Medroxyprogesterone acetate therapy for patients with adenocarcinoma of the endometrium who wish to preserve the uterus-usefulness and limitations

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Summary

Background: To determine the effectiveness of medroxyprogesterone acetate therapy for women with endometrial adenocarcinoma who wish to preserve their uterus.

Study design: Fifteen patients with endometrial carcinoma (12 with grade 1 endometrioid adenocarcinoma, 2 with grade 2 adenocarcinoma and 1 with adenoacanthoma) were treated with high-dose medroxyprogesterone acetate alone as primary therapy and their clinical responses evaluated.

Results: Seven of the 12 cases (58%) with grade 1 adenocarcinoma and one of the two (50%) with grade 2 carcinoma responded initially to medroxyprogesterone acetate. The median length of treatment required for regression was 29 weeks. Three patients who initially responded relapsed. Thirteen patients are alive without evidence of disease as of December 1999 (10 to 146 months, median; 4 years and 11 months) and one is continuing medroxyprogesterone acetate therapy as a final follow-up. One patient was lost to follow-up. Two patients have conceived having three healthy infants.

Conclusion: Treatment of endometrial carcinoma with high-dose medroxyprogesterone acetate could be an alternative to hysterectomy, although the successful rate is limited.

Key words: Endometrial carcinoma; Medroxyprogesterone acetate; Fertility.

Introduction

Endometrial carcinoma is one of the most frequent malignancies occurring in the female genital tract, and its incidence has been increasing in Japan [1]. Endometrial carcinoma occurs usually in postmenopausal women, with only 1.5-14.4% of the patients being of child bearing age or under the age of 40 [2, 3]. These patients, however, tend to have a history of irregular menstruation, chronic anovulation and infertility [2]. Endometrial carcinoma in younger patients also tends to be well differentiated [2, 4]. The standard treatment for endometrial carcinoma is laparotomy with abdominal hysterectomy and bilateral salpingo-oophorectomy. Therefore, there is a dilemma between being successfully treated and the preservation of one's fertility, which is of great importance to young nulliparous patients.

Atypical hyperplasia is considered to be the precursor lesion of endometrial carcinoma and has a risk of progressing to carcinoma in approximately 25% [5, 6]. Therefore, it is recommended that patients with atypical hyperplasia, especially older women, undergo a hysterectomy. A more function-retaining treatment for endometrial hyperplasia using progestin, however, supports its usefulness as a curable treatment method in young patients [5, 7, 8]. More limited evidence suggests that well-differentiated endometrioid adenocarcinoma of the endometrium may also be treated effectively with progestin alone [8, 9, 10]. In a recent review [11] on women under age 40 with well-differentiated adenocarcinoma, 13 of 21 patients appeared to respond to progestin alone.

In this study, we aimed to determine whether or not a conservative high-dose MPA therapy for Japanese women with endometrial adenocarcinoma was also effective, and to determine whether or not these women would be able to bear children if the treatment was successful.

Materials and Methods

Fifteen patients with endometrial carcinoma visited Kitasato University Hospital with serious interest in preserving their uteri and fertility. With this in mind, they were treated with MPA from January 1987 to February 1999 after having been informed about all possible options including the more effective method of surgical treatment. The histological diagnosis was made by using a specimen obtained by dilatation and curettage which was performed under anesthesia and classified using the histological classification of tumors of the female genital tract (WHO, 1994) [12]. Clinical stage of malignancy was assessed using the classification of the International Federation of Gynecology and Obstetrics (FIGO, 1982) [13], and patients having positive endocervical curettage were considered to have stage II. The patients with endometrial carcinoma consisted of 12 with grade I (G1) endometrioid adenocarcinoma, one with grade 2 (G2), and two with adenoacanthoma. MPA 400-800 mg daily per os (p.o.) was prescribed continuously for at least 12

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Table 1. — *The Patients treated with MPA and their outcome of follow-up*

Case	Clinical stage	Histology	MPA treatment	Finding of surgical specimen	Outcome of Follow-up
Regression					
1*	Ia	G1 adenoca.	400 mg/day x 45 weeks	Atrophic endometrium with focal EC	A+W, 146 months
2**	II	G1 adenoca.	400 mg/day x 11 weeks, 600 mg/day x 22 weeks, cyclic MPA x 6 courses	Atrophic endometrium with focal EC	A+W, 72 months
3	Ia	G1 adenoca.	600 mg/day x 30 weeks, cyclic MPA x 6 courses	–	A+W, 55 months
4	II	G1 adenoca.	600 mg/day x 34 weeks, cyclic MPA x 5 courses	–	A+W, 35 months
5	Ia	G1 adenoca.	600 mg/day x 64 weeks, cyclic MPA x 1 course,	–	A+W, 30 months
6	II	G1 adenoca.	600 mg/day x 30 weeks, cyclic MPA continuous	–	A+W, 10 months
7	Ia	G1 adenoca.	600 mg/day x 30 weeks	–	A+W, 10 months
8***	Ia	G2 adenoca.	600 mg/day, 36 weeks	–	Lost to follow-up
Persistent					
9	II	G1 adenoca.	400 mg/day x 23 weeks	Atrophic endometrium with focal EC	A+W, 143 months
10	Ia	G1 adenoca.	400 mg/day x 17 weeks	Atrophic endometrium with focal EC	A+W, 95 months
11	II	G1 adenoca.	800 mg/day x 63 weeks	Myometrial invasion less than 1/3, cervical invasion	A+W, 31 months
12	II	G1 adenoca.	600 mg/day x 56 weeks, continuous	–	A+W, 16 months
13	II	G2 adenoca.	600 mg/day x 12 weeks	Atrophic endometrium with focal EC	A+W, 47 months
14	II	Adenoaca.	600 mg/day x 12 weeks	Marked decidual change of atypical endometrium	A+W, 63 months
Progressive					
15	II	G1 adenoca.	600 mg/day x 41 weeks	Deep myometrial invasion, cervical invasion, right ovarian metastasis	A+W, 24 months

Adenoca. = adenocarcinoma; Adenoaca = adenocanthoma; A+W = alive and well
* = recurrent 23 weeks after MPA therapy; ** = recurrent 19 weeks after MPA therapy; *** = recurrent 28 weeks after MPA therapy.

weeks, which is the recommended duration of MPA therapy to obtain clinical response [14]. Prescription of MPA was maintained for 8 to 12 weeks even after regression of the lesion. Cyclic MPA therapy which consisted of 10 mg daily p.o. for 14 consecutive days followed by 14 non-prescription days was given additionally after high-dose MPA therapy followed by inducing ovulation in five cases.

Endometrial cytology with sampling devices (Endocyte®) inserted into the uterine cavity, and endometrial biopsy (samples obtained with 4-direction curettage) were conducted to detect the effects of MPA treatment at 4-week intervals. Specimens of endometrial cytology were mainly used to review the effectiveness of MPA therapy when those from endometrial curettage were not able to be obtained. Lesions were defined as having regressed, persisted, or progressed based on the specimen available during or after completion of treatment according to the following criteria: Regression was classified to have occurred if the last endometrial sample obtained by dilatation and curettage following hysteroscopy showed a normal endometrium. Persistence of the lesion was classified to have occurred if the last biopsy or cytology showed viable carcinoma. Progression of the lesion was considered to have occurred if new lesions appeared. Finally, recurrence was classified to have occurred if a lesion that had initially regressed appeared again. Fourteen patients were followed-up on with an observation period which lasted until December 1999.

Patients' clinical history, response and prognosis of the treatment and the pregnancy outcome clowing successful treatment were evaluated by reviewing the patient records.

Results

The patients ranged in age from 24 to 38 years (mean 30.2). Eleven patients complained of menometrorrhagia. All women were nulligravida, and seven women had complained of infertility on presentation. Chronic anovulation was confirmed by a basal body temperature in 4 of 11 cases (36%). Six patients were in stage I and nine were in stage II. Fourteen patients were followed for periods from 10 to 146 months with a mean of 59 months from the beginning of MPA therapy. One patient declined a hysterectomy after a diagnosis of recurrence and was lost to follow-up.

Seven of the 12 patients with G1 adenocarcinoma and one of the two with G2 carcinoma were documented as regressing to a normal endometrium including atrophic endometrium in three cases and secretory in five. The median length of treatment required for regression was 29 weeks with a range of 18 to 64 weeks. Three patients developed recurrence of the carcinoma 19 to 28 weeks after discontinuation of MPA therapy (mean - 23 weeks). Four patients were treated with more than four courses of additional cyclic MPA therapy and one of them relapsed. Regression was not experienced in the patient with adenocanthoma. None of 12 patients with G1 adenocarcinoma have progressed to grade 2 or 3 carcinoma. Persistent carcinoma was observed in seven cases 12 to 63 weeks after

the start of MPA therapy (mean – 32 weeks). One of the 15 cases developed a new lesion in the ovary. Two cases diagnosed as being recurrent, five as being persistent and one as being progressive underwent hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy. In six cases, focal carcinoma of 2-15 mm (mean – 5 mm) in diameter coexisted with the atrophic endometrium. Myometrial invasion of more than the inner half and endocervical invasion by the carcinoma was confirmed in one case and two cases, respectively. In one case diagnosed as being progressive, deep myometrial invasion (more than half) as well as endocervical stromal invasion were observed. The right ovary was 11.0x9.5x6.0 cm in size. Histology diagnosed as G1 endometrioid adenocarcinoma was consistent with the primary lesion. Lymph node metastasis was not found in any of the cases. All women treated by MPA with or without hysterectomy are alive without further recurrent disease.

Two cases with grade 1 carcinoma conceived after successfully completing MPA treatment. The age at the time of diagnosis of endometrial carcinomas was 36 (case 3) and 34 years (case 4), and they were both nulligravidous. Case 3 with stage la carcinoma received high-dose MPA therapy for 30 weeks followed by six courses of cyclic MPA therapy. After completion of MPA therapy, she was treated by inducing ovulation with clomiphen citrate followed by follicle stimulating hormone and human chorionic gonadotropin according to standard protocol. She conceived having a twin pregnancy 13 months after the completion of MPA treatment. Case 4 with stage II cancer received high-dose MPA therapy for 34 weeks and five courses of cyclic MPA therapy. After completetion of MPA therapy, clomiphen citrate was prescribed and she conceived four months after MPA treatment. The courses of their pregnancies were uncomplicated. They delivered normal and healthy infants (gestational age: 35 weeks and 38 weeks, respectively). The details of these patients have been reported elsewhere [15].

Discussion

In this series, all of the 15 cases were under age 40 and nulligravidous. Seven of 12 with G1 endometrioid adenocarcinoma and one of two with G2 had regressed after MPA therapy. Three of them however recurred 19, 23, and 24 weeks after regression, respectively. Six patients with persistent disease and one with progressive disease as well as two recurrent patients underwent hysterectomy and their postoperative courses have been non-contributory.

The patients with endometrial carcinoma under 40 years of age are frequently nulliparous and are often very interested in preserving their fertility, although they assume some risk undergoing this function-retaining therapy. Our results are consistent with those of a recent case series reported in the literature in which 13 of 21 premenopausal women with well-differentiated carcinoma showed an initial response to progestin therapy [11]. Randall and Kurman [8] evaluated the efficacy of conservative management of atypical hyperplasia and well-differentiated adenocarcinoma of the endometrium in women under age 40.

Sixteen of 17 patients (94%) with atypical hyperplasia and nine of 12 (75%) with well-differentiated adenocarcinoma regressed. Bokhman *et al.* [10] reported the results of progestin therapy for 19 cases with stage I endometrial carcinoma (mean age was 28.0 years). Complete regression of the tumor was obtained in 15 patients (79%) after 3-6 months treatment, and they concluded that progestin therapy may be applied in young women with stage I endometrial carcinoma. These data and our results confirm that patients with well-differentiated endometrial carcinoma can be treated successfully by using progestin alone. However, these studies suggest that progestin treatment has some unfavorable risk. Not all patients respond to treatment. In our series, seven of 15 patients ultimately underwent hysterectomy because they did not show an initial favorable response. Kim *et al.* [11] reported that eight of 21 patients (38%) also did not respond to progestins. In our series, two of seven unresponsive patients were considered to be non responsive to progestin after only 12 weeks of treatment. The median length of treatment required to achieve regression was 29 weeks in our series. Therefore, some of the patients who were considered to fail in the treatment may have received an inadequate course of MPA treatment. Another problem is that three patients who responded initially to MPA therapy in our series relapsed later and two of them underwent hysterectomy, although they did not have metastatic disease. Kim *et al.* [11] reported one case that was found to have metastatic disease after complete response to progestin, and concluded that progestin therapy delayed definitive surgical treatment for this patient and may have adversely affected her prognosis. They postulated the magnitude of the risk of disease progression occurring during or after progestin therapy is approximately 5%.

In our series only MPA was prescribed as the progestin, because other progestins are not allowed to be used in Japan. In the literature [8-11, 16, 17], megestrol acetate, hydroxyprogesterone caproate and norethisterone were used as progestins. Randall and Kurman [8] reported the effects of megestrol acetate and MPA with a variety of dosages and schedules, and did not formulate a firm recommendation for the regimen of treatment. The optimal duration of MPA treatment and follow-up after MPA therapy is unclear. In our series, three patients whose lesions regressed first with MPA therapy relapsed nine, 23 and 24 weeks after treatment. These patients had a history of anovulation. From these experiences, it is plausible that long-term surveillance of patients following regression is necessary. We tried to add cyclic MPA therapy to five patients whose carcinoma remitted completely with high-dose MPA therapy and recurrence was experienced in only one of them. On the other hand, two of three cases without additional cyclic MPA therapy revealed a recurrence. It is suggested that additional cyclic MPA therapy following successful high-dose MPA may decrease the incidence of recurrence.

The most important therapeutic objective of function-retaining for young patients with endometrial carcinoma is to preserve fertility and to bear children. Two of six women in our series who attempted to conceive following their course of treatment had successful pregnancies. Kim and colleagues [11] reported that three of 13 patients who responded to progestin therapy were able to have successful pregnancies with six viable infants. They concluded that premenopausal women with endometrial carcinoma might be treated successfully with progestin therapy as the primary therapy to preserve childbearing potential. Randall and Kurman [8] reported that 25 patients with complex atypical hyperplasia and endometrial carcinoma were treated with progestin; seven women conceived and five (20%) had full-term pregnancies. However, many patients identified in the literature [18, 19] and ours were successful in conceiving only after treated by assisted reproductive technology for ovulatory failure. Young women who have recovered from endometrial carcinoma may have a low pregnancy rate due to the high incidence of chronic anovulation and infertility. Therefore, it is important to induce ovulation. Kimming *et al* [19] described an infertile woman with endometrial carcinoma who was treated with progestin, and immediately after documenting regression of the disease she was treated with gamete intra-fallopian transfer and delivered viable triplets.

Our data support that primary therapy with high-dose MPA may be an alternative treatment for women with G1 endometrial carcinoma who want to preserve their fertility and who may have a chance of having a healthy infant. The patients, however, must receive a prolonged prescription of progestin (probably more than 7 months) and careful monitoring with periodic endometrial cytology and biopsy. These patients may have a risk of developing extrauterine metastasis of the tumor. The mechanism of action and sensitivity of MPA therapy for endometrial carcinoma is left for future basic study.

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