Clinical Trial of High-Dose Oral Medroxyprogesterone Acetate in the Treatment of Metastatic Breast Cancer and Review of the Literature

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Recent studies have suggested that there are benefits from the use of high-dose parenteral medroxyprogesterone acetate (MPA) in the treatment of metastatic breast cancer. The present study was designed to assess the efficacy and toxicity of high-dose oral MPA in women with clinical parameters suggesting potentially hormonally sensitive metastatic breast cancer. The first 28 patients received 800 mg/day, and 11 of them had received no previous hormone (NPH) therapy. The response rate (complete plus partial) was 63% for those receiving NPH and 12% for those receiving previous hormone (PH) therapy. Toxicity was significant at these doses, especially for women treated for more than 5 weeks. Toxic effects included excessive weight gain, Cushingoid facies, worsening of diabetes mellitus, and other stigmata suggestive of hypercorticism. Nineteen other patients were treated at 400 mg/day with a 60% response rate for 10 NPH patients and 44% for patients with PH treatment. Toxicity was less severe in these patients. The median time to treatment failure was 23 weeks, and to survival, 119 weeks for all treated patients. Moderately high (400 mg/d) and higher dose (800 mg/d) oral MPA are capable of inducing reasonable response rates in patients with NPH treatment. The toxicity of these regimens was significant—profound weight gain was dose limiting in some patients. While effective, high-dose oral MPA is unlikely to supplant tamoxifen as first-line therapy in metastatic breast cancer.

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HORMONE MANIPULATIONS remain the mainstay of therapy in many patients with metastatic breast cancer. With minimal toxicity hormone treatments induce significant antitumor responses in 30% to 60% of patients (depending on patient selection factors) with a median duration of 12 to 16 months.[1] Progestins have recently emerged as an important group of hormones in the treatment of breast cancer.[2–4] Medroxyprogesterone acetate (MPA) has been used for several years at low dosages,[5] but the recent use of higher dosages parenterally has yielded encouraging results.[6–10] The experience with high-dose MPA given orally has been limited.[11–16] This trial described in this article was undertaken to assess the role of high-dose oral medroxyprogesterone acetate (HDO-MPA) in the treatment of patients with advanced breast cancer.

Materials and Methods

Fifty-one peri-menopausal or postmenopausal women with measurable, metastatic breast cancer were prospectively studied between 1980 and 1983. This study was conducted after approval by the University of Miami Institutional Review Board in accordance with an assurance filed with and approved by the Department of Health and Human Services. Before treatment, all patients were informed of potential benefits as well as risks and hazards, and they signed formal informed consent forms. The criteria for patient selection generally included a positive estrogen receptor status (ER) and/or a previous response to an hormone manipulation. Three patients without previous hormone manipulations were entered into the study with borderline or unknown ER status because of a long disease-free interval and indolent presentation. Patients were not excluded from the study on the basis of age or site of metastatic disease. Early in the study, a positive ER was

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TABLE 1. Patient Characteristics

Characteristic	Previous hormones	No previous hormones
No. of patients	27	21
Median age	55	59
Age range	36 to 77	46 to 77
No previous therapy	—	11
Previous hormone therapy only	14	—
Previous chemotherapy only	—	1
Previous hormone therapy and chemotherapy	13	—
Previous adjuvant chemotherapy	1	9
Estrogen receptor status		
Positive	21 (78)	18 (86)
Negative	1 (4)*	–
Borderline	–	1 (5)†
Unknown	5 (18)*	2 (9)†

(Numbers in parentheses indicate percentage.)
* All previous hormone responders.
† All with long disease-free interval and indolent disease.

defined as greater than 700 fmol/gm of tissue. The units were later changed, and positive ER was defined as greater than 10 fmol/mg protein.

Baseline studies of each patient included a history and physical examination, bone and liver scans, chest and other appropriate radiographs, complete blood cell count, liver and renal function tests, serum electrolytes, calcium, cholesterol, triglycerides, and urinalysis. The patients were reevaluated at 6- to 8-week intervals at which time blood tests were repeated; other tests were given as well if needed to assess response and/or progression. The first 29 consecutive patients were treated with HDO-MPA 800 mg daily in divided doses. The toxicity encountered was significant; therefore, the next 19 patients were started at a dose of 400 mg daily. This change was also supported by emerging data from other studies[13] indicating no significant benefit in response rate using the higher dose. Three patients responding to the initial dose of 800 mg were deescalated to 400 mg later in their clinical course. The drug treatment was continued until objective evidence of progression, intolerable side-effects, or toxicity were seen.

Standard response criteria were used. A complete response (CR) was defined as the disappearance of all clinical evidence of disease. Partial response (PR) was defined as a reduction of at least 50% in measurable lesions and no evidence of disease progression for a minimum of 2 months. No response (NP) was defined as an increase of 25% or more in measurable lesions or evidence of new sites of disease. Standard criteria for the response of bone disease were used.[17] The times to treatment failure and survival were measured from the time of the initiation of HDO-MPA.

Results

Of the 51 patients entered, three were ineligible; two with far advanced disease were treated on compassionate grounds, and one, on review, had pleural effusion as the only evidence of evaluable (but not measurable) disease. The characteristics of the patient population are shown in Table 1. One patient was removed from the study after 5 weeks of treatment because of toxicity. The response to treatment could not be assessed; therefore, she is included only in the analysis of toxicity. Of all 47 patients evaluable for response, four (8.3%) achieved a CR, 15 (31.3%) achieved a PR, and eight (16.7%) had stable disease. The responses to treatment in the PH and NPH groups are outlined in Table 2. The combined CR and PR was 61.9% in the NPH group compared to 22.2% in the PH group ($P < 0.05$). There were 15 patients with and 33 patients without visceral metastases. The response rate tended to be higher in patients without visceral metastases (45% *versus* 27%; $P = 0.19$). Twenty patients had progressive disease, 14 of whom had PH. The median time to treatment failure (TTF; Fig. 1) measured from the initiation of therapy to relapse in responding or stable disease patients and to off-study in nonresponders was 23 weeks. The median TTF for responders was 46 weeks. Although the median TTF for patient with stable disease was 32 weeks, it could not be determined if these patients derived biologic benefit or if they simply had more slowly growing tumors than patients with progressive disease. The TTF for the four patients achieving CR were 54, 69, 100, and 195 weeks. The first patient was taken off study while in CR because of recurrent phlebitis.

The median survival from on-study to death was 119 weeks. Dose and PH treatment appear to have had an interactive effect on survival. The median survival in patients with PH on high-dose therapy was 56 weeks, while the median survival in the other three groups

TABLE 2. Response to Treatment

	CR	PR	CR + PR	Stable	Progression
Previous hormones	1 (4)*	5 (19)	6 (23)	6 (23)	14 (54)
No previous hormones	3 (14)	10 (48)	13 (62)	2 (9)	6 (29)
Total	4 (8)	15 (31)	19 (39)	8 (17)	20 (42)

* Numbers in parentheses indicate percentage.

CR: complete response; PR: partial response.

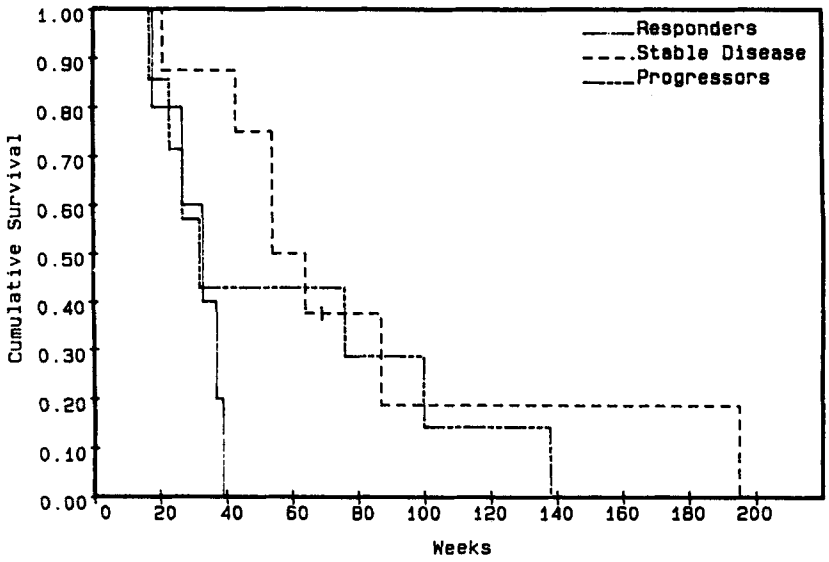

FIG. 1. Time to treatment failure.

(NPH-800, PH-400, and NPH-400) combined was 148 weeks ($P < 0.001$, generalized Wilcoxon statistic). The reasons for this apparent adverse interactive effect of high-dose therapy in previously treated patients remains obscure, although patient numbers in these subsets are small.

Table 3 presents the response rates in both treatment groups (PH and NPH) as a function of dose. No statistically significant conclusions can be drawn because of small numbers in the four subsets and because the dose-response was not evaluated through controlled, randomized study design. There was, however, a trend toward a higher response rate (CR and PR combined) in patients receiving 400 mg *versus* 800 mg of HDO-MPA (52% *versus* 31% $P = 0.13$).

Twenty-nine patients (60.4%) had some evidence of significant side effects or toxicity. Table 4 outlines the frequency of side effects or toxicity. Four patients were removed from the study because of severe toxicity. One patient gained 60 pounds and developed diabetes mellitus and Cushingoid facies; another gained 27 pounds and refused further therapy; a third had recurrent superficial thrombophlebitis; and the fourth patient had transient cerebrovascular insufficiency within 5 weeks of the onset of therapy. Of these four patients, one was taken off study while in CR, two others were stable, and in the fourth, response could not be assessed. They had been on therapy for 54, 33, 18, and 5 weeks, respectively. All four patients had received 800 mg of HDO-MPA daily. No patient treated with 400 mg of HDO-MPA was removed from study because of toxicity.

There appeared to be an association between the duration of treatment and the appearance of side effects. Table 5 correlates the mean duration of treatment and the frequency of toxicity. The mean duration of treatment in the 19 patients without significant toxicity was 16.6 weeks compared to 40.6 weeks in those with at least one symptom (Student's t test, $P < 0.001$).

Discussion

While the precise mechanism or mechanisms of action of progestins in breast cancer treatment remain uncertain, several possibilities exist. High doses of MPA

TABLE 3. Response to Treatment According to Dose and Previous Therapy

	CR	PR	Stable	Progression	Total
800 mg/day					
Previous hormones	0	2 (12)*	3 (18)	12 (70)	17
No previous hormones	3 (27)	4 (36)	1 (9)	3 (27)	11
Total	3 (10)	6 (21)	4 (14)	16 (55)	28
400 mg/day					
Previous hormones	1 (11)	3 (33)	3 (33)	2 (22)	9
No previous hormones	0	6 (60)	1 (10)	3 (30)	10
Total	1 (5)	9 (48)	4 (21)	5 (26)	19

CR: complete response; PR: partial response.

* Numbers in parentheses indicate percentage.

TABLE 4. Side Effects and Toxicity

Symptoms	No. of patients	Percent
Weight gain (>10 lb)	18	(38)
Cushingoid facies	9	(19)
Development or worsening of DM*	4	(8)
Facial rash	3	(6)
High blood pressure	2	(4)
Nervousness	2	(4)
Atypical chest pain	1	(2)
Phlebitis	1	(2)
Pain flare	1	(2)
Tremulousness	1	(2)
Transient cerebrovascular insufficiency	1	(2)

* Includes one patient with impairment of glucose tolerance test.
DM: diabetes mellitus.

have been shown to interfere with the hypothalamo-pituitary-adrenal axis, primarily decreasing the circulating levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and, secondarily, the estrogen level.[18] It also reduces the cortisol level probably by suppressing ACTH.[18] Hedley *et al.* concluded that plasma MPA concentrations could not be correlated with plasma hormone levels or clinical response[19] although they studied all patients at one dose level (600 mg/day) and did not study adrenal steroidogenesis. Van Neelan *et al.* studied patients at three different dose levels of MPA in an attempt to correlate dose-response with studies of adrenal steroidogenesis. They concluded that suppression of androstenedione levels (and consequently serum estrone levels) did occur with higher MPA doses and might account for its biologic antitumor effect.[20,21] Mahlke *et al.* also found a correlation between MPA serum levels and response, but also found that even nonresponders had suppressed cortisol levels.[22]

In addition to its effects on the pituitary adrenal axis, MPA binds with high affinity to the glucocorticoid, androgen, and progesterone receptors, whereas it does not compete with estradiol for estrogen receptor binding.[23] It has been suggested that MPA acts in neoplastic cells by androgen receptor binding, which is found in hormone-responsive tumors thus characterized by the presence of ER.[23] In addition, there might be several other mechanisms of action such as the acceleration of estrogen metabolism and a decrease in the conversion of androgens to estrogens. Furthermore, the clinically observed androgenic and glucocorticoid effects may also alter the hormone milieu, leading to clinical responsiveness. The dual mechanism of action through endocrine manipulation and direct action in the tumor cell through the steroid receptors makes MPA an attractive drug in the treatment of breast cancer.[24]

The precise role of progestins in breast cancer treatment remains to be established. While MPA has been successfully used in the past in the treatment of advanced breast cancer, older studies at lower dosages showed no advantage over more established therapies.[5] Pannuti *et al.* reported excellent results with the parenteral use of higher doses of MPA.[7] Several other confirming European studies followed.[8,25] Depending on clinical characteristics, a response rate varying from 21% to 61% has been reported, with an overall 41% response rate among 1021 patients.[25] Estrogen receptor status, site of metastases, and previous therapy were found to be important determinants.[25] Although there is debate regarding the optimum dose and schedule of administration of parenteral MPA, a critical review of the subject and a literature review showed that 500 mg intramuscularly (IM) daily for 4 weeks followed by 500 mg IM twice weekly were as effective as higher doses.[25] However, in a recent, prospective randomized trial of parenteral MPA, Cavalli *et al.* found a response rate of either 33% or 15% in 186 patients treated with 1000 mg or 500 mg daily, respectively. This difference was maintained across different prognostic subgroups, although the survival was the same for both groups.

Weight gain, moon facies, increased appetite, vaginal bleeding, muscle cramps, and increased blood pressure were found.[26] It has previously been demonstrated that parenteral administration (IM) of high doses of MPA resulted in a slow but cumulatively efficient absorption phase, whereas oral administration leads to fast absorption but low global bioavailability and marked interpatient variability.[27] After 10 days, the oral administration

TABLE 5. Duration of Treatment and Side Effects

	Duration of treatment in weeks				
	2–10	11–20	21–40	>40	Total
Patients with no toxicity	8 (42)*	7 (37)	1 (5)	3 (16)	19
Patients with at least one toxicity symptom	3 (10)	5 (17)	11 (38)	10 (35)	29
Patients with weight gain ≥10 lb	0	4 (22)	7 (39)	7 (39)	18
Patients with cushingoid facies	0	1 (11)	4 (44)	4 (44)	9

* Numbers in parentheses indicate percent.

of 1000 mg daily results in similar plasma levels attained by 4 weeks of administration of 500 mg IM.[27] Because of interpatient variability in response to MPA, Pannuti *et al.* suggested the "routine" analysis of plasma MPA levels,[28] although this need has been questioned by others.[19]

The experience with HDO-MPA has been limited. Guarnieri *et al.* treated 26 previously treated postmenopausal patients with oral MPA 2000 mg twice daily for 30 days followed by 1000 mg daily for 60 days. The objective response rate was 27% with a median duration of response of 8 months and a median survival of 16.8 months. Side effects were mild, although diarrhea was seen in 14 patients.[14] Izuo *et al.* treated 110 postmenopausal women with different dosages of oral MPA varying from 600 to 2400 mg/day. The highest response rate (38.2%) was found at the 1200 mg/day dose level with a significantly better response in patients with bone disease.[11]

Endocrinologic studies performed in this trial showed a significant decrease in LH, FSH, and ACTH and a consequent decrease in endogenous estrogen (estrone), progesterone, and hydrocortisone levels. There was an increase in the urinary excretion of 17 hydroxysteroids and to a lesser extent, 17 ketosteroids.[11] The same group of investigators randomized 87 evaluable postmenopausal patients without previous hormone treatment to receive MPA 1200 mg daily or the antiestrogen, mepitiostane. Objective response rates were 40 and 35%, lasting 45 and 39 weeks, respectively.[29] Beretta *et al.* treated 134 women in three consecutive studies with oral MPA (600 mg/d); IM MPA (500 mg/d); and oral tamoxifen (20 mg/d). The response rates (CR + PR) were 26.2, 25.6, and 28.1%, respectively.[15] The European Organization for Research in Treatment of Cancer (EORTC) randomized 201 patients to receive 300 *versus* 900 mg of MPA orally. The overall response rates were 16% and 23%, respectively ($P = 0.08$). The time to progression was significantly longer in those treated with the high dose ($P = 0.02$), whereas response duration and survival were not.[13] Hortobagyi *et al.* treated 39 postmenopausal patients with positive or unknown ER with HDO-MPA at 800- or 400-mg/day doses with an overall response rate of 44%. A weight gain of more than 10 pounds (47%), increased appetite (66%), muscle cramps (41%), and increased blood pressure (39%) were the most common side effects.[15]

Our study confirms the efficacy of HDO-MPA in patients previously treated with hormones as well as patients without previous hormone manipulations. The response rate (CR plus PR) of 61.9% in patients without previous hormone manipulation agrees with most other rates from hormone therapies when used as the first treatment in women with a positive ER status. The response rate of 22.2% in patients with previous hormone therapy is also consistent with that seen in secondary or tertiary hormone manipulations. The duration of disease control is likewise similar to that reported for other hormone manipulations. The shorter duration of disease control in the PH group is not surprising given the usual shorter duration of response to secondary or tertiary (compared with primary) therapeutic maneuvers in metastatic breast cancer.

The advantages of oral over parenteral administration of MPH are obvious, and there appears to be no difference in the response rate in the published literature. The advantages of higher doses are not as clear. Although our trial was not comparative between 800 and 400 mg/day, trends do not appear to support the higher dose. Even in the large, controlled EORTC study previously cited, differences between 300 mg and 900 mg were modest, although there were trends favoring the higher dose.[13] As in other series,[15,26,30] some significant side effects were seen in our trial. Although the inconvenience of parenteral administration and the formation of gluteal abcesses are eliminated by the oral administration of MPA, other patterns of toxicity have become more apparent. Weight gain (occasionally severe) Cushingoid facies, facial rash, worsening or development of diabetes mellitus or arterial hypertension, as well as nervousness and tremulousness were found in our patients. These symptoms are also found in patients treated with glucocorticoids. Some of the side effects found were severe enough to warrant the discontinuation of treatment.

Although the most troubling side effects of progestins in this population of women was weight gain, this may well be turned to unique advantage in some clinical patient subgroups. Thus, Pannuti *et al.* have repeatedly commented on the marked subjective improvement, increased sense of well-being, and reversal of anorexia seen in their breast cancer patients and even in patients with hormonally "insensitive" tumors.[31] Similarly dramatic anabolic and palliative effects were more recently reported using massive doses of the related progestin megestrol acetate.[32–34] In standard doses this compound would appear to yield a response rate and toxicity patterns similar to MPA.[4] It is interesting that Wander *et al.* compared the two drugs and suggested that comparable oral doses would be 160 to 200 mg/d megestrol acetate or 1 to 1.5 g/day of MPA.[34] If that is the case, the oral MPA doses comparable to the 1600 mg of megesterol acetate used by Tchekmedyan *et al.* have not yet been explored.[33] The 4 g/day induction dose used in a small series reported by Guarnieri *et al.* is the highest we have been able to find in our literature review. This dose was not only associated with a 27% objective response rate,

but also an 88% subjective response rate with an 8-month response duration and an overall median survival of 16.8 months. Therapy was complicated by an increased prevalence of diarrhea.[14]

High-dose oral MPA is another effective hormone manipulation in the treatment of both previously treated and previously untreated patients with metastatic breast cancer. The drug's major side effects of appetite stimulation and weight gain might limit its usefulness in obese breast cancer patients or in the adjuvant situation, but could make it more useful in anorectic cancer patients. Given the data cited, it would appear that a maximum tolerated dose (MTD) of HDO-MPA has not yet been reached, and a Phase I trial would appear to be indicated. Once an MTD has been established, a controlled, randomized trial against more conventional doses of MPA would appear to be indicated. Combination chemohormone therapy also needs further investigation. In three consecutive, randomized trials of chemotherapy with or without parenteral MPA a trend favoring the chemohormone therapies was found. The median duration of response was significantly longer.[35] Another interesting approach is the use of sequential hormone therapy using estrogens or antiestrogens to induce progesterone receptors followed by therapy with progestins. This approach has resulted in promising trends in some of the Phase II trials reported.[36,37] These will need to be confirmed in Phase III trials.

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