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# Medroxyprogesterone Acetate and Prednisone in Advanced Breast Cancer. A Randomized Trial

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**Abstract**—*In a randomised trial patients with progressive metastatic breast cancer were allocated to one of three different treatments. A: Prednisone* 10 mg x 3 *daily. B: Medroxyprogesterone acetate (MPA) orally* 500 mg *daily. C: MPA i.m.* 1000 mg *daily for* 3 weeks *followed by* 500 mg *i.m. weekly. The study included* 150 *patients and was well-balanced with respect to different prognostic parameters. Most patients* (83%) *were postmenopausal, and* 95% *had previously received chemo- or hormonal therapy. In the MPA treated patients, analysis of serum MPA levels was performed once a month. The response rates were* 4.6, 7.9 *and* 12.5% *in treatments A, B and C, respectively. This difference was not statistically significant* ($P > 0.05$). *Furthermore, the follow-up of serum MPA levels revealed no significant difference between responders and non-responders. Analysis of time to progression did not indicate any advantage of MPA over prednisone, irrespective of MPA schedule. In accordance with these data, there was no difference as regards survival in the three groups. In conclusion, the study indicated that MPA is not superior to prednisone in this group of heavily pretreated patients with advanced breast cancer.*

## INTRODUCTION

METASTATIC breast cancer represents a therapeutic challenge as the patients at present cannot be offered curative treatment. Different chemotherapeutic regimens prolong the survival, but on progression, which inevitably occurs sooner or later, other treatment modalities should be considered. In this situation, hormonal manipulation offers an attractive second-line choice as the side effects are mostly small or negligible, a fact of utmost importance to these heavily pretreated patients.

Recent years have seen a considerable number of studies investigating the effect of medroxyprogesterone acetate (MPA) [1–5], but its role in the treatment of metastatic breast cancer has not yet been fully elucidated. Different treatment schedules and doses have been applied and response frequencies ranging from 9 to 54% have been reported [6]. There is still confusion as to the best route of administration, and the optimal dosage has not been determined. The same applies to the possible correlation between serum levels and response.

Most trials have only reported on the frequency of response and in fact it has not yet been proven that MPA prolongs the survival. This problem is important both from a clinical and an economic point of view as the MPA treatment is rather expensive in high dose schedules.

The main purpose of the present study was to compare the survival of patients treated by two different routes of MPA administration with patients given prednisone. A further objective was to analyse the possible correlation between serum MPA level and response.

## MATERIALS AND METHODS

Following informed consent 150 women with metastatic breast cancer entered the study between 1981 and 1984. The patients were randomly allocated to one of three different treatments,

A: Prednisone 10 mg orally × 3 daily.
B: MPA 500 mg orally × 1 daily.
C: MPA 1000 mg i.m. daily except Saturdays

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and Sundays for 3 weeks followed by 500 mg i.m. weekly.

Treatment continued till progression. The randomisation was balanced in blocks of 10 at the three participating centres (Aarhus, Herlev, Odense). The criteria for acceptance in the protocol were progressive metastatic breast cancer and a life expectancy of at least 3 months. Patients with brain metastases, diabetes or other diseases requiring hormonal treatment were ineligible for the study. The same applied to patients previously treated with prednisone or MPA.

The study was well-balanced in the three regimens with respect to different patient characteristics, including the dominant site of the disease (Table 1). It appears that 83% were postmenopausal. Most patients had previously received adjuvant radiotherapy (73%) or treatment with cytostatic drugs (72%) mostly in combination regimens. Hormonotherapy in the form of antiestrogen treatment had previously been given to 95% of the patients. The table also shows that 81% of the patients were ambulatory.

*Serum MPA*

Serum MPA levels were measured 2 and 4 weeks after start of treatment and then every 4th week in the treatment period. The method for analysis of MPA in serum by use of the RIA method is described in detail elsewhere [7].

*Response*

The response was evaluated after at least 2 months of treatment according to UICC criteria [8]. The study included both measurable and evaluable lesions. Twenty-one patients died within 2 months and consequently they were not accessible for assessment of response, another eight were not evaluable. However, the exclusion of these patients does not change the conclusions of the study. The time to progression was calculated from the day of entering the protocol.

*Survival*

All patients who entered the study were included in the analysis irrespective of time of death. The survival was calculated as Kaplan–Meyer plots and analysed for differences by the Mantel–Haenszel test by use of the BMDP program implemented on a CDC173 computer at the Regional EDP Centre at Aarhus University.

## RESULTS

Table 2 shows the response rate according to the dominant lesion site. The response frequencies were 12.5 in the MPA i.m. group compared with

*Table 1. Patient characteristics at protocol admission*

| | Regimen | | |
|---|---|---|---|
| | A | B | C |
| Total no. of patients | 52 | 48 | 50 |
| Menopausal status | | | |
| Premenopausal | 4 | 2 | 3 |
| Menopausal | 2 | 8 | 7 |
| Postmenopausal | 46 | 38 | 40 |
| Age (median) | 62 | 61 | 63 |
| Range | 38–80 | 38–77 | 36–79 |
| Disease-free interval (months) (median) | 23 | 24 | 27 |
| Previous treatment | | | |
| Radiotherapy | 40 | 36 | 34 |
| Chemotherapy | 33 | 37 | 38 |
| Hormonal therapy | 51 | 45 | 46 |
| Dominant site | | | |
| Viscera | 25 | 26 | 26 |
| Bone | 16 | 18 | 18 |
| Soft tissue | 11 | 4 | 6 |
| Performance score (ECOG) | | | |
| 0 | 16 | 16 | 20 |
| 1 | 18 | 19 | 11 |
| 2 | 8 | 5 | 9 |
| 3 | 3 | 6 | 5 |
| 4 | 2 | 0 | 2 |
| Not investigated | 5 | 2 | 3 |

*Table 2. Response rate according to regimen in 121 evaluable patients*

| | Regimen A No. | A % | B No. | B % | C No. | C % |
|---|---|---|---|---|---|---|
| CR | 1 | (2.3) | 1 | (2.6) | 3 | (7.5) |
| PR | 1 | (2.3) | 2 | (5.3) | 2 | (5.0) |
| NC | 19 | (44.2) | 11 | (28.9) | 17 | (42.5) |
| PD | 22 | (51.2) | 24 | (63.2) | 18 | (45.0) |
| Total no. | 43 | | 38 | | 40 | |

4.6% in the prednisone arm and 7.9% in the group treated with oral MPA. The difference is not significant (chi-square test). Further analysis of response rates at different lesion sites (soft tissue, bone, viscera) revealed the highest response rate in soft tissue. This applied to all three treatments, but no significant difference between them appeared, although the figures suggested a higher response rate in the MPA i.m. group, irrespective of lesion site.

The serum MPA concentration (Fig. 1) showed a high interindividual variation especially in the group treated with MPA orally, but there was no indication of a systematic difference between responders and non-responders. The serum level in the MPA i.m. group appeared more stable, but this group also failed to demonstrate any difference between the responders and non-responders. A more detailed analysis of serum MPA subsets revealed that the high serum levels (> 100 ng/ml) all belonged to non-responders except for one case.

The Kaplan–Meier plots in Fig. 2 illustrate the time to progression according to treatment. The median values were 3, 2, 5 and 4 months, respectively. The curves suggest a small advantage of MPA i.m. over the two other regimens, although the difference was not significant ($P = 0.09$) (Mantel–Haenzel test), but approx. 20% of the patients in this regimen were still progression-free at 1 yr on treatment.

Figure 3 depicts the crude survival in the three treatment groups. The plots suggest a worse course in the prednisone group as also indicated by the median values of 6 (5–7, 95% confidence limits) months in the prednisone group compared with 8.5 (6.5–10.5) and 10 (8–12) months in the two other groups. However, statistical analysis using the Mantel–Haenzel test revealed no significant difference ($P = 0.3\%$) and a very small fraction of long term survivors (> 2 yr) was found in all three groups.

All three regimens were well-tolerated and several patients reported a subjective improvement. The side-effects in 108 evaluable patients appear from Table 3. It should be noticed that treatment was not stopped because of side-effects in any case. The rather serious side-effect, gluteal abscess, reported in earlier studies was not observed in the

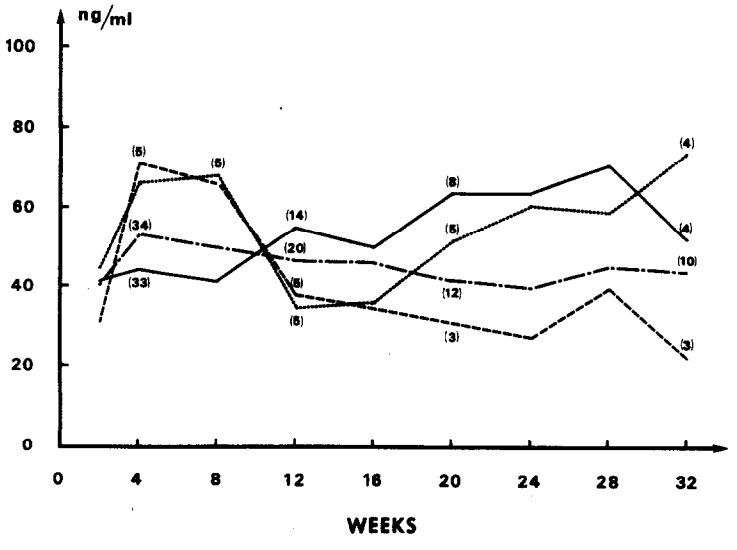


*Fig. 1. Serum MPA concentrations. The curves represent mean values. (——) MPA orally non-responders. (– – –) MPA orally responders. (— – —) MPA i.m. non-responders and (----) MPA i.m. responders. The number of patients is indicated in brackets.*

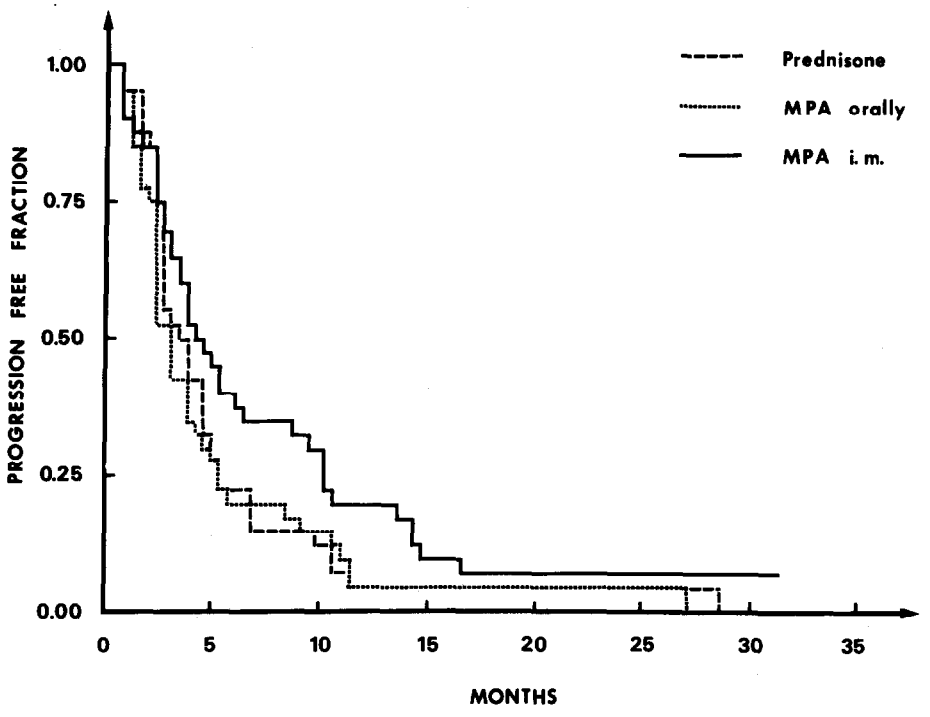


*Fig. 2. Time to progression according to treatment. The Kaplan–Meier plot represents 52, 48 and 50 patients, respectively. The difference is not significant ($P > 0.05$).*

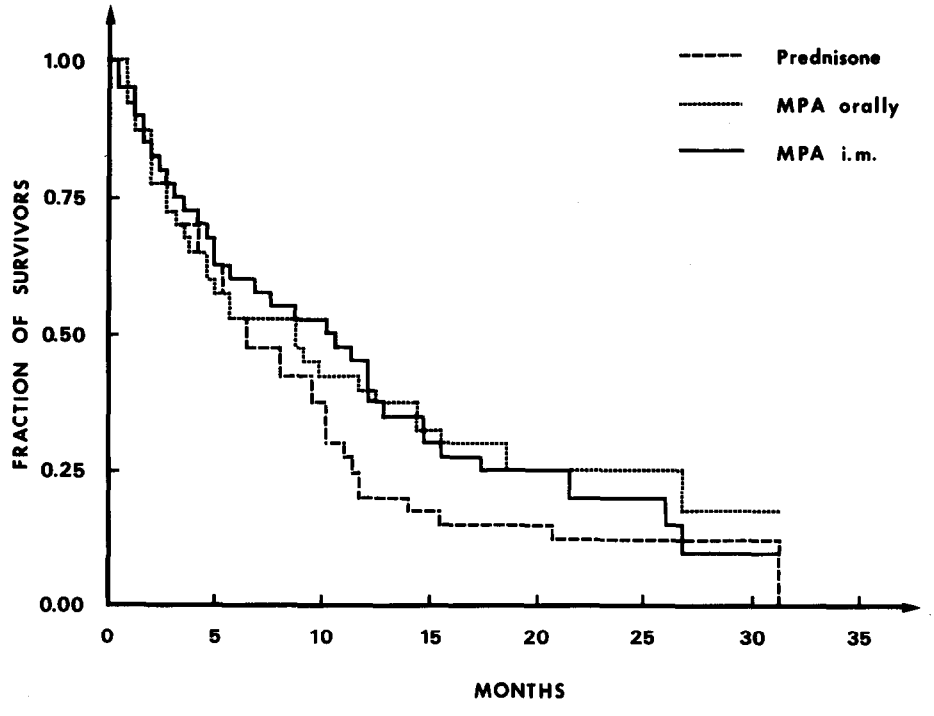


*Fig. 3. Survival of 150 patients according to treatment. The difference between the Kaplan–Meier plots is not significant ($P > 0.05$).*

MPA i.m. regimen, and no patients complained of pain at the injection site. The well-known prednisone side-effects (weight gain and moon face) were observed as expected in patients treated with this drug, but the same side-effects also appeared in patients given MPA, although at a lower frequency. Euphoria/dysphoria also occurred in all three groups.

*Table 3. Side effects*

| | Regimen A 37 patients | | B 36 patients | | C 35 patients | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Gluteal abscess | – | – | – | – | – | – |
| Moon face | 16 | (43.2) | 5 | (13.8) | 2 | (5.7) |
| Weight gain | 9 | (24.3) | 7 | (19.4) | 4 | (11.4) |
| Gastric intolerance | 4 | (10.8) | 6 | (16.6) | 1 | (2.8) |
| Euphoria/dysphoria | 2 | (5.4) | 1 | (2.7) | 3 | (8.5) |

## DISCUSSION

The current literature on MPA in advanced breast cancer is characterized by rather diverging results. Response rates of 40–50% have been reported by some authors [9, 10] but most studies have described a somewhat lower rate in the order of 30% [11–13]. A recent survey [6] has underlined the fact that the response rate seems to increase with a decreasing number of patients included in the study. An obvious explanation of the conflicting results is the diversity of patient selection, response criteria and previous treatment. Some studies lack information of these data as well as specification of dominant site of disease, which evidently hampers a precise evaluation of the results.

The present study included heavily pretreated patients and this fact may explain the low response rates. Another possible explanation may be that the dose of MPA was too low. This may be the case in orally treated groups, but the rather low response rate also observed in the patients treated with MPA i.m. is less likely to be explained by an inadequate dose. These patients received a sufficient loading dose for 3 weeks followed by maintenance therapy. Using almost the same dose schedule, Cavalli *et al.* [14] reported a response rate of 33%. However, in their material 18% of the patients had not previously received hormonal therapy compared with only 5% in our study.

The route of administration as well as the dosage may be important to the clinical effect. The i.m. route provides a stable plateau concentration due to the depot effect, whereas oral administration is associated with great fluctuations of serum level. However, interindividual variations are marked irrespective of administration route. In the present study, we found no significant difference in response rate neither between the two administration routes nor between the responders and non-responders, but the serum levels in the patients treated with MPA i.m. were somewhat lower than might be expected. The lack of difference between responders and non-responders is in accordance with the results described by Pannuti *et al.* [15] and raises the question of the mechanism of action. Recent investigations by Blossey *et al.* [16] and Van Veelen *et al.* [17] have indicated that the drug suppresses the pituitary adrenal axis. If this mechanism is important to the effect, high interindividual variations of serum levels sufficient to provide this blockage are to be expected and may explain the lack of correlation between clinical response and serum level.

Although high dose MPA may ensure a higher response rate than conventional dose regimens, the advantage of high MPA dose in terms of survival has not been established. On the contrary, the randomised study by Cavalli *et al.* [14] indicated no significant difference in survival between high and low dose schedules. The present study confirms these results and questions the advantage of MPA over prednisone. This also applies to the subjective improvement which was described by many patients in both the MPA and prednisone groups. The latter drug may have some serious side-effects which, however, were not observed in the present study.

An objection to the present study may be that the patients were heavily pretreated and that a low response rate and poor survival therefore could be expected on any treatment. However, in our opinion MPA is not the drug of first choice in metastatic breast cancer, and this also applies to postmenopausal women. Pretreated patients thus appear to be the target population for such treatment and they should consequently be included in clinical trials to define the proper role of MPA in metastatic breast cancer. The present study showed no advantage of MPA compared to prednisone which can be given at a much lower cost.

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