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REVIEW

Optimal treatment of actinic keratoses

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Abstract: The most compelling reason and primary goal of treating actinic keratoses is to prevent malignant transformation into invasive squamous cell carcinoma, and although there are well established guidelines outlining treatment modalities and regimens for squamous cell carcinoma, the more commonly encountered precancerous actinic lesions have no such standard. Many options are available with variable success and patient compliance rates. Prevention of these lesions is key, with sun protection being a must in treating aging patients with sun damage as it is never too late to begin protecting the skin.

Keywords: actinic keratosis, photodynamic therapy, topical chemotherapy, field therapy

Introduction

Actinic keratoses (AKs) are common (estimated prevalence of 39.5 million in 2004 alone, 26 million of which were in patients over 65 years of age) epidermal lesions that have the potential to progress to invasive squamous cell carcinoma (SCC), with the highest incidence in the aged population. Chronic exposure to ultraviolet radiation in fair-skinned patients is the most important risk factor for the development of AKs. Clinically, they can vary from small erythematous scaly macules to pigmented rough patches to hyperkeratotic cutaneous horns in sun-exposed areas.[1] They are the second most common diagnosis made by dermatologists in their practices and account for more than 5.2 million office visits a year, leading to over $920 million spent on treatments.[2,3] The annual rate of transformation of AKs to SCC is controversial with reports ranging from 0.025%–20%, and with no clinical way of determining which lesions will progress, clinicians are obligated to treat all AKs encountered.[4]

As the burden of AKs is high, preventive measures have been actively sought after. Sunscreen has shown to be an effective AK prevention method reducing up to 24% AK lesions over time, even compared with beta carotene and topical tretinoin cream 0.05%.[5,6] Nicotinamide (vitamin B3) 500 mg daily or twice daily for 4 months has also shown a 29%–35% relative reduction in AK count when studied. Celecoxib 200 mg twice daily for 9 months was shown not effective for preventing AKs but data does suggest a preventive effect in nonmelanoma skin cancers.[7]

A number of treatment options are available to treat the AK lesions, thus reducing the risk for progression as well as providing symptomatic relief in the cases that are irritating and/or pruritic. Therapies can be divided into lesion-directed therapy that targets specific AK lesions or field-directed therapy that is used for treatment of multiple clinical lesions in an area as well as subclinical AKs. This review will

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summarize both targeting options of AK treatment and the various modalities utilized (Tables 1 and 2).

Lesion-targeted therapies

The most commonly used therapy for AK treatment is cryotherapy either sprayed with a cryogun or placed directly on the lesion with a cotton swab.[8] Spray therapy has been shown to effectively cure 98.8% of lesions followed up over 1–8.5 years.[9] The cure rate is technique dependent; however, 1–5 seconds of spray showed a 39% cure rate whereas 20 seconds or more increased the cure rate to 83% in one study.[10] Side effects such as hypopigmentation increases to up to 29% with increased freeze time (>20 seconds) limiting the cosmetic outcome.[10] Some practitioners opt for more than one cycle of therapy to increase efficacy. Side effects include blistering, hypopigmentation, hyperpigmentation, scarring, and infection as well as discomfort during the freezing cycle.[11] Electrodessication and curettage is also an option for lesion-directed therapy that is often utilized for hyperkeratotic AKs and those with follicular involvement as other therapies cannot penetrate as deep as electrodessication and curettage, providing 95%–99% clearance.[12] Immunocompromised patients with AKs are also more likely to have a better outcome with electrodessication and curettage as well.[13]

Field-directed therapies

When lesions become less well defined and more confluent in nature, field therapy can become an attractive option as it can target both clinical and subclinical lesions over larger areas. Subclinical AKs that have the same histologic atypia as clinically visible AKs are common in patients with aged and sun-damaged skin.[14] Because they can exceed the number of clinically visible AKs by ten-fold, these untreated subclinical lesions can lead the practitioner to believe they are recurrent lesions after spot treating rather than new clinically apparent AKs erupting.[15] Among patients with multiple AKs as is usually the case, the cumulative lifetime risk of at least one invasive SCC is estimated at 6%–10% depending on the number of lesions and duration of lesion persistence.[16,17] Thus, it is appropriate to treat all lesions, both clinical and subclinical, to prevent progression to invasive cancer.

Field therapies can be divided into patient-administered options such as topical therapies and physician-administered options such as photodynamic therapy (PDT), laser resurfacing, dermabrasion, and medium- to deep-depth chemical peels (Table 1). Compliance is a concern with patient-administered therapy as it requires patient adherence to the treatment regimen that can be uncomfortable and time consuming. Early discontinuation of therapy decreases efficacy and lesion clearance rates.[18] The physician-administered options can be expensive and require training and expertise in this area as well as the necessary procedural equipment.[14]

Comparative clinical trials regarding overall safety, efficacy, and recurrence data are not easily interpretable in the various treatment options as studies looking at each of these points are not uniform in reporting. Study endpoints used include 100% clearance of AKs, a 75% reduction in AKs after treatment that may be more clinically relevant, length of time of evaluation, recurrence percentages, and the type of AKs cleared (clinical, subclinical, or both). A more standardized approach is needed with a set definition of "clearance" or "cure rate" to allow a more objective comparison of therapeutic options.

Current approved topical therapies include 5-fluorouracil (5-FU) 0.5%–5% cream, imiquimod 5% and 3.75%, diclofenac sodium gel 3%, and ingenol 0.015% and 0.05% gel. Since the 1960s, when it was observed that oral administration of 5-FU for breast and rectal cancer incidentally resolved AKs, topical 5-FU has been approved for the treatment of AKs. The mechanism of action for 5-FU involves inhibition of thymidylate synthetase, which leads to a reduction in DNA synthesis and cell death. Topical 5-FU therapy is available as a cream or solution in 0.5%–5% concentrations. Side effects of 5-FU include application site reactions such as erythema, erosions, edema, and dryness.[19,20] Petroleum jelly, cold compresses, or a mild hydrocortisone 2.5% cream can be provided for comfort during therapy that will not decrease clearance of AKs.[21] The 0.5% 5-FU cream is prescribed once daily and the 5% 5-FU cream twice daily for 3–4 weeks, giving around a 58% total lesion clearance and 75% clearance of lesions by 75% patients.[22]

Topical imiquimod cream is a toll-like receptor-7 agonist that induces synthesis and release of interferon-γ, interleukin-12, and tumor necrosis factor, activates Langerhans cells, and recruits macrophages that lead to apoptosis of AK cells.[23] Imiquimod 5% cream was approved in 2004 as a twice a week application for 16 weeks for the treatment of AKs on the balding scalp and face. Imiquimod 3.75% cream was approved for the same indication in 2010 applying once nightly for 2 weeks of treatment, followed by 2 weeks of no treatment (rest period), followed by another 2 weeks of treatment. Side effects include irritation, redness, and rarely flu-like symptoms and lymphadenopathy.[8] Imiquimod 3.75% cream offers the advantages of a shorter total treatment duration and the ability to treat a larger area

Table 1 Field-directed therapeutic options for actinic keratoses

Treatment modality	Formulation	Treatment regimen	Advantages	Side effects	Molecular target	Efficacy	Cost*
Patient-administered treatments							
5-fluorouracil	0.5%–5% cream, solution	5% cream twice daily or 0.5%–1% cream daily for 3–4 weeks	Over 50 years of data to support usage, high cure rate with compliance, good cosmetic result 2 weeks after therapy	Burning, pruritus, erythema, peeling, scaling, potential scarring	Inhibition of thymidylate synthetase, reducing DNA synthesis and increased cell death	58% patients achieved 100% clearance while 75% patients achieved 75% clearance with 5% cream[22]	0.5% cream 30 g: $228.89 1% cream 30 g: $279.97 5% cream 40 g: $345.99 (name brand); $249.98 (generic) 5% solution 10 cc: $126 (name brand); $101.99 (generic)
Imiquimod	3.75%, 5% cream	Twice a week for 16 weeks using 5% cream. Daily for one week, then off a week, then on for a week using 3.75% cream daily	Believed to induce immune memory that may prevent recurrence, milder erythema than 5-fluorouracil	Erythema, crusting, pruritus, induration, scaling; rarely flu-like symptoms, fever, fatigue, angioedema	Toll-like receptor-7 agonist that induces interferon-γ, interleukin-12, and tumor necrosis factor	45% patients achieved 100% clearance 8 weeks posttreatment with 5% cream while 60% achieved 75% clearance[24,25] 35% patients achieved 100% clearance 8 weeks posttreatment with 3.75% cream while 60% achieved 75% clearance[24,25]	3.75% one box (28 each): $601.01 5%, $650.82 three packages for one treatment course (name brand); $434.38 (generic)
Diclofenac	3% cream in 2.5% hyaluronan gel	Nightly for 60–90 days	Limited irritation and erythema	Allergic reaction to those allergic to aspirin or NSAIDS, contact sensitization erythema	Inhibits cyclooxygenase-2	50% patients achieved 100% clearance after 60–90 days treatment[29]	1% gel 100 g tube: $559.97
Ingenol	0.015% gel for face and scalp; 0.05% gel for trunk and extremities	Daily application for 3 days face and scalp; 2 days for trunk and extremities	Short treatment application duration for patient	Redness, scaling, vesiculation, dyspigmentation, swelling, pruritus, crusting	Macrocyclic diterpene ester with nonspecific cellular necrosis and neutrophil-mediated antibody-dependent cellular cytotoxicity	42.2% patients achieved 100% clearance with 0.015% gel on face and scalp; 63.9% had 75% clearance at 8 weeks[31] 34.1% patients achieved 100% clearance with 0.05% gel on body; 49.1% had 75% clearance at 8 weeks[31]	0.05% gel two packets: $608.06 0.015% gel three packets: $608.06
Physician-administered treatments							
PDT/blue light	ALA incubated 1–2 hours, blue light exposure 16 minutes 40 seconds	1–3 treatment sessions every 4–6 weeks	High clearance rates and compliance; photorejuvenation with good cosmetic results	Pain, erythema, edema, stinging, crusting may last up to 4 weeks after treatment; must practice strict sun protection 24–48 hours after treatment	Free radicals are produced after light activation of protoporphyrin IX	66% patients achieved complete clearance 8 weeks after ALA/PDT treatment[47] 65% patients achieved complete clearance 3 months after MAL/PDT treatment[34]	Average $550 per treatment session $165.31 per ALA stick
Chemical peels	Trichloroacetic acid 35% or 50%, with or without Jessner's solution	Every 4 weeks	Photorejuvenation with excellent cosmetic results	Pain, erythema, edema, stinging; initially effective but recurrences high; requires skill and user experience	Nonspecific cell necrosis	Not established	Average $125–$250 per session

(*Continued*)

Table 1 (*Continued*)

Treatment modality	Formulation	Treatment regimen	Advantages	Side effects	Molecular target	Efficacy	Cost*
Dermabrasion		Not clearly established	Low incidence recurrence, good cosmetic results	Pain, erythema, edema, stinging; requires skill and user experience	Nonspecific physical destruction	Not established	Average $100–$500 per session
Laser	Carbon dioxide, Erb:YAG	Not clearly established	Added cosmetic photorejuvenation	Pain, erythema, bruising, dyschromia, scarring; requires user experience; low clearance rates	Laser target specific to each laser	Not established	Dependent on office and laser type

Note: *Epocrates Essentials (ePocrates Rx). ePocrates, Inc; Ver 4.5.
Abbreviations: ALA, aminolevulinic acid; Erb:YAG, erbium-doped yttrium aluminum garnet; MAL, methyl 5-aminolevulinate; NSAIDs, nonsteroidal antiinflammatory drugs; PDT, photodynamic therapy.

compared to imiquimod 5% cream (200 cm^2 versus 25 cm^2, respectively).[23] However, complete clearance rate for the 5% cream is higher at 45% when used twice weekly versus 35% with the 3.75% cream used daily at 8 weeks posttreatment.[24,25] Using the 5% cream three times a week for 16 weeks can increase complete clearance up to 57%.[26]

Diclofenac 3% topical gel with hyaluronan is a nonsteroidal anti-inflammatory agent that inhibits cyclooxygenase-2, an enzyme increased in sun-exposed skin, AKs, and SCCs that supports tumor growth by promoting angiogenesis and inhibiting apoptosis.[27,28] Treatment regimens vary from twice daily application for 60–90 days with a 50% efficacy compared with 20% efficacy with hyaluronan alone. Adverse events include pruritus, paresthesia, rash, edema, and contact dermatitis.[29]

Ingenol mebutate is a diterpene ester found in the sap of the plant *Euphorbia peplus*. The method of action is not fully understood but in vivo models have shown a two-fold mechanism involving cellular necrosis as well as neutrophil-mediated antibody-dependent cellular cytotoxicity of residual cells.[30] Complete clearance for AKs on the face and scalp treated with ingenol mebutate 0.015% gel for 3 days was 42.2% at the 8-week follow-up visit and 34.1% for AKs on the trunk and extremities using ingenol mebutate 0.05% gel for 2 days.[31] Local reactions of redness, scaling, vesiculation, dyspigmentation, swelling, pruritus, and crusting peaks at 4–8 days, which can last up to 30–55 days.[31] The short therapeutic regimen is an attractive option for increased compliance and therefore outcomes, but longer term data is not available.

With all topical therapies, it is recommended to avoid the orbital of the eye to avoid painful swelling, avoid ultraviolet radiation, instruct patients to wash hands after application, and start with one body part at a time such as face, scalp, or single extremity to avoid systemic absorption or severe irritation. To increase compliance and adherence to therapy, full disclosure of anticipated course and results including pictures of the inflammation should be given to patients.

Approved for lesion-directed therapy in 1999, PDT involves applying 5-aminolevulinic acid or methyl 5-aminolevulinate topically, which undergo conversion to a photosensitizer protoporphyrin IX in abnormal keratinocytes. Free radicals are produced after light activation, which result in targeted tissue destruction.[32] It is used off-label for field therapy. Pretreatment with dermabrasion, curettage, or urea cream can increase efficacy. Food and Drug Administration-approved regimens include using 20% 5-aminolevulinic acid solution and blue light for 16 minutes and 40 seconds or 16.8% methyl 5-aminolevulinate with red light for

Table 2 Lesion-targeted versus field-directed therapies

	Lesion type targeted	Approaches	Advantages	Disadvantages
Lesion-targeted therapy	Isolated, singular lesions	Liquid nitrogen, electrodessication and curettage	– Localized side effects – Less downtime after treatment – High efficacy – Cheap – Readily available	– Addresses only clinically apparent lesions – Can require multiple treatments – Efficacy is technique dependent – Painful during procedures – Can leave scarring
Field-directed therapy	Diffuse clinical and subclinical lesions	5-fluorouracil, imiquimod, diclofenac, ingenol, photodynamic therapy, chemical peels, dermabrasion, laser	– Field cancerization treatment – Improved cosmetic outcome – More diffuse and larger areas can be treated at once	– More diffuse side effects – Unpredictable patient response – Patient compliance with patient administered therapies – Longer downtime – More expensive and not all covered under insurance plans – Potential for scarring

7–10 minutes.[32] The efficacies can vary depending on pretreatments, incubation periods, type of light used and parameters, and photosensitizing agent but can be up to 66% with good cosmetic results including cosmetic photorejuvenation that can be appealing to patients.[14,33,34] Patients must wear protective eyewear while exposed to the light and practice strict sun protection with hats, sunscreen, and ultraviolet radiation avoidance at least for 24–48 hours after treatment.

For all resurfacing modalities, evidence to support use is limited to case reports, descriptive series, and expert opinions with no randomized controlled trials. Many are operator dependent and rely on the experience of the provider. Regarding peels, trichloroacetic acid 35% (medium) or 50% (deep) with or without Jessner's solution (resorcinol, lactic acid, and salicylic acid in ethanol) have mostly been used. Side effects include peeling, erythema, crusting, dyschromia, scarring, and discomfort. One prospective trial showed comparable treatment clearances of 83%–92% using trichloroacetic acid peels, a course of 5-FU, or carbon dioxide laser.[35,36] A study of five patients using two to three passes of erbium-doped yttrium aluminum garnet laser showed histological reversal of actinic damage 3 months after treatment and an 86%–96% decrease in number of AKs.[37]

Combining therapeutic modalities

As there is no universal standard monotherapy established, combination therapy has the potential to improve efficacy, increase patient satisfaction, and potentially have a cosmetic benefit. Combining 5-FU with other therapies has shown promising results. One-week treatment with 0.5% 5-FU followed by cryotherapy for facial AKs resulted in 30% complete clearance, compared to 8% of subjects who received vehicle followed by cryotherapy at 6 months.[38] In another study, 59.5% of patients whose AKs were treated with both cryotherapy and imiquimod 3.75% achieved complete clearance of those lesions when evaluated 20 weeks posttreatment in comparison to 29.8% of patients whose AKs were treated with cryotherapy alone.[39] In a survey of 293 dermatologists from an American Medical Association database, only 10% of patients with AKs were treated with combined cryotherapy and field-directed therapy even though complete clearance of lesions was more common when field-directed therapy was used in conjunction with cryotherapy.[40]

Combining 70% glycolic acid with 5-FU showed a 92% reduction in the number of AKs compared to a 20% reduction with the chemical peel alone.[41] Using 20% aminolevulinic acid PDT followed 1 month later by 5% imiquimod twice a week for 16 weeks showed a 90% lesion clearance versus 75% for PDT alone at 6 months after treatment.[42] Topical therapies can also be combined together especially in cases of recalcitrant lesions. Once daily application of imiquimod and 5-FU for an average of 1–12 weeks histologically resolved AK lesions in ten out of ten patients in a recent study of treatment-refractory AKs.[43] A similar study showed topical 5-FU in the morning and imiquimod 5% applied at night for 1 week of therapy, repeated monthly for up to 3 months, achieved greater than 90% complete clearance; however, 17% patients withdrew due to adverse effects.[44]

Combining field and lesion specific treatment modalities has the benefit of utilizing intense localized destruction to more aggressive lesions while at the same time providing a more tolerable course for the background of actinic damage.

For instance, curettage of hyperkeratotic lesions can be combined with a topical chemotherapy regimen or PDT for smaller lesions and subclinical damage. This personalization is key in efficacy and overall patient satisfaction. The risks of inflammation, scarring, dyschromia, and patient discomfort are synergistic, however, in combining multiple therapies and should be discussed fully with patients. Also, higher costs must be considered with potential insufficient insurance coverage given the lack of standardized combination treatment protocols.

General treatment recommendations and decision making

As there is no way to clinically determine which lesions will transform into invasive SCC, recur after treatment, and metastasize (the 5-year recurrence rate of SCC is 8% and metastasis rate is 5%), all efforts to eradicate AKs are recommended.[14,17,45] As presented, many options are available for both spot and field therapies (Table 1). Since there are no specific guidelines available guiding physicians in either types of treatment, physicians should consider the number, duration, localization, extent, and clinical course of lesions; patient's age, comorbidities, risk factors such as immunosuppression, history of skin cancer, or continued sun exposure; cost of therapy; physician's familiarity with treatment procedure; and patient's personal preference in deciding an appropriate therapy.[14]

It cannot be overemphasized that follow-up is crucial no matter what therapy is chosen. There are no established guidelines stating when this should occur; regardless, patient follow-up needs to take place at least on an annual if not semiannual basis to determine if lesions have resolved, new AK lesions have occurred, and to screen for more invasive lesions. Clinical features suggestive of malignancy include induration and inflammation, diameter greater than 1 cm, rapid enlargement, bleeding, erythema, and ulceration.[46] Other risk factors for progression of AK to SCC include hyperkeratotic lesions; lesions on lips, nose, ears, eyelids; male gender; older age; prior history of skin cancer; skin type Fitzpatrick I and II; continued sun exposure; and status post organ transplantation (immunosuppression).[14]

At each encounter, education on sun protection with hats, sun protective clothing, sunscreen greater than SPF 15 applied every 2–3 hours, and avoiding midday sun exposure is of utmost importance as prevention is the best treatment of all.

Disclosure

The author reports no conflicts of interest in this work.

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