Pergamon

European Journal of Cancer Vol. 33, No. 1, pp. 66–74, 1997

Printed in Great Britain
0959-8049/97 $17.00+0.00

PII: S0959-8049(96)00276-6

Original Paper

An Overview of Randomised Studies Comparing 5-HT_3 Receptor Antagonists to Conventional Anti-emetics in the Prophylaxis of Acute Chemotherapy-induced Vomiting

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Ten years after it was demonstrated in the ferret that cisplatin-induced emesis could be blocked by the selective 5-HT_3 receptor antagonist MDL 72222, 5-HT_3 receptor antagonists have become routine anti-emetic agents for chemotherapy-induced emesis. However, although in association with highly emetogenic, mainly cisplatin-containing regimens, the use of these agents is well justified, the net benefit of 5-HT_3 receptor antagonists in association with moderately emetogenic regimens has not been that well clarified. Here, we present an overview of 30 randomised studies comparing 5-HT_3 antagonists with the conventional anti-emetics in the prophylaxis of acute vomiting induced by cytotoxic chemotherapy. A meta-analysis showed that 5-HT_3 antagonists reduce the risk of acute vomiting in comparison to conventional anti-emetics both with cisplatin treatments (15 trials; odds ratio 0.60; 95% confidence interval 0.51–0.70) and with moderately emetogenic treatments (11 trials; odds ratio 0.47; 95% confidence interval 0.39–0.58). The risk of acute vomiting seems to be further reduced when 5-HT_3 antagonists are combined with dexamethasone.

Key words: chemotherapy, cisplatin, emesis, serotonin antagonists, ondansetron, granisetron, tropisetron, metoclopramide

Eur J Cancer, Vol. 33, No. 1, pp. 66–74, 1997

INTRODUCTION

RECENT ANTI-EMETIC research has emphasised the role of serotonin (5-hydroxytryptamine, 5-HT) in the pathophysiology of chemotherapy-induced emesis. Cytotoxic chemotherapy appears to release serotonin from the enterochromaffin cells in the upper gastrointestinal tract [1, 2]. The initiation of the emetic reflex is most likely produced via 5-HT_3 receptors located on vagal afferent nerves in the gut [3]. In 1986 Miner and Sanger performed an important study demonstrating block of cisplatin-induced emesis in the ferret by the selective 5-HT_3 receptor antagonist MDL 72222 [4]. This observation led to the development of several highly selective 5-HT_3 receptor antagonists for the control of cancer chemotherapy-related emesis. Today there are three highly selective 5-HT_3 receptor antagonists commercially available: ondansetron (GR38032F), granisetron (BRL43694) and tropisetron (ICS 205-930). There are differences in the affinities and specificities of ondansetron, granisetron and tropisetron for 5-HT_3 receptors in different experimental conditions [5, 6]. However, these differences have not been shown to be clinically relevant [7]. The doses and schedules of ondansetron have varied in different anti-emetic trials. A single prophylactic dose has been recommended for granisetron (3 mg i.v.) and tropisetron (5 mg i.v. or orally).

Cisplatin is one of the most highly emetogenic agents in common use. Cisplatin can induce two distinct patterns of emesis: acute and delayed. Acute emesis occurs 2–6 h after

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Received 13 Feb. 1996; revised 31 May 1996; accepted 12 Jul. 1996.

the start of chemotherapy infusion. The severity of acute emesis is directly related to the cisplatin dose. Administration of cisplatin results in a median of 10 emetic episodes within the first 24 h if no anti-emetics are used [8, 9]. Delayed emesis occurs more than 24 h after the chemotherapy, although the division between the two phases is not clearly defined. Acute phase nausea and vomiting parallels plasma serotonin release. Whilst there is a significant urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion increase 4–8 h after the start of cisplatin infusion [2, 10], there is no increased serotonin release during the delayed phase.

Serotonin may trigger the early, intense period of emesis, but although serotonin may have some effect during the delayed phase, it may not be the major cause [11]. Until the introduction of the selective 5-HT_3 antagonists, high-dose intravenous metoclopramide with dexamethasone and diphenhydramine or lorazepam was the treatment of choice for cisplatin-induced emesis. With this combination, complete protection from acute emesis has been obtained in 60% of patients at first cycle of cisplatin chemotherapy [12]. Unfortunately, extrapyramidal symptoms, nervousness and sedation, related to incidental blockade of dopamin receptors, were the unpleasant side-effects of high-dose metoclopramide especially in younger patients [8].

Most commonly used chemotherapy regimens are considered as moderately emetogenic [13]. Cyclophosphamide, especially in combinations with anthracyclines, is used widely in the treatment of solid tumours. The emetic profile of cyclophosphamide differs from that of cisplatin. Cyclophosphamide induces a single prolonged pattern of emesis with a late onset at 9–18 h after chemotherapy [14]. Cyclophosphamide-induced vomiting and particularly nausea may persist for several days. Urinary 5-HIAA excretion following the administration of cyclophosphamide is not markedly increased compared with the acute phase of cisplatin [15]. It was found that 80–90% of patients receiving cyclophosphamide-containing chemotherapy at a dose equal to or higher than 450 mg/m^2 experience vomiting if no anti-emetics are used [16, 17]. Dexamethasone and oral metoclopramide have been the standard anti-emetics for cyclophosphamide-containing chemotherapy, with 50–80% of patients reporting no emetic episodes over the first 24 h [18, 19].

During the development of all the 5-HT_3 antagonists, control of vomiting has been measured by counting the number of vomits and retches. Control is classified as complete with no vomits or retches. Since patients often consider nausea to be even more distressing than vomiting, control of vomiting alone is probably an inadequate measure of therapeutic success [20]. However, no consensus on the criteria for assessment of nausea has been reached. An ideal anti-emetic study should be double blind to avoid unintentional bias in assessment of anti-emetic efficacy. Cross-over design studies do allow patient and physician preference to be assessed. As the natural course of chemotherapy-induced emesis is to worsen progressively with successive chemotherapy courses, the cross-over design is particularly open to carryover effects and may favour the first anti-emetic treatment of the sequence [21]. In the parallel-group design patients should be carefully stratified according to factors

Table 1. 5-HT_3 receptor antagonists in the prophylaxis of acute vomiting induced by cisplatin compared to high-dose metoclopramide. Response as % of patients with no emetic episodes during the first 24 h. "Total" indicates the pooled number of patients and the weighted average response rate

Reference	No.of patients Study arm/ Comparator arm	Cisplatin dose (mg/m^2)	5-HT_3 antagonist	Response (%)	Comparator*	Response (%)
Hainsworth [22]	136/138	>100	Ondansetron	40	HD-MCP	30
De Mulder [23]	95†	50-100	Ondansetron	40	HD-MCP	25
Marty [24]	76†	80-100	Ondansetron	46	HD-MCP	16
Tsavaris [25]	42/42	100	Ondansetron	26	HD-MCP	26
Warr [26]	74/75	>50	Granisetron	46	HD-MCP+ DEX + DIPH	44
Marty [27]	143/138	>49	Granisetron	70	HD-MCP + DEX	67
Sismondi [28]	98†	Mean dose 60	Granisetron	67	HD-MCP+ DEX + LOR + ORP	48
Heron [29]	119/121	>50	Granisetron	56	HD-MCP + DEX	52
Chiou [30]	20/20	ND	Granisetron	80	HD-MCP	45
Sorbe [31]	131/128	50-89	Tropisetron	63	HD-MCP + DEX	64
Sorbe [32]	33/33	50-75	Tropisetron	82	HD-MCP + DEX	82
Chang [33]	(60/59)†	>50	Tropisetron	48	HD-MCP+ DEX + DIPH + LOR	29
Italian group [34]	136/131	>50	Ondansetron+ DEX	79	HD-MCP+ DEX + DIPH	60
Navari [35]	40/40	70-100	Ondansetron+ DEX	92	HD-MCP+ DEX + LOR+ DIPH	90
Cunningham [36]	117/120	mean dose 70	Ondansetron+ DEX	73	HD-MCP+ DEX + LOR	56
Total	1320/1314			60		49

*HD-MCP, high-dose metoclopramide; DEX, dexamethasone; DIPH, diphenhydramine; LOR, lorazepam; ORP, orphenadrine.
†Cross-over study; ND, no data.

(age, sex, previous chemotherapy, alcohol consumption) affecting chemotherapy induced vomiting [21].

The anti-emetic activity of 5-HT_3 receptor antagonists has been proven in many clinical studies since the late 1980s. The present knowledge and clinical experience support the use of 5-HT_3 antagonists for acute emesis in association with highly emetogenic chemotherapy regimens. However, what is the actual net benefit of the use of 5-HT_3 antagonists in association with moderately emetogenic chemotherapy regimens seems somewhat controversial. In this article, we describe an overview of the randomised studies published until April 1996 comparing 5-HT_3 receptor antagonists with the conventional anti-emetics in the prophylaxis of acute vomiting induced by cytotoxic chemotherapy.

MATERIALS AND METHODS

In April 1996, a search was performed on the Medline database with the following criteria: randomised trial published in English, comparison between a 5-HT_3 antagonist and any other anti-emetic therapy for adult patients receiving cytotoxic chemotherapy. A total of 27 articles describing the results of 28 trials were found. Two additional trials were identified from the abstract book of the ESMO meeting held in November 1994. Results of eleven trials comparing the efficacy of 5-HT_3 antagonist and dexamethasone with a 5-HT_3 antagonist as a single agent were also evaluated.

The reports were summarised using a standardised summary form. The following criteria were used for final acceptance of the trial: (1) a randomised trial; (2) a 5-HT_3 antagonist in at least one arm; (3) possible to categorise the emetogenicity of the chemotherapy; and (4) the number of patients in each arm and the number (or percentage) of patients vomiting during the first 24 h given in the article. The anti-emetic regimens, number of patients, number of patients vomiting, and type of chemotherapy were then recorded (Tables 1–4)

Within a trial, the odds for complete protection of vomiting were calculated for each treatment arm, i.e. the reported number of patients not vomiting during the first 24 h was divided by the number of those vomiting. Within each trial, the odds of vomiting when receiving the study drug (generally a 5-HT_3 antagonist) divided by the odds of not vomiting when receiving the comparator regimen resulted in an odds ratio. An odds ratio of 1.0 indicates no difference in the anti-emetic efficacy of the two anti-emetic regimens. A value less than 1.0 means better control in the study arm, whereas a value higher than 1.0 indicates superiority of the conventional regimen. Tests of heterogeneity among different trials were performed, but such tests are of limited value. Furthermore, substantial heterogeneity does not invalidate the results of meta-analysis. It merely necessitates the investigation for possible sources of heterogeneity. For this purpose, the trials were adjusted for the mean odds of vomiting in each trial. The odds ratios were combined using the Mantel–Haenszel procedure (see reference [60]). The common odds ratio together with 95% confidence intervals (CIs) are reported. All calculations of the odds ratios, the 95% confidence intervals and combination of the odds ratios were performed with the StatXact^{TM} program (Cytel Software Corp., Cambridge, MA).

RESULTS

Acute vomiting after cisplatin chemotherapy was avoided in 49% of 1314 patients receiving high-dose metoclopramide-based anti-emetic cocktails whereas 60% of 1320 patients receiving 5-HT_3 antagonists either alone or combined with dexamethasone were free of vomiting during the first 24 h. For both types of treatment the percentage of patients responding to anti-emetic therapy varied greatly from trial to trial (Table 1). The odds ratios of vomiting in each trial varied from 0.22 to 1.03 resulting in combined OR of 0.60 (95% CI 0.51–0.70) (Figure 1).

For 4–5 days low-dose cisplatin treatment there were only four trials comparing the efficacy of 5-HT_3 antagonists and conventional anti-emetics in a randomised setting. The response rate for 5-HT_3 antagonists in these studies is in the same range as for higher dose cisplatin, but the metoclopramide and alizapride regimens provided only 23% (range 9–35%) protection (Table 2). The odds ratios in these four trials varied from 0.03 to 0.57 with a combined OR of 0.28 (95% CI 0.17–0.44) (Figure 2).

Chemotherapy was classified as moderately emetogenic in 11 trials. For these regimens, the most commonly used conventional anti-emetic therapy consisted of low-dose (20–80 mg) metoclopramide. The conventional anti-emetics resulted in 51% (range 22–89%) total protection as compared to 68% (range 45–82%) with 5-HT_3 antagonists as single agents (Table 3). The odds ratios of vomiting in each trial varied from 0.20 to 1.69 resulting in combined OR of 0.47 (95% CI 0.39–0.58) (Figure 3).

In 11 trials, 5-HT_3 antagonists as single agents were compared to the same dose of 5-HT_3 antagonist with dexamethasone. In ten of the trials, the combinations were

Table 2. 5-HT_3 receptor antagonists in the prophylaxis of emesis in patients treated with low to moderate doses. (15–40 mg/m^2) of cisplatin for 4–5 days. Response as % of patients with no emetic episodes over the total chemotherapy treatment time. "Total" indicates the pooled number of patients and the weighted average response rate

Reference	No. of patients Study arm/ Comparator arm	5-HT_3 antagonist	Response (%)	Comparator*	Response (%)
Sledge [37]	23/22	Ondansetron	30	MCP	9
Bremer [38]	72/63	Granisetron	49	ALIZ + DEX	35
Nicolai [39]	18/18	Ondansetron+ DEX	83	ALIZ + DEX	11
Räth [40]	56/57	Ondansetron+ DEX	57	MCP + DEX	19
Total	169/160		53		23

* MCP, metoclopramide; ALIZ, alizapride; DEX, dexamethasone.

Table 3. 5-HT$_3$ receptor antagonists as single agents compared to conventional antiemetic therapy in the prophylaxis of acute emesis induced by moderately emetogenic chemotherapy. Response as % of patients with no acute emesis. "Total" indicates the pooled number of patients and the weighted average response rate

Reference	No. of patients Study arm/ Comparator arm	5-HT$_3$ antagonist	Response (%)	Comparator*	Response (%)
Marschner [41]	50/59	Ondansetron	60	MCP 60 mg i.v. before chemotherapy and repeated 10 mg po 8 and 16 later	47
Jones [42]	100†	Ondansetron	73	DEX 8 mg i.v. + DEX 4 mg po before chemotherapy and repeated 4 mg po 6, 12 and 18 h later	66
Kaasa [43]	40/42	Ondansetron	65	MCP 60 mg i.v. before chemotherapy and repeated 20 mg po 8 and 16 h	41
Bonneterre [44]	35/33	Ondansetron	66	MCP 60 mg i.v. and 20 mg po before chemotherapy and repeated 20 mg po 8 and 16 h later	27
Jantunen [45]	52/48	Ondansetron	77	Levomepromazine 10 mg po or MCP 20–100 mg i.v. + LOR 1–2 mg po as single agents or with DEX 10–20 mg i.v. before chemotherapy and MCP 10 mg po 8 and 16 h	56
Levitt [46]	85/80	Ondansetron	82	MCP 10 mg po + DEX 10 mg i.v. before chemotherapy and MCP 10 mg po 8 and 16 hours later	89
Clavel [47]	123/131	Ondansetron	57	Alizapride 150 mg i.v. before chemotherapy and 50 mg po 8–12 h later	31
Marty [27]	133/133	Granisetron	68	DEX 12 mg + Chlorpromazine 25 mg i.v. or i.m. before chemotherapy and chlorpromazine 25 mg po every 4–6 h	47
Italian group [48]	137/136	Granisetron	72	DEX 8 mg i.v. + 4 mg po before chemotherapy and 4 mg po 6, 12 and 18 h later	71
Medler [49]	118/111	Granisetron	74	Prochlorperazine 10 mg po b.d.	41
Anderson [50]	51/51	Tropisetron	45	MCP 20 mg i.v. or MCP 20–100 mg i.v. + LOR 2–4 mg po before chemotherapy and MCP 20 mg po every 4–6 h	22
Total	924/924		68		51

* MCP, metoclopramide; DEX, dexamethasone; LOR, lorazepam. † Cross-over study. po, oral; b.d., twice daily.

Table 4. 5-HT_3 receptor antagonists with dexamethasone versus 5-HT_3 receptor antagonists as single agents in the prophylaxis of acute emesis induced by cisplatin or moderately emetogenic chemotherapy. "Total" indicates the pooled number of patients and the weighted average response rate

Reference	No. of patients Study arm/ Comparator arm	Chemotherapy dose (mg/m^2)	5-HT_3 antagonist	Response with dexamethasone (%)	Response as single (%)
Hesketh [51]	127/118	Cisplatin >100	Ondansetron	61	46
Smith [52]	27*	Cisplatin 100-120	Ondansetron	96	96
Roila [53]	89*	Cisplatin 50-120	Ondansetron	91	64
Joss [54]	97/110	Cisplatin+ moderately emetogenic	Ondansetron	76	56
Smyth [55]	84*	Cisplatin 100	Ondansetron	58	42
Heron [29]	117/119	Cisplatin >50	Granisetron	66	56
Latreille [56]	194/98	Cisplatin >50	Granisetron	64	39
Italian group [48]	135/137	Moderately emetogenic	Granisetron	93	72
Carmichael [57]	141/137	Moderately emetogenic	Granisetron	85	76
Sorbe [58]	28/35	Cisplatin mean dose 60	Tropisetron	75	40
Adams [59]	63/63	Moderately emetogenic	Tropisetron	89	75
Total	1102/1017			76	59

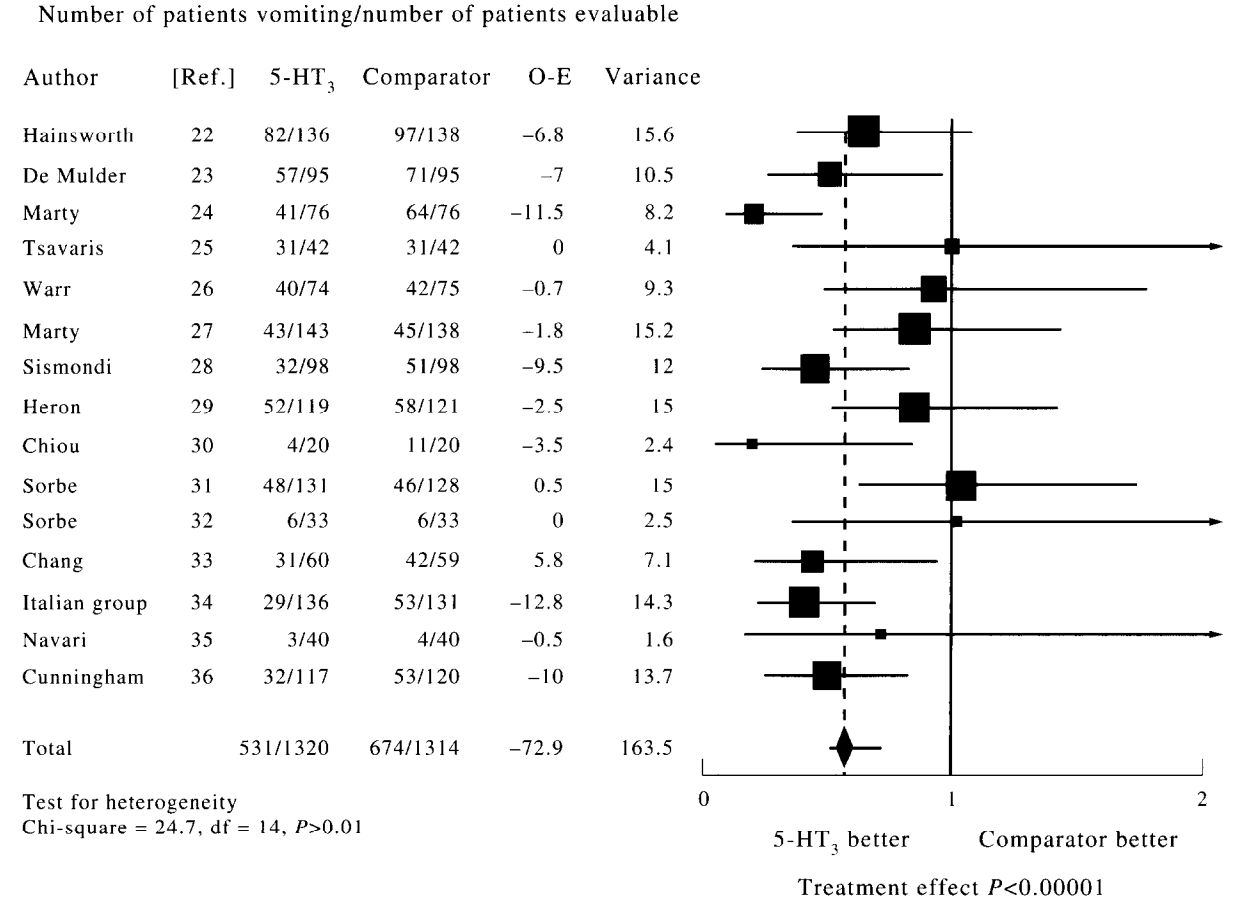

Figure 1. Risk of acute vomiting for patients receiving cisplatin in 15 randomised trials comparing 5-HT_3 antagonists to high-dose metoclopramide treatments. Odds ratios with 95% confidence intervals are given. "Total" indicates the pooled odds ratio of all trials calculated by the Mantel–Haenszel method [60].

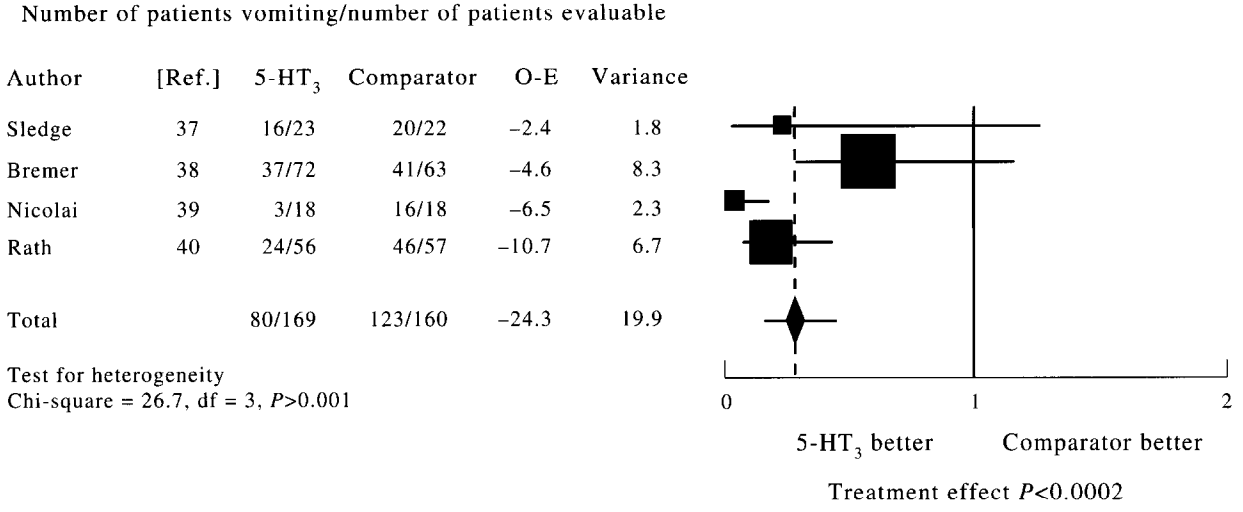

Figure 2. Risk of vomiting for patients receiving low-dose cisplatin for 4–5 days in four randomised trials comparing 5-HT$_3$ antagonists to conventional anti-emetic treatments. Odds ratios with 95% confidence intervals are given. "Total" indicates the pooled odds ratio of all trials calculated by the Mantel–Haenszel method [60].

superior to the 5-HT$_3$ antagonists as single agents (Table 4). The superiority of combination was also evident in the combined odds ratio of 0.42 (95% CI 0.34–0.51) (Figure 4).

DISCUSSION

5-HT$_3$ receptor antagonists have been in clinical use for chemotherapy-induced emesis since 1987. During the last eight years, a great number of phase II and randomised anti-emetic studies have been published. Lately, the anti-emetic studies have concentrated on comparisons between different 5-HT$_3$ antagonists. Based on the results of the randomised studies, several conclusions can be made. For example, the efficacy of the new anti-emetic agents correspond to the efficacy of high-dose metoclopramide treatment. However, they lack the unpleasant side-effects and complicated dosing schedules of high-dose metoclopramide. Randomised clinical trials provide unbiased evidence of relative treatment efficacy in a selected patient population.

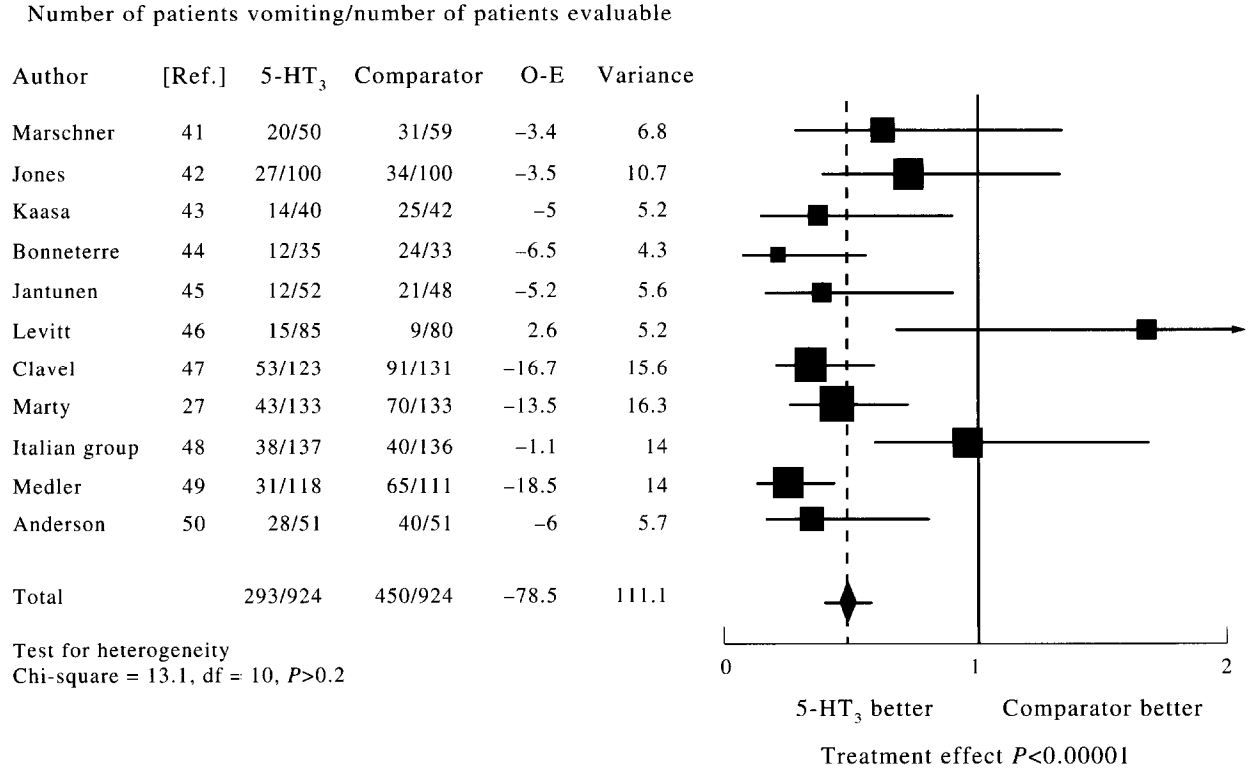

Figure 3. Risk of acute vomiting for patients receiving moderately emetogenic chemotherapy in 11 randomised trials comparing 5-HT$_3$ antagonists to conventional anti-emetic treatments. Odds ratios with 95% confidence intervals are given. "Total" indicates the pooled odds ratio of all trials calculated by the Mantel–Haenszel method [60].

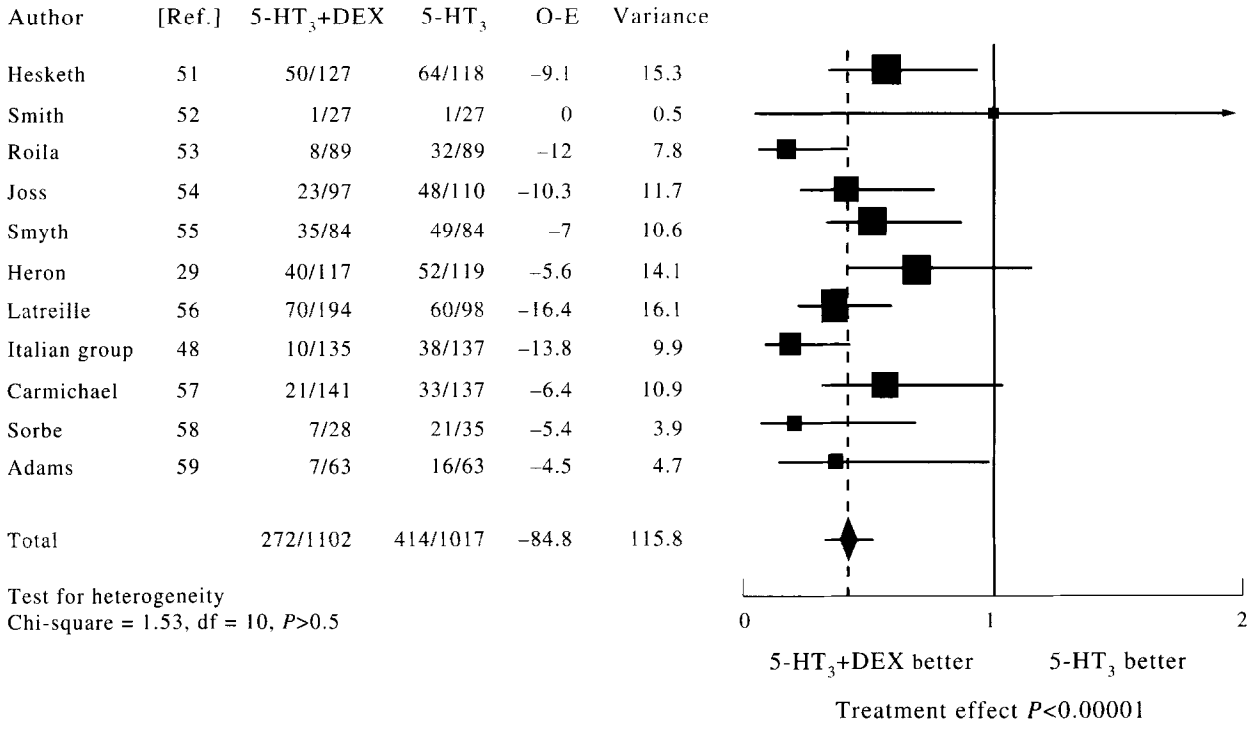

Figure 4. Risk of acute vomiting for patients receiving cytotoxic chemotherapy in 11 randomised trials comparing the combination of 5-HT_3 antagonist and dexamethasone to 5-HT_3 antagonist as a single agent. Odds ratios with 95% confidence intervals are given. "Total" indicates the pooled odds ratio of all trials calculated by the Mantel–Haenszel method [60].

However, it is very important to remember that the efficacy rates of these studies do not directly correspond to the efficacy rates observed in routine clinical work. In the randomised anti-emetic studies, patients usually receive cytotoxic agents for the first time and the results are usually reported from only one cycle. In routine clinical work, the efficacy of an anti-emetic is often lost during repeated chemotherapy cycles, especially with cisplatin treatments. The efficacy of 5-HT_3 antagonists may not be maintained over repeated cycles of chemotherapy [61].

According to this study, 5-HT_3 antagonists reduce the risk of acute cisplatin-induced vomiting (odds ratio 0.60) compared to different high-dose metoclopramide treatment schedules and combinations. Even better results have been achieved with the combination of 5-HT_3 antagonists and dexamethasone. There are many oncological clinics, where high-dose metoclopramide has never been in routine clinical use because of its side-effects. Especially in these clinics, the efficacy of 5-HT_3 antagonists has been most impressive compared to other anti-emetics. The combination of 5-HT_3 antagonist and dexamethasone is the most efficacious anti-emetic treatment for cisplatin-induced acute emesis. The results from the studies, where cisplatin was infused for 4–5 days are even more favourable for the use of 5-HT_3 antagonist (odds ratio 0.28).

Although the meta-analysis showed that 5-HT_3 antagonists reduce the risk of acute vomiting induced by moderately emetogenic chemotherapy compared to conventional anti-emetics (odds ratio 0.47), the comparisons of 5-HT_3 antagonists against inadequate doses of metoclopramide may give them an unfair advantage. In studies where 5-HT_3 antagonists have been compared to dexamethasone, no difference has been found in the efficacy of these treatments [42, 48]. The combination of 5-HT_3 antagonist and dexamethasone prevents acute vomiting in 90% of patients receiving moderately emetogenic chemotherapy [48, 62], thus showing a clear advantage for this combination. If the price of 5-HT_3 antagonists is reduced it is quite possible that 5-HT_3 antagonists will become the routine anti-emetic treatment for moderately emetogenic chemotherapy due to their favourable adverse event profiles and simple administration schedules.

Development of 5-HT_3 antagonists has been a major advance in the field of clinical oncology. However, the problem of chemotherapy-induced vomiting and nausea has not yet been solved. More efficient anti-emetic agents are needed for delayed emesis. Acute emesis is still a problem in cisplatin treatments and with high-dose chemotherapies requiring bone marrow or stem cell transfusions. Instead of new 5-HT_3 antagonists, more information is needed about the basic pathophysiology of chemotherapy-induced emesis for developing new anti-emetic drugs and treatments.

1. Cubeddu LX, Hoffman IS, Fuenmayor NT, *et al.* Efficacy of ondansetron (GR 38032F) and the role of serotonin in cisplatin-induced nausea and vomiting. *N Engl J Med* 1990, **322**, 810–816.
2. Wilder-Smith OH, Borgeat A, Chappuis P, Fathi M, Forni M. Urinary serotonin metabolite excretion during cisplatin chemotherapy. *Cancer* 1993, **72**, 2239–2241.
3. Andrews PLR, Bhandari P. The 5-hydroxytryptamine receptor antagonists as antiemetics: preclinical evaluation and mechanism of action. *Eur J Cancer* 1993, **29A** (Suppl 1), S11–S16.

4. Miner WD, Sanger GJ. Inhibition of cisplatin-induced vomiting by selective 5-hydroxytryptamine m-receptor antagonism. *Br J Pharmacol* 1986, **88**, 497–499.
5. Andrews PL, Bhandari P, Davey PT, Bingham S, Marr HE, Blower PR. Are all 5-HT_3 receptor antagonists the same? *Eur J Cancer* 1992, **28A** (Suppl 1), S2–S6.
6. Freeman AJ, Cunningham KT, Tyers MB. Selectivity of 5-HT_3 receptor antagonists and anti-emetic mechanisms of action. *Anti-Cancer Drugs* 1992, **3**, 79–85.
7. Morrow GR, Hickok JT, Rosenthal SN. Progress in reducing nausea and emesis. *Cancer* 1995, **76**, 343–357.
8. Gralla RJ, Itri 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**, 905–909.
9. Cupissol DR, Serrou B, Caubel M. The efficacy of granisetron as a prophylactic anti-emetic and intervention agent in high-dose cisplatin-induced emesis. *Eur J Cancer* 1990, **26** (Suppl. 1), 23–27.
10. Cubeddu LX, Hoffmann IS. Participation of serotonin on early and delayed emesis induced by initial and subsequent cycles of cisplatinum-based chemotherapy: effects of antiemetics. *J Clin Pharmacol* 1993, **33**, 691–697.
11. Navari R, Madajewicz S, Anderson N, *et al.* Oral ondansetron for the control of cisplatin-induced delayed emesis: a large, multicenter, double-blind, randomized comparative trial of ondansetron versus placebo. *J Clin Oncol* 1995, **13**, 2408–2416.
12. 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.
13. Jones AL, Lee GJ, Bosanquet N. The budgetary impact of 5-HT_3 receptor antagonists in the management of chemotherapy induced emesis. *Eur J Cancer* 1992, **29A**, 51–56.
14. Fetting JH, Grochow LB, Folstein MF, Ettinger DS, Colvin M. The course of nausea and vomiting after high-dose cyclophosphamide. *Cancer Treat Rep* 1982, **66**, 1487–1493.
15. Cubeddu LX, Hoffmann IS, Fuenmayor NT, Malave JJ. Changes in serotonin metabolism in cancer patients: its relationship to nausea and vomiting induced by chemotherapeutic drugs. *Br J Cancer* 1992, **66**, 198–203.
16. Beck TM, Ciociola AA, Jones SE, *et al.* Efficacy of oral ondansetron in the prevention of emesis in outpatients. *Ann Intern Med* 1993, **118**, 407–413.
17. Cubeddu LX, Pendergrass K, Ryan T, *et al.* Efficacy of oral ondansetron, a selective antagonist of 5-HT_3 receptors, in the treatment of nausea and vomiting associated with cyclophosphamide-based chemotherapies. *Am J Clin Oncol* 1994, **17**, 137–146.
18. 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.
19. Pollera CF, Nardi M, Marolla P, *et al.* Effective control of CMF-related emesis with high-dose dexamethasone: results of a double-blind crossover trial with metoclopramide and placebo. *Am J Clin Oncol* 1989, **12**, 524–529.
20. Cooper S, Georgiou V. The impact of cytotoxic chemotherapy—perspectives from patients, specialists and nurses. *Eur J Cancer* 1992, **28A**, 536–538.
21. Tonato M, Roila F, Del Favero A. Methodology of antiemetic trials: a review. *Ann Oncol* 1991, **2**, 107–114.
22. Hainsworth J, Harvey W, Pendergrass K, *et al.* A single-blind comparison of intravenous ondansetron, a selective serotonin antagonist, with metoclopramide in the prevention of nausea and vomiting associated with high-dose cisplatin chemotherapy. *J Clin Oncol* 1991, **9**, 721–728.
23. De Mulder PH, 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**, 834–840.
24. Marty M, Pouillart P, Scholl S, *et al.* Comparison of the 5-hydroxytryptamine$_3$ (serotonin) antagonist ondansetron (GR 38032F) with high-dose metoclopramide in the control of cisplatin-induced emesis. *N Engl J Med* 1990, **322**, 816–821.
25. Tsavaris NB, Charalambidis G, Ganas N, *et al.* Ondansetron and metoclopramide as antiemetic treatment during cisplatin-based chemotherapy—a prospective study with special regard to electrolyte imbalance. *Acta Oncol* 1995, **34**, 243–246.
26. Warr D, Wilan A, Venner P, *et al.* A randomised, double-blind comparison of granisetron with high-dose metoclopramide, dexamethasone and diphenhydramine for cisplatin-induced emesis. *Eur J Cancer* 1992, **29A**, 33–36.
27. Marty M. A comparison of granisetron as a single agent with conventional combination antiemetic therapies in the treatment of cytostatic-induced emesis. The granisetron study group. *Eur J Cancer* 1992, **28A**(Suppl. 1), S12–S16.
28. Sismondi P, Danese S, Guercio E, *et al.* Patient preference for granisetron over conventional antiemetics for the prophylaxis of cisplatin-induced nausea and vomiting. *Ann Oncol* 1994, **5** (Suppl. 8), S208.
29. On behalf of the Granisetron Study Group, Heron JF, Goedhals L, Jordaan JP, Cunningham J, Cedar E. Oral granisetron alone and in combination with dexamethasone: a double-blind randomized comparison against metoclopramide plus dexamethasone in prevention of cisplatin-induced emesis. *Ann Oncol* 1994, **5**, 579–584.
30. Chiou TJ, Wei CH, Hsieh RK, Fan FS, Liu JH, Chen PM. Comparison of intravenous granisetron with metoclopramide in the treatment of chemotherapy-induced emesis. *Chuang Hua I Hsueh Tsa Chih Taipei* 1995, **56**, 23–30.
31. Sorbe BG, Högberg T, Glimelius B, *et al.* A randomized, multicenter study comparing the efficacy and tolerability of tropisetron, a new 5-HT_3 receptor antagonist, with a metoclopramide-containing antiemetic cocktail in the prevention of cisplatin-induced emesis. *Cancer* 1994, **73**, 445–454.
32. Sorbe B, Hallen C, Frankendal B. An open, randomized study to compare the efficacy and tolerability of tropisetron with that of a metoclopramide-containing antiemetic cocktail in the prevention of cisplatin-induced emesis. *Cancer Chemother Pharmacol* 1994, **33**, 298–302.
33. Chang TC, Hsieh F, Lai CH, *et al.* Comparison of the efficacy of tropisetron versus a metoclopramide cocktail based on the intensity of cisplatin induced emesis. *Cancer Chemother Pharmacol* 1996, **37**, 279–285.
34. The Italian Group for Antiemetic Research. Difference in persistence of efficacy of two antiemetic regimens on acute emesis during cisplatin chemotherapy. *J Clin Oncol* 1993, **11**, 2396–2404.
35. Navari RM, Province WS, Perrine GM, Kilgore JR. Comparison of intermittent ondansetron versus continuous infusion metoclopramide used with standard combination antiemetics in control of acute nausea induced by cisplatin chemotherapy. *Cancer* 1993, **72**, 583–586.
36. Cunningham D, Dicato M, Verweij J, *et al.* Optimum antiemetic therapy for cisplatin induced emesis over repeated courses: ondansetron plus dexamethasone compared with metoclopramide, dexamethasone plus lorazepam. *Ann Oncol* 1996, **7**, 277–282.
37. Sledge GW, Einhorn L, Nagy C, House K. Phase III double-blind comparison of intravenous ondansetron and metoclopramide as antiemetic therapy for patients receiving multiple-day cisplatin-based chemotherapy. *Cancer* 1992, **70**, 2524–2528.
38. Bremer K. A single-blind study of the efficacy and safety of intravenous granisetron compared with alizapride plus dexamethasone in the prophylaxis and control of emesis in patients receiving 5-day cytostatic therapy. The Granisetron Study Group. *Eur J Cancer* 1992, **28A**, 1018–1022.
39. Nicolai N, Mangiarotti B, Salvioni R, Piva L, Faustini M, Pizzocaro G. Dexamethasone plus ondansetron versus dexamethasone plus alizapride in the prevention of emesis induced by cisplatin-containing chemotherapies for urological cancers. *Eur Urol* 1993, **23**, 450–456.
40. Räth U, Upadhyaya BK, Arechavala E, *et al.* Role of ondansetron plus dexamethasone in fractionated chemotherapy. *Oncology* 1993, **50**, 168–172.
41. Marschner NW, Adler M, Nagel GA, Christmann D, Fenzl E, Upadhyaya B. 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.

42. Jones AL, Hill AS, Soukop M, *et al.* Comparison of dexamethasone and ondansetron in the prophylaxis of emesis induced by moderately emetogenic chemotherapy. *Lancet* 1991, **338**, 483–487.
43. 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. International Emesis Study Group. *Eur J Cancer* 1990, **26**, 311–314.
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. Jantunen IT, Flander MK, Heikkinen MI, Kuoppala TA, Teerenhovi L, Kataja VV. Comparison of ondansetron with customary treatment in the prophylaxis of nausea and emesis induced by non-cisplatin containing chemotherapy. *Acta Oncol* 1993, **32**, 413–415.
46. Levitt M, Warr D, Yelle L, *et al.* Ondansetron compared with dexamethasone and metoclopramide as antiemetics in the chemotherapy of breast cancer with cyclophosphamide, methotrexate, and fluorouracil. *N Engl J Med* 1993, **328**, 1081–1084.
47. French Ondansetron Study Group, Clavel M, Bonneterre J, d'Allens H, Paillarse J-M. Oral ondansetron in the prevention of chemotherapy-induced emesis in breast cancer patients. *Eur J Cancer* 1995, **31**, 15–19.
48. The Italian Group for Antiemetic Research. Dexamethasone, granisetron, or both for the prevention of nausea and vomiting during chemotherapy for cancer. *N Engl J Med* 1995, **332**, 1–5.
49. Medler EM, Gruben D, Johnsonbaugh RE, Friedman CJ, Pellier P. Acute antiemetic response to oral granisetron superior to oral prochlorperazine in patients receiving moderately emetogenic chemotherapy. *Ann Oncol* 1994, 5(Suppl. 8), S205.
50. Anderson H, Thatcher N, Howell A, Logan K, Sage T, de Bruijn KM. Tropisetron compared with a metoclopramide-based regimen in the prevention of chemotherapy-induced nausea and vomiting. *Eur J Cancer* 1994, **30A**, 610–615.
51. Hesketh PJ, Harvey WH, Harker WG, *et al.* A randomized, double-blind comparison of intravenous ondansetron alone and in combination with intravenous dexamethasone in the prevention of high-dose cisplatin-induced emesis. *J Clin Oncol* 1994, **12**, 596–600.
52. Smith DB, Newlands ES, Rustin GJ, *et al.* Comparison of ondansetron and ondansetron plus dexamethasone as antiemetic prophylaxis during cisplatin-containing chemotherapy. *Lancet* 1991, **338**, 487–490.
53. 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.
54. Joss RA, Bacchi M, Buser K, *et al.* Ondansetron plus dexamethasone is superior to ondansetron alone in the prevention of emesis in chemotherapy-naive and previously treated patients. *Ann Oncol* 1994, **5**, 253–258.
55. 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.
56. Latreille J, Stewart D, Laberge F, *et al.* Dexamethasone improves the efficacy of granisetron in the first 24 h following high-dose cisplatin chemotherapy. *Support Care Cancer* 1995, **3**, 307–312.
57. Carmichael J, Bessel EM, Harris AL, Hutcheon AW, Dawes PJ, Daniels S. Comparison of granisetron alone and granisetron plus dexamethasone in the prophylaxis of cytotoxic-induced emesis. *Br J Cancer* 1994, **70**, 1161–1164.
58. Sorbe B, Högberg T, Himmelmann A, *et al.* Efficacy and tolerability of tropisetron in comparison with a combination of tropisetron and dexamethasone in the control of nausea and vomiting induced by cisplatin-containing chemotherapy. *Eur J Cancer* 1994, **30A**, 629–634.
59. Adams M, Soukop M, Barley V, *et al.* Tropisetron alone or in combination with dexamethasone for the prevention and treatment of emesis induced by non-cisplatin chemotherapy: a randomized trial. *Anti-Cancer Drugs* 1995, **6**, 514–521.
60. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959, **22**, 719–748.
61. De Wit R, Schmitz PIM, Verweij J, *et al.* Analysis of cumulative probabilities shows that the efficacy of 5-HT_3 antagonist prophylaxis is not maintained. *J Clin Oncol* 1996, **14**, 644–651.
62. Soukop M, McQuade 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.