Treatment of Actinic Keratoses

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Histopathologically, actinic keratosis (AK) is an epidermal lesion consisting of dysplastic keratinocytes and is classified as an in situ squamous cell carcinoma.[1,2] Lesion development is directly related to lifetime UV light exposure. Spots usually occur on long-term sun-exposed skin and may appear as a single lesion or affect the entire exposed surface, known as field cancerization. In white individuals, the prevalence of AKs has been increasing.[3] The risk for malignant transformation depends on patient immunocompetence. For immunocompetent individuals, the risk for an AK developing into an invasive squamous cell carcinoma is approximately 10%, though lower levels of risk have been reported. However, in patients who are immunosuppressed, risk levels can be as high as 40% to 50%.[1,4,5]

Much of our careers as dermatologists will be spent treating AKs. Cryotherapy is a mainstay treatment of AK, and for most clinicians it is the de facto treatment of individual lesions. Topical therapies are highly utilized alternatives to cryotherapy with numerous agents now approved by the US Food and Drug Administration. The main advantages of topical therapy are treatment of field cancerization in addition to treatment of clinically evident lesions. 5-Fluorouracil (5-FU) received approval from the US Food and Drug Administration for the treatment of AKs in 1970 and is the oldest available topical therapy. Additionally, imiquimod (IMQ) was approved in 1997, diclofenac in 1999, photodynamic therapy (PDT) in 2004, and most recently ingenol mebutate in 2012. (Additional alternative therapies include lasers and chemical peels, which I will not discuss.)

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No treatment algorithm currently exists for first-line or second-line therapies due to a lack of comparative studies, which makes it challenging to identify which treatment is best for an individual patient. I will review the most relevant comparative studies with a focus on treatment efficacy. The discussion will be limited to immunocompetent patients with AKs on the head and neck, which hopefully will form an outline of the most effective options for the treatment of AKs. At the end, I will discuss how I approach the use of these medications.

Treatment Efficacies

Cryotherapy, 5-FU, and IMQ—The stand-alone reported efficacies for the top treatment modalities are variable. Cryotherapy has a clearance rate of 75% to 98% with recurrence rates at 1-year follow-up of 2% to 12%.[1,6,7] However, there is no standardization for treatment duration, frequency, or intensity. In a study of 421 AK lesions, Thai et al[8] reported that a 5-second freeze-thaw cycle had a 39% lesion cure rate, whereas a treatment of more than 20 seconds had an 83% lesion cure rate. Freezes also included a 1-mm rim of clinically healthy skin. In general, most dermatologists undertreat with cryotherapy for concern of producing blisters and scars. When 5-FU is used twice daily for 2 to 4 weeks, it is reported to have a field clearance rate of 50% with a recurrence rate up to 50% within 1 year.[1,9,10] Similarly, reports for IMQ include field clearance rates of 45% to 85% and recurrence rates within 1 year of 10% to 20%.[1,11]

A randomized study by Krawtchenko et al[1] compared the efficacy of cryotherapy, 5-FU, and IMQ in immunocompetent patients with AKs. Patients were randomized to 1 to 2 courses of lesion-directed cryotherapy with a 20- to 40-second freeze-thaw cycle (n=25), 5-FU twice daily for 4 weeks (n=24), or 1 or 2 courses of IMQ 3 times weekly for 4 weeks each (n=26). The initial clinical clearance rate 4 to 8 weeks following completion of therapy was

68% (17/25) for cryotherapy, 96% (23/24) for 5-FU, and 85% (22/26) for IMQ. The sustained clearance rate of the initially cleared lesions at 1-year follow-up was 28% (7/25) for cryotherapy, 54% (13/24) for 5-FU, and 73% (19/26) for IMQ. Histologic and cosmetic outcomes also were evaluated and shown to be superior for IMQ. The authors concluded that IMQ treatment of AKs resulted in superior outcomes and should be considered as first-line therapy.[1]

However, a comparison study of cryotherapy and IMQ showed lesion response rates of 85.0% (306/360) for cryotherapy and 66.9% (234/350) for IMQ at 1-year follow-up.[12] The cryotherapy-treated arm underwent freezing (20–30-second freeze-thaw cycles) of up to 10 lesions per session, with up to 4 sessions every 3 months. In contrast, 1 to 2 courses of IMQ (applied 3 times weekly for 3–4 weeks) were given. Lesion clearance rate was higher with repeated cryotherapy, but cosmetic outcome was better with IMQ. Overall, closely followed patients treated with repeated cryotherapy achieved excellent AK clearance rates.[12]

Gupta et al[13] published a critical review and meta-analysis of the effectiveness of IMQ and 5-FU in the treatment of AKs. Only studies with lesion clearance as a primary end point and dosage regimens similar to what was approved were included. The average efficacy rate (standard deviation) was 52% (18%)(6 studies; 145 participants) for 5-FU and 70% (12%)(4 studies; 393 participants) for IMQ. The authors concluded that both IMQ and 5-FU are effective for the treatment of AKs; however, IMQ may have a higher clearance of AK lesions than 5-FU.[13] In my experience, IMQ is slightly superior to 5-FU for AKs, though it also has limitations that I will discuss.

Photodynamic Therapy—At my institution, PDT has enjoyed increasing approval among both patients and clinicians, regardless of whether it is used with aminolevulinic acid (ALA) or methyl 5-aminolevulinate; however, it does require the purchase of equipment. The results of an investigator-initiated, single-blind, split-face comparison study of ALA-PDT and IMQ for the treatment of AKs showed a mean lesion count reduction (8 weeks posttreatment) of 59.2% for ALA-PDT and 41.4% for IMQ (n=50/61 completed study; mean AK count per side of face was n=11.7 for IMQ and n=12.2 for ALA-PDT).[14] A limitation of the study was the small amount of IMQ applied. A 20% solution of ALA was applied with an incubation time of 1 hour and patients were treated with 2 sessions.[14] Most patients need more than 1 treatment to achieve an adequate result, and on average I send patients for 2 to 3 treatments.

A randomized, pilot, comparative study by Serra-Guillén et al[15] compared methyl 5-aminolevulinate–PDT, IMQ cream 5%, and sequential application of both therapies in patients with AKs. The sequential application of PDT (1 session) and IMQ (1 cycle) resulted in a superior AK clearance rate compared to monotherapy with either agent.[15] I have not tried a combined approach, but this combination is a novel idea for immunocompetent patients with severe field cancerization (commonly seen in Arizona) or immunosuppressed patients with a high level of disease burden.

Diclofenac Gel—There is one study comparing the efficacy and tolerability of diclofenac sodium gel 3% and IMQ cream 5% in the treatment of AKs. At 1-year follow-up, the lesion response rate for diclofenac gel was 12% (n=25), which was inferior to IMQ. Interestingly, IMQ had a low lesion response rate of 22% (n=24).[16]

Ingenol Mebutate Gel—Ingenol mebutate gel 0.05% for the trunk and extremities and 0.015% for the face and scalp were approved early this year for the treatment of AKs. There are no comparative studies available. A pivotal paper published in the *New England Journal of Medicine* showed a complete clearance rate of 42.2% (n=277) with ingenol mebutate versus 3.7% (n=270) with placebo (assessed at 57 days).[17] In an observational follow-up trial of patients who achieved a complete response, 87.2% (n=108) of lesions in the treatment field were still clear at 1-year follow-up.[17,18] These numbers look comparable to 5-FU with the advantage of a 3-day, once-daily application period of the 0.015% strength to the face and scalp. However, the medication has not yet acquired the safety record of 5-FU.

My Approach to Treatment of AKs

There are a handful of comparative studies that show somewhat different efficacies between the treatment options for AKs, though nothing dramatic. The role of cryotherapy has not changed with the advent of topical treatments. It remains highly utilized, effective, and cheap. However, I rarely administer a 20-second freeze-thaw cycle, especially on the face. It is important to be aware of your level of aggressiveness with cryotherapy to make adjustments as the situation dictates. Seeing patients regularly for follow-up is important when treating several lesions. When patients have more than 10 to 15 AKs on examination, I start thinking about field-directed therapy.

Comparative studies in addition to my personal experiences showed that IMQ is slightly more effective than 5-FU. However, I still reach for 5-FU first because it is less expensive than IMQ and it works

well. The packaging of IMQ also is not ideal for large areas and the sachets make it hard for nondexterous elderly patients to use. Most patients struggle with compliance when using 5-FU because of irritation and the application period takes weeks, which is similar to IMQ. Ingenol mebutate gel 0.015% has the advantage of being applied once daily for 3 days to the face and scalp. However, the price is prohibitive for use right now. If compliance is a problem, I use PDT, which has an efficacy close to IMQ. Insurance usually covers PDT fairly well. Although purchasing equipment for PDT is required, it is a good investment. For the highly cosmetically sensitive patient, best results are seen with IMQ or PDT. I only consider using diclofenac gel for patients who are intolerant of other options; there usually are more efficacious alternatives.

Conclusion

Not having a standard of care for the treatment of AKs is reasonable. As a resident, you should become familiar and experienced with all of the modalities. The ability to speak with patients about the pros and cons of each option and to discuss the patient's expectations will help you to choose the best treatment option. Based on the comparative studies, many of the treatments work well.

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