CASE STUDY

48-YEAR-OLD WOMAN WITH MULTIPLE CONFLUENT ACTINIC KERATOSES OF THE FACE AND SCALP*

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BACKGROUND

The patient is a 48-year-old attorney with skin type II and a family history of skin cancer. She is an established patient of the dermatology practice and has been seen semi-annually during the last 7 years for treatment and screening of actinic damage. Over the course of the last 5 to 6 months, she has developed a large number of small erythematous papules across her forehead and extending to both temples, forming a strip approximately 15 to 20 cm long and 3.5 cm wide (Figure 1).1 The lesions are confluent in some areas of the forehead. After some research on the Internet, the patient called the physician’s office to request an appointment for what she referred to as “chronic contact dermatitis.” A recent biopsy of a single lesion within the same general region of her forehead revealed large keratinocytes with atypical nuclei in the lower portion of the epidermis. Based on the patient’s background skin, she is diagnosed with chronic photodamage. Considering her sun-damaged skin and fair complexion, her dermatologist also considers it likely that her “contact dermatitis” actually represents widespread, confluent actinic keratoses (AK) lesions that are too numerous to count. On the basis of her Internet research, the patient questions the diagnosis of AK, and a small biopsy is performed from a representative area of the lateral forehead. The biopsy exhibits features consistent with AK, including focal parakeratosis with loss of granular layer; the loss of the orderly arrangement of the epidermis; and large, moderately atypical keratinocytes.

TREATMENT PLAN

Therapeutic options that could be considered for this patient include cryotherapy, topical therapies, and photodynamic therapy (PDT).

5-Fluorouracil (5-FU) is a pyrimidine analog that inhibits RNA processing and thymidylate synthesis. It therefore acts as an antimetabolite that interferes with DNA and RNA synthesis of atypically dividing keratinocytes. Topical administration of 5-FU is approved by the US Food and Drug Administration (FDA) for field therapy of AKs on the face and scalp. 5-FU is available as 1%, 2%, and 5% solutions, a 5% cream, and a 0.5% cream in a porous microsponge vehicle for facial application.2 5-FU is the most widely used topical treatment for AK; it treats visible and subclinical lesions, and therefore, can be used as surveillance of these subclinical lesions.3 It may produce intense skin irritation or inflammation, accompanied by patient complaints of burning, stinging, or pain. Treatment also increases photosensitivity, and patients must wear sunscreen and protective clothing to avoid direct sunlight during treatment and for a few weeks after. Topical application of 5-FU may cause severe and potentially life-threatening systemic symptoms in patients who lack the enzyme dihydropyridine dehydrogenase, which is important in the metabolism of 5-FU and related substances.4

Imiquimod is a topical immunomodulator that activates an immune response by stimulating the synthesis and release of proinflammatory cytokines (including interferons and tumor necrosis factor α), which promote cellular immune responses against viruses and cancer cells.5 6 Imiquimod is usually applied topically twice weekly for 16 weeks or 3 times weekly for 12 weeks, and is US FDA approved for treatment on skin areas up to 25 cm² (this is roughly equivalent to the size of a palm

*Based on a case study developed with Jonathan S. Weiss, MD, for a national grand rounds series.
or 1 cheek area). Skin irritation, itching, or burning occur in a large percentage of patients. Some rare systemic flu-like symptoms have been reported, especially when imiquimod is used to treat large skin surfaces or when it comes in contact with mucous membranes. The response to imiquimod also varies considerably from patient to patient, and it is difficult to predict how well any particular patient will respond.

Diclofenac 3% gel is a topical nonsteroidal anti-inflammatory drug (NSAID) that is US FDA approved to treat skin areas of up to 25 cm². Its precise mechanism of action in AK is not completely understood, but it may suppress the progression of carcinogenesis. Diclofenac gel must be used twice daily for 60 to 90 days to produce significant improvement, and the greatest degree of improvement may occur after approximately another month. As with other NSAIDs, diclofenac is associated with the potential for anaphylaxis and gastrointestinal bleeding. Diclofenac also produces photosensitivity, and sunlight exposure should be limited.

Photodynamic therapy is US FDA approved only for the treatment of individual lesions and not as field-directed therapy. However, it is often used as a field-directed therapy in actual clinical practice. PDT employs a topical preparation of aminolevulinic acid, which is applied directly to the AK lesions and converted intracellularly to protoporphyrin IX, a potent photosensitizer. After an incubation period, a light source is used to activate the protoporphyrin IX, which yields a cytotoxic product. PDT may produce burning and stinging that may be difficult for some patients to tolerate. Patients remain photosensitive for some time after treatment, with the length of time depending on the specific preparation.

Cryotherapy was considered to be a less attractive treatment option for this patient. Although cryotherapy nearly always results in the complete elimination of the treated lesion with a very low recurrence rate and with a single office visit, it is more appropriate for treating small numbers of well-demarcated AK lesions. Many patients develop hyperpigmentation or hypopigmentation, and there is also a potential risk of scarring. As an attorney who frequently meets with clients or appears in court, the patient was very concerned about the risk of hyperpigmentation, hypopigmentation, or scarring with cryotherapy.

OUTCOME AND FOLLOW-UP

-DECISION POINT-

Which treatment would you choose for this patient?

Because of her large number of confluent AK lesions and the large skin area involved, she would be considered a candidate for any of the topical treatments that were described previously. The patient described here may need more than 1 course of therapy with topical treatments. It is generally recommended that patients return for follow-up within 3 to 6 months to make sure that the treatment was effective. Retreatment may be needed, and it is generally felt that with topical therapy the patient will see reductions in the numbers of AKs on subsequent treatments until eradication of the AKs demonstrates the efficacy of these products.

DISCUSSION

Several factors may be considered when choosing a particular therapy, including the severity and extent of the lesions, the patient’s age, cosmetic concerns, occupa-
tion, and social obligations. Controlled clinical trials have demonstrated the effectiveness of several treatment strategies for patients with multiple AK lesions.

5-FU has been used since the 1970s to treat AK. It produces complete clearance in approximately 50% of patients when used as field therapy, usually with a 2- to 4-week course of therapy.² 5-FU also may be used in combination with lesion-directed therapy. A recent randomized, double-blind, placebo-controlled clinical trial evaluated the efficacy and safety of 0.5% 5-FU cream before cryotherapy in patients with 5 or more AKs on the face. Lesions were evaluated at baseline and after 1, 2, and 3 treatment cycles.⁷ During each treatment cycle, patients applied 5-FU cream or placebo cream for 7 days, after which any remaining lesions were counted and removed using liquid nitrogen. As shown in Figure 2, pretreatment with 5-FU 0.5% cream for 7 days before cryotherapy significantly increased AK clearance after the first cryotherapy treatment and reduced the number of lesions over time.⁷

One limitation of imiquimod is that treatment is applied for up to 16 weeks. Two recent studies suggest a shorter imiquimod regimen may be as effective as the conventional treatment regimen. One vehicle-controlled, double-blind, randomized clinical trial of patients with AK of the head examined a shorter regimen of imiquimod therapy (3 times/week for 4 weeks), with a second course of treatment for those without complete clearance after the completion of the first course.⁸ Overall, complete clearance of all lesions was noted for approximately 54% of patients who...
received imiquimod and 15% of patients who received placebo ($P < .001$). Partial clearance also occurred more often in patients who were treated with the short-course imiquimod strategy (Figure 3). In the second study, which also examined a 4-week imiquimod regimen with a second course of treatment if required, imiquimod was associated with a complete clearance rate of 55% versus 2.3% with placebo ($P < .0001$).

A randomized, double-blind clinical trial of patients with AK compared treatment with diclofenac 3% gel for 90 days versus a placebo gel in patients with 5 or more AK lesions at baseline. The results of this study are summarized in Figure 4. A target lesion number score of 0 indicates complete resolution of all lesions within the treated area. The cumulative lesion number score is the number of remaining lesions, plus any new lesions that appeared after treatment. For a subjective investigator-graded improvement index and patient-graded improvement index a score of 4 indicates complete improvement from baseline. As shown in Figure 4, diclofenac produced significantly greater improvement from baseline than placebo for all 4 outcome measures.

The efficacy of PDT is comparable to that of 5-FU, and treatment may also improve the cosmetic appearance of the skin. In a recent randomized, vehicle-controlled clinical trial of 243 patients with AK, clinical response after 8 weeks (which was defined in this study as clearing of at least 75% of AK lesions) was noted for 77% of patients, which increased to 89% of the patients after 12 weeks.

No randomized, controlled clinical trials have directly compared the efficacy of 5-FU, imiquimod, diclofenac, and PDT for the treatment of AK. One small clinical trial compared the efficacy and safety of 5-FU 5% cream for 2 to 4 weeks versus imiquimod 5% cream for 16 weeks in 39 patients with 4 or more AK lesions of the face, forehead, or scalp. As shown in Figure 5, the total number of AK lesions for up to 24 weeks was significantly lower for patients who were treated with 5-FU. 5-FU also was more effective than imiquimod for exposing subclinical AK lesions. A comparison of published response rates using data from the prescribing information provided by the manufacturers. A comparison of published response rates using data from the prescribing information provided by the manufacturers.

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**Table. Comparison of Response Rates Reported for AK Treatments, According to Prescribing Information Provided by the Manufacturers**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Efficacy, Complete Clearance</th>
<th>Efficacy, % Clearance</th>
<th>US FDA Approved for Field Therapy</th>
<th>Length of Treatment with Healing Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU†</td>
<td>38%–58%</td>
<td>84%–92%</td>
<td>Yes</td>
<td>3–6 wk</td>
</tr>
<tr>
<td>Imiquimod</td>
<td>45%–57%</td>
<td>83%</td>
<td>25 cm²</td>
<td>12–24 wk</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>41%–58%</td>
<td>NA</td>
<td>25 cm²</td>
<td>12–16 wk</td>
</tr>
<tr>
<td>PDT</td>
<td>73%</td>
<td>90%</td>
<td>No</td>
<td>1–4 wk</td>
</tr>
</tbody>
</table>

*Information from respective prescribing information.
†Compilation of data from the 5-FU 0.5% cream and 5% cream formulations.
5-FU = 5-fluorouracil; AK = actinic keratosis; FDA = Food and Drug Administration; PDT = photodynamic therapy.
manufacturers of the different products suggests that the response rates of the various medications are generally similar to one another (Table). These comparisons are not scientifically rigorous, but they provide some idea of efficacy and tolerability of the different agents. Several points should be noted. Imiquimod and diclofenac were studied only in application to skin areas of 25 cm². In studies of imiquimod, only patients with 4 to 8 lesions within the 25 cm² area were eligible for enrollment. PDT was applied to individual lesions, and the effect on subclinical lesions is unknown. The results for 5-FU were obtained after 2 to 4 weeks of therapy with varying strengths of medication, at doses of 0.5% once daily to 5% twice daily.

CONCLUSIONS

Topical therapy and PDT are important treatments for patients with widespread AK. Several choices may be appropriate for any particular patient. Therapy should be selected based on the patient’s clinical characteristics, as well as personal or lifestyle factors that may be important in treatment adherence.

REFERENCES