Facial Resurfacing for Nonmelanoma Skin Cancer Prophylaxis

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Objective: To determine the effect of facial skin resurfacing for treatment of actinic keratoses (AKs) and prophylaxis against new primary basal and squamous cell carcinomas in individuals with previous nonmelanoma skin cancer (NMSC) or severe photodamage.

Design: Randomized, prospective 5-year trial.

Setting: Dermatology and otolaryngology clinics of a Veterans Affairs hospital.

Patients: Thirty-four patients with a history of facial or scalp AKs or basal or squamous cell carcinoma were enrolled. Five of 7 eligible patients who declined study-related treatment were used as controls. Twenty-seven patients were randomized to 3 treatment arms; 3 patients were discontinued from the study.

Interventions: Carbon dioxide laser resurfacing, 30% trichloroacetic acid peel, or 5% fluorouracil cream applied twice daily for 3 weeks.

Main Outcome Measures: Reduction in the number of AKs was measured 3 months after treatment. The incidence of new NMSC in treated areas was assessed between January 1, 2001, and June 30, 2005. Times from baseline to diagnosis of first skin cancer were compared between the treatment and control groups.

Results: Treatment with fluorouracil, trichloroacetic acid, or carbon dioxide laser resulted in an 83% to 92% reduction in AKs (P < .03), a lower incidence of NMSC compared with the control group (P < .001), and a trend toward longer time to development of new skin cancer compared with the control group (P = .07). However, no significant differences were noted among the treatment groups.

Conclusion: All 3 modalities demonstrated benefit for AK reduction and skin cancer prophylaxis compared with controls and warrant further study in a larger trial.

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substantial actinic damage or a history of NMSC. Preliminary studies have shown that resurfacing of the face can prevent or delay the occurrence of these lesions, especially in high-risk patients. We compared 2 skin resurfacing regimens, carbon dioxide laser resurfacing and 30% trichloroacetic acid peel, with topical 5% fluorouracil cream to determine whether any modality was superior for AK reduction and skin cancer prevention during a 5-year study.

METHODS

This study was approved by the institutional review boards of the Veterans Affairs Palo Alto Health Care System (VAPAHCS) and Stanford University Medical Center. Eligible patients included those evaluated in the VAPAHCS dermatology clinic between October 1, 2000, and October 30, 2002, with a history of facial or scalp NMSC and numerous AKs or significant photodamage alone (Fitzpatrick skin types I, II, and III). Demographic data and the occurrence of previous facial and nonfacial skin malignancies were recorded, as were the number, types, and locations of AKs at the time of enrollment. History of SCC or basal cell carcinoma (BCC) in treated and non-treated areas was noted, as were those with NMSC present at the time of enrollment, unless treated. No topical therapy or LN2 cryotherapy was permitted on face and scalp within 5 years of enrollment were excluded, as were those with a history of facial or scalp NMSC and numerous AKs or significant photodamage alone (Fitzpatrick skin types I, II, and III). The diagnosis of AK was made on clinical grounds and was confirmed by an experienced dermatologist (S.M.S.). Patients were prospectively randomized to 1 of 3 treatment arms: carbon dioxide laser skin resurfacing, 30% trichloroacetic acid peel, or full-face treatment with 3% fluorouracil cream. Patients who had undergone facial resurfacing procedures (laser or chemical peel) within 5 years of enrollment were excluded, as were those with NMSC present at the time of enrollment, unless treated. No topical therapy or LN2 cryotherapy was permitted on face and scalp sites for at least 2 months before enrollment.

The number and locations of existing AKs were charted on a diagram of the head at enrollment and throughout the 24-month follow-up period (Figure 1). The diagnosis of AK was made on clinical grounds and was confirmed by an experienced dermatologist (S.M.S.). Patients were prospectively randomized to 1 of 3 treatment arms: carbon dioxide laser skin resurfacing, 30% trichloroacetic acid peel, or full-face treatment with 3% fluorouracil cream. Patients were examined by the same investigators (Z.A.C., B.M.H., and S.M.S.) every 3 months, at which time the number of AKs present on the treated areas was noted. Any newly diagnosed lesions were either treated with LN2 if clinically considered to be an AK or biopsied if clinically suggestive of BCC or SCC.

Full-face carbon dioxide laser resurfacing was performed in the otolaryngology clinic at VAPAHCS. Resurfacing encompassed the forehead, nose, cheeks, and chin; the neck was not treated but was feathered with the laser to prevent a line of demarcation. Resurfacing was performed in a minor procedure room under local anesthesia. All the patients received 2 passes with the carbon dioxide laser (Ultrapulse; Coherent Inc, Santa Clara, Calif.). The first pass was made over the entire skin of the face at a setting of 6 W. The second pass was perpendicular to the first pass, at a setting of 5 W, and avoided nasal skin. Perioperative care included the application of topical 0.05% tretinoin cream to the face each night for 1 month before the procedure and again at 3 weeks after skin resurfacing. Patients received valacyclovir hydrochloride, 500 mg twice daily, 2 days before resurfacing and continuing through postoperative day 10. After the procedure, patients received an occlusive dressing and ciprofloxacin, 500 mg twice per day, for 5 days. Patients continued prophylactic treatment with 0.05% tretinoin cream to the face each night for 1 month before the procedure and again at 3 weeks after skin resurfacing. Patients received valacyclovir hydrochloride, 500 mg twice daily, 2 days before resurfacing and continuing through postoperative day 10. After the procedure, patients received an occlusive dressing and ciprofloxacin, 500 mg twice per day, for infection prophylaxis. Acetaminophen with or without hydrocodone bitartrate was provided as needed for pain. After the second postprocedural day, patients were instructed to wash their face 3 times per day with superflatted, fragrance-free cleanser; soak the treated areas with diluted acetic acid 3 to 4 times per day; and apply bland hydrophilic ointment until reepithelialization occurred. Patients in all 3 treatment arms were instructed to avoid excessive sun exposure for 3 months and to undertake strict photoprotection measures.

Chemical full-face resurfacing was performed using 30% trichloroacetic acid (Spectrum Quality Products, New Brunswick, NJ). Patients underwent the same preoperative and postoperative regimen as those undergoing laser resurfacing, except for ciprofloxacin prophylaxis. Trichloroacetic acid resurfacing was performed in the dermatology clinic at VAPAHCS and involved standard skin preparation with acetone-soaked sponges to defat the skin. This was done to ensure even penetration of the 30% trichloroacetic acid, which was applied to the face using a 2 × 2-inch gauze pad. The solution was feathered into the hairline, vermilion zone, and superior neck to avoid a visible line of demarcation. Application was discontinued on the presence of an even frost on the skin surface, indicating that protein agglutination had taken place.

Treatment with 5% fluorouracil cream involved twice-daily application for 3 weeks, as tolerated. The patient performed this application at home. A low-potency corticosteroid preparation, 0.05% desonide lotion, was used for 1 to 2 weeks after fluorouracil treatment to decrease redness and irritation.

After treatment, all the patients in the treatment arms of the study were instructed to apply sunscreen with a sun protective factor of at least 30 each morning and 0.05% tretinoin cream to the face or scalp each night. Any AKs remaining at the first 3-month follow-up evaluation were treated with LN2. In the control group, LN2 cryotherapy was similarly used for AKs and surgical excisions performed for new NMSC; strict photoprotection with sunscreen and hats was recommended as well.

Treated patients were evaluated every 3 months for a minimum of 24 months. At each visit, AKs were treated with LN2, and any lesions suggestive of BCC or SCC were biopsied. Patients were also monitored for any adverse events at each visit. At the end of the 24-month study, patients continued routine general dermatology clinic surveillance for AKs and NMSC. The VAPAHCS medical and pathologic records were reviewed for each patient through June 30, 2005, to evaluate for any subsequent development of skin cancer in treated areas.

Data were tabulated using Microsoft Excel 2003 (Microsoft Corp, Redmond, Wash), and statistical analyses were performed using Analyze-it (version 1.73; Analyze-it Software Ltd, Leeds, England) and Prism 4 for Windows (version 4.03; Graph-
Patients Received

Patients Received

Had a Protocol

Completed Treatment

10

6

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Figure 2. Patient allocation diagram. Of 34 patients enrolled in the study, 7 never scheduled treatment, 5 of whom were followed up as controls. The remaining 27 patients were randomized to 1 of 3 treatment arms: 5% fluorouracil cream, 30% trichloroacetic acid peel, or carbon dioxide laser resurfacing. These patients compose the intention-to-treat population.

Pad Software Inc, San Diego, Calif). Nonparametric tests were performed to accommodate the relatively small sample size. Individuals who enrolled but did not begin treatment were used as a control population for evaluating cancer rates in this population but were not included in the evaluation of AK formation. The Wilcoxon signed rank test was used to compare numbers of AKs at various points for each of the treatments.

Rates of cancer formation were evaluated in 2 ways. First, cancer incidence rates were calculated as a ratio of the total number of cancers to the total number of patient-years followed in each group. This total number of patient-years was based on the number of days each patient was followed up. Rates of cancer formation per patient-year of follow-up were compared using χ² analysis. Second, the number of days from baseline/treatment to diagnosis of the first NMSC was evaluated using Kaplan-Meier curves that accounted for patient dropouts. These curves were compared among the groups using a log-rank test.

RESULTS

A total of 34 VAPAHCS patients (33 men and 1 woman, all white) were enrolled in the study; 7 withdrew before treatment. Of the remaining 27 patients, 9 were prospectively randomized to treatment with fluorouracil, 10 to trichloroacetic acid peel, and 8 to carbon dioxide laser resurfacing. Exclusion of patients from further analysis also occurred for the following reasons: inadvertent use of 5% fluorouracil for 3 months rather than 3 weeks in the fluorouracil arm (1 patient) and incomplete facial resurfacing due to intolerance to the procedure in the carbon dioxide laser resurfacing arm (2 patients). Of the 7 untreated patients, 1 underwent full-facial carbon dioxide laser resurfacing outside the study, and 1 did not return for any dermatology appointments, leaving 5 individuals in the untreated control group. Approximately 50% of the patients reported noncompliance with regular posttreatment application of tretinoin and sunscreen; similar rates of photoprotection adherence were noted in the control group. Figure 2 summarizes the overall allocation scheme for all the patients enrolled in the study.

After excluding 3 patients because of protocol violations, the 24 evaluable patients were aged 54 to 91 years (mean, 72.8 years) (Table 1). Before study entry, all but 3 patients had a history of NMSC, and 6 had a history of NMSC in areas other than the face or scalp. No significant differences in mean age were found among the 3 study arms (Table 1). All the patients were men, consistent with the demographics of the VAPAHCS population.

Patients were followed up for 24 months after the procedure at 3-month intervals. One patient with a history of BCC in the trichloroacetic acid arm had no AKs at enrollment and was therefore excluded from the AK count analysis. No significant differences were noted among the fluorouracil, trichloroacetic acid, and carbon dioxide arms (P = .31). However, the percentage reductions in mean AK count 3 months after facial resurfacing with fluorouracil, trichloroacetic acid, and carbon dioxide were all significant: 83% (P = .008), 89% (P = .004), and 92% (P = .03), respectively (Table 2). No adverse effects, such as postinflammatory pigmentation alteration, scarring, or purpura, were noted in the 3 treatment arms.

Of the 8 patients in the fluorouracil arm who received appropriate treatment, 2 were lost to follow-up before the 24-month point. One patient developed 5 SCCs during follow-up. Of the 10 patients in the trichloroacetic acid arm, 2 died of unrelated medical issues, 1 was lost to follow-up, and 1 violated protocol by starting topical imiquimod use immediately after his 3-month follow-up appointment. Only 1 patient in the trichloroacetic acid arm developed NMSC in the treated areas, which was an SCC in situ diagnosed 3 months after treatment. Of the 6 patients in the laser-resurfacing arm, 1 was lost to follow-up before the 24-month point and 3 developed 1 BCC each in the treated areas during follow-up (range, 14-39 months after treatment).

In the intention-to-treat analysis, skin cancer incidence data were calculated using the total number of days each patient was followed up to determine the number of patient-years of observation for each group. Cancer incidence rates in the patient population were 1.57, 0.21, 0.04, and 0.15 per patient-year in the control, fluorouracil, trichloroacetic acid, and carbon dioxide laser-resurfacing arms, respectively (Table 2). The rate of NMSC development in the trichloroacetic acid arm was lower by 3.75- to 5.25-fold compared with the other 2 treatment groups; however, given the small sample size, there were no statistically significant differences among the 3 treatment groups (χ² = 2.66; P = .26). Notable, though, was the nearly 40-fold lower rate of subsequent NMSC in the trichloroacetic acid arm compared with the control population and that a significant difference existed between each treatment group and the control (P < .001 for all 3 treatment modalities).

Kaplan-Meier curves were generated to illustrate the number of days to the first NMSC diagnosis (Figure 3) and were compared using the log-rank test and log-rank test for trend. Patients who dropped out of the follow-up portion of the study were considered to be censored and are noted in the curves accordingly. Whereas a significant difference was not noted between the curves (P = .07), the log-rank test for trend was significant (P = .02), with a shorter interval to first cancer formation in the control arm. Subjective assessment of patient
preference for the treatment modality revealed less discomfort, fewer patient complaints, and faster time to healing in the trichloroacetic acid arm compared with the laser-resurfacing or fluorouracil arms.

Prevention of AKs and NMSC is important for patients with a history of significant actinic damage and skin cancer. Approximately 3.7 million office visits for AK are estimated to occur each year in the United States, equating to an incidence rate of 1.5 per 100 person-years. New primary NMSC is estimated to occur in 6% to 44% of patients with a history of BCC or SCC, particularly in those with a history of multiple lesions. In a critical review of the literature and a meta-analysis of subsequent NMSC in patients with a history of NMSC, Marcil and Stern described an 18% 3-year cumulative risk of SCC.

### Table 1. Demographic and Follow-up Data for the 24 Evaluable Study Patients*

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Previous Facial Skin Cancer</th>
<th>Previous Treatments</th>
<th>Study Treatment</th>
<th>Initial AK Count</th>
<th>AK Count at 3 mo</th>
<th>AK Reduction, %</th>
<th>Total Follow-up, mo</th>
<th>New Skin Cancer</th>
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<tbody>
<tr>
<td>1/M/91 SCC LN2</td>
<td>Fluorouracil</td>
<td>Fluorouracil</td>
<td>50</td>
<td>11</td>
<td>78</td>
<td>9.0</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>2/M/63 None LN2, fluouracil</td>
<td>Fluorouracil</td>
<td>Fluorouracil</td>
<td>25</td>
<td>9</td>
<td>64</td>
<td>52.8</td>
<td>None</td>
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</tr>
<tr>
<td>3/M/80 None LN2</td>
<td>Fluorouracil</td>
<td>Fluorouracil</td>
<td>84</td>
<td>0</td>
<td>100</td>
<td>43.7</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>4/M/83 BCC (&gt;3), SCC LN2</td>
<td>Fluorouracil</td>
<td>Fluorouracil</td>
<td>50</td>
<td>14</td>
<td>72</td>
<td>35.7</td>
<td>SCC (18 mo, 28 mo, 32 mo ×3)†</td>
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</tr>
<tr>
<td>5/M/83 BCC (2) LN2</td>
<td>Fluorouracil</td>
<td>Fluorouracil</td>
<td>98</td>
<td>18</td>
<td>81.6</td>
<td>39.8</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>6/M/79 BCC (&gt;3), SCC LN2</td>
<td>Fluorouracil</td>
<td>Fluorouracil</td>
<td>67</td>
<td>0</td>
<td>100</td>
<td>51.0</td>
<td>None</td>
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<td>7/M/60 None None</td>
<td>Fluorouracil</td>
<td>Fluorouracil</td>
<td>65</td>
<td>10</td>
<td>84.6</td>
<td>47.8</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>8/M/61 None LN2, fluouracil, trichloroacetic acid</td>
<td>Fluorouracil</td>
<td>Fluorouracil</td>
<td>56</td>
<td>8</td>
<td>85.7</td>
<td>6.0</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>9/M/69 SCC (2) LN2</td>
<td>Fluorouracil</td>
<td>Trichloroacetic acid</td>
<td>65</td>
<td>13</td>
<td>80</td>
<td>18.0</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>10/M/63 BCC LN2</td>
<td>Fluorouracil</td>
<td>Trichloroacetic acid</td>
<td>30</td>
<td>7</td>
<td>76.7</td>
<td>31.5</td>
<td>SCC at 3.5 mo</td>
<td></td>
</tr>
<tr>
<td>11/M/63 None LN2</td>
<td>Fluorouracil</td>
<td>Trichloroacetic acid</td>
<td>127</td>
<td>6</td>
<td>95.3</td>
<td>21.1</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>12/M/64 BCC (2) SCC LN2</td>
<td>Fluorouracil</td>
<td>Trichloroacetic acid</td>
<td>112</td>
<td>10</td>
<td>91.1</td>
<td>46.1</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>13/M/79 SCC LN2</td>
<td>Fluorouracil</td>
<td>Trichloroacetic acid</td>
<td>133</td>
<td>11</td>
<td>91.7</td>
<td>54.1</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>14/M/85 BCC (&gt;3), SCC LN2</td>
<td>Fluorouracil</td>
<td>Trichloroacetic acid</td>
<td>80</td>
<td>6</td>
<td>92.5</td>
<td>3.3</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>15/M/66 BCC (2), SCC LN2</td>
<td>Fluorouracil</td>
<td>Trichloroacetic acid</td>
<td>30</td>
<td>3</td>
<td>90</td>
<td>27.3</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>16/M/71 SCC (2) LN2</td>
<td>Fluorouracil</td>
<td>Trichloroacetic acid</td>
<td>104</td>
<td>4</td>
<td>96.2</td>
<td>9.0</td>
<td>None</td>
<td></td>
</tr>
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<td>17/M/72 None LN2, fluouracil, trichloroacetic acid</td>
<td>Fluorouracil</td>
<td>Fluorouracil</td>
<td>72</td>
<td>9</td>
<td>87.5</td>
<td>53.0</td>
<td>None</td>
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<tr>
<td>18/M/69 BCC (&gt;3) LN2</td>
<td>Fluorouracil</td>
<td>Trichloroacetic acid</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>49.8</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>19/M/77 None LN2, fluouracil, trichloroacetic acid</td>
<td>Fluorouracil</td>
<td>Fluorouracil</td>
<td>88</td>
<td>0</td>
<td>100</td>
<td>43.1</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>20/M/70 BCC (&gt;3), SCC LN2</td>
<td>Fluorouracil</td>
<td>Trichloroacetic acid</td>
<td>57</td>
<td>0</td>
<td>100</td>
<td>44.7</td>
<td>BCC at 31 mo</td>
<td></td>
</tr>
<tr>
<td>21/M/54 BCC (&gt;3) LN2</td>
<td>Fluorouracil</td>
<td>Trichloroacetic acid</td>
<td>77</td>
<td>0</td>
<td>100</td>
<td>15.1</td>
<td>BCC at 14 mo</td>
<td></td>
</tr>
<tr>
<td>22/M/62 None LN2, carbon dioxide</td>
<td>Fluorouracil</td>
<td>Fluorouracil</td>
<td>64</td>
<td>9</td>
<td>85.9</td>
<td>44.7</td>
<td>BCC at 39 mo</td>
<td></td>
</tr>
<tr>
<td>23/M/54 None LN2, trichloroacetic acid</td>
<td>Fluorouracil</td>
<td>Fluorouracil</td>
<td>51</td>
<td>13</td>
<td>74.5</td>
<td>44.5</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>24/M/71 BCC LN2</td>
<td>Fluorouracil</td>
<td>Carbon dioxide</td>
<td>131</td>
<td>11</td>
<td>91.6</td>
<td>52.4</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AK, actinic keratosis; BCC, basal cell carcinoma; LN2, liquid nitrogen; SCC, squamous cell carcinoma.

*Patients 1, 8, 9, and 21 were lost to follow-up before the 24-month surveillance period, and patients 11 and 16 died of unrelated medical causes. Patient 14 violated protocol by starting imiquimod therapy after the 3-month posttreatment visit.

†Patient 4 had a total of 5 new skin cancers.

### Table 2. AK Reduction and NMSC Incidence Rates for the Treatment and Control Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group</th>
<th>Fluorouracil Group</th>
<th>Trichloroacetic Acid Group</th>
<th>Carbon Dioxide Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>71.0 ± 8.6</td>
<td>75.0 ± 11.9</td>
<td>76.1 ± 7.4</td>
<td>64.7 ± 9.5</td>
</tr>
<tr>
<td>AK count, mean ± SD</td>
<td>NA</td>
<td>61.8 ± 22.4</td>
<td>83.7 ± 38.4</td>
<td>78.0 ± 29.2</td>
</tr>
<tr>
<td>Baseline</td>
<td>NA</td>
<td>8.6 ± 6.3</td>
<td>7.7 ± 3.3</td>
<td>5.5 ± 6.2</td>
</tr>
<tr>
<td>AK reduction, mean ± SD, %</td>
<td>83.2 ± 12.9</td>
<td>90.0 ± 6.6</td>
<td>92.0 ± 10.3</td>
<td>90.0 ± 10.3</td>
</tr>
<tr>
<td>No. of cancers</td>
<td>24</td>
<td>5</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Cancer incidence*</td>
<td>15.24</td>
<td>23.83</td>
<td>26.10</td>
<td>20.37</td>
</tr>
<tr>
<td>P-value</td>
<td>1.57</td>
<td>0.21</td>
<td>0.04</td>
<td>0.15</td>
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<tr>
<td>χ²</td>
<td>0</td>
<td>13.05</td>
<td>22.55</td>
<td>13.95</td>
</tr>
<tr>
<td>P value</td>
<td>&gt;.99</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: AK, actinic keratosis; NA, not applicable; NMSC, nonmelanoma skin cancer.

*Cancer incidence is expressed as the total number of new NMSCs diagnosed in the treated facial area divided by the total number of patient-years followed in each group. The total number of patient-years was based on the number of days each patient remained in the study follow-up. Rates of cancer formation per patient-year followed were compared using χ² analysis.
after index SCC and a 44% 3-year cumulative risk of BCC after index SCC or BCC. This represented a 10-fold increased incidence of subsequent NMSC compared with the incidence of first tumors in a comparable general population. In addition, patients with AKs are at markedly increased risk of developing melanoma and NMSC, and the economic health care burden of AK and NMSC is substantial. Based on a Medicare retrospective claims database analysis, the estimated annual mean expenditure for NMSC and AK was $562 and $202 million, respectively, in 1998 US dollars.20,24

Destructive procedures remain the standard treatment for AKs. The most common modality involves cryotherapy with LN2, resulting in a depth-controlled tissue injury. However, despite an overreliance by dermatologists on LN2, there are, to our knowledge, no published studies that justify this expensive treatment modality as an efficient means to reduce the financial impact of AKs and NMSC on the health care system. Some third-party payers have mandated that fluorouracil be used first, with localized freezing only for refractory lesions.7 More recently, the novel immunomodulator imiquimod has been reported to be effective in the treatment of AKs.25 In a study by Stockfleth et al,25 patients with a 5- to 16-year history of recurrent AKs were treated thrice weekly with 5% imiquimod cream for 6 to 8 weeks. All 6 patients were clinically and histologically completely cleared of AKs at the end of treatment. Several phase 3, randomized, double-blind, vehicle-controlled studies11,26,27 have subsequently confirmed the efficacy of imiquimod for the treatment of AKs, with mean reduction rates of 72.2% to 86.6% reported.

Coleman et al28 showed that skin resurfacing using standard dermabrasion techniques provided successful prophylaxis against AKs, with a mean time to appearance of the first postdermabrasion AKs of 4 years. However, dermabrasion did not prevent perinasal BCC in this study, likely related to the difficulty of treating the central face with this modality. Owing to the cost of the equipment, the time and training required, and the equivalent to superior results with laser resurfacing, dermabrasion is no longer used by most dermatologists for AK treatment.

Trimas et al13 reported their experience with the carbon dioxide laser for cancer prophylaxis in 14 patients, with follow-up of 6 to 24 months. No patient developed recurrent AKs or required retreatment for new AKs. Massey and Eliezri19 showed similar beneficial effects from carbon dioxide laser resurfacings in 2 patients who developed malignancy outside of the laser treatment field (but not inside it) during follow-up of 33 and 52 months. In contrast, Fulton et al29 showed recurrence of AKs or NMSC in 5 (14%) of 35 patients within 6 months of laser resurfacing. Recurrence was most common in patients with Fitzpatrick skin types I and II. In this study,29 3 to 4 passes were performed for each patient, and any suspicious lesions were curetted at the time of resurfacing.

In a retrospective analysis, Iyer et al15 reviewed 24 patients with multiple AKs treated with carbon dioxide, erbium:YAG, or carbon dioxide plus erbium:YAG laser. Most patients had at least 3 passes with the carbon dioxide laser and 2 passes with the erbium:YAG laser plus spot treatment for any residual suspicious lesions. The authors15 found a significant decrease in the number of AKs, with 21 (87%) of 24 patients remaining free of AKs at 1 year, and similar to the present study, the absolute number of AKs after treatment declined significantly. Although in 1 study carbon dioxide laser resurfacing was associated with fewer complications than chemical peel or dermabrasion, both laser and trichloroacetic acid may lead to hypopigmentation or hyperpigmentation.12,30

Trichloroacetic acid acts as a chemical cauterant by coagulating protein in the skin.31 In general, laser resurfacing and chemical peel with trichloroacetic acid are extremely safe procedures associated with limited morbidity; however, if concentrations of trichloroacetic acid greater than 50% are used, scarring may result.32 Trichloroacetic acid has been used for the treatment of AKs on the face and scalp and has provided patients with excellent cosmetic results. Furthermore, histologic evaluation of skin treated with trichloroacetic acid has shown it to be effective in treating photodamage.33 Trichloroacetic acid was noted to be as effective as fluorouracil in preventing the recurrence of AKs for at least 1 year.18 Low-concentration (≤30%) trichloroacetic acid peel has less morbidity than topical fluorouracil, and in the present study and as noted by Lawrence et al,18 patients preferred chemical resurfacing to fluorouracil use because of its convenient single application, minimal adverse effects, and rapid healing time.

Our results with trichloroacetic acid peel are comparable with those of a split-face study of 15 patients by Lawrence et al18 comparing fluorouracil with a chemical peel containing Jessner solution and 35% trichloroacetic acid. In this study, both fluorouracil and the chemical peel resulted in an approximately 75% reduction of AKs. Thirty-two months after treatment, 8 patients were available for reevaluation. One SCC was identified in the peel arm and 2 in the fluorouracil arm; AKs recurred in all 8 patients during follow-up.16

In the present study, all the patients were instructed to use topical 0.05% tretinoin cream nightly after treatment. It is known that regular use of tretinoin can de-
crease the number of AKs, but no significant benefit has been demonstrated with daily tretinoin use before and after trichloroacetic acid peel. An estimated 50% of patients in this study population had difficulty complying with the tretinoin regimen irrespective of treatment arm or timing of use. Several patients cited irritation as the reason for noncompliance, and others simply forgot to apply the medication or claimed that the pharmacy would not fill the prescription. Similarly, all the patients (treated and controls) were instructed to use sunscreen daily, and again, they gave a variety of reasons for nonadherence to photoprotective measures. In general, treated patients were more compliant with sunscreen use than tretinoin use. Although the variability in compliance with posttreatment tretinoin and sunscreen use is a limitation of this study, we do not believe that any significant difference in posttreatment regimen adherence existed among the 3 study arms or biased our results for AK reduction or NMSC development.

In our patient population, 21 (87%) of 24 treated patients had a history of NMSC, and 15 (62%) of 24 had a history of NMSC on the face and scalp. Eleven patients (46%) had a history of at least 2 NMSCs in the treated areas before study entry. In a study of a similar high-risk population of predominantly elderly patients, men were found to have an incidence of 1.7 new NMSCs per year, significantly greater than the 0.04 to 0.22 yearly incidence we found in each of our treatment arms but similar to our control subjects. In the trichloroacetic acid peel arm, 1 cancer per 26.1 years would be expected compared with 1 cancer per 6.79 and 4.77 years in the carbon dioxide and fluouracil arms, respectively. In the control population, 21 cancers developed in 3 (60%) of 5 patients with a mean follow-up of 43 months (range, 29-56 months). This corresponds to a rate of 1.57 new NMSCs per year, or more than 1 new cancer every 8 months.

This study was limited by a relatively small number of participants. In addition, there was a potential bias in the control group because patients were not randomized into this group. For example, 12% of the patients in the treatment group did not have a history NMSC compared with the control group, in which all the patients had a history of NMSC and thus may have been at increased risk for subsequent NMSC development. Despite these limitations, the reductions observed in NMSC development suggest efficacy in skin cancer prevention for each of the treatments.

In conclusion, although no significant differences were observed among the treatment arms in terms of AK reduction, all the groups showed significant clearing of AKs at 3-month follow-up. Long-term AK reduction was noted, although not formally analyzed, because LN2 cryotherapy was provided as necessary at follow-up dermatology visits. Although the number of treated patients was small, a markedly lower rate of development of new primary NMSC in the trichloroacetic acid arm was observed compared with the fluorouracil and laser-resurfacing arms. All the modalities demonstrated significantly decreased rates of cancer incidence compared with internal and historical controls. Similarly, a trend toward a longer interval before development of the first new NMSC was noted in the treatment groups compared with the control group. Again, the study is limited by the small sample size, variability in sunscreen and tretinoin use, and a potential bias in the control group. However, the data suggest that 1-time facial resurfacing provides sufficient cutaneous malignancy prophylaxis to reduce the need for frequent and multiple destructive procedures.

Long-term skin cancer and AK surveillance continue to be important, and repeated resurfacing procedures or courses of topical agents, such as fluorouracil or imiquimod, may be necessary. A larger study comparing trichloroacetic acid resurfacing for AK reduction and NMSC prophylaxis would help validate the superiority of this resurfacing technique over the carbon dioxide laser and assess its cost-effectiveness compared with photodynamic therapy or imiquimod treatment. Improved patient compliance in the trichloroacetic acid arm, ease of performance in the outpatient setting, and subjective measures of better tolerance for this procedure make it an attractive alternative to repeated courses with topical agents or laser resurfacing.

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