ACTINIC KERATOSIS: A CLINICAL UPDATE

JOSEPH L. JORIZZO, M.D.

Actinic keratosis (AK) is seen commonly in dermatology practice. Although it is still being debated, many believe that AK actually represents an incipient form of squamous cell skin cancer (SCC).1,2 When evaluating a biopsy under a microscope, the histologic features of a hyperplastic AK and SCC are similar. AKs are, at the very least, considered to be precancerous. More than 1 million new cases of skin cancer are diagnosed in the United States each year; and of those, an estimated 200,000 to 300,000 individuals are diagnosed with SCC each year, therefore, it is important to treat AKs to avoid the progression to invasive SCC.

Studies have shown that more than 5 million Americans have at least one AK.3 Risk factors include fair-skin phenotype, geographic location (ie, closeness to equator), immunosuppression (eg, HIV-positive patients, those receiving organ transplants, and patients with cancer) and supplementary sources of ultraviolet radiation (ie, artificial tanning and occupational exposure). The prevalence dramatically increases with age, which is indicative of the strong correlation between the amount of cumulative sun exposure and the occurrence of AK, as well as the fact that immune surveillance lessens with age. In a survey conducted in Tennessee, 26.5% of men and 10.2% of white women had one or more AKs. By age 75, 63.6% of the men had AKs.4 Prevalence also increases with proximity to the equator. In Australia up to 60% of the population older than 40 years has AKs.5,6

AK PROGRESSION TO SCC

One concern in the treatment of AK is preventing progression to invasive SCC, a disease that may account for up to 34% of deaths from skin cancer among persons aged 65 to 84 years.8 The progression of AKs to SCC occurs in 0.1% to 10% of cases,7,10 and 3% of these SCC metastasize.11 Although AK lesions have markers that show all the features of SCC, they are held in check at the early stage by cellular immunity. Decreasing immune surveillance with increasing age and immunosuppression from chemotherapy, HIV infection or immunosuppressant medications in transplant patients results in increased development of AKs. Immunosuppression is an important factor in the concept of AKs, in situ SCC and invasive SCC as a continuum, and should be kept in mind when treating patients with AKs.

Chronic progression of AKs to SCC correlates with the evolution of histologic features. Characteristics include epidermal hyperplasia with a partial-thickness proliferation of keratinocytes exhibiting cytologic atypia, loss of polarity, nuclear pleomorphism and disordered maturation. As it progresses to invasive SCC, proliferations may be long and slender or bulbous extensions into the papillary dermis. In Figure 1, underlying solar elastosis in the dermis coupled with extension of atypical cells along adnexal structures suggests SCC; however, the atypia is not full thickness and considered to be premalignant. Given enough time, 0.1% to 10% of AKs will progress to SCC.7,10,12

PREVENTION OF AK

Prevention is fundamental in the management of AKs and photoaged skin. It is important to inform patients of the risks of AK and advise them to avoid excessive exposure to sunlight during peak sunlight hours (10 a.m. to 4 p.m.); avoid prolonged periods around reflective surfaces, such as water; wear protective clothing and a wide-brimmed hat; and apply a broad-spectrum (UVA/UVB) sunscreen (sun protection factor 15 or higher) liberally.11,13-15 Reliable data now show that ultraviolet light induces a suppressor T-cell subset,16,17 which suppresses immunesurveillance and allows for progression of AKs to SCC. Using daily sunscreens that block UVA and UVB light can greatly reduce the incidence of AKs and subsequent skin cancer.13-18

TREATMENT GOALS AND OPTIONS

When treating photoaged skin, the primary goal is eradication of AKs to prevent future morbidity. However, it is becoming more common for patients to expect dermatologists to provide comprehensive wellness care for diseases of the skin, so the secondary goal is to improve the cosmetic appearance, self-esteem and, ultimately, quality of life. This can be done with elective treatments, such as chemical peels and laser resurfacing, which may reduce signs of photodamage, including fine lines/wrinkles, textural alterations, diffuse dyschromias, yellowing and mottling of the skin.19
A variety of treatment options are available for the treatment of AKs — cryosurgery, curettage/shave removal, chemical peels, photodynamic therapy (PDT) and topical therapies. Combination therapy often is most effective. When selecting a treatment, there are several factors to consider, including a patient’s overall risk of SCC; the types, number and locations of lesions; patient preference; cosmetic prognosis; and cost.

**Cryosurgery**

Cryosurgery is one of the most convenient methods to treat AKs, and most dermatology offices are equipped with liquid nitrogen. It is often more efficient to examine patients with such an agent at hand, particularly for those with a history of hypertrophic AK. AK lesions are more sensitive to cryotherapy compared to normal cells, and it can treat multiple lesions quickly. Studies have shown that cryotherapy has up to a 99% success rate 1-year post-surgery. Adverse effects include local erythema, blisters, crusts, weeping, pain and secondary infection. Hypopigmentation is a common and undesirable sequelae of cryotherapy. It can be reduced by using the least possible amount of cryosurgery and then properly taking care of the wound to prevent secondary infection or other effects that could lead to hypopigmentation. Provide patients with instructions for care of wounds and reinforce the importance of compliance.

**Curettage/Shave Removal**

Extensive photodamage often parallels the number of suspicious lesions that patients present with, thus it can be difficult to distinguish between AK and SCC clinically. Removal of AK lesions with curettage/shave removal permits histologic examination and a 95% to 99% success rate has been reported. Adverse effects include pain, scarring, and hypo- or hyperpigmentation.

**PDT**

Photodynamic therapy is a novel modality used to treat AK that has shown promise in respect to efficacy and tolerance. Aminolevulinic acid (ALA) plus light involves the topical application of 20% ALA. It preferentially localizes in the abnormal AK/SCC cells and upon exposure to blue light, ALA is converted to protoporphyrin IX, which produces oxygen intermediates that destroy the abnormal AK/SCC cells. Efficacy of ALA is well established.

**Topical Therapy**

Topical therapy is available in a variety of creams and solutions. The tolerability of reactions, duration, size availability, and cost differs for each product as shown in Table 1.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>AK</td>
<td>Imiquimod 5%</td>
</tr>
<tr>
<td>AK</td>
<td>3% diclofenac gel</td>
</tr>
<tr>
<td>AK</td>
<td>0.5%-FU</td>
</tr>
</tbody>
</table>

**Imiquimod 5%**. This novel immune response modifier can be used to treat multiple AK lesions and does not require surgery. Although the exact mechanism of action remains unclear, it appears that this treatment uses the immune system to reject these AK lesions from below. A phase III, randomized, multi-centered (18 centers), double-blind, parallel group, vehicle-controlled study (n=308) evaluated the efficacy of imiquimod 5% cream compared with vehicle in the treatment of AKs on the face and scalp. The 3% diclofenac gel was used for 90 days and the 5-FU cream for 28 days. Evaluation of efficacy showed 99% clearance with 3% diclofenac and 98% clearance with 5-FU; however, less inflammation was demonstrated with 3% diclofenac gel, despite the longer treatment period of 60 to 90 days. This generated significant patient satisfaction. Also, photosensitivity or phototoxicity is not induced with 3% diclofenac gel alone or in combination with sunscreens.

**3% diclofenac gel**. 3% diclofenac gel is a well-known, nonsteroidal anti-inflammatory drug used for arthritis that can be used to treat AK, although the mechanism of action is unknown. This novel formulation (3% diclofenac in 2.5% hyaluronan gel) can be used to treat multiple AKs and does not require surgery. A comparison study (n=30) was conducted by Smith et al, which evaluated the efficacy and tolerability of 3% diclofenac sodium gel and 5-fluorouracil (5-FU) cream in the treatment of AK of the face and scalp. The 3% diclofenac gel was used for 90 days and the 5-FU cream for 28 days. Evaluation of efficacy showed 99% clearance with 3% diclofenac and 98% clearance with 5-FU; however, less inflammation was demonstrated with 3% diclofenac gel, despite the longer treatment period of 60 to 90 days. This generated significant patient satisfaction. Also, photosensitivity or phototoxicity is not induced with 3% diclofenac gel alone or in combination with sunscreens.

**0.5%-FU**. Topical 0.5%-FU inhibits DNA synthesis, leading to impaired AK growth when compared to growth of normal cells. It is available in once-daily formulation and can be used to treat multiple and subclinical lesions; surgery is not required. Typical adverse effects, such as burning, itching, redness, flaking and peeling, can be managed with the application of topical hydrocortisone (0.5% to 1.0%). Weiss et al conducted a randomized, double-blind, multicentered, parallel-group study (n=177) to evaluate safety and efficacy of 0.5%-FU compared with vehicle once daily for 1, 2 or 4 weeks. Efficacy was assessed by lesion counts and clearance and...
safety was gauged by monitoring for adverse events. Of those treated with 0.5%-FU at 4 weeks, 88.7% had a reduction in lesions and 47.5% achieved total clearance, which was significantly higher compared to vehicle (34.4% and 3.4%, respectively). Mild-to-moderate facial irritation was the primary adverse event, which lasted 15 to 17 days post-treatment.30

Interval (pulse) therapy with 5-FU. Although there is a known risk of burning, itching and inflammation with all formulations of topical FU, there has been well documented evidence that FU acts as chemotherapy and suppresses inflammation when used alone or in combination. An excessive inflammation response is not necessary when using FU to achieve reduction of AK,31 and all AK treatments typically involve a localized inflammatory response, which can be socially disruptive. Interval (pulse) therapy with 5-FU can potentially overcome such adverse, unwelcome reactions, without reducing efficacy. It often involves varying the frequency of application, which allows for delivering a lower than recommended dose. In a study by Pearlman, 10 patients completed an interval (pulse) therapy study using topical 5-FU for multiple facial AKs and applying it 1 to 2 days per week for an average of 6 to 7 weeks.32 This method cleared 98% of the lesions. Irritation was limited to erythema without disruption to their social or business lives due to altered appearance. At 9 months, six available patients remained 86% clear of lesions. This study suggests efficacy can be obtained without excessive irritation.

Chemical Peels
Chemical peels are useful for cosmetic facial rejuvenation and eliminating photoaging skin and AKs (See Figure 2).33,34 Peels may be performed at superficial, medium or deep levels, depending on the extent of damage. Side effects include stinging, irritation and inflammation. Combination therapy with 5-FU also can be considered.35,36

Combination Therapy
There is no ideal monotherapy for the treatment of AK, thus combination therapy is often used because it has the potential to enhance treatment efficacy. Diverse combination therapies are available, including cryotherapy plus a choice of topical therapy; shave removal followed by topical therapy; and topical retinoids followed by 5-FU. There are ongoing studies of the efficacy of different combination therapies. One such study was a recent prospective, multi-centered, randomized, double-blind, vehicle-controlled clinical trial (n=144, ≥5 facial AK lesions). Investigators examined the 6-month outcome of a 1-week course of 0.5%-FU followed by cryosurgery.37 Topical 0.5%-FU was used once daily for 7 days. At 4 weeks follow-up, the remaining lesions were treated with cryosurgery. The primary endpoints were reduction in AKs from baseline to 4 weeks and 6 months. At 4 weeks, the mean AK lesion count reduced by 62.4% in the 0.5%-FU group versus 28.8% in the vehicle group, and complete clearance was achieved in 16.7% of patients in the 0.5%-FU group versus 0% in the vehicle group. At 6 months, the mean lesion count was reduced by 67% in the 0.5%-FU plus cryosurgery group, and significantly more patients had complete clearance (30%) in the 0.5%-FU plus cryosurgery group than vehicle group (7.7%). Although the mean lesion count was reduced with the addition of cryosurgery at week 4, there was still a high occurrence of AKs at 6-month follow-up, showing the need for continued surveillance.

COSMETIC CONSIDERATIONS
Individuals desire products that do not feel heavy or greasy, thus new formulations are being developed to address these concerns. This can be seen with the latest “microsphere” vehicle formulation of 0.5%-FU, which has a more favorable irritation profile than the precursors and is preferred by patients.30 In addition, treatments, such as chemical peels, which enhance appearance while treating AKs, are being used more often.19 Other options include laser resurfacing, non-invasive lasers, radiofrequency devices, hyaluronic acid gels, poly-L-lactic acid injections, permanent fat injections and botulinum toxin injections.38-43 By including

---

FIGURE 2. Chemical Peels
Patient photographs courtesy of Dr. Steven B. Hopping, Washington, DC.
### TABLE: Topical Therapy Options for AK

<table>
<thead>
<tr>
<th>Concentration (Formula)</th>
<th>Application</th>
<th>Available Sizes</th>
<th>AWP*</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% imiquimod cream</td>
<td>Twice weekly for 16 wk</td>
<td>12 packets</td>
<td>$268.38</td>
</tr>
<tr>
<td>Microsphere-encapsulated 0.5% FU cream</td>
<td>Once daily for 1–4 wk</td>
<td>30-g tube</td>
<td>$143.73</td>
</tr>
<tr>
<td>5% FU cream</td>
<td>Twice daily for 2–4 wk</td>
<td>40-g tube</td>
<td>$249.05</td>
</tr>
<tr>
<td>5% FU solution</td>
<td>Twice daily for 2–4 wk</td>
<td>10-mL bottle</td>
<td>$249.05</td>
</tr>
<tr>
<td>1% FU cream</td>
<td>Twice daily for 2–6 wk</td>
<td>30-g tube</td>
<td>$139.15</td>
</tr>
<tr>
<td>3% diclofenac gel</td>
<td>Twice daily for 30–90 d</td>
<td>50-g tube</td>
<td>$198.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100-g tube</td>
<td>$301.51</td>
</tr>
</tbody>
</table>

*AWP reflects brand name price. AK = actinic keratosis; AWP = average wholesale price; FU = fluorouracil. Data from Jorizzo et al. and Amerisource database.

### CONCLUSIONS

When managing the treatment of AK, it is important to remember that it can never be considered “cured.” Long-term surveillance is necessary, especially because the incidence of AK increases with age and is often seen with other signs of aging. Although the primary goal in AK treatment is always to prevent future morbidity from cancer, aesthetic and wellness considerations are also important to patients. Overall patient outcomes can be significantly improved by providing a treatment plan that provides individualized patient care and comprehensive wellness for the skin.

Address correspondence to: Joseph L. Jorizzo, M.D., Professor and Former (Founding) Chair, Department of Dermatology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157. E-mail: jjorizzo@wfubmc.edu.

### References