GENERAL GYNECOLOGY

Topical 5-fluorouracil for treatment of cervical intraepithelial neoplasia 2: a randomized controlled trial

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OBJECTIVE: The objective of the study was to evaluate the efficacy of intravaginal application of 5% 5-fluorouracil (5-FU) for the treatment of cervical intraepithelial neoplasia (CIN) 2 in women.

STUDY DESIGN: Women aged 18-29 years with CIN 2 were recruited for this randomized controlled trial of observation vs treatment with intravaginal 5-FU. Women in the observation group returned in 6 months for a Papanicolaou smear, colposcopy, and a human papillomavirus (HPV) deoxyribonucleic acid test. Women in the 5-FU group were treated with intravaginal 5-FU once every 2 weeks for a total of 16 weeks and were similarly evaluated at 6 months. All women who had a baseline visit were included in the intention-to-treat analysis. Values of $P < .05$ were considered statistically significant.

RESULTS: Between August 2010 and June 2013, 60 women were randomized and had a baseline visit for intervention (n = 31) vs observation (n = 29). Of women who had cervical biopsy results at 6 months, regression of disease was demonstrated in 93% of women in the 5-FU group (26 of 28) and 56% of women in the observation group (15 of 27). Under the intention-to-treat analysis, a relative risk for cervical disease regression of 1.62 (95% confidence interval [CI], 1.10—2.56) was found between the 5-FU and observation arms ($P = .01$). When the cervical biopsy, Papanicolaou smear, and HPV results were combined for the 6 month follow-up visit, 50% of the 5-FU group (14 of 28) had a documented normal biopsy, normal Papanicolaou smear, and negative HPV test compared with 22% in the observation group (6 of 27) (relative risk, 2.25; 95% confidence interval, 1.05—5.09; $P < .05$). There were no moderate or severe side effects in the intervention group.

CONCLUSION: Topical 5-FU appears to be an effective medical therapy for CIN 2 in young women. 5-FU is readily available and may be considered as an off-label treatment option for young women with CIN 2 who are interested in the treatment of disease but want to avoid excisional procedures.

Key words: cervical intraepithelial neoplasia, 5-fluorouracil, medical therapy

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Historically, most women with cervical intraepithelial neoplasia (CIN) 2 and 3 underwent excisional therapy or ablation of the cervical transformation zone.[1-3] However, 5-26% of women have disease recurrence, even with negative surgical margins.[4] Additionally, excisional treatment procedures have been associated with increased risk of premature delivery[5-8] as well as anxiety, pain, bleeding, and health care expenditure.[8-11] Because nearly half of CIN 2 lesions regress in young women, current guidelines endorse close observation of young women as a preferable management strategy for CIN 2 and acceptable management strategy for CIN 3.[1,2,12-14] Although expectant management is appealing, approximately one-third of CIN 2 cases will persist and the remaining may progress to CIN 3 on follow-up.[12-14] There are no medical therapies recommended to promote the clearance of

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human papillomavirus (HPV) or cervical dysplasia.

Topical 5-fluorouracil (5-FU) is used for the treatment of skin cancers and lesions caused by HPV, including genital warts, vulvar intraepithelial neoplasia and vaginal intraepithelial neoplasia.[15-17] The 5-FU treatment of genital disease is an off-label use of the medication because it has not been approved by the Food and Drug Administration or recommended by the American College of Obstetricians and Gynecologists for this use.

Initial treatment regimens were associated with severe side effects such as pain and chronic ulceration.[18] These side effects were likely a dose-related response because standard treatments require multiple daily applications; studies limiting topical 5-FU to less frequent application or diluted doses have reported favorable side effect profiles.[19-21]

The objective of this study was to assess the efficacy, safety, and acceptability of intravaginal 5-FU as a primary treatment for CIN 2 in young women.

Materials and Methods

This was a prospective nonblinded, randomized trial of intravaginal 5% 5-FU vs standard-of-care observation in young women with CIN 2 (no placebo). The primary outcome was regression of disease 6 months after the diagnosis of CIN 2. Secondary outcomes included high-risk HPV status at 6 months, 12 month pathological findings, and safety and acceptability data.

This study was approved by the University of North Carolina (UNC) Institutional Review Board. All participants underwent written informed consent procedures.

Women (aged 18-29 years) presenting to the UNC's Women's Hospital Clinics with satisfactory colposcopic examinations, a biopsy-confirmed diagnosis of CIN 2, and in whom follow-up observation with cytology and colposcopy every 6 months was planned were approached for study enrollment. Women who were non-English speaking, human immunodeficiency virus (HIV) infected, immunosuppressed, pregnant, planning pregnancy, or breast-feeding during the study time period or were unwilling to use condoms and another form of birth control during the treatment time period were excluded from the study.

Dual contraception (condoms plus 1 of the following: oral, intravaginal, injectable, implantable, or intrauterine conception) was required for the 5-FU group because of its potential teratogenic effects demonstrated in intravenous administration.[22] Women were counseled regarding teratogenic risk during the consent process.

Order of randomization was generated based on a simple randomization table with a 1:1 allocation ratio, and assignments were placed into sequentially numbered opaque envelopes. After verbal interest was reported by a potential participant on the phone, women were randomized to an observation or treatment group (5-FU) by study staff. Participants in the observation group were given the option to have their written consent forms mailed and completion of a background survey by phone. They were scheduled for appointments in 6 months from biopsy date and received standard phone and written appointment reminders from the health care facility in addition to reminders from study staff. Reminders consisted of phone calls, texting, or e-mailing, depending on the preference of the participant.

The 5-FU group presented to the study site for written consent procedures and received written and verbal instructions for insertion of 2 g of 5-FU via vaginal applicators every 2 weeks for a total of 8 doses. This dosing schedule was based on its reported safety, tolerability, and efficacy in a prior trial of intravaginal 5-FU for the prevention of recurrence of CIN after excisional procedure in HIV-infected women.[21] However, because our study's patient population was not potentially immunocompromised, we chose a shorter course of 16 weeks as per other treatment studies for HPV-related diseases.[7,8,23,24]

The 5-FU participants were instructed to insert 2 g of topical 5% 5-FU cream (Efudex; Valeant Pharmaceuticals International, Quebec, Canada) at night with a vaginal applicator, which could be twisted onto the study tube for the removal of 5-FU cream. After the medication was inserted into the vagina proximal to the cervix, participants placed a tampon per vagina overnight to keep the cream at the cervix. Participants were instructed to remove the tampon in the morning, shower, and frequently hand wash and change panty liners over the next 2 days to avoid irritation from the cream.

Women were supplied home pregnancy tests for use prior to each application of cream. Condoms or abstinence from sexual activity 48 hours after use of the cream was also recommended to diminish any potential irritation to the participant's sexual partner. All supplies were provided to the participants. Use of study drug was delayed if a participant was having her menstrual cycle.

Participants in the 5-FU group returned for a safety and acceptability visit at the study site after 8-16 weeks of use of intravaginal 5-FU to complete a survey and pelvic examination. A single unblinded coinvestigator assessed adherence and genital symptoms and performed a colposcopic examination of vaginal and cervical tissue as per the National Institutes of Health Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events: Female Genital Grading Table for Use in Microbicide Studies (Table 3 for a listing of criterion.).[25]

The interview included an acceptability questionnaire in which participants were surveyed regarding emotions felt while using the cream and side effects to their sexual partner; logistical concerns surrounding use of the cream were scored on a 5 point Likert scale. Prior to the 6 month visit, all participants received hospital-based and study-based reminders similar to the observation group described above.

At the 6 month visit, colposcopically guided cervical biopsies were performed at the site previously biopsied and diagnosed with CIN 2 on original histology 6 months prior for both intervention and control arms. In all participants, additional biopsies were obtained if there was clinical concern for other areas of dysplasia. We completed similar