**Actinic Keratoses Update**

Linda Susan Marcus, MD

Actinic keratoses (AKs) are no longer considered precancerous lesions and are formally considered the earliest stage in the development of skin cancer. This definition must be incorporated into texts, lectures, and all publications as it reflects the importance of AKs biologically, the way they are treated, and prevention. Treatments and goals in caring for AKs are diverse and depend on the patient’s profile. Combination therapy is the ideal. A review of the types of AK lesions and appropriate uses of current treatment modalities (eg, curettage, shave, excision, cryosurgery, topical chemotherapies, photodynamic therapy, laser/intense pulsed light rejuvenation, chemical peels, retinoids, and combination therapy) is discussed. Preventive measures, including broad spectrum UVA/UVB sunscreens, protective clothing, tanning beds, and oral therapies are included. As new therapies in treatment and prevention evolve, adaptation in patient care must be made.

**DESCRIPTION**

Actinic keratoses are skin-colored or reddish-brown epidermal lesions that are flat or slightly elevated, rough, scaly, mottled, and crusty as in Figure 1. Variants may be hyperkeratotic, hornlike, sandpaperlike, pigmented, unique, or coalescing as in Figure 2. When found on the lips, they are referred to as actinic cheilitis.

**PATHOLOGY**

Histologically, there is dysplasia of the epidermis with abnormal keratinocytes in the basal layer, abnormal cellular polarity in the lower epidermis, nuclear atypia, and mitotic figures, which extend up the granular and cornified layers but not into the dermis. As in Figure 3, there can be parakeratosis and hyperkeratosis.

**ETIOLOGY**

Early UV light exposure is the main cause of actinic damage and AKs. Lesions appear after the age of 40 years, but have been seen as early as 20 years. They are more prevalent in fair skinned, light eyed individuals who live in sunny climates.

**PHOTOCARCINOGENESIS AND PATHOGENESIS**

UVB radiation contributes to C to T and CC to TT mutations in p53 (60% of AKs). There is suppression of protective cutaneous immunity with the release of inflammatory mediators, which affects cytokines, mast cells, prostaglandins, immunosuppression, and Langerhan cells. Interleukin (IL) 1, IL-10, and tumor necrosis factor α are released. Urocanic acid is isomerized from the trans to the cis form, which suppresses contact hypersensitivity responses to hapten via its action on mast cells. Prostaglandin E2 synthesis suppresses cutaneous immune responses.

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The author reports no conflict of interest in relation to this article.

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UVA radiation can damage DNA, suppress the immune system, cause oxidative stress, and reduce collagen and elastin fibers. In vitro studies show it increases p38 mitogen-induced protein kinase activity and expression of Bcl-XL.4

The human papillomavirus has been implicated with oncogenic potential and predisposes to the initiation of skin cancer, but it does not maintain itself as AKs progress to SCC.5

Genetic tumor markers prove AKs are in the continuum of skin cancer involving p53, which allows for the replication of DNA-damaged cells. No apoptosis allows cancerous cells to survive, and field cancerization causes further lateral spread.⁶

Further UVB exposure causes adjacent monoclonal colonies to be affected. Nelson et al⁷ reported 53% of AKs to have p53 mutation; 16% have the Ras oncogene. Death receptor CD95 is increased in AKs but decreased in SCC; therefore, AKs do not metastasize.⁶⁻⁸

Ironically, vitamin D plays a role in skin cancer prevention; a gene for vitamin D receptor (VDR) is polymorphic and can increase or decrease transcriptional activity when the receptor is occupied. This affects vitamin D’s effect on tumor growth, which can influence susceptibility to develop AKs. In an Australian study,⁹ VDR polymorphisms of the TaqI and ApaI genotypes are predisposed to AKs versus FokI types.

**TREATMENT MODALITIES**

When choosing a treatment modality, consideration must be given to the type of lesion (eg, hyperkeratotic/flat, scaly/thick/thin); number (eg, unique, coalescing, field/covert); and location as represented in Figure 4. The patient’s age, health, compliance, and social circumstances (feasibility) should be considered as well as efficacy, tolerability, convenience, cosmesis, and cost. The goals of therapy are diagnostic, therapeutic, palliative, maintenance, and prevention. Multiple therapies may be used in one patient at any one visit and definitely throughout the continued courses of follow-up care.¹⁰⁻¹¹
Biopsy
A biopsy is important to make a diagnosis or to confirm a diagnosis of a related disease. Bowen disease, SCC, cutaneous horn, basal cell carcinoma, pigmented actinic versus melanoma, or benign lesions (eg, seborrheic keratosis, lichen planus–like keratosis, scaly lentigo).

Curettage or Shave
For curettage or shave, there must be an appropriate depth to make a diagnosis versus punch biopsy (fast/simple). This technique is good for pathological diagnosis. Light electrodessication may be used.

Excisions
Excisions are rarely done by a dermatologist unless the diagnosis is questionable; however, it is useful for treatment of cutaneous horn.

Cryosurgery
Cryosurgery is the most frequent modality used and is the gold standard of the destructive therapies. It achieves 98% cure rates. It is fast, simple, and has the ability to treat many lesions expeditiously (>15).

Topical Chemotherapy
Topical chemotherapy has a field therapy advantage and is useful to treat an entire clinical and subclinical area for clusters, large surface areas, and poorly visualized lesions. It allows for treatment of preclinical lesions of UV-mutated cells in an anatomical field, provides excellent cosmesis, and is beneficial in prevention, treatment, and prophylaxis.

The choice of drug depends on the patient, social commitments, cooperation, expectations, finances, time, and the extent of the lesions. The regimen may be tailored to each individual to accommodate a situation.

The oldest agent is 5-fluorouracil (5-FU), which is applied in small amounts to the entire area 2 times a day for 2 to 4 weeks as in Figure 5. Fluorinated pyrimidine 5-FU blocks the methylation of deoxouridine acid to thymidyl acid of DNA, altering only fast-dividing cancerous cells. It is available in solutions of 1%, 2%, and 5% and in creams of 1% and 5%. There is also a cream with 0.5% that utilizes a microsphere delivery system to trap the active ingredients on the skin’s surface for increased efficacy. In addition, 5-FU may be used as maintenance therapy, cycle therapy, or prior to cryosurgery; elicits erythema, scaliness, crusts (avoided with milder preparations); and the reaction is self-limited. Topical steroids or hyaluronic acid (HA) gels used posttreatment may abate the reaction faster.

Diclofenac sodium 3% in HA 2.5% gel may have a place in mild problems as well as pre- and postcryosurgery.

Imiquimod is the newest standard for treating AKs. It was approved by the US Food and Drug Administration (FDA) in 2004 as a 5% preparation applied twice daily for up to 16 weeks (commonly 8–12). Other preparations have been studied and may be available soon. Imiquimod is an immune response modifier that induces mRNA encoding cytokines such as α-interferon, tumor necrosis factor, and IL-12 for a cytotoxic T-lymphocyte response. It has a direct action is unknown; it may involve prostaglandin levels in UV-exposed skin and upregulation of COX-2, which may promote proliferation. (Cyclooxygenase is the rate-limiting enzyme step in prostaglandin synthesis). No severe reaction is seen. Patient compliance is a problem due to the length of therapy. In addition, diclofenac sodium 3% in HA 2.5% gel may have a place in mild problems as well as pre- and postcryosurgery.

Figure 4. Patient with field actinic keratoses.

Figure 5. Patient with actinic keratoses 3 weeks posttreatment with 5-fluorouracil.
Actinic Keratoses

Proapoptotic effect in changing cancerous cells as a result of bypassing transduction paths, activating caspase-3 downstream of membrane-bound death receptor activation. It evokes a severe reaction without much pain and gives excellent cosmetic results upon healing. Dermatologists tweak the frequency of applications. Imiquimod may give longer-lasting results, but some studies say it is similar to 5-FU. As in Figure 6, it is excellent field therapy for subclinical lesions, but requires follow-up care and hand holding.14-16

Photodynamic therapy (PDT) is an in-office procedure that shortens the treatment course and is especially good for field therapy as in Figure 7. It was, however, originally approved for only 6 lesions, which is not feasible since it is costly and time consuming. A natural photosensitizer, 5-aminolevulinic acid (5-ALA) accumulates in damaged skin cells after application. It is converted by light to protoporphyrin IX, a photosensitizer, which generates cytotoxic free oxygen radicals and destroys dystrophic cells. It is contraindicated in porphyria.17-19

In a single-use disposable stick, ALA 20% is applied 20 to 60 minutes (short contact) to the area for incubation prior to exposure to blue light (420 nm) for 16 minutes and 40 seconds; with intense pulsed light using a 560-filter, double pulse at 3.5-, 3-, and 5-millisecond durations with a 10-millisecond delay; or with a 7-mm spot size at 3.5 J/cm² using a pulsed dye laser.20 In addition, 532-nm lasers may also be employed to activate chemicals and destroy actinic lesions. Penetration can be enhanced by longer incubation, pretreatment microdermabrasion, peels, or acetone scrubs. Regimens can be customized.20-22

Methyl 5-aminolevulinate cream 160 mg/g needs a 3-hour incubation period (with occlusion) prior to exposure to red light (630 nm) at 75 J/cm². This may increase efficacy due to the correlation to the spectrum of protoporphyrin IX action; however, it is not very user-friendly.21

Photodynamic therapy may cause burning, edema, or redness for 3 to 10 days. Anti-inflammatories, HA, moisturizers, and sunscreen may be used postprocedure. Natural sunlight activates ALA. Its advantages are that it is fast, can be used for field therapy, and clears 89% of patients, although retreatment may be needed depending on the patient and protocol.18,19

Chemical peeling destroys undesirable skins cells. Mild, medium, or deep peels are used depending on the goal of treatment, lifestyle of the patient, economics, and time. Jessner solution, trichloracetic acid 50%, β- and α-hydroxy acids, vitamin C, and antioxidants may be used as monotherapy, maintenance, or in conjunction with other modalities.
Dermabrasion or laser resurfacing with a CO2 laser can be used to remove skin cells and actinically damaged cells. The number of treatments depends on the depth of destruction desired. It involves downtime, pain, erythema, and swelling. Dermabrasion can be used for photodamaged skin, with rejuvenizing therapy at one time.23

Topical retinoic acid was approved for treatment of photodamage in Fitzpatrick skin type I in the 1990s. There are cream and gel formulations that are applied at night along with sunscreen during the day. The mechanism of action is unknown; however, retinoids are needed in maintenance of epithelial differentiation and maturation. They indirectly down regulate protooncogenes and may have a role in maintenance by increasing cellular turnover and differentiation.24 Retinoids can be used as adjunctive therapy to enhance penetration of other topical regimens such as 5-FU, especially on thicker lesions (scalp). Retinoids should be stopped a few days prior to lasers, peels, and PDT to avoid increased skin sensitivity.

PROPHYLAXIS
Laser, peels, 5-FU, retinoic and glycolic acid, and antioxidants creams may remove early damaged cells and halt progression; therefore, these therapies may be used as prophylaxis.23

PREVENTION AND MAINTENANCE: SUNSCREEN AND SUN AVOIDANCE
The key to long-term treatment of AKs is prevention and maintenance with the use of a sunscreen containing a sun protection factor (SPF) of at least 30 that blocks against UVB rays and one that blocks against UVA rays (the deeper more damaging rays [90%-95% of light from the atmosphere]), which remain constant throughout the year.4 Greatest in the summer, UVB is most intense from 10:00 AM to 4:00 PM.

The minimal erythema dose (MED) is the minimum exposure to UV radiation to produce sunburn and depends on skin type, geographical location, and time of year. (Fitzpatrick skin types I–III burn easily, within 20 minutes or less).

The UV index is a mathematical computer-generated number, taking into consideration ozone, elevation, latitude, cloud coverage, time of year, and day for peak UV level at noon (0–11). The UV Index was created by the World Health Organization, World Meteorological Organization, United Nations Environmental Programme, International Commission on Non-Ionizing Radiation Protection, and the National Weather Service.25 Table 1 depicts how the grades are indicated and reported with weather information. Indirect, damaging rays from snow, sand, concrete, water, and buildings are not considered.

Therefore, the UV index is not really an indication of exposure; artificial sources and year-round exposure are indicative. A daily sunscreen regimen is necessary because a low UV index may give a false sense of security. There should be no indoor tanning. In fact, many states now have warnings and age requirements on tanning booths, indicating that it is a hazardous procedure.

Sunscreen
The SPF in sunscreen indicates protection from UVB rays (280–320 nm) and is a ratio of how long it takes skin to redden as compared without sunscreen. If it takes 2 minutes for unprotected skin to redden, an SPF of 15 will protect the skin for 30 minutes, absorbing 29 of 30 U of UVB rays. A person cannot stay in the sun for 30 minutes without sunscreen. Using a higher SPF increases protection incrementally from 97% to only 98%, but sometimes it seems to make a difference in those with sensitive skin.

An SPF is tested at 2 mg/cm2, and the FDA may institute a 50+ system. Sunscreen should be applied in the amount of 0.5 mg/cm2 with each application (about the size of a shot glass or golf ball). Ingredients found in sunscreens include cinnamates (octyl methyl cinnamate and cinoxate), oxybenzone, sulisobenzone, and salicylate.25 UVA rays (320–400 nm) pass through window panes. Tests for UVA protection include the Protection Factor of UVB test and Persistent Pigment Darkening test; however, these are not standard. The star system is supposed to indicate protection quality.26 Ingredients such as zinc oxide 6% (which may be obtained colorless) and titanium dioxide are physical sunblocks. Avobenzone (Parsol 1785) must be stabilized, and ecamsule is good. Octocrylene increases photostability and fills in the gap between UVB/UVB range/duration. Diethylhexyl 2,6-naphthalate and benzophenone are patented and derived with a photostabilizing solvent to stabilize avobenzone and increase duration; however, how long is the duration? Patients must reapply sunscreen every

### Table 1

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<th>UV Index</th>
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<td><strong>Index Level</strong></td>
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2 hours while outside. Chemical absorbers work by absorbing light, but are unstable in light; the trend is toward white pigments that reflect UV radiation, not absorb it.\(^{26,27}\)

On March 31, 2006, there was a class action lawsuit against Chattem, Inc; Johnson & Johnson Services, Inc; Neutrogena; Playtex Products, Inc; Schering-Plough; Sun Pharmaceuticals Industries; and Tanning Research Laboratories, Inc, because of the companies’ use of misleading terms such as long-lasting, waterproof, sunblock, and all-day protection on their products. The FDA asked for a voluntary removal of this terminology.\(^{25}\)

### Clothing and Physical Protection

Sun-protective clothing is beneficial because it is non-greasy and dry. The material should be dark, have a tight weave, and little tension. The clothing must have long sleeves and pants to cover the body well, decrease perspiration, be nonstick, and ventilate. Three-inch wide-brimmed hats do not protect against indirect light; therefore, the nape of the neck should be covered.

The American Society for Testing and Materials adapted an Australian code for a UV protection factor (UPF) to rate fabrics (fiber, weight, construction, color, fit, wet/dry), which is measured by a spectrophotometer and compared with nonprotective fabric. A UPF of 30 blocks 29 of 30 U of UV radiation, or 97% as seen with an SPF.\(^{25}\)

The FDA is not involved in UPF rating and is maintained by an honor system. Sun-protective garments are sold in the United States, and there are chemicals that can be added to the laundry to increase the SPF in fabrics to absorb UV radiation.\(^{25,28}\)

Wraparound sunglasses with UV protection are an important part of sun protection.\(^{25}\) Photosensitive film protectors for car and home windows have been available since 1998. Film blocks 99% of UV rays up to 380 nm; a UV shield blocks 99.9%. Physical barriers to the sun are important, including umbrellas, trees, and shade structures found on playgrounds; however, sunscreen must be used even on cloudy days.\(^{27}\)

### Other Sources of Sun Protection

Other pharmacologic and dietary chemicals inhibit or reverse the effects of UV radiation and can be used both topically and orally as chemopreventatives. Many are found in plants and inhibit the development of cancer by interfering with the mechanism of action of UV radiation on cells. Most of these are generally safe, simple, inexpensive, and compatible with other medications. Included are nutritional supplements with antioxidants that block cell damage from UV light; however, sunscreen should still be used. Polypodium leucotomos, a Central American fern, is taken orally but is not proven as a sunscreen. Adjunctive natural plant therapy such as feverfew, a flower antioxidant with anti-inflammatory activity, decreases erythema because it reduces prostaglandin synthesis and is protective of DNA. Green tea, *Camellia sinensis*, blocks erythema up to twice the MED for 72 hours after application, but does not absorb UV light and may be added to sunscreens. Vitamins C and E, L-ascorbic acid, and \(\alpha\)-tocopherol, are antioxidants. When ferulic acid is added as a stabilizer and applied for 4 days, one study showed protection of 2 to 10 MED.\(^{30}\) Vitamin D UV radiation causes AKs (skin cancer) and also produces vitamin D, which inhibits tumor development. Can supplements help to protect against the sun? More studies are needed to judge the efficacy of topical calcipotriol.\(^{29}\) Tumeric acts similarly to COX-2, which enhances DNA repair. Tamarind xyloglucan, aloe vera, and DNA repair enzymes that have been implicated as immunologic photoprotectors. Cat’s claw, found in AC-11, enhances DNA repair, decreases oxidative DNA damage in humans, and is anti-inflammatory. It also decreases the effect of UV radiation in DNA and induces skin repair. Dihydroxymethylornithine inhibits ornithine decarboxylase, the rate-limiting step in tumor promotion. In addition, T4 endonuclease V repairs DNA damage in bacteria and is being investigated. COX inhibitors and celecoxib/anti-inflammatory drugs may decrease incidence of AKs when used regularly.\(^{30-33}\)

### THE FUTURE

Using the immune protection factor to protect cutaneous immunity from the damaging effects of radiation differs from the usual approach of sun protection, which relies on blocking mechanisms and opens the door to new formulations. DNA fragments are being used as signals to create more melanin in the body and act as a biologic sunscreen or aid in repair.

An Israeli company was working on an encapsulated particle sunscreen. Quantum physics has been used to trap single photons of UV energy in a silicon, non-particle coating that captures UVA, UVB, and UVC to dissipate as heat. Ingenol mebutate gel is an Australian product that is due for FDA submission in mid-2010 and augments neutrophil killing ability on abnormal cells by damaging mitochondria. The benefits of this product in treating superficial basal cell carcinoma have been proven histologically. It is to be applied for only 2 to 3 days, with studies performed on 4 to 8 lesions per 25 cm\(^2\). There is 38% clearance using a 0.025% preparation with excellent tolerability and 100% clearance with a 0.125% preparation that causes irritation. What will be the adequate preparation and how much irritability will be tolerable? This is being studied. Only time will
tell what will be the next innovative approach to a challenging and constant problem.32-37

CONCLUSION
Actinic keratoses are the earliest changes in the continuum of skin cancer and must be treated to prevent further progression. The choice of therapy depends on many factors including the lesion, patient, goal of treatment, time, cosmetic result, and cost. Multiple modalities can and should be used over time in a single patient when forming a treatment plan. Treatment and curing an individual lesion, prophylaxis, and maintenance of the skin play a part in caring for the patient with AKs, as well as prevention, which is an ongoing process. Plans include destructive, chemical, maintenance, and preventive methods. The mainstay of prevention is avoiding the sun and using chemical and physical means (Table 2). Education is primary in helping the public understand the importance of sun safety and to avoid tanning. There are many new and interesting ideas about prevention and treatment of AKs in this ever-evolving field that must be respected.

REFERENCES
16. Tanghetti E. Efficacy and tolerability of 5% 5-fluorouracil cream and imiquimod 5% cream in the management of actinic keratoses. Poster presented at: 64th Annual Meeting of the American Academy of Dermatology, March 3-7, 2006; San Francisco, CA.

Table 2

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<td>Cryotherapy</td>
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Abbreviations: AK, actinic keratoses; PDT, photodynamic therapy.
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