Optimizing Management of Actinic Keratosis and Photodamaged Skin: Utilizing a Stepwise Approach

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The incidence of photodamaged skin and skin lesions of all degrees of severity, from actinic keratosis (AK) to skin cancers, has dramatically increased. Actinic keratoses are pathologic, reflecting damage of essential skin cell functions and potentially progressing to invasive squamous cell carcinoma (SCC). The rate of progression is uncertain but may be as high as 10%. Because it is impossible to predict which AKs will progress to SCC, all lesions should be treated. Options include topical therapies, cryotherapy, curettage, and photodynamic therapy. Unfortunately, many individuals do not seek treatment or avoid it because of irritation, discomfort, and concern for scarring. Combining field-directed therapy and cryotherapy has been more effective than cryotherapy alone. Incorporating patient education with treatment may optimize outcomes. We propose a comprehensive 5-step approach for managing AK lesions and photodamaged skin that includes periodic clinical skin examinations; treating AK lesions with a combination of field- and lesion-directed therapy; and patient education regarding sun-protective measures and regular skin self-examinations.

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Skin cancers represent one-third of all cancers affecting individuals in the United States. One of 6 Americans will develop skin cancer during their lifetime; most will be nonmelanoma skin cancers (NMSCs), such as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).[1] The increasing incidence of NMSCs in the United States likely is attributable to increased sun exposure, particularly as Americans spend more time outdoors for leisure activities.[2] From 1990-1999, actinic keratosis (AK), resulting mainly from photodamaged skin, was diagnosed in 47 million visits to dermatologists, comprising 14% of all visits to US dermatologist offices.[3] In an analysis of the National Ambulatory Medical Care Survey, annual visits for AK rose from an estimated 4.9 million during 1995-1997 to 5.2 million during 2000-2003.[4]

Actinic keratosis lesions often are diagnosed when patients present to the clinician with concerns of cosmetic effects of sun damage or a different dermatologic issue. Managing the potential progression of AK to invasive SCC requires increased vigilance in screening and prescribing safe and effective treatment options. Education may help patients understand the risks for unprotected sun exposure and untreated photodamaged skin and increase their willingness to initiate treatment before cancerous lesions emerge.

Presentation of AK and Progression to SCC

Long-term, excessive, and unprotected exposure to solar radiation initiates a process that begins with

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subclinical lesions, progresses to AK, and potentially advances to SCC.[5] Actinic keratosis develops after exposure to UVB radiation (290–320 nm), which damages DNA in epidermal cells; promotes mutations in the tumor protein p53 gene, *TP53*; and results in immunosuppression.[6,7] Despite widespread public discussion on the risks for unprotected sun exposure, the incidence of SCC is nearing epidemic proportions.[8] The number of BCC and SCC cases diagnosed in the United States is unknown because lesion rates are not reported; however, the American Cancer Society estimates the total annual number of NMSCs at more than 1 million.[9,10] Of these, 800,000 to 900,000 are BCC and 200,000 to 300,000 are SCC.[10]

Actinic keratosis lesions may appear as rough, scaly, often hyperkeratotic macules or papules with discrete or diffuse borders. They may be pigmented or erythematous and present as plaques.[11] They may feel similar to gritty sandpaper. Histologically, they may be recognized by the presence of atypical keratinocytes deep in the epidermis. Individuals with fair skin primarily are affected by AK lesions, which commonly are found on sun-exposed areas of the body such as the face, bald scalp, ears, hands, and lateral forearms. The Table summarizes the principal risk factors for NMSC and melanoma.

Knowing how AKs progress to invasive SCC may help clinicians plan treatment strategies to prevent the 1300 to 2300 annual deaths from SCC in the United States.[12] A number of studies have reported progression of AK to invasive SCC in 0.025% and 16.0% of cases, and extrapolation studies have estimated the rate at 8.0%.[13-16] A retrospective study of 6691 patients found that 91 had pathologically confirmed AK lesions at the same site as subsequent SCCs.[17] The mean progression time from AK lesions to invasive SCCs was 24.6 months. These investigators predicted that approximately 10% of AK lesions would become invasive SCCs within 2 years, suggesting that clinicians treat AK lesions promptly after diagnosis.[17] We believe that the progression rate is low; however, the presence of multiple risk factors may increase the likelihood of developing invasive SCC.

Although most AK lesions will not progress to invasive SCC, patients often have multiple lesions and predicting which lesions will progress to invasive SCC is not possible.[13,18,19] The relationship between AK and SCC is strong; studies have shown that SCC was linked to an AK lesion 72% to 97% of the time.[18,19] Because of this association, the American Academy of Dermatology, the American Cancer Society, and the Skin Cancer Foundation recommend that individuals with AK see a dermatologist to screen for cutaneous malignancies.[20]

The importance of sun protection has been widely disseminated; however, many individuals who develop AK lesions from sun exposure do not seek treatment.[20] Moreover, many patients with AK lesions resist or oppose treatment because they equate therapy with skin irritation and slow healing. Patient education may encourage more individuals to consult a dermatologist and increase the willingness of patients to accept treatment after AK has been identified.[17]

We recommend a 5-step approach to treating AK lesions and photodamaged skin. This approach considers a number of factors, including the need for early detection and identifying the most effective treatment option.

5 Steps for Optimizing Management of AK Lesions and Photodamaged Skin

Our 5-step program addresses the challenge of providing optimal care for patients with AK lesions and photodamaged skin as well as those at risk for cancerous lesions: (1) periodic clinical skin examinations; (2) field-directed therapy consisting of topical medications; (3) lesion-directed therapy consisting of specific destructive procedures; (4) patient education on sun protection and the need for prompt treatment of AK, BCC, and SCC; and (5) regular skin self-examinations (Figure 1).

Step 1: Periodic Clinical Skin Examinations—The benefits of mass screening programs for skin cancer generally have been acknowledged, though recommendations on frequency vary. The American Academy of Dermatology and the Skin Cancer Foundation recommend annual complete skin examinations for all patients, and the American Cancer Society recommends annual skin examinations for all patients 40 years and older and every 3 years for patients aged 20 to 39 years. The US Preventive Services Task Force and the American Academy of Family Physicians have noted a lack of evidence for or against routine complete skin examinations but urge clinicians to be alert to potentially malignant lesions, especially in patients with risk factors for melanoma, and to consider referral of patients with marker lesions (ie, atypical nevi) to a skin cancer specialist.[21]

Clinicians should be especially assiduous in eliciting information that would permit an assessment of each patient's lifetime sun exposure and history of painful sunburns. A case-control study in 966 individuals found an association between the recall of painful sunburns before 20 years of age and an increased risk for AK lesions and several NMSCs.[22]

During screening, patients should remove all clothing and concealing cosmetics, and examiners

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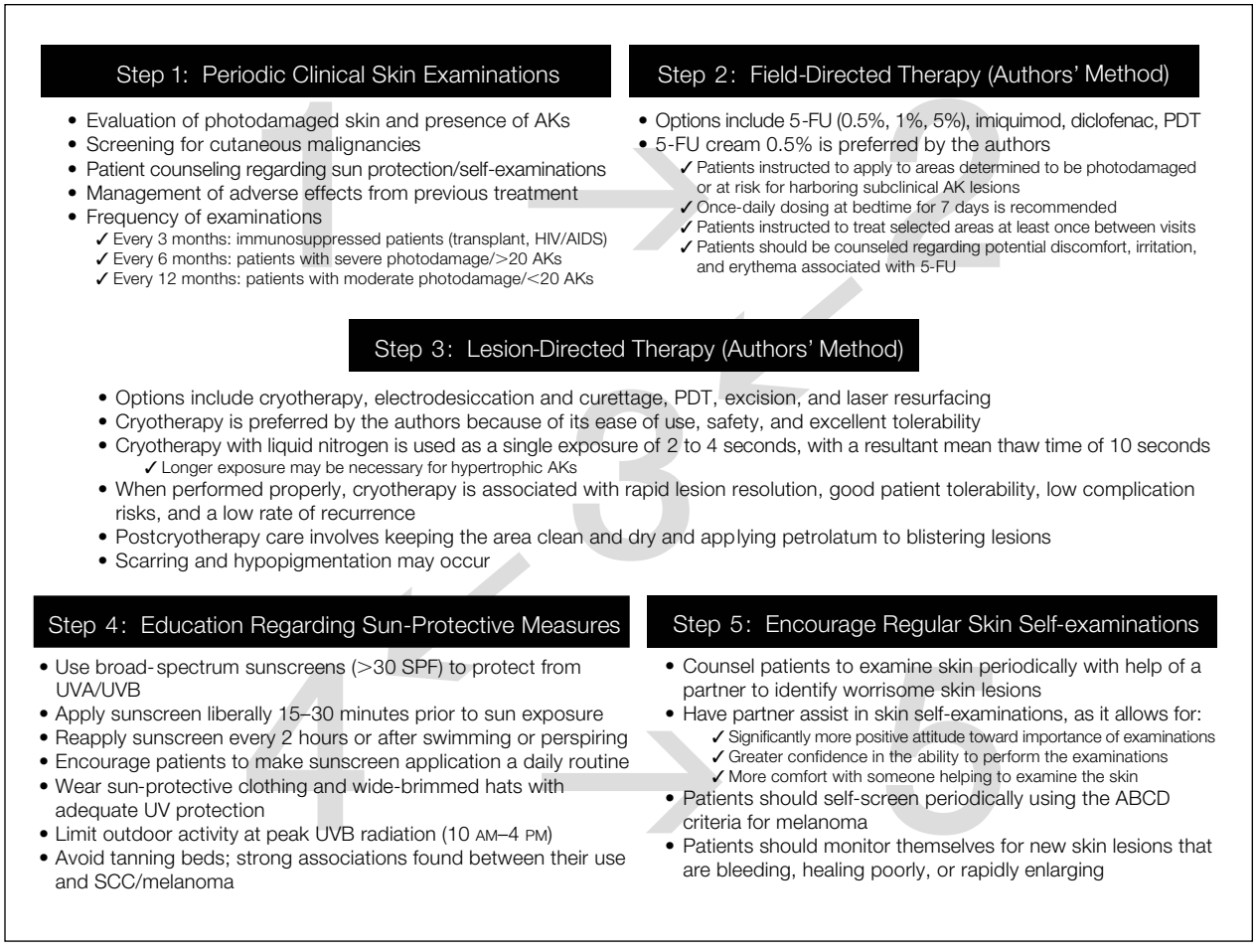

Figure 1. A 5-step approach for providing optimal care for patients with actinic keratosis lesions and photodamaged skin. AK indicates actinic keratosis; HIV, human immunodeficiency virus; 5-FU, 5-fluorouracil; PDT, photodynamic therapy; SPF, sun protection factor; SCC, squamous cell carcinoma. The ABCD system for identifying lesions, nevi, or keratoses suggestive of melanoma consists of the following: A=asymmetry (the 2 halves of the lesion do not match); B=border (uneven or irregular); C=color (not uniform); and D=diameter (>6 mm and/or growing).

should systematically inspect the entire skin surface.[1] Daylight is ideal, but full-spectrum halogen or a combination of incandescent (tungsten) and fluorescent illumination also is satisfactory.[23] Figure 2 illustrates typical presentations of AK lesions and SCCs.

Steps 2 and 3: Field- and Lesion-Directed Therapy—Field-directed therapy is appropriate for patients with multiple or diffuse AK lesions. Topical medication is applied to larger affected areas that may include several lesions, some that may not be clinically apparent. Several topical medications are approved for the treatment of AK and include 5-fluorouracil (5-FU), imiquimod, and diclofenac.

Lesion-directed therapy, or destructive procedures, requires the clear and specific identification of target lesions. Common destructive modalities include cryotherapy, electrodesiccation and curettage, and photodynamic therapy.

Used as monotherapy, all AK treatments have limitations, including incomplete clearance of lesions, risk for recurrence, limited tolerability, and cosmetic adverse effects, that make the therapy less acceptable to patients. Hypertrophic AK lesions were excluded from phase 3 US Food and Drug Administration–approved studies of all field-directed therapies for AK. These lesions respond better to destructive therapies such as cryotherapy. Field-directed therapies are suited for detecting and treating subclinical AK lesions that are missed on routine skin examinations. These factors suggest that combining the 2 most efficacious modalities of treatment will maximize AK clearance, reduce recurrence, and minimize adverse effects. We prefer combination therapy with 5-FU cream 0.5% and cryotherapy for most of our patients, with imiquimod used as an interval regimen for special situations, such as transplant recipients and for actinic cheilitis.

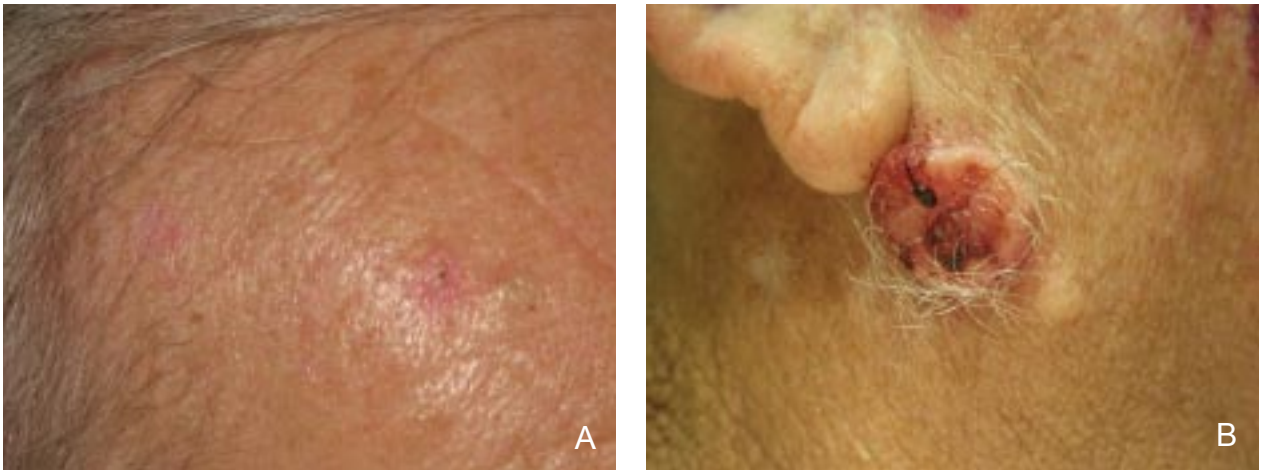

Figure 2. Typical clinical presentations of actinic keratosis lesions (A) and squamous cell carcinomas (B).

Combination therapy with 5-FU followed by cryotherapy was proposed by Abadir[24] in 1983. The rationale for combination therapy was that although topical 5-FU at a 5% concentration applied for a minimum of 3 to 4 weeks is a complete method of treatment, it can become intolerable for many patients. As an alternative, 10 days of topical treatment twice daily with 5-FU 5% was proposed, followed by treating areas that developed erythema with cryotherapy. This method permitted clinicians to assure patients that the undesirable cosmetic effects would be minimized after cryotherapy.[24]

Our preferred treatment protocol—using 5-FU at a much lower concentration (0.5%) for 1 week followed by cryotherapy—was evaluated in a randomized vehicle-controlled study of pretreatment with 5-FU cream 0.5%.[25] The study included 3 treatment cycles at 6-month intervals (start of study, 6 months, and 12 months), with each cycle consisting of 7 days of 5-FU cream 0.5% applied to the face and other potentially affected areas. Follow-up occurred 4 weeks later when all remaining AK lesions were counted and cryotherapy was performed. Proportional reductions from baseline facial lesions were significantly higher in the 5-FU cream 0.5% group versus the vehicle group during all 3 treatment cycles (62.6% vs 28.8%, $P<.001$; 86.3% vs 57.8%, $P<.001$; 77.8% vs 64.7%, $P=.007$, respectively). Incidence of treatment-related adverse events was similar between the 2 treatment groups, with the exception of application site reactions and rash. Over time, application site reactions decreased in the active treatment group, and no serious adverse events were considered treatment related.[25]

The use of other topical treatments in combination with cryotherapy, although used in dermatology practices, has not been extensively discussed in the literature. Imiquimod was compared with vehicle in 63 study participants after target AK lesions had been treated with cryotherapy. The difference between the imiquimod- and vehicle-treated groups did not attain significance for the proportion of patients completely clear of target AK lesions at week 12 (79% vs 76%) or for achieving clearance of subclinical (58% vs 34%, $P=.06$) and total (23% vs 9%, $P=.21$) AK lesions.[26]

Step 4: Education Regarding Sun-Protective Measures—Individuals with fair skin appear to be the most vulnerable to solar radiation and UV light.[27] The association between sun exposure and AK lesions was confirmed in a population-based survey (N=20,637) reporting that in white men and women (age range, 65–74 years), the prevalence of AK lesions was higher in those who had high sun exposure compared with low sun exposure (55.4% vs 18.5% and 37.3% vs 11.9%, respectively).[28]

The reduction in the incidence of AK lesions with sunscreen use has been studied in the United States and elsewhere.[29-31] An Australian study evaluating white participants with AK lesions found a mean (standard error) increase of 1.0 (0.3) AK lesions in participants using base cream compared with 0.6 (0.3) AK lesions in participants using sunscreen with a sun protection factor of 17.[31] Similarly, a 78% decrease in the lifetime incidence of BCC and SCC has been reported in individuals who regularly use sunscreen with a sun protection factor of 15 during the first 18 years of life.[30]

Step 5: Encourage Regular Skin Self-examinations—Self-examination is an effective tool for identifying several types of cancers, including breast and testicular cancer.[32] However, unlike these cancers, self-examination of the skin often requires others to inspect areas of the skin that are not easily seen. A recent study showed a strong positive relationship between the beneficial effects provided by the

partner being included in the skin self-examination skills training and the quality of the marital/partner relationship.[32]

Self-examination for signs of malignant melanoma is particularly important. The ABCD system for identifying lesions, nevi, or keratoses suggestive of melanoma has been proposed as an easy mnemonic for patients and a practical reminder to clinicians to be aware of these lesions: A=asymmetry (the 2 halves of the lesion do not match); B=border (uneven or irregular); C=color (not uniform); D=diameter (>6 mm and/or growing).[9] Individuals are urged to seek prompt attention for moles or lesions that evolve or change, bleed, are painful, heal poorly, have rough patches of skin with scaly crusted growths, or exhibit other anomalies.

Comment

Effective management of the adverse consequences of sun exposure requires a collaborative effort by clinicians and patients. Just as lifestyle choices such as smoking, diet, and inactivity constitute risk factors for a range of chronic diseases, sun exposure should be understood to constitute a risk factor for skin disorders and diseases ranging from mild photoaging to cancerous lesions of varying severity. While the most effective therapy is prevention, educating patients to seek medical attention at the earliest sign of a worrisome lesion may result in improved outcomes and lower morbidity associated with treatment.

Clinicians need to adopt treatment strategies that effectively deal with the target lesions and are acceptable to patients. Patients may be unwilling to undergo lengthy and irritating treatment regimens, even though their condition may affect their health and quality of life. Treating AK lesions with cryotherapy is highly effective but may be impractical for patients who have many lesions. Conversely, 5-FU at higher concentrations results in good clearance of AK lesions but may have unacceptably high adverse effects. Combination therapy with a topical therapy, such as a 1-week course of 5-FU cream 0.5% followed by cryotherapy, has been shown to reduce the overall number of AK lesions in a treatment field, both in clinical studies and anecdotal experience.

Our 5-step management approach for AK lesions and photodamaged skin emphasizes patient involvement, encouraging patients to return for periodic skin examinations and to remain vigilant with regular skin self-examinations, all with a goal of reducing the risk for skin cancer.

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