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ORAL HIGH-DOSE PROGESTINS AS TREATMENT FOR ADVANCED BREAST CANCER

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Abstract

Fifty-two postmenopausal, previously treated advanced breast cancer patients who received oral high-dose progestins (medroxyprogesterone acetate [MPA] and/or megestrol acetate [MA]) were retrospectively reviewed. MPA was given to 45 patients and MA to 17 (10 earlier treated with MPA); 48 were evaluable for clinical response to progestin treatment, 43 for MPA and 5 for MA. Two complete responses and 10 partial responses (25%) with median duration of 9.5 months were seen. Forty percent of the patients obtained stable disease ≥6 months with a median duration of 8.0 months. In patients with estradiol receptor positive (n=31) and estradiol and progesterone receptor positive (n=19) tumors the response rates were 35% and 37% respectively. No differences in serum levels of MPA or MA were observed in the different responding groups. The serum levels of MA were twice as high as MPA in spite of a dose of 160 mg/day of MA compared to 1000 mg/day of MPA. A long disease-free interval, and positive receptor status of primary or metastatic lesions seemed to predict response to endocrine therapy even late in a therapeutic sequence. Side effects occurred in 11/45 (24%) of MPA treated patients and in 1/15 (7%) of MA treated patients. No difference in serum levels of MPA was found between patients with side effects and patients without side effects.

Key words: Advanced breast cancer, progestin treatment, medroxyprogesterone acetate, megestrol acetate.

High-dose progestins have recently been introduced as treatment for advanced breast cancer. Medroxyprogesterone acetate (MPA) and megestrol acetate (MA) can be administered orally, and both have a favorable side effect profile, and give the same clinical response as other forms of endocrine therapy (1–4). Their mechanism of action is not clear; suppression of adrenal steroid hormone synthesis (5, 6), alterations in steroid hormone metabolism in tumor cells (7, 8) and liver (9), possible reduction of the amount of estradiol receptor (ER) in tumor cells (10), and a direct cytostatic/cytotoxic effect (11), have been suggested.

In this retrospective study we reviewed previously treated patients with advanced breast cancer for evaluation of the therapeutic efficacy and side effects of oral progestins. The role of several prognostic factors—age, disease-free interval, ER, progesterone receptor (PgR), and metastatic site—were evaluated in relation to results of progestins as late therapy in an endocrine treatment sequence. For some of the patients response and side effects have been related to serum levels of the two progestins. In 10 patients the effect of MA in previously treated with MPA were studied.

Material and Methods

Patient characteristics. Forty-eight postmenopausal patients with metastatic breast cancer, started with progestin therapy from December 1980 to November 1985, were evaluable (Table 1). Another 4 patients were evaluable for side effects. The inclusion criteria in this study of patients treated with oral high-dose progestins were: previous response to endocrine treatment; previous failure of endocrine treatment if the patient had clinical characteristics (disease-free interval >2 years, soft tissue and bone localization of disease, slow-growing disease) and/or receptor status (ER and PgR ≥10 fmol/mg cytosol protein) predicting a probable response; previous adjuvant endocrine therapy with tamoxifen (TAM) in patients with clinical characteristics as mentioned.

All the patients (n=48) had received TAM previously, 5 as adjuvant therapy, the rest for metastatic disease, 22 had also been treated with aminoglutethimide (AG) and 28 had received chemotherapy. Steroid receptor contents were measured in the primary tumor (ER n=19, PgR

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n=16), in the metastatic tumor only (ER n=16, PgR n=16) or in both (ER n=5, PgR n=4). When the receptor status of both the primary and metastatic tumor was known, the receptor status of the metastatic tumor was used in the evaluation.

All the patients had a life expectancy of 2 months or more, 4 patients had a Karnofsky index lower than 30 and all the patients had progressive disease at the time when the progestin therapy was started. Six patients had bone metastases only. The UICC criteria for response were used (12), but SD was defined as stable disease lasting for at least 6 months.

Treatment schedules. The progestins were given orally as tablets, either as MPA (n=43) 500 mg bid (n=36), 300 mg bid (n=7) (Provera 100 mg, Upjohn or Farlutal 250 mg or 500 mg, Farmitalia) or MA (n=5) 160 mg once daily (Megace 40 mg, Bristol Myers). Ten of the patients treated with MPA later received MA. No other endocrine or chemotherapy was allowed during progestin therapy.

Blood sampling and progestin determination. Blood samples were obtained 4–6 h after the morning dose, after 14 days or more of treatment, and serum levels of MPA (n=24) and MA (n=11, 8 patients previously treated with MPA included) were determined by RIA described by Ortiz et al. (13), with some modifications (14). Serum levels are given as ng/ml serum, and with a detection limit of 5 ng/ml for both MPA and MA. Mean coefficient of variation (interassay, for 3 different levels) of MPA and MA, were 14% and 19% respectively.

Receptor measurements. All receptor measurements (ER, PgR) were performed in the same laboratory using methods described earlier (15). Tumors were classified as negative when the receptor concentrations were less than 10 fmol/mg cytosol protein.

Statistical methods. The survival times of the patients were plotted using the Kaplan-Meier method. The Mann-Whitney test was used to test for difference in age, disease-free interval, time from first recurrence to MPA/MA start, length of survival and serum levels of MPA in the differently responding groups, as well as serum levels in patients with and without side effects of MPA therapy.

Results

An objective response rate of 25% was found, including 2 complete responses (CR) and 10 partial responses (PR). Nineteen patients (40%) obtained stable disease (SD) lasting ≥6 months. Median duration of response (range) was 9.5+ months (6+–37) and 8.0 months (6–36) for CR+PR and SD respectively (Table 2).

Response rates of 36% and 35% were found in patients with ER+tumors (n=31) and PgR+tumors (n=20) respectively. The response rate was 37% in patients with ER+/PgR+tumors (n=19) (Table 3). Thirty-two percent of the patients with ER+metastatic tumors (n=19) responded to the therapy, and 50% showed an SD. Patients with ER+/PgR+metastatic tumors showed a similar response.

The patients in the 3 responding groups had similar age distribution (Table 4).

Median disease-free survival of the objective responders was 67 months, and 23 and 24 months, for patients with SD and PD respectively. However, the patients with objective responses did not have a significantly longer

Table 1

Pretreatment characteristics of the evaluable patients

No. of patients	48
Age at diagnosis (years)	Median (range): 58.5 (34–87)
DFI[1] (stage I–III) (months) n=44.	Median (range): 24 (5–240)
Previous therapy	
Hormonal therapy	
Tamoxifen	Adjuvant: n=5
	Metastatic disease: n=43
Aminoglutethimide	Metastatic disease: n=22
Prednisone (in CMFP[2])	Adjuvant: n=5
	Metastatic disease: n=8
Prednisone alone	Metastatic disease: n=12
Oophorectomy	Adjuvant n=16
	Metastatic disease: n=3
Chemotherapy	Adjuvant: n=13
	Metastatic disease: n=15
Previous recurrences (No.)	Median (range): 2 (0–6)
Time from first recurrence to start of MPA/MA (months) n=44	Median (range): 31.5 (2–130)
Time from start of progestin therapy to death (months) n=28.	Median (range): 11.5 (0.5–49)

DFI[1] = disease-free interval.
CMFP[2]: C = cyclophosphamide, M = methotrexate, F = 5-fluorouracil, P = prednisone.

Table 2

Response rate and duration of response in 48[1] patients with advanced breast cancer

	Responders		Median duration of response (range) (months)
	No.	%	
CR[2]	2	4	–
PR[3]	10[a]	21	–
CR+PR	12[a]	25	9.5+(6+–37
SD[4]	19[b]	40	8.0 (6 –37)
PD[5]	17	35	–

[1]43 patients were treated with medroxyprogesterone acetate (MPA) and 5 with megestrol acetate (MA).
CR[2] = complete response.
PR[3] = partial response.
SD[4] = stable disease ≥6 months.
PD[5] = progressive disease +SD <6 months.
[a] One of the patients on MA therapy.
[b] Four of the patients on MA therapy.

Table 3

Response rates of patients in relation to receptor status (ER[1] and PgR[2]) in primary and/or metastatic tumor[3]

	No.	CR[4] No.	PR[5] No.	CR+PR %	SD[6] No.	(%)
Receptor status						
ER+/PgR+	(19)	1	6	37	6	(35)
ER+/PgR−	(9)	0	2	22	5	(56)
ER+/PgR?	(3)	0	2		0	
ER−/PgR+	(1)	0	0		1	
ER−/PgR−	(3)	0	0		2	
ER?/PgR?	(13)	1	1	15	5	(39)

ER[1] = estradiol receptor.
PgR[2] = progesterone receptor.
[3] Knowing both receptor status of the primary and metastatic tumor, receptor status of metastatic tumor was used (n=5).
CR[4] = complete response.
PR[5] = partial response.
SD[6] = stable disease ≥6 months.

Table 4

Response rate related to age, DFI[1] and time from first recurrence to medroxyprogesterone acetate (MPA)/megestrol acetate (MA) therapy start (stage I–III, n=44)

	CR[2]+PR[3] (n=10)	SD[4] (n=18)	PD[5] (n=16)
Age[6] (years)			
Mean (sd)	54.7 (12.8)	58.7 (11.7)	59.9 (13.5)
Median	56.5	59.0	58.0
Range	34–72	39–84	36–87
DFI (months)			
Mean (sd)	87.6 (76.7)	48.7 (66.8)	34.4 (37.6)
Median	67.0	23.0	24.0
Range	12–240	5–240	6–153
Time from first recurrence to MPA/MA start (months)			
Mean (sd)	51.0 (42.0)	44.1 (31.9)	33.4 (31.0)
Median	42.5	32.0	28.5
Range	10–127	4–105	2–129

DFI[1] = disease-free interval.
CR[2] = complete response.
PR[3] = partial response.
SD[4] = stable disease ≥6 months.
PD[5] = progressive disease +SD <6 months.
[6] Age in all 49 patients.
sd = standard deviation.

disease-free survival than those with SD (p=0.465) and PD (p=0.454) (Table 4).

Median time from first recurrence to start of progestin treatment was 42.5 for CR+PR patients and 32.0 months for SD patients, and 28.5 months for the PD group (p=n.s.) (Table 4).

Twenty-eight percent of the patients with soft tissue (n=25) as dominant metastatic site showed an objective response. The corresponding values for visceral (n=9) and bone metastases (n=14), were 33% and 14% respectively.

Response rates were similar in patients who had received TAM only (n=26, 6 CR+PR, 12 SD) and those who had received both TAM and AG (n=22, 6 CR+PR, 7 SD) prior to progestin treatment.

Twenty-five of the patients had previously received corticosteroids. Our response data might indicate that there is no obvious cross-resistance between these 2 modalities.

Sequential use of MPA and MA (with different therapeutic modality between the two progestins) in 10 patients resulted in 1 CR, 3 SD≥6 months, and 3 SD≤4 months with MA therapy after MPA treatment. In one patient (NH) with soft tissue metastasis treatment with MPA (600 mg) for 3 months resulted in a PD, but during the following MA therapy a CR was obtained lasting for 12+ months (Table 5).

Mean serum levels (±SD) of MPA (n=24) was 142.0 ng/ml (58.5) and of MA (n=11) 355.4 ng/ml (183.8). No significant differences between responders and non-responders were observed. For the patients receiving both MPA (1000 mg) and later MA (160 mg), the serum level of MA were twice as high as MPA (Table 5).

No significant difference in survival was observed between objective responders and SD patients after start of progestin therapy (Figure). In the PD group a shorter survival was observed. Median survival of the objective responders was 16.5 months, 22.0 months for the SD group and 9.0 months for the PD group.

Side effects occurred in 11 patients (24%) on MPA and one (7%) on MA, but no fatal side effects were observed (Table 6). One patient on MPA had to reduce the dose from 1000 to 600 mg/day due to tremor, which then subsided. Therapy was stopped in 2 patients on MPA and one on MA due to hypertension, fluid retention and diabetes mellitus. The mean serum level (±SD) of MPA in patients who experienced side effects (n=7) was 123.7 ng/ml (±44.3) compared to 148.3 ng/ml (±61.4) in those without side effects (n=18).

Discussion

An objective response rate of 25% on progestin treatment is lower than reported earlier (3), but all patients in our study were previously treated adjuvantly or for metastatic disease with TAM (100%), AG (47%) and chemotherapy (57%). Our response rate corresponds to the response rates of 16–28% in previously treated patients reported by Sedlacek & Horwitz (3). High-dose progestins given as first treatment have shown similar effects as TAM (2, 4).

Our data cannot be used to evaluate the role of receptor data to predict a response to progestin treatment used late

Table 5

Response rates and duration of response of sequential use of medroxyprogesterone acetate (MPA) and megestrol acetate (MA) in 10 patients with advanced breast cancer

Patients	MPA			MA		
	Response	Duration (months)	Serum level (ng/ml)	Response	Duration (months)	Serum level (ng/ml)
EE	SD	6.0	161	PD	–	278
IP	SD[1]	8.0	195	PD[5]	4.0	403
GRG	SD	8.0	142	PD[5]	4.0	322
SH	SD	13.5	*ND	SD	7.0	470
AP	PR[6]	25.0	ND	NE[2, 7]	–	335
LT	PR	7.0	ND	NE[2]	–	ND
ØN	CR[3]	13.0	ND	SD	6.0	285
BG	SD[4]	12.0	ND	SD	9.0	138
NH	PD[6]	–	ND	CR	12+	520
HL	PD[1]	4.0	82	PD[1, 5]	3.0	ND

[1] Therapy stopped due to side effects.
[2] Too short follow-up.
[3] Sequential use of tamoxifen (TAM) and MPA.
[4] Chlorambucil and MPA in combination.
[5] PD = stable disease SD less than 6 months.
[6] Provera 600 mg/day, treated 3 months for soft tissue metastatic disease.
[7] Serum levels after 4 days.
* ND = not determined.

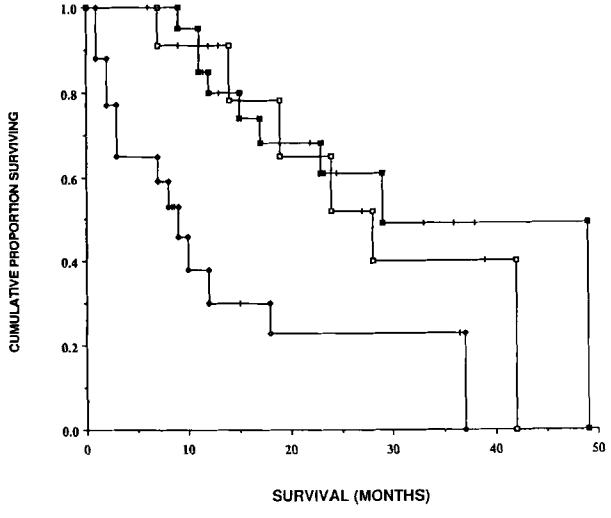

Figure. Survival (cumulative proportion) of the patients with objective response (CR+PR) ○, stable disease (SD) ●, and progressive disease (PD) ◊ after progestin treatment (Kaplan-Meier). (The tick marks on the curves show the follow-up times of patients alive.)

Table 6

Side effects of 52 patients during progestin treatment, 45 were given MPA and 15 MA*

	MPA (n=45) n=11	MA (n=15**) n=1
Cushing-like syndrome	3	0
Vaginal spotting	1	0
Icting	1	0
Diabetes	0	1[2]
Sweating	2	0
Tremor	1[1]	0
Hairloss	1	0
Hirsutism	1	0
Hypertension	1[2]	0
Fluid retention	1[2]	0
Dyspnoea	3	0
Weight gain	7	0

[1] Dose reduction due to side effect.
[2] Therapy stopped due to side effect.
* More than 1 side effect occurred in same patients.
** 8 of the 15 were also evaluated for MPA side effects.

in the therapeutic sequence, as only 4 patients with receptor negative tumors were available. However, when only patients with receptor positive tumors were evaluated the response rate in our material increased from 25% to 36–37% (Table 3). A protracted disease-free interval and possibly time from first recurrence to start of progestin therapy is suggestive of a response to progestin therapy (Table 4) (16).

The high rate of patients showing SD ≥6 months (40%) (Table 2) is of definite clinical value in the treatment of a non-curable disease, as also suggested by others (17).

The serum levels of MA were higher than MPA levels

(Table 5), although the daily dose of MA was 160 mg compared to 1000 mg of MPA. This suggests that the pharmacokinetic profiles of the two drugs are different. A preliminary report from a randomized study showed no difference in effect between MPA and MA (18). The serum levels of MPA and MA after at least 14 days of treatment were as expected (5, 14, 19, 20). As also reported by Hedley et al. (19) no significant difference in MPA concentration was observed between responders and non-responders. This is, however, in conflict with the results of others (1, 4). In our MA treated group the number of responding patients is too small to evaluate the relation of response to serum levels. In a previous study no correlation was found between serum levels of MA and patients response (5).

Cross-resistance between the two progestins was tested in 10 patients. The fact that one patient obtained a CR and 3 SD$\geq$6 months and 3 SD$\leq$4 months after sequential use of MPA and MA treatment, could indicate that the two drugs have different modes of action in tumor cells. Other possibilities are that resistance to progestins can be a reversible process with time or that this could reflect differences in serum and tissue levels of the two drugs (MA>MPA). Similar results of MA therapy after intramuscular MPA treatment have been reported by Blackledge et al. (1).

Side effects were less important (no fatal) and less frequent in our study than reported by Goss et al. (21). MA seems to give less side effects (7%) than MPA (24%) (Table 6), but the number of patients is small and side effects can be difficult to evaluate correctly. In agreement with Hedley et al. (19) no difference in MPA serum levels was observed in patients with and without side effects.

In conclusion the two progestins, MA and MPA, are well tolerated, safe drugs, and effective used late in a sequence of endocrine manipulations, as 65% of the patients experienced some kind of positive effect of the treatment. A long disease-free interval and a positive receptor status of primary or metastatic lesions might indicate a response to endocrine therapy even late in a therapeutic sequence. A possible non-cross resistance of the two progestins in some patients should be further explored.

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