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A Randomized Comparison of Megestrol Acetate (MA) and Medroxyprogesterone Acetate (MPA) in Patients with Advanced Breast Cancer

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Abstract—*The efficacy and side-effects of megestrol acetate and medroxyprogesterone acetate in postmenopausal patients with advanced breast cancer were compared in a prospectively randomized study. The dosage of MA was 2 × 80 mg p.o. or MPA 2 x 500 mg p.o. daily, given as a secondary hormonal treatment, mostly after previous treatment with tamoxifen.*

Ninety-eight patients entered the study and 92 were evaluable for effect, 48 patients on MA and 44 on MPA. Age, main tumor site and prior treatment were not different, but there was a preponderance of ER-negative tumors in the MA group. Responses appeared to be more frequent in the MPA-treated group (25% vs. 43%), predominantly in bone lesions, 12% for MA and 45% for MPA. Median progression-free survival was comparable, 15 vs. 10 months, and overall survival was not different (20 vs. 16 months).

Toxicity was frequent, occurring in 83% vs. 74% of patients: increased appetite, nausea and dizziness in more than 20%, and a preponderance of pyrosis and breathlessness on MA and hot flashes, sweating and tremors on MPA. Cushingoid symptoms were present in about a quarter of the patients treated for more than 3 months. The occurrence of thrombo-embolic episodes and cardiovascular events was evenly distributed. Patients on MPA had more often increase in body weight, systolic blood pressure and serum creatinine than those treated with MA.

It is concluded that MPA may be more effective for treatment of bone metastases, at the expense of more progestational side-effects. The occurrence of Cushingoid effects is frequent but similar in both arms, while the incidence of cardiovascular or thrombo-embolic events cannot be related to the use of either compound.

INTRODUCTION

MOST postmenopausal patients presenting with advanced breast cancer are initially treated with tamoxifen, due to its minor side-effects. When a second-line treatment with progestins is considered, however, most patients in Europe will receive medroxyprogesterone acetate (MPA), while in the U.S.A. most patients are treated with megestrol acetate (MA). Usually, MA is given orally as 2 × 80 mg daily. There is some dispute about the most effective dose and way of administration of MPA. MPA is given i.m. in some centers, but may also be given orally [1, 2]. We wanted to compare both the efficacy and side-effects of both drugs given in an optimal dosage. Earlier, we and others have demonstrated that adrenal suppression by oral MPA is maximal at 1000 mg daily [3, 4]. Others have shown that further suppression of adrenal steroids is not achieved by doses of MA over 200 mg/day [5]. Therefore, we choose to compare the efficacy and side-effects of MPA 2 × 500 mg vs. MA 2 × 80 mg orally.

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PATIENTS AND METHODS

Entered into the study were 98 postmenopausal patients with locally advanced or metastatic breast cancer. Patients with rapidly progressive disease, liver metastases or pulmonary lymphangitis were not eligible for hormonal treatment. All patients had received first-line hormonal treatment, mostly with tamoxifen, and all patients had measurable or evaluable disease.

Excluded were patients aged 80 years or more, WHO performance grade 3 or a life expectancy less than 3 months, or patients with a second malignancy. Osteoblastic bone lesions, pleural effusion or ascites, and pulmonary lymphangitis were considered not evaluable. Tumor response was evaluated according to standard WHO/UICC criteria. The survival and progression-free period were calculated from the moment the treatment was started.

In patients who were treated for a period of at least 3 months, the patient's body weight, blood pressure, liver and kidney function tests, blood glucose and serum calcium were followed. An increase in body weight of over 5%, or a rise in systolic or diastolic blood pressure of over 10 mmHg on two separate visits, were scored as treatment-related events. The biochemical parameters were evaluated according to standard WHO criteria. Major toxicity like deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI) and cerebrovascular accident (CVA) or acute death were registered, as well as a number of minor symptoms. For their presence a specific questionnaire was followed.

All differences in analog scale parameters were compared according to Wilcoxon's test. The incidence of side-effects was analyzed by chi-square analysis.

RESULTS

The number of eligible patients entering the study, their mean age, performance status, prior hormonal therapy, main disease sites, ER status and response to treatment are given in Table 1. All patient characteristics were distributed evenly over both groups, apart from a slight preponderance of locally advanced primaries in the MPA arm and ER negative tumors in the MA arm. Six patients were considered not evaluable for response. Two patients were not evaluable for MA: one was taken off treatment because of a transient ischemia attack, and the other for severe depressive symptoms, which cleared after treatment was stopped. Four patients were not evaluable for MPA: one patient was taken off treatment for a pulmonary embolism, and one crossed over to MA for neuropsychiatric symptoms (agitation and feelings of depersonalization). Two elderly patients suffered from sudden death within 3 months of the start of treatment.

The effect of treatment for the main metastatic sites is shown in Table 2. The overall response for MA was 25% and for MPA 43%. Most responses were found in soft tissue disease for MA [eight out of 14 (57%)] and in skeletal lesions for MPA [10 out of 22 (45%)]. The latter difference was significant, but the confidence intervals for the overall remission percentage showed a large overlap:

Table 1.

	MA	MPA
Eligible	50	48
Evaluable for response	48	44
Median age	64	65
range	49–79	51–80
Performance score (%)		
0	37	25
1	48	61
2	15	14
Prior hormonal treatment		
tamoxifen	45	38
other	3	6
Site of tumor deposits (%)		
primary	14	20
lymph nodes	4	9
skin	11	7
lung	11	7
pleura	4	—
bone	50	50
liver	6	7
ER (%)		
positive (>10 fmol/mg protein)	20	25
negative	15	2*
unknown	16	73
Response (%)		
PR	12 (25)	16 (36)
CR	—	3 (7)
stable	21 (44)	11 (25)
progressive	15 (31)	14 (32)

*$P < 0.05$.

14–40% for MA and 28–59% for MPA. The median duration of the progression-free period was 15 months for MA and 10 months for MPA (not significant). The median overall survival is 20 vs. 16 months (MA vs. MPA), and the median survival for non-progressive patients on MA was 24 vs. 20 months on MPA (not significant). There was no difference in response rate for the ER-positive or ER-unknown patients. Progesterone receptors were not measured systemically.

The response to previous hormone therapy may predict the chance for a subsequent response on second-line treatment. Therefore, two groups of patients were compared, those who progressed within 3 months on tamoxifen and those who were stable or responded for a longer period of time. Patients who responded to tamoxifen had a median PFS on progestin therapy of 14 months vs. 12 months for patients who progressed on tamoxifen (not significant). The percentage of patients responding to progestin was not larger in the tamoxifen responsive group than in the progressive group (36 vs. 31%).

Side-effects could be evaluated in 92 patients, 48 on MA and 44 on MPA, and were present in respectively 83 and 74% (Table 3). Only 19 patients

Table 2.

	Response (%)	Stable	Progression	All
Response to MA for main disease sites				
Soft tissue	8 (57)	5	1	14
Lung	1 (14)	3	3	7
Bone	3 (12.5)	11	10	24
Liver	—	2	1	3
Total	12 (25)	21	15	48
Response to MPA for main disease sites				
Soft tissue	6 (37.5)	7	3	16
Lung	3 (100)	—		3
Bone	10* (45)	3	9	22
Liver	—	1	2	3
Total	19 (43)	11	14	44

*$P < 0.05$ vs. MA.

Table 3. *Side-effects*

	MA		MPA	
	n	%	*n*	%
Eligible patients	50		48	
Not evaluable for side-effects	2		4	
Evaluable	48		44	
No side-effects observed	8	(17)	11	(26)
Side-effects present in	40	(83)	33	(74)
Number of evaluable patients		48		44
Side-effects (%):				
increased appetite		25		23
fatigue		12		19
breathlessness		8*		—
nausea		21		23
pyrosis		10*		2
obstipation		6		2
nycturia		4		7
pruritus		6		9
hot flashes		4		12*
sweating		12		31*
tremor		6		17*
thirst		12		9
muscle cramps		17		12
restlessness		2		7
depression		8 (1)		9
agitation		—		(1)
headache		10		7
dizziness		23		19
disturbed vision		6		2
Cushingoid appearance		25		25
ankle edema		20		6

*$P < 0.05$. (1) treatment stopped for these side-effects.

were free of symptoms, eight on MA and 11 on MPA treatment. There was a preponderance of pyrosis and a feeling of breathlessness on MA contrasting with hot flashes, sweating and tremors on MPA, while a number of side-effects occurred with the same frequency in both groups, e.g. nausea, fatigue, dizziness and muscle cramps in more than 20% of patients. A Cushingoid appearance was seen in a quarter of the patients who were treated for more than 3 months in both groups, while edema was found in 10 patients on MA and three on MPA ($P < 0.05$). Major events like thrombo-embolic or cardiovascular episodes are summarized in Table 4. One patient in each study arm was taken off treatment for these complications, one patient for a TIA on MA and one for a pulmonary embolism on MPA. The relation with either treatment is difficult to state in this elderly population.

Table 5 shows a number of biochemical parameters in patients who were treated for at least 3 months. There were more patients on MPA who had an increase in body weight of over 5% or systolic blood pressure of over 10 mmHg. Serum creatinine rose more in patients on MPA, as did blood hemoglobin levels. Leukocytes rose during MA and platelet levels during treatment with both drugs. Non-fasting blood glucose levels fell in both groups.

Table 4. *Cardiovascular and thrombo-embolic events*

	MA	MPA
	50	48
Cardiac decompensation	1	—
Angina pectoris	1	—
Total AV block	1	—
Acute death e.c.i.	—	(2)
Transient ischemic attack	(1)	—
Thrombophlebitis	1	1
Deep venous thrombosis	1	1
Pulmonary embolism	—	(1)
Total	6	5

(1) treatment was stopped for this reason.

Table 5. Side-effects

	MA	MPA
Total No. of patients	48	44
Body weight increase ≥5% (% of pts)	26	59†
Median weight increase (kg)	1	4
BP increase ≥10 mmHg		
systolic (%)	26	58†
diastolic (%)	36	36
Serum creatinine (mmol/l)		
baseline	82	74
treated	78	92*†
Hemoglobin (mmol/l)		
baseline	8.2	8.1
treated	8.4	8.4*
Leukocytes (× 10^9/l)		
baseline	6.8	7.3
treated	8.0*	7.1
Platelets (× 10^9/l)		
baseline	269	230
treated	303*	256*
Blood glucose (mmol/l) (not fasting)		
baseline	6.1	5.3
treated	5.1*	4.9*
Median follow-up (months)	9	9

*$P < 0.05$ vs. baseline.
†$P < 0.05$ vs. MA.

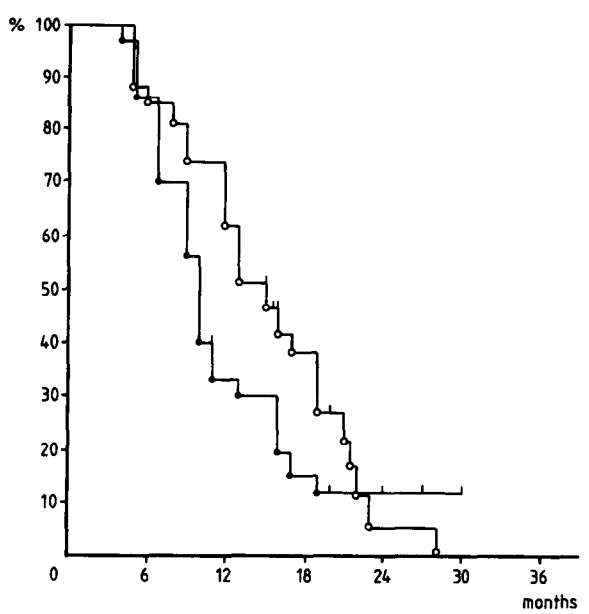

Fig. 1. Progression-free survival during treatment with MA (○) or MPA (●).

DISCUSSION

Efficacy

With the dosage of each drug chosen in this study, there was a difference in antitumor effect, in favor of MPA. A remission percentage of 40% was also found in a previous study with MPA, used as a first-line hormonal treatment [6]. Other studies found less than 25% in second line [1, 2, 7, 8]. For MA, response rates of 26–43% were described in second line [9–11]. The dosages given in this study were considered sufficient, as no author thus far has described increased response rates for higher dosages of MA [5, 9, 12] or for MPA [7, 8] in randomized studies. One author reported a 61% response rate using very high dosages of MPA [13]. No correlation was found between drug levels and response [14]. Higher progestin dosages than the ones used in this study result in higher serum levels, but their biological effects as measured by the suppression of adrenal steroids is not enhanced, either by MA [5] or MPA [2–4]. Studying the same population, nearly similar suppression of adrenal steroids and estrone was found [15].

Evidently, there is little cross resistance or selection of hormone-unresponsive clones by the preceding treatment with tamoxifen. We could not establish a predictive value for the response to first-line treatment with tamoxifen. According to some authors, tumors responding to tamoxifen have a better chance for response to subsequent treatment with progestins [16]. Tamoxifen may induce the presence of progesterone receptors within the tumor, which would be in favor of this particular treatment sequence [17].

Although MPA seems to give a higher response rate than MA, the efficacy is the same when patients with stable disease are included, reaching 69% vs. 68% of patients without progression. There appears

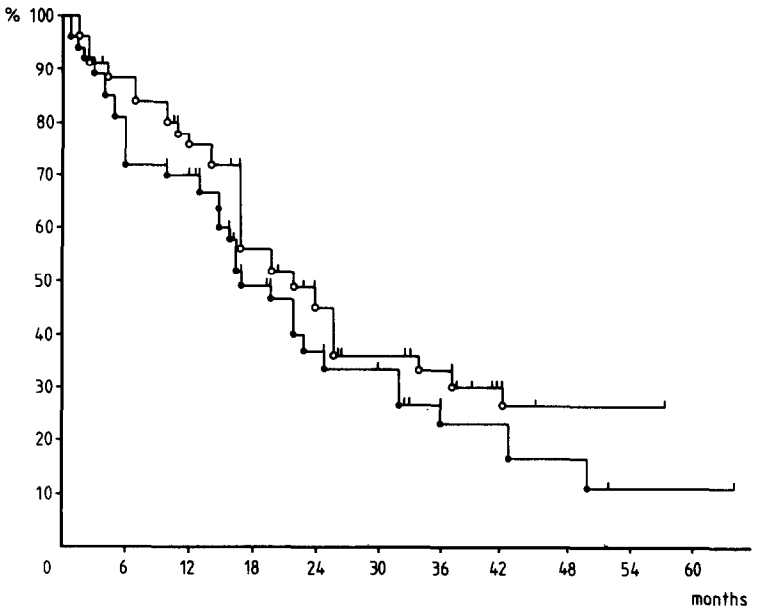

Fig. 2. Overall survival during treatment with MA (○) or MPA (●).

to be a better response of bone metastases to MPA compared with MA. In a previous study, osteosclerotic responses were also seen more often with MPA than tamoxifen [6]. Presumably, MPA does have a stronger anabolic effect on bone than MA.

Side-effects

Progestins may influence mood, appetite and may give a sense of wellbeing, which may positively affect the patient's quality of life, an important issue in patients with cancer. Progestins may also induce a shift in fluid distribution, leading to hypertension, edema, and increased body weight. Moreover, their corticosteroid effects may elevate blood glucose, and produce Cushingoid symptoms. Anabolic effects may lead to higher hemoglobin, leukocyte and platelet counts, but may also induce changes in blood coagulation, resulting in thrombo-embolic complications.

Side-effects were frequent in this study, occurring in 75–80% of patients, although most of these side-effects were moderate and not of great concern to the patients. In most other studies, where comparison of side-effects was not the main issue, a much lower incidence is reported. In case of MA, this mainly concerns increased body weight [11, 18–20]. Higher dosages induced high blood pressure, dyspnea and cardiac decompensation which was considered to be dose-dependent [9, 21]. For MPA, apart from weight increase which was correlated with the treatment duration, Goss *et al.* reported adverse effects in 64% and dose reduction for Cushingoid effects in 20%, while 10% of the patients had to stop treatment for undue toxicity [22].

Severe cardiovascular and thrombo-embolic events occurred in both arms of this study and cannot with any degree of certainty be attributed to the hormonal treatment, as they might occur spontaneously in these predisposed elderly patients with breast cancer. In a large overview, the incidence of thrombo-embolic events by progestins is stated to be about 2.6%, hypertension 19% and heart failure 1.2% [21].

We have no simple explanation for the evident rise in serum creatinine in patients treated with MPA. There was no relation with body weight or hypertension. Some authors have interpreted this as an 'anabolic' effect [1], but a deterioration of renal function or impaired secretion of creatinine by the tubules is more probable. Progestins are known to cause a relaxation of ureteral muscle tonus, e.g. during pregnancy, but there appears to be a direct effect on the kidneys as well.

A fall in non-fasting blood glucose was found in both arms of the study. Increased insulin levels during MA have been reported [12], which may well explain the lower glucose levels as well as the increased amount of body fat, due to the uncontrollably enhanced appetite by these hypoglycemic periods in some patients.

In conclusion, responses appeared to be more frequent after MPA, but no difference in efficacy was present when stable patients were included in the response percentages. The response of skeletal lesions was seen more clearly in MPA than in MA treated patients. The progression-free survival and overall survival were comparable. Minor side-effects were frequent for both drugs, especially gastrointestinal effects and dyspnea with MA and progestin-like symptoms with MPA. Cushingoid symptoms, thrombo-embolic and cardiovascular events were distributed evenly over both study arms. MPA

leads more often to increased body weight, systolic blood pressure and serum creatinine. MPA thus seems to be marginally more effective at the cost of more, mostly minor, side-effects in this category of patients.

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