What Is the Role of Field-Directed Therapy in the Treatment of Actinic Keratosis? Part 1: Overview and Investigational Topical Agents

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Actinic keratosis (AK) constitutes the initial epidermal lesion in a disease continuum that may progress to invasive squamous cell carcinoma (SCC). A number of treatment options are available to clear lesions, and thus reduce the risk for progression. Field-directed approaches are primarily used to clear multiple AKs and subclinical lesions. Current field-directed approaches still have a number of unmet needs, and a number of investigational agents are being evaluated. Topical therapy can be improved by shortening treatment periods; enhancing tolerability, compliance, and patient satisfaction; reducing recurrence rates; and lowering cost. This 2-part review will explain the role of field-directed therapy in the treatment of AK. Part 1 focuses mainly on investigational agents that are being studied for topical patient-administered, field-directed therapy.

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Actinic keratosis (AK) constitutes the initial epidermal lesion in a disease continuum that may progress to invasive squamous cell carcinoma (SCC), most commonly located on chronically sunlight-exposed adult skin.[1,2] Based on data from the US National Ambulatory Medical Care Survey for 1999-2000, AK is the second most common diagnosis at visits to dermatologists in the United States, only slightly exceeded by acne, which occurs in 5.15 million visits or 15.3% of all dermatology visits for each diagnosis.[3] Sixty percent of dermatology visits for AK are by the US Medicare population.[4] In an analysis that applied age-adjusted crude prevalence of AK to the 2004 US population, an estimated 58 million patients had at least 1 AK lesion and 26 million of these patients were 65 years or older.[5]

Actinic keratosis can present as a discrete well-defined lesion; however, multiple less-defined subclinical lesions over large areas of skin are more common, and additional lesions often become evident over time. A German study of patients with multiple AK lesions on the extremities found the average number of lesions to be 11.[6] Many patients have dozens or hundreds of lesions,[7,8] though counts often are unreliable, even when performed by experienced dermatologists, because multiple AK lesions may be confluent.[9] In addition, lesion counts can

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This article is the first of a 2-part series. The second part will appear next month.
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change as new AK lesions appear and existing AK lesions regress,[10] possibly due to immune rejection or the patient inadvertently scraping off the lesion.[11]

Subclinical AK lesions are common, particularly in patients with sun-damaged skin.[12] Subclinical lesions have the same histopathologic features as clinically visible AK, which includes focal areas of abnormal keratinocyte proliferation and differentiation, but are not yet discernible on the skin surface. Subclinical AK may exceed the number of visible lesions by 10-fold, and the emergence of untreated subclinical lesions over time may account for many apparent recurrences, as they visibly manifest as clinically new lesions.[13] Subclinical lesions can be distinguished from normal skin by reflectance-mode confocal microscopy[14,15] based on criteria including irregular keratinocyte cell borders,[14] keratinocyte pleomorphism, parakeratosis, and architectural disarray.[15] Subclinical lesions also can be identified by pink fluorescence under a UV Woods lamp after topical application of 5-aminolevulinic acid or methylaminolevulinate acid,[16] or by focal erythema following multiple topical applications of imiquimod or 5-fluorouracil (5-FU).[17,18]

The proper diagnosis and treatment of AK are essential because the lesions can potentially progress to invasive SCC. Among persons with multiple AK lesions, the cumulative lifetime risk for having at least 1 invasive SCC has been estimated at 6% to 10%,[19] but the cumulative risk depends on the number of lesions and the length of time that the lesions persist.[20] Therefore, it is important to effectively resolve both clinical and subclinical lesions as quickly as possible. Quaedvlieg et al[21] reviewed randomized and retrospective studies to identify risk factors for progression. The authors found the clinical features suggestive of an increased risk for malignancy to be induration and inflammation, diameter of greater than 1 cm, rapid enlargement, bleeding, erythema, and ulceration (coined as IDRBEU).[21] Other risk factors for progression of AK to SCC include large hyperkeratotic lesions or lesions on the lips, nose, ears, or eyelids; male gender; older age; prior history of skin cancer; skin type (ie, Fitzpatrick skin types I and II); continued sun exposure; and status post–organ transplantation (specifically immunosuppression).[22]

Nevertheless, because there is no way to clinically determine which lesions will transform and potentially invade the dermis, recur after treatment, and metastasize[20,23] (the 5-year recurrence rate of primary cutaneous SCC is 8% and the 5-year metastasis rate is 5%),[19] it is recommended that all AK lesions be treated.[24] Because the overwhelming majority of lesions do not progress to SCC, some dermatologists have a different perception and believe that the treatment of each individual lesion may be impractical and unnecessary; nevertheless, patients with many lesions should be closely monitored so that evolving SCC can be detected and treated expeditiously.

For the primary prevention of AK lesions, dermatologists recommend that patients avoid sun exposure and use sunscreen at any age, which decreases the risk for AK and subsequent SCC.[25] They also recommend wearing protective clothing, such as hats[25] and sunglasses; remaining in the shade as much as possible; and avoiding artificial sources of UV radiation (ie, tanning beds).[26] In addition, diet has been shown to have an effect on the development of AK, as reported in a prospective, controlled, randomized clinical trial in which a low-fat diet significantly decreased the incidence of AK ($P=.001$).[27] A small longitudinal study in humans showed a possible association between consumption of moderate amounts of oily fish (an average of 1 serving every 5 days) and red wine, which contains the chemopreventive agent resveratrol (average of one-half glass a day), and a lower incidence of AK lesions.[28] Both animal[29-31] and human[32] studies have demonstrated increasing evidence that systemic (ie, oral) nonsteroidal anti-inflammatory drugs are chemopreventive against SCC and AK lesions through the potent inhibition of cyclooxygenase-2, which is particularly overexpressed in SCC and AK types of lesions.[32] However, systemic cyclooxygenase-2 inhibitors have no labeled indication for AK and some have an unfavorable safety profile.

Secondary prevention includes self-examination to detect changes suggestive of dermal invasion plus screening and early diagnosis in combination with counseling to put the recommendations for primary prevention into practice. Even if preventive measures are used, a number of treatment options are available when patients present with AK.

Overview of Treatment Options

The primary goal of the treatment of AK is to eliminate the risk for progression to invasive SCC. There are many options available for treating AK, and to determine the most appropriate management approach for each patient, dermatologists often consider various factors including the following: (1) the number, duration, localization, extent, and clinical course of the lesions; (2) the patient's age, comorbidities, and other risk factors such as immunosuppression, history of skin cancer, or continued sun exposure; (3) the cost of a particular therapy; (4) the physician's familiarity with the treatment procedure; and (5) the patient's personal preference. Figure 1 presents a simple approach to management.[5,33] When multiple AKs are present on relatively large areas of skin or when

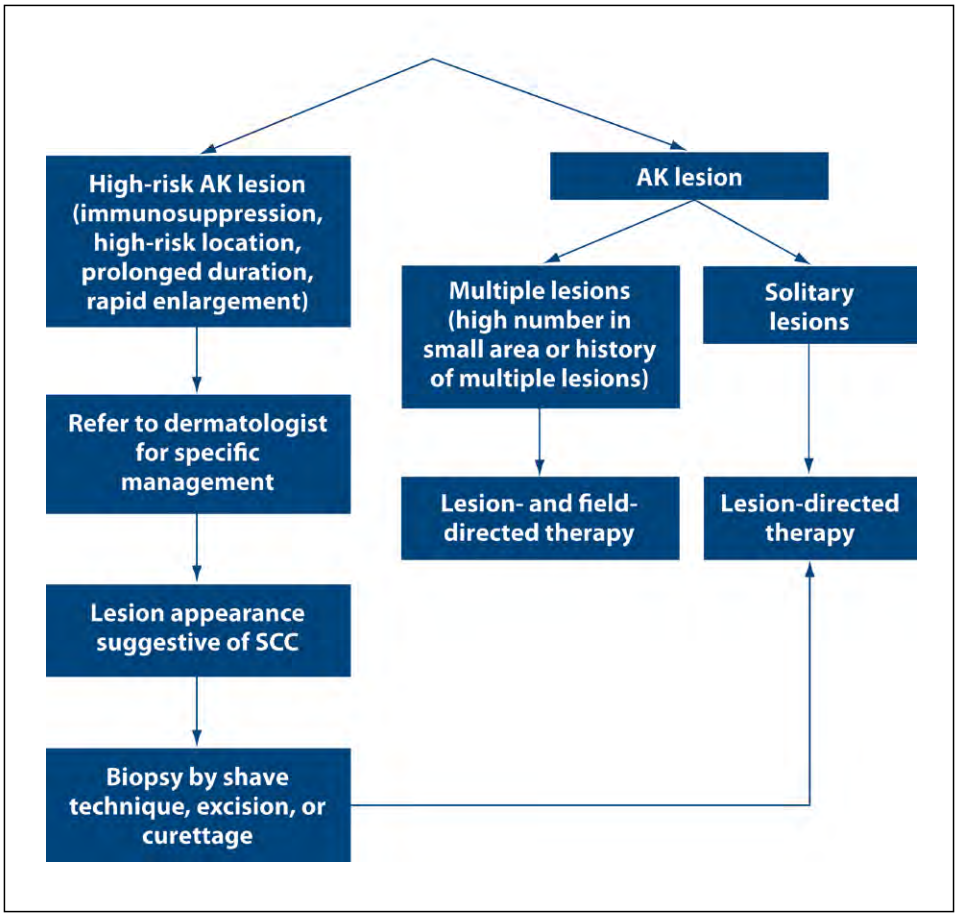

Figure 1. Simple algorithm for selecting treatment of actinic keratosis (AK). SCC indicates squamous call carcinoma. Adapted from Stockfleth E, Ferrandiz C, Grob JJ, et al; for the European Skin Academy.[33]

there is the suspicion of subclinical lesions due to extensive sun damage, field-directed therapy should be considered.[5] Data from the Medicare Current Beneficiary Survey and the US National Ambulatory Medical Care Survey showed that of the $920 million spent on AK treatment annually, 51% of reimbursements are for destructive (ie, lesion directed) procedures, 43% are for office visits, and 6% are for topical (ie, field directed) therapy.[4] Patients with multiple AK lesions (Figure 2) also can be treated with combined lesion- and field-directed therapy. A national survey conducted in 2004-2005 of 293 dermatologists (1184 AK patients) from an American Medical Association database found that approximately 74% of patients treated for AK received lesion-directed therapy only, specifically cryotherapy, and approximately 26% received field-directed therapy (16% received field-directed therapy alone and

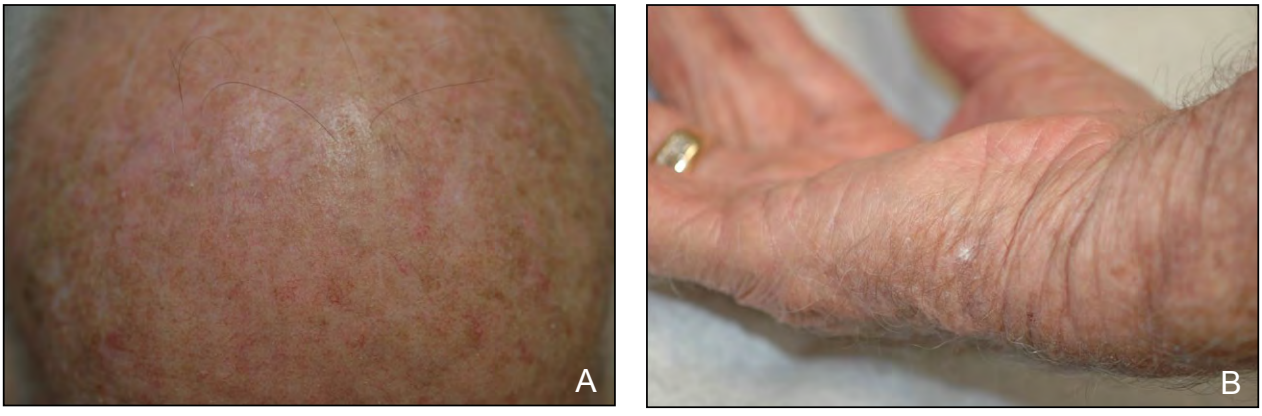

Figure 2. Multiple actinic keratosis lesions on the scalp (A) and on the hand (B), which is an atypical location.

10% received combined cryotherapy and field-directed therapy).[34] Complete clearance of lesions was more common when field-directed therapy was used in conjunction with cryotherapy. The authors noted that nearly two-thirds of patients indicated a clear preference for field-directed therapy.[34]

Regardless of the chosen treatment approach, follow-up is necessary to determine if all lesions have cleared to identify recurrences as well as new lesions and to screen for SCC, particularly in patients at an increased risk. However, there are no data concerning any magnitude of benefit from follow-up in patients with AK,[2] though many studies include follow-up data with respect to the rate of recurrence.

Field-Directed Therapy

Field-directed therapy primarily is used for multiple visible or palpable AK lesions on contiguous areas of skin, for subclinical lesions, or for an entire sun-damaged area at risk for subclinical lesions. Dermatologists also tend to use field-directed therapy for patients with new and recurring AK lesions or for those who have a mean duration of more than 1 year since the last AK episode.[35] Field-directed therapy provides the distinct benefit of treating subclinical lesions, which reduces risk factors for further AK development within the field.

Field-directed therapy is divided into 2 categories: (1) patient-administered topical therapies and photodynamic therapy (PDT), both used to treat multiple lesions over relatively large areas, and (2) resurfacing procedures, such as nonablative and ablative laser resurfacing, dermabrasion, and deep and medium-depth chemical peels. Resurfacing procedures are relatively costly and require considerable expertise, equipment, and experience. Resurfacing procedures are useful for large areas with many AK lesions and severe sun damage.[13] The advantages and disadvantages of field-directed therapies are summarized in the Table.

An evidence-based approach to the management of AK was developed by the Oregon Health and Science University's Evidence-Based Practice Center, Portland, for the Agency for Healthcare Research and Quality in 2001.[22] For patients who have multiple recurrent AK lesions, the authors concluded that available data are insufficient to determine if immediate field-directed therapy for all lesions or a strategy of selective treatment of AK developing suspicious characteristics results in different outcomes, particularly with respect to morbidity or mortality from SCC. They recommended resolving the issue with controlled trials of different strategies for the long-term management of patients who have multiple AK lesions. No specific treatment approach was recommended.[22]

In the interim, dermatologists can access the American Academy of Dermatology (AAD),[36] British Association of Dermatologists,[2] and European Dermatology Forum[24] guidelines for the treatment of AK. The most recent AAD guidelines were published in 1995,[36] but current treatment options were summarized on ActinicKeratosesNet.[37] The AAD guidelines recommend that dermatologists provide cost-effective treatment, noting that many surgical and nonsurgical therapies for AK are available and the selected method depends on a number of variables, including the presence of factors that place lesions at increased risk for progression to SCC.[36] No specific recommendation is made regarding field-directed therapy. The 2007 British Association of Dermatologists' guidelines for the treatment of AK summary of recommendations state that PDT may be helpful when there are multiple or confluent AK lesions, though PDT is likely to be more expensive than most other therapies.[2] The 2006 European Dermatology Forum guidelines for the treatment of AK also provide no specific recommendation regarding field-directed therapy but do observe that dermatologists should primarily consider the needs of individual patients, using the guidelines as a source of support for therapeutic strategies.[24]

Topical Therapy

Patient-administered topical therapies that currently are available include various 5-FU formulations, imiquimod cream 5% and 3.75%, and diclofenac sodium gel 3%. Although these agents are used for field-directed therapy, they also may be used for lesion-directed therapy. Clinical experience shows that they usually achieve complete clearance of lesions in up to 50% of patients; partial responses are observed in approximately 70% of patients. The prolonged application periods, particularly with diclofenac and imiquimod (Figure 3), and severe local skin responses, particularly with 5-FU, may result in suboptimal compliance,[5,38-40] which is clinically noteworthy because early discontinuation reduces the likelihood of lesion clearance.[5] Patient compliance is not typically assessed in clinical studies of topical agents for AK; however, a study measuring compliance with topical 5-FU therapy for AK among a clinic population showed that adherence dropped over the 4-week active treatment period from 92% during the first week to 82% by the end of the active treatment period.[41] Compliance may be improved by discussing side effects before initiating treatment, keeping treatment options simple, and informing patients that there usually is minimal or no scarring.[5] Shorter-duration topical therapies would potentially improve patient compliance.

Advantages and Disadvantages of Field-Directed Therapies[2,5,13,33-37]

Therapy	Advantages	Disadvantages
Laser resurfacing	Allows more precise control of lesion ablation; good cosmetic effect; low risk for scarring and other complications when dermatologist has laser experience	Series of office visits may be required; requires local anesthesia; healing time longer than with other methods
Dermabrasion	Low incidence of recurrence or new lesions for extended time period; good cosmetic effect	Complex procedure; requires local or topical anesthesia; topical prescription medication may be required to prevent infection; potential for scarring; prescription medication may be required to relieve pain
Chemical peel	Initially highly effective; AEs tend to be mild with experienced and skilled operator; AEs are relatively brief (typically 4–7 days); can provide a more youthful appearance to skin	Recurrence or additional AK lesions may appear shortly after treatment; AEs include discomfort, erythema, blistering, crusting, peeling, scarring, and dyschromia; may require local anesthesia
Photodynamic therapy	Complete clearance rates can exceed 90%; noninvasive; good cosmetic results; does not permanently discolor skin; AEs are uncommon and tend to be mild with an experienced and skilled operator	2-step process; may require multiple sessions; severe stinging and burning during treatment in some patients; pain may be considerable; potential AEs include initial erythema, edema, burning sensation, pain, and crusting followed by hypopigmentation or hyperpigmentation, ulceration, or scaling; erythema and edema may persist for 1–4 weeks; photosensitivity
5-FU	Mainstay of topical therapy for 40 years; gold standard to which other topical treatments are compared; noninvasive chemotherapy; erythema reveals subclinical lesions, which can be cleared with 5-FU; high cure rates when compliance is good; most effective for head and neck AKs; AEs such as erosions usually heal within 2 weeks after cessation of treatment (a smooth complexion appears); usually no residual scarring or discoloration; AEs may be reduced and compliance can improve with concurrent topical corticosteroids and/or pulse therapy	Recurrence rates of up to 55% have been reported; AEs may be severe and can include local irritation presenting as dryness, erythema, erosions, ulcerations, pain, or periorbital edema; must be applied carefully; inflammation and potential scarring make 5-FU undesirable to many patients; AEs usually begin after first week of treatment and can persist for 2–4 weeks following treatment; typical pattern is 4–6 weeks of initial erythema progressing to vesiculation and erosion; difficult to predict which patients will have most severe reactions; AEs are associated with high rates of noncompliance and also with discontinuation of treatment

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Table (continued)

Therapy	Advantages	Disadvantages
Topical imiquimod	Mechanism of action believed to induce immune memory, which may minimize recurrence; can be well-tolerated; noninvasive immunomodulatory therapy; can reveal and treat subclinical lesions; little or no scarring and no skin discoloration; shorter treatment period (2-week treatment cycles) with imiquimod cream 3.75%	16-week treatment period with imiquimod cream 5% is long and may reduce compliance; local cutaneous reactions are common, including erythema, pruritus, burning, pain, erosions, edema, scabbing, induration, and ulceration; sometimes unpredictable local AEs with some patients manifesting very few AEs, while others may experience substantial reactions; in most studies, dose reduction was required due to local reactions; rare reports of systemic AEs, including fatigue, flulike symptoms, and angioedema
Topical diclofenac	Moderate efficacy when treating mild lesions; may be effective in preventing AK lesions (long-term follow-up studies are needed); noninvasive therapy; may possibly reduce recurrence rates; may possibly reveal subclinical lesions; well-tolerated with minimal AEs that resolve after cessation of treatment; good cosmetic effects; tolerability tends to be high due to limited local irritation and inflammation; AEs typically are mild to moderate and rarely severe enough to cause treatment discontinuation	60- to 90-day treatment period is long and may reduce compliance; complete clearance may not be evident for up to 30 days following cessation of therapy; AEs include erythema, pruritus, rash, and dry skin; potential allergic reaction in aspirin-sensitive patients; contact sensitization a potential problem; patients should be advised to avoid sun exposure

Abbreviations: AE, adverse effect; AK, actinic keratosis; 5-FU, topical 5-fluorouracil.

Investigational Agents for Field-Directed Therapy

The prolonged courses of therapy required with topical imiquimod, 5-FU, and diclofenac, as well as the irritation profiles of 5-FU and imiquimod, may underlie the less than optimal compliance that has been associated with these agents, which can adversely affect lesion clearance. Investigational topical agents, including one involving a short treatment period, are being evaluated as field-directed therapy for AK.

Ingenol Mebutate—Ingenol mebutate (PEP 005) is a diterpene ester in development for the treatment of AK. (See Addendum.) Ingenol mebutate is derived from the plant *Euphorbia peplus*,[42] which has been used as a traditional treatment of a variety of skin cancers and precancerous skin lesions. The mechanism of action in AK is not fully understood, though in vivo and in vitro models have shown that ingenol mebutate has a dual mechanism of action: (1) local induction of lesion cell death by disrupting the plasma membrane and mitochondria of tumor cells,[42] and (2) generation of proinflammatory cytokines and massive infiltration of neutrophils and other inflammatory cells, which raise an immune response.[43,44]

A single application of ingenol mebutate gel 0.01% to discrete AK lesions demonstrated a favorable safety profile with greater clearance than vehicle alone.[45] Phase 2 dose-escalation studies indicated that ingenol mebutate gel 0.05% applied once daily for only 2 consecutive days to AK lesions on nonfacial areas

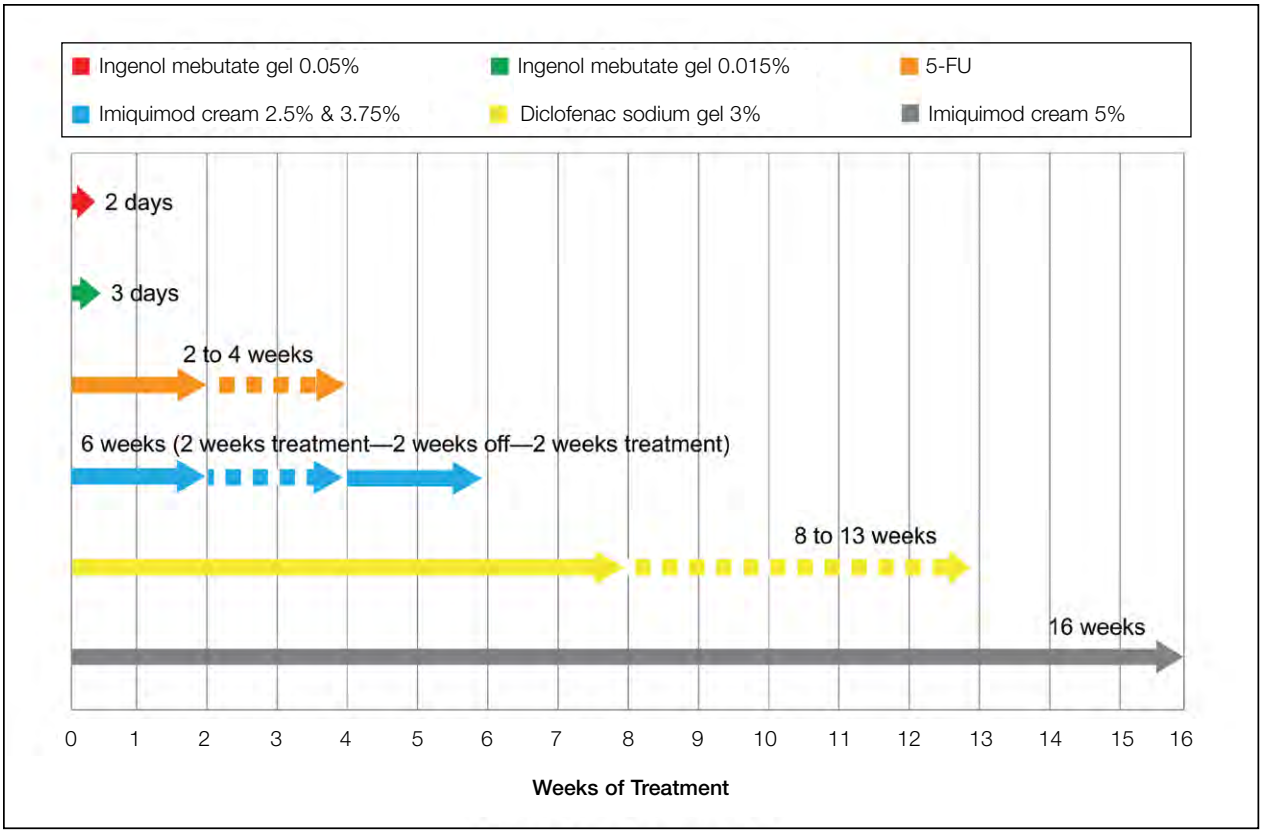

Figure 3. Duration of treatment with currently approved, patient-administered topical agents for field-directed therapy. Depending on the formulation, 5-fluorouracil (5-FU) usually is applied once or twice daily for 2 to 4 weeks. Diclofenac sodium gel 3% usually is applied twice daily for 8 to 13 weeks. Imiquimod cream 5% usually is applied once daily 2 or 3 times a week for 16 weeks; imiquimod cream 2.5% or 3.75% is applied once daily for two 2-week treatment cycles separated by a 2-week no-treatment period. Ingenol mebutate gel 0.015% is applied for 3 consecutive days (for actinic keratosis of the face and scalp) and ingenol mebutate gel 0.05% is applied for 2 consecutive days (for actinic keratosis of the trunk and extremities).

may be a suitable concentration and dosage regimen for field-directed therapy of multiple lesions. Patients experienced a complete clinical response in 71% of AK lesions.[46,47] Ingenol mebutate gel 0.015% applied to face and scalp lesions once daily for 3 consecutive days produced complete clearance of lesions in 50% of 265 patients, and the median number of lesions was reduced by 85%.[48] The most common local skin responses were erythema, scabbing, crusting, scaling, flaking, and dryness, which peaked between days 3 to 8 and generally resolved within 2 to 4 weeks after treatment.[45,46] In 4 multicenter, randomized, double-blind studies, randomly assigned patients with AKs on the face or scalp or on the trunk or extremities self-applied ingenol mebutate or vehicle gel to a 25-cm^2 contiguous field once daily for 3 consecutive days for lesions on the face or scalp or for 2 consecutive days for the trunk or extremities. In a pooled analysis of the 2 trials involving the face and scalp, the rate of complete clearance was higher with ingenol mebutate than with placebo vehicle (42.2% vs 3.7%; $P<.001$). Local reactions peaked at day 4, rapidly decreased by day 8, and continued to decrease, approaching baseline scores by day 29. In a pooled analysis of the 2 trials involving the trunk and extremities, the rate of complete clearance was higher with ingenol mebutate than with placebo vehicle (34.1% vs 4.7%; $P<.001$). Local skin reactions peaked between days 3 and 8 and declined rapidly. Ingenol mebutate gel has the potential to enhance compliance (>98% adherence to treatment regimen in these studies) and thereby outcomes, not only because of its substantially shorter course of therapy but also because of the abbreviated period of irritation compared with currently available topical agents; currently, no compliance data are available.[49]

Resiquimod—Resiquimod is an imidazoquinolinamine nonspecific immune modulator with greater potency at inducing cytokine expression than imiquimod.[50] In a European phase 2, dose-ranging study (N=132) of 4 concentrations of resiquimod gel, each applied topically once daily 3 times weekly for

4 weeks to AK lesions within a 25-cm^2 area on the face or scalp, the rate of complete clearance after one course of therapy was 40.0% with the 0.01% gel; 74.2% with the 0.03% gel; 56.3% with the 0.06% gel; and 70.6% with the 0.1% gel.[51] Patients with residual lesions received a second course of treatment. The 2 lowest concentrations were better tolerated. The discontinuation rate due to local skin responses and systemic adverse reactions after the first course of treatment with each concentration of resiquimod gel was 0%, 13%, 31%, and 38%, respectively. The authors concluded that efficacy in clearance of AK lesions was similar among the resiquimod concentrations evaluated, but resiquimod gel 0.01% and 0.03% were better tolerated than the higher concentrations.[51]

Epigallocatechin Gallate—The green tea polyphenol epigallocatechin gallate, derived from *Camellia sinensis*, has been shown to inhibit the growth of many cancer cell lines and to suppress the phosphorylation of the epidermal growth factor receptor.[52] In the United States, a randomized, double-blind, placebo-controlled, phase 2 trial tested an ointment formulation among patients with AK on the arms; they applied the treatment daily for 12 weeks or until all AK lesions within the treatment field had regressed. However, the trial was discontinued due to the low conditional power for a positive result.[53]

Betulinic Acid—Betulinic acid is a naturally occurring pentacyclic triterpenoid that exhibits potential antitumor properties through its inhibition of topoisomerase. It is found in the bark of several species of plants, including white birch. A multicenter, double-blind, placebo-controlled phase 2 study in Germany enrolled patients to assess the efficacy and tolerability of betulinic acid applied twice daily to AK lesions of the face and head for as long as 3 months.[54]

Piroxicam—Piroxicam is a nonselective nonsteroidal anti-inflammatory drug that blocks cyclooxygenase-1 and cyclooxygenase-2 activity. An Italian open-label study in 2010 assessed the efficacy and safety of piroxicam gel 1% applied twice daily for 12 weeks to 31 AK lesions; complete regression occurred in approximately half of the lesions. Adverse effects included pruritus, mild erythema, dry skin, and rarely rash.[55]

Fluorouracil/Salicylic Acid (LAS 41005)—LAS 41005 combines 5-FU 0.5% (5 mg/g) with salicylic acid 10% (100 mg/g)(for its keratolytic effect) in a topical gel formulation applied once or twice daily for the treatment of AK. A 120-day phase 3 study of LAS 41005 for AK lesions on the face and forehead or bald scalp (excluding eyelids, lips, and mucosa) was conducted in Germany and completed in 2009.[56] Study results currently are not available.

Conclusion

The proper diagnosis and treatment of AK is essential because the lesions can potentially progress to invasive SCC. Because there is no way to clinically determine which lesions can potentially transform and invade the dermis, recur after treatment, and metastasize, most dermatologists treat all AK lesions. Field-directed therapy is primarily used for multiple visible or palpable lesions on contiguous areas of skin, for subclinical lesions, and for entire sun-damaged areas at risk for subclinical lesions. Topical agents that currently are available necessitate prolonged courses of field therapy, often produce skin irritation, and are associated with less than optimal compliance, which can adversely affect lesion clearance. Investigational topical agents, including one involving a short treatment period, are being evaluated for field-directed therapy of AK.

ADDENDUM

After the manuscript was accepted for publication, ingenol mebutate gel 0.015% and 0.05% were approved for the topical treatment of AK. The 0.015% formulation is indicated for the face and scalp and should be applied once daily for 3 consecutive days. The 0.05% formulation is indicated for the trunk and extremities and should be applied once daily for 2 consecutive days.[49]

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