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Fertility sparing treatment of complex atypical hyperplasia and low grade endometrial cancer using oral progestin

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HIGHLIGHTS

- Our CAH or G1EC patients <45 y had a 55% complete response rate to oral progestin.
- Increasing age was associated with a lower likelihood of complete response.
- The benefit of continuing progestin >1 y in the absence of a histologic response may be limited.

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ABSTRACT

Objective. Oral progestin is an alternative to hysterectomy for women with complex atypical hyperplasia (CAH) or grade one endometrial cancer (G1EC) who wish fertility preservation. We evaluated treatment efficacy and fertility outcomes in this population.

Methods. Women <45 y treated with oral progestin for CAH or G1EC were identified from two cancer centers. Data were obtained from medical records and telephone questionnaires. Time until complete response (CR), and from CR until recurrence was censored for patients without events and analyzed for associations with patient and treatment characteristics; cumulative incidence functions were used to estimate event probability over time.

Results. 44 patients were identified, 19 (43%) with CAH and 25 (57%) with G1EC. Median age was 36.5 y (26–44). 24 (55%) achieved CR (median time: 5.7 months). Older age was associated with a lower likelihood of CR (HR 0.84, p = 0.0003, 95% CI, 0.8–0.9). CR probability appeared to plateau after 12 months of therapy. Among those with CR, 13 (54%) recurred (median time 3.5 y). 24 patients (55%) underwent hysterectomy; 3 (13%) were upstaged. 11 (25%) underwent fertility treatment with the following outcomes: 6 (55%) no pregnancy, 2 (18%) at least one live infant, and 3 (27%) spontaneous abortion. One achieved a live birth without intervention.

Conclusion. Oral progestin is an effective temporizing fertility-sparing treatment for women with CAH/G1EC. Fertility specialist involvement is recommended due to the low live birth rate without intervention. Progestin therapy should be re-evaluated at 1 year in non-responders due to a low probability of success. Hysterectomy is recommended after childbearing due to a high recurrence rate.

Introduction

The standard of care for treatment of endometrial cancer is hysterectomy and bilateral salpingo-oophorectomy, with subsequent disease-free five-year survival rates up to 99.2% among women with stage 1A grade 1 disease [1]. However, 3–5% of women diagnosed with endometrial cancer are under the age of 40, of which 70% are nulliparous [2]. The subfertility of this population is often due to the same risk factors associated with the development of endometrial carcinoma: polycystic

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ovarian syndrome, ovarian dysfunction, chronic anovulation, obesity [3], as well as hyperinsulinemia, which increases the risk of endometrial cancer independent of body mass index [4]. Many women diagnosed with CAH or G1EC have a strong desire to preserve fertility. The scope of the problem is expected to increase with rising rates of obesity, diabetes, and delay of childbearing.

The most studied fertility-preserving treatment of early endometrial cancer and CAH in young women is oral progestin. Definitive treatment guidelines do not exist, but it is generally accepted that progestin therapy should be restricted to patients with grade 1 disease or less, presumed stage 1A with no evidence of myometrial invasion or extrauterine disease on imaging, and motivation to achieve pregnancy soon after disease regression [5]. Traditionally it has been felt that these patients could be safely treated with progestin, but to date there have been five deaths reported in the literature due to disease progression or an undetected synchronous malignancy [6–10].

Many questions remain regarding the optimal dose and duration of treatment [11,12], understanding clinical and pathologic features that predict treatment success to improve patient selection [13,14] and more recently the possibility of progestin re-treatment following relapse [15]. The objective of this research was to assess the efficacy of progestin treatment in our population of patients. Secondary outcomes of interest were clinical characteristics associated with treatment success and fertility outcomes in patients who had a complete response (CR).

Table 1
Baseline characteristics of the study population (n = 44).

Variable	N (%)	Median (range)
Age at diagnosis (years)	44	36.5 (26–44)
Nulliparous	35 (81)	
Body mass index	25	30 (20–66)
<26 kg/m^2	10 (40)	
≥26 kg/m^2	15 (60)	
Oligomenorrhea (n = 43)	26 (61)	
Menorrhagia (=43)	29 (68)	
Diabetes mellitus type II (n = 43)	5 (12)	
Family history Lynch syndrome-associated cancer in a first degree relative (n = 31)[a]	7 (23)	
Pelvic imaging		
Ultrasound	8 (18)	
MRI	6 (14)	
Both	21 (48)	
Neither	9 (20)	
Progestin therapy		
High dose (MPA[b] ≥ 100 mg/day or MA[c] ≥ 80 mg/day)	11(26)	
Low dose (MPA < 100 mg/day or MA < 80 mg/day)	31 (74)	
Unknown	2	

[a] Cancers of colorectum, endometrium, stomach, small intestine, hepatobiliary system, kidney, ureter, ovary, and sebaceous tumors.
[b] MPA = Medroxyprogesterone acetate.
[c] MA = megestrol acetate.

Methods

Women with CAH or G1EC under the age of 45 years who were treated with oral progestin for the purpose of fertility preservation were identified from clinical databases from the Princess Margaret Hospital and Odette Cancer Center in Toronto, Canada, from 2000 to 2011. Diagnosis and response to treatment were based on endometrial curettage or office endometrial biopsy and reviewed by a gynecologic pathologist. Patients underwent multiple surveillance biopsies (median 4, range 2–12) at variable intervals (due to the retrospective nature of this study) while on progestin therapy and after CR. Clinical and demographic data were obtained from medical records. If insufficient, additional fertility data was obtained from telephone questionnaires. Progestin regimens were categorized as high-dose and low-dose; high dose was defined as ≥100 mg medroxyprogesterone acetate (MPA) or ≥80 mg megestrol acetate (MA) daily. CR was defined as no evidence of abnormal endometria on pathology. Univariate and multivariate Cox regression models were used to determine clinical characteristics associated with an increased likelihood of CR.

Continuous variables were described using medians, ranges and interquartile ranges; categorical variables were described using frequencies and proportions. Time until CR was measured from the progestin start date. Time until recurrence was measured from the date of CR (patients without a CR were excluded from the analysis). Patients without an event of interest by their last follow-up date were censored in both analyses. There were no competing risk events in either analysis. Plots of cumulative incidence functions estimating the probability of an event over time were generated using the cmprsk package in R 2.15.1. SAS 9.3 TS Level 1M1 was used to generate all descriptive statistics and to implement Cox models relating time until events with patient and treatment characteristics using proc phreg and proc lifetest. Statistical significance was set to 0.05.

Results

Forty-four patients met the inclusion criteria. Baseline characteristics are described in Table 1. The majority (80%, N = 35) had imaging prior to treatment. Two patients had possible superficial myometrial invasion on MRI; the remainder had no radiologic evidence of myometrial invasion or extrauterine disease. The median follow-up from the start of progestin treatment was 39 months (range 5–128). 26% of patients were on high-dose progestin and 74% on low-dose progestin. Forty-two patients (95%) had discontinued progestin treatment by their last follow-up date. The median time on treatment for these patients was 9.5 months (range 2–53). Two patients were still on their initial round of progestin treatment by their last follow-up visit because they had not achieved a CR to treatment at 12.7 and 14.7 months.

Twenty-four patients (55%) had a CR to progestin treatment by their last follow-up date. The probability of CR was not significantly different between the patients with G1EC and those with CAH (HR 0.98, 95% CI 0.44–2.22, p = 0.97). The median time to CR was 5.7 months (range 2–24); 92% responded within 12 months of treatment. The estimated median time until CR from the progestin start date was 11.1 months based on the data from all 44 patients. The lower limit of the 95% confidence interval is 6.2 months; the upper limit cannot be calculated due to lack of follow-up. A cumulative incidence function representing the probability of a complete response over time is depicted in Fig. 1. CR

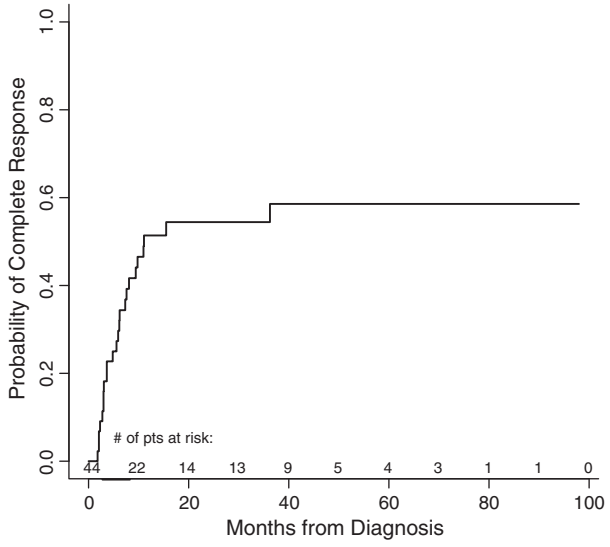

Fig. 1. Cumulative incidence function representing the probability of a complete response over time.