ONCOLOGY

Combined medroxyprogesterone acetate/levonorgestrel—intrauterine system treatment in young women with early-stage endometrial cancer

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OBJECTIVE: The purpose of this study was to evaluate the efficacy of the combined oral medroxyprogesterone acetate (MPA)/levonorgestrel-intrauterine system (LNG-IUS) treatment in young women with early-stage endometrial cancer who wish to preserve their fertility.

STUDY DESIGN: A prospective observational study was conducted. The study population comprised women aged ≤40 years who were diagnosed with endometrioid endometrial cancer, grade 1, tumor size <2 cm presumably confined to the endometrium. A LNG-IUS was inserted in the uterine cavity of each woman, and all of the women received oral MPA (500 mg/d). Dilation was conducted every 3 months.

RESULTS: From September 2008 to December 2012, 16 patients were enrolled. The overall complete remission rate was 87.5% (14/16 patients); the average time to complete remission was 9.8 ± 8.9 months (range, 3—35 months). In the initial 3 months of treatment, complete remission was observed in 25% of cases (4/16 patients), partial response in 25% (4/16), and no change in 50% (8/16); there were no cases of progressive disease. Three patients achieved pregnancies. The average follow-up period was 31.1 ± 11.8 months (range, 16—50 months), and there were no treatment-related complications.

CONCLUSION: Combined oral MPA/LNG-IUS treatment is considered to be effective and favorable for young patients with early-stage endometrial cancer who want to preserve their fertility.

Key words: endometrial cancer, levonorgestrel-intrauterine system (LNG-IUS), medroxyprogesterone acetate, progesterone

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Endometrial cancer (EC) is the most frequent gynecologic malignancy in developed countries, and the incidence is rising steadily. Although most cases are diagnosed in postmenopausal women, up to 14% of those afflicted are premenopausal, among whom 4% are <40 years old. Ominously moreover, cases that involve this younger cohort have been increasing continuously over the past several years.[1-3]

The standard treatment for EC is total hysterectomy with bilateral salpingo-oophorectomy, peritoneal cytology, and/or lymph node dissection, which is very effective. The 5-year survival rate for those with the early-stage EC, in fact, is >93%.[4] However, the permanent infertility that results from such treatment is a very significant drawback for younger women. So far, for women with clinical stage IA and grade I lesions who desire to preserve their fertility, conservative treatment such as the administration of high-dose oral progesterone has been recommended.[5-15] The recent prospective multicenter study showed that, in 28 patients who had EC at presumed stage IA and who were treated daily with 600-mg medroxyprogesterone acetate (MPA), the complete response (CR) rate was 55%.[15] In addition, several recent studies reported the use of a progesterone-containing intrauterine system to treat patients at a high risk of perioperative complications who cannot tolerate systemic progesterone because of its adverse effects.[16,17] The result is unsatisfactory, especially compared with the high cure rate (>93%) of surgically treated early-stage EC that has been noted already. Therefore, to achieve a therapeutic progesterone level with less adverse systemic effects of high-dose progestin, we tried the combination of a lower dose of systemic progesterone and local progesterone therapies: combined 500-mg MPA/levonorgestrel-intrauterine system (LNG-IUS) daily.

In a recent pilot study on the combined treatment of MPA/LNG-IUS, an enhanced treatment effect that did not increase side-effects was thought to have been attained; complete remission occurred in 4 of 5 patients during the median follow-up period of 10.2 ± 3.6 months (range, 6—16 months). Despite this promising result, the number of subjects (5 women) was not sufficient to confirm the treatment effect.[18]

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Thus, in the present study, we aimed to verify the combined treatment effects of MPA/LNG-IUS therapy on early-stage EC in young women who were desirous of preserving their fertility.

Patients and Methods

A prospective observational study was conducted from September 2008 to December 2012; 16 patients with EC at CHA Gangnam Medical Center were enrolled. Inclusion criteria were ≤40 years old with the histologically proven well-differentiated endometrioid EC, tumor size <2 cm that was presumed International Federation of Gynecology and Obstetrics stage IA limited to the endometrium, and a strong desire to preserve their fertility.

The histologic diagnosis was made with dilation while the patient was anesthetized; all slides were reviewed by 2 specialist pathologists. All patients were evaluated by pelvic examination, ultrasound scan, abdomen and pelvis computerized tomography, and magnetic resonance imaging. The tumor size was measured by the maximum dimensions of tumor in any plane on magnetic resonance imaging. That the tumor size of <2 cm and clinical stage of tumor was confined to the endometrium were established. Also, the lack of pelvic/aortic lymph node involvement or extrauterine lesions was confirmed for all of the subjects.

All patients were informed fully of the merits, disadvantages, and risks of surgical and hormonal treatments; their voluntary informed consent to participate in the present study (as approved by the institutional review board of CHA Gangnam Medical Center) was obtained.

The LNG-IUS was inserted in the uterus, and each patient was administered 500 mg of MPA orally once per day. Follow-up evaluation and treatment response assessment were implemented at 3-month intervals with history-taking, physical examination, transvaginal ultrasonography, and dilation after removal of LNG-IUS. The histologic diagnosis of all obtained samples was carried out by specialist pathologists. Treatment response was defined based on a comparison of the index sample with the last available specimen during and after the completion of treatment.

In endometrial biopsy, *CR* is defined as a condition without any hyperplastic or cancerous lesion. *Partial response* (PR) is defined as the presence of residual lesion with degeneration or atrophy of endometrial glands or endometrial hyperplasia. *No change* (NC) is defined as the presence of residual lesion without degeneration or atrophy of endometrial glands. *Progressive disease* (PD) is defined as according to the appearance of grade 2 or 3 endometrial carcinoma.

At the treatment evaluation every 3 months, cases with PR and NC continued a further 3 months of the same treatment procedure, whereas cases with PD underwent surgery. Meanwhile, for patients with CR who wanted to become pregnant, in vitro fertilization (IVF) was immediately carried out; to those who wanted to postpone pregnancy, oral contraceptive pills were administered for prevention of recurrence.

Results

Sixteen eligible subjects were treated with combined oral MPA/LNG-IUS. None of them had any obstetric history; their mean age was 34.8 ± 4.3 years (range, 29–40 years), and their average body mass index was 24.4 ± 5.9 kg/m^2 (range, 17.0–36.3 kg/m^2). The overall complete remission rate was 87.5% (14/16 patients); the average time to complete remission was 9.8 ± 8.9 months (range, 3–35 months). In the initial 3 months of combined treatment, CR was observed in 25% of patients (4/16 patients); PR was observed in 25% of patients (4/16), and NC was observed in 50% of patients (8/16); there were no cases of PD.

A total of 14 patients had a CR after conservative treatment, 9 of whom have attempted to conceive with or without IVF and 5 of whom did not want to conceive immediately, so they had been administered oral contraceptive pills or maintained LNG-IUS in uterine cavity as a maintenance therapy. There was no recurrence among the subjects with CR with a maintenance therapy. Seven patients underwent IVF. Two of the patients who had undergone IVF in the course of pregnancy trials showed recurrent cancer (case 4, 6 months after achieving CR; case 5, 7 months after achieving CR). Including these 2 patients, 5 patients underwent surgery: 1 patient had NC after 9 months of treatment; 2 patients gave up pregnancy and wanted to surgical therapy (cases 3, 4, 5, 6, and 10). They are currently under observation after successful surgical treatment. All of their postoperative stages were IA.

Three patients have achieved successful pregnancy (case 7, 14, and 16). One patient had spontaneous pregnancy, and two other patients conceived with IVF. One pregnancy terminated in miscarriage at the ninth week; two other patients are pregnant without complication.

The average follow-up period was 31.1 ± 11.8 months (range, 16–50 months), and there were no cases of adverse effect, serious complications, or death related to treatment (Table; Figure).

Comment

During the last years, conservative treatments such as the administration of high-dose oral progesterone or progesterone-containing intrauterine system frequently have been proposed for early-stage EC.[5-17,19] Most studies have reported approximately 57-76% response rates for 100-800 mg of oral progesterone (megestrol acetate or MPA:MPA) per day. Nonetheless and unfortunately, such evidence is not sufficient, particularly for the purposes of treatment-effect comparison, because most of the studies have been based on retrospective analysis and a limited number of subjects. No definitive standard treatment protocols have been established with respect to the types and appropriate amounts of progesterone, the treatment period, follow-up methods, posttreatment fertilization methods, and maintenance therapies for the prevention of recurrence, among other protocols, because of the absence of large-scale studies to date. Recently, Ushijima et al[15] presented the first results of a prospective multicenter study. They had administered 600 mg of progesterone (MPA) and low-dose aspirin daily for 26 weeks to 28 patients who were