Effect of a 1-Week Treatment With 0.5% Topical Fluorouracil on Occurrence of Actinic Keratosis After Cryosurgery

A Randomized, Vehicle-Controlled Clinical Trial

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Background: No long-term randomized controlled clinical trial has compared the efficacy of cryosurgery alone vs cryosurgery following fluorouracil applications for the treatment of actinic keratosis.

Objective: To determine the 6-month outcome of a 1-week course of 0.5% fluorouracil followed by cryosurgery.

Design: Prospective, multicenter, randomized, double-blind, vehicle-controlled clinical trial performed in community and academic outpatient clinics.

Patients: A total of 144 patients with 5 or more visible or palpable actinic keratoses on the face.

Interventions: Topical 0.5% fluorouracil or vehicle once daily for 7 days. At the 4-week follow-up visit, residual lesions were treated with cryosurgery.

Main Outcome Measure: Reduction in facial actinic keratoses from baseline to 4 weeks and 6 months.

Results: At 4 weeks, mean actinic keratosis lesion count was reduced by 62.4% in the 0.5% fluorouracil group vs 28.8% in the vehicle group (P<.001), and complete clearance was achieved in 16.7% of patients in the 0.5% fluorouracil group vs 0% of those in the vehicle group (P<.001). At 6 months, mean lesion count was reduced by 67.0% in the 0.5% fluorouracil plus cryosurgery group vs 45.6% in the vehicle plus cryosurgery group (P=.01), and significantly more patients in the 0.5% fluorouracil plus cryosurgery group than in the vehicle plus cryosurgery group had complete clearance (30% vs 7.7%; P<.001).

Conclusions: A 1-week course of topical 0.5% fluorouracil before cryosurgery is significantly more effective in reducing patients’ numbers of actinic keratosis lesions 6 months after treatment than cryosurgery alone. The high occurrence rate of actinic keratosis lesions at 6 months suggests a need for follow-up.

Arch Dermatol. 2004;140:813-816

MORE THAN 1 MILLION new cases of skin cancer will be diagnosed in the United States and an estimated 9800 individuals will die from skin cancer this year. Actinic keratosis (AK) skin lesions have an estimated 10% rate of progression to invasive squamous cell carcinoma. Because AK has the potential to evolve into an aggressive disease, treatment of all AK lesions has been recommended.

Effective treatments for AK lesions include chemical destruction by topical medications such as 5-fluorouracil or physical destruction by cryosurgery, curettage, electrosurgery, and in some cases, excision or dermabrasion. The most commonly used treatment modality in the United States is cryosurgery with liquid nitrogen. Fluorouracil is an antineoplastic antimetabolite that has been known for approximately 40 years to have beneficial effects on AK lesions. Clinical trials have repeatedly found topical fluorouracil to be effective for the treatment of AK lesions when applied in concentrations of 0.5%, 1%, and 5%.

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The long-term outcomes of cryosurgery and the effect of a regimen using topical fluorouracil before cryosurgery have not been evaluated in randomized or controlled trials. A 1-week course of topical 0.5% fluorouracil is effective and well tolerated in the treatment of AK. The pre-
Methods

PATIENTS

Eligible patients were 18 years or older and had 5 or more visible or palpable AK lesions on the face. Women were eligible if they were postmenopausal or using appropriate contraceptive methods and not pregnant or lactating. Patients were excluded if they had basal or squamous cell carcinomas, other potentially confounding skin conditions, or known allergies to ingredients of the test drug formulation; or if they had been treated for AK lesions with topical medications within the 5 previous months, had cryosurgery within the previous 4 weeks, or were engaged in activities that involved excessive or prolonged exposure to sunlight. Patient recruitment took place from October 2001 to February 2002.

STUDY DESIGN

This is a 12-month, multicenter, randomized, double-blind, vehicle-controlled clinical trial with a preplanned 6-month interim analysis (presented in this report) after completion of the first cycle of treatment. The study was performed in community and academic outpatient clinics. Eligible patients were randomly assigned in a 1:1 ratio at baseline (day 1) to apply topical 0.5% fluorouracil cream (Carac; Dermik Laboratories, Berwyn, Pa) or vehicle cream once daily for 7 days to the face plus 1 or more of the following investigator-designated areas: scalp, ears, neck, and/or lips (defined at screening as the treatment area). Eligible patients at each site were assigned by the investigator the next available (ie, lowest available) treatment allocation number from a computer-generated randomization schedule. All study personnel, investigators, and patients were blinded to actual treatment assignment. The fluorouracil and vehicle creams, which were indistinguishable in texture, color, and smell, were supplied in identical tubes, patient kits, and labeling.

Any residual AK lesions in the treatment area were treated after the 4-week assessment with liquid nitrogen cryosurgery as a single spray of 1 to 2 seconds with a Cryrac device (Brymill Inc, Vernon, Conn), with a resultant mean thaw time of about 10 seconds. Patients then returned for follow-up 6 months (± 2 weeks) after initial topical treatment.

The study protocol was approved by institutional review boards at all participating institutions, and written informed consent was obtained from all patients before study enrollment.

EFFICACY AND TOLERABILITY OUTCOME MEASURES

Efficacy variables were the numbers of facial AK lesions, the proportion of patients with complete clearance of AK lesions, and the occurrence (ie, presence) rate of AK lesions. The same evaluator counted visible and/or palpable AK lesions before initial treatment and at the 4-week and 6-month follow-up visits.

Severe application site reactions (erythema, edema, dryness, pain, erosion, burning, and pruritus) and eye irritation (burning, sensitivity, itching, stinging, and watering) were recorded at each visit, as were any other adverse events.

STATISTICAL ANALYSIS

A sample size of 70 patients per treatment group was calculated to provide greater than 90% power to detect a difference in clearance rates at 4 weeks, based on the assumption of a 20% clearance in the fluorouracil group and a 3% clearance in the vehicle group. Assuming a standard deviation of 25% and a dropout rate of 25% by 6 months, this sample size would also provide greater than 80% power to detect a significant difference (at the .025 level to adjust for multiple analyses) in occurrence at 6 months between the fluorouracil and vehicle groups.

The primary efficacy end points were the reduction (absolute and percentage) in AK lesions at the 4-week follow-up visit, the proportion of patients with complete clearance of AK lesions at the 4-week follow-up visit (before cryosurgery), and the occurrence rate at the 6-month follow-up visit. The clearance rate at 6 months was also determined.

Efficacy analyses were performed for all patients of this intent-to-treat study who had at least 1 postbaseline efficacy measurement. Between-group comparisons for AK lesion

Table 1. Baseline Demographics and Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Topical 0.5% Fluorouracil +</th>
<th>Vehicle + Cryosurgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 72)</td>
<td>(n = 70)</td>
</tr>
<tr>
<td>Age, mean (range), y</td>
<td>62.6 (33-88)</td>
<td>62.6 (43-84)</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>62 (86)</td>
<td>57 (81)</td>
</tr>
<tr>
<td>Female</td>
<td>10 (14)</td>
<td>13 (19)</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>71 (99)</td>
<td>67 (96)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (1)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Complexion, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light</td>
<td>48 (67)</td>
<td>47 (67)</td>
</tr>
<tr>
<td>Medium</td>
<td>24 (33)</td>
<td>23 (33)</td>
</tr>
<tr>
<td>Dark</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lesion count, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All areas</td>
<td>22.6 (18.2)</td>
<td>19.6 (13.4)</td>
</tr>
<tr>
<td>Face</td>
<td>13.7 (9.3)</td>
<td>13.1 (7.6)</td>
</tr>
<tr>
<td>Lips</td>
<td>1.8 (0.8)</td>
<td>2.0 (0.7)</td>
</tr>
<tr>
<td>Ears</td>
<td>3.0 (1.9)</td>
<td>2.0 (1.1)</td>
</tr>
<tr>
<td>Neck</td>
<td>5.1 (4.3)</td>
<td>3.4 (2.7)</td>
</tr>
<tr>
<td>Scalp</td>
<td>13.6 (14.5)</td>
<td>10.4 (10.7)</td>
</tr>
</tbody>
</table>

Numbers of patients with actinic keratosis lesions who were randomized to treatment with topical 0.5% fluorouracil or vehicle before cryosurgery and evaluated at 4-month and 6-month follow-up visits.

(REPRINTED) ARCH DERMATOL/VOL 140, JULY 2004 WWW.ARCHDERMATOL.COM

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counts and percentage reduction of AK lesions were performed using a Wilcoxon rank sum test. A Mantel-Haenszel $\chi^2$ test was used to compare the proportion of patients in each group with total clearance of AK lesions at the 4-week and 6-month follow-up visits. Occurrence at 6 months was analyzed by comparison of the number of AK lesions and the percentage reduction in AK lesions using a Wilcoxon rank sum test. Changes from baseline within a treatment group were analyzed using a paired $t$ test.

Statistical outcomes for the between-group comparisons at 4 weeks were considered significant with $P<.05$. For the between-group comparison of occurrence rates at 6 months, the analysis was considered significant with $P<.025$.

## RESULTS

### PATIENTS

Of the 144 patients enrolled in the study, 72 were randomly assigned to receive topical 0.5% fluorouracil and 72 to receive vehicle (Figure 1), and 142 were included in the intent-to-treat study population. Of these, 1 patient who did not return for follow-up and 1 who withdrew consent prior to treatment were not included in the efficacy analyses. The 143 patients who received any study treatment were included in the safety analyses. There were no important differences in patient demographics or baseline characteristics between treatment groups (Table 1).

### CLINICAL EFFICACY

At 4 weeks, patients treated with topical 0.5% fluorouracil cream once daily had significantly fewer AK lesions on the face than those in the vehicle group (4.3 vs 9.1, respectively; $P<.001$). Both the absolute and percentage reduction in AK lesions from baseline were significantly greater in the topical 0.5% fluorouracil group than in the vehicle group ($P<.001$) (Table 2). The proportion of patients with complete clearance of facial AK lesions at 4 weeks was 16.7% in the topical 0.5% fluorouracil group and 0% in the vehicle group ($P<.001$) (Table 2). Patients with residual lesions at the 4-week follow-up visit received cryosurgery to remove all remaining lesions.

Six months after the initial treatment, 30% of patients in the topical 0.5% fluorouracil plus cryosurgery group were clear of facial AK lesions compared with 7.7% of patients in the vehicle plus cryosurgery group ($P<.001$). The mean number of AK lesions present was significantly less and the percentage reduction significantly greater ($P=.01$ for both end points) for patients in the topical 0.5% fluorouracil plus cryosurgery group than for patients in the vehicle plus cryosurgery group (Table 2), although the mean absolute change from baseline was not significantly different. Of the 12 patients in the topical 0.5% fluorouracil treatment group who were clear of AK lesions at the 4-week follow-up visit (and therefore did not require cryosurgery), 11 had an assessment at 6 months. Five of the 11 patients remained clear at 6 months.

### TOLERABILITY

Eye irritation occurred in as many patients in the vehicle group (10 [14%]) as in the topical 0.5% fluorouracil group (10 [14%]) and was rated as mild for all but 1 patient in the fluorouracil group who had moderately severe irritation. Application site reactions were reported in 13 patients (18%) in the topical 0.5% fluorouracil group and in 3 patients (4%) in the vehicle group ($P=.02$). No patient discontinuations were due to adverse events.

The results of this study indicate a need to evaluate patients 6 months after treatment for AK lesions, especially if cryosurgery alone is used. More than 90% of patients who had cryosurgery but did not receive pretreatment with 0.5% fluorouracil had lesions at 6 months. Treatment with topical 0.5% fluorouracil be-
fore cryosurgery significantly reduced the proportion of patients with AK lesions compared with patients receiving cryosurgery alone, and thus reduced the need for retreatment during long-term follow-up.

The initial 4-week treatment results confirmed the finding of other controlled trials that topical 0.5% fluorouracil is effective in reducing AK lesions when used once daily for 1 week.17,18 The clearance rates of 16.7% and 0% (fluorouracil vs vehicle) at 4 weeks were close to the assumed rates of 20% and 3% used in determining statistical power of the study. The power of the study is therefore adequate to support the conclusion that a 1-week course of 0.5% fluorouracil is significantly more effective than vehicle.

The results at 6 months demonstrate that a short course of topical fluorouracil before cryosurgery significantly improves long-term outcomes. These results were achieved even though the statistical analysis was adjusted to account for the fact that this was an interim analysis. One possible explanation for this improvement in long-term efficacy may be that subclinical AK lesions may have become clinically evident after fluorouracil treatment, allowing earlier removal with cryosurgery. Fluorouracil also may have successfully treated incipient lesions, thus preventing their progression.

Although it is commonly accepted that cryosurgery eradicates AK lesions, we could find no randomized or controlled prospective trials in the literature that studied longer-term outcomes of cryosurgery for AK. An open observational study found a long-term cure rate of 98.8% with cryosurgery, based on 12 recurrences of 1018 treated lesions in 70 patients.9 It was not stated if patients in this study received other treatment at any time or if new lesions occurred. Because of the differences in study design, no comparison can be made with the results of the current study, which found a higher incidence of AK lesions at 6 months.

Only anecdotal evidence of sequential use of topical fluorouracil and cryosurgery in treatment of AK lesions has previously been reported.19 Abadir20 described a method in which patients were treated with topical 5% fluorouracil twice daily for 10 days, after which areas showing actinic damage were sprayed with liquid nitrogen. Although the method was described as successful, no quantitative outcomes were provided. The present study provides quantitative support for the use of topical fluorouracil and cryosurgery for the treatment of AK lesions and suggests that this novel approach can reduce the occurrence of new lesions. Although most patients are treated intermittently with cryosurgery, they maintain a high number of lesions. Interval therapy for 1 week with topical fluorouracil may therefore reduce the number of lesions requiring cryosurgery.

In conclusion, the results of our study support the need for a 6-month follow-up visit for patients treated for AK lesions. Most patients will have lesions again within 6 months of receiving cryosurgery for multiple AK lesions. A 1-week course of topical 0.5% fluorouracil before cryosurgery significantly increases the proportion of patients who are clear of facial AK lesions at 6 months, thus reducing the need for retreatment.

Accepted for publication January 2, 2004.

This study was supported by a grant from Dermik Laboratories.

We thank the following investigators who participated in the clinical trial: Alicia Bucko, DO, Albuquerque, NM; Steven M. Davis, MD, San Antonio, Tex; Alan Menter, MD, Dallas, Tex; Toivo Rist, MD, Knoxville, Tenn; Joel S. Shavin, MD, Snellville, Ga; and Daniel Stewart, DO, Clinton Township, Mich.

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