GYNECOLOGY

While women await surgery for type I endometrial cancer, depot medroxyprogesterone acetate reduces tumor glandular cellularity

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BACKGROUND: Multiple population-level studies have demonstrated an adverse effect of long wait times to surgery on survival for women with endometrial cancer. Other retrospective and nonrandomized prospective studies have shown that preoperative administration of depot medroxyprogesterone acetate decreases tumor glandular cellularity, which may be a surrogate marker for clinically meaningful tumor response.

OBJECTIVE: We sought to determine whether preoperative injection with depot medroxyprogesterone acetate decreases tumor glandular cellularity when compared to placebo injection in women awaiting hysterectomy for endometrial intraepithelial neoplasia or type I endometrial cancer, and to determine whether depot medroxyprogesterone acetate injection affects quality of life while waiting for surgery.

STUDY DESIGN: This was a double-blind, randomized controlled trial of 400-mg depot medroxyprogesterone acetate injection or 0.9% saline injection at the preoperative visit. Patients with recent use of progesterone analogs were excluded. A sample size of 76 patients (38 per arm) was calculated to detect a 20% difference in decreased glandular cellularity between arms. Pathologic characteristics including the primary outcome, tumor glandular cellularity, from patients' diagnostic biopsies were reviewed by 2 dedicated gynecologic pathologists and compared to posttreatment hysterectomy specimens. On the night prior to surgery, patients completed the Functional Assessment of Cancer Therapy-Endometrial Survey (Version 4) to report quality of life while waiting for surgery. In comparing characteristics between the intervention and control groups, *t* tests were used for continuous variables, and χ^2 or Fisher exact tests were used where appropriate for categorical data.

RESULTS: From March 2015 through March 2016, 148 women were screened and 76 patients were enrolled. In all, 38 patients were randomized to and received depot medroxyprogesterone acetate injection and 38 were randomized to and received placebo injection. Demographics were similar between groups. Patients who received depot medroxyprogesterone acetate injection experienced a larger decrease in tumor glandular cellularity (mean change −64 [−31.8%] vs −14 [−5.5%] cells per quarter high-powered field in depot medroxyprogesterone acetate vs placebo groups, $P = .002$). This effect was most pronounced in women waiting ≥3 weeks for surgery. Several additional histologic and immunohistochemical markers of tumor differentiation and decreased cell proliferation were more pronounced in the depot medroxyprogesterone acetate group than in the placebo group. There were no significant differences in quality of life between groups on the Functional Assessment of Cancer Therapy-Endometrial Survey. Only 5.3% of patients who were approached declined to participate due to concerns regarding an intramuscular injection.

CONCLUSION: Administration of depot medroxyprogesterone acetate prior to surgery for type I endometrial cancers caused greater tumor effect than placebo injection. Injection of depot medroxyprogesterone acetate was acceptable to and well tolerated by patients. Depot medroxyprogesterone acetate may represent a meaningful bridge to surgery in women who can expect long wait times.

Key words: endometrial cancer, progesterone analogs, wait time to surgery

Introduction

Uterine cancer is the second most common gynecologic malignancy in the world, with increasing incidence globally as countries undergo socioeconomic transitions.[1] Type I endometrial cancers arise from estrogen-driven precursors and account for 80−90% of endometrial carcinomas.[2] Due to population aging and the worsening obesity crisis, the incidence of type I endometrial carcinoma is expected to increase in the United States.[3] Five-year overall survival is approximately 95% for stage I disease, as surgery is curative for most patients.[4]

Long wait times for surgery have been negatively associated with survival in breast cancer, bladder cancer, rectal cancer, and melanoma.[5−8] Recent work examining multiple cancer registries has confirmed an association between long wait times and decreased survival in uterine cancer, including low-risk type I endometrial cancers.[9−13] These findings are increasingly important in North America, as wait times for surgery for endometrial cancer are increasing.[10,14]

Progesterone analogs are used to treat early type I endometrial cancers in women who desire to preserve fertility or cannot undergo surgery, and may represent a meaningful bridge to surgery for women subject to a long wait time. Progesterone analogs can restore the pathologic characteristics of normal endometrium, and recent work has identified tumor glandular cellularity as an important prognostic factor in tumor response to medical management.[15,16]

The objective of this study was to determine whether preoperative injection with depot medroxyprogesterone acetate (DMPA) decreases tumor glandular cellularity in women awaiting hysterectomy for endometrial

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AJOG at a Glance

Why was this study conducted?

Although it is known that long wait times to surgery for type I endometrial cancer are increasing and affect prognosis, most patients do not receive preoperative hormonal treatment. An effective preoperative hormonal treatment may mitigate risk in women who have long wait times to surgery.

Key findings

This study found that depot medroxyprogesterone acetate injection had significant tumor effect on type I endometrial cancers compared to placebo injection while women waited for surgery, without compromising quality of life.

What does this add to what is known?

This study contributes to an increasing literature showing the efficacy of progesterone analogs in treating type I endometrial cancer, and it is the first randomized study to examine preoperative use rather than using progesterone analogs with curative intent.

intraepithelial neoplasia or grade-1 to -2 endometrioid adenocarcinoma compared to placebo injection. Our secondary objective was to examine quality of life for women awaiting hysterectomy for endometrial cancer.

Materials and Methods

We performed a double-blind, randomized controlled trial at Women and Infants Hospital of Rhode Island in Providence, RI. Research approval was obtained from the institutional review board prior to recruitment (reference number 792629). This trial was registered on the ClinicalTrials.gov protocol registration and results system (NCT02335203). An investigational new drug exemption was obtained from the US Food and Drug Administration with reference number 125366.

From March 2015 through March 2016, patients referred to the Women and Infants Program in Women's Oncology with a new diagnosis of complex atypical hyperplasia, endometrial intraepithelial neoplasia, or grade-1 or -2 endometrioid adenocarcinoma of the uterus were approached for screening by a physician or research assistant.

Inclusion criteria were age ≥18 years, biopsy-proven histologic diagnosis (either by endometrial biopsy or dilation and curettage), ability to give informed consent in English, and plan for hysterectomy. Grade-3 endometrioid adenocarcinoma was not included as it is thought to be a more aggressive subtype compared to grade-1 or -2 tumors.[17]

Exclusion criteria included allergy to medroxyprogesterone acetate, evidence of extrauterine cancer on physical exam or imaging, a plan for management that did not include hysterectomy, history of breast cancer, hepatic disease, uncontrolled hypertension (defined as persistent systolic blood pressure ≥170 mm Hg or diastolic blood pressure ≥110 mm Hg), osteoporosis, or strong osteoporotic risk factors including anorexia nervosa, rheumatoid arthritis, and chronic glucocorticoid use. Women who had undergone treatment with any progesterone analog in the 6 weeks prior to diagnostic endometrial sampling or study enrollment were also excluded.

After written informed consent was obtained by a physician or research assistant, enrolled participants were randomized to receive either 400-mg intramuscular DMPA injection or placebo (0.9% sodium chloride injection). Women received the injection at the same clinic visit. This dose of DMPA was chosen based on a prior study performed by the Gynecologic Oncology Group in a group of women awaiting surgery for endometrioid adenocarcinoma of the uterus.[15] DMPA injection was chosen over alternative progesterone analogs due to the ease of administration as a 1-time injection, prior work on the subject by the Gynecologic Oncology Group, and the lack of need for an invasive procedure as with intrauterine device insertion.

Randomization lists were computer-generated by the pharmacy staff with a 1-to-1 allocation ratio in blocks of 4. The pharmacy prepared syringes containing 400-mg DMPA in a 1-mL solution or 1 mL of 0.9% sodium chloride labeled only with the study name and a sequentially ordered study identification number. The numbered syringe was dispensed to the medical assistant working at the clinic. Because the syringes did not appear identical, the medical assistant administered the injection intragluteally to prevent the patient from knowing her exposure status. The medical assistant was not involved in data analysis and was instructed to not allow the patient to observe the syringe. All other study personnel were blind to the assignment.

At enrollment, study participants were provided with a paper copy of the Functional Assessment of Cancer Therapy-Endometrial Survey (FACT-En) (Version 4), a validated quality-of-life instrument for patients with endometrial cancer.[18] Patients were instructed to complete the FACT-En the night prior to surgery and bring it with them to the hospital. This survey queries symptoms over the previous 7 days, and includes 43 items covering physical, social or family, emotional, and functional well-being, as well as questions specific to endometrial cancer. Questions are answered on a Likert-like scale and assigned a point value. Points are summed for each domain and an overall score is calculated, with a higher value reflecting better quality of life.

Patients underwent hysterectomy and staging per the standard of care of their gynecologic oncologist. Participation in this study had no impact on the timing of surgery. The completed FACT-En was collected during the patient's hospitalization. Patients who did not complete the survey preoperatively or bring it to the hospital were provided with a copy to be completed within 24 hours postoperatively. Adverse events and complications were recorded and reviewed by the principal investigator on a rolling basis.

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