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Oral Ondansetron in the Prevention of Chemotherapy-induced Emesis in Breast Cancer Patients

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A multicentre randomised, double-blind parallel group study has been carried out in order to confirm the anti-emetic efficacy of orally administered ondansetron. A total of 259 chemotherapy-naive breast cancer patients treated with a 5-fluorouracil, doxorubicin, cyclophosphamide (FAC) or 5-fluorouracil, epirubicin, cyclophosphamide (FEC) regimen were randomly assigned to ondansetron (OND) 8 mg tablet or alizapride (ALI) 150 mg intravenous (i.v.) injection, prior to chemotherapy. These treatments were then followed by OND 8 mg tablet or ALI 50 mg tablet, respectively, 8 to 12 h later. Oral treatment was then continued twice a day over 3–5 days. The number of emetic episodes (EE = vomits + retches) and the grade of nausea were recorded; quality of life was assessed using a specific questionnaire. Of the 254 patients analysed for efficacy, complete or major control (success: 0–2 EE) over the 24 h following start of chemotherapy was obtained in 81% of the OND group compared with 47% of the ALI group ($P < 0.001$). A significant difference in favour of OND was also observed for nausea ($P < 0.0001$). For on days 2 to 4 emesis, the arm containing OND was superior to that with ALI (worst day analysis): 77% success versus 63% ($P < 0.002$). The overall control of emesis (from day 1 to day 4) was better with OND (64% patients success in the OND group versus 41% in the ALI group; $P < 0.0001$). At the end of the study the number of patients wishing to receive the same anti-emetic treatment for their next course was 83% for OND compared with 54% for ALI ($P < 0.0001$). In terms of quality of life in relation to emesis phenomena, OND was significantly superior to ALI ($P = 0.04$). Both treatments were well tolerated. In the prevention of the prolonged emesis induced by FAC/FEC-type emetogenic chemotherapy, orally administered OND was superior to ALI, given as an i.v. injection and followed by tablets.

Key words: $5HT_3$ antagonists, anti-emetics, cytotoxic-induced emesis, randomised trial
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INTRODUCTION

IN THE treatment of breast cancer, 5-fluorouracil, doxorubicin, cyclophosphamide (FAC) or 5-fluorouracil, epirubicin, cyclophosphamide (FEC) chemotherapy regimens are commonly used treatments showing a similar anti-cancer efficacy [1]. These protocols are considered moderately emetogenic, inducing nausea and vomiting in 60–90% of patients not treated with an anti-emetic [2].

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Ondansetron is a highly selective $5HT_3$ receptor antagonist, and is effective in patients treated with highly emetogenic chemotherapies [3–5]; furthermore, its superiority in the prevention of nausea and vomiting induced by a FAC–FEC chemotherapy regimen has been demonstrated in a comparative study with metoclopramide [6].

Its efficacy has also been demonstrated when given orally to patients following a similar type of chemotherapy, although the observed difference in activity over metoclopramide did not reach statistical significance [7]. A recent American study also demonstrated the efficacy of orally administered ondansetron compared with placebo in cyclophosphamide-treated patients [8].

Alizapride is a neuroleptic, anti-emetic benzamide whose mode of action is similar to that of metoclopramide. Its anti-emetic efficacy has been confirmed by various clinical studies [9], and it is widely used in cytotoxic-induced emesis.

The aim of this study was to provide complementary data on the efficacy of orally administered ondansetron: thus, it compared ondansetron administered orally with alizapride given intravenously followed by oral administration in FAC–FEC chemotherapy regimen given for the treatment of breast cancer.

PATIENTS AND METHODS

Patient selection

Thirty-six French cancer centres included patients according to the following criteria: female patients aged 18 years or over, undergoing their first course of cytotoxic chemotherapy for breast cancer using one of the following regimens: FAC—5-fluorouracil 500–600 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500–600 mg/m^2. FEC—5-fluorouracil 500–600 mg/m^2, epirubicin 50–75 mg/m^2, cyclophosphamide 500–600 mg/m^2.

The patients were not eligible for inclusion if any of the following applied: serious disease other than the cancer being treated, another cause of nausea or vomiting other than the chemotherapy, a clinical hepatic disorder, a persistent chronic alcoholism, emesis or anti-emetic treatment during the 24 h preceding the entry into the study.

This protocol was approved by the Ethics Committee of Lyon. The study was conducted in accordance with the principles of the Helsinki Declaration. All patients gave their written informed consent.

Anti-emetic regimen

The patients were randomised to one of the two following groups:

- Ondansetron group: one capsule containing 8 mg ondansetron tablet, 2 h prior to the start of chemotherapy, and a single intravenous placebo injection 30 min before chemotherapy, followed 8–12 h later by one capsule containing 8 mg ondansetron tablet, administered morning and evening during the following 3–5 days (the decision of the treatment duration was left to the investigator).
- Alizapride group: one placebo capsule, 2 h before the beginning of chemotherapy, and a single intravenous injection of 150 mg alizapride 30 min before chemotherapy, followed 8–12 h later with a capsule containing 50 mg alizapride tablet, administered morning and evening during the following 3–5 days (the decision of the treatment duration was left to the investigator).

Assessment criteria

During chemotherapy and for the following 3 days, the emetic episodes were recorded on a diary card. An emetic episode was defined as a single vomit or retch, alone or any number of continuous vomits or retches. Emetic episodes were by definition separated by the absence of both vomiting or retching for at least one minute. The response to treatment was graded as complete control (no episode), major (one to two episodes), minor (three to five episodes) or failure (more than five episodes or rescue medication). Those patients showing a complete or major response were regrouped into success (up to two episodes).

The primary efficacy assessment criteria was the anti-emetic response assessed during the 24 h following the start of chemotherapy. The control of delayed emesis was assessed through the anti-emetic response on the worst day (days 2–4) for each patient.

Nausea graded as none, mild, moderate or severe was assessed before treatment, 4, 8 and 24 h after the start of chemotherapy. The four-item graded scale was related to effects of nausea on the patients' daily activities (grade of nausea: none, mild, moderate, severe). The patient also carried out a self-assessment of nausea by means of a vertical visual analogue scale from 0 mm (absence of nausea) to 100 mm (nausea as severe as can be imagined) before the anti-emetic treatment and after.

The overall patient satisfaction was assessed at the follow-up examination (1–4 weeks after the beginning of chemotherapy) by asking the patient if she wished to receive the same anti-emetic treatment during the next course of chemotherapy.

Quality of life was assessed using two specific scales, the FLIC (functional living index in cancer [10]) for the impact of cancer and the FLIE (functional living index in emesis [11]) for the impact of emesis. This questionnaire was completed by the patient before chemotherapy and 4 days after. It included a total of 40 questions, 22 for the FLIC and 18 for the FLIE. The patients gave each question a score from one to seven which, depending on the questions, corresponded either to a better quality of life or to a worse condition. The total score for each questionnaire was obtained by calculating the average score of each question.

The adverse events were recorded during the week following the beginning of chemotherapy. A cause–effect relationship with the study treatment was established by the investigator and, in case of a serious adverse event, a drug surveillance enquiry was made to establish the causal link with the study drug.

Statistical analysis

This was a multicentre, randomised, parallel group, double-blind study. In order to show a difference between the assumed success rates of 70% for ondansetron and 50% for alizapride, with a 5% level of significance and 95% power (one-sided test), 128 patients in each treatment group would be required.

All the patients were included in the analysis of efficacy if they had complied with the conditions of the protocol during the first 24 h of the study. The efficacy of the study treatments were compared over the first 24 h after the start of chemotherapy, during the worst day between days 2 and 4 and finally, at the end of the anti-emetic treatment.

The quantitative variables were compared using a variance analysis or the Wilcoxon rank sum test. Comparisons of the qualitative variables were carried out using a Fisher's exact test, χ^2 test or a maximum likelihood test according to the theoretical population size. The comparisons between the scores obtained with the quality of life questionnaire were carried out with Student's t-test.

RESULTS

Of the 259 patients recruited into the study, 5 were excluded from the analysis of efficacy for the following reasons: non-compliance with the anti-emetic therapy ($n = 3$), non-compliance with the chemotherapy regimen ($n = 1$), lack of records of assessment criteria ($n = 1$).

The characteristics at entry in the study of the 254 patients analysed for efficacy, along with the chemotherapy regimen received, are presented in Table 1 with 123 patients in the ondansetron group and 131 patients in the alizapride group. All patients were included in the safety analysis (ondansetron, $n = 125$; alizapride, $n = 134$).

Efficacy

Control of emetic episodes. Table 2 shows that the control of acute emesis, in the 24 h following the start of chemotherapy, was significantly better with ondansetron, successful in 81% of patients compared with 47% with alizapride ($P < 0.0001$).

This rate of failure on day 1 was 11% for ondansetron and 41% for alizapride ($P < 0.0001$).

The efficacy of ondansetron was equally superior in the control of days 2–4 emetic episodes (Table 3) with the success rate on

Table 1. Study population at entry in the trial*

	Ondansetron (n = 123)	Alizapride (n = 131)
Age, years (mean ± standard deviation)	51.9 ± 0.9	52.9 ± 0.9
Body surface area, m^2 (mean ± standard deviation)	1.66 ± 0.01	1.65 ± 0.01
Alcohol consumption > 4 units† per day: n(%)	0 (0)	1 (0.7)
Histological type (n)		
Ductal	109	116
Lobular	11	6
Colloid	0	1
Other	3	7
Data missing	—	1
Chemotherapy regimens: n (%)		
FEC‡	100 (81.3)	103 (78.6)
FAC	23 (18.7)	28 (21.4)

* There is no statistically significant difference between the two study groups. † One alcohol unit = one glass of liqueur or one glass of wine (12.5 cl) or one tankard of beer (25 cl). ‡ FEC = FEC 50 or FEC 75.

Table 2. Comparison of the anti-emetic effect over 24 h following the beginning of chemotherapy between the two treatment groups

Anti-emetic response	Ondansetron (n = 123)		Alizapride (n = 131)	
Control of the emetic episodes* (vomiting and retches): n (%)				
Complete (0 episodes)	70 (57)	81%	40 (31)	47%
Major (1–2 episodes)	30 (24)		22 (17)	
Minor (3–5 episodes)	10 (8)		16 (12)	
Failure (> 5 episodes or rescue medication)	13 (11)		53 (41)	

*P = 0.001 (χ^2 test)

the worst day being 77% of patients compared with 63% for alizapride ($P < 0.002$). The difference is even more significant when the rates of failure are considered: 10% for ondansetron versus 29% for alizapride ($P < 0.0001$).

The complete results of the control of emetic episodes during the whole study period (days 1–4) are presented in Table 4. The results show a significant difference in favour of ondansetron ($P = 0.0001$).

Table 3. Comparison of efficacy in delayed emesis on days 2–4 (worst day analysis)

Anti-emetic response:	Ondansetron (n = 123)		Alizapride (n = 131)	
Control of emetic episodes* (vomiting and retches): n (%)				
Complete (0 episodes)	76 (62)	77%	63 (48)	63%
Major (1–2 episodes)	19 (15)		20 (15)	
Minor (3–5 episodes)	16 (13)		10 (8)	
Failure (> 5 episodes or rescue medication)	12 (10)		38 (29)	

* P = 0.002 (χ^2 test).

Table 4. Comparison of the overall control of emetic episodes during the whole course (days 1–4)

Anti-emetic response	Ondansetron (n = 123)		Alizapride (n = 131)	
Control of emetic episodes* (vomiting and retches): n (%)				
Complete (0 episodes)	60 (49)	64%	32 (24)	41%
Major (1–2 episodes)	19 (15)		22 (17)	
Minor (3–5 episodes)	14 (11)		14 (11)	
Failure (> 5 episodes or rescue medication)	30 (24)		63 (48)	

* P = 0.0001 (χ^2 test)

Control of nausea. The severity of nausea, assessed 24 h after the start of chemotherapy and on the worst day from days 2–4, shows that, during these two assessments, ondansetron was significantly superior to alizapride in its anti-nausea effect (Table 5).

Self-evaluation at 24 h by means of the visual analogue scale confirmed the superiority of ondansetron with a grade of nausea of 25.8 ± 2.8 mm versus 44.5 ± 3.4 mm for alizapride ($P < 0.0001$).

Global control of emesis (day 1). The percentages of patients with no emetic episodes, and with nausea graded none or mild, were 50% for the ondansetron group and 28% for the alizapride group ($P < 0.0001$).

Patient satisfaction with anti-emetic treatment

At the follow-up examination, a greater percentage of patients in the ondansetron group declared they wished to receive the same treatment during their next chemotherapy regimen (83% versus 54%; $P < 0.001$).

Assessment of quality of life (Table 6)

There was less deterioration in the quality of life due to emesis (scale FLIE) in the patients receiving ondansetron ($P = 0.04$), which was statistically significant. The deterioration of quality

Table 5. Control of nausea at 24 h and on the worst day after the start of chemotherapy: results expressed as percentage of patients for each grade of nausea

	At 24 h*		Worst day†	
Grade of nausea	Ondansetron n = 123 %	Alizapride n = 131 %	Ondansetron n = 123 %	Alizapride n = 131 %
None	40	26	35	28
Mild	31	21	20	18
Moderate	20	21	28	16
Severe	10	31	18	39

*$P < 0.0001$ (χ^2 test).
†P = 0.01 (χ^2 test).

Table 6. Evaluation of quality of life: FLIC questionnaire for cancer-related quality of life and FLIE for emesis-related quality of life

	FLIC		FLIE	
	Ondansetron	Alizapride	Ondansetron	Alizapride
Before chemotherapy, mean scores given for each question (number of patients)	4.99 (122)	5.24 (130)	6.79 (121)	6.83 (125)
After chemotherapy, mean scores given for each question (number of patients)	4.46 (119)	4.50 (126)	5.37 (120)	4.87 (125)
Mean differences in the scores given for each question (number of patients)	0.55* (119)	0.73 (125)	1.45† (119)	1.93 (121)

* non-significant. † $P = 0.04$ (Student's t test). FLIC, functional living index in cancer; FLIE, functional living index in emesis.

of life due to cancer (scale FLIC) was not different between the two groups.

Safety

In both treatment groups, drug-related adverse events were minor with headache being the most frequently reported adverse event (2 patients in the ondansetron group, 3 patients in the alizapride group).

DISCUSSION

Treatment groups were well balanced with respect to the distribution of the main prognostic factors that are known to affect the control of nausea and vomiting (age, alcohol consumption and chemotherapy regimen): thus the statistical comparisons were not biased by the influence of these factors.

The results noted for the anti-emetic response on the day of chemotherapy are similar to those of a previous trial [6], comparing injectable forms of ondansetron and metoclopramide. Another study on the effects of orally administered ondansetron also showed results in favour of ondansetron [7], but the difference did not reach statistical significance. The present study shows that orally administered ondansetron is superior to alizapride in the prevention of nausea and acute vomiting, induced by moderately emetogenic chemotherapies, i.e. FAC–FEC. An anti-emetic treatment, administered by the oral route, may have benefits for the elderly patient, as well as those receiving chemotherapy in an ambulatory setting.

The results obtained on days 2–4 (worst day) in the ondansetron group were better than in the alizapride group. These results were similar to those obtained in a previous study [6]. This superiority of ondansetron was obtained with an 8 mg oral dose given twice daily; furthermore, it has been demonstrated that the efficacy of this dose was similar to that of the same dose of 8 mg ondansetron administered orally three times/day [12].

Evaluation of the two treatments during the whole course permitted an overall assessment of the emetic disorders felt by the patient throughout the course of chemotherapy. The superiority of ondansetron is highly significant, with many more patients failing on alizapride compared with ondansetron. It is known that patients who fail during their initial course of chemotherapy are more likely to experience nausea and vomiting during subsequent cycles [2].

The results noted for nausea, a phenomenon equally distressing for the patients, provide evidence of the superiority of ondansetron over alizapride, in the control of both acute nausea and possibly delayed nausea where a carry over from day 1 is not excluded. Both modes of evaluating nausea in this study (four item-graded scale and visual analogue scale) gave similar results.

More patients were satisfied with their anti-emetic treatment in the ondansetron group. These results confirm those obtained in two previous studies [13, 14], and are similar to those already reported, in terms of patient preference during studies carried out using cross-over designs [3, 6]; the difficulties inherent in the analysis of cross-over studies, particularly with the possibility of having a period or carry-over effect, led to a study design based on parallel groups.

Despite the better anti-emetic efficacy observed with ondansetron in terms of nausea and vomiting, the control of emesis induced by FAC/FEC chemotherapy with ondansetron alone is still suboptimal, and could be improved by using a corticoid in combination [15].

The assessment of quality of life in relation to emesis phenomena clearly demonstrates the superiority of ondansetron over alizapride. This confirms the findings noted in a previous American study [11]. The evaluation in terms of quality of life does not show any difference for the quality of life linked with cancer (FLIC scale): this instrument should be used again on several consecutive chemotherapy courses, in order to confirm the sensitivity of the questionnaire when administered over a longer period of evaluation.

Both treatments were well tolerated, the rare, drug-related adverse events reported in the two groups being minor and transient.

In conclusion, this trial, carried out in a homogeneous population of women treated for breast cancer, has demonstrated the efficacy of orally administered ondansetron, and its superiority over alizapride, initially administered intravenously, and followed by oral administration in the control of emesis, induced by a moderately emetogenic FAC–FEC chemotherapy regimen.

1. French Epirubicin Study Group. A prospective randomised phase III trial comparing combination chemotherapy with cyclophosphamide, fluorouracil, and either doxorubicin or epirubicin. *J Clin Oncol* 1988, **6**, 679–688.
2. Gralla RJ. Approaches to management of nausea and vomiting in the clinical setting–in emesis and cancer therapy. *Clinician* 1988, **6**, 26–38.
3. Marty M, Droz JP, Pouillart P, Paule B, Brion N, Bons J. GR38032F, a 5HT3 receptor antagonist, in the prophylaxis of acute cisplatin-induced nausea and vomiting. *Cancer Chemother Pharmacol* 1989, **23**, 389–391.
4. 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 cisplatinum-induced emesis. *N Engl J Med* 1990, **322**, 816–821.
5. Miner WD, Sanger GJ. Inhibition of cisplatin-induced vomiting by selecting 5-hydroxytryptamine M-receptor antagonism. *Br J Pharmacol* 1986, **88**, 497–499.

6. 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.
7. 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.
8. Beck MT, Ciociola AA, Jones SE, *et al.* Efficacy of oral ondansetron in the prevention of emesis in outpatients receiving cyclophosphamide based chemotherapy. *Ann Intern Med* 1993, **118**, 407–413.
9. Cupissol D, Caubel M. Synthèse des travaux concernant l'alizapride dans les chimiothérapies. In Jacquillat C, Weil M, Khayat D, eds. Neo-adjuvant Chemotherapy. Colloque INSERM. London, John Libbey Eurotext, 1988, 911–918.
10. Schipper H, Clinch J, McMurray A, Levitt M. Measuring the quality of life of cancer patients: the functional living index-cancer: development and validation. *J Clin Oncol* 1984, **2**, 472–483.
11. Hirsch JD, Lee JT, Grapski R. Quality of life with intravenous ondansetron versus standard antiemetic therapy in patients receiving emetogenic cancer chemotherapy. 28th Annual Meeting of the American Society of Clinical Oncology, San Diego, 17–19 May 1992. *Proc ASCO* 11 1992, 393, 1368 (abstract).
12. Dicato MA, Kaasa S, Campora E, *et al.* Efficacy of twice daily versus three times daily oral ondansetron in the prevention of chemotherapy induced emesis: a randomized, single-blind, multicentre study. *Clin Oncol* 1992, **4**, 275–279.
13. Depierre A, Lebeau B, d'Allens H. Comparison of ondansetron with a combined regimen of alizapride and methylprednisolone in the prophylaxis of cisplatin-induced emesis in patients with lung cancer. 3rd International Congress on Neo-adjuvant Chemotherapy. Paris, Springer, 1991, 23–35.
14. Harousseau JL, Gisselbrecht C, Paillarse JM. Comparison of ondansetron and alizapride in the prophylaxis of lymphoma chemotherapy-induced emesis. 3rd Internatinal Conference on Neo-adjuvant Chemotherapy. Paris, Springer, 1991, 9–21.
15. 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.

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A Phase III Study of Recombinant Interleukin-2, 5-Fluorouracil and Leucovorin Versus 5-Fluorouracil and Leucovorin in Patients with Unresectable or Metastatic Colorectal Carcinoma

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135 patients with locally advanced or metastatic colorectal cancer were entered into a phase III trial evaluating the efficacy of chemoimmunotherapy [recombinant interleukin 2 (rIL2)/5-fluorouracil (5-FU) and leucovorin (LV)] versus chemotherapy alone (5-FU/LV). A cycle of chemoimmunotherapy comprised a constant intravenous infusion of rIL2 at a dose of 18 × 10^6 U/m²/24 h for 120 h, followed by three bolus injections of 5-FU (600 mg/m²) and LV (25 mg/m²) at weekly intervals. Patients receiving chemotherapy alone received 5-FU/LV at the same dose at weekly intervals for 6 weeks followed by a rest period of 2 weeks, constituting one cycle of therapy. A maximum of 6 months therapy was given in both arms of the study. The response rates (complete and partial responses) were 17% in patients receiving rIL2/5-FU/LV versus 16% in those in the 5-FU/LV arm of the study. Median survival and progression-free survival were comparable for the two groups of patients, although there was a trend for a prolongation of survival in patients receiving chemoimmunotherapy compared with chemotherapy alone, beyond 12 months. Retrospective subgroup analyses revealed a significantly increased survival in poor prognosis patients (ECOG 1) treated with rIL2/5-FU/LV when compared to those receiving chemotherapy alone. Therefore, further studies evaluating the dose and duration of chemoimmunotherapy in patients with metastatic colorectal cancer seem warranted.

Key words: recombinant interleukin-2, chemotherapy, advanced colorectal cancer, randomised trial
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INTRODUCTION

COLORECTAL CANCER continues to be a major cause of morbidity and mortality in Western societies. Surgical resection remains the mainstay of treatment, but approximately 40% of patients have lymph node metastases and one-fifth have distant metastases at the time of initial diagnosis [1]. Furthermore, the corrected 5-year survival rate is approximately 50% [2, 3] and, in specialised centres, has remained static over the last 50 years [4]. Although surgical resection of metastatic disease has been attempted, only a small number of patients with advanced