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Short communication

Methylprednisolone as antiemetic treatment in breast-cancer patients receiving cyclophosphamide, methotrexate, and 5-fluorouracil: a prospective, crossover, randomized blind study comparing two different dose schedules

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Summary. The antiemetic response and side effects resulting from treatment with methylprednisolone (MPA) given on two different dose schedules were evaluated in 20 women with breast cancer who were undergoing chemotherapy consisting of cyclophosphamide, methotrexate and 5-fluorouracil (CMF). This randomized, crossover, double-blind study compared the antiemetic efficacy of a single dose of 125 mg MPN with that of two such doses. The study demonstrated the superiority of the latter protocol in preventing CMF-induced nausea and vomiting. The rate of antiemetic response to single vs double doses was as to follows: complete protection, 17% vs 30%; partial and minimal protection, 39% vs 55%; and no protection, 44% vs 15% of the courses, respectively ($P = 0.0087$). No difference in the antiemetic response rate was found between the first and the second course. Treatment with MPN was well tolerated, and no difference in the incidence of side effects was found between the single-dose and the double-dose schedule. We recommend the use of two doses of 125 mg MPN as prophylactic antiemetic treatment in breast-cancer patients receiving CMF chemotherapy.

Introduction

Combination chemotherapy consisting of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) is one of the common protocols used in the treatment of breast cancer, but there is no satisfactory antiemetic therapy [10]. Without effective antiemetic treatment, more than 50% of patients suffer from severe nausea and vomiting [8]. Given alone or in combination with other antiemetic drugs, methylprednisolone (MPN) provides effective protection against chemotherapy-induced emesis [2, 4, 7]. The optimal dose of MPN for the prevention of emesis induced by CMF chemotherapy has not yet been determined. A recent study showed no difference in the antiemetic efficacy of 125 vs 375 mg MPN [9]. The aim of the present study was to compare two MPN dose schedules (125 mg × 1 vs 125 mg × 2) in breast-cancer patients undergoing CMF chemotherapy.

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Patients and methods

A randomized, crossover, double-blind study comparing two schedules for the administration of MPN as antiemetic prophylactic treatment in breast-cancer patients receiving CMF chemotherapy was carried out in the Day Care Unit of the Oncology Department of Hadassah University Hospital in cooperation with the Cytotoxic Reconstitution Unit of the Pharmacy Department of the same institution. The antiemetic protocol consisted of two arms; one included a single dose of 125 mg MPN and the other, two such doses of MPN. The first dose was given at 2 h prior to CMF treatment and the second (MPN or placebo), immediately before the chemotherapy. MPN was given by slow i.v. injection. Each patient received the two regimens of MPN in two sequential chemotherapy courses according to a randomized crossover design [6].

The patients included in this study were women with breast cancer of stages I–II (T1–2, N0–1, M0) who were scheduled to receive their first course of adjuvant CMF chemotherapy, which comprised 600 mg/m^2 cyclophosphamide, 40 mg/m^2 methotrexate, and 600 mg/m^2 5-fluorouracil given by i.v. push injection every 3 weeks. Patients with a history of peptic disease were excluded.

The antiemetic efficacy of MPN was determined according to the degree of protection provided against from nausea and vomiting. Scores were assigned according to the severity of nausea (none, 0; mild, 1; moderate, 2; and severe, 3) and to the incidence of vomiting (none, 0; 1–4 episodes, 1; 5–10 episodes, 2; and >10 episodes, 3). The antiemetic response was defined as the sum of nausea and vomiting scores as follows: complete protection, no nausea and no vomiting (scores 0 and 0); partial protection, an absence of nausea associated with 1–4 episodes of vomiting (scores 0 and 1) or mild nausea either in the absence of vomiting (scores 1 and 0) or associated with 1–4 vomiting episodes (scores 1 and 1); minimal protection, mild nausea along with 5–10 episodes of vomiting (scores 1 and 2) or moderate nausea associated with

Table 1. Distribution of nausea and vomiting according to chemotherapy course and MPN dose schedule

Score		Incidence of side effects[a]			
		Chemotherapy course		MPN dose schedule (mg)	
		First (20 patients)	Second (18 patients)	125×1 (18 patients)	125×2 (20 patients)
Nausea:					
None	0	25% (5)	28% (5)	22% (4)	30% (6)
Mild	1	30% (6)	22% (4)	22% (4)	30% (6)
Moderate	2	20% (4)	22% (4)	17% (3)	25% (5)
Severe	3	25% (5)	28% (5)	39% (7)	15% (3)
P value		0.533		0.026	
Vomiting episodes:					
None	0	50% (10)	50% (9)	33% (6)	65% (13)
1–4	1	25% (5)	11% (2)	16% (3)	20% (4)
5–10	2	10% (2)	28% (5)	20% (5)	10% (2)
>10	3	15% (3)	11% (2)	22% (4)	5% (1)
P value		0.783		0.012	

[a] Values in parentheses represent numbers of patients

Table 2. Rate of antiemetic response to MPN according to chemotherapy course and MPN dose schedule

Antiemetic response	Response rate[a]			
	Chemotherapy course		MPN dose schedule (mg)	
	First (20 patients)	Second (18 patients)	125×1 (18 patients)	125×2 (20 patients)
Complete	25% (5)	22% (4)	17% (3)	30% (6)
Partial	30% (6)	34% (6)	28% (5)	35% (7)
Minimal	10% (2)	22% (4)	11% (2)	20% (4)
None	35% (7)	22% (4)	44% (8)	15% (3)
P value	0.964		0.009	

[a] Values in parentheses represent numbers of patients

1–4 (scores 2 and 1) or 5–10 vomiting episodes (scores 2 and 2); and no protection, mild nausea associated with >10 episodes of vomiting (scores 2 and 3) or severe nausea accompanied by 5–10 (scores 3 and 2) or >10 episodes of vomiting (scores 3 and 3).

In addition to their antiemetic response, the patients' general feeling, appetite, and daily activity during treatment were evaluated. Scores were given to these variables as follows: normal appetite, 1; increased appetite, 2; decreased appetite, 3; good general feeling, 1, bad general feeling, 2; very bad general feeling, 3; normal daily activity, 1; decreased daily activity, 2; and significantly decreased daily activity, 3. The side effects evaluated included facial flush, nervousness, disturbed sleep, headache, and anxiety. The antiemetic response and the side effects were evaluated over the period between the two courses of chemotherapy. The results were analyzed according to the MPN dose and the chemotherapy course. Statistical analysis was performed using Wilcoxon matched-pair tests.

Results

A total of 20 women with breast cancer of stages I–II (T1–2, N0–1, Mo) who were undergoing adjuvant CMF chemotherapy took part in this study. The median age was 43.5 years (range, 30–54 years). In all, 18 patients received 2 courses of CMF chemotherapy and 2 received only 1 course. In the latter 2 cases, the chemotherapy was changed from CMF to CAF (doxorubicin instead of methotrexate) for the second course; thus, 18 patients were evaluated for 2 courses and 2, for 1 course. In the first chemotherapy course, 11 women received a double dose (125 mg×2) and 9 were given a single dose (125 mg×1) of MPN. In the second course, 9 patients received the double dose and 9 were given the single dose.

The incidence and severity of nausea and vomiting during the first and second chemotherapy courses were as follows (Table 1): no nausea, 25% vs 28%; mild to moderate nausea, 50% vs 44%; severe nausea, 25% vs 28%

Table 3. Onset and duration of emesis following treatment according to chemotherapy course

	Median onset and duration of emesis (h)[a]	
	First course	Second course
Nausea:		
Start	7.5 (0–24)	8.5 (0–24)
End	31 (2–72)	48 (8–72)
Duration	30 (2–72)	30 (0–65)
P value	0.173	
Vomiting:		
Start	12 (6–24)	10.5 (7–24)
End	22 (6–48)	24 (14–72)
Duration	8 (0–24)	13 (3–63)
P value	0.180	

[a] Values in parentheses represent ranges

Table 4. Appetite, general feeling, and daily activity of patients after treatment according to chemotherapy course and MPN dose schedule

	Incidence[a]			
	Chemotherapy course		MPN dose schedule (mg)	
	First (20 patients)	Second (18 patients)	125×1 (18 patients)	125×2 (20 patients)
Appetite:				
Normal	25% (5)	33% (6)	17% (3)	40% (8)
Increased	25% (5)	–	22% (4)	5% (1)
Decreased	50% (10)	67% (12)	61% (11)	55% (11)
P value	0.53		0.09	
General feeling:				
Good	45% (9)	39% (7)	39% (7)	45% (9)
Bad	25% (5)	33% (6)	28% (5)	30% (6)
Very bad	30% (6)	28% (5)	33% (6)	25% (5)
P value	0.66		0.18	
Daily activity:				
Normal	40% (8)	35% (6)	33% (6)	40% (8)
Decreased	35% (7)	53% (9)	45% (8)	40% (8)
Significantly decreased	25% (5)	12% (3)	22% (4)	20% (4)
P value	1.00		0.23	

[a] Values in parentheses represent numbers of patients

Table 5. Side effects of MPN according to chemotherapy course and MPN dose schedule

Side effect	Incidence of side effects					
	Chemotherapy course			MPN dose schedule (mg)		
	First (20 patients)	Second (18 patients)	*P* value	125×1 (18 patients)	125×2 (20 patients)	*P* value
Facial flush	35%	50%	0.31	33%	50%	0.31
Nervousness	40%	39%	1.00	39%	40%	1.00
Disturbed sleep	45%	39%	0.73	33%	53%	0.31
Headache	35%	22%	0.40	39%	22%	0.46
Anxiety	55%	39%	0.22	44%	53%	0.68

($P = 0.53$); no vomiting, 50% vs 50%; 1 to 10 episodes of vomiting, 35% vs 39% and >10 vomiting episodes, 15% vs 11% ($P = 0.78$), respectively. The results obtained for single vs double doses of MPN were as follows: no nausea, 22% vs 30%; mild to moderate nausea, 39% vs 55%; severe nausea, 39% vs 15% ($P = 0.026$); no vomiting, 33% vs 65%; 1–10 episodes of vomiting, 45% vs 30%; and >10 vomiting episodes, 22% vs 5% ($P = 0.012$).

The rates of antiemetic response recorded for the first and second courses, respectively, were as follows (Table 2): complete protection, 25% vs 22%; partial and minimal protection 40% vs 56%; and no protection, 35% vs 22% ($P = 0.9645$). The results obtained for single and double doses of MPN were as follows: complete protection, 17% vs 30%; partial and minimal protection, 39% vs 55%; and no protection, 44% vs 15% ($P = 0.0087$).

The timing of nausea and vomiting following the first and second courses of chemotherapy, respectively, was as follows (Table 3): median onset of nausea, 7.5 and 8.5 h (median duration, 30 h; $P = 0.17$); and median onset of vomiting, 12 and 10.5 h (median duration, 8 and 13 h, respectively; $P = 0.18$). The median duration of emesis following MPN doses of 125 mg×1 vs 125 mg×2 was 39.5 vs 29 h for nausea ($P = 0.735$) and 12 vs 16 h for vomiting ($P = 0.65$). No difference was found in the timing of nausea or vomiting according to either chemotherapy course or MPN dose schedule (Table 3).

The appetite, general feeling, and daily activity of patients during the treatment were scored as: normal appetite, 29%; increased appetite, 13%; decreased appetite, 58%; good general feeling, 42%; bad general feeling 29%; very bad general feeling 29%; normal daily activity, 38%; decreased daily activity, 43%; and significantly decreased daily activity, 19% of the courses. No difference was found in the incidence of these variables according to chemotherapy course or MPN dose schedule (Table 4). The incidence of side effects during the treatment was: facial flush, 42%; nervousness, 39%; disturbed sleep, 42%; headache, 29%; and anxiety, 47%. No difference was found between the first and second courses or between the two different doses of MPN (Table 5).

Discussion

Nausea and vomiting are serious problems in breast-cancer patients undergoing adjuvant CMF chemotherapy [10]. Much effort has been expended during the last decade to overcome problems with emesis; metoclopramide, phenothiazines, delta-9-tetrahydrocannabinole, corticosteroids, and, recently, 5-HT_3 receptor antagonists have been investigated to define the optimal antiemetic treatment for these patients [3, 4, 7].

Three antiemetic protocols for breast-cancer patients receiving CMF chemotherapy have been studied in our department: high-dose metoclopramide with dexamethazone, chlorpromazine with MPN, and MPN vs metoclopramide [5–7]. MPN given alone or in combination with other antiemetic drugs was found to be effective and well tolerated, but the optimal dose has not yet been determined. The aim of the present study was to compare a single dose of 125 mg MPN with two such doses. The results demonstrate that the double-dose protocol was superior to the single-dose treatment and did not increase the incidence or severity of associated side effects. The antiemetic protection provided by the double dose vs the single-dose schedule was: complete protection, 30% vs 17%; partial and minimal protection, 55% vs 39% and no protection, 15% vs 44% ($P = 0.0087$). The significance of these findings is enhanced by the observation that there was no difference in the antiemetic protection noted during the first vs the second chemotherapy course. Moreover, 13 of 18 patients (72%) preferred the double dose of MPN. The common side effects of the treatment included facial flush, nervousness, disturbed sleep, headache, and anxiety; although their incidence was high – between 29% and 47% – they were mild and were partly attributable to the patients' receiving their first course of chemotherapy [10].

Our results disagree with those reported by Roila et al. [9], who found no difference between doses of 125 and 375 mg MPN in protecting patients against CMF chemotherapy-induced emesis. In conclusion, we found the administration of two doses of 125 mg MPN to be an effective and well-tolerated treatment, which we recommend for breast-cancer patients receiving CMF chemotherapy.

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