Editorial

What's New in the Treatment of Actinic Keratoses?

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Actinic keratoses (AKs) are common dysplastic keratinocytic epidermal lesions caused by long-term UV exposure. Actinic keratosis is the second most common diagnosis seen by dermatologists. The prevalence of AK was reported to be 11% to 25% in 2008 and up to 60% in individuals over the age of 40 years in the northern hemisphere.[1] Actinic keratoses primarily affect fair-skinned, middle-aged individuals. Childhood sun exposure, immunosuppression, and age increase risk for developing AK. In the United States alone, the direct cost of AK therapy is estimated to be more than $1 billion per year and indirect costs are nearly $300 million.[2] Given its prevalence, much research has been dedicated to understanding and treating AKs. As a result, our awareness of the nature of AKs has dramatically changed over the last decade.

Historically, AK was classified as a premalignant lesion. In recent years, however, more evidence is accumulating that AKs are part of a spectrum of lesions ranging from sun-damaged skin to squamous cell carcinoma (SCC) in situ. Some practitioners consider AK to be the earliest clinically recognizable manifestation of SCC.[1,3-5] Chromosome analysis has revealed that AK and SCC have an altered p53 gene and altered expression of the B-cell lymphoma 2 gene, *BCL2*, an anti-apoptotic gene.[1,5,6] The exact percentage of cutaneous SCCs that arise in or near an AK varies from 25% to 80%, but studies have revealed a direct correlation of abnormal gene expression in the progression of normal skin to AK to SCC.[3,5]

Not all AK lesions will progress to SCC, but it is not possible to predict which AK lesions will progress and which will not. The relative risk for developing SCC increases with the number of AK lesions from less than 1% with 5 or fewer lesions to 20% with greater than 20 lesions.[1,2,7] Squamous cell carcinoma has a metastatic risk of 0.5% to 3.3%.[6] It is accepted that the presence of AK is a biomarker of risk for patients and therefore must be treated to avoid possible morbidity and mortality.[1,4,7] Additionally, there is high interobserver variation among experienced dermatologists.[1,7-9] Although there are no distinct clinical boundaries between AK and invasive SCC, histologically there is usually clear differentiation.[1]

Given the knowledge that AKs are part of a continuous spectrum of sun-damaged skin to SCC, AKs generally are treated and there are many options available. Lesion-directed treatment is one option in the setting of single lesions and can include cryotherapy, laser therapy, curettage, photodynamic therapy, and dermabrasion. These treatments may be painful and result in hypopigmentation as well as other cosmetically unacceptable outcomes. Furthermore, efficacy is variable depending on technique; there are no standard guidelines for cryosurgery with liquid nitrogen, and clearance rates of 39% to 98.8% have been reported.[10] Trials examining its efficacy found overall individual complete response rates of greater than 67%, but this number varied greatly depending on freeze time.[11,12]

It is widely accepted that AK is a field disease that is rarely limited to a single clinically apparent lesion.[3] To this end, field-directed therapy is an alternative that aims to eliminate not only clinically visible lesions but also subclinical lesions within the treatment area. Imiquimod cream, which acts as a toll-like receptor 7 agonist, disrupts tumor proliferation by modifying the immune response and stimulating apoptosis. Initially approved in a 5% concentration, imiquimod demonstrated 84% lesion reduction of AKs after one 16-week cycle of twice-weekly application.[13] More recently, a newer 3.75% concentration of imiquimod cream was approved for the treatment of AKs on the face or balding scalp. In one trial (N=479), participants applied cream daily for two 2-week treatment cycles separated by a 2-week rest period (2 weeks on, 2 weeks off, 2 weeks on). Participants achieved a median lesion reduction of 82% and 35.6% demonstrated complete clearance.[14] Although imiquimod 3.75% and 5% have not been examined head-to-head, the efficacy data for the 3.75% formulation are similar to the 5% formulation, with the advantage of a substantially shorter treatment time with the 3.75% formulation.

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Dr. Frankel reports no conflict of interest. Dr. Goldenberg is a consultant and speaker for Graceway Pharmaceuticals, LLC, and a consultant for LEO Pharma.

A novel therapy, ingenol mebutate (PEP 005), has shown promising results in the treatment of AKs. Ingenol mebutate gel induces necrosis and institutes a neutrophil-mediated, antibody-dependent cellular cytotoxicity of residual disease cells.[15-17] Ingenol mebutate has shown complete clearance rates of 70% after 2 days of treatment in phase 2 studies with a 25-cm^2 area.[3,4] Preliminary phase 3 data are available with PEP 005 used on the face, scalp, arm, chest, and back of the hand; complete and partial clearance rates of 27.8% to 42% and 44.4% to 55.0%, respectively, were reported.[18] Furthermore, common adverse effects such as redness, irritation, and burning resolved within 2 to 4 weeks, and adherence rates were high.[4]

Photodynamic therapy also is being used as field therapy, either alone or in conjunction with other topical therapies.[19] Photodynamic therapy is a noninvasive treatment that uses a topical photosensitizer such as aminolevulinic acid or methyl aminolevulinate to generate reactive oxygen species that cause selective and localized destruction of abnormal cells.[20,21] Aminolevulinic acid plus blue light is indicated for the treatment of minimally to moderately thick AKs of the face and scalp. As described in the package insert, the technique involves 2 steps starting with application of aminolevulinic acid in the physician's office to either face or scalp lesions 14 to 18 hours prior to blue light exposure.[22] Methyl aminolevulinate plus red light is indicated for the treatment of nonhyperkeratotic AKs of the face and scalp. In one study, methyl aminolevulinate photodynamic therapy resulted in complete clearance of 86.2% of lesions when combined with curettage compared to only 60% complete clearance with curettage alone.[23] Response rates have been inversely correlated with lesion thickness.[10] Photodynamic therapy has consistently shown excellent cosmesis.[10,23-25]

In many cases, undesirable side effects of treatment result in nonadherence, skewing our ability to really understand which therapies are most effective. Compliance studies, therefore, are important regarding AK treatment options. One might ascertain that there is a niche for a topical treatment with a mild to moderate side-effect profile, high complete clearance rate, optimal cosmetic results, and short duration of treatment.[3] Direct comparator studies of the currently available treatments would be beneficial in aiding the diagnostician in choosing the best option for the patient with multiple AKs. However, as Nolan and Feldman[26] aptly pointed out, despite clinical efficacy of a given treatment regimen, if patient adherence is not taken into account, clinical trial data may not translate into the best treatment option for a given patient.

The incidence of nonmelanoma skin cancer (NMSC) has been rising by more than 5% annually since 1964.[2] The potential transformation of AK to NMSC poses the greatest risk to affected individuals. As the current armamentarium of therapies against AK expands, the practitioner today has many options to treat this common problem. However, the prudent dermatologist would be wise to stress prevention, including sunscreen use and avoidance of artificial sources of UV light, as well as education regarding regular skin self-examinations.[10] In this way we can hope to stem the tide of the ever-increasing incidence of NMSC and its burden on our healthcare system.

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