The influence of a chronic high alcohol intake on chemotherapy-induced nausea and vomiting. *Proc Am Soc Clin Oncol* 1986;5:257.
26. Walsh TD. Antiemetic drug combinations in advanced cancer. *Lancet* 1982;i:1018.
27. Roila F, Tonato M, Basurto C, Picciafuoco M, Bracarda S, Donati D, et al. Protection from nausea and vomiting in cisplatin-treated patients: high-dose metoclopramide combined with methylprednisolone versus metoclopramide combined with dexamethasone and diphenhydramine: a study of the Italian Oncology Group for Clinical Research. *J Clin Oncol* 1989;7:1693–700.
28. Roila F, Tonato M, Basurto C, Canaletti R, Morsia D, Passalacqua R, et al. Antiemetic activity of two different high doses of metoclopramide in cisplatin-treated cancer patients: a randomized double-blind trial of the Italian Oncology Group for Clinical Research. *Cancer Treat Rep* 1985;69:1353–7.
29. Kris MG, Gralla RJ, Tyson LB, Clark RA, Kelsen DP, Reilly LK, et al. Improved control of cisplatin induced emesis with high-dose metoclopramide and with combinations of metoclopramide, dexamethasone and diphenhydramine. Results of consecutive trials in 255 patients. *Cancer* 1985;55:527–34.
30. Cubeddu LX, Hoffmann IS, Fuenmayor NT, Finn AL. Efficacy of ondansetron (GR38032F) and the role of serotonin in cisplatin induced nausea and vomiting. *N Engl J Med* 1990;322:810–6.
31. Bonneterre J, Hecquet B. 5-HT_3 receptor antagonists in the prophylaxis of acute vomiting induced by moderately emetogenic chemotherapy. A randomized study. *Eur J Cancer* 1994;30A:1041–2.
32. Del Favero A, Roila F, Tonato M. Reducing chemotherapy-induced nausea and vomiting. *Drug Saf* 1994;9:410–28.
33. Dilly SG on the behalf of the Granisetron Study Group. A double-blind cross-over study to compare the efficacy and safety of granisetron and ondansetron in the prophylaxis of nausea and vomiting induced by 5-day fractionated chemotherapy [abstract book]. Proceedings of the Antiemetic Control: Maximizing the Benefits Satellite Symposium to the 7th European Conference on Clinical Oncology and Cancer Nursing; 1993 Nov 14–18; Jerusalem. Macclesfield (UK): Adelphy Communication, 1993:25–7.
34. Gralla RJ. Antiemetic treatment for cancer chemotherapy: problems and progress. *Support Care Cancer* 1994;2:275–6.