High-Dose Medroxyprogesterone Acetate in Advanced Breast Cancer

Clinical and Pharmacokinetic Study With a Combined Oral and Intramuscular Regimen

REINHARD BECHER, MD, ANTONIUS A. MILLER, MD, KLAUS HÖFFKEN, MD, UDO GERHOLD, HERBERT HIRCHE, AND CARL G. SCHMIDT, MD

Seventy-five patients with advanced and intensively pretreated breast cancer received high-dose medroxyprogesterone acetate (MPA) using a schedule consisting of an intramuscular (IM) loading dose (1 g MPA IM days 1 to 10) and an oral maintenance treatment (200 mg/day three times a day) thereafter. A reinduction was performed in part of the responding patients at time of early relapse (1 g MPA IM for 10 consecutive days). MPA serum levels above 100 ng/ml were achieved during induction treatment and maintained for 3 to 4 months during the oral phase of therapy before decreasing to approximately 50 ng/ml. Two complete remissions (duration, 17.2 and 62 months), 15 partial remissions (median duration, 7 months), and 21 cases of disease stabilization (median duration, 5.5 months) were achieved. The median survival time was significantly longer for responders (19.9 months) than nonresponders (4.8 months). Although a higher proportion of postmenopausal patients responded, the remission duration in premenopausal women was remarkably long. Favorable sites of response were soft tissue, lymph nodes, and bone lesions. Reinduction treatment yielded a second response (two partial remissions, three no change) in five of six patients indicating that high-dose conditions were necessary to maintain response. This schedule allows to restrict higher doses of MPA on a long-term basis to responding patients.

Cancer **63:1938–1943, 1989.**

CONVENTIONAL DOSES of medroxyprogesterone acetate (MPA) have not resulted in reproducible therapeutic benefits in patients with advanced breast cancer. The same drug, however, was reported to be more effective if given in high doses with response rates ranging from 20% to 52%.[1] The first successful treatment schedules with MPA in high doses were based on daily intramuscular (IM) injections, which were inconvenient and often caused gluteal abscesses.[2,3] Therefore, oral treatment modalities with MPA were developed, which were similarly effective.[4] Because of the rapid elimination of MPA,[5] oral treatment requires strict compliance by the patients. Even then, however, MPA serum levels may still show high individual variation.[6] After discontinuation of the drug in oral regimen, MPA plasma levels drop quickly below the margin of 100 ng, which is considered necessary to obtain optimal efficacy. After IM application,[6] however, relatively stable serum levels can be maintained for several weeks. Based on these pharmacokinetic features, a Phase II study was designed, which made use of the characteristics of both kinds of application. The intention was to reduce the daily dosage of oral MPA and to increase the stability of MPA plasma levels by giving an IM loading course.

Patients and Methods

Patients

Between 1979 and 1983, a total of 88 female patients with histologically proven advanced breast cancer were treated according to the protocol described below; 75 patients (85%) were evaluable. The remaining 13 patients were excluded for the following reasons: discontinuation

From Innere Universität und Poliklinik (Tumorforschung), Westdeutsches Tumorzentrum, FRG.

The authors thank C. Massion for typing the manuscript and M. Weiss for reviewing the English language.

Address for reprints: Reinhard Becher, MD, Innere Universität und Poliklinik (Tumorforschung), Westdeutsches Tumorzentrum, Hufelandstrasse 55, D4300 Essen 1, FRG.

Accepted for publication December 13, 1988.

of treatment (four patients for noncompliance without severe side effects, one because of intolerable weight gain of more than 20 kg, and one because of congestive heart failure), inadequate treatment (one patient), and loss of follow-up without documentation of side effects (six patients). The hormonal receptor status was unknown in the majority of patients. At the time of entry into the study, all patients had objectively measurable and progressive lesions and a minimal performance status of 60% according to the Karnofsky scale.[6] Patients with exclusive pleural effusions, ascites, and/or osteoblastic lesions were not considered evaluable. Patients with brain or predominantly hepatic metastases were excluded from high-dose MPA treatment. The menopausal status was defined at the date of mastectomy. All patients had been pretreated with hormonal and/or various cytostatic modalities. Hormonal pretreatment consisted mostly of tamoxifen as first-line treatment and aminoglutethimide as second-line treatment. First-line cytostatic treatment consisted mostly of a combination of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF schedule). Some patients had received a combination containing adriamycin as second-line chemotherapy. The characteristics of patients are summarized in Table 1.

TABLE 1. Patient Characteristics

No. of patients	Total	88 (100%)
	Evaluable	75 (85%)
	Alive at time of evaluation	6 (8%)
Age (yr)	Range	34–81
	Mean ± SD	55.6 ± 11
Hormonal status (at diagnosis) (n)	Premenopausal	38
	Postmenopausal	37
Pretreatment (n)	No pretreatment	0
	Chemotherapy only	10
	Hormonal therapy only	25
	Both	40
Relapse-free interval (mo)	Total group	0–192 (median, 19)
	Premenopausal	0–192 (median, 20)
	Postmenopausal	0–74 (median, 19)
Metastatic pattern (n)*	Cutaneous/lymph	38 (51%)
	Pleuropulmonal	24 (32%)
	Bone lesions	52 (69%)
	Liver	8 (11%)
	1 site of metastasis	35 (47%)
	2 or more sites	40 (53%)

SD: standard deviation.
* Sum is higher than 100% due to multiple metastatic lesions.

Treatment Schedule

On days 1 to 10, all patients received a loading dose of 1 g MPA/d as a deep intragluteal injection. The site of injection was alternated each day. From day 11 on, MPA (Clinovir, Upjohn GmbH, Heppenheim, FRG) was continued orally with 200 mg MPA/d 3 times daily. Patients were evaluated for response after a minimum of 4 weeks of treatment. Selected responding patients (six patients) received a second IM loading dose of 1 g MPA for 10 days at the time of early relapse. In these cases only the duration of the first response was included in the evaluation of overall response rates (Tables 2 and 3).

Response Criteria

The efficacy of treatment was assessed according to the criteria defined by the International Union Against Cancer (UICC).[7] Complete remission was defined as disappearance of all measurable lesions. Partial remission was defined as a 50% decrease of all measurable lesions or recalcification of lytic bone marrow metastases. Stable disease (no change) was defined as no progression of lesions (frequently bone lesions) without appearance of new lesions for a period of at least 2 months. Duration of response was evaluated from start of treatment to the first documentation of disease progression.

TABLE 2. Response Rate, Median Duration of Response, and Median Survival After High-Dose MPA Treatment According to Menopausal Status

	Total (n = 75)			Premenopausal (n = 38)			Postmenopausal (n = 37)		
	Response N (%)	Duration (mo)	Survival (mo)	Response N (%)	Duration (mo)	Survival (mo)	Response N (%)	Duration (mo)	Survival (mo)
CR	2 (3)	39.6	27.0	1 (3)	62	65.4	1 (3)	17.2	27.0
PR	15 (20)	7	19.5	4 (11)	8	39.0	11 (30)	7	18.2
NC	21 (28)	5.5	20.1	10 (26)	5	8.6	11 (30)	8.5	29.1
PD	37 (49)	—	4.8	23 (60)	—	4.8	14 (37)	—	4.9

CR: complete remission; PR: partial remission; NC: no change; PD: progressive disease.

In patients who received reinduction treatment, the duration of response was determined at the first time of progression.

TABLE 3. Response and Duration of Response in Relationship to Relapse-Free Interval, Site of Metastasis, and Pretreatment

Parameter	Total no. of patients	No. of responders (%)	Duration of response median (mo)
Relapse-free interval			
≥2 yr	30	15 (50)	8.5
<2 yr	45	23 (51)	6.5
Site of metastases			
Cutaneous or lymph	38	20 (53)	8.7
Pleuropulmonal	24	12 (50)	5.5
Osseous	52	27 (52)	6.7
Pretreatment			
Hormonal	25	18 (72)	8.5
Cytostatic	10	5 (50)	6
Both*	40	15 (38)	5.5

None of the values of duration of response were significant.
* Sequential and/or simultaneous use of chemotherapy and hormones.

Pharmacokinetic Studies

Plasma levels of MPA were determined by high-performance liquid chromatographic (HPLC) analysis in 12 patients and monitored between 10 to 40 weeks (median, 20 weeks). Blood samples were drawn into heparinized glass tubes, daily for the initial 10 days, weekly for the following 8 weeks, and monthly thereafter, until disease progression. Samples were immediately cooled on ice, centrifuged for 10 minutes at 1500 × *g* and 4°C, the plasma transferred and stored at −20°C until analysis.

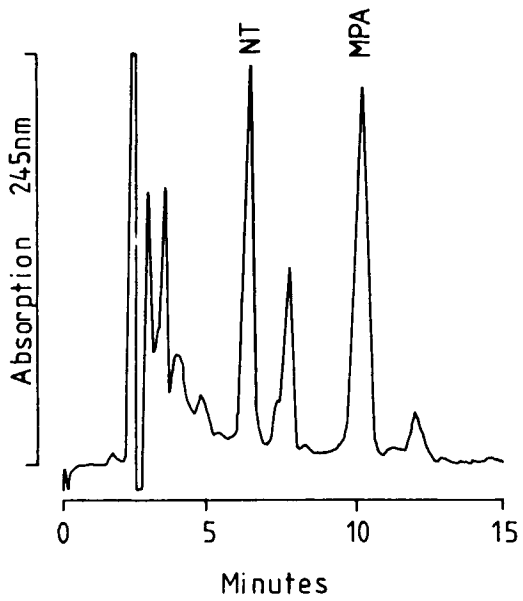

FIG. 1. HPLC chromatogram of patient plasma taken 3 weeks after beginning of treatment. MPA: medroxyprogesterone acetate; NT: nortestosterone (internal standard; MPA concentration, 122 ng/ml).

Nortestosterone was used as an internal standard, as shown in Figure 1. One milliliter of chloroform in disposable columns filled with C18 reversed-phase material was used to extract MPA from 1 ml plasma (Baker Chem, Phillipsburg, NJ). The extraction efficiency was 95%. The eluant was dried under a stream of nitrogen, and the dry residue reconstituted with 100 μl of methanol. Of this solution, 10 to 20 μl was used for HPLC analysis. The chromatograph consisted of an M6000 pump and a U6K manual injector (Millipore/Waters, Milford, MA). The separation was achieved in a reversed-phase column (Hibar RP18, 5-μm particle size, 4 × 250 mm, from Merck, Darmstadt) with methanol:water:acidic acid 350:145:5 (v:v:v) as solvent. Isocratic conditions with a flow rate of 1 ml/min were employed. For quantification, a variable UV detector set to the absorption maximum of MPA (245 nm) was used (Spectroflow 773 from Kratos Instruments, Westwood, NJ). The detector was connected to an HP3390A integrator (Hewlett Packard, Palo Alto, CA), which reported integrated peaks. All samples were analyzed in duplicate.

Statistical Methods

Median survival and duration of response for different groups of patients were calculated by the standard methods of survival analysis.[8] Differences between the medians of several groups were tested by the general Wilcoxon rank-order statistic.[9]

Results

Response

Objective tumor reduction (CR and PR) was achieved in 17 patients (23%) and stabilization of disease (NC) in 21 patients (28%). The duration of response was clearly longer in the two patients with complete tumor reduction (Table 2). No significant difference regarding response duration was seen between patients with PR and NC. One premenopausal patient with histologically confirmed peritoneal metastases including a nonresectable mass in the pancreatic area achieved clinical CR for 5 years before relapse. The percentage of objectively responding patients (CR + PR) was higher in postmenopausal women (12 of 37) as compared with premenopausal patients (five of 38). The median duration of partial response, however, was similar in both groups (8 and 7 months).

Survival was longer in responding patients and corresponded to the quality of remission (Table 2, Fig. 3), except for the postmenopausal subset in which the median

survival was slightly longer in the NC group compared with patients with PR. Response rates and duration of responses were correlated to various prognostic criteria, such as relapse-free interval, sites of metastases, and type of previous chemotherapy. Table 3 shows that patients with any of these conditions may respond. The duration of the relapse-free interval did not influence the probability of response or its duration. The metastatic site was of little impact on treatment results because remissions were achieved in patients with cutaneous, lymphatic, pleuropulmonal, and bone lesions, except for the few cases with additional liver metastases who showed no objective response. Although patients responded after extensive pretreatment including different chemotherapy techniques with or without adriamycin, response rates and their duration were slightly higher if patients had received prior hormonal treatment only. Results were unfavorable after both hormonal and cytostatic pretreatment but were not statistically significant ($P > 0.4$).

Reinduction

In six patients, a reinduction therapy with 1 g MPA/d for 10 successive days IM was performed at the time of early relapse. Two patients were premenopausal and four were postmenopausal; their mean age was 55 years. The metastatic sites of these patients were as follows: cutaneous or lymphatic (three), cutaneous and osseous (one), osseous (one), and pulmonal (one). Three patients had received prior cytostatic treatment. The reinduction treatment yielded partial remissions lasting 14 weeks and 15 weeks in two postmenopausal patients and stable disease in three patients, which lasted 11 weeks in one premenopausal patient and 36 weeks and 54 weeks in two postmenopausal patients.

Toxicity

The side effects of the treatment were tolerable. High-dose MPA treatment was discontinued in two patients because of intolerable weight gain in the first and because of treatment-resistant congestive heart failure in the second. No treatment-related deaths were observed. A detailed list of recorded side effects is shown in Table 4.

Pharmacologic Studies

MPA plasma concentrations in 12 patients during the initial IM induction phase and during the oral maintenance of treatment are shown in Figure 2. Plasma levels above 100 ng/ml MPA were achieved during the IM injection phase and were sustained for 16 weeks. During the phase of oral maintenance, plasma levels dropped to a concentration of approximately 50 ng MPA/ml, with a relatively high degree of variation, if no IM reinduction was performed.

TABLE 4. Side Effects of High-Dose MPA Treatment (n = 75 Patients)

Side effects	No. of patients
Weight increase (>3000 g)	26
Systolic blood pressure (increase >20 mmHg)	15
Dyspnea	17
Peripheral edema	12
Pain relief during PD (bone lesions)	8
Nausea	5
Pruritus	4
Vaginal bleeding	4
Cushing syndrome	3
Congestive heart failure	5
Peripheral neuropathy	5
Abscess after IM injection	1
Hirsutism	1

PD: progressive disease.

Discussion

In a group of 12 responding patients, the MPA plasma levels were found to reach 100 ng/ml during the IM period of treatment and peak levels of 150 ng and more during the early phase of oral maintenance. If compared with the literature[1] the rate of objective responses observed in our study seems to be relatively low. However, in contrast to other investigators,[2] we treated poor-risk patients who had already received intensive previous treatment. Second, we applied the UICC criteria[7] strictly for response of bone lesions that require partial recalcification. Thus, most of our patients with bone lesions and relief of pain without progression were classified as NC. This accounted for the relatively high percentage of NC patients (Table 2), which

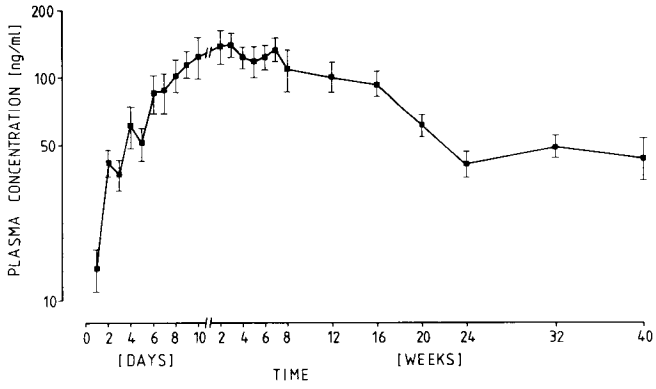

FIG. 2. Plasma concentrations of 12 patients during treatment with MPA (days, initial IM drug administration; weeks, continuous oral therapy). Values are means ± SEM.

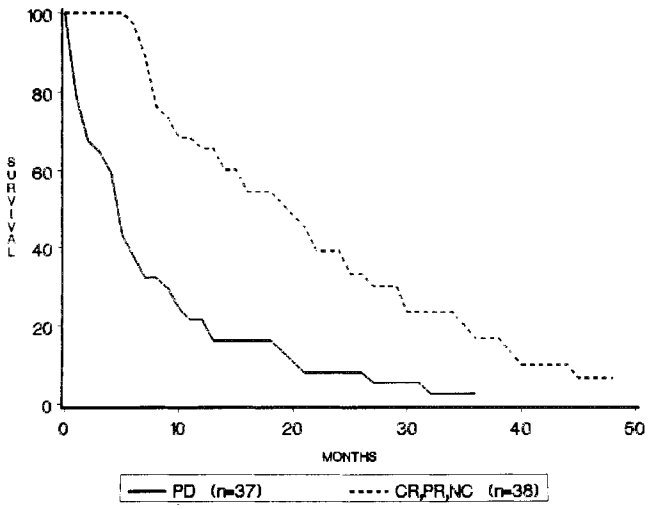

FIG. 3. Survival of responders (CR, PR, and NC) and nonresponders to high-dose MPA treatment. Differences between both groups were significant ($P < 0.05$).

exceeded objective remissions in our study. Our patient characteristics were similar to those in the study reported by De Lena, *et al.*[3] who observed objective remissions in 28% of patients. Remarkably high objective remission rates as observed by Pannuti[10] included patients with bone lesions as responders who had relief of pain for more than 3 months without recalcification. Although the clinical value of partial remissions *versus* an NC status may be similar, standard criteria for the evaluation of response should be adapted to enable comparison of published data. Especially with high-dose MPA treatment, an objective evaluation is necessary because this drug may exert an analgesic effect on patients with bone lesions independent of treatment response.[3] One of the patients in the current study exhibited massive progression of diffuse bone lesions during a period of substantial relief of pain. IM deposits of MPA lead to rather stable serum levels for a period of approximately 3 months. Therefore, we administered a reinduction course of 1 g MPA for 10 days IM in previously responding patients at the time of early relapse. Six patients with favorable prognostic criteria were selected for this procedure. The observation that five of six patients responded again with PR or NC indicates that high-dose MPA was responsible for the success of treatment. Similar results were found by Pannuti *et al.*[2] after treatment with HD-MPA during a limited period of 30 days. Here, the schedule was only repeated at time of relapse in responding patients, and additional response was achieved in four of 15 patients.

Based on our results, postmenopausal patients with low risk type metastases may respond favorably to a reinduction course. In the five cases reported here, the duration of response more than doubled with the second response or stabilization of disease (one PR, four NC). In addition, this study also revealed that even without reinduction, many responses lasted longer than the period of 3 to 4 months during which high-dose MPA conditions were maintained. This indicates that after high-dose induction treatment, a maintenance treatment at lower MPA plasma levels may be sufficient for most patients. Because objective criteria are not available to ascertain which patients need continuous high-dose MPA, an IM reinduction course should only be considered for responding patients at the time of early relapse. Such a procedure could remarkably reduce the MPA plasma levels and reduce the frequency of side effects.

When compared with oral treatment schedules (*e.g.*, 1 g MPA/d), our sequential IM and oral regimen permits a reduction of approximately 30% in the total MPA dosage in responding patients. The IM injection of MPA also leads to a higher degree of treatment safety in case of compliance problems with patients.

Several authors[2,11] reported a preferential effect of high-dose MPA on bone lesions. In our study, although the percentage of bone lesions was high (Table 1), we found similar responses for all types of metastases, as shown in Table 3, probably due to the strict use of the UICC criteria for evaluation. None of the few patients with concomitant liver metastases responded to MPA.

The side effects of MPA were tolerable. Weight gain and an increase of appetite were observed in almost all patients and welcomed by most of them. It led to the termination of treatment in only one patient. Difficult to assess was a favorable psychic effect of MPA observed in several patients. It was similar to that seen with prednisone treatment. Serious cardiopulmonal complications with congestive heart failure, observed also by Goss *et al.*,[12] led to the discontinuation of MPA treatment in one case.

The rank order in which high-dose MPA should be used in the sequential treatment of advanced breast cancer is a matter of continuing discussion. A recent randomized clinical trial of tamoxifen *versus* MPA with a crossover after progression showed that patients did not respond to tamoxifen after treatment with high-dose MPA.[13] A similar observation was made by Alberto *et al.*[14] in which patients showed low response to aminoglutethimide after treatment with high-dose MPA. Therefore, we would suggest that high-dose MPA be used in late stages of the disease. Some of its side effects (*e.g.*, weight gain, psychic stabilization, analgesic effect), which could be disturbing to patients in earlier stages of the disease, may then be welcomed.

REFERENCES

1. Ganzina F. High-dose medroxyprogesterone acetate (MPA) treatment in advanced breast cancer. A review. *Tumori* 1979; 65:563–585.

2. Pannuti F, Martoni A, Lenaz GR, Piana F, Nanni P. A possible new approach to the treatment of metastatic breast cancer: Massive doses of medroxyprogesterone acetate. *Cancer Treat Rep* 1978; 62:499–504.

3. De Lena M, Brambilla C, Valagussa P, Bonadonna G. High-dose medroxyprogesterone acetate in breast cancer resistant to endocrine and cytotoxic therapy. *Cancer Chemother Pharmacol* 1979; 2:175–180.

4. Wander HE, Blossey C, Köbberling J, Nagel GA. Hochdosiertes Medroxyprogesteronacetat beim metastasierenden Mammakarzinom: Beziehung zwischen Krankheitsverlauf und Hormonprofilen. *Klin Wochenschr* 1983; 61:553–560.

5. Salimtschik M, Mouridsen HT, Loeber J, Johansson E. Comparative pharmacokinetics of medroxyprogesterone acetate administered by oral and intramuscular routes. *Cancer Chemother Pharmacol* 1980; 4:267–269.

6. Pannuti F, Camaggi CM, Strocchi E, Giovannini M, Di Marco AR, Costanti B. Medroxyprogesterone acetate (MPA) relative bioavailability after single high-dose administration in cancer patients. *Cancer Treat Rep* 1982; 66:2043–2049.

7. Hayward JL, Carbone PP, Heuson JC, Kumaoka S, Segaloff A, Rubens RD. Assessment of response to therapy in advanced breast cancer. A project of the programme on clinical oncology of the International Union Against Cancer, Geneva, Switzerland. *Cancer* 1977; 39:1289–1294.

8. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Statist Assoc* 1958; 53:437–481.

9. Breslow N. A generalized Kruskal-Wallis test for comparing k samples subject to unequal patterns of censorship. *Biometrica* 1970; 57:579–594.

10. Pannuti F. Die hochdosierte Gestagenbehandlung in der Therapie des fortgeschrittenen Mammakarzinoms. *Onkologie* 1979; 2:54–60.

11. Robustelli Della Cuna G, Calciati A, Bernardo Strada MR, Bumma C, Camprio L. High-dose medroxyprogesterone acetate (MPA) treatment in metastatic carcinoma of the breast: A dose–response evaluation. *Tumori* 1978; 64:143–149.

12. Goss PE, Ashley S, Powles TJ, Coombes RC. High-dose oral medroxyprogesterone acetate in heavily pretreated patients with metastatic breast cancer. *Cancer Treat Rep* 1986; 70:777–779.

13. van Veelen H, Willemse PHB, Tjabbes T, Schweitzer MJH, Sleijfer DT. Oral high-dose medroxyprogesterone acetate versus tamoxifen: A randomized crossover trial in postmenopausal patients with advanced breast cancer. *Cancer* 1986; 58:7–13.

14. Alberto P, Mermillod B, Kaplan E *et al.* A clinical trial of aminoglutethimide in advanced postmenopausal breast carcinoma: Low response in patients previously treated with medroxyprogesterone. *Eur J Cancer Clin Oncol* 1985; 21:423–428.