ONCOLOGY

Oncology 1999;56:283–290

# A Randomized Controlled Comparative Study of Oral Medroxyprogesterone Acetate 1,200 and 600 mg in Patients with Advanced or Recurrent Breast Cancer

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Study Group for the Chemo-Endocrine Therapy of MPA for Breast Cancer

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**Key Words**
Dose comparison study · Randomized controlled trial · Breast cancer, advanced or recurrent · Medroxyprogesterone acetate

**Abstract**
A randomized controlled comparative study of oral medroxyprogesterone acetate (MPA) 1,200 mg (arm I) and 600 mg (arm II) was conducted in 80 patients with advanced or recurrent breast cancer. There were no significant differences between arm I and arm II in terms of response rate, duration of response and survival, or in terms of incidence and severity of adverse reactions. The lowest serum MPA concentration in responders tended to be higher than that in nonresponders. In the cohort of this study, the lowest concentration in partial response was 17.4 ng/ml, suggesting that this level may be the required minimum serum concentration.

## Introduction

Medroxyprogesterone acetate (MPA) is a progesterone analogue synthesized in 1958. MPA is characterized not only by its excellent direct effect on tumors such as breast and endometrial cancer, but also by its favorable effects, such as improvement of performance status and stimulation of appetite [1]. Pannuti et al. [2] first reported the clinical activity of MPA in breast cancer in the 1970s. The usefulness of this agent in single use and in combination chemotherapy has since been confirmed [3, 4].

In clinical studies carried out in Europe and the US a wide range of daily dosages of MPA (500–3,000 mg) was used, but the optimal dosage has yet to be defined [5]. A dose comparison study conducted in Japan at the dosage range of 600–2,400 mg documented a higher response rate in the 1,200-mg group compared with the lower and higher dosage groups [6]. These results cannot be regarded as confirmatory, however, as this was not a randomized controlled study. Other studies subsequently reported

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0030–2414/99/0564–0283$17.50/0

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was obtained with MPA at dosages of 600 and 800 mg and suggested that lower dosages be considered to minimize the risk of adverse events [7–9].

The aim of the present multicenter randomized controlled study was to compare the clinical efficacy of MPA 1,200 and 600 mg in patients with advanced or recurrent breast cancer.

## Patients and Methods

*Patients*

The study was performed in 34 centers in Japan (Appendix 1) between January 1992 and June 1993. Patients included in the study were females with advanced or recurrent breast cancer and with measurable or evaluable lesions who had not received previous treatment, who had failed to respond to previous treatment or who were unaffected by previous treatment. Patients who had undergone surgery within 1 month before the start of study or those with complications or a past history of hypertension, diabetes or arteriosclerosis were excluded, because they were considered at high risk for MPA-induced thrombosis.

*Methods*

Patients were registered over the telephone by a central registration method and were randomly assigned to treatment groups at the Case Registration Center. Prior to case registration, details of treatment were fully explained to patients or their families and informed consent was obtained either verbally or in writing.

Patients received oral therapy with MPA at a dosage of either 1,200 mg/day (arm I) or 600 mg/day (arm II) for as long as possible with the aim of continuing administration beyond 12 weeks. Therapeutic efficacy was assessed in accordance with the Standards for Assessment of the Therapeutic Effects in Advanced and Recurrent Breast Cancer Patients (Japan Breast Cancer Society, 1992) and the Criteria for the Evaluation of the Clinical Effects of Solid Cancer Chemotherapy (Japan Society for Cancer Therapy, 1986). These criteria are essentially the same as the WHO criteria except for minor revisions made for Japanese patients. Assessment of the effect was reviewed extramurally by an evaluation committee organized by members of the protocol committee.

Duration of survival and treatment response were assessed at final follow-up made in June 1996. The median duration from case registration to the end of follow-up was 201.4 weeks. Serum concentrations of MPA were measured by high-performance liquid chromatography [10] at 8 weeks after the start of the treatment. Plasma cortisol levels were measured before the start of the treatment and at 8 weeks thereafter.

To test for blood coagulation and fibrinolytic activity, the fibrin degradation products D-dimer, $\alpha_2$-plasmin inhibitor plasmin complex, antithrombin III, protein C and plasminogen activator inhibitor I were measured before the start of the treatment and 2, 4, 8, 12 weeks after the start of the treatment.

*Patient Eligibility*

Of the 80 patients registered in the study, 10 were considered ineligible for inclusion, because of an insufficient duration of with-

| | Arm I (n = 37) | Arm II (n = 32) | Total (n = 70) | p value ($\chi^2$ test) |
|---|---|---|---|---|
| Mean age, years | 55.6 | 55.9 | 55.8 | 0.9340[a] |
| Menopausal status | | | | |
| Pre | 8 | 8 | 16 | 0.6777 |
| Peri | 3 | 5 | 8 | |
| Post | 20 | 17 | 37 | |
| Castrated | 6 | 3 | 9 | |
| Advanced/recurrent | | | | |
| Advanced | 4 | 3 | 7 | 0.9999 |
| Recurrent | 33 | 30 | 63 | |
| Disease-free interval, years | | | | |
| 0 | 4 | 3 | 7 | 0.7123 |
| <1 | 3 | 6 | 9 | |
| <2 | 10 | 9 | 19 | |
| <3 | 6 | 3 | 9 | |
| ≥3 | 14 | 12 | 26 | |
| Histology | | | | |
| Pap. tub. | 10 | 9 | 19 | 0.6446 |
| Solid tub. | 6 | 4 | 10 | |
| Scirrhous | 15 | 17 | 32 | |
| Others | 4 | 3 | 7 | |
| Unknown | 2 | 0 | 2 | |
| Site | | | | |
| Breast | 2 | 2 | 4 | 0.7874 |
| Skin and subcutaneous | 7 | 9 | 16 | |
| Lymph node | 12 | 8 | 20 | |
| Lung | 6 | 6 | 12 | |
| Pleura | 9 | 3 | 12 | |
| Liver | 2 | 2 | 4 | |
| Bone | 19 | 16 | 35 | |
| Number of sites | | | | |
| 1 | 23 | 22 | 45 | 0.5819 |
| 2 | 9 | 9 | 18 | |
| ≥3 | 5 | 2 | 7 | |
| ER | | | | |
| + | 18 | 18 | 36 | 0.7180 |
| – | 8 | 8 | 16 | |
| Unknown | 11 | 7 | 18 | |
| PgR | | | | |
| + | 10 | 13 | 23 | 0.4824 |
| – | 10 | 6 | 16 | |
| Unknown | 17 | 14 | 24 | |
| PS | | | | |
| 0 | 22 | 21 | 43 | 0.4296 |
| 1 | 8 | 10 | 18 | |
| 2 | 1 | 1 | 2 | |
| 3 | 4 | 1 | 5 | |
| 4[b] | 2 | 0 | 2 | |
| Previous treatment | | | | |
| Yes | 21 | 19 | 40 | 0.9999 |
| Chemotherapy | 4 | 3 | 7 | |
| Chemotherapy + Endo. | 13 | 11 | 24 | |
| Endo. | 4 | 5 | 9 | |
| No | 16 | 14 | 30 | |

ER = Estrogen receptor status; PgR = progesterone receptor status; PS = performance status; Endo = endocrine therapy.

[a] t test.

[b] Pain because of bone metastases.

| | CR | PR | NC | PD | CR + PR | p value ($\chi^2$ test) |
|---|---|---|---|---|---|---|
| Arm I | 0 | 6 | 12 | 13 | 6/31 (19.4, 7.5–37.5) | 0.9999 |
| Arm II | 3 | 3 | 10 | 12 | 6/28 (21.4, 8.3–41.0) | |

Figures in parentheses represent percentage followed by 95% confidence interval.

drawal from previous therapy (2 patients), previous radiotherapy (4 patients), bone lesion not identified as metastatic from breast cancer (1 patient), active double cancer (1 patient), complication with hypercalcemia and performance status 4 (1 patient) and previous treatment with MPA (1 patient). Of the remaining 70 eligible cases, 59 were judged as 'complete' and 11 as 'incomplete'. Incomplete cases included 1 patient who was diagnosed as having a venous return disorder during MPA administration and whose treatment was discontinued (discontinuation case), 2 patients with protocol violation and 2 patients lost to follow-up (dropout cases), and 6 patients whose bone lesions were inadequately studied with x-ray (incomplete observation cases). The response rate and duration of survival were assessed in all complete cases. Adverse reactions were assessed in all evaluable cases (i.e. complete cases, discontinued cases and incomplete observation cases).

*Patient Details*

The demographic characteristics of the eligible patients are shown in table 1. There were no significant differences between treatment groups in terms of age, menopausal status, advanced or recurrent cancer, disease-free interval, histology, sites of tumor, number of tumor sites, estrogen receptor status, progesterone receptor status, performance status or numbers of patients with or without previous treatment.

*Statistics*

Demographic characteristics, tumor response rate and the incidence of adverse reactions were compared between treatment groups by the $\chi^2$ test, t test and Fisher's direct probability test. Duration of response and survival were compared by the generalized Wilcoxon test and log-rank test.

## Results

*Therapeutic Results*

Response rates for complete cases are given in table 2. The response rate [complete response (CR) + partial response (PR)] was 19.4% (6/31) in arm I and 21.4% (6/28) in arm II, with no significant differences noted between the two treatment groups. By comparison, the response rate for 70 eligible cases was 16.2% (6/37) in arm

ences were noted between treatment groups.

There were no significant differences between the two treatment groups in terms of the response rate as a function of tumor sites (table 3). CRs were obtained in the breast and lymph node only in arm I patients, while CRs were obtained in the skin and subcutaneous tissue only in arm II patients. PRs in the pleura occurred only in arm I patients.

The median overall duration of response was 66.9 weeks (range 23.6–106.1) in arm I and 46.0 weeks (range 24.6–120.6) in arm II, and there were no significant differences between the two treatment groups. Kaplan-Meier survival curves initiated from the start of treatment showed no significant differences in survival between the two treatment groups (fig. 1).

*Adverse Events*

The incidences and types of adverse events occurring during the study were similar irrespective of MPA dosage and, again, no significant differences were noted between treatment groups (table 4). MPA treatment was discontinued in 1 patient receiving 1,200 mg/day because of tenderness and purple coloration of the limbs; a venous return disorder was subsequently diagnosed at the vascular surgery department.

*Laboratory Results*

There was a considerable interpatient variation in serum concentrations of MPA in both of the treatment groups. Nevertheless, the median serum concentration of MPA was nearly 2-fold higher in arm I compared with arm II (63.5 vs. 35.9 ng/ml; fig. 2a). Median serum MPA concentrations by response were 49.7 ng/ml in CR, 47.2 ng/ml in PR, 56.9 ng/ml in no change (NC) and 39.0 ng/ml in progressive disease (PD), showing no significant difference between responders (CR + PR) and nonresponders (NC + PD) (fig. 2b). The lowest serum MPA concentrations by response were 44.4 ng/ml in CR, 17.4 ng/ml in PR, 22.0 ng/ml in NC and 8.0 ng/ml in PD.

Plasma cortisol levels decreased after MPA administration in nearly all patients in both treatment groups (fig. 3). However, there was no correlation between the extent of this decrease and the antitumor effect of MPA. Levels of antithrombin III and protein C increased significantly in both treatment groups, but there were no significant changes in other test items of blood coagulation and the fibrinolytic system.

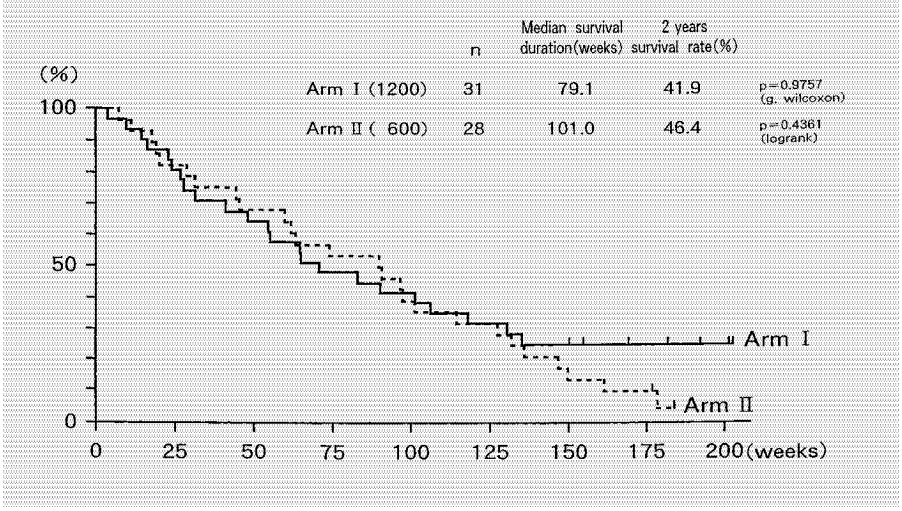


**Fig. 1.** Survival curves. The cumulative survival rates are shown by the Kaplan-Meier method. —— = Cumulative survival rate of arm I; – – – = cumulative survival rate of arm II.

**Table 3.** Response rates as a function of tumor site (complete cases)

| | CR | PR | NC | PD | CR + PR | p value ($\chi^2$ test) |
|---|---|---|---|---|---|---|
| Breast | | | | | | |
| Arm I | 1 | 0 | 1 | 0 | 1/2 (50.0, 1.3–98.7) | 1.000 |
| Arm II | 0 | 1 | 0 | 1 | 1/2 (50.0, 1.3–89.7) | |
| Skin and subcutaneous tissue | | | | | | |
| Arm I | 0 | 1 | 4 | 2 | 1/7 (14.3, 0.4–57.9) | 0.3602 |
| Arm II | 3 | 1 | 2 | 2 | 4/8 (50.0, 15.7–84.3) | |
| Lymph node | | | | | | |
| Arm I | 2 | 2 | 4 | 3 | 4/11 (36.4, 10.9–69.2) | 0.6314 |
| Arm II | 0 | 1 | 4 | 2 | 1/7 (14.3, 0.4–57.9) | |
| Lung | | | | | | |
| Arm I | 0 | 1 | 2 | 3 | 1/6 (16.7, 0.4–64.1) | 0.9999 |
| Arm II | 0 | 1 | 2 | 1 | 1/4 (25.0, 0.6–80.6) | |
| Pleura | | | | | | |
| Arm I | 0 | 2 | 4 | 3 | 2/9 (22.2, 2.8–60.0) | 0.999 |
| Arm II | 0 | 0 | 1 | 2 | 0/3 (0.0, 0.0–70.8) | |
| Liver | | | | | | |
| Arm I | 0 | 0 | 1 | 0 | 0/1 (0.0, 0.0–70.8) | – |
| Arm II | 0 | 0 | 0 | 1 | 0/1 (0.0, 0.0–70.8) | |
| Bone | | | | | | |
| Arm I | 0 | 2 | 8 | 3 | 2/13 (15.4, 1.9–45.5) | 0.9999 |
| Arm II | 0 | 1 | 5 | 4 | 1/10 (10.0, 0.3–44.5) | |

Figures in parentheses represent percentage followed 95% confidence interval.

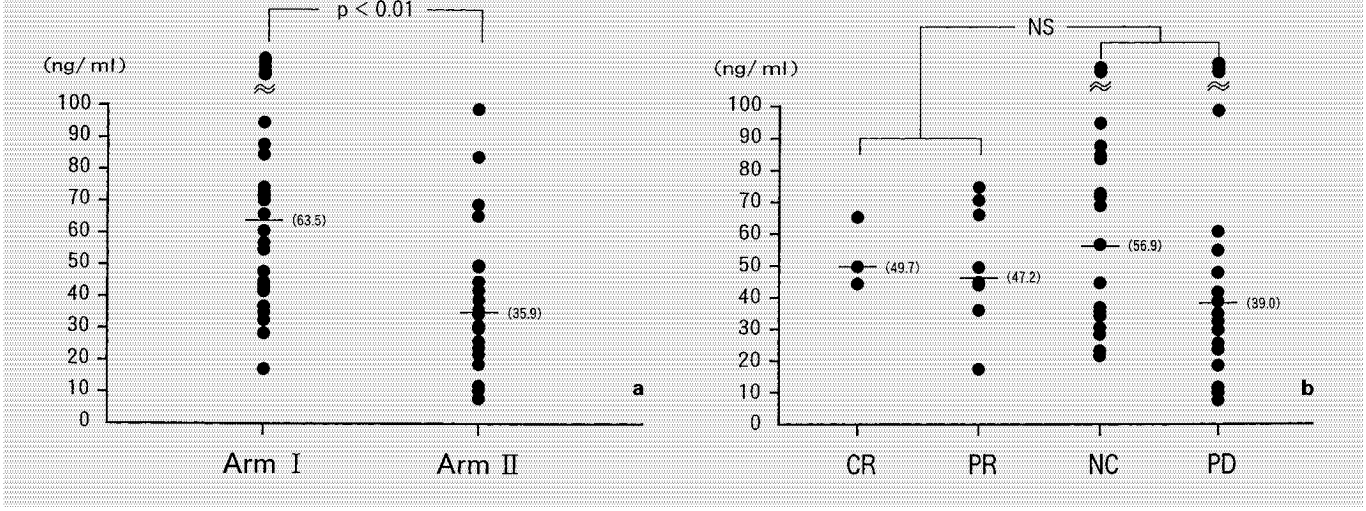


**Fig. 2.** Serum MPA concentration 8 weeks after the start of the treatment. **a** Concentration by arm. **b** Concentration by response.

## Discussion

A multicenter randomized controlled trial was conducted to compare the efficacy and safety of MPA at dosages of 1,200 and 600 mg/day in patients with advanced or recurrent breast cancer.

There were no differences noted in this study between the two dosage groups in terms of the response rate to MPA treatment (arm I: 19.4%; arm II: 21.4%). These results correspond with findings obtained in other dose comparison studies performed elsewhere. For example, no significant differences in response rates were reported by Hortobagyi et al. [11] at MPA dosages of 800 and 400 mg, by Gallagher et al. [12] at dosages of 1,000 and 300 mg, by Davila et al. [13] at dosages of 800 and 400 mg, and by Langecker et al. [14] at dosages of 1,400 and 400 mg [14]. Enomoto et al. [15] reported that the response rate of MPA 1,200 mg was somewhat superior to 600 mg but there were no significant differences between the two doses in combination with cyclophosphamide and epirubicin. Ganzina [16] reported that the response rate in patients treated with MPA at 200 mg or less was 17% and thus concluded that so-called 'low dose MPA therapy' cannot achieve a satisfactory response rate. However, 'high dose MPA therapy' using higher doses appears to produce no marked difference in the response rate of different doses.

CR was obtained in the skin in the MPA 600-mg treatment group (3 responses), and in the breast (1 response) and lymph node (2 responses) in the 1,200-mg treatment

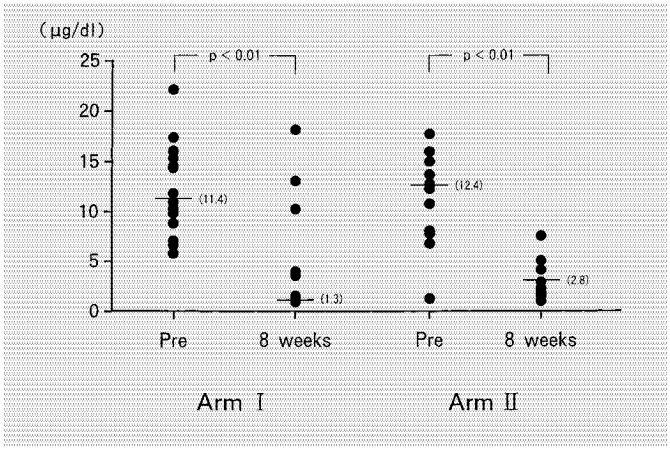


**Fig. 3.** Plasma cortisol concentration before the start of the treatment and 8 weeks later.

**Table 4.** Adverse events (evaluable patients)

| Adverse event | Arm I | Arm II | p value ($\chi^2$ test) |
|---|---|---|---|
| Increase in body weight | 12/36 (33) | 12/30 (40) | 0.8546 |
| Increase >5 kg | 6/36 (16.7) | 4/30 (13.3) | |
| Vaginal bleeding | 4/36 (11) | 6/30 (20) | 0.5105 |
| Moon face | 7/36 (19) | 4/30 (13) | 0.7831 |
| Edema | 4/36 (11) | 2/30 (7) | 0.8224 |
| Total | 22/36 (61) | 18/30 (60) | 0.9999 |

Figures in parentheses represent percentage.

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