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# Introduction

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## Introduction

Nausea and vomiting are frequent, serious and often persistent side effects of cancer chemotherapy and radiotherapy. Indeed, patients rank nausea and vomiting as the worst side effects of chemotherapy.[1]

Emesis following chemotherapy is classified as acute, occurring during the first 24 h following chemotherapy, and delayed, which is normally less severe and lasts from 24 h up to 5 or more days after treatment. In addition, some patients who suffer nausea and vomiting after chemotherapy subsequently experience anticipatory emesis before receiving further courses of chemotherapy.[2]

The incidence and severity of chemotherapy-induced emesis varies according to the emetogenic potential of the chemotherapy administered and several patient factors. High-dose cisplatin (50 mg/m$^2$) is more emetogenic than the majority of drugs (Figure 1). If anti-emetics are not administered over 90% of patients will experience up to 25 emetic episodes in the first 24 h following cisplatin treatment.[3] Clinical assessments of an anti-emetic are therefore divided into highly emetogenic and less emetogenic regimens.

Some patient variables other than the emetogenic potential of the chemotherapy administered, are also relevant. Young patients are more prone to vomiting[4] and women experience more emesis than do men.[5] Patients who are susceptible to motion sickness,[6] or who have previously experienced emesis due to anti-neoplastic therapy, may also experience more nausea and vomiting.[3] However, patients with a history of high alcohol consumption vomit less easily.[7]


Cisplatin
Cyclophosphamide
Doxorubicin
Methotrexate
5-Fluorouracil
Vincristine

**Figure 1.** Emetogenic potential of chemotherapeutic agents.

Despite the use of conventional anti-emetics, approximately 40% of patients experience significant emesis. Furthermore, drugs such as metoclopramide often induce distressing extrapyramidal reactions as a result of dopamine receptor antagonism.[8] Ondansetron prevents emesis by blocking 5-hydroxytryptamine$_3$ (5-HT$_3$) receptors at two sites: vagal afferent nerves that innervate the gastrointestinal tract; and the same vagal nerves in the chemoreceptor trigger zone and hindbrain vomiting system.

### Ondansetron *vs* metoclopramide

Before the introduction of the 5-HT$_3$ receptor antagonists, metoclopramide was generally regarded as the most effective anti-emetic in adult cancer patients. Therefore six randomized double-blind comparative studies were carried out to compare ondansetron with metoclopramide. Due to the variable potency of chemotherapy to induce emesis, ondansetron has been studied in patients receiving: highly emetogenic (cisplatin) chemotherapy, less emetogenic (non-cisplatin) chemotherapy and radiotherapy. These studies were carried out using published[9] and widely accepted response criteria (Table 1).

**Table 1.** Definitions of response

| | |
|---|---|
| Emesis | |
| Complete response | No emetic episodes[a] |
| Major response | 1–2 emetic episodes |
| Minor response | 3–5 emetic episodes |
| Failure | >5 emetic episodes |
| Nausea | |
| None | |
| Mild | Did not interfere with normal daily life |
| Moderate | Interfered with daily life |
| Severe | Bedridden due to nausea |

[a] Emetic episode = one vomit or one retch—vomit not productive of liquid (dry heave).

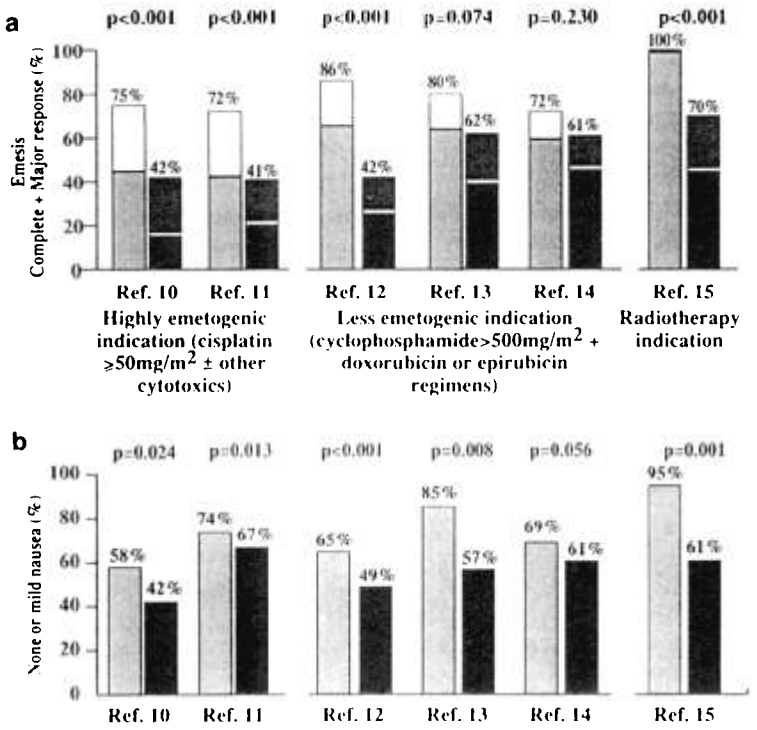


**Figure 2.** Summary of results of six studies of efficacy of ondansetron (□ and ▨) and metoclopramide (■ and ▩) against **a** emesis and **b** nausea (day 1).[10-15] Highly emetogenic indications were: cisplatin >50 mg/m² ± other cytotoxics); less emetogenic indications were: cyclophosphamide >500 mg/m² + doxorubicin or epirubicin regimens. For emesis, M = major control; C = complete control.

Emesis was considered to be successfully treated in patients who experienced two or fewer emetic episodes (including retching). Nausea was successfully treated in those who graded it as none or mild (i.e., nausea did not interfere with normal daily life).

In the cisplatin studies, ondansetron was given as an 8 mg intravenous loading dose before chemotherapy followed by a 1 mg/h infusion for 24 h. Patients receiving less emetogenic chemotherapy or radiotherapy were given an intravenous or oral loading dose of ondansetron (8 mg) followed by 8 mg orally every 8 h. In all studies, ondansetron was superior to metoclopramide in the control of nausea and emesis over the first 24 h after treatment when symptoms are normally most severe (Figure 2).

In the non-cisplatin studies, ondansetron was given orally three times a day for up to 5 days. A meta-analysis of the combined data from these studies shows that ondansetron is superior to metoclopramide over this period (Figure 3); this reached statistical significance on days 2 and 4.[16]

Ondansetron was well tolerated in these studies. Unlike metoclopramide, ondansetron did not include any extrapyramidal reactions. The only side effects that occurred more frequently after ondansetron administration were headaches and constipation, in 11 and 4% of patients, respectively (Table 2).

## Ondansetron plus dexamethasone

Corticosteroids have been shown to enhance the anti-emetic effects of drugs such as metoclopramide[17] and alizapride.[18] Two randomized, double-

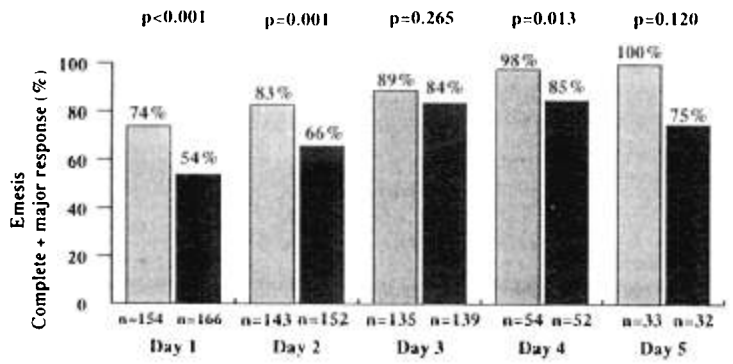


**Figure 3.** Efficacy of ondansetron (□) compared with metoclopramide (▩) over days 1–5 following non-cisplatin chemotherapy (combined data: meta-analysis).

**Table 2.** Number of patients reporting adverse events in ondansetron *vs* metoclopramide studies

| | No. of patients (%) | | | |
|---|---|---|---|---|
| | Ondansetron | | Metoclopramide | |
| | group | ($n$ = 461) | group | ($n$ = 403) |
| Extrapyramidal reaction | 0 | 0% | 12 | 3% |
| Headaches | 50 | 11% | 24 | 6% |
| Tiredness | 22 | 5% | 33 | 8% |
| Constipation | 1 | 4% | 5 | 1% |
| Diarrhoea | 1 | 2% | 21 | 5% |
| Abnormal liver function tests | 10 | 2% | 9 | 2% |

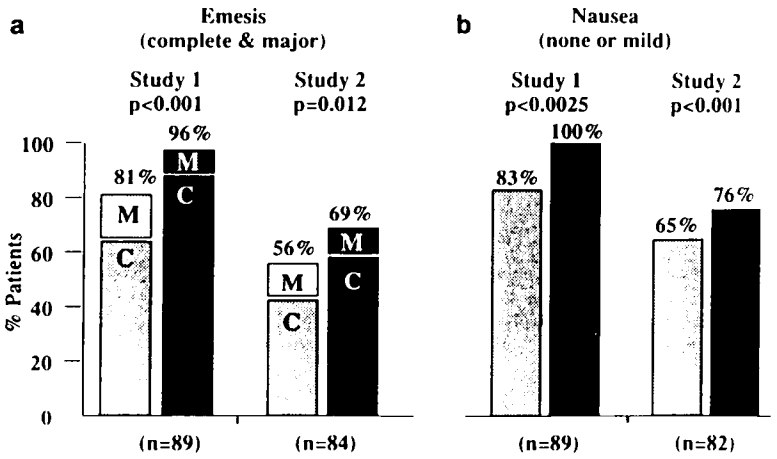


**Figure 4.** Efficacy of ondansetron plus dexamethasone (■ and □) compared with ondansetron alone (■ and ■) in the control of **a** emesis and **b** nausea following high-dose cisplatin chemotherapy. For emesis, M = major control, C = complete control.

blind crossover studies were therefore performed to investigate whether control of acute emesis could be enhanced by the addition of dexamethasone to ondansetron in patients receiving high-dose cisplatin.[19,20] In both studies ondansetron plus dexamethasone was significantly superior to ondansetron alone (Figure 4). Ondansetron plus dexamethasone is also superior to ondansetron alone in patients receiving multi-day chemotherapy (cisplatin,[21] POMB[22]). Furthermore, ondansetron given alone or in combination with dexamethasone was well tolerated, with no significant differences between the two treatment regimens.

## Simplified dosing

Three further randomized double-blind studies[23] have demonstrated that a single intravenous dose of ondansetron (8–32 mg) is as effective as the continuous infusion schedule used in the initial studies (Figure 5).

One of the studies carried out in the United States showed that a 32 mg intravenous single dose was superior to an 8 mg intravenous single dose in patients receiving very high doses of cisplatin. Since it is known that the degree of emesis is related to several prognostic factors as well to the cisplatin regimens, the selection of an appropriate single

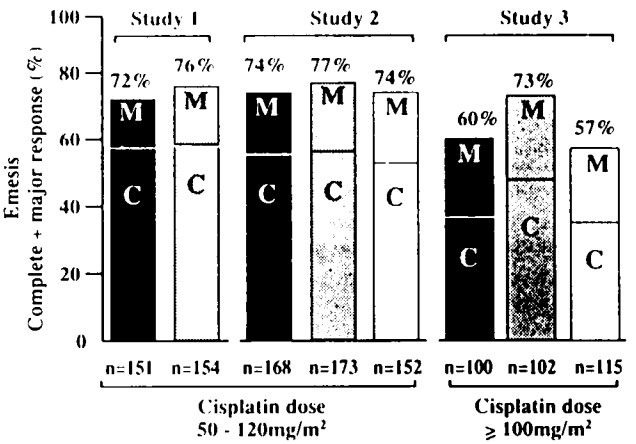


**Figure 5.** Control of acute cisplatin-induced emesis with ondansetron given as a continuous infusion (8 mg + 24 mg) (■); as an intermittent dose (0.15 mg kg × 3) (■); as single dose of 32 mg (□); or a single dose of 8 mg (□). For emesis, M = major control, C = complete control.

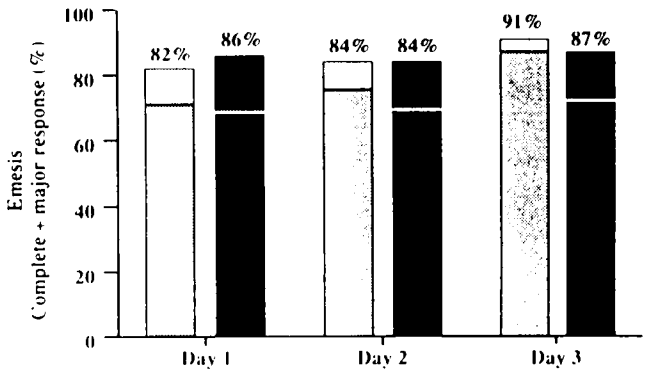


**Figure 6.** Comparison of anti-emetic efficacy of ondansetron twice daily (□ and ▨) *vs* three times daily (■ and ■).

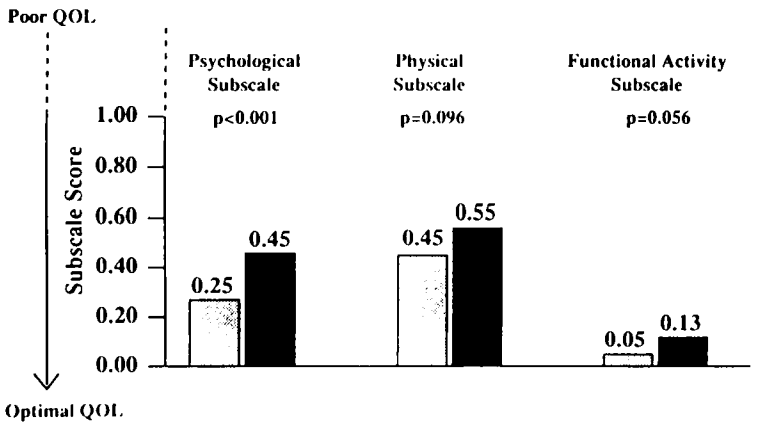


**Figure 7.** Quality of life (QOL) assessments in patients receiving ondansetron (□) or metoclopramide (■) over one to six courses of chemotherapy.

intravenous prophylactic dose of ondansetron (8 -32 mg) should be based on the anticipated emetogenic challenge and patient factors. In addition, it has been shown that following an initial 8 mg intravenous dose, 8 mg orally twice daily is as effective as the same dose given three times a day[24] (Figure 6).

### Ondansetron and quality of life

A recent study comparing ondansetron plus dexamethasone with metoclopramide plus dexamethasone in patients scheduled to receive six courses of chemotherapy for breast cancer, assessed patients' quality of life using a validated questionnaire, the Rotterdam Symptom Checklist.[25] The study showed that emesis in patients given ondansetron was significantly better controlled than in those patients given metoclopramide, and that this response was significantly better maintained over the six courses of chemotherapy. Moreover, patients given ondansetron had a better quality of life, particularly psychological well being, compared with those given metoclopramide (Figure 7).

## Conclusions

Ondansetron is an extremely effective and well tolerated anti-emetic in adult patients receiving chemotherapy or radiotherapy. It is therefore a major advance in the supportive care of these patients.

### References

1. Coates A, Abraham S, Kaye SB, *et al.* On the receiving end: patient perception of the side effects of cancer therapy. *Eur J Cancer Clin Oncol* 1983; **19:** 203-8.
2. Gralla RJ, Tyson LB, Kris MG, *et al.* The management of chemotherapy induced nausea and vomiting. *Med Clin N Amer* 1987; **71:** 289-301.
3. Gralla RJ, Iri LM, Pisko SE, *et al.* Anti-emetic efficacy of high dose metoclopramide: randomized trials with placebo and prochlorperazine in patients with chemotherapy induced nausea and vomiting. *N Engl J Med* 1981; **305:** 905-9.
4. Roila F, Tonato M, Basurto C. Protection from nausea and vomiting in cisplatin-treated patients: high-dose metoclopramide combined with dexamethasone and diphenhydramine: a study. *J Clin Oncol* 1989; 7: 1693-700.
5. Roila F, Tonato M, Basurto C. Anti-emesis activity of high doses of metoclopramide in cisplatin treated cancer

patients: a randomized double blind trial. *J Clin Oncol* 1988; **5:** 111-49.
6. Morrow GR. Chemotherapy related nausea and vomiting: etiology and management. *CAA Cancer Treat J* 1989; **39:** 89-104.
7. D'Acquisto RW, Tyson LB, Gralla RJ. The influence ofchronic high alcohol intake on chemotherapy-induced nausea and vomiting. *Proc Am Soc Clin Oncol* 1986; **5:** 257.
8. Kris MG, Tyson LB, Gralla RJ, *et al.* Extrapyramidal reaction with high-dose metoclopramide. *N Eng J Med* 1983; **309:** 433-4.
9. Kris MG, Gralla RJ, Tyson B, *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:** 108-14.
10. 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:** 816-21.
11. 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. *Ann Intern Med* 1990; **113:** 834-40.
12. 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:** 1063-9.
13. 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:** 311-4.
14. Marschner NW, Adler M, Nagel GA, *et al.* Double-blind randomized trial of the anti-emetic efficacy and safety of ondansetron and metoclopramide in advanced breast cancer patients treated with epirubicin and cyclophosphamide. *Eur J Cancer* 1991; **27:** 1137-40.
15. Priestman TJ, Roberts JT, Lucraft H, *et al.* Results of a randomized, double-blind comparative study of ondansetron and metoclopramide in the prevention of nausea and vomiting following high-dose upper abdominal irradiation. *Clin Oncol* 1990; **2:** 71-5.
16. Schmoll HI. The role of ondansetron in the treatment of emesis induced by non cisplatin-containing chemotherapy regimes. *Eur J Cancer Oncol* 1989; **25(Suppl 1):** 535-9.
17. Kris MG, Gralla RJ, Tyson LB, *et al.* Improved control of cisplatin-induced with high dose metoclopramide and with combinations of metoclopramide, dexamethasone and diphenydramine. *Cancer* 1985; **5:** 141-9.
18. Pollera CF, Nardi M, Marolla P, *et al.* Randomized trial comparing alizapride alone or with dexamethasone vs a metoclopramide dexamethasone combination for emesis induced by moderate-dose cisplatin. *Cancer Chemother Pharmacol* 1987; **19:** 335-8.
19. Roila F, Tonato M, Cognetti F, *et al.* Prevention of cisplatin induced emesis: a double-blind multicenter randomized crossover study comparing ondansetron and ondansetron plus dexamethasone. *J Clin Oncol* 1991; **9:** 675-8.
20. Smyth JF, Coleman RL, Nicolson M, *et al.* Does dexamethasone enhance control of acute cisplatin-induced emesis by ondansetron? *Br Med J* 1991; **303:** 1423-6.
21. Arechevala E, Aulizky W, Boeckmann W, *et al.* A randomised double-blind comparative of ondansetron (OND) plus dexamethasone (DEX) with metoclopramide (MCP) plus DEX as anti-emetic prophylaxis during multi-day cisplatin therapy. *Proc Am Soc Clin Oncol* 1992; **11** Abstract no. 1369.
22. Smith DB, Newlands ES, Rustin GJS, *et al.* Comparison of ondansetron and ondansetron plus dexamethasone as anti-emetic prophylaxis during cisplatin-containing chemotherapy. *Lancer* 1991; **338:** 487-90.
23. Brown GW, Paes D, Bryson J, *et al.* The effectiveness of a single intravenous dose of ondansetron. *Oncology* 1992; **49:** 273-8.
24. Dicato MA. Oral treatment with ondansetron in an outpatient setting. *Eur J Cancer* 1991; **27(Suppl 1):** S18-9.
25. Soukop M, McQade B, Hunter E, *et al.* Ondansetron compared with metoclopramide in the control of emesis and quality of life during repeated chemotherapy for breast cancer. *Oncology* 1992; **49:** 295-304.