32. Jones BJ, Costall B, Domeney AM, *et al.* The potential anxiolytic activity of GR 38032F, a 5-HT$_3$ receptor antagonist. *Br J Pharmacol* 1988, **93**, 985.
33. Hartig PR. The molecular biology of 5-HT receptors. *Trends Pharmacol Sci* 1989, **10**, 64.
34. Bhandari P, Gupta YK, Seth SD. Effect of diethyl-dithiocarbamate on cisplatin-induced emesis in dogs. *Asia Pacific J Pharmacol* 1988, **3**, 247.

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Ondansetron

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Ondansetron is the first selective antagonist of the 5-hydroxytryptamine receptors (type 3) marketed for the prevention of emesis induced by antineoplastic agents. Ondansetron has been shown to be more active and less toxic than high-dose metoclopramide in patients submitted to cisplatin chemotherapy. Furthermore, when dexamethasone was added to ondansetron, its antiemetic efficacy increased significantly. In the prevention of emesis induced by a high single dose of cisplatin or by repeated low doses, ondansetron combined with dexamethasone has been shown to be the more efficacious and less toxic antiemetic treatment. However, in the prevention of delayed emesis from cisplatin, its role is still to be defined. In patients submitted to moderately emetogenic chemotherapeutic agents, ondansetron has shown an efficacy superior or equal to standard doses of metoclopramide, but is less toxic. Moreover, when compared with dexamethasone, its antiemetic efficacy and tolerability is similar; in this group of patients ondansetron should be used only when steroids fail. Ondansetron toxicity is generally mild; in particular, it does not induce extrapyramidal reactions. The most frequent side-effects are headache and constipation.
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INTRODUCTION

ONDANSETRON IS a potent, highly selective antagonist of the 5-hydroxytryptamine (5-HT) receptors (type 3) which has been found markedly efficacious in preventing vomiting induced by cisplatin, cyclophosphamide and radiation in ferrets [1]. The site of antiemetic action of ondansetron is still not precisely known. Cytotoxic drugs and radiation can induce damage in the enterochromaffin cells in the gastrointestinal tract and consequently the release of serotonin that can stimulate vagal and splanchnic nerve receptors that in turn elicit the activation of the vomiting centre. Ondansetron can act by blocking the afferent stimulus from the gut or directly at the chemoreceptor trigger zone. In fact, it has been shown that regions in or adjacent to the area postreme are particularly rich in 5-HT$_3$ receptors and that low doses of ondansetron injected directly into this region in ferrets inhibited emesis induced by cisplatin [2]

Ondansetron plasma half-life is approximately 3–3.5 h, while in the elderly it is prolonged to 5 h due to a reduction of plasma clearance. Ondansetron is extensively metabolised (less than 5–10% is recovered unchanged in the urine) and excreted both in the urine and faeces [3].

The drug is moderately bound to plasma protein (70–75%). Interpatient variability of plasma concentrations is considerable and there is no apparent correlation between plasma levels of ondansetron and antiemetic efficacy, although plasma levels may not necessarily reflect drug interaction at the target receptors [3].

Ondansetron is supplied both in parenteral and oral formulation. When administered orally its bioavailability is about 60%.

Even when administered at high doses for 2 years ondansetron has shown no mutagenic or oncogenic potential [4].

STUDIES IN CISPLATIN-TREATED PATIENTS

Cisplatin induces nausea and vomiting in almost all patients during the first 24 h after its administration (acute emesis).

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Since 1981, when for the first time the use of high-dose intravenous metoclopramide was shown efficacious in the prevention of cisplatin-induced emesis, much progress has been made. In fact, when metoclopramide is used in combination with dexamethasone and diphenhydramine or lorazepam, complete protection from acute emesis has been obtained in 60–70% of patients at first cycle of cisplatin chemotherapy [5–7]. However, despite the use of these combinations many problems remain to be solved: (1) 30–40% of patients still suffer from acute emesis despite treatment. Response to therapy is poorer in some subgroups of patients such as females, younger people and patients with previous experience of nausea and vomiting induced by chemotherapy; (2) complete protection from vomiting decreases significantly in the subsequent cycles of chemotherapy; (3) sedation, diarrhoea, nervousness and especially extrapyramidal reactions in about 5% of patients are unpleasant side-effects of these combinations; (4) finally, a variable percentage of patients (20–90%) suffer from delayed emesis (nausea and vomiting appearing after the first 24 h after cisplatin administration). The treatment of choice of delayed emesis induced by cisplatin is still an unresolved matter; in fact, only a few controlled studies have been performed.

An oral combination of dexamethasone and metoclopramide [8] can be considered the standard antiemetic therapy for prevention of delayed emesis from cisplatin, but despite this treatment over 40% of patients still have this side-effect.

The availability of a new class of drugs such as the 5-HT_3 antagonists may offer a solution to some of the above-mentioned problems.

Studies with a single high dose of cisplatin (≥ 50 mg/m^2)

Ondansetron was initially evaluated in several pilot studies with various schedules and doses. Most frequently it was administered both as a 15-min bolus infusion repeated 3 times every 2–8 h or followed by a continuous infusion for 24 h [9–15].

In these studies ondansetron showed a fairly good antiemetic activity (35–55% complete protection from vomiting, including patients with emesis refractory to standard antiemetics) and tolerability.

When administered as a repeated bolus infusion the results obtained using ondansetron every 2–4 h were similar to those obtained by administering it every 6 or 8 h. Furthermore, doses of 0.15–18 mg/kg seemed more efficacious than doses of 0.01–0.04 mg/kg.

On the basis of these results and on those of a subsequent double-blind study [16] the dose of 0.15 mg/kg (or 8 mg) in bolus followed by two further bolus doses every 2 or 4 h or by a continuous infusion of 1 mg/h for 24 h were chosen for the larger phase III comparative studies.

At present, three controlled studies [17–19] (Table 1) comparing ondansetron with high-dose metoclopramide have been published. In all of these, ondansetron has shown better antiemetic activity and lower toxicity than metoclopramide and, in the two crossover studies, was preferred by the patients. Complete protection from vomiting in 40–45% of patients was obtained, but, as has already been shown for metoclopramide, an increase of the antiemetic efficacy of ondansetron when combined with dexamethasone was found both in ferrets and in pilot studies in man [20–22]. The usefulness of such a combination was confirmed by a double-blind crossover study comparing ondansetron alone (0.15 mg/kg intravenously every 2 h × 3 doses) vs. ondansetron (at the same dose and schedule) plus dexamethasone (20 mg intravenously) [23]. This combination was significantly superior to the single drug (91 vs. 64% complete protection from vomiting) and was preferred by the patients. Side-effects were mild and not significantly different between the two antiemetic treatments (Table 2). Recently these results have been confirmed by two other multicentre studies [24, 25].

However, as shown in Table 2, complete protection from vomiting, although always superior with the ondansetron plus dexamethasone combination, varies from one study to another. This can be explained considering the different characteristics of the patients enrolled in these studies (i.e. dose of cisplatin, sex, etc.), that can significantly influence the response to the antiemetic treatment.

The next logical step in the search for the best treatment in the prevention of cisplatin-induced emesis was to compare ondansetron plus dexamethasone to a standard three-drug antiemetic combination.

Table 1. Ondansetron vs. high-dose metoclopramide

No. of patients	Cisplatin doses (mg/m^2)	Antiemetics	C.P. (%)	Results	Reference
97	80–100	OND 8 mg bolus + 1 mg/h c.i. × 24 h	46	OND > MTC < toxicity > preference	[17]
		MTC 3 mg/kg bolus + 0.5 mg/kg/h c.i. × 8 h	17		
121	50–100	OND 8 mg bolus + 1 mg/h c.i. × 24 h	72*	OND > MTC < toxicity > preference	[18]
		MTC 3 mg/kg bolus + 0.5 mg/kg/h c.i. × 8 h	41*		
307	100	OND 0.15 mg/kg i.v. × 3	40	OND > MTC < toxicity	[19]
		MTC 2 mg/kg i.v. × 6	30		

OND = Ondansetron; MTC = metoclopramide; C.P. = complete protection; * ≤ 2 emetic episodes; c.i. = continuous infusion; i.v. = intravenously.

Table 2. Ondansetron vs. ondansetron + dexamethasone

Study	No. of patients	Cisplatin doses (mg/m^2)	Antiemetics	C.P. (%)	Results	Reference
DBxo	102	76.5	OND 0.15 mg i.v. × 3	64	OND + DEX > OND > preference	[23]
			OND as above + DEX 20 mg i.v.	91		
DBxo	31	120	OND 8 mg × 3 orally	29.6*	OND + DEX > OND > preference	[24]
			OND as above + DEX 8 mg × 3 orally	77.8*		
DBxo	100	100	OND 8 mg i.v. + 1 mg/h for 24 h	42	OND + DEX > OND > preference	[25]
			OND as above + DEX 20 mg i.v.	58		

DBxo = Double-blind crossover; C.P. = complete protection; * ≤ 2 emetic episodes; OND = ondansetron; DEX = dexamethasone; i.v. = intravenously.

The first of these studies has recently been reported [26]. It is a multicentre randomised double-blind study in 289 patients submitted to ≥ 50 mg/m^2 of cisplatin chemotherapy. Ondansetron plus dexamethasone was significantly more efficacious than metoclopramide plus dexamethasone plus diphenhydramine. In particular, complete protection from vomiting was obtained in 78.7 and 59.5% of patients, respectively, in day 1 after cisplatin administration.

Furthermore, complete protection from vomiting was significantly better with ondansetron plus dexamethasone even on day 2 (83.9 vs. 68.0%) and day 3 (86.3 vs. 71.2%) after cisplatin administration, while all patients were receiving the same antiemetics for prophylaxis of delayed emesis.

The adverse events were significantly inferior with ondansetron plus dexamethasone; in particular, slight sedation was referred by 2.1% of patients treated with ondansetron and by 11.8% of those receiving high-dose metoclopramide, while extrapyramidal reactions were observed only with metoclopramide.

In conclusion, ondansetron plus dexamethasone seems to be the most efficacious and least toxic antiemetic therapy for prevention of cisplatin-induced emesis.

Recently, some large studies have evaluated the problem of the optimal dose and schedule of ondansetron [27–29]. In two double-blind studies [27, 28] a single 32 mg intravenous dose of ondansetron administered before cisplatin showed a similar efficacy and toxicity with respect to an 8 mg loading dose followed by a 24 h infusion of 1 mg/h.

One of these studies [28] involving 535 patients included a third arm in which patients received a single 8 mg intravenous dose before cisplatin chemotherapy. Control of emesis was similar in all groups with complete protection from vomiting in about 55% of patients.

Unfortunately, another double-blind American study [29] evaluating 699 patients did not confirm these results. In fact, the efficacy of an 8 mg intravenous single dose and 0.15 mg every 4 h × 3 of ondansetron was shown to be inferior to a 32 mg intravenous single dose.

In conclusion, more studies are needed to clarify the optimal dose and schedule of ondansetron. However, considering that one single dose simplifies antiemetic therapy and improves patient compliance, the 32 mg intravenous single dose may be considered the best choice in clinical practice.

Studies with repeated low doses of cisplatin (20–40 mg/m^2)

Few studies have been published in this particular group of generally young patients with testicular cancer. It is a common experience that repeated high doses of metoclopramide induce a high rate of extrapyramidal reactions and, therefore, the use of ondansetron can be especially helpful.

In two pilot studies [30, 31] ondansetron at doses of 0.15 mg/kg every 2–6 h three times daily for 4–5 days, showed an overall complete protection from vomiting in about 30% of patients and few adverse events.

A double-blind dose-finding study [32] in 90 patients showed that doses of 0.15–0.30 mg/kg three times daily of ondansetron were significantly more efficacious than 0.015 mg/kg doses. In Table 3 the results of the two published double-blind comparative studies are reported [33, 34]. Ondansetron was more efficacious than metoclopramide both when used alone and when combined with dexamethasone. Furthermore, while the incidence of extrapyramidal reactions in metoclopramide-treated patients was very high, inducing in one study [34] interruption of the antiemetic treatment after the first 2 days of cisplatin chemotherapy in 23% of patients, the tolerability of repeated doses of ondansetron was very good.

Therefore, in this particular group of patients, the combination of ondansetron plus dexamethasone, offering a very good activity and low toxicity, should be considered the antiemetic therapy of choice.

Studies on delayed emesis caused by high-dose cisplatin

Very few studies have been performed with ondansetron in the prevention of cisplatin-induced delayed emesis and only three double-blind trials have been published. In one of these [35], 48 patients with one or two episodes of vomiting during the initial 24-h post-cisplatin period were randomised to receive ondansetron (16 mg orally three times daily) or placebo for 4 days. The overall, but not the day to day, protection from vomiting was significantly superior with ondansetron but no statistical difference in the control of nausea was found.

No conclusions on the efficacy of ondansetron can be drawn from a second study [36] which compared in 25 patients the antiemetic activity of two doses of orally administered ondansetron (2 vs. 16 mg) and did not show any significant difference.

Table 3. Ondansetron in patients treated with cisplatin (20–25 mg/m^2 × 4–5 days)

Study	No. of patients	Antiemetics	C.P. (%)	Results	Reference
DB	45	OND 0.15 mg/kg i.v. × 3/day	78*	OND > MTC < toxicity	33
		MTC 1 mg/kg i.v. × 3/day	14*		
DB	95	OND 32 mg i.v./day + DEX 20 mg i.v./day	55	OND + DEX > MTC + DEX < toxicity	34
		MTC 2 mg/kg i.v. × 2/day + DEX 20 mg i.v./day	19		

OND = Ondansetron; MTC = metoclopramide; DEX = dexamethasone; C.P. = complete protection; *results at first day of chemotherapy; DB = double-blind, i.v. = intravenously.

Finally, in a comparison with oral metoclopramide (20 mg three times daily), oral ondansetron (8 mg three times daily) showed a similar efficacy in controlling delayed emesis, while nausea was significantly better controlled with metoclopramide [18].

In conclusion, the role of ondansetron in the prevention of delayed emesis is still to be defined; in particular, comparative studies vs. the available most effective antiemetic treatment (metoclopramide plus dexamethasone) are lacking.

STUDIES IN PATIENTS TREATED WITH MODERATELY EMETOGENIC ANTINEOPLASTIC DRUGS

Relatively few antiemetic therapy trials have been conducted in selected patients submitted to antineoplastic agents not containing cisplatin. Furthermore, several of these pilot studies included patients treated with antineoplastic combinations with different emetogenic power.

At present, both in the prevention of emesis induced by intravenous cyclophosphamide plus methotrexate plus 5-fluorouracil (CMF) or doxorubicin alone or in combination, high doses of steroids (methylprednisolone or dexamethasone) repeated every 4–6 h until at least 12 h after chemotherapy administration are the most efficacious and least toxic antiemetic drugs [37–40]. Instead, metoclopramide has shown contrasting results in the prevention of emesis induced by moderately emetogenic drugs [38, 39, 41].

The antiemetic activity of ondansetron has been evaluated in this group of patients in several pilot studies showing good efficacy even in patients refractory to the usual antiemetic drugs. The dose used was generally 8 mg orally three times daily (the first dose was sometimes administered intravenously).

Recently, two studies comparing different oral dosages of ondansetron have been published. One of these [42], in patients treated with doxorubicin plus cyclophosphamide, compared oral doses of 1, 4 and 8 mg three times daily. Ondansetron was very efficacious and its efficacy appears dose-related, with an 8 mg dose inducing 85% complete protection from vomiting. The other [43], performed in 324 patients receiving cyclophosphamide, doxorubicin or epirubicin plus other non-cisplatin cytostatics, compared 8 mg intravenously prior to chemotherapy followed by 8 mg orally twice daily vs. 8 mg three times daily. Both twice and three times daily dosing schedules provided similar control of nausea and emesis and were well tolerated. Therefore, from these studies it can be concluded that an 8 mg twice-daily oral dose of ondansetron would be optimal and convenient in the prevention of emesis in out-patient treatment with these chemotherapy regimens.

At present, three multicentre double-blind trials have been performed in breast cancer patients treated with the FAC and FEC combinations [44–46]. In these studies ondansetron was compared to metoclopramide administered at doses of 20 mg three times a day, orally (first dose 60 mg intravenously) (Table 4). Complete protection from vomiting was always superior with ondansetron, even if statistically significant in only one study. Both drugs were well tolerated, and only metoclopramide induced extrapyramidal reactions (5% of patients).

At present, only one comparative double-blind trial has been published comparing ondansetron with dexamethasone [47].

In 112 patients, receiving intravenous anthracycline and/or cyclophosphamide and/or etoposide, dexamethasone (8 mg intravenously before chemotherapy and 4 mg every 6 h

Table 4. Ondansetron vs. metoclopramide

Study	No. of patients	Chemotherapy	Antiemetic first dose†	Results* (%)	Comment	Reference
DB xo	65	FAC or FEC	OND 4 mg i.v. + 4 mg o.s.	86	OND > MTC > preference	44
			MTC 60 mg i.v. + 20 mg o.s.	42		
DB	93	CTX + DOX or Epi-DOX	OND 8 mg i.v.	80	OND > MTC	45
			MTC 60 mg i.v.	62		
DB	122	CTX + DOX or Epi-DOX	OND 8 mg o.s.	72	OND = MTC	46
			MTC 60 mg i.v.	61		

* ⩽2 emetic episodes; DB = double-blind; xo = crossover; MTC = metoclopramide; OND = ondansetron, †subsequent oral doses: OND 8 mg every 8 h, MTC 20 mg every 8 h; i.v. = intravenously.

reduced to 1 mg/dose between days 1 and 5) was shown to have an efficacy similar to ondansetron (4 mg intravenously and 4 mg every 6 h days 1–5) in controlling acute and delayed emesis and no significant differences were shown in the number of adverse events.

On the basis of this data and considering the cost of ondansetron, dexamethasone may remain the antiemetic of choice for prevention of emesis induced by moderately emetogenic antineoplastic drugs.

More studies are necessary to better evaluate the activity of ondansetron in this group of patients.

SIDE-EFFECTS

The safety profile of ondansetron seems very satisfactory. Side-effects are generally mild and infrequent. No extrapyramidal reactions have been published except in one report in which the patient had already received antidopaminergic drugs [48]. The most frequent side-effects are represented by headache (about 20% of patients) and constipation (5–10% of patients). A transitory increase in transaminase levels shown in pilot studies is probably secondary to cisplatin chemotherapy; in fact, when ondansetron was compared with metoclopramide the incidence of this side-effect was similar in the two groups of patients [49].

Furthermore, a retrospective study showed a dose-related effect and cumulative-dose effect of cisplatin on hepatic transaminase values [50].

CONCLUSIONS

Ondansetron is an efficacious antiemetic drug in preventing chemotherapy-induced nausea and vomiting. The drug is well tolerated and side-effects are mild.

For the prevention of acute emesis induced by a high single dose of cisplatin ($\geqslant 50$ mg/m^2) or by low doses (20–40 mg/m^2) repeated for 4–5 days the combination of ondansetron plus dexamethasone is the most efficacious and least toxic antiemetic therapy available today.

Is, therefore, this combination to be used routinely in all of these patients?

If we consider the relevant toxicity caused by high-dose metoclopramide-containing regimens when administered during consecutive days the answer could be yes. However, in the case of prevention of emesis induced by a high single dose of cisplatin even the metoclopramide combination, although significantly inferior to ondansetron plus dexamethasone, protects many patients from nausea and vomiting. Furthermore, the incidence of extrapyramidal reactions is low and generally easily controlled by appropriate therapy. Therefore, considering the high cost of ondansetron, the definitive choice can be based only on a cost-benefit analysis which is still lacking.

For the prevention of delayed emesis induced by cisplatin, the activity of ondansetron is not well defined. In particular, comparative studies, using ondansetron alone or in combination with dexamethasone, with standard antiemetic regimens are needed.

Finally, for the prevention of emesis induced by moderately emetogenic drugs ondansetron is still indicated only in those patients refractory to steroids. In this group of patients the activity of ondansetron combined with steroids vs. steroids alone needs to be studied.

1. Tyers MB, Bunce KT, Humphrey PPA. Pharmacological and anti-emetic properties of ondansetron. *Eur J Cancer Clin Oncol* 1989, **25**, S15–S19.
2. Higging GA, Kilpatrick GJ, Bunce KT, *et al.* 5-HT$_3$ receptor antagonists injected into the area postrema inhibit cisplatin-induced emesis in the ferret. *Br J Pharmacol* 1989, **97**, 247–255.
3. Blackwell CP, Harding SM. The clinical pharmacology of ondansetron. *Eur J Cancer Clin Oncol*, 1989, **25**, S21–S24.
4. Tucker ML, Jackson MR, Scales MDC, *et al.* Ondansetron: preclinical safety evaluation. *Eur J Cancer Clin Oncol* 1989, **25**, S79–S93.
5. Kris MG, Gralla RJ, Clark RA, *et al.* Antiemetic control and prevention of side effects of anti-cancer therapy with lorazepam or diphenhydramine when used in combination with metoclopramide plus dexamethasone. *Cancer* 1987, **60**, 2816–2822.
6. Roila F, Tonato M, Basurto C, *et al.* Protection from nausea and vomiting in cisplatin-treated patients: high-dose metoclopramide combined with methylprednisolone versus metoclopramide with dexamethasone and diphenhydramine: a study of the Italian Oncology Group for Clinical Research. *J Clin Oncol* 1989, 7, 1693–1700.
7. Roila F, Basurto C, Bracarda S, *et al.* Double-blind crossover trial of single vs divided dose of metoclopramide in a combined regimen for treatment of cisplatin-induced emesis. *Eur J Cancer* 1991, **27**, 119–121.
8. Kris MG, Gralla RJ, Tyson LB, *et al.* Controlling delayed vomiting: double-blind randomized trial comparing placebo, dexamethasone alone, and metoclopramide plus dexamethasone in patients receiving cisplatin. *J Clin Oncol* 1989, 7, 108–114.
9. Kris MG, Gralla RJ, Clark RA, *et al.* Dose-ranging evaluation of the serotonin antagonist GR-C507/75 (GR38032F) when used as an antiemetic in patients receiving anticancer chemotherapy. *J Clin Oncol* 1988, **6**, 659–662.
10. Kris MG, Gralla RJ, Clark RA, *et al.* Phase II trials of the serotonin antagonist GR38032F for the control of vomiting caused by cisplatin. *J Natl Cancer Inst* 1989, **81**, 42–46.
11. Grunberg SM, Stevenson LL, Russell CA, *et al.* Dose ranging Phase I study of the serotonin antagonist GR38032F for prevention of cisplatin-induced nausea and vomiting. *J Clin Oncol* 1989, 7, 1137–1141.
12. Hesketh PJ, Murphy WK, Lester EP, *et al.* GR38032F (GR-C507/75): a novel compound effective in the prevention of acute cisplatin-induced emesis. *J Clin Oncol*, 1989, 7, 700–705.
13. Marty M, Droz JP, Pouillart P, *et al.* GR38032F, a 5HT$_3$ receptor antagonist, in the prophylaxis of acute cisplatin-induced nausea and vomiting. *Cancer Chemother Pharmacol* 1989, **23**, 389–391.
14. De Haan LD, De Mulder PHM, Beex LVAM, *et al.* The efficacy of GR38032F an antagonist of 5-Hydroxytryptamine-$_3$ (5-HT$_3$) in the prophylaxis of cisplatin (CDDP)-induced nausea and vomiting. *Eur J Cancer Clin Oncol* 1988, **24**, 1383–1384.
15. Roila F, Bracarda S, Tonato M, *et al.* Ondansetron (GR38032F) in the prophylaxis of acute and delayed cisplatin-induced emesis. *Clin Oncol* 1990, **2**, 268–272.
16. Lane M, Grunberg SM, Lester EP, *et al.* A double-blind comparison of three dose levels of i.v. ondansetron in the prevention of cisplatin-induced nausea and vomiting. *Proc ASCO* 1990, **9**, 329.
17. Marty M, Pouillart P, Scholl S, *et al.* Comparison of the 5-hydroxytryptamine-$_3$ (serotonin) antagonist ondansetron (GR38032F) with high-dose metoclopramide in the control of cisplatin-induced emesis. *N Engl J Med* 1990, **322**, 816–821.
18. De Mulder PHM, Seynaeve C, Vermorken JB, *et al.* Ondansetron compared with high-dose metoclopramide in prophylaxis of acute and delayed cisplatin-induced nausea and vomiting. A multicenter, randomized, double-blind, crossover study. *Ann Intern Med* 1990, **113**, 834–840.
19. Hainsworth J, Harvey W, Pendergrass K, *et al.* A single-blind comparison of intravenous ondansetron, a selective serotonin antagonist, with intravenous metoclopramide in the prevention of nausea and vomiting associated with high-dose cisplatin chemotherapy. *J Clin Oncol* 1991, **9**, 721–728.
20. Hawthorn J, Cunningham D. Dexamethasone can potentiate the anti-emetic action of a 5-HT$_3$ receptor antagonist on cyclophosphamide induced vomiting in the ferret. *Br J Cancer* 1990, **61**, 56–60.
21. Cunningham D, Turner A, Hawthorn J, *et al.* Ondansetron with and without dexamethasone to treat chemotherapy-induced emesis. *Lancet* 1989, **1**, 1323.

22. Smith DB, Newlands ES, Spruyt OW, *et al.* Ondansetron (GR38032F) plus dexamethasone: effective anti-emetic prophylaxis for patients receiving cytotoxic chemotherapy. *Br J Cancer* 1990, **61**, 323–324.
23. Roila F. Tonato M, Cognetti F, *et al.* Prevention of cisplatin-induced emesis: a double-blind multicenter randomized cross-over study comparing ondansetron and ondansetron plus dexamethasone. *J Clin Oncol* 1991, **9**, 675–678.
24. Smith DB, Newlands ES, Rustin GJS, *et al.* Comparison of ondansetron and ondansetron plus dexamethasone as antiemetic prophylaxis during cisplatin-containing chemotherapy. *Lancet* 1991, **338**, 487–490.
25. Smyth JF, Coleman RE, Nicolson M, *et al.* Does dexamethasone enhance control of acute cisplatin induced emesis by ondansetron? *Br Med J* 1991, **303**, 1423–1426.
26. Roila F, Tonato M, Favalli G, *et al.* A multicenter double-blind study comparing the antiemetic efficacy and safety of ondansetron (OND) plus dexamethasone (DEX) vs metoclopramide (MTC) plus DEX and diphenhydramine (DIP) in cisplatin (CDDP) treated cancer patients (pts). *Proc ASCO* 1992, **11**, 394.
27. Marty M, d'Allens H et le Groupe Multicentrique Français. Etude randomisèe en double-insu comparant l'efficacité de l'ondansetron selon deux modes d'administration: injection unique et perfusion continue. *Cahiers Cancer* 1990, **2**, 541–546.
28. Seynaeve C, Paes D, Verweij J, *et al.* Ondansetron, effective as a single intravenous dose in the prevention of acute cisplatin-induced emesis. Abstract of Internist Days '91 of the Dutch Internists Association, Veldhoven, Koningshof, 1991, 104.
29. Beck TM, Madajewicz S, Navari RM, *et al.* A double blind, stratified, randomized comparison of intravenous (i.v.) ondansetron administered as a multiple dose regimen versus two single dose regimens in the prevention of cisplatin-induced nausea and vomiting. *Proc ASCO* 1992, **11**, 378.
30. Hainsworth JD, Omura GA, Khojasteh A, *et al.* Ondansetron (GR38032F): a novel antiemetic effective in patients receiving a multiple-day regimen of cisplatin chemotherapy. *Am J Clin Oncol (CCT)* 1991, **14**, 336–340.
31. Einhorn LH, Nagy C, Werner K, *et al.* Ondansetron: a new antiemetic for patients receiving cisplatin chemotherapy. *J Clin Oncol* 1990, **8**, 731–735.
32. Burton G, Huang A, Lazarus H, *et al.* A double-blind randomized comparison of three doses of i.v. ondansetron for prevention of emesis induced by multi-day cisplatin therapy. *Proc ASCO* 1990, **9**, 328.
33. Sledge GW, Einhorn LH, Nagy C, *et al.* Randomized trial of ondansetron and metoclopramide as antiemetic therapy for cisplatin-based chemotherapy. *Proc ASCO* 1990, **9**, 323.
34. Weissbach L for the Multi-day Cisplatin Emesis Study Group. Ondansetron. *Lancet* 1991, **338**, 753.
35. Gandara DR. Progress in the control of acute and delayed emesis induced by cisplatin. *Eur J Cancer* 1991, **27** (Suppl. 1), S9–S11.
36. Grunberg SM, Groshen S, Stevenson LL, *et al.* Double blind randomized study of 2 doses of oral ondansetron (GR38032F) for the prevention of cisplatin-induced delayed nausea and vomiting. *Proc ASCO* 1990, **9**, 327.
37. Markman M, Sheidler V, Ettinger DS, *et al.* Antiemetic efficacy of dexamethasone. Randomized, double-blind, crossover study with prochlorperazine in patients receiving cancer chemotherapy. *N Engl J Med* 1984, **311**, 549–552.
38. Basurto C, Roila F, Bracarda S, *et al.* A double-blind trial comparing antiemetic efficacy and toxicity of metoclopramide versus methylprednisolone versus domperidone in patients receiving doxorubicin chemotherapy alone or in combination with other antiblastic agents. *Am J Clin Oncol (CCT)* 1988, **11**, 594–596.
39. Roila F, Basurto C, Minotti V, *et al.* Methylprednisolone versus metoclopramide for prevention of nausea and vomiting in breast cancer patients treated with intravenous cyclophosphamide, methotrexate, 5-fluorouracil: a double-blind randomized study. *Oncology* 1988, **45**, 346–349.
40. Chiara S, Campora E, Lionetto R, *et al.* Methylprednisolone for the control of CMF-induced emesis. *Am J Clin Oncol (CCT)* 1987, **10**, 264–267.
41. Edge SB, Funkhouser WK, Berman A, *et al.* High-dose oral and intravenous metoclopramide in doxorubicin/cyclophosphamide induced emesis. *Am J Clin Oncol (CCT)* 1987, **10**, 257–263.
42. Fraschini G, Ciociola A, Esparza L, *et al.* Evaluation of three oral dosages of ondansetron in the prevention of nausea and emesis associate with cyclophosphamide—doxorubicin chemotherapy. *J Clin Oncol* 1991, **9**, 1268–1274.
43. Dicato MA. Oral treatment with ondansetron in an outpatient setting. *Eur J Cancer* 1991, **27** (Suppl.1), S18–S19.
44. Bonneterre J, Chevallier B, Metz R, *et al.* A randomized double-blind comparison of ondansetron and metoclopramide in the prophylaxis of emesis induced by cyclophosphamide, fluorouracil, and doxorubicin or epirubicin chemotherapy. *J Clin Oncol* 1990, **8**, 1063–1069.
45. Kaasa S, Kvaloy S, Dicato MA, *et al.* A comparison of ondansetron with metoclopramide in the prophylaxis of chemotherapy-induced nausea and vomiting: a randomized, double-blind study. *Eur J Cancer* 1990, **26**, 311–314.
46. Marschner NW, Adler M, Nagel GA, *et al.* Double-blind randomised trial of the antiemetic efficacy and safety of ondansetron and metoclopramide in advanced breast cancer patients treated with epirubicin and cyclophosphamide. *Eur J Cancer* 1991, **27**, 1137–1140.
47. Jones AL, Hill AS, Soukop M, *et al.* Comparison of dexamethasone in the prophylaxis of emesis induced by moderately emetogenic chemotherapy. *Lancet* 1991, **338**, 483–487.
48. Dobrow RB, Coppock MA, Hosenpud JR. Extrapyramidal reaction caused by ondansetron. *J Clin Oncol* 1991, **9**, 1921.
49. Smith RN. Safety of ondansetron. *Eur J Cancer Clin Oncol* 1989, **25**, S47–S50.
50. Hesketh PJ, Twaddell T, Finn A. A possible role for cisplatin in the transient hepatic enzyme elevations noted after ondansetron administration. *Proc ASCO* 1990, **9**, 323.