

Medroxyprogesterone Acetate Treatment Reduces Serum Interleukin-6 Levels in Patients with Metastatic Breast Carcinoma

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BACKGROUND. The serum interleukin (IL)-6 concentration was very low in patients with metastatic breast carcinoma who had received oral medroxyprogesterone acetate (MPA) treatment as compared with those who had not. Accordingly, the authors conducted a prospective study to determine whether MPA treatment reduces the serum level of IL-6 in patients with this disease.

METHODS. In 21 consecutive Japanese patients who were scheduled to receive oral MPA treatment at doses of 600, 800 or 1200 mg/day, serum concentrations of IL-6 were determined with a sensitive enzyme-immunoassay prior to the administration of MPA and again at 4 weeks after the treatment was started. In addition, plasma levels of MPA were determined by high-performance liquid chromatography (HPLC).

RESULTS. Four weeks after the oral MPA therapy was started, serum IL-6 levels decreased in all 21 patients regardless of whether or not they responded to the treatment. Although the extent of decrease in the serum IL-6 (Δ IL-6) did not correlate with the daily dose of MPA, it correlated closely with the plasma MPA level in these patients. Subjective improvement in appetite and weight gain were more frequent in the Δ IL-6 > 3 pg/mL group compared with the Δ IL-6 \leq 3 pg/mL group (80% vs. 45% and 70% vs. 45%, respectively). Similar results were obtained for improvement in patients' sense of well-being (100% vs. 55%).

CONCLUSIONS. Oral MPA treatment reduces serum IL-6 concentration in patients with metastatic breast carcinoma, but the decrease is not associated with response to MPA. This observation may indicate a potential of this agent for producing subjective improvement. *Cancer* 1996; 78:2346-52. © 1996 American Cancer Society.

KEYWORDS: breast carcinoma, medroxyprogesterone acetate, serum interleukin-6.

Medroxyprogesterone acetate (MPA) is a well-established therapeutic agent for patients with metastatic breast carcinoma. This agent is a synthetic steroid derived from progesterone and has marked progestogenic activity in both animals and humans. High dose oral MPA is effective, with an overall remission rate of 40% or greater in metastatic breast carcinoma patients.¹⁻² It has also been shown that only high plasma levels of MPA are likely to induce tumor regression.³ However, the mechanism for the antitumor activity of MPA is still controversial and appears to be complex. A decrease in the concentration of the estrogen receptor (ER) and the estrogen-binding capacity of the ER after MPA treatment would be expected to make the estrogen-targeted tissues less responsive to estrogen.⁴⁻⁵ Furthermore, MPA has suppressive effects on the hypothalamo-pituitary-adrenal (HPA) axis, and the antitumor activity of MPA has been correlated with the extent of endogenous

cortisol suppression and subsequent estrogen deprivation in patients with metastatic breast carcinoma.⁶⁻⁸ However, the mechanism underlying this effect of MPA is not known.

Cancer patients with progressive disease frequently complain of unexplained fever and weight loss. Some become so emaciated that their deaths appear to be caused primarily by cachexia. These clinical features generally indicate a poor prognosis. The mechanisms that underlie this complex syndrome of nutritional and metabolic disorders are poorly understood. Interleukin (IL)-6 is a multipotent cytokine that initiates numerous biologic activities. This cytokine has recently been implicated in disease processes such as those just mentioned.⁹⁻¹¹ For example, the serum levels of IL-6 are elevated in patients with lymphoma, and there is an association between endogenous overproduction of IL-6 and the presence of B symptoms.¹² In metastatic renal cell carcinoma, the serum IL-6 levels are increased as compared with normal individuals, and elevated serum IL-6 levels are an adverse prognostic factor in patients with this disease.¹³

During an investigation into the serum levels of IL-6 in patients with metastatic breast carcinoma, we noticed that serum IL-6 concentration was extremely low in patients who had received oral MPA treatment as compared with those who had not. On the basis of this preliminary observation, we conducted a prospective study to determine whether MPA treatment reduces the serum level of IL-6 in patients with this disease.

PATIENTS AND METHODS

Patient Population

Twenty-one patients with histologically confirmed metastatic breast carcinoma who were scheduled to receive oral MPA treatment participated in this study. All patients had previously received tamoxifen therapy, and four also received 5-fluorouracil (Table 1). MPA was administered as second-line hormonal therapy to these patients without any other anticancer or endocrine agents (a daily dose of 600, 800, or 1200 mg was assigned randomly), and the clinical results were evaluated 4-8 weeks after the start of the treatment on the basis of standard Eastern Cooperative Group criteria.¹⁴ A complete response (CR), defined briefly, was the complete disappearance of all evidence of disease. A partial response (PR) was defined as a decrease of 50% or greater in the sum of the products of the two greatest dimensions of measurable lesions. No change (NC) was defined as a decrease in tumor size of less than 50%, no change, or an increase of less than or equal to 25%. Progressive disease (PD) was defined as an increase of greater than 25% in the size of any

measurable lesion. The appearance of a new lesion was always considered to be evidence of PD.

All patients also underwent weekly assessment of body weight with the same printing scale. In addition, the toxic effects of the treatment, its influence on appetite, and the subjective improvement in patients' sense of well-being were determined by a questionnaire. This study was approved by Kamamoto University Institutional Ethics Committee, and informed consent was obtained from each patient.

Blood Sampling and Storage

Blood samples were taken from the antecubital vein before the administration of MPA and again at 4 weeks after the beginning of MPA therapy. The serum and plasma samples were stored at -70 °C until the assays were performed.

Determination of Serum IL-6

Serum IL-6 concentration was measured with a commercially available enzyme-immunoassay (Cytoscreen, BioSource International, Camarillo, CA) according to the manufacturer's recommended protocol. This is a sensitive assay; the minimal detectable dose of IL-6 is 0.104 pg/mL. When the concentration of a sample was greater than the upper limit of the standard curve (>10 pg/mL), it was diluted with a standard dilution buffer. The intra-assay coefficients of variation (CV) for the high, middle, and low sample levels were 4.3%, 6.6%, and 8.2%, respectively. The interassay CV for the high, middle, and low sample levels were 5.4%, 7.5%, and 9.2%, respectively.

As a control, we measured the serum IL-6 concentration in 22 blood samples from apparently healthy, normal Japanese women. The mean value obtained was 1.24 ± 0.17 pg/mL (mean \pm standard error [SE]; range, 0.11 to 3.5 pg/mL).

Determination of Plasma MPA

Blood samples for the MPA measurement were taken again at 4 weeks after the start of therapy because previous reports had indicated that the steady state is achieved after 2 to 3 weeks of daily oral MPA administration.¹⁵ The plasma MPA concentration was determined by a high-performance liquid chromatography method, described previously.¹⁶ The antibody used was kindly provided by the Kyowa Hakko Kogyo Company, Tokyo, Japan.

Statistics

All data are expressed as the mean \pm SE. For comparing differences in the serum IL-6 concentration between two different groups, the nonparametric Wilcoxon signed rank test was used. The correlation coef-

TABLE 1
Clinical Characteristics of 21 Patients with Metastatic Breast Carcinoma Receiving Oral Medroxyprogesterone Acetate Treatment

Patient no.	Age (yrs)	Major site of metastasis	Preceding agents	Daily dose of MPA	Serum IL-6 (pg/mL)		Δ IL-6 (pre-post)	Plasma MPA (ng/mL) (post)	Outcome
					Pre	Post			
1	53	Lung, liver	TAM	1200	42.2	8.6	33.6	116	PD
2	75	Bone, ax node	TAM	1200	12.21	4.81	7.4	76	NC
3	64	Lung	TAM, 5-FU	1200	9.56	9.17	0.39	41	PR
4	45	SC node	TAM	1200	8.71	7.59	1.12	61	CR
5	44	Lung	TAM	1200	7.24	2.72	4.52	97	NC
6	56	SC node, lung	TAM	1200	4.82	2.13	2.69	56	NC
7	58	Bone	TAM	1200	3.57	2.18	1.39	73	NC
8	65	Lung	TAM	800	14.12	3.2	10.92	108	PR
9	65	SC node	TAM	800	10.9	2.41	8.49	125	PD
10	35	Lung, bone	TAM	800	7.91	6.59	1.32	53	NC
11	48	Lung	TAM, 5-FU	800	5.86	0.95	4.91	77	NC
12	60	Bone	TAM, 5-FU	800	5.68	3.02	2.66	59	NC
13	51	Lung	TAM	800	4.42	1.32	3.1	85	PR
14	50	Lung, ax node	TAM	800	3.75	3.19	0.56	32	PD
15	72	Lung, liver, ax node	TAM, 5-FU	600	30.34	28.74	1.6	64	NC
16	35	Lung	TAM	600	13.31	2.62	10.69	92	PR
17	44	Bone	TAM	600	9.02	2.71	6.31	106	PD
18	48	SC node	TAM	600	4.67	4.38	0.29	36	PR
19	57	Bone	TAM	600	4.13	0.63	3.5	80	PR
20	43	SC node, ax node	TAM	600	2.23	0.24	1.99	41	PR
21	60	Bone	TAM	600	1.94	0.78	1.16	52	NC

MPA: medroxyprogesterone acetate; Ax node: contralateral axillary lymph node; SC node: supraclavicular lymph node; TAM: tamoxifen; 5-FU: 5-fluorouracil; PD: progressive disease; NC: no change; PR: partial response; CR: complete response; IL-6: interleukin-6; Δ IL-6: difference between pre- and posttreatment levels of serum IL-6 in each patient; Pre: before beginning of MPA treatment; Post: 5 weeks after beginning of treatment.

ficients were calculated by linear regression analysis. Two-sided *P* values below 0.05 were regarded as statistically significant.

RESULTS

Influence of MPA Treatment on Serum Levels of IL-6

The pretreatment serum IL-6 level of 21 patients with metastatic breast carcinoma was 9.83 ± 2.10 pg/mL. This value was significantly higher than that for normal individuals (1.24 ± 0.17 , $P = 0.0002$). As shown in Table 1 and Figure 1, the serum IL-6 concentrations decreased 4 weeks after the beginning of MPA treatment in all 21 patients, regardless of whether they responded (CR or PR) or not (NC or PD) to the therapy. The mean serum IL-6 level was significantly lower in the posttreatment samples (4.66 ± 1.33) than in the pretreatment samples (9.83 ± 2.10 , $P = 0.044$). Nevertheless, the mean posttreatment level was significantly higher than that for normal individuals (1.24 ± 0.17 , $P = 0.012$).

Correlation between Serum IL-6 and Plasma MPA

Figure 2 shows the correlation between the decrease in the serum IL-6 concentration (Δ IL-6 =

$[\text{IL-6}_{\text{pretreatment}}] - [\text{IL-6}_{\text{posttreatment}}]$) and the daily oral dose of MPA. The decrease in the serum IL-6 concentration (Δ IL-6) tended to be greater in the 1200 mg group (7.30 ± 4.48) than in the 600 mg group (3.65 ± 1.39) or the 800 mg group (4.56 ± 1.45), although the differences were not statistically significant. However, a highly significant correlation was found between the extent of reduction in the serum IL-6 (Δ IL-6) levels and the plasma concentrations of MPA (r [correlation coefficient] = 0.668, $P = 0.0009$) (Fig. 3).

Correlation between Serum IL-6 and Patient Parameters

Of the 21 patients, 13 (62%) had a subjective improvement in appetite, and 12 (57%) experienced more than 2 kg weight gain (range, 2.2–3.8 kg). Sixteen of the 21 patients (76%) had a subjective improvement in their sense of well-being. Table 2 shows the correlation between the decrease in serum IL-6 (Δ IL-6) levels and the improvements in these patient parameters after 4 weeks of MPA therapy. The respective results for the patients who exhibited Δ IL-6 ≤ 3 pg/mL ($n = 11$) and Δ IL-6 > 3 pg/mL ($n = 10$) were as follows: improvement in appetite, 45% and 80%; weight gain (> 2 kg),

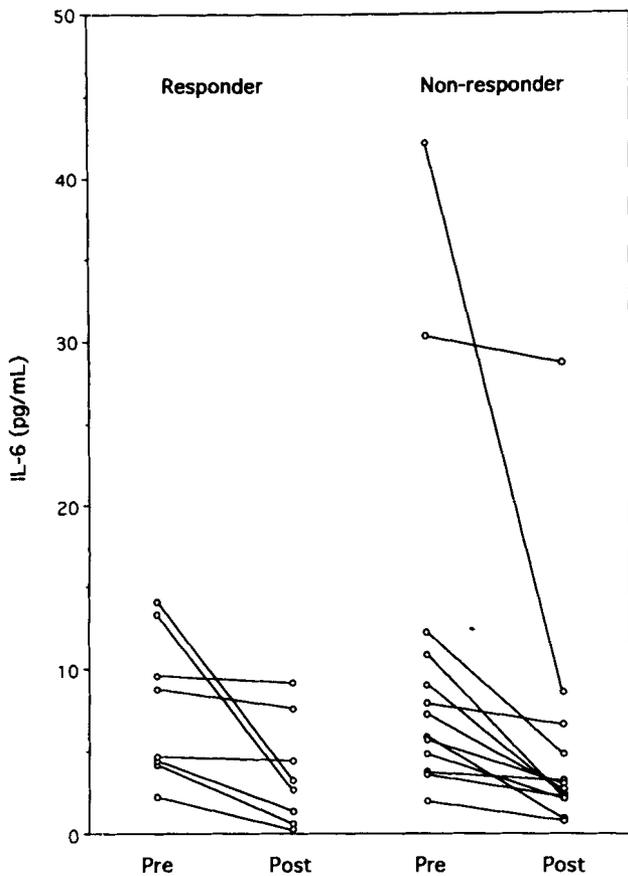


FIGURE 1. Changes are shown in the serum levels of interleukin (IL)-6 between the pretreatment and posttreatment samples on an individual basis in the responder and nonresponder groups of patients. The posttreatment serum IL-6 levels were measured in the serum samples obtained 4 weeks after the start of medroxyprogesterone acetate treatment. The responder group comprised the patients who exhibited either complete or partial response, and the nonresponder group comprised the patients who had either no change or progressive disease.

45% and 70%; and improvement in sense of well-being, 55% and 100%.

DISCUSSION

The serum IL-6 levels in patients with metastatic breast carcinoma were considerably higher than those in normal individuals. It is still unclear what is responsible for this increase in the serum IL-6 in patients with metastatic breast carcinoma. Constitutive IL-6 production has been demonstrated in a variety of tumor cells, including breast carcinoma cells.¹⁷⁻²¹ Stromal and inflammatory cells activated within the tumor, such as macrophages, monocytes, neutrophils, fibroblasts, and endothelial cells, may also produce enough IL-6 to increase serum IL-6 levels.²² Such local production of IL-6 may be responsible for the increase

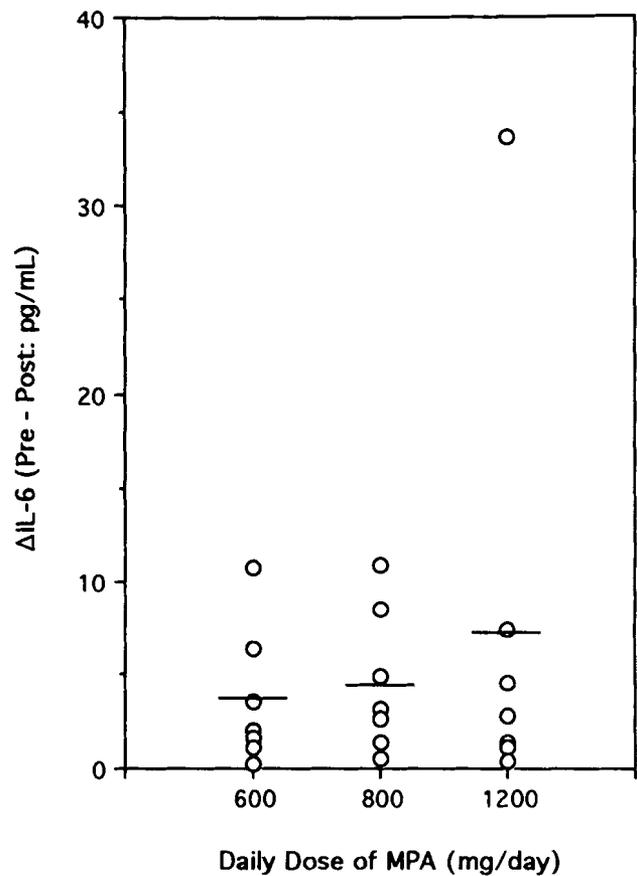


FIGURE 2. The correlation is shown between the decrease in the serum interleukin (IL)-6 levels and the daily oral dose of medroxyprogesterone acetate (MPA). The difference between the basal and posttreatment levels of serum IL-6 in each patient (Δ IL-6) was plotted as a function of the daily dose of MPA. The horizontal line represents the mean level of Δ IL-6 in each dosage group.

in the circulating IL-6 levels in patients with metastatic breast carcinoma. In fact, our previous study demonstrated that tumor tissue extracts from patients with advanced breast carcinoma contained a significantly larger amount of IL-6 than those from patients with early stage disease or normal mammary glands.²³

This prospective study clearly demonstrated that the oral administration of MPA reduces the serum level of IL-6. The decrease in the serum IL-6 concentration was observed not only in patients who responded to the therapy but also in those who did not, indicating that the decrease in the serum IL-6 concentration was not due to disease improvement. Rather, it is more reasonable to postulate that the decrease in the serum IL-6 is attributable to a direct pharmacologic effect of MPA. This is further supported by the findings of the current study that the extent of decrease in the serum IL-6 concentration correlates with

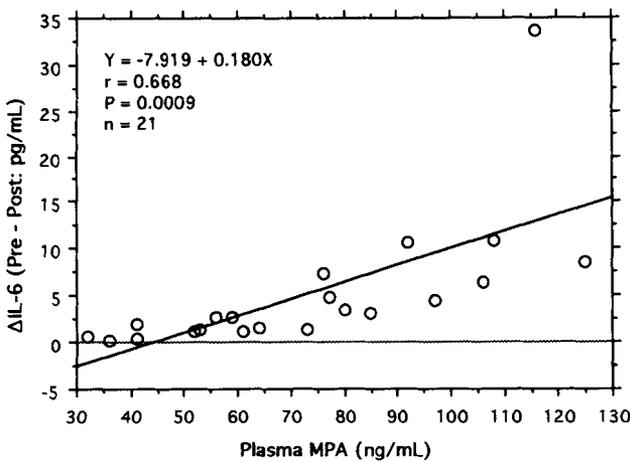


FIGURE 3. The correlation is shown between the decrease in the serum interleukin (IL)-6 levels and the plasma concentration of medroxyprogesterone acetate (MPA). The difference between the basal and posttreatment levels of serum IL-6 in each patient (Δ IL-6) was plotted as a function of the plasma concentration of MPA. Y: coordinate axis; r: correlation coefficient; n: number of patients.

TABLE 2
Correlation between the Decrease in the Serum Interleukin-6 Levels and Study Parameters for Patients with Metastatic Breast Carcinoma

Study parameters	No. of patients (%)	
	Δ IL-6 \leq 3 pg/mL (n = 11)	Δ IL-6 > 3 pg/mL (n = 10)
Improvement in appetite	5 (45)	8 (80)
>2.0 kg weight gain	5 (45)	7 (70)
Improvement in sense of well-being	6 (55)	10 (100)

Δ IL-6: difference between pre- and posttreatment levels of serum interleukin-6 in each patient.

the plasma MPA concentration, which is more important in determining the optimal tumor response than in determining the MPA dose.³

A dose-response relationship has been demonstrated with MPA, and a minimum daily dosage, the so-called "high dose," is necessary for optimal antitumor effects. An oral dose of about 1000 mg/day usually yields a high enough MPA plasma concentration for antitumor activity.¹⁵ However, as shown in this study, the plasma MPA levels vary considerably among individuals even if they receive the same dose. This phenomenon is probably due to individual variations in the absorption and excretion of this drug.²⁴

Although the mechanism for the antitumor activity of MPA is still controversial, it is clearly character-

ized by a dual mechanism; (1) a direct action on the tumor cells predominantly via its specific progesterone receptor, and (2) a systemic effect resulting from the suppression of the HPA axis, leading to endogenous cortisol suppression and subsequent estrogen deprivation in patients with metastatic breast carcinoma. The first direct action of MPA via the progesterone receptor may be based on a progesterone-mediated antitumor effect; progesterone has generally been associated with cell differentiation because it inhibits the proliferative effects of estrogen and directs the tissue toward its normal function.²⁵ However, with respect to the latter effect of MPA, it is still unknown what MPA-mediated alterations underlie the suppression of the HPA axis.

Cytokines are now recognized as having an important role in the modulation of the neuroendocrine system.²⁶⁻²⁷ IL-1 and tumor necrosis factor (TNF)- α have been reported to stimulate hormonal secretion in the HPA axis.²⁸ Recently, IL-6 has also been found to share the biologic activity of these cytokines, especially with regard to certain stimulatory effects.²⁹⁻³⁰ IL-6 acts on the HPA axis, resulting in an increase in cortisol, which in turn acts on liver cells to enhance IL-6 induction of acute-phase protein synthesis.¹¹ Thus, it seems reasonable to postulate that the MPA-induced reduction of the circulating IL-6 levels may contribute, at least in part, to the suppression of the HPA axis in patients with metastatic breast carcinoma.

As stated previously, various human tumor cells actually produce IL-6, and this molecule can act as an autocrine or paracrine growth factor for tumor cells.¹⁷⁻²¹ It has also been reported that increased levels of IL-6 in serum or tumor tissue correlate well with disease severity in various human malignancies.^{12-13,23,31} In human breast carcinoma cells, IL-6 has been shown to have a unique effect on cellular morphology. Of the various cytokines tested, only IL-6 has been confirmed to cause a striking conversion of ductal breast carcinoma cells from an epithelial shape to a fibroblastoid phenotype, accompanied by a decrease in cell-cell association and an increase in cell motility.³²⁻³³ In addition, IL-6 stimulates the production of endothelin-1, which may play a role in stimulating the growth of human breast carcinoma cells in autocrine and paracrine fashion.³⁴ Thus, it is possible that MPA may also exert its antitumor effect by reversing the IL-6-stimulated growth of human breast carcinoma cells. However, our data failed to support this hypothesis; no correlation was found between the decrease in serum IL-6 levels and patients' responses to MPA therapy.

Our data suggest that the decrease in the serum IL-6 levels may be associated with subjective im-

provement in patients with metastatic breast carcinoma. Previous studies showed that megestrol acetate has a potential role in producing subjective improvement, sense of well-being, and increase in appetite and weight.³⁵⁻³⁶ Weight gain has been previously reported as an undesirable side effect in patients treated with megestrol acetate for breast carcinoma.³⁷ However, several investigators have suggested that megestrol acetate has the potential for producing subjective improvement and increase in weight as a desirable event, thereby improving the quality of survival.^{35-36,38}

In conclusion: This is the first study demonstrating that oral MPA treatment reduces serum IL-6 concentration in patients with metastatic breast carcinoma. The decrease in the serum IL-6 levels is not associated with patients' response to MPA. This observation may be associated with a potential of this agent for producing subjective improvement.

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