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CLINICAL TRIAL REPORT

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Chemotherapy-induced emesis: management of early and delayed emesis in milder emetogenic regimens

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Abstract The objective of the present study was to examine the problem of the control of nausea and vomiting induced by non-cisplatin containing cyclophosphamide-based chemotherapy regimens in breast cancer patients. This was randomized, double-blind, parallel-group and placebo-controlled study comparing the efficacy of three antiemetic therapeutic regimens (ondansetron for 3 days, ondasetron plus metoclopramide, and ondansetron given in a single dose) in breast cancer patients receiving cyclophosphamide-based chemotherapy regimens on an outpatient basis. Both the primary and the secondary efficacy were measured. The primary efficacy variable was the number of emetic episodies (considering early and delayed emesis). The secondary efficacy variable measured was the quality of life. Two-by-two tables using the chi-square test and relative-risk concept were elaborated for statistical analysis. There was no difference between high-dose ondansetron and ondansetron plus metoclopramide among patients given CMF (cyclophosphamide, methotrexate, 5-fluorouracil). The single-dose ondansetron regimen showed the worst results. In patients given an FEC regimen (cyclophosphamide, epirubicin, 5-fluorouracil) the antiemetic efficacy was best for the high-dose ondansetron regimen, followed by the ondansetron plus metoclopramide regimen, and was worst for single-dose ondansetron administration. Despite the use of different antiemetic schedules, nausea and emesis are significant problems in patients receiving cyclophosphamide-based chemotherapy. Their adequate control should be the aim of any antiemetic approach.

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Introduction

Two of the most troublesome, most feared, and most commonly encountered side effects associated with the administration of antineoplastic chemotherapy are nausea and vomiting. Uncontrolled nausea and vomiting may result in serious physiologic debilitation or in psychologic distress so severe that the patient may refuse potentially curative treatment [2]. Chemotherapy regimens containing cyclophosphamide in combination with either epirubicin, methotrexate, or 5-fluorouracil are effective in reducing the recurrence rate of breast cancer and extending the survival of patients with the disease [5]. This chemotherapy is usually given on an outpatient basis and can induce nausea and vomiting in over 80% of patients [3]. Cytotoxic drugs are given in combinations that may enhance their emetogenic potential.

Advances in the control of chemotherapy-induced nausea and emesis have been made during the last decade following improvements in our understanding of the pathophysiology of cytotoxic drug-induced nausea and vomiting [6]. Different studies suggest that serotonin acts as an important neurotransmitter in the initiation of chemotherapy-induced emesis. Serotonin (5-hydroxytryptamine3, 5-HT_3) receptors have been identified in both the central and the peripheral nervous system and have been of interest since the discovery of selective antagonists for these receptors [8].

Ondansetron, a potent agent, highly antagonistic to the 5-HT_3 receptor, is reportedly superior to other regimens in patients receiving highly emetogenic chemotherapy regimens [8]. However, the results are not so conclusive in terms of delayed emesis in patients

receiving non-cisplatin-based chemotherapy regimens. To define more specifically the antiemetic role and the optimal dosing schedule of ondansetron in patients receiving intermediately emetogenic regimens, we performed a double-blind, randomized clinical trial comparing three different therapeutic approaches.

Patients and methods

Patient selection

This was a randomized, double-blind, parallel-group, and placebo-controlled study comparing the effect of three antiemetic therapeutic regimens in breast cancer patients receiving cyclophosphamide-based chemotherapy regimens given intravenously on an outpatient basis. The patients were to receive one of the following chemotherapy treatments (doses expressed per square meter of body-surface area): CMF (cyclophosphamide at 500 mg on day 1, methotrexate at 50 mg on days 1 and 8, and 5 fluorouracil at 600 mg on days 1 and 8) every 28 days and FEC (cyclophosphamide at 500 mg on day 1, epirubicin at 75 mg on day 1, and 5-fluorouracil on day 1) every 21 days.

Patients were eligible for this study if they had received no previous chemotherapy, were at least 18 years old, and had a Karnofsky performance status of at least 60%. All patients selected were available for follow-up and each patient gave written consent before entering the study. Patients were excluded if they had severe concurrent illness, had jaundice or showed laboratory evidence of hepatic dysfunction not attributable to metastatic involvement. Patients who required other rescue treatments were also excluded.

Randomization and antiemetic therapy—experimental protocol

After eligibility criteria had been ascertained and written informed consent had been obtained, the patients were enrolled in the study and randomly assigned to receive either of the three designed antiemetic therapeutic protocols in a blinded fashion.

The first treatment (A) consisted of 8 mg of ondansetron in 20 ml of saline given as an intravenous infusion over a period of 5 min at 15–20 min before chemotherapy followed by capsules of ondansetron (8 mg) given every 8 h daily for 3 days (per os). The second treatment (B) consisted of an intravenous infusion of ondansetron (given as described for protocol A) followed by capsules of metoclopramide (MCT, 10 mg) given every 8 h daily for 3 days. The third treatment protocol (C) consisted of 8 mg of ondansetron given as an intravenous infusion in 20 ml of saline (as described for protocols A and B) followed by placebo capsules given orally every 8 h for 3 days. To ensure that the oral treatment (ondansetron, MCT, or placebo) could not be identified, the tablets were put in identical capsules. Once a given patient had been assigned to either of the three designed protocols, she continued receiving the same antiemetic therapy.

The number of vomiting and retching episodes were recorded on a daily basis by the patients on diary cards for 5 days after chemotherapy administration. The primary efficacy variable was the number of emetic episodes. An emetic episode was defined as vomiting or as retching. By definition, emetic episodes were separated by the absence of both vomiting and retching for at least 1 min. The treatment response was defined by the number of emetic episodes: a complete response indicated no emetic episode, a major response indicated one or two emetic episodes, a minor response indicated three to five emetic episodes, and treatment failure indicated more than five emetic episodes. Emesis was considered to have been successfully treated in patients who experienced two or fewer emetic episodes (complete or major control emesis).

Two phases of emesis were considered in the patients selected. Early emesis was defined as that occurring in the immediate period after cytotoxic drug administration (less than 24 h), and delayed emesis was defined as that following the acute phase. It should be borne in mind that each phase may have different underlying mechanisms and that several pathways may operate to produce the overall emetic profile.

The secondary efficacy variable was the quality of life, which was assessed using a general questionnaire for emesis: the functional living index (FLIC) [10]. These questionnaires were completed by patients during a 5-days period following the chemotherapy. The degrees of nausea and disability were recorded each day on a seven-point scale. The FLIC is a multidimensional (physical well-being, ability, emotional state, social interactions, and family situation) quality-of-life assessment instrument. Also, questions are included that measure the compliance of the patients with the therapy. All patients entering the study answered the questionaires. Adverse effects other than emesis were recorded on the daily cards by the patients in response to a general question.

Statistical analysis

Two-by-two tables were elaborated for the statistical analysis. The chi-square statistic with Mantel-Haenszel correction and Fisher analysis, if necessary, were used to test the significance of the differences between treatment groups. We also used the relative-risk concept. Generally an association is suggested by a relative risk larger or smaller than 1.0. The further the relative risk is from 1.0, the stronger the apparent association. Statistical significance using a confidence level $(1 - \alpha)$ of 95% and a power $(1 - \beta)$ of 80% was assessed by values for the chi-square tests that were low ($P < 0.05$) or by confidence limits for the relative risk that did not include 1.0.

Results

A total of 116 cycles of CMF and 66 cycles of FEC chemotherapy were evaluable for analysis. The distribution of patients according to various prognostic factors for chemotherapy-induced emesis (age, alcohol intake) was similar in each of the three treatment groups.

No severe or unexpected event was reported by the patients. Constipation and hot flushes tended to be more frequent among patients receiving ondansetron for 3 days (protocol A) than in patients assigned to protocols B or C. However, there was no significant difference between the groups ($P = 0.1421$ and $P = 0.1001$ for constipation and hot flushes, respectively).

Primary response—number of emetic episodes

CMF regimen

For the CMF chemotherapy regimen we found no difference between the high-dose ondansetron schedule (A) and the ondansetron plus MCT regimen (B) in the control of early or delayed emesis (Fig. 1; Tables 1, 2). During the first 24 h, 77.8% of the patients on

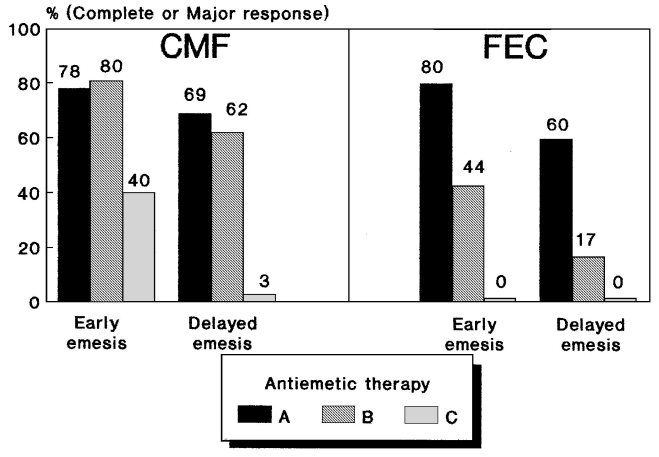

Fig. 1 Antiemetic efficacy of the three antiemetic protocols (*A* Ondansetron given for 3 days, *B* ondansetron plus MCT, *C* ondansetron given in a single dose) in patients receiving chemotherapy (CMF and FEC regimens; see Tables 1 and 2 for the statistical significance of differences)

Table 1 Comparison of the antiemetic efficacy of three antiemetic regimens in patients receiving CMF and FEC chemotherapy

CMF:			
Antiemetic protocols	A 36 cycles *n*(%)	B 50 cycles *n*(%)	C 30 cycles *n*(%)
Early emesis:			
C + M response[a]	28 (77.8)	40 (80.0)	12 (40.0)
Failure rate[b]	8 (22.2)	10 (20.0)	18 (60.0)
Delayed emesis:			
C + M response[a]	25 (69.4)	31 (62.0)	1 (3.3)
Failure rate[b]	11 (31.6)	19 (38.0)	29 (96.7)
FEC:			
Antiemetic protocols	A 30 cycles *n*(%)	B 18 cycles *n* (%)	C 18 cycles *n* (%)
Early emesis:			
C + M response[a]	24 (80.0)	8 (44.4)	0 (0)
Failure rate[b]	6 (20.0)	10 (55.6)	18 (100.0)
Delayed emesis:			
C + M response[a]	18 (60.0)	3 (16.7)	0 (0)
Failure rate[b]	12 (40.0)	15 (83.3)	18 (100.0)

[a] Including complete and major responses
[b] Including minor responses and treatment failures

ondansetron regimen (A) and 80% of those on ondansetron plus MCT (B) reported complete or major protection (two or less emetic episodes). This difference was not statistically significant. However, only 40% of the patients on the ondansetron single-dose schedule (C) reported complete or major emesis control ($P = 0.002$ and $P = 3 \times 10^{-4}$, respectively).

Table 2 Statistical comparison of the efficacy of three antiemetic regimens in patients receiving CMF and FEC chemotherapy

CMF:	A vs B	B vs C	A vs C
Early emesis:			
P[a]	0.990	3×10^{-4}	0.002
RR (95% CI)[b]	1.1 (0.5–2.5)	3(1.6–5.6)	2.7(1.4–5.3)
Delayed emesis:			
P[a]	0.677	3×10^{-6}	1×10^{-6}
RR (95% CI)[b]	0.8(0.4–1.5)	2.5(1.8–3.7)	3.2(1.9–5.2)
FEC:	A vs B	B vs C	A vs C
Early emesis:			
P[a]	0.012	0.003*,[c]	1×10^{-6}
RR[b]	0.4(0.2–0.8)	1.8(1.2–2.7)	5(2.4–10.2)
Delayed emesis			
P[a]	0.004	0.229[c]	4×10^{-5}
RR[b]	0.5(0.3–0.8)	1.2(0.9–1.5)	2.5(1.6–3.9)

*$P < 0.05$
[a] Probability as determined by the chi-square test
[b] Relative risk (with 95% confidence interval)
[c] Fisher exact test applied

FEC regimen

For patients receiving the FEC regimen the best antiemetic approach was high-dose ondansetron (A; Fig. 1; Tables 1, 2). Furthermore, in these patients the worst results were obtained after the single administration of 8 mg of Ondansetron (low-dose ondansetron schedule, C).

Quality of life

Assessment of the quality of life was undertaken along the 5-day study period using the FLIC questionnaire for emesis as pointed out in patients and methods. In general, single-dose ondansetron administration resulted in poor antiemetic control along the 5-day study period. When patients receiving CMF chemotherapy were considered, there were huge differences in quality of life between patients receiving single-dose ondansetron therapy (C) and those assigned to protocols A or B ($P < 0.0001$ in any of the follow-up days). As occurred for the objective response, there was no difference between high-dose ondansetron (A) and the ondansetron plus MCT regimen (B) among CMF patients (Fig. 2).

Among FEC patients, the worst results were reported by the patients given a single dose of ondansetron (C), even on the 1st day of follow-up (Fig. 3), ($P < 0.0001$ and $P = 0.0440$ for C versus A and C versus B, respectively). Although patients receiving

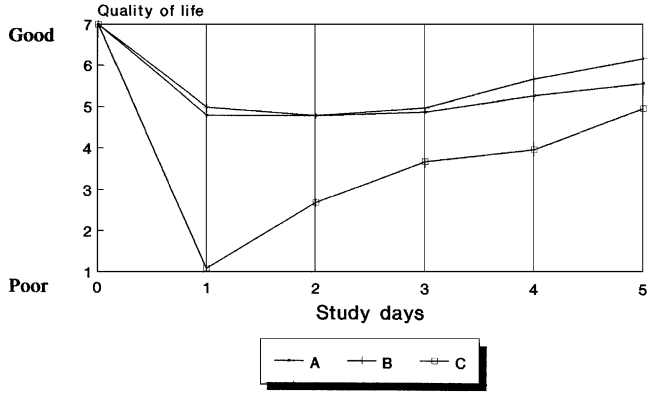

Fig. 2 Assessment of the quality of life along the 5-day study period in patients receiving CMF chemotherapy (*A* Ondansetron given for 3 days, *B* ondansetron plus MCT, *C* ondansetron given in a single dose)

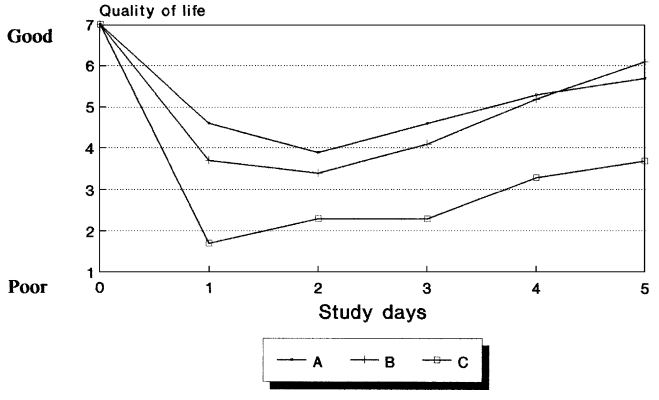

Fig. 3 Assessment of the quality of life along the 5-day study period in patients receiving FEC chemotherapy (*A* ondansetron given for 3 days, *B* ondansetron plus MCT, *C* ondansetron given in a single dose)

ondansetron for 3 days (A) showed a better response in terms of quality of life, only on day 3 of follow-up was the difference statistically significant ($P = 0.032$). No patient complained of emesis after day 5, which is congruent with the moderate emetogenic capability of the chemotherapy treatments given.

In summary, there was no difference between high-dose ondansetron and ondansetron plus MCT among patients receiving CMF in terms of either objective response or subjective assessment of the quality of life. The single-dose ondansetron regimen showed the worst results. The FEC regimen was, as expected, more emetogenic. In this case the antiemetic efficacy was best for the high-dose ondansetron regimen (A), followed by the ondansetron plus MCT regimen (B), and was worst for single-dose ondansetron administration (C).

Discussion

It is well known that the nausea and emesis associated with antineoplastic therapy is of variable intensity and duration and is dependent on the agent, dose, and additional drugs used [2]. The emetic response to cyclophosphamide-based chemotherapy is less intense than that to, for example, platinum-based regimens [6]. However, the control of nausea and vomiting induced by CMF and FEC is a rarely examined problem [4]. A latent period of 8–10 h before the onset of nausea and emesis is usually observed following the administration of cyclophosphamide [2]. The addition of agents such as epirubicin may shorten the latent period and intensify the nausea and emesis.

The question of the optimal dose and schedule of ondansetron continues to be investigated. The studies performed during the clinical development of ondansetron used multidose schedules based on traditional methods of administration of antiemetics and on the pharmacocinetics of ondansetron. The serum half-life of ondansetron is short (approx 3 h) [7]. Another interesting observation, which was consistent in the phase I, II, and III studies, was that most ondansetron failures of treatment occurred within approx 20–24 h of chemotherapy administration. Although ondansetron has been found to be effective as an antiemetic in different clinical trials of highly emetogenic combination-therapy regimens that include cisplatin, its role in milder emetogenic regimens has not been fully defined. Moreover, it has been demonstrated that alternative antiemetic regimens are as effective as the administration of ondansetron [9].

Despite the use of different antiemetic schedules, nausea and emesis are significant problems in the population receiving cyclophosphamide-based chemotherapy. Interestingly, although CMF chemotherapy is generally regarded as being only weakly emetogenic, 50% of patients given a placebo in different studies have experienced emesis [5]. This finding is consistent with our results. The failure rates in our series were 31.3% and 51.4% for CMF and FEC cycles, respectively.

Our results seem to indicate that in patients receiving CMF chemotherapy, there is no need to use ondansetron for 3 or more days and that a single dose of ondansetron followed by MCT for 3 days is probably as effective in controlling both early and delayed emesis. There was no statistically significant difference in efficacy between the two regimens. Most authors who have reported the higher efficacy of ondansetron as an antiemetic in cyclophosphamide-based chemotherapy have made comparison between ondansetron and a placebo [1].

In our experience, the administration of a single 8-mg dose has been shown to be ineffective in controlling nausea and vomiting (both early and delayed

emesis), whatever the chemotherapy schedule considered. These data confirm those reported by Hainsworth et al. [7].

The results of this study indicate that ondansetron given for 3 days provides significant benefits to patients receiving FEC chemotherapy, whereas the combination of ondansetron plus MCT can control emesis CMF-treated patients. This finding is also in agreement with previously reported results [4]. However, it must be taken into account that even in FEC-treated patients given ondansetron for 3 days the failure rates were 20% and 40% for early and delayed emesis, respectively, showing the need for further improvement in antiemetic treatment.

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