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Adjuvant Therapy for Operable Breast Cancer with Medroxyprogesterone Acetate Alone in Postmenopausal Patients or in Combination with CMF in Premenopausal Patients

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Abstract—*The present paper concerns two multicenter studies on adjuvant therapy with medroxyprogesterone acetate (MAP) for operable N+ breast cancer. The patients entered the study between April* 1979 *and March* 1986. *One hundred and fifty-one premenopausal patients were randomly assigned to receive either polychemotherapy (CMF) or CMF + MAP. One hundred and thirty-eight postmenopausal patients were randomized to receive either MAP h.d. or no treatment. CMF was administered according the following schedule: cyclophosphamide* mg 100/ms *p.o.* 1–4 *days; methotrexate* mg 40/ms *i.v. and fluorouracil* mg 600/ms *i.v.* 1*st and* 8*th days. The cycle was repeated six times every* 28 *days. MAP was administered at* 1000 mg × 2*/daily p.o. for* 30 *days and afterwards* 500 mg × 2*/daily for* 5 *months. In the premenopausal study after a median follow-up of* 36 *months no difference was observed in the incidence of recurrence, site of recurrence, actuarial* 5*-year disease-free survival (DFS) or overall survival (OS). In the postmenopausal study a statistically significant lower number of recurrences was observed in MAP-treatment patients after a median follow-up of* 37 *months. The effect of MAP was limited to patients with* ≤ 3 *metastatic axillary lymph nodes. In addition, there are suggestions that only patients with ER+ tumors draw some advantage from the treatment. On the other hand, no difference exists in the OS. The treatments were substantially well tolerated. The MAP + CMF regimen induces lower vomiting compared to the CMF alone. The most frequent MAP side-effects were vaginal spotting* (16%) *and tremors* (12%).

We conclude that MAP h.d., like tamoxifen and aminoglutethimide, can improve the DFS of operable N+ breast cancer in postmenopausal patients.

INTRODUCTION

IT IS well-known that the presence of metastatic foci in the axillary lymph nodes (N+) at the moment of the diagnosis of breast carcinoma makes prognosis in these patients very severe.

During the 1970s many studies were carried out on the use of adjuvant chemotherapy in these female patients. On the whole it has been proven that it can improve the disease-free survival in at least some patient sub-groups [1]. The CMF regimen in particular has determined a significant improvement in disease-free survival and in overall 10-year survival in premenopausal patients [2].

Less interest was placed in those years on the use of additive hormonal therapy in adjuvant terms.

The Italian Chemo-Radio-Surgical Co-operative Group started a prospective and randomized study in 1976 which assessed the effect of medroxyprogesterone acetate (MAP) in high doses intramuscularly (1 month of treatment for three cycles every 6 months) in patients with N+ breast carcinoma compared with a group of control patients who received only post-operative radiotherapy. After 3 years the actuarial statistical analysis did not show any significant differences in disease-free survival

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between the two groups of patients [3].

On the basis of the previous experience and of data from the literature, the Chemo-Radio-Surgical Co-operative Group set up a study in April 1979 to assess the usefulness of adding hormone therapy with high-dose MAP to chemotherapy with CMF in premenopausal patients or of having only hormone therapy with MAP at high doses administered orally and continuously in postmenopausal patients.

At the start of the study a total of 12 courses of chemotherapy were planned in premenopausal patients. From January 1980 the number of CMF cycles was reduced to six cycles on the basis of a study which showed no difference in disease-free survival and overall survival between treatment with CMF 12 cycles and CMF six cycles [2].

The results of the study on both premenopausal and postmenopausal patients are reported here.

MATERIALS AND METHODS

The present study concerns patients with operable T1, T2 and T3a, N0, N1 breast carcinoma. Patients with N2 were also admitted to the study as long as it only involved lymph nodes which were fixed to one another and not fixed to the surrounding structures. All the patients had metastases at the axillary lymph nodes upon histological examination. Patients with T3b or T4 as well as patients who were previously treated for carcinoma of the contralateral breast or for another tumor with the exception of basal or squamous cell carcinoma of the skin or of the cervix, were excluded. The surgical operation had to involve a radical mastectomy or modified radical mastectomy. The search for the 17-beta-estradiol and progesterone receptors, conducted according the dextran-charcoal method, was done every time it was possible to do so. Patients whose tumor contained $\geq$ 10 fmole of ER per mg cytosol protein were considered as having a ER positive tumor and those with $<$10 fmols/mg ER a negative tumor.

The premenopausal patients or the ones in menopause for less than a year were randomized to receive either polychemotherapy (CMF) or polychemotherapy plus hormone therapy (CMF + MAP at high doses). The patients who had been in postmenopause for more than a year were randomized to receive either no treatment or hormone therapy (MAP at high doses).

CMF consisted of the following drugs and dosages: cyclophosphamide 100 mg/ms orally from the 1st to 14th days + fluorouracil 600 mg/ms and methotrexate mg 40/ms intrvenously on the 1st and 8th days with a cycle to be repeated every 28 days. MAP was administered at a dose of 1000 mg twice daily orally for 1 month and then 500 mg twice daily orally for 5 months. The adjuvant treatment was started in a period between 20 and 45 days after the surgical operation and the total duration was six cycles of CMF and/or 6 months of MAP therapy.

Table 1. Premenopausal study

	CMF	CMF + MAP
Randomized patients	80	71
Evaluable patients	77 (96%)	68 (96%)
Non-evaluable patients	3	3
Reasons:		
Ineligibility	—	3
Lost to follow-up	1	—
Refusal of treatment	1	—
Other reasons	1*	—

*Patient died of acute leukemia after 4 months.

The patients were checked monthly during the treatment and every 3 months subsequently. Instrumental tests were carried out periodically (chest X-ray every 6–9 months, bone scintigraphy and hepatic echography once a year for the first 3 years).

The analysis of the disease-free survival and of the overall survival was performed using the 'product-limit' analysis and the statistical comparisons were done with the Wilcoxon and Mantel–Cox tests. Times were measured from the date of mastectomy.

RESULTS

Premenopausal patients

One hundred and fifty-one patients were randomized up to 30 March 1986. One hundred and forty-five patients were considered evaluable for the analysis (Table 1). Six patients were considered not to be evaluable: three patients were excluded as they were ineligible for the study (reasons for ineligibility: previous malignant tumor, previous irradiation, primary tumor T4). One refused the treatment, no follow-up information was available for one patient and one patient died of acute leukemia after four cycles of CMF. The characteristics of the evaluable patients are reported in Table 2. The two groups of patients proved to be well-balanced as regards the prognostic factors considered. Eleven patients in the CMF group and 16 patients in the CMF + MAP group were admitted to the study when 12 courses of CMF were scheduled. The remaining patients were randomized to receive six courses of CMF. The median follow-up period was 36 months (range 4–81).

Relapse was observed in 28/77 (36%) of the patients treated with CMF and in 20/68 (29%) of the patients treated with CMF + MAP. This difference is not statistically significant, nor is the distribution of the sites of the first relapse. The actuarial analysis of the disease-free survival at 5

Table 2. Characteristics of premenopausal patients

	CMF (77 patients)	CMF + MAP (68 patients)
Age (years)		
Median	45	45
Range	(33–55)	(29–57)
Size of the tumor		
T1	15	7
T2	52	48
T3	10	13
Nodal status		
N0	17	15
N1	56	50
N2	4	3
Number positive nodes		
Median	3	3
Range	(1–25)	(1–18)
1–3	45	42
>3	32	26
Surgical treatment		
Radical mastectomy	52	42
Modified radical mastectomy	25	26
Hormonal receptors		
ER+	19	17
ER−	9	8
Not determined	49	43

Table 3. Results of premenopausal study

	No. of patients	Recurrence No. (%)	*P**	5yDFS %	*P*†
All patients					
CMF	77	28 (36%)	0.375	53	0.779
CMF + MAP	68	20 (29%)		61	
$N \leq 3$					
CMF	45	11 (24%)	0.543	68	0.922
CMF + MAP	42	8 (19%)		75	
$N > 3$					
CMF	32	17 (53%)	0.51	31	0.728
CMF + MAP	27	12 (44%)		45	

*Pearson test.
†Wilcoxon test.

years does not show any significant differences between the two groups (Table 3, Fig. 1). Even the comparison between the two treatments within the sub-groups of patients with a differing number of metastatic lymph nodes or according to the receptor status of the tumor does not show any significant difference.

At the present moment no significant difference has emerged even as regards overall survival. 15/77 (19%) patients in the CMF group and 10/68 (15%) in the CMF + MAP group have died. The 5-year overall survival is 72% for CMF and 73% for CMF + MAP.

Postmenopausal patients

One hundred and thirty-eight patients were randomized, and 128 patients can be considered evaluable (Table 4). Ten patients were considered not to be evaluable: seven patients were excluded as they were ineligible [reason for ineligibility: N− (3), M1 (2), T4 primary tumor (1), previous cancer in contralateral breast (1), two because of violations of the protocol, and one because she never actually began the treatment]. The characteristics of the assessable patients are reported in Table 5.

The two groups were well-balanced for prognostic factors. The lower median number of positive lymph nodes (2) in the control group as compared with the MAP group (3) is not statistically significant ($P < 0.2$).

The median follow-up period was 37 months (range 4–83).

Relapse was observed in 36/66 (55%) of the control patients and 23/62 (37%) of the patients treated with MAP at high doses. This difference turned out to be statistically significant ($P = 0.048$).The analysis of the relapse site shows that a higher number of simultaneously distant and local recurrences occurs in the control group (Table 6). The actuarial analysis of the 5-year disease-free survival does not show any significant difference between the two groups (Fig. 2) even though the MAP-treated group has a higher disease free survival (50%) than the control group (24%). The comparison of the two treatments on the basis of the number of lymph nodes shows that a significant difference exists in favor of MAP in the group with 1–3 lymph nodes (Table 7 and Fig. 3).

As regards the receptor status, we should point out that in the RE+ subgroup, although statistical significance was not reached, only one out of 12 patients treated with MAP had relapse, as opposed to eight out of 16 untreated.

So far 23/66 (35%) and 16/62 (26%) with no treatment and MAP have died respectively (no significant difference). The overall 5-year survival of the two groups of patients is not significantly different: 48% for the control group and 62% for the group treated with MAP at high doses ($P = 0.34$).

Side-effects

In the premenopausal study the treatment was interrupted because of toxicity in five cases in the CMF group and in two cases in the CMF + MAP group. Leukopenia was the main reason for treatment suspension (3 patients in the CMF group and 1 patient in CMF + MAP). Other causes were severe nausea and vomiting in two patients and asthenia with hypotension in one case. Five more patients refused to complete the treatment program:

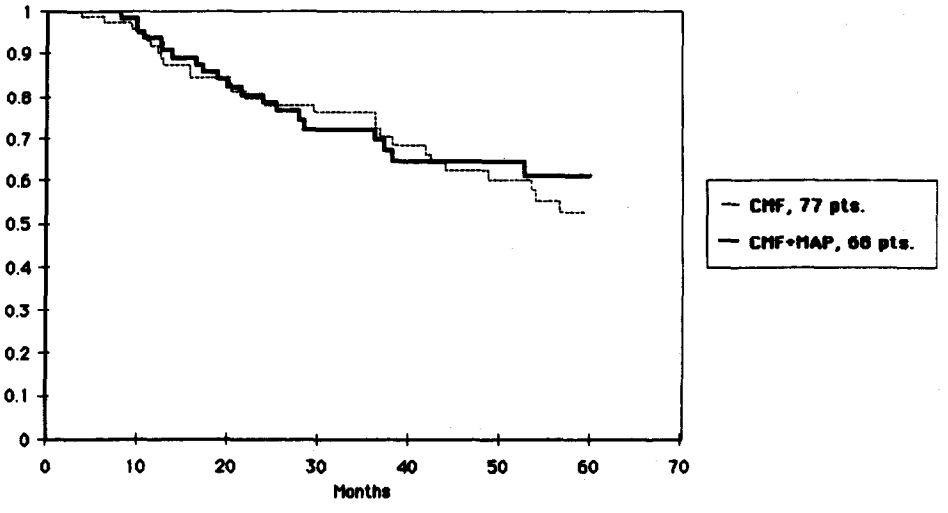

Fig. 1. Premenopausal patients. Disease-free survival (Wilcoxon P = 0.77; Mantel-Cox P = 0.55).

Table 4. Postmenopausal study

	Control	MAP
Randomized patients	69	69
Evaluable patients	66 (96%)	62 (90%)
Non-evaluable patients	3	7
Reasons:		
Ineligibility	2	5
Protocol violation*	1	1
Treatment not done	—	1

*One patient received Rx therapy and the other one received CMF.

Table 5. Characteristics of postmenopausal patients

	No treatment (66 patients)	MAP (62 patients)
Age		
Median	59	59
Range	(40–79)	(41–72)
Size of tumor		
T1	9	7
T2	48	41
T3	9	14
Nodal status		
N0	7	11
N1	50	41
N2	9	14
Number of positive nodes		
Median	2	3
Range	(1–14)	(1–26)
1–3	39	38
>3	26	24
Surgical treatment		
Radical mastectomy	41	38
Modified radical mastectomy	25	24
Hormonal receptor		
ER+	16	12
ER−	4	4
Not determined	46	46

Table 6. Postmenopausal study. Site of first recurrence

	Control	MAP
Only local		
Local cutaneous	9	9
Loco-regional nodes	4	—
Only distant		
Bone	3	11
Pleura	—	1
Lung	1	—
Liver	3	—
Soft tissues	2	—
Local + distant	13*	1†
Unspecified	1	1
Total	36	23

*Bone + soft tissue (6), bone + lung (2), bone + liver (1), bone + pleura (1), lung + nodes (1), liver + soft tissue (2).
†Bone + liver.

Table 7. Results of postmenopausal study

	No. of patients	Recurrence No. (%)	P*	5yDFS %	P†
All patients					
MAP	62	23 (37%)	0.048	50	0.131
No treatment	66	36 (55%)		24	
$N \leq 3$					
MAP	38	8 (21%)	0.058	69	0.051
No treatment	39	16 (41%)		42	
$N > 3$					
MAP	24	15 (62%)	0.267	25	1.00
No treatment	26	20 (80%)		0	

*Pearson test.
†Wilcoxon test.

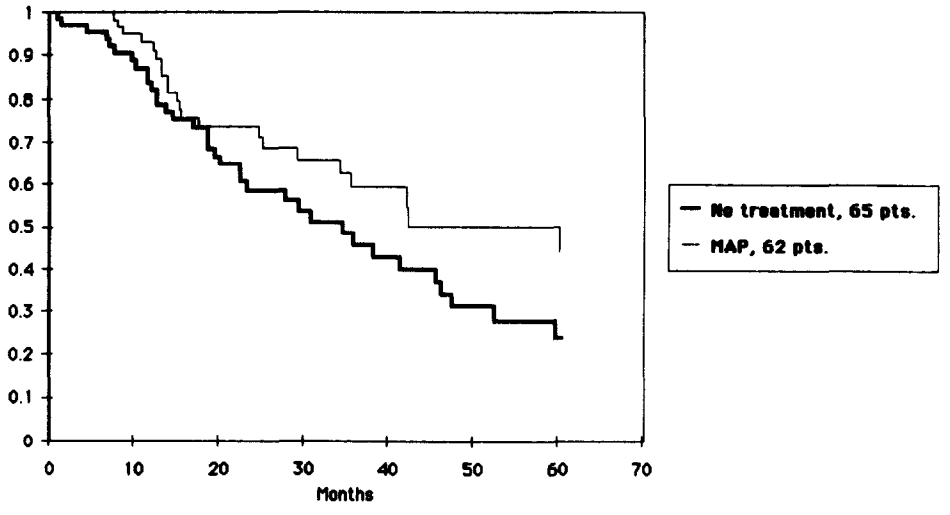

Fig. 2. Postmenopausal patients. Disease-free survival (Wilcoxon P = 0.13; *Mantel-Cox* P = 0.09).

four in the CMF group and one in the CMF + MAP group.

In the postmenopausal study one patient stopped MAP after 2 months treatment because of tremor and severe cramps. Another patient was hospitalized because of lipotymia after 3 months treatment which was suspended.

The incidence of side-effects reported during the treatments is shown in Table 8. The association of MAP and CMF brought about a significant reduction in nausea and vomiting, and a tendency towards a lower incidence of leukopenia. On the other hand, the combination caused a series of side-effects (vaginal spotting, cramps, tremors and sweating) which are characteristic of MAP treatment and which have also been observed when this progestin was used alone. Amenorrhea was reported with the same incidence in the two groups of premenopausal patients.

DISCUSSION

The results of the present study demonstrate that the addition of a hormone treatment like high-dose MAP does not improve the effect of chemotherapy alone with CMF in premenopausal patients. This result runs parallel to what was noted in the NSABBP study in which the addition of tamoxifen (TAM) for 2 years to the PAM + fluorouracil regimen did not bring about an improvement in the disease-free survival or in the overall survival in patients whose age was less than or equal to 49 years [4]. In Ludwig's study as well, which compared polychemotherapy (CMFP) vs. CMFP + oophorectomy in premenopausal patients with N+ > 3, the addition of hormonal treatment did not improve the chemotherapy results [5]. The failure of the addition of hormonal therapy to chemotherapy in having an effect cannot be easily explained. Various hypotheses may be made. One may suppose there is a pharmacological interference between the hormonal and cytotoxic agents with the result of a reduced activity of one or both the treatments. In this way the lack of differences in the incidence of amenorrhea between the two treatments could be interpreted. A higher proportion of amenorrhea in the CMF + MAP group as compared with the CMF group could have been expected but an incidence of 46% and 42% was registered in CMF and CMF + MAP respectively. The possibility of an incomplete survey of this side-effect makes this hypothesis uncertain. Another hypothesis, as recently suggested by others [6], considers the possibility of the existence in the tumor of cell clones resistant to both treatments or of a small proportion of cells sensitive to only one treatment, or the possibility that hormonal treatment interferes with tumor cell kinetics making the cell less sensitive to chemotherapy. Our results thus confirm that in premenopause the combination of hormonal therapy and chemotherapy must be considered an experimental treatment and should not be extended to routine practice.

Table 8. Side-effects

	CMF (%)	CMF + MAP (%)	MAP (%)
Leukopenia	50	39	—
Anemia	10	3	—
Thrombocytopenia	5	4	—
Nausea	76*	55	—
Vomiting	65	47†	—
Diarrhea	5	3	—
Alopecia	28	26	—
Stomatitis	4	6	—
Amenorrhea	46	42	—
Anorexia	14	4	—
Body weight increase	—	11	6
Sweating	—	10	9
Cramps	—	6	6
Vaginal spotting	—	24	16
Thrombophlebitis	—	1	1
Tremors	—	13	12

*$P < 0.01$ (chi-square test).
†$P < 0.05$ (chi-square test).

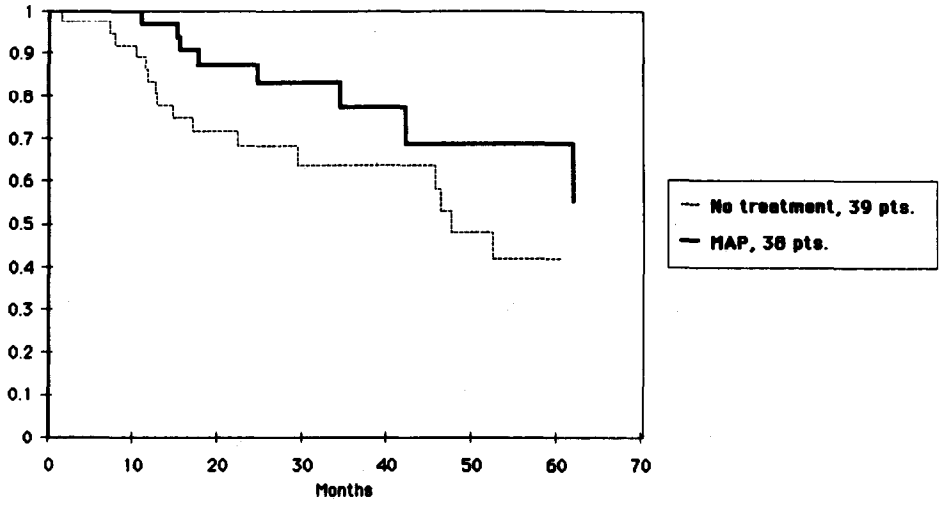

Fig. 3. Postmenopausal patients with N ≤ 3. *Disease-free survival* (*Wilcoxon* P = 0.05; *Mantel–Cox* P = 0.09).

In the study of postmenopausal patients, MAP at high doses induced a lower number of relapses and this effect seems to be limited to the sub-group of patients with a number equal to or less than three metastatic lymph nodes. There are also signs that the effect of hormonal treatment may be limited to patients with ER+ tumor.

Unfortunately, only in 22% of the postmenopausal patients in the study were hormonal receptors determined.

Our results in postmenopausal patients seem to be a confirmation of the results which have recently emerged from other studies that have used TAM [7–9] or aminoglutethimide (AG) [10]. The NATO study in particular has noted an improvement in both disease-free survival and overall survival in patients treated for 2 years with TAM 6 years after mastectomy, irrespective of the menopausal status, the number of lymph nodes and the receptor status [7]. In another study postmenopausal patients treated with the combination of TAM and prednisone for 12 months had a better 3-year disease-free survival than the control patients, but at the same time they had a lower disease-free survival than the patients treated with CMFP + TAM [11]. In this study the effect of a hormonal treatment appears to be limited to ER+ tumors. In the already cited NSABBP study the combination of TAM + chemotherapy (PF) gave better results as compared with PF alone in postmenopausal patients with ER+ tumors [4]. An interim analysis of a study comparing AG + hydrocortisone vs. placebo for two years in postmenopausal patients N+ indicates that endocrine treatment significantly reduces the number of recurrences [10].

The shortness of the median follow-up makes our results susceptible to further variations. In particular it should be clarified whether the advantages in terms of disease-free survival are maintained later on in time and whether or not this is reflected in the overall survival. In connection with this problem there is the one of the duration of hormonal treatment. In our study MAP h.d. was administered for 6 months in opposition to TAM and AG which were administered for at least in 12–24 month periods in the previously mentioned studies. The duration of endocrine adjuvant treatment and the MAP doses to be used are still completely open to discussion.

The MAP treatment was substantially well tolerated even if the incidence of vaginal spotting and tremors cannot be neglected. Its association with CMF determined a reduction in some side-effects (nausea and vomiting in particular) and a lower number of early treatment suspensions. In addition there is the suggestion of a moderate protection from myelodepression with the combination of CMF + MAP as compared to CMF alone.

Although these results ought not to be considered definitive and require further confirmation, the suggestions that arise from our study are that use of the hormonal treatment like MAP h.d. in postmenopause may be considered useful in patients with limited lymph nodal involvement, excluding, however, those patients with hormone receptor negative tumor.

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