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A Randomized, Double-Blind, Placebo-Controlled Trial of 5-Fluorouracil for the Treatment of Cervicovaginal Human Papillomavirus

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ABSTRACT

Objective: To compare intravaginal 5-fluorouracil (5-FU) and placebo for the treatment of cervical and/or vaginal human papillomavirus (HPV).

Methods: A randomized, placebo-controlled trial was performed. Women with HPV detected visually or by Papanicolaou (Pap) test and confirmed by colposcopic biopsy were randomized to receive either intravaginal 5-FU cream or an intravaginal placebo cream. Women with cervical or vaginal intraepithelial neoplasia were excluded. The primary outcome measure was cytologic regression of HPV as determined by Pap test screening 4 to 6 months after treatment. The secondary outcome was cytologic evidence of disease progression at both the 4–6-month and 12-month follow-up evaluations. Data were analyzed using the Chi square test with significance established at $P < 0.05$.

Results: A total of forty patients were randomized, and thirty patients had a follow-up Pap test 4 to 6 months after treatment. Of those patients treated with 5-FU, 28% demonstrated regression of HPV on cytologic evaluation, compared with 69% of those treated with placebo ($P < 0.05$). Twelve-month follow-up cytology was available from 18 of the study participants. There were no significant differences in the frequency of cytologic progression or regression between groups at 12 months.

Conclusion: Four to six months post treatment, the use of intravaginal 5-FU for the treatment of cervical or vaginal HPV is associated with a lower rate of regression than the use of placebo. Infect. Dis. Obstet. Gynecol. 7:186–189, 1999. © 1999 Wiley-Liss, Inc.

KEY WORDS

condyloma; human papillomavirus; 5-fluorouracil

Human papillomavirus (HPV) is a commonly occurring, sexually transmitted virus that has been identified as a cause or cofactor in the development of lower genital tract dysplasia and carcinoma.[1] Most HPV infections are asymptomatic and are identified through cytologic screening or more advanced DNA technologies. A smaller percentage manifest as external or internal genital warts. The treatment of lower genital tract HPV can be difficult because the disease tends to be recurrent or persistent even after lesions are destroyed.[2] Treatment strategies for HPV without evidence of dysplasia are controversial, especially for subclinical disease that is identified through routine cytologic screening. Although spontaneous regression rates of HPV related atypia and dysplasia may be as high as 76%,[3] there is also evidence demonstrating the progression of HPV lesions to carcinoma in situ and invasive cancer.[3–5] This malignant potential has prompted some investigators to recommend treat-

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ment of subclinical HPV to prevent subsequent carcinogenesis.[6]

The antimetabolite 5-fluorouracil (5-FU) has been recommended for the treatment of subclinical HPV, genital warts, and lower genital tract dysplasia.[7–9] It has the advantage of being an inexpensive treatment that does not require special equipment or anesthesia. However, 5-FU is associated with significant side effects, including acute vulvovaginitis, chronic epidermal or mucosal erosions, and acquired adenosis.[10–13]

Some clinicians prescribe 5-FU for clinical and subclinical HPV despite the adverse side effect profile and evidence to suggest that HPV often undergoes spontaneous regression or resolution. It is the purpose of this study to evaluate the effectiveness of intravaginal 5-FU cream versus placebo cream for the treatment of vaginal or cervical HPV.

METHODS

Between February 1996 and March 1997, a randomized, double-blind, placebo-controlled study was conducted at the Medical University of South Carolina's outpatient colposcopy clinic, a referral center for patients with abnormal cervical cytologic screening results. The protocol was approved by the institutional review board, and all patients gave written informed consent before inclusion in the study. Subjects eligible for inclusion were females between the ages of 18 and 45 years who had a screening Pap test demonstrating abnormalities consistent with HPV and also had colposcopic-directed biopsies confirming HPV. Patients with a colposcopic biopsy revealing cervical intraepithelial neoplasia (CIN) were excluded from participation. Additionally, only those patients using some form of barrier, hormonal, or surgical contraception were included. Other exclusion criteria included pregnancy, known hypersensitivity to 5-FU, known human immunodeficiency virus, and clinical evidence of vaginitis or cervicitis.

Patients who met the inclusion criteria were randomized in a 1:1 ratio to receive either intravaginal 5-FU or placebo. The research pharmacist generated the randomization list using a computer-generated randomization table. The 5-FU cream used was a marketed 5% cream preparation (Efudex, Roche Laboratories, Basel, Switzerland). The placebo cream was compounded by the research pharmacist using a similar cream base which made the two preparations indistinguishable by sight or smell. The treatment and placebo creams were dispensed in prefilled intravaginal applicators, and the appropriate quantity of applicators for the entire treatment protocol was placed in a single envelope. The envelopes were numbered sequentially according to the randomization list. Subjects were instructed by study nursing personnel in the technique for medication application. Intravaginal applications were administered weekly for 4 weeks, then every other week for two additional doses. This dosing regimen has been reported by previous authors.[7] The dosing schedule was reinforced with a treatment calendar on which days of treatment were circled. Compliance with treatment was monitored by having each subject mark her treatment calendar the day she used the medication. Repeat cytologic assessment by Pap test was performed within 4–6 months after randomization and recorded for analysis. Subsequent follow-up Pap test results were recorded for up to 18 months after enrollment.

The primary outcome measure was the frequency of cytologic regression of HPV as determined by Pap test screening 4 to 6 months after randomization. Secondary outcomes included any cytologic evidence of progression of disease; this was calculated for the 4–6- month follow-up interval and also for the 12–18-month follow-up interval. Data were analyzed using the Chi square test with significance established at $P < 0.05$.

RESULTS

Forty patients were randomized to receive either intravaginal 5-FU or placebo. Thirty patients (5-FU = 14, placebo = 16) presented for follow-up cytologic evaluation between 4 and 6 months after initiation of intravaginal therapy. Of those patients treated with 5-FU, 28% demonstrated regression of HPV on cytologic evaluation, compared with 69% of those treated with placebo ($P < 0.05$). Additionally, 64% of those patients treated with 5-FU had cytologic evidence of progressive dysplasia, compared with 31% of those exposed to placebo only ($P = 0.07$). No patients in either group demonstrated cytologic progression beyond mild dysplasia (CIN I) on the initial 4–6-month follow-up Pap test.

Twelve-month follow-up cytology was available for 18 of the study participants (5-FU = 10, placebo = 8). There were no significant differences in the

frequency of cytologic progression or regression between groups. Only five of the 18 demonstrated cytologic abnormalities, none of which progressed beyond mild dysplasia.

DISCUSSION

Our randomized, controlled trial of intravaginal 5-FU versus placebo for the treatment of subclinical vaginal or cervical HPV indicates that 4 to 6 months after treatment, patients using placebo demonstrate regression of HPV more frequently than those treated with 5-FU. One year out from treatment, there seems to be no difference between treatment groups with respect to disease progression or regression. Our findings do not support the high response rate identified by Krebs in his study of 5-FU for the treatment of vaginal condyloma.[7] In his series of 20 patients, a similar dosing regimen of 5-FU was prescribed, and 85% of patients had no evidence of disease by colposcopy and cytology at 3 months posttreatment; there were no control patients in this study for comparison. In a comparative treatment study for condyloma acuminata, Ferenczy found 5-FU to be more effective than CO_2 laser ablation for the treatment of condyloma acuminata.[13] Based on these previous studies, our findings of poorer outcomes among the 5-FU users was unexpected.

The less desirable outcome associated with 5-FU treatment in our study may even suggest an adverse effect of 5-FU on subclinical HPV. Perhaps the antimetabolite action of 5-FU transiently interrupts the normal immune function that is responsible for spontaneous regression. Another study using 5-FU or trichloroacetic acid (TCA) as a "prophylactic" treatment following laser ablation of subclinical cervicovaginal HPV demonstrated a similar "worsening" of HPV among subjects treated with 5-FU, but not among those who were treated with nothing or with trichloroacetic acid.[14] In this observational study, the group treated with laser plus 5-FU had recurrence/persistence rates of 68% at 3 months compared with the control group (laser treatment only) with 19% and the laser-plus-TCA group with 15%. In our study, 69% of the placebo users had regression of the disease at the 4–6-month follow-up visit. This is consistent with the high spontaneous regression rates reported by others.[3, 15]

Our data on longer term outcomes are severely limited by poor follow-up compliance among our study subjects. Of the original 40 patients who were randomized, only 18 returned during the 12–18-month follow-up interval. Five of the 18 patients screened at 12–18 months had either persistent HPV or mild dysplasia; the remainder had normal cytology. Although there was no difference between the treatment and placebo groups, we cannot make any conclusions based on this small number.

We had no reports of serious side effects other than minor vulvar irritation reported by one patient. The remainder of patients who returned for the first follow-up visit reported and documented compliance with the study treatment protocol We do not believe that the poor follow-up rates are related to treatment compliance or adverse side effects, but are more likely the result of serving a largely indigent, referral population.

In conclusion, our study demonstrates that the use of 5-FU for the treatment of HPV infections of the cervix and vagina is associated with a lower rate of regression than the use of placebo. Given this lack of efficacy and data supporting the high rate of spontaneous resolution of HPV, it is appropriate to follow these patients with regular cytologic screening and avoid the use of caustic therapy that may indeed have an undesirable effect on subclinical disease.

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