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ACTINIC KERATOSIS:

CHANGING THE TREATMENT PARADIGM

JO0519

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ORIGINAL ARTICLE

JO0519

Addressing the Challenges of Treating Actinic Keratosis

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Actinic keratosis (AK) represents one of the most common diagnoses in our dermatology practices. The incidence of AK lesions continues to rise, along with that of non-melanoma skin cancers. Numerous risk factors have now been implicated, including chronic sun exposure, history of sunburns, fair skin, advanced age, male gender, and immunosuppression. Although an individual lesion's likelihood of progression to malignancy remains very low, AKs seldom occur in isolation. Indeed, the condition can most accurately be described as a "field disease", with a mix of clinical and subclinical lesions present in the same region. Studies have shown that the majority of squamous cell carcinomas arise in sites of pre-existing AKs, highlighting the importance of diagnosis and appropriate management.

The selection of treatment depends on several factors including the number of AK lesions, patient adherence, tolerability of side effects, treatment availability, and cost. Although procedural techniques—such as cryosurgery—remain the mainstay of treatment for individual lesions, the popularity of field-directed therapies has increased in recent years. Such medications aim to address the entire disease burden of an area, treating multiple AKs and subclinical lesions under the same regimen. Options include topical therapies (5-fluorouracil, imiquimod, ingenol mebutate) as well as light-based therapies (photodynamic therapy). Observation and careful monitoring may also be appropriate, although this approach can be burdensome for the patient and physician. Individual AKs can regress spontaneously, although there is a high risk of recurrence, with data showing 15-53% recurrence rates for single lesions 1 year after regression.[1]

Despite the advantages of field-directed therapies, agents often carry the limitations of prolonged treatment courses and high incidences of local skin reactions. The severity of these cutaneous effects may range from mild erythema and pruritus to erosions and even ulceration. The healing time of sequelae can last up to several weeks, and some therapies, such as topical imiquimod, also carry the risk of systemic flu-like symptoms.

Novel topical therapies aim to reduce treatment time and improve tolerability. Light-based therapies have now expanded to the use of natural daylight, which may prove more time-efficient and cost-efficient, as well as more comfortable. In addition, investigational therapies remain an area of active clinical research. By using novel mechanisms of action, these agents may allow for circumvention of the inevitable skin irritation tied to classic modalities. The success of these agents can significantly impact treatment algorithms in the future.

The management of AKs remains a long-term undertaking between patient and clinician. Importantly, an emphasis on prevention and further progression is not to be overlooked, as routine counseling (use of broad-based sunscreens, wide-brimmed hats, avoidance of exposure during peak hours) remains an integral component to the treatment algorithm.

With an increasing array of treatment modalities, dermatology providers who are engaged and educated in the development of therapies for AKs will have an exciting opportunity to tailor treatments to specific patient requirements for optimal efficacy and tolerability.

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Actinic Keratosis:
Current Therapies and Insights Into New Treatments

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ABSTRACT

Actinic keratosis (AK) develops on chronically sun-exposed skin and constitutes one of the most common diseases managed by dermatologists. The incidence of AKs continues to rise among aging as well as younger sun damaged populations worldwide, underscoring the importance of effective therapy options. Various treatments are available, including light-based therapies, topical therapies, and destructive therapies. Herein, we review the current management options for AKs and discuss emerging therapeutic agents.

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INTRODUCTION

Actinic keratosis (AK) lesions are common epidermal neoplasms that present as erythematous, hyperkeratotic, scaly papules on a background of chronic sun damage. It is widely accepted that AKs represent the initial manifestations in a continuum that may eventually progress to squamous cell carcinoma (SCC).[1,2] Given the high prevalence of AKs and the potential for malignant transformation, early detection by clinical evaluation and treatment are commonly indicated. The National Ambulatory Medical Care Survey on outpatient medical care in the US found that AK was the second-leading diagnosis at dermatology visits and constituted 14.6% of visits to dermatologists between 1993 and 2010.[3] In 2004 alone, the prevalence of AKs in the US was estimated to be 39.5 million.[4]

Actinic keratoses typically arise on chronically sun-exposed skin surfaces such as the face, balding scalp, and dorsal forearms and hands.[1,2] As the number of neoplastic cells in the epidermis increases, the lesion becomes clinically palpable.[2] Importantly, it has been shown that subclinical AKs also exist in areas of chronically sun-exposed skin, a phenomenon termed "field cancerization".[1] In addition to treating clinically apparent AK lesions, preventative treatment and photoprotection strategies should also be directed at these areas of subclinical actinic damage. To the dermatologist, treating what is on the way is as important as what is present today.

Histologically, AKs are characterized by a disorganized neo-plastic proliferation of epidermal keratinocytes. These keratinocytes display increased number of mitoses, disorganized differentiation and orientation, and nuclear pleomorphism wherein the nuclei are enlarged, irregular, and/or hyperchromatic with pale or vacuolized eosinophilic cytoplasm.[2] Lesions can be categorized into the following six types based on histology: hypertrophic, atrophic, bowenoid, acantholytic, lichenoid, and pigmented.[1]

Actinic keratoses are graded on the extent of epidermal keratinocytic dysplasia using a three-tiered classification system. Keratinocytic intraepidermal neoplasia (KIN) I describes a flat lesion with focal cellular atypia of basal and suprabasal keratinocytes limited to the lower third of the epidermis. More advanced is KIN II, which describes a hyperkeratotic papule with atypia that extends to the lower two-thirds of the epidermis. Finally, KIN III, equivalent to SCC in situ, describes a plaque with diffuse atypical keratinocytes extending through the full thickness of the epidermis.[5]

The most critical risk factor associated with the development of AKs is cumulative ultraviolet (UV) damage.[6] Other risk factors include fair skin (Fitzpatrick skin types I and II), male gender, baldness in men, older age, geographic latitude (proximity to the equator), and immunosuppression.[6-9] Countries such as Australia, which have large Caucasian populations and are located close to the equator, have prevalence rates as high as 40–50% in adults 40 years and older.[1] Other risk factors include

genetic syndromes with increased sensitivity to UV radiation (either from melanin deficiency or chromosomal instability), such as albinism, xeroderma pigmentosum, Bloom syndrome, Cockayne syndrome, and poikiloderma congenitale.[6] The presence of cutaneous human papilloma virus has also been implicated in the development of AKs, possibly as an oncogenic cofactor or result of true infection.[10]

PATHOGENESIS

Excessive and cumulative exposure to UV radiation induces genetic damage, inflammation, immunosuppression (loss of tumor surveillance), and mutagenesis in epidermal keratinocytes, which eventually gives rise to AKs through clonal expansion.[11,12] UV light promotes the production of arachidonic acid, pro-inflammatory cytokines, adhesion molecules, and mast cell-derived mediators.[11] The majority of UV exposure occurs from UVA (320–400 nm), which penetrates the skin more deeply than UVB (290–320 nm). UVA produces reactive oxygen species (ROS), such as superoxide anions, hydroxyl radicals, and hydrogen peroxide. These ROS trigger oxidative damage in nucleic acids, membrane lipids, and proteins, thereby disrupting normal cellular signal transduction pathways and causing abnormal proliferation. The effects of UVA also result in 8-hydroxyguanine adducts, leading to signature transitions of thymine (T) -> guanine (G).[12,13] UVB produces cytosine (C)-containing cyclobutane pyrimidine dimers and pyrimidine-pyrimidone 6-4 photoproducts that result in signature transitions of C -> T and CC -> TT.[11,13] This generation of DNA photoproducts disrupts normal replication and transcriptional processes.

The most significant UV-induced mutations occur in tumor suppression genes. The initial mutation serves as a pivotal event that increases susceptibility to the accumulation of mutations in additional tumor suppressor genes and proto-oncogenes, thereby facilitating the unrestrained proliferation of neoplastic keratinocytes.[11] Some mutations implicated in the development of AK and the progression to SCC include RAS oncogenes, C-MYC proto-oncogenes, as well as the tumor suppressor genes p16 (INK4a), p14 (ARF), and p15 (INK4b).[14]

In particular, mutations in the p53 tumor suppressor gene are commonly present in AKs, SSCs, and normal perilesional skin from sun-exposed sites.[15-17] This evidence suggests that the p53 mutation is an early step in AK development. Under normal conditions, the p53 gene is activated by DNA damage to arrest the cell cycle and allow for the repair of damaged DNA. In the event of irreparable damage, p53 also triggers apoptosis of keratinocytes with premalignant or malignant properties in order to prevent clonal expansion.[11,13] The protective role of the p53 gene in preventing carcinogenesis by UV radiation was demonstrated in p53-heterozygous mice, who showed increased susceptibility to skin cancer, an effect that was even

further exaggerated in p53-homozygous knockout mice.[18] It has also been shown that UVB-induced point mutations lead to p53 inactivation, compromising the gene's tumor suppressive functions and creating genetically compromised keratinocytes.[11,12]

EVOLUTION TO SQUAMOUS CELL CARCINOMA

Actinic keratoses may regress spontaneously, remain stable, or progress to invasive SCC.[19,20] Approximately 26% of lesions regress, although the mechanism of regression is not well understood.[19] Anywhere between 0.025% and 16% of AKs can transform to invasive SCC.[21] Extrapolation studies suggest the overall risk of progression is approximately 8%, although the likelihood varies with age, gender, chronic UV exposure, and location of AKs.[22,23] Given the variable reporting on the risk of transformation, the decision to treat should be made in the context of individual risk factors.[21]

Histological evidence endorses a strong association between AK and SCC. In a review of 165 SCC cases, 80% of SCC were found to be contiguous with or arise in close proximity of AKs.[24] A review of 1011 cases of SCC found that 97.2% of SCCs contained SCC in situ at the periphery or within the confines of the SCC itself.[25] The authors suggested that had all specimens been removed with adequate margins, 100% of specimens would contain evidence of SCC in situ, demonstrating the histopathological progression of AK to SCC.

While it is not possible to accurately predict which AK lesions will progress to SCC, certain clinical parameters may indicate an increased risk of malignancy. In a systematic review of studies of malignant transformation of AK to SCC, predictive factors included induration/inflammation, diameter greater than 1 cm, rapid enlargement, bleeding, erythema, and ulceration.[26] In lesions that develop palpability, induration, or ulceration, biopsy is commonly indicated to rule out malignant transformation.[27]

TREATMENT

A wide range of management options exist for AKs. Therapies can be broadly divided according to the number of lesions targeted: destructive and surgical therapies that target individual lesions, and field treatments that target widespread lesions.

Cryosurgery

Cryosurgery with liquid nitrogen remains a preferred treatment for isolated AK lesions. With cryosurgery, liquid nitrogen at -196°C is applied to the affected lesion using either a spray device or cotton tip applicator. The cold temperatures lead to intracellular and extracellular ice crystal formation, which damage AK cells through cryolysis, vascular stasis, and apoptosis.[28]

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The duration of freezing is tied to treatment efficacy. In a prospective study of 90 patients with a total of 421 AKs, the overall clearance rate at 3-month follow-up was 67.2% [SEM = +/-3.5%; 95% confidence interval (CI) = 60.4–74.1%], and longer freeze times were associated with improved responses.[29] A clearance rate of 39% was achieved in lesions treated with a freeze time <5 seconds, 69% with a freeze time >5 seconds, and 83% with a freeze time >20 seconds. However, longer durations of freezing may result in greater discomfort and risks of localized cutaneous reactions, such as hypopigmentation.

Surgical Management
Surgical therapies, such as shave excision or curettage with electrodessication, are typically reserved for hyperkeratotic lesions. The advantage of acquiring a histopathologic specimen (eg, when concern arises for SCC) must be weighed against the increased risk of scarring.

Dermabrasion has also been used to treat actinic damage, most commonly on the forehead or bald scalp.[30] The technique utilizes a handheld device to manually abrade the skin and remove affected epidermal cells. In a study of 23 patients, dermabrasion led to 96% clearance at 1-year post-treatment, with clearance rates diminishing to 54% at 5 years post-treatment.[31] Wide areas of actinic damage can be covered with the technique, but pain control measures are commonly required.

Photodynamic Therapy
Photodynamic therapy (PDT) is based on the application of a photosensitizer to the treatment area, exposure to a particular wavelength of light, and the resulting formation of oxygen species that are toxic to atypical keratinocytes. The most commonly used photosensitizers are 5-aminolevulinic acid (ALA) and, outside the US, methyl aminolevulinate (MAL). These agents serve as precursors to protoporphyrin IX, which accumulates in the target cells during the incubation period. When exposed to the appropriate wavelength of light, protoporphyrin IX transforms into reactive oxygen species, resulting in apoptosis of the neoplastic cells. Protoporphyrin IX has absorption peaks at 404–420 nm (blue light) and 635 nm (red light), which is the basis for the light sources used in treatment regimens with ALA and MAL, respectively.[32] The phototoxic reaction of PDT is associated with the local skin reactions of erythema, crusting, burning, and/or pruritus, which typically resolve within 10 days.

There are many regimens for treatment with PDT, including variations on the incubation time of the photosensitizer. The ideal conversion of exogenous porphyrins to protoporphyrin IX occurs after two hours of incubation, and efficacy studies have supported at least a two-hour incubation period for optimal lesion reduction.[33]

Daylight PDT
In contrast to conventional PDT, daylight PDT utilizes ambient visible light in order to activate the photosensitizer. Prior to treatment, an organic, broad-spectrum sunscreen is applied to all sun-exposed areas. MAL cream is then applied to the treatment area, and the patient is exposed to daylight within 30 minutes. The duration of daylight exposure is typically 2 hours, during which protoporphyrin IX and ROS are formed.[34] Afterwards, the MAL cream is rinsed off to avoid further phototoxic reaction, and patients are instructed to spend the remainder of the day indoors.

Daylight PDT has demonstrated favorable comparisons to conventional PDT in clinical trials.[35,36] In an Australian study of 100 subjects with AKs of the face and/or scalp, subjects underwent a single treatment of both daylight PDT and conventional PDT using a split-face design.[36] At 12-week follow-up, the clearance rate of mild lesions with daylight PDT was non-inferior to conventional PDT (89.2% vs 92.8%, respectively; 95% CI -6·8 to -0·3). However, pain scores were significantly lower with daylight PDT relative to conventional PDT (0.8 vs 5.7 on a 10-point scale; P<.001).

Similar outcomes were observed in a European split-face study of 108 subjects with AKs of the face or scalp, during which subjects underwent a single treatment with both daylight PDT and conventional PDT.[35] At 12-week follow-up, the response rate with daylight PDT was non-inferior to conventional PDT (70% vs 74%, respectively; 95% CI [-9.5; 2.4). Importantly, daylight PDT was effective in both sunny and cloudy conditions and was associated with better pain scores than conventional PDT (0.7 vs 4.4 on a 10-point scale; P<.001).

Imiquimod
Imiquimod is a toll-like receptor-7 agonist that causes the activation of several cellular proteins, including nuclear factor-kappa B (NF-κB).[37] Increases in NF-κB lead to the release of pro-inflammatory cytokines and induction of the innate and cellular immune response. This heightened immune response is directed against antigens expressed by atypical keratinocytes, leading to lesion destruction where imiquimod has been applied.

Topical imiquimod originally came to market as a 5% cream, which is applied twice weekly for up to 16 weeks. In a meta-analysis of 5 trials involving 1293 subjects, complete clearance was achieved in 50% of patients.[38] The most common adverse events were erythema (27%), scabbing or crusting (21%), flaking (9%), erosion (6%), edema (4%), and weeping (3%). In addition to local skin irritation, imiquimod may also produce flu-like symptoms, such as fever, chills, myalgia, and fatigue.

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A 3.75% cream formulation is also available, which is applied nightly for 2 weeks followed by a 2-week rest period, then followed by another 2-week treatment period. The lower concentration is designed for a shorter treatment duration as well as a larger treatment area (200 cm^2 vs 25 cm^2 for the 5% cream). However, clinical efficacy may be reduced, with large scale clinical trials only demonstrating a clearance rate of 36%.[39]

Diclofenac
Diclofenac is a nonsteroidal anti-inflammatory drug that inhibits cyclooxygenase-2 (COX-2) and prostaglandin synthesis. The exact mechanism behind AK clearance remains unclear, but it is believed that diclofenac induces anti-inflammatory and anti-angiogenic effects, which may induce anti-proliferative and apoptosis mechanisms.[40]

Topical diclofenac 3% is available in a gel combination with 2.5% hyaluronan. The gel is applied twice daily for 60–90 days. In a meta-analysis of 3 trials involving 364 patients, treatment with 3% diclofenac in 2.5% hyaluronan gel led to complete clearance in 40% of subjects.[41] An advantage of diclofenac treatment is the relatively mild cutaneous effects relative to other therapies such as 5-FU.[42]

Ingenol Mebutate
Ingenol mebutate, an extract from the sap of the *Euphorbia peplus* plant, is a newer addition to the array of AK treatments. The agent operates through a two-fold mechanism that induces both rapid cell necrosis and delayed immunostimulatory effects. Within the first few hours, ingenol mebutate causes cell death through the disruption of the plasma membrane and mitochondrial swelling, a process that is later followed by neutrophil-mediated, antibody-dependent cellular cytotoxicity.[43] Due to the rapid effects, ingenol mebutate treatment courses are substantially shorter than other topical agents. A 3-day course of 0.015% gel is used for facial/scalp lesions, and a 2-day course of 0.05% gel is used for trunk/extremity lesions.

In a randomized controlled trial of 547 subjects with AKs of the face and/or scalp, ingenol mebutate led to clearance in 42% (vs 3.7% with placebo; *P*<.001).[44] Of 458 patients with AKs of the trunk and/or extremities, clearance was achieved in 34% (vs 4.7% in placebo; *P*<.001). Local skin reactions peaked at day 4 following face/scalp treatment and between days 3 and 8 following trunk/extremity treatment, with reactions decreasing to baseline by day 29.

5-Fluorouracil
5-fluorouracil (5-FU) is a pyrimidine analogue that inhibits the enzyme thymidylate synthetase, thereby blocking DNA synthesis.[45] This disruption of cell division preferentially affects neoplastic cells, providing for the treatment of AKs.

Topical 5-FU is available in a cream formulation at 5%, 1%, or 0.5%, or in a solution formulation at 5% and 2%. The most common treatment regimen is application of the 5% cream twice daily for 2–4 weeks. In a meta-analysis of 5 randomized controlled trials, treatment with 5% 5-FU led to an average clearance rate of 49%.[46] As with other field treatments, 5-FU is associated with inflammation, erosion, and ulceration during treatment, which may last 1-2 weeks after the application period has ended.

The relative efficacies of different AK therapies were evaluated in a meta-analysis by Gupta et al.[47] The following eight agents were examined: 5-ALA PDT, MAL-PDT, cryosurgery, diclofenac in hyaluronan gel, 5-FU, imiquimod, ingenol mebutate, and placebo. Thirty-two trials were included, and agents were graded based on their ability to achieve complete clearance. Results ranked the agents as follows: 5-FU > ALA-PDT ≈ imiquimod ≈ ingenol mebutate ≈ MAL-PDT > cryosurgery> diclofenac in hyaluronan gel > placebo.

Investigational Therapies
Investigational therapies are being studied with the goal of improving drug tolerability and patient compliance. KX2-391 ointment 1% is a novel field treatment currently in clinical trial development. The agent functions as a dual Src tyrosine kinase and tubulin polymerization inhibitor, thereby blocking the growth of human keratinocytes and inducing apoptosis in dividing cells.[48] In a phase II open-label study, once-daily application of KX2-391 ointment 1% was examined using either a 3-day or 5-day treatment regimen (n=84 in each cohort).[49] At day 57, 43% of subjects in the 5-day cohort achieved complete clearance, compared with 32% in the 3-day cohort. Within the 5-day cohort, 52% of subjects with AKs on the face and 33% of subjects with AKs on the scalp attained clearance. Local skin reactions were mostly mild and transient. Based on these results, phase III placebo-controlled trials using once daily KX2-391 ointment 1% for 5 days are currently underway (ClinicalTrials.gov Identifier: NCT03285477).

SR-T100 gel is an anti-proliferative agent derived from the medicinal herb *Solanum undatum*. The active ingredients, solamargine and solasonine, penetrate the cell membrane through simple diffusion and induce cell death by apoptosis. In a phase III double-blind vehicle-controlled trial, 16-week treatment with once-daily application of SR-T100 gel led to clearance in 32.4% of patients, although these results were not significantly higher than in the placebo group (17.1% clearance; *P*=0.111).[50]

VDA-1102 ointment is an anti-neoplastic agent containing a voltage-gated anion channel/hexokinase 2 modulator, which prevents glycolysis and triggers apoptosis. A phase 2b trial

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examining 12-week treatment with 10% or 20% VDA-1102 ointment is ongoing (ClinicalTrials.gov Identifier: NCT03538951).

CONCLUSION

Treatment options for AKs continue to expand as pharmaceutical developers aim to improve clinical efficacy and reduce post-treatment downtime. At present, therapies with the highest levels of lesion clearance—such as 5% 5-FU—are inevitably tied to local skin irritation. Daylight PDT has demonstrated encouraging results and may offer comparable efficacy to conventional PDT with only minimal associated pain. In addition, exploring agents with improved tolerability remains an active area of research. Investigational therapies currently in trial development are utilizing novel mechanisms in order to circumvent the limitations of classic modalities.

DISCLOSURES

Dr. Rigel has served as a consultant and advisory board member for LEO Pharma. Dr. Kircik has served either as an investigator, advisory board member, speaker, or consultant for Almirall, LEO Pharma, and Ortho Dermatologics. Dr. Bhatia has served either as an investigator, advisory board member, speaker, or consultant for Allergan, Biofrontera, Dermira, Dusa, Exeltis, Ferndale, ISDIN, LaRoche-Posay, LEO Pharma, PharmaDerm, Regeneron, Sanofi, SunPharma, and Valeant. Dr. Hashim and Tinley Chen have no conficts.

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