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Double-Blind Controlled Trial of the Antiemetic Efficacy and Toxicity of Methylprednisolone (MP), Metoclopramide (MTC) and Domperidone (DMP) in Breast Cancer Patients Treated With i.v. CMF

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Abstract—*Sixty-two patients treated for the first time with i.v. CMF were included in a double-blind comparative study aimed at evaluating the efficacy of 3 different drugs (methylprednisolone (MP), metoclopramide (MTC), and domperidone (DMP)) in preventing chemotherapy-induced nausea and vomiting.*

Complete protection from vomiting/nausea was obtained in 85%/80% in the group treated with MP; in 60%/65% in the group treated with MTC and in 38%/42% in the group treated with DMP. Average number of vomiting episodes was 2.4 with MP, and 1.7 with MTC and 6.2 with DMP. Older patients seem to be a prognostically unfavorable subgroup. Side-effects were mild and infrequent.

We conclude that MP and MTC are probably equally efficacious antiemetic treatments in patients undergoing i.v. CMF chemotherapy, but due to the risk of extrapyramidal reactions with MTC, MP probably should be the treatment of choice in these patients.

INTRODUCTION

We conducted a double-blind controlled trial to compare the antiemetic efficacy of methylprednisolone (MP), metoclopramide (MTC) and domperidone (DMP) administered for 11½ hr after cancer chemotherapy in patients treated with i.v. cyclophosphamide–methotrexate–5FU (CMF).

MATERIALS AND METHODS

Women with breast cancer hospitalized in the Division of Medical Oncology, Perugia, from April, 1984, to April, 1985, who were receiving CMF chemotherapy as an adjuvant or for metastatic disease were entered in the study. Patients were eligible for randomization if their performance status was ≥ 60 and if they had not received any prior chemotherapy.

Patients were excluded from the study if they had other possible causes of nausea and vomiting or contraindications to antiemetic drugs used. The aim of the study was fully explained to each participating patient, and informed consent was obtained.

Antiemetic treatment was randomized among the following regimens.

Treatment A

MTC, 20 mg i.v., ½ hr before and 2½, 5½, 8½ and 11½ hr after chemotherapy.

Treatment B

DMP, 20 mg i.v., ½ hr before, 5½ and 11½ hr after chemotherapy.

Treatment C

MP, 125 mg i.v., ½ hr before, 5½ and 11½ hr after chemotherapy.

Every patient entered the study only at the time of the first course of chemotherapy. Saline was administered as placebo at 2½ and 8½ hr after chemotherapy in patients receiving DMP or MP. Vomiting was measured by the number of emetic episodes; the intensity of nausea was expressed

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Table 1. Characteristics of the patients

Treatment	MTC	MP	DMP
No. patients	20	21	21
Average age	56.0	52.1	53.1
< 50	5 (25%)	9 (42.9%)	7 (33.3%)
⩾ 50	15 (75%)	12 (57.1%)	14 (66.7%)
Performance status			
60–80	3 (15%)	1 (4.8%)	1 (4.8%)
90–100	17 (85%)	20 (95.2%)	20 (95.2%)
Stage of disease			
N.E.D.*	17 (85%)	19 (90.5%)	19 (90.5%)
Advanced	3 (15%)	2 (9.5%)	2 (9.5%)

*No evidence of disease.

by the following scale: 0 = absence of nausea; 1 = slight; 2 = moderate; 3 = severe nausea. Such evaluations were performed at 2, 4, 6, 8, 11, 14 and 24 hr after chemotherapy.

Statistical analysis

Chi-square tests and 2-way ANOVA models were performed to evaluate the results. All *P*-values correspond to a 2-tailed significance test.

RESULTS

Efficacy

Sixty-two consecutive patients were studied. The characteristics of these patients are reported in Table 1. All prognostic factors were well balanced among the 3 groups of patients. The 3 antiemetic regimens were statistically different for protection from vomiting and nausea ($\chi^2 = 10.06$; $P < 0.01$ and $\chi^2 = 6.59$; $P < 0.05$, respectively). Complete protection from vomiting/nausea was observed in 85%/80% of patients treated with MP; in 60%/65% of those treated with MTC and in 38%/42% of those treated with DMP (see Table 2).

In order to examine which treatment was the more efficacious, a multifactorial analysis was performed. MP and MTC were apparently more efficacious than DMP in protecting patients from vomiting and nausea. In fact, complete antiemetic protection was significantly inferior among patients treated with DMP when compared to those treated with MP ($P = 0.01$), and the mean number of vomiting episodes was significantly higher among the patients treated with DMP as compared to those treated with MP ($P = 0.001$) and MTC ($P = 0.001$).

As regards nausea, both from the point of view of complete protection and the maximal intensity of nausea evaluated by score, the patients treated with DMP showed significantly higher mean levels than patients treated with MP ($P = 0.02$ and $P = 0.02$, respectively). In addition, mean number of vomiting episodes was significantly higher in the older patients (4.3) than in the younger ones (1.9; $P = 0.001$), suggesting that the age of patients may influence the results of therapy. However there were no significant differences in complete protection from nausea and maximal intensity of nausea as regards age levels.

Another interesting observation is that the mean number of emetic episodes in the younger patients treated with MP was 0 while in the older ones it was 4.2, whereas the mean number in the younger and older patients treated with MTC was 2.6 and 1.4, respectively. In conclusion, it would seem that MP was more efficacious in the younger patients and MTC in the older ones, but this result requires confirmation in a larger clinical trial.

All 3 treatments were well-tolerated, with MP showing the lowest toxicity. Slight sedation and headache were noted by 20–30% of the patients treated with MTC or DMP, and only 2 patients treated with MTC presented an extrapyramidal reaction which rapidly reversed after administration of diazepam.

DISCUSSION

Our study is the first double-blind controlled trial that shows activity of MP and MTC in preventing nausea and vomiting from i.v. CMF. DMP is clearly less efficacious than the other 2 drugs and probably has no place in the prevention of emesis in CMF treated cancer patients.

Previous antiemetic studies have shown the lack of efficacy of both 'standard' [1] and high-dose i.v. [2] MTC in CMF-treated patients. The discrepancy found among the results of our study and the previous ones may well be due to the different dosing schedule we used (MTC every 3 hr instead of every 6 hr) and to the more prolonged duration of treatment. The last doses of drugs in our study were, in fact, administered 11½ hr after chemotherapy, allowing a more complete protection of patients from late vomiting episodes induced by cyclopho-

Table 2. Results

	MTC	MP	DMP
No. of patients	20	21	21
Complete antiemetic protection	12 (60%)	18 (85.7%)	8 (38.1%)
Major antiemetic protection (≤ 2 emetic episodes)	4 (20%)	1 (4.8%)	1 (4.8%)
Minor antiemetic protection (3–5 emetic episodes)	2 (10%)	1 (4.8%)	7 (33.3%)
No effect (> 5 emetic episodes)	2 (10%)	1 (4.8%)	5 (23.8%)
No nausea	13 (65%)	17 (80.9%)	9 (42.8%)
No. emetic episodes			
Average	1.7	2.4	6.2
Range	(0–11)	(0–44)	(0–48)
Maximal intensity of nausea			
Average	0.7	0.3	1.0
Range	(0–3)	(0–2)	(0–3)

sphamide, which usually begin 12 hr after chemotherapy.

Our study also shows that the older patients are more prone to nausea and vomiting than younger patients: the number of emetic episodes was higher than in the younger patients. This phenomenon may be relevant with respect to the therapy but cannot be clearly interpreted and should be confirmed in a larger study.

In conclusion, our study suggests that both MTC and MP are equally efficacious in the prevention of nausea and vomiting in CMF treated patients, but the lower toxicity of MP makes it the drug of choice in these patients. However, this antiemetic regimen seems particularly suitable for hospitalized patients because of the necessity of repeated infusions over a relatively long period of time. Furthermore, older patients may need an even more intensive or a different antiemetic treatment.

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REFERENCES

1. Morran C, Smith DC, Anderson DA, McArdle CS. Incidence of nausea and vomiting with cytotoxic chemotherapy: a prospective randomized trial of antiemetics. *Br Med J* 1979, **1**, 1323–1324.
2. David M, Durand M, Chauvergne J, Mauriac L, Bui BN, Noerni B. Cyclophosphamide, methotrexate, and 5-FU (CMF)-induced nausea and vomiting: a controlled study with high-dose metoclopramide. *Cancer Treat Rep* 1984, **68**, 921–922.