Clinical implication of medroxyprogesterone acetate against advanced ovarian carcinoma: a pilot study

K. Niwa[1], *M.D.*; K. Onogi[1], *M.D.*; Y. Wu[1], *M.D.*; H. Mori[2], *M.D.*; R.C. Harrigan[3], *Ph.D.*; T. Tamaya[1], *M.D.*

Departments of [1]Obstetrics & Gynecology and [2]Tumor Pathology, Gifu University Graduate School of Medicine, Gifu-City (Japan)
[3]Division of Complementary and Alternative Healthcare, John A. Burns School of Medicine, University of Hawaii (USA)

Summary

Purpose of investigation: The present study was performed to identify the effects of medroxyprogesterone acetate (MPA) plus adjuvant chemotherapy on advanced epithelial ovarian carcinoma (FIGO Stage III/IV). *Methods:* A total of 50 patients were enrolled in this study. A relatively low dose of MPA (200 mg/day) after surgery was administered in combination with platinum-based chemotherapy and the treatment was continued for two years. Patients' backgrounds were also analyzed. *Results:* Relapse-free survival ($p < 0.05$) and overall survival ($p < 0.001$) rates in FIGO Stage III/IV ovarian cancer patients with MPA combined chemotherapy were significantly longer than the control group. The effect was more prominent in the higher progesterone receptor expression group. The chemotherapy regimens (cyclophosphamide, doxorubicin and cisplatin vs paraplatin plus cyclophosphamide or paclitaxel) did not affect prognosis. *Conclusion:* MPA with platinum-based chemotherapy as an adjuvant therapy might improve the prognosis in FIGO Stage III/IV epithelial ovarian cancer cases. A randomized controlled study is still needed for further analyses.

Key words: Medroxyprogesterone acetate; Progesterone receptor; Ovarian cancer; Survival.

Introduction

Ovarian cancer is a gynecological malignancy with the highest mortality rate in Japan as well as in Western countries [1]. Most women with this advanced disease are offered some form of chemotherapy after surgery, but the 5-year survival rate after diagnosis is assumed to be approximately 30% [2]. Although paclitaxel has been introduced into the treatment for ovarian cancer, the superiority of the chemotherapy including paclitaxel to the conventional chemotherapy [cyclophosphamide, doxorubicin and cisplatin (CAP) or AP] has not yet been demonstrated [3]. As a result, combination treatment, including surgery, chemotherapy, hormonal and anti-angiogenetic therapy is needed to obtain a better prognosis, since ovarian cancer is frequently known to be hormone-dependent and angiogenetic.

Epidemiological studies have shown a decreased incidence with increased parity [4], and the use of oral contraceptives has also exerted a protective effect on the incidence of ovarian tumors [5]. Thus, progesterone is thought to have a suppressive effect on ovarian neoplasms.

The ovary is the principal source of estradiol and progesterone, and it is also recognized as a target organ for gonadal sex steroid hormones, thus acting by means of an auto-, intra- or paracrine mode [6]. Elevated sex-steroid hormones in epithelial ovarian cancer are reported to be related with the tumor volume and prognosis [7]. Progesterone has been reported to possess a preventive and growth-inhibiting effect on ovarian tumors [8, 9]. This point correlates with our present observation, especially regarding tumors with a progesterone receptor (PR) expression. The presence of PR itself has been shown to be a prognostic factor [10].

A variety of progestational agents have been shown to be effective in the treatment of recurrent and metastatic endometrial carcinoma [11]. Although the clinical response rate of progesterone to ovarian cancer patients has been reported to be 7% or lower [12], the value is suggested to be based on the use of progesterone alone to advanced or refractory ovarian cancer patients. In the present study, we used progesterone combined with platinum-based chemotherapy as a first-line treatment to treat epithelial ovarian cancer patients who had had cytoreductive surgery.

Regarding endometrial cancer patients, 400-600 mg/day of MPA orally has usually been administered. In a GOG study for recurrent or advanced endometrial cancer patients [13], the response rate of oral MPA at the dose of 200 mg/day was equally effective as that of 1000 mg/day. MPA was effective after oral administration at the dose of 200 mg/day, when the serum level was determined [14]. To avoid the most adverse effect of hypercoagulation by MPA, the dose of oral MPA in this study was determined at 200 mg/day.

The main aim of this study was to clarify the clinical implication of MPA, particularly in response to treatment and clinical outcome in a single institutional series of primary untreated advanced ovarian cancer patients.

Patients and Methods

Patients. The clinical records of 50 ovarian cancer patients who were admitted, treated, and followed-up at the Department of Obstetrics & Gynecology of Gifu University Hospital between January 1993 and December 2001 were evaluated for

Revised manuscript accepted for publication October 1, 2007

clinical prognostic factors (patient's age, tumor stage), the survival status and causes of death (cancer association, cancer independent, unclear). Staging was performed according to the FIGO classification.

The standard surgical intervention consisted of bilateral salpingo-oophorectomy, total abdominal hysterectomy and partial omentectomy. Paraaortic and pelvic lymphadnectomy and cytology of ascites or peritoneal washing cytology were also routinely performed. In addition, all patients had undergone tumor reductive surgery and were suboptimally debulked. Any patients with benign lesions, metastatic ovarian tumors, borderline tumors, stromal and germ cell tumors were excluded from the study.

Pathological study. Histological examination revealed the following subtypes according to the WHO classification [15]: serous 27 (54.0%); mucinous 13 (26.0%); clear cell seven (14.0%); endometrioid two (4.0%); others (transitional cell cancer) one (2.0%). Staging was performed according to FIGO. Thirty-seven patients (74.0%) were in Stage III and ten (26.0%) in Stage IV.

Immunohistochemistry. Four micrometer sections, fixed in 10% formalin and paraffin-embedded, were mounted on poly-L-lysin-coated slides (Sigma, St. Louis, MO). The sections were then deparaffinized, rehydrated and, to quench endogenous peroxidase activity, incubated for 30 min with 3% H_2O_2 in methanol. After a short rinse in Tris-buffer, the sections were boiled in a microwave oven for 3 x 5 min in citrate buffer. Following rolling and rinsing in Tris-buffered saline, normal horse serum (for ER-α, β) and goat serum (for PR antibody) were applied on the sections for 20 min to block non-specific binding. The sections were then incubated overnight at 4°C with monoclonal antibodies directed against ER–α, β and PR. The localization of antigen-antibody complex was performed with the avidin-biotin-peroxidase complex (ABC) technique using a Vectastain ABC kit. Peroxidase activity was demonstrated by 5-min incubation in 3,3'-diaminobenzidine tetrahydrochloride and H_2O_2 dissolved in citrate buffer.

The following monoclonal antibodies were used: ER-α, β (Dako, Denmark); and PR (PgR-ICA monoclonal, Abot, IL). The evaluation of all tissue sections was performed without any prior knowledge of clinical parameters by different cytopathologists by means of microscopy. Immunoreactive score for ER-α, β and PR was calculated basically based on Krajewska *et al*. [16]. Briefly, the intensity of immunostaining was as follows: none = 0, weak = 1, moderate = 2, strong = 3, and the percentage of positive tumor cells was as follows: none = 0, < 10% = 1, 10-50% = 2, 51-80% = 3, > 80% = 4.

Survival. Relapse-free survival (RFS) was also defined as the period from the initial surgery to the time of recurrence or death, whichever occurred first. Overall survival (OS) was calculated from the date of the first surgery to the date of death or the last contact. Medians and life tables were computed using the product-limit estimate by the Kaplan-Meier method.

Chemotherapy. All patients underwent six cycles of platinum-based chemotherapy three to four weeks after primary surgery. Chemotherapy was performed in two regimens; 12 (24.0%) with CAP [cyclophosphamide 320 mg/m^2, doxysorubicin 30 mg/m^2, cisplatin 50 mg/m^2], and 38 (76.0%) with paraplatin (AUC = 5) and cyclophosphamide (500 mg/m^2) or paclitaxel (150 mg/m^2).

MPA therapy. MPA was offered to all ovarian cancer patients in this study. The investigators told them the following: "The drug might be not effective for your disease, but it may be useful for your disease". After approval from the Gifu University Hospital Ethical Committee and informed patient consent, MPA was commenced. MPA and chemotherapy were used synchronously for the patients in the MPA group. The regimen was as follows: MPA (200 mg/day) was administered from one month after the surgery for patients without hypercoagulation. If the patient's data of coagulation tests showed beyond the normal limitations, MPA therapy was stopped and aspirin (100 mg/day) was added. The administration of such drugs continued up to two years after the start.

Clinical response and follow-up. Clinical data were obtained from the patients' records and follow-up data were obtained from the clinical registers. The patients were followed-up every three to four months during the first three years, and then every six months at the Department of Gifu University Hospital.

Statistical analysis. Fisher's exact probability or the chi-square test was used to analyze the cases according to several clinicopathological features.

Table 1. — *Patient characteristics*.

	Total	MPA group	Control	p-value
Number of patients	50	22	28	
Mean age	57.7 ± 12.4	61.1 ± 12.4	55.0 ± 12.4	p = 0.08
Tumor grade				
1	24	12	12	p = 0.22
2 and 3	26	10	16	
Histologic type				
Serous	27	11	16	p = 0.084
Mucinous	13	6	7	
Clear cell	7	4	3	
Endometrioid	2	1	1	
Others (TCC*)	1	0	1	
FIGO stage				
III vs IV	37 vs 13	14 vs 8	23 vs 5	p = 0.14
Residual tumor				
(+)	30	12	18	p = 0.74
(–)	20	10	10	
Chemotherapy **				
CAP	12	5	7	p = 0.98
CBDCA plus CPA or PTX	38	16	22	

* TCC, transitional cell carcinoma; ** CAP, cyclophosphamide, doxysorubicin and cisplatin; CBDCA, carboplatin; CPA, cyclophosphamide; PTX, paclitaxel.

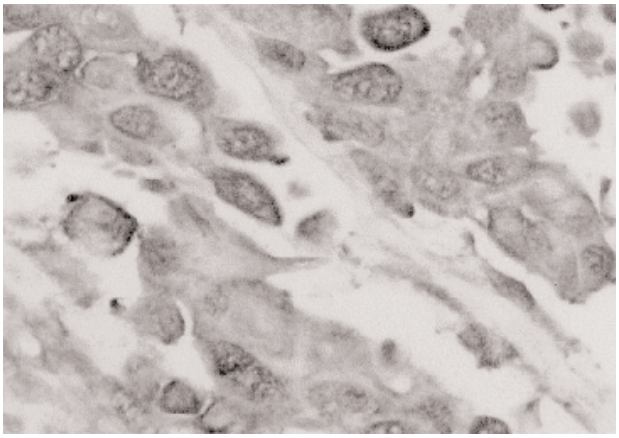

Figure 1. — Immunohistochemical staining for PR in a representative section of high-grade serous carcinoma is shown. High PR expression was restricted mainly to the tumor cells (original magnification x 200).

Fig. 2

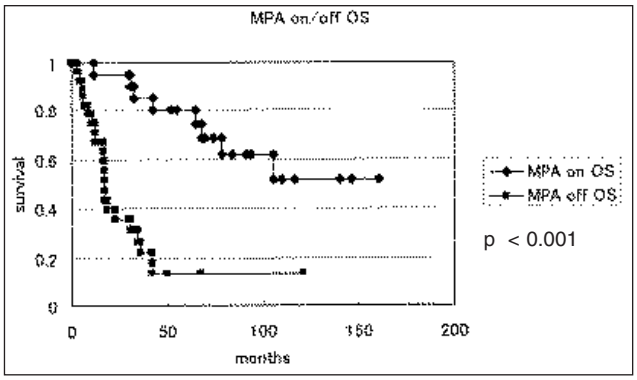

Fig. 3

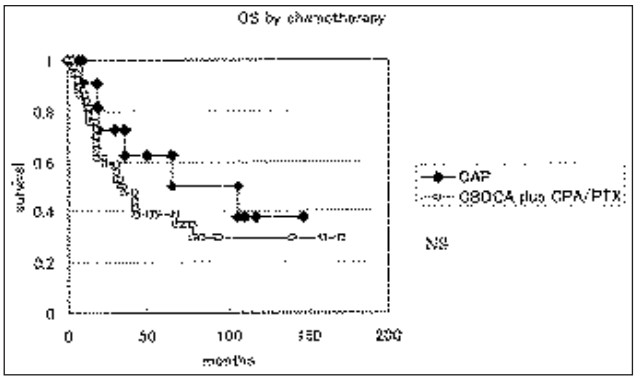

Fig. 4

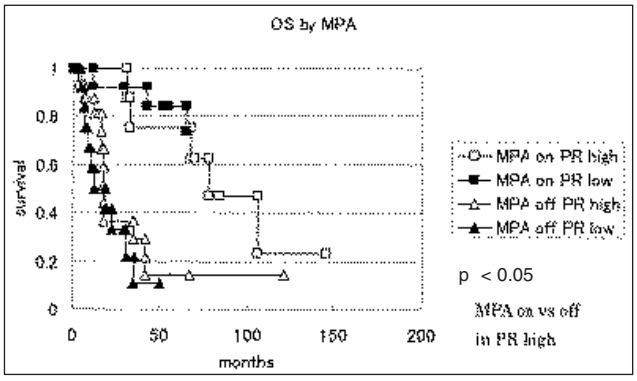

Figure 2. — Kaplan-Meier curves for overall survival (0S) rates of patients with ovarian carcinoma categorized according to MPA administration or not. The OS of patients treated with MPA plus chemotherapy was significantly higher than for the control group ($p < 0.001$).

Figure 3. — Kaplan-Meier curves for overall survival (0S) rates of patients with ovarian carcinoma categorized according to chemotherapy regimens. No significant differences were found between CAP and CBDCA plus CPA or PTX.

Figure 4. — Kaplan-Meier curves for overall survival (0S) rates of patients with ovarian carcinoma categorized according to PR expression and MPA therapy. The OS with MPA was significantly better than without ($p < 0.05$) in the high PR expression group.

Results

Patient characteristics and background. Follow-up data were available from 50 patients. As of June 2007, the median follow-up period was 4.5 years, and the mean follow-up period was 4.4 ± 4.3 years. The background ratios including histological grades, residual tumors, and chemotherapy between the control and MPA group showed no differences (Table 1).

Immunohistochemical expression. Immunohistochemical staining for PR is shown in Figure 1. Immunohistochemical expression scores in the MPA and control groups are summarized in Table 2. No differences were found in the ER-α, β and PR scores between the two groups.

Survival analysis. Figure 2 shows the OS for the MPA and control groups. The MPA group did significantly better than the control group (Figure 2, $p < 0.001$). The RFS group treated with MPA also did significantly better than that without ($p < 0.01$, data not shown). Figure 3 reveals the OS by different chemotherapy regimens. No significant difference was found in the OS (CAP vs paraplatin plus cyclophosphamide or paclitaxel). Figure 4 shows the OS by MPA on/off related with PR expression. The OS for PR high expression with MPA was significantly better than without ($p < 0.05$).

Table 2. — *Immunohistochemical expression scores in the MPA and control groups*.

Groups	ER-α score	ER-β score	PR score
MPA group (n = 22)	6.5 ± 1.6*	3.5 ± 1.6	5.4 ± 1.4
Control (n = 28)	6.2 ± 1.6	3.3 ± 1.4	5.1 ± 1.2

*Mean ± SD

Discussion

In the present study, a relatively low-dose MPA combined with platinum-based chemotherapy significantly improved the survival as well as recurrence rates of advanced stage (FIGO Stage III/IV) epithelial ovarian cancer patients. These results imply that MPA combined with platinum-based chemotherapy could improve the prognosis of advanced epithelial ovarian cancer. In the present study, the chemotherapy regimens did not affect the prognosis. The effect of MPA was more prominent in the PR high expression group.

The possible mechanisms of progesterone on ovarian cancer are proposed to be 1) the induction of apoptosis of cancer cells [8], 2) the inversion of multi-drug resistance of cancer cells [17], 3) inhibition of angiogenesis [18], 4) causing cells to starve to death by inhibition of the synthesis and esterification of cholesterol (19), 5) inhibition of ovarian cancer growth by release of FSH and LH through negative feedback [19].

There is a clinical report that progesterone was used to treat ovarian cancer and the response rate was 7% [12]. However, such evidence is basically based on the use of progesterone alone to treat advanced ovarian cancer or for those patients who had no longer responded to other drugs. In the present study, we used MPA combined with

systemic chemotherapy as a first-line treatment to treat epithelial ovarian cancer patients who had undergone cytoreductive surgery. Since MPA inhibits angiogenesis and the growth of cancer cells, the administration of MPA after cytoreductive surgery may inhibit the angiogenesis and growth of cancer cells that remain in the abdominal cavity in advanced ovarian cancer patients. Related with anti-angiogenic effects of MPA, it has also been reported to improve the long-term survival for chemo-resistant breast cancer [20] and the quality of life for non-hormone-sensitive cancer patients [21].

The presence of PR itself is thought to be a prognostic factor [10]. As the expression of ER-α, β and PR showed the same tendencies (Table 2), the differences for PR expressions between the MPA and control groups seemed small. In the MPA-treated group, however, the efficancy of MPA on the higher PR expression subgroup was more prominent than the lower PR expression subgroup (Figure 4).

Although the number of cases in this study was relatively small, adding MPA to systemic chemotherapy in advanced ovarian cancer patients statistically induced better survival. A randomized controlled study is still needed for further analyses.

References

[1] Tamakoshi K., Kondo T., Yasuya H., Hori Y., Kikkawa F., Toyoshima H.: "Trends in the mortality (1950-70) and incidence (1975-1993) of malignant ovarian neoplasm among Japanese women: analses by age, time, and birth cohort". *Gynecol. Oncol*., 2001, *83,* 64.

[2] Warwick J., Kehoe S., Earl H., Luesly D., Redman R., Chan K.K.,: "Long-term follow-up of patients with advanced ovarian cancer treated in randomized clinical trials". *Br. J. Cancer,* 1995, *72,* 1513.

[3] The international Collaborative Ovarian Neoplasm Group: "Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial". *Lancet,* 2002, *360*, 505.

[4] Adami H.O., Hsieh C.C., Lambe M., Trichopoulos D., Leon D., Persson I. *et al*.: "Parity, age at first childbirth, and risk of ovarian cancer". *Lancet,* 1994, *344,* 1250.

[5] La Vecchia C., Franceschi S.: "Oral contraceptive and ovarian cancer". *Eur. J. Cancer Prev.,* 1999, *8,* 297.

[6] Longcope C.: "Endocrine function of the postmenopausal ovary". *J. Soc. Gynecol. Invest.,* 2001, *8,* S67.

[7] Wimalasena J., Meehan D., Cavallo C.: "Human epithelial ovarian cancer cell steroid secretion and its control by gonadotropins". *Gynecol. Oncol.,* 1991, *41*, 56.

[8] Bu S.Z., Yin D.L., Ren X.H., Jiang L.Z., Wu Z.J., Gao Q.R. *et al*.: "Progesterone induces apoptosis and up-regulation of p53 expression in human ovarian carcinoma cell lines". *Cancer,* 1997, *79,* 1944.

[9] Rodriguez G.C., Walmer D.K., Cline M.: "Effect of progestin on the ovarian epithelium of macaques: cancer prevention through apoptosis?". *J. Soc. Gynecol. Invest.,* 1998, *5,* 271.

[10] Hempling R.E., Piver M.S., Eltabbakh G.H., Recio F.O.: "Progesterone receptor status is a significant prognostic variable of progression-free survival in advanced epithelial ovarian cancer". *Am. J. Clin. Oncol.,* 1998*, 21*, 447.

[11] Piver M.S., Barlow J.J., Lauin J.R., Blumenson L.E.: "Medroxyprogesterone acetate versus hydroxyprogesterone caproate in women with metastatic endometrial adenocarcinoma". *Am. J. Clin. Oncol.,* 1980, *45*, 268.

[12] Ver Der Vange N., Greggi S., Burger C.W., Kenemans P., Vermorken J.B.: "Experience with hormonal therapy in advanced epithelial ovarian cancer". *Acta. Oncol*., 1995, *34*, 810.

[13] Thigpen J.T., Brady M.F., Alvarez R.D., Adelson M.D., Homesley H.D., Manetta A., et al.: "Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose response study by the Gynecologic Oncology Group". *J. Clin. Oncol.,* 1999, *17,* 1736.

[14] Bonte J., Janssens J.P., Ide P.: "Modalities and results of a combined anti-estrogenic therapy by means of tamoxifen and medroxyprogesterone in gynecologic cancerlogy". *Eur. J. Gynecol. Oncol.,* 1986, *7,* 45.

[15] Serow S.F., Scully R.E., Sobin L.H.: "International classification of tumors. Histological typing of ovarian tumours". WHO, Geneva, 1973, 37.

[16] Krajewska M., Fenoglio-Preiser C.M., Krajewski S., Song K., Macdonald J.S., Stemmerman G. *et al*.: "Immunohistochemical analysis of Bcl-2 family proteins in adenocarcinoma of the stomach". *Am. J. Pathol.,* 1996, *149,* 1449.

[17] Mallick S., Horwitz S.B.: "A role for progesterone in multi-drug resistance". In: Parlik E.J. (ed.) Estrogens, Progestins, and Their Antagonists. Boston, Birkhauser, 1996, 123.

[18] Yamamoto T., Terada N., Nishizawa Y., Petrow V.: "Angiostastic activities of medroxyprogestrerone acetate and its analogues". *Int. J. Cancer,* 1994, *56,* 393.

[19] Kammerman S., Demopoulos X.Y., Raphael C., Ross J.: "Gonadotropic hormone binding to human ovarian tumors". *Hum. Pathol.,* 1981, *12* (suppl.), 886.

[20] Zaucha R., Sosinska-Mielcarek K., Jassem J.: "Long-term survival of a patient with primarily chemo-resistant metastatic cancer treated with medroxyprogesterone acetate". *Breast,* 2004, *13,* 321.

[21] Simons J.P., Aaronson N.K., Vansteenkiste J.F., ten Velde G.P, Muller M.J. *et al*.: "Effects of medroxyprogesterone acetate on appetite, weight, and quality of life in advanced-stage non-hormone-sensitive cancer: a placebo-controlled multicenter study". *J. Clin. Oncol.,* 1996, *14*, 1077.

Address reprint requests to:
K. NIWA, M.D.
Department of Obstetrics and Gynecology,
Gifu University Graduate School of Medicine,
1-1 Yanagido, Gifu-city,
Gifu 501-1194 (Japan)
e-mail: kniwa@gifu-u.ac.jp.