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High-Dose Medroxyprogesterone Acetate in Breast Cancer Resistant to Endocrine and Cytotoxic Therapy

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Summary. *The therapeutic effects of high-dose (1000 or 1500 mg/day) medroxyprogesterone acetate (MPA) were evaluated in a consecutive series of 81 women with advanced breast cancer. All patients were resistant to either endocrine treatment and/or chemotherapy. Complete plus partial remission was obtained in 23 of 81 (28%) patients, with a median duration of 6 months and a median survival of 13.5 months. The highest response rate was observed with lung metastases (41%), followed by soft tissue (31%) and osteolytic bone involvement (13%). Complete plus partial response was not significantly influenced by the dose regimen utilized (32% with 1000 mg/day vs. 21% with 1500 mg/day). Responders survived longer than nonresponders. The responsiveness to MPA was correlated with the prior disease-free interval ($\geqslant$ 2 years: 47%, $<$ 2 years: 19%) and with menopausal status (17% in premenopausal vs. 32% in postmenopausal patients), but was independent of prior response to other hormonal manipulations and chemotherapy. An increase in body weight was observed in 56% of cases and gluteal abscess in 16%. The incidence of this latter side effect was correlated with the dose (1000 mg: 13%; 1500 mg: 21%). This study shows that high-dose MPA can produce objective remission with improved survival in about one-third of postmenopausal women who are resistant to cytotoxic drugs and other endocrine therapies. Our results are not superior to those obtained with conventional oral MPA.*

Introduction

The recent determination of estrogen-binding protein, or estrogen receptor (ER), in the cell cytoplasm constitutes an interesting development in the endocrine treatment of various stages of breast cancer. While the number of reports on the selective application of various forms of endocrine treatment on the basis of ER determinations is increasing, the clinical use of progestational agents in advanced breast cancer has remained limited. Progestogens, and in particular medroxyprogesterone acetate (MPA), have been known for a relatively long time to produce objective tumor regression in women with disseminated breast cancer, and to be practically devoid of severe untoward effects [3]. In the past few years, Pannuti et al. [11, 12] and a few other investigators [1, 19] have reported that the response rate to MPA can be increased by using very high daily doses, ranging from 1000 to 2000 mg, for 1 months.

The aim of this paper is to report our experience with two high doses of MPA administered for a relatively short period in patients who had become resistant to combination chemotherapy and to other endocrine treatments.

Patients and Methods

Patient Selection

Patients selected for treatment with high-dose MPA had disseminated breast carcinoma. Before starting MPA, all patients had one or more physically and/or radiologically measurable parameters for drug response. In particular, no patient had pleural effusion or osteoblastic bone involvement as the sole clinical evidence of advanced cancer. Women with brain metastases, with a performance status below 50, or with life expectancy of less than 6 weeks were all excluded from the study.

Between March 1975 and November 1977, a consecutive series of 81 women was treated with MPA. All patients are considered evaluable for the analysis of drug response and form the subject of this report. Table 1 summarizes the main characteristics of evaluable patients. Most women (78%) were in postmenopausal status, either natural or artificial. The vast majority of patients (98%) had previously been treated with combination chemotherapy, including CMF and adriamycin plus vincristine (AV), and 37% had also received one or more endocrine manipulations. Two dose schedules were used, 1500 mg and 1000 mg MPA a day. The two treatment groups are fairly comparable in terms of dominant site of disease, menopausal status, and prior chemotherapy.

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Table 1. Main characteristics of patients

	Total (81)		1500 mg (28)		1000 mg (53)	
	No.	%	No.	%	No.	%
Median age (years) (Range)	55 (28–75)		52 (31–66)		56 (28–75)	
Dominant site						
Soft tissue	31	38	12	43	19	36
Visceral	28	35	8	28.5	20	38
Osseous	22	27	8	28.5	14	26
Menopausal status						
Pre-	18	22	8	29	10	19
Post-	63	78	20	71	42	81
Previous systemic therapy						
Chemotherapy	79	98	28	100	51	96
Endocrine therapy	30	37	10	36	20	38
Castration	16		6		10	
Androgens	4		2		2	
Estrogens	6		2		4	
Antiestrogens	3		0		3	
Progestins[a]	1		0		1	

[a] Norethisterone acetate

Treatment Schedule

MPA (as Depo-Provera, 150 mg/ml) was administered according to two different dose schedules; at the end of the treatment induction the two groups of patients had received about the same total dose. Group I received MPA at a dose of 1500 mg/day for 27 consecutive days, while group II received 1000 mg/day for 40 consecutive days. In 21 patients with either stable disease or partial response, maintenance therapy was given with 500 mg twice weekly. The hormone was administered in two IM injections each day about 12 h apart and the patients were advised to have the preparation injected deeply into each buttock in turn.

Evaluation of Response

All patients were treated on an outpatient basis. Metastatic lesions were measured before and after treatment through physical examinations and chest and skeletal roentgenograms. Complete blood counts and blood chemistry tests were also repeated after MPA therapy. In only four patients were the estrogen receptors determined.

The objective criteria used in our Institute to evaluate the drug response in metastatic breast cancer are listed below.

1. Complete Remission (CR). Complete disappearance of all lesions and recalcification of all osteolytic metastases for at least 1 month.

2. Partial Remission (PR). A decrease of 50% or more in the product of the two largest perpendicular diameters of all measurable lesions, or partial recalcification of osteolytic metastases (with regression or no change in osteoblastic metastases) for a minimum of 1 month.

3. Objective Improvement. A decrease of 25%–50% of the product of the two largest perpendicular diameters of all measurable lesions, with no change in osseous metastases. A CR or PR of one or two parameters with no change in other organs or sites was also defined as an objective improvement.

4. No Response. No appreciable change in measurable lesions or objective improvement of one lesion without concomitant tumor regression in other sites.

5. Progression. An increase of 25% or more over the original product of the two largest perpendicular diameters of measurable lesions, irrespective of concomitant regression in other tumor sites, occurrence of new lesions, or progression of osteolytic metastases.

6. Relapse. Appearance of new lesions or increase in the product of the two largest perpendicular diameters of measurable lesions by 50% over the size recorded at the initiation of therapy following a period of initial response or a period of no change.

Results

Table 2 shows the therapeutic results in the entire series and in the two groups given different dose schedules of MPA.

While a total of 35% showed objective tumor regression, CR plus PR was observed in 28% of patients. The response to MPA was not significantly influenced by the treatment schedule. It is interesting to note that no patient receiving 1500 mg/day achieved CR. The median duration of CR plus PR was 6 months (range: 2–15 months) with no appreciable difference between the two treatment groups (1000 mg: 7 months; 1500 mg: 5.5 months). Both patients who were ER-negative showed no response to MPA, while PR was observed in one of two women who were ER-positive. Table 3 shows the incidence of CR plus PR related to individual sites of disease involvement. In the present series, the highest percentage of tumor regression was observed in lung, skin, nodes, pleura, and breast, while only 13% of women showed partial or complete recalcification of osteolytic lesions. It is noteworthy that in no instance did liver metastases show signs of objective regression. Table 3 shows that in the present series a considerable lower percentage of response was observed at the level of soft tissue involvement in the group treated with 1500 mg/day than in that receiving 1000 mg/day.

Table 4 analyzes the response rate in relation to disease-free interval and menopausal status. There was a positive correlation between a long disease-free interval ($\geqslant$ 2 years) and response to MPA. Only three of the 18 (17%) premenopausal women showed a response to MPA. All three patients with amenorrhea induced by MPA failed to show any evidence of tumor response. Therefore, complete plus partial tumor regression was observed in the present series primarily in postmenopausal women (32%), with no substantial difference between early (1–5 years) and late (> 5 years) meno-

Table 2. Objective response

	Total (81)	1500 mg (28)	1000 mg (53)
Progression	41	17	24
No change	12	3	9
Improvement	5	2	3
Partial ⩾ 50%	20	6	14
Complete	3	0	3
Complete + partial	23 (28%)	6 (21%)	17 (32%)
Total with response	28 (35%)	8 (29%)	20 (38%)

Table 3. Complete plus partial response at the sites of disease involvement

	Total		1500 mg		1000 mg	
	No.	%	No.	%	No.	%
Soft tissue	98	32	39	18	59	41
Breast	33	24	17	12	16	37.5
Skin	38	39	15	27	23	48
Nodes	27	30	7	14	20	35
Lung	17	41	3	33	14	43
Pleura	7	29	3	33	4	25
Liver	7	0	2	0	5	0
Bone	32	13	11	0	21	19

Table 4. Complete plus partial response to MPA related to disease-free interval and menopausal status

	Total	
	No.	%
≥ 2 Years	28	47
< 2 Years	53	19
Menopausal status		
Pre-	18	17
Post-	63	32
1–5 Years	28	29
> 5 Years	35	34

Table 5. Complete plus partial response to MPA related to previous systemic treatment

Prior therapy	Patients		Response to prior therapy		Response to MPA	
			No.	%	No.	%
Endocrine	30	CR + PR	5	17	2/5	40
		None	25	83	8/25	32
Chemotherapy	79	CR + PR	32	41	11/32	34
		None	47	59	10/47	21

pausal status. There was no direct correlation between response to either type of prior systemic treatment (endocrine treatment and chemotherapy) and response to MPA. In particular, 32% of the women showed complete plus partial response in the absence of objective tumor regression to prior hormonal manipulations (Table 5).

The influence of high-dose MPA on pain produced by bone involvement and/or soft tissue infiltration was not systematically recorded. However, of 27 patients with pain, nine obtained relief from their symptoms. It is interesting to note that in seven of nine women pain decreased after MPA in the absence of documented objective tumor response.

Survival is illustrated in Fig. 1, and the median duration was 13.5 months. It is noteworthy that while complete plus partial responders had not reached the median 2 years from starting MPA, all other patient categories showed a median survival of only 10 months. Once more, no appreciable difference was noted between women receiving 1500 mg and those receiving 1000 mg MPA.

Short-term treatment with high-dose MPA was essentially devoid of major side effects. However, an increase in body weight, ranging from 3 to 10 kg, was observed in 56% of patients (1500 mg: 43%; 1000 mg: 62%). This was due to increased adipose tissue in the abdominal and cervicodorsal regions, as observed by Pannuti et al. [17]. Almost all patients noticed a dramatic increase in appetite. Furthermore, gluteal abscess occurred in a total of 13 women (16%) and in four cases this required surgery. This complication was dose-related, since it occurred in 13% of patients receiving 1000 mg/day, as against 21% of those treated with 1500 mg/day. In four women receiving 1500 mg/day multiple abscesses were observed. The occurrence of abscess led

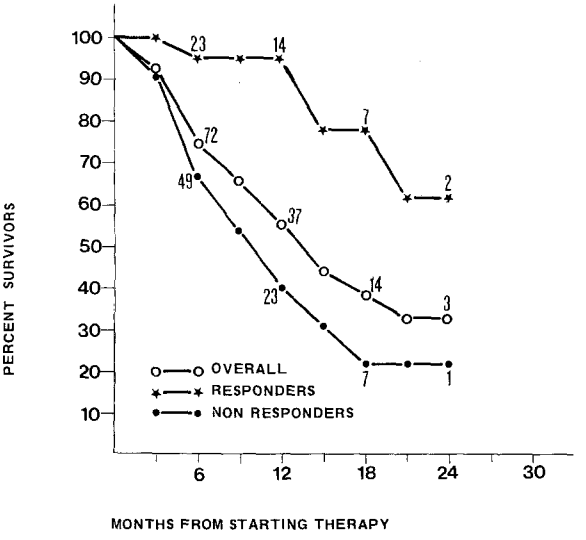

Fig. 1. Overall survival from start of MPA

to discontinuation of treatment in seven patients. Minor vaginal bleeding developed in two women. MPA induced amenorrhea in three of eight menstruating females. Muscle cramps were observed in about 20% of patients during treatment and for a few weeks thereafter. Laboratory studies failed to reveal any evidence of hepatic dysfunction related to MPA administration. No patient developed hypercalcemia.

Discussion

The results of our prospective study show that MPA induced objective tumor response in about 30% of women with disseminated breast cancer who were resistant to hormonal manipulation and to combination chemotherapy. Patients with a disease-free interval of longer than 2 years, who were postmenopausal and had lesions either in the soft tissue or in the lung and pleura were the ones who benefited most from treatment with MPA. Thus, our series of patients indicates that even after the vast majority of conventional treatments for advanced disease have failed, MPA can still provide a useful tumor response followed by improved survival.

In breast cancer, progestational agents have been much less extensively investigated than androgens, estrogens, and antiestrogens. The progesterone derivatives that have been used most often are norethisterone acetate [5, 6, 20] or enanthate [2] and medroxyprogesterone acetate [4, 7, 8, 10, 21–23]. As with other endocrine treatments, published results often revealed marked discrepancies. In fact, the response rate ranged from 3.6%–41% for norethisterone and from 0%–36% for MPA. Most probably, the differences reflected patient selection (e.g., age, extent of disease, prior therapy) as well as criteria for the assessment of therapeutic results and methods of reporting data. Therefore, the duration of remission also varied in different reports, and ranged from 3.5–5.5 months for norethisterone and from 7–12 months for MPA. All authors working with progestational agents agreed that the objective response was correlated with long disease-free interval, postmenopausal status, and absence of visceral involvement.

In recent years, the treatment of breast cancer with MPA has been somewhat revitalized by the publications of Pannuti et al. [11, 12, 16]. They used Farlutal Depot (Farmitalia) (200 mg/ml) and, following empiric criteria, administered high daily doses (1500 and 2000 mg) for 30 days. The total daily dose was given in two IM injections 12 h apart. In premenopausal women [14], CR plus PR accounted for 93% (13 of 14) and in postmenopausal women [17] for 43% of the patients (19 of 44). The most recent [17] response rate published for dominant soft tissue and bone involvement was 67%, that for lung 12%, while all three patients with pleural metastases showed objective response. No regression was observed in patient with liver and brain deposits. A high incidence (94%) of pain relief was also noticed, and symptoms were reduced, even in the absence of objective tumor response. In addition, an increase in the performance status was observed. In postmenopausal women, the median duration of response was 7 months, with a median duration of survival of 15.5 months for responders. About one-third of the women had previously been treated with chemotherapy and/or endocrine therapy. Amenorrhea occurred in all premenopausal subjects [14]. A number of reversible side effects were reported [11, 17]: increased body weight (77%), gluteal abscess (33%), sweating (23%), fine tremor (21%), vaginal bleeding (10%), muscle cramps (4%), and thrombophlebitis (2%). Furthermore, transient increases in the arterial blood pressure, leukocyte and platelet counts, blood urea nitrogen, and serum Na and K were observed [11, 15]. Some of the reported side effects were less pronounced when MPA was administered orally in a daily dose of 2000 mg for 30 days [16]. Similar therapeutic (CR plus PR: 56.8%) and toxic results with high-dose MPA therapy were also reported by Amadori et al. [1], who administered MPA IM at a dose of 1000 mg/day for 45–50 consecutive days to 44 women previously untreated with chemotherapy.

To test whether the good results obtained with MPA could be explained only by the high dose regimen utilized, two controlled studies were recently performed. Robustelli et al. [19] randomly allocated 101 postmenopausal women previously untreated with chemotherapy to receive MPA either at 1000 mg/day or at 500 mg/day for 30 consecutive days. CR plus PR was observed in 41% and 44%, with median duration of response of 9 and 8 months, respectively. A very similar incidence of CR plus PR (43.5%) with a median duration of response of 4 vs. 5 months was obtained by Pannuti et al. [18] in 92 postmenopausal patients randomized to receive either 1500 mg/day or 500 mg/day for 30 days. In this last series, 18 of 92 (20%) women had previously been treated with chemotherapy. In both studies the incidence and the severity of side effects were lower after the 500-mg/day regimen than after the higher doses.

When a high-dose regimen of MPA (500 mg or more daily) is used, suppression of ovulation, pituitary gonadotrophins, and adrenal sex steroids is probably greater than is achieved with a lower dosage. However, this possibility could explain only in part the good results reported by Pannuti et al. [13], Amadori et al. [1], and Robustelli et al. [19]. They administered MPA to women who had received practically no previous treatment with chemotherapy, and even in the absence of prior hormone therapy. Furthermore, partial response also included no change in osseous lesions for at least 3

months [17]. Therefore, different methods of patient selection and different criteria of drug response have probably also played an important role in the incidence of therapeutic response. This factor was also evident in the series treated with norethisterone. In 154 women previously untreated with chemotherapy, only 87 (56%) of whom had received prior hormone therapy, Edelstyn [6] reported objective remission in 41. Conversely, CR plus PR was obtained in only 23.3% and 25%, respectively, in the series of Ansfield et al. [2] and Rubens et al. [20], where practically all patients had previously received endocrine and cytotoxic treatments. Our results with MPA are in agreement with those of Mattsson [9], who has observed PR in 28% of 25 postmenopausal women for a median duration of 7^+ months after 1000 mg/day for 30 days, and are slightly superior to those reported in the past by Muggia et al. (22%), who administered 100 mg three times weekly [10]. In both these series, as in our own, patients had very advanced disease refractory to cytotoxic and/or endocrine treatment.

From the current evidence, progestational agents can definitely be considered useful compounds in the treatment of advanced breast cancer, although the results obtained in our series do not support the idea that high IM doses of MPA are superior to conventional oral doses. The results available indicate that although CR is rare even after high doses of progestogens, useful PR can be achieved in postmenopausal women having soft tissue, pulmonary, pleural, and osseous involvement, even when patients have become refractory to prior hormone and cytotoxic therapies. This is of practical importance, while a more appropriate place for progestational agents in the palliative therapy of mammary carcinoma will probably be found when hormone receptors are available in all patients at the time of therapeutic decision.

Since treatment with progestogens, especially when administered at high doses, is expensive, a randomized trial with tamoxifen followed by a cross-over treatment upon failure appears to be indicated in postmenopausal women with positive receptors and no hepatic involvement. Such a study will also provide the opportunity to test the value of maintenance treatment in patients responding to MPA when given at 500 mg/day for 30 days. In premenopausal patients, the incidence of response reported by Pannuti et al. with 1500–2000 mg daily [14] is superior to that currently reported after castration. In addition, in this subgroup of patients a prospective controlled trial would allow a better definition of the relative merits of the two treatments.

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