Updates on Treatment Approaches for Cutaneous Field Cancerization

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Abstract

Purpose of Review Field cancerization describes the phenomenon that multiple heterogenous mutations may arise in an area exposed to chronic carcinogenic stimuli. Advances in the understanding of cutaneous field cancerization have led to novel therapeutic approaches to the management of actinic keratoses (AKs). Herein, we review the literature on the pathophysiology and emerging research of field cancerization in dermatology.

Recent Findings The classification systems for grading AK lesions are being refined with investigations focusing on their clinical utility. There is a growing shift toward field-directed treatment for AKs as the importance of field cancerization becomes clearer. Current field-directed therapies are being optimized and novel therapeutic modalities are being studied.

Summary Field cancerization underlies the transformation of photodamaged skin into AKs and potentially cutaneous squamous cell carcinoma (cSCC). Clinically meaningful classification systems for AKs are needed to better inform decisions regarding treatment. As we learn more about the role of field characterization in photodamage, AKs, and cSCCs, therapeutic strategies are becoming more field-directed rather than lesion-directed.

Keywords Field cancerization · Actinic keratosis · Cutaneous squamous cell carcinoma · Photodamage · Photodynamic therapy

Introduction

Field Cancerization Concept

Field cancerization describes the phenomenon that multiple heterogenous mutations may arise in an area exposed to chronic carcinogenic stimuli [1••]. As one or more cells undergo irreversible genetic changes that persist over multiple cycles of cell division, a dysplastic field emerges [1••]. Invasive properties are not evident initially, but as somatic mutations accumulate from carcinogen exposure, subclonal proliferations may eventually induce carcinoma [1••, 2]. The term "field cancerization" was first coined and described in a landmark study by Slaughter et al. in 1953 in reference to

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oropharyngeal squamous cell carcinoma (SCC) [3]. Areas adjacent to the tumor appeared grossly normal but histopathologic examination demonstrated dysplastic changes and foci of oropharyngeal SCC in situ [3]. The findings of discrete primary tumors and islands of dysplastic epithelium suggested that the tumors had simultaneously developed independent of each other, rather than from the clonal proliferation of a single mutant cell [2].

The concept of field cancerization is especially relevant in dermatology, as it describes how actinic keratosis (AK) lesions develop and subsequently transform into cutaneous SCC (cSCC), the second most common malignancy in the US [4]. A committee of European dermatologists defined field cancerization as the anatomical area including or adjacent to AKs with visibly photodamaged skin, characterized by pigmentary changes, rough texture, atrophy, or telangiectasia [5].

Field cancerization has significant therapeutic implications and clinical consequences in dermatology. AKs are typically viewed as precancerous; however, treatment of individual lesions often does not address mutations in nearby cells that may be transforming into cancer [2]. AKs are one of the most prevalent diagnoses in dermatology and are expected to increase with the aging population and increased exposure to sunlight [6]. In 2015, over 35 million cases of AKs were

treated in the Medicare Part B fee-for-service population, up from 29.7 million in 2007, highlighting the treatment burden of this condition [7]. AKs have been estimated to cost the US healthcare system $920 million annually [8]. There is up to 0.075% risk per lesion-year of AK transformation to cSCC, increasing to 2.57% at 4 years [9, 10].

Currently, there is no reliable method to discern AKs that will transform into cSCCs from those that will either remain benign or resolve without treatment, complicating the treatment algorithm of AKs. Various approaches are being investigated for this unanswered question including imaging techniques and genotyping [5, 11]. The Department of Veterans Affairs Topical Tretinoin Chemoprevention (VATTC) trial is a 5-year multicenter clinical trial that followed individual AK lesions. By 1 year, 55% of AKs had regressed, and at 5 years, 70% were not present [10]. Of note, some AKs not present at the 1 year follow-up were present at later follow-up visits, which is consistent with the reported regression and recurrence of AKs [10]. Of the primary cSCCs that were diagnosed, 65% of those arose from lesions that were initially diagnosed as AKs [10]. Interestingly, 36% of basal cell carcinomas (BCCs) were diagnosed from lesions that were previously diagnosed as AKs, indicating that either BCCs and cSCCs may share a common underlying pathogenesis or the initial AK diagnosis was incorrect [10]. Another study estimated that approximately 10% of AKs will undergo malignant transformation into cSCC with the average time for conversion being 24.6 months (range 2 to 65 months) [12]. Without intervention, resulting cSCC may subsequently lead to significant healthcare expenditure, patient morbidity, and patient mortality. In 2013, it was estimated that each year in the US, cSCC causes between 4000 and 9000 deaths and bears a $4 billion economic burden [6]. While the risk of a single AK transformation to cancer is overall low, patients typically have many AKs or at least multiple fields of precancerous, photodamaged skin.

Understanding field cancerization is important for elucidating the malignant transformation process from normal skin to cSCC. Determining the risk of cSCC development from a single lesion as well as risk for a field may improve patient outcomes by identifying those patients who would benefit most from earlier treatment [2]. Herein, we discuss the emerging research of field cancerization in dermatology, with emphasis on the most recent research literature on the pathogenesis, classification, and treatments of AKs.

Pathogenesis

Photodamage is caused by chronic ultraviolent (UV) radiation exposure from sunlight and is associated with detrimental consequences to the skin, such as atrophy and increased risk of cancer [13]. UVA irradiation (320–400 nm) is associated with indirect damage to DNA by oxidative injury via reactive oxygen species (ROS) [14]. UVB irradiation (290–320 nm) causes direct damage to DNA by inducing structural rearrangements of nucleotides, such as thymidine dimerization, leading to physical distortions in the DNA strands [15]. The collective DNA damage and mutations over time interfere with replication and transcription, resulting in cutaneous cancerization of the field and clinically manifesting as varying degrees of photodamaged skin [16]. Field cancerization of the skin begins when UV radiation induces a sporadic somatic mutation in epidermal keratinocytes (Fig. 1) [1••]. With chronic exposure to UV radiation, clonal expansion occurs and mutations accumulate, leading to AKs on sun-exposed skin [1••]. As UV radiation non-selectively damages DNA, AKs may have varying mutations and may be at different stages of development [5]. The transformation of AKs to cSCC is thought to occur in a stepwise fashion with progressive development of epidermal neoplasia, which has been classified clinically by Olsen et al. and histologically by Rowert-Huber et al. [17, 18]. For clinical research purposes, AKs are graded based on thickness and the degree of hyperkeratosis: AK 1 is better palpated than visualized, AK 2 is visible, and AK 3 is hyperkeratotic [17]. Histologically, AKs are graded based on the extent of epidermal atypical keratinocytes: AKI is limited to epidermal basal layer, AKII extends to the lower two thirds of the epidermis, and AKIII involves the full epidermal thickness [18]. Histologically graded AKI was recently found to be the most common precursor to cSCC as progression occurs through direct invasion from proliferating atypical keratinocytes, such that any grade of AKs may be invasive [19••].

In photodamaged skin, AKs, and cSCCs, evidence of the TP53 tumor suppressor protein was observed in keratinocytes and has been recorded in 69 to over 90% of invasive cSCC [20, 21]. Other implicated mutations in field-cancerized islands include the oncogenes c-myc, Ras, H-ras, c-jun, WNT, and KNSTRN and the tumor suppressors, p16INK4, NF-κB, Notch1, Notch2, Hes1, and Erdr1 [2, 16, 20, 22, 23]. Some studies have genotyped AKs and cSCC to identify potential key biomarkers which may be useful for diagnosis, prevention, or treatment [11, 24, 25].

Since AKs and cSCC share many genetic features, AKs are used as a risk marker for cSCC; however, there is emerging evidence that AKs may also herald other types of skin cancer [1••]. One study found evidence of histologically present AKs in 57% (35/61) of cSCC specimens, 33% (21/64) of basal cell carcinoma specimens, and 25% (6/24) of malignant melanoma specimens [1••]. The extent of field damage may be even larger than reported as only 0.1 mm of the distal lateral margin was assessed for discontiguous foci of dysplasia [1••]. The relationship between AKs and other cutaneous malignancies is unclear, but these findings are significant as they suggest that any cutaneous malignancy may be surrounded by an expanding pre-neoplastic field [1••]. Another study
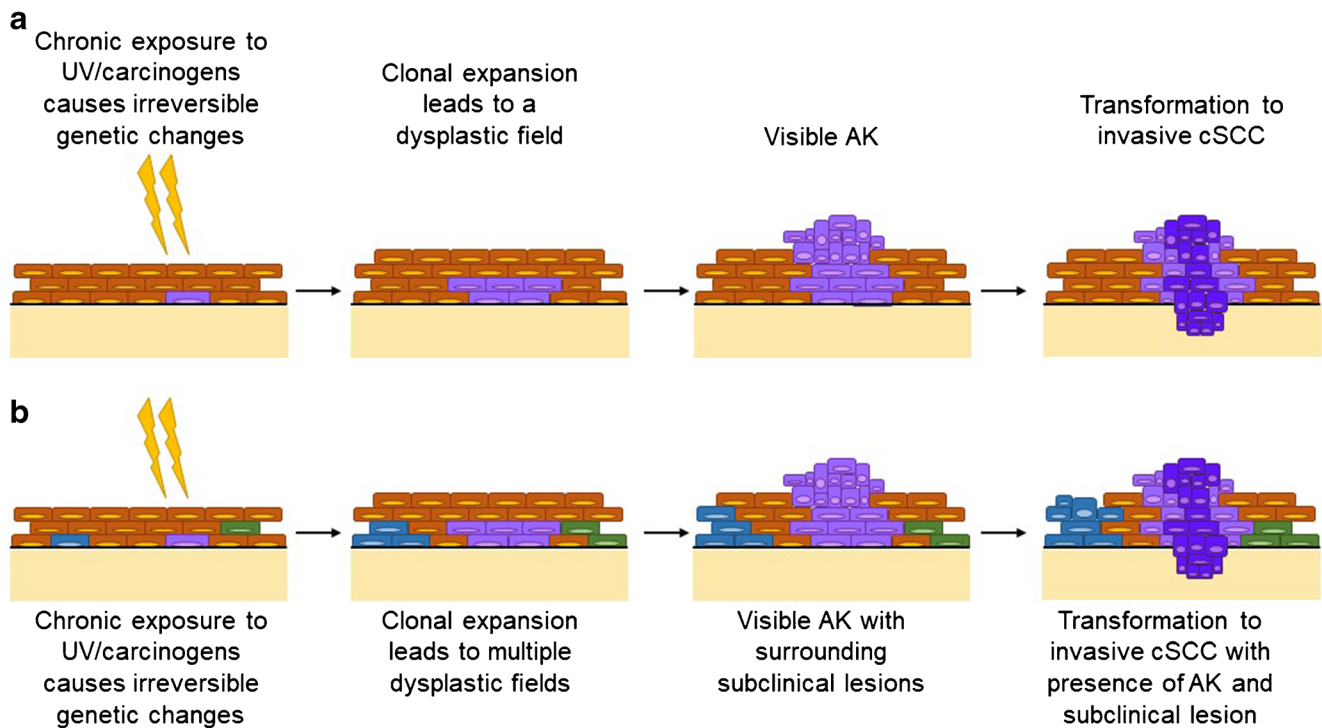
Fig. 1 Field cancerization theory. **a** Previous theory of cSCC formation. **b** Current field cancerization theory. UV ultraviolet, cSCC cutaneous squamous cell carcinoma, AK actinic keratosis

demonstrated a 42% risk of developing subsequent cSCC within 5 years of the original diagnosis and a 72% increase in risk if the patient had two or more cSCCs at the initial time of diagnosis [2, 26]. Thus, a patient with a known diagnosis of cSCC is at increased risk of developing additional cSCCs.

AK Classification

The wide variety of clinical and histological presentations of AKs presents a challenge to developing a uniform grading system that predicts whether a lesion will regress or progress. Grading of AKs based on thickness was found to be inconsistent among experts [5, 17]. Grading based purely on histology is not specific enough as histological findings may overlap with other keratinocyte diseases such as Bowen's disease and seborrheic keratosis [18]. Additionally, there is no evidence to support that the stepwise progression from AKI to AKIII is necessary for the transformation of atypical keratinocytes into cSCC [27]. Other classification schemes based on lesion size, number of lesions, and histological findings are focused on individual lesions, an approach that does not consider the process of field cancerization and spontaneous mutations [28].

In 2017, two scales were developed and validated to measure AKs in the context of field cancerization, the Actinic Keratosis Area and Severity Index (AKASI) and the Actinic Keratosis Field Assessment Scale (AK-FAS) [29, 30]. The AKASI evaluates AK parameters including severity on the head, area of extent, and clinical features (i.e., distribution, erythema, and thickness) [29]. The AK-FAS is used to grade AK severity based on AK area (as opposed to number of lesions), hyperkeratosis severity, and sun damage severity [30]. These scales are not widely used in the clinical setting, possibly due to their recent introduction.

One of the major issues with grading is the heterogeneous nature of field cancerization, which leads to a variety of grades within a single lesion [31]. Two thirds (67%) of AKs have more than one grade [31]. The diverse grading within a lesion also means that histopathological information from one biopsy may not be extrapolated to the entire field. One solution is to classify AKs based on their development; this requires a better understanding of the role of field cancerization in AK and cSCC development [27]. The predictive value of field disarray in lesion progression also requires further investigation as earlier identification of lesions with malignant potential may result in better patient outcomes and decrease the financial burden of this disease.

Management/Treatment

The ideal management of field cancerization is through patient education on the importance of UV exposure avoidance (i.e., using high SPF sunscreen that protects against UVA and UVB rays) to minimize photodamage [2]. Recently, oral nicotinamide (vitamin B3) has been advocated for use as skin cancer chemoprevention due to its protective effects against UV-induced cutaneous damage, reducing the rate of new AKs in high-risk patients [32]. The therapeutic mechanisms of nicotinamide involve enhancement of DNA repair via blockade of UV-induced ATP depletion [32]. This chemopreventative method may supplement behavioral modifications in patients at higher risk of developing AKs.

If the patient has already developed AKs, then treatment is usually offered in routine clinical practice. As there is no reliable way to determine which AKs will become cSCCs, the prevailing recommendation by expert consensus is to treat all lesions [2]. Treatment for AKs may be lesion-directed or field-directed. Lesion-directed therapies are adequate for well-defined lesions and may be useful when complete clearance is not achieved by other methods [33]. Recently, there has been a shift toward field-directed therapy using topical agents, photodynamic therapy (PDT), chemical peels, laser resurfacing, etc. [34, 35•, 36]. Since field cancerization causes multifocal areas of dysplasia and precancerous changes, a single diagnosis of cSCC signifies increased risk of subsequent cSCC and therefore may require long-term follow-up [2]. Subsequent cSCC may be recurrence of the primary cSCC or may arise as a new primary cancer due to the heterogeneity of field cancerization (Fig. 2) [2]. Currently available field-directed therapies are being optimized and new field-directed topical agents and laser therapies are discussed below. In

Fig. 2 Field cancerization and local recurrences of tumors

addition, Table 1 describes clinical trials currently being conducted in the US for AK treatment.

Currently Available

5-Fluorouracil and Imiquimod

5-fluorouracil (5-FU) and imiquimod are two topical agents that are well-established and commonly used for field-directed therapies for AKs [37]. 5-FU is available in cream formulation with 0.5%, 1%, and 5% strengths. The 5% cream is applied twice daily for 2 to 4 weeks whereas 0.5% and 1% creams are applied daily for 3 to 4 weeks [38]. Imiquimod is available as 3.75% and 5% creams. The 3.75% cream is applied once daily for 8 h for two 2-week treatment cycles separated by a 2-week no-treatment period whereas the 5% cream is applied two times per week for 8 h for 16 weeks [39, 40].

More recent studies combine AK therapies, use different concentrations, or report rare adverse events [41–46]. Combination therapy studies include 5% 5-FU and 0.005% calcipotriol, which was found to reduce the number of AK lesions by 87.8% compared with 26.3% for 5% 5-FU and white petrolatum in mice [45]. This effect was thought to be related to an activation of CD4$^+$ T cell-mediated immunity [45]. Different concentrations of imiquimod, 2.5% and 3.75%, were studied in a meta-analysis of four phase III clinical trials [46]. These doses are lower than the typical 5% imiquimod for use as short-term cycle therapy or an expanded treatment area [46]. The two concentrations showed dose-related effects on Combined Investigator's Global Integrated Photodamage score and both performed significantly better than the control cream [46]. While 5-FU and imiquimod are considered safe, there have been recent case reports of rare adverse reactions. One report described fever, fatigue, mucositis, dehydration, and significant weight loss, thought to be related to a dihydropyrimidine dehydrogenase deficiency, leading to decreased drug clearance and systemic 5-FU accumulation after 0.5% topical 5-FU [42]. Another case report described a patient with blistering, peeling, and painful erythema after overapplying the topical 5% 5-FU she was prescribed [44].

Photodynamic Therapy

PDT consists of topical application of a photosensitizing agent that is activated by light. In the case of aminolevulinic acid (ALA), one of the more commonly used photosensitizing agents in the US, precursors of the heme pathway are converted to protoporphyrin IX (PpIX) in the skin [47]. PpIX generates ROS when exposed to light irradiation, typically red or blue light, leading to cell death and an inflammatory response [47]. Red light PDT has been a staple in European PDT and is being reintroduced to the US market. Red light penetrates deeper than other wavelengths of visible light and
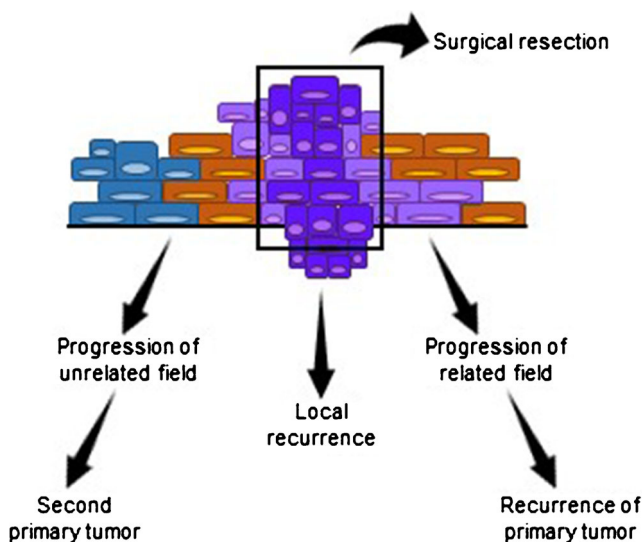
Table 1 Ongoing clinical trials for AK investigation in the USA. *NA* not available

	Study title (identifier)	Phase	Interventions	Study design	Primary outcome (time frame)
PDT	Daylight Photodynamic Therapy for Actinic Keratosis (NCT03322293)	1	Drug: ALA Topical 20% Topical Solution Device: BLU-U blue light phototherapy illuminator	Randomized Single-blind	Reduction in treatment symptoms (12 weeks)
	Protocols for Painless Photodynamic Therapy (PDT) of Actinic Keratoses (NCT02124733)	3	Procedure: ALA-PDT with altered incubation time (0 vs 1 h)	Randomized Single-blind	AK clearance (3 months)
	Photodynamic Therapy Incubation Times for Actinic Keratosis (NCT03066843)	NA	Drug: ALA Device: blue light therapy with altered incubation time (0 vs 1 h)	Randomized Single-blind	Change in number of AK lesions (baseline and 8 weeks)
	DUSA: Cyclic PDT for the Prevention of AK & NMSC in Solid Organ Transplant Recipients (NCT03110159)	1, 2	Drug: Levulan® Kerastick® Drug: BLU-U blue light photodynamic therapy	Single-group Open-label	Primary prevention of AKs and NMSCs (3 years) Time to occurrence of AKs and NMSCs (3 years)
	Biomarker Database Registry for Photodynamic Therapy (NCT03319251)	NA	PDT	NA	AK clearance (3 months) Vitamin D levels (baseline)
VDA-1102: anti-neoplastic agent	Study to Evaluate the Efficacy, Safety, and Tolerability of Topical VDA-1102 Ointment in Subjects With Actinic Keratosis (Phase2b) (NCT03538951)	2	Drug: 10% VDA-1102 Drug: 20% VDA-1102	Open-label Multi-center	Complete clearance rate (16 weeks) Complete facial clearance rate (16 weeks)
SOR007: uncoated nanoparticulate paclitaxel ointment	Study of SOR007 Ointment for Actinic Keratosis (NCT03083470)	2	Drug: SOR007 (uncoated nanoparticulate paclitaxel) Ointment: 0.15%, 1.0%, 2.0% Other: SOR007 ointment vehicle	Randomized Double-blind	Incidence of treatment emergent adverse events (28 days)
SR-T100: antiproliferative agent	Efficacy and Safety Phase II Study of SR-T100 to Treat Actinic Keratosis (NCT01516515)	2	Drug: vehicle gel Drug: SR-T100 with 2.3% of SM	Randomized Double-blind	Total clearance rate (24 weeks)
KX2-391: Src tyrosine kinase inhibitor	A Ph2a, Open-Label, Multicenter, Activity & Safety Study of KX2–391 Oint in Subj. w Actinic Keratosis on the Face or Scalp (NCT02838628)	2	Drug: KX2-391	Single-group Open-label	Complete response rate (57 days)
	A Multi-Center Study to Evaluate the Efficacy and Safety of KX2–391 Ointment 1% on AK on Face or Scalp (AK003) (NCT03285477)	3	Drug: KX2-391 ointment 1% Drug: placebo	Randomized Double-blind Multi-center	Complete response rate (57 days)
	A Multi-Center Study to Evaluate the Efficacy and Safety of KX2–391 Ointment 1% on AK on Face or Scalp (AK004) (NCT03285490)	3	Drug: KX2-391 ointment 1% Drug: placebo	Randomized Double-blind Multi-center	Complete response rate (57 days)
5-FU	Evaluating Skin Appearance Following 5-Flourouracil Cream for Treatment of Actinic Keratosis and the Effects of Topical Agents (NCT03279328)	4	Drug: topical steroid ointment Other: Vaseline Drug: skin barrier moisturizer	Randomized Open-label	Skin barrier biophysical properties (2 h)
CAP	Using a Cold Atmospheric Plasma Device to Treat Skin Disorders (NCT02759900)	NA	Device: non-thermal, atmospheric plasma	Single-group Open-label	Clinical improvement (1 month)
Other	Validation of SHADE a Mobile Technology for Monitoring of Ultraviolet Exposure (NCT03315286)	NA	Device: SHADE Ultraviolet Sensor Behavioral: Standard of care counseling	Randomized Double-blind	Quantification of AK (6 months)

has a higher fluence rate compared to blue light; this may cause more pain during light treatment [48, 49]. PDT has minimal downtime although patients become more sensitive to light, which warrants precaution for sun exposure and medications that cause photosensitivity [50, 51]. There is evidence that PDT may be able to correct dysplastic, photodamaged skin by altering cancer-associated gene expression [52••]. PDT has been reported to have desirable cosmetic effects when used to treat AKs through activation of processes involved in wound healing [52••, 53]. A phase III study using ALA and red light to treat an entire field found long-lasting skin rejuvenation in areas of asymptomatic photodamage in addition to being effective for the treatment of mild-to-moderate AK lesions [53].

PDT may not be as effective for AKs on the extremities due to the thermal dependence of endogenous PpIX generation [54••]. However, thermal PDT, which uses higher temperatures during incubation of the photosensitizer, results in better outcomes in field treatment of the extremities, shorter incubation times, and does not increase side effects [54••, 55–57, 58••]. Higher temperatures were achieved by wrapping the extremity tested with a heating pad to set "medium" which achieved maximal temperatures ranging from 37.2 to 43.4 °C during incubation compared with a baseline of 29.6 to 33.6 °C [54••].

Since patients may experience discomfort during PDT, various strategies have been studied to mitigate this adverse effect, use of including of alternate light sources, pretreatments, and different photosensitizers. A variation to conventional PDT is to use daylight as an alternative light source to activate PpIX [59–61]. This method allows continuous and gradual activation of the photosensitizer with daylight rather than with red or blue light, resulting in decreased pain while still maintaining clearance rates similar to conventional PDT [59–65]. Metal halide white light may be an alternative to daylight PDT [66]. This therapeutic option is significant as daylight PDT is dependent on weather conditions and requires patient ability to go outside for light exposure. Other methods to reduce pain include a two-step irradiance treatment and using green light due to its decreased depth of tissue penetration [67, 68].

Recent investigations are evaluating combination therapies, comparing PDT protocols, and developing new photosensitizers. Microneedling as a pretreatment decreased ALA incubation time and decreased pain with similar efficacy to the conventional 1-h ALA incubation time method [69•]. Microneedling may assist with drug delivery as it may create microchannels to bypass the stratum corneum [69•]. Calcipotriol, a synthetic vitamin D derivative, may be used before PDT [70]. Patients undergoing PDT who were pretreated with calcipotriol were found to have fewer side effects and a higher clearance rate of AKs compared to those who received PDT only [71–73]. Calcipotriol pretreatment is thought to boost the amount of PpIX in the skin, thereby

enhancing efficacy of field treatment [72]. Vignion-Dewalle et al. recently published a comprehensive in silico analysis of various PDT protocols using different lights to determine the regimen that offers the best complete response rate at 3 months [74••]. The following top four protocols performed similarly: daylight PDT on a clear sunny day, daylight PDT on an overcast day, PDT with white LED lamp, and PDT with blue light [74••]. The development of new photosensitizers may be coupled with light therapy to form an alternative treatment. One example is photochemical internalization in which an amphiphilic photosensitizer along with a cytotoxic molecule or ribosomal-inactivation protein is given [75]. The cytotoxic compound is taken up into the cell and with light exposure, causes death by endosome rupture. Photochemical internalization is being studied in head and neck cancers but has not yet been reported for use in skin cancer [76].

Needed to Study

SR-T100

SR-T100 gel, not to be confused with the radiotherapy SRT-100, is a topical antiproliferative agent, with active ingredients solamargine, solasodine, and solasonine, thought to treat AKs through modulation of the tumor necrosis factor receptor signaling pathway [77]. A study in Taiwan reported 32% complete clearance rate and 72% partial clearance rate for the group receiving SR-T100 gel compared with 12% complete clearance and 37% partial clearance rate for the control group [78]. The odds ratio for complete clearance was 2.14 and 4.36 for partial clearance [78]. The study gel was applied to an area that covered the AK and then covered by an occlusive dressing for 8 h daily for 16 weeks. In terms of safety, the rate of adverse events, 55.3% (42/76) for SR-T100 and 51.4% (19/37) for vehicle, and the rate of serious adverse events, 13.2% (10/76) for SR-T100 and 13.5 (5/37) for vehicle, were not statistically different. Serious adverse events were concluded to be unrelated to the study drug. Rates of erythema, burning/stinging, and erosion were higher in the SR-T100 group compared to the vehicle group. While these initial results are promising, more studies are necessary to evaluate the field effects of this drug. SR-T100 is currently under investigation in a phase II clinical trial in the US (Table 1).

2,4,6-Octatrienoic Acid

2,4,6-octatrienoic acid is a parrodiene derivative that has been shown to activate peroxisome proliferator-activated receptor-γ (PPARγ), reducing oxidative damage and inducing DNA repair enzymes thereby treating the field [79]. As far as the authors know, this is the only study that has used this agent to treat AKs. Patients in a phase IV study applied a topical cream containing 2,4,6-octatreinoic acid and urea twice daily

for 2 months [80]. At the 3-month follow-up visit, 82.5% of patients achieved complete elimination of their AK lesions [80]. No side effects were reported although images provided in the article show common side effects such as erythema and crusting [80]. Patients were followed clinically and therefore lack histologic confirmation of lesion treatment. Further research with longer follow-up, periods, side effect reporting, and confirmation of AK treatment are necessary for this product.

Nonthermal Atmospheric Pressure Plasma

Nonthermal atmospheric pressure plasma, also known as cold atmospheric pressure plasma (CAP), is a new therapy being investigated for treatment of AKs. CAP demonstrated therapeutic potential in vitro and in animal models [81]. The mechanism of action is not fully understood but is thought to be related to ROS generation affecting cells undergoing DNA replication (i.e., cancer cells) [81]. This modality involves direct cutaneous contact of ionized gas without thermal damage to the skin [81]. One study using 120 s of CAP therapy twice weekly for seven applications on seven patients with extensive AKs showed promising potential as it resulted in clinical improvement and rejuvenating effects without adverse events or limitations on the maximum treatment area [82]. Another case series of five patients treated 17 lesions; 1 month after a single treatment lasting 1 to 2 min, nine lesions completely resolved, three improved significantly, and five showed no major changes [83•]. Additionally, no side effects were noted [83•]. There is currently one study underway evaluating a CAP device for the treatment of various skin disorders, including AKs (Table 1). The preliminary results using CAP as a therapy for AKs are encouraging but more research is needed to study the mechanism, efficacy, safety, and optimal protocol for CAP.

Lasers

Cutaneous laser resurfacing may be used on an entire skin field to induce new collagen formation and remodeling. Fractional lasers target evenly spaced microthermal zones to minimize thermal damage [84]. Ablative lasers function at higher wavelengths to destroy the epidermis and dermis compared with nonablative lasers [35•].

Lasers are being investigated as monotherapy and as adjunctive applications in AK treatment [84]. One split-face study using ablative fractional laser (AFXL) therapy compared to no treatment for AKs found a significant reduction of AKs at 1 month; however, at the 3-month follow-up, reduction of AKs on either side of the face was similar due to spontaneous regression on the non-treated side [85]. In this study, the Ultrapulse CO_2 laser ActiveFX handpiece (Lumenis) was used with the settings 70 mJ per pulse, power

at 9 W, and density of 4 [85]. In porcine skin, treatment with AFXL was found to induce more dermal deposition of ingenol mebutate [86]. Another study using AFXL in human 3D AK skin equivalents improved MAL uptake and improved PDT outcomes [87]. Fractional Q-switched 1064-nm Nd:YAG laser, a non-ablative laser typically used for tattoo and pigment treatment, is being studied for AK treatment [88]. After four sessions, complete clearance was observed in five out of six patients at the 3-month follow-up [88]. Evidence thus far appears to favor lasers as an adjunct to current therapies as they may facilitate delivery of topical agents, although the ideal monotherapy laser and settings have not been clearly defined yet.

Er:YAG ablative fractional laser-assisted MAL-PDT (AFL-PDT) as a combination therapy has shown positive results [89]. AFL-PDT was found to have an 84.8% response rate at 12 months and a 7.5% recurrence rate which was significantly better than the MAL-PDT only group with a 51.1% response rate and 22.1% recurrence rate [89]. Interestingly, no significant differences in pain were found across the treatment groups [89]. Another study found fractional CO_2 followed by ALA-PDT to produce significantly higher clearance rates than ALA-PDT alone, 89.8% versus 71.2% at 12 weeks and better cosmesis as rated by the investigator and patients [90]. In terms of side effects, the laser group experienced slightly more intense pain and prolonged erythema [90]. Laser use for the treatment of AKs has shown favorable results but more studies are needed to determine efficacy and safety in a larger number of patients as well as determine how lasers best fit in the field-directed AK treatment algorithm.

Chemical Peels

Chemical peels are another resurfacing technique, commonly used for cosmetic purposes, that is being studied for AK therapy. It is applied topically to cause chemical ablation of the skin, causing the superficial layers to slough off, inducing regeneration of the epidermis and dermis. One study compared one session of either ALA PDT or 35% trichloroacetic acid (TCA) peel [91]. Adverse events of TCA included persistent erythema, bacterial superinfection in one patient, and scarring in six patients [91]. Patients treated with ALA PDT demonstrated a complete clearance rate of 73.7% at the 12-month follow-up, compared with 48.8% in the TCA group [91]. Additionally, better Physician Global Assessment scores were noted with the MAL PDT group, with 54.5% of patients achieving completely clear or almost clear in target areas versus 11.8% in the TCA group [91]. Further studies with larger sample sizes, combination therapy with TCA, treatment confirmation with histology, and preventative studies may be needed to assess the role of chemical peels in AK management.

Conclusions

Cutaneous field cancerization describes the process by which chronic UV exposure induces DNA damage and multifocal dysplastic cells. Genetic alterations, progressive invasion of atypical keratinocytes, and crusty, scaly growths may be observed. As a result, recent advances in field cancerization research have furthered understanding of the underlying pathophysiology of AKs and cSCCs. Examining cancer development through a field approach may lead to discoveries in other disease processes including basal cell carcinoma and melanoma. Furthermore, field-directed therapy is desirable for treating AKs as there are high recurrence rates of cSCC when therapy is lesion-directed. PDT, topical treatments, and lasers continue to be commonly employed therapies that are safe and efficacious. As current therapies for AKs are being optimized and new treatments are being developed, we expect efficacy of field therapy to improve. The combination of laser and topical treatments may enhance efficacy in the clinical setting. Comparing the genetic profile of pre- and post-AK treatment areas may reveal important biomarkers for disease progression or regression and allow for gene-targeted approaches.

Limitations of current research on field cancerization include the heterogenous nature of these lesions which pose a problem for classification methods, extrapolation of biopsy results to other lesions, and successful treatment of cSCC. Many clinicians use cryotherapy, a lesion-directed therapy, and may less often use or study field approaches. There is an unmet need for a better classification system for AKs that provides clinical predictability of lesion progression. Future studies should further elucidate the pathogenesis of field cancerization. Factors that differentiate the AKs that transform into cSCCs from those that remain benign or regress need further exploration. Finally, current and developing treatment options for AKs are abundant and studies are necessary to determine the safest and most effective therapies.

Field cancerization explains the continuum of photodamaged skin to cutaneous cSCC. Understanding this process will help guide future management such that patients may benefit the most.

Compliance with Ethical Standards

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Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

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