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Management of Actinic Keratosis

Neal Bhatia [1]

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Abstract
Purpose of Review Approaching treatment for actinic keratosis must start with defining the disease, often as a point in a spectrum of disease between normal skin and progression of cumulative photoexposure. With many of the available topical therapies, dermatologists are fixated on reactions and not on outcomes, which influences patient expectations and long-term strategies, instead of understanding the mechanisms of action of therapies, integration into combination regimens with lesional destruction, and long-term maintenance to reduce skin cancer risks.
Recent Findings New vehicles and percentages of active ingredients, new photodynamic therapy protocols, and systemic chemoprevention with nicotinamide and retinoids are also going to be reviewed in this article.
Summary Considerations for treatment of actinic keratoses start with answers to questions about SCC and the greater assessment of the precursor disease of photodamage.

Keywords Actinic · Keratosis · Carcinoma · Photodamage · Chemoprevention · Photodynamic

Introduction

The fundamental basis for managing actinic keratosis (AK) starts with defining the disease: Should an AK be considered (a) a symptom of photodamage, which is in fact the disease that cannot be cured but may or may not require treatment? (b) a benign neoplasm with "pre-malignant potential" that can either regress, persist, or progress to squamous cell carcinoma (SCC)? or (c) non-invasive SCC that should be treated to avoid recurrence or invasion [1, 2]? One step further is the concept of an AK as point in a spectrum of disease that starts from normal skin and progresses with cumulative photoexposure. Some have classified an AK in the early stages as similar to SCC in situ given many similarities in molecular biological and cytological markers, as well as expression of tumor markers and mutations [3], whereas another analysis of the process suggested that "AK is the initial clinical manifestation of a disease continuum that progresses to frank SCC" [4]. Nevertheless, most dermatologists believe in the clinical description that an AK is "pre-cancerous" to suggest that there are defined steps to progression to malignant transformation, although the concept that histologically it is in a position somewhere in the spectrum from normal skin to photodamage to cancer tends to guide treatment and prevention strategies. How we define this to patients and ourselves will help define expectation for incorporating these strategies, both in the office and over the long-term. A survey was performed between June 1 and July 31, 2016, by dermatologists at Penn State Hershey College of Medicine involving 571 patients inquiring to evaluate the differences in patients' decisions on whether to receive treatment for AK related to information presentation or choice framing [5•]. The question that posed when an AK was presented as a "precancer" had the highest proportion (92.2%) responding the preferred treatment. In contrast, two questions presenting the risk of AK as not progressing to cancer yielded the lowest proportion of individuals who chose treatment (57.7%) and (60.9%) [5•]. These results collaborate with the more common and accessible definitions of AK that patients find as follows: "Actinic

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✉ Neal Bhatia
bhatiaharbor@gmail.com

[1] Therapeutics Clinical Research, San Diego, CA, USA

Keratosis is a premalignant condition of thick, scaly, or crusted patches of skin." [6].

A simple analogy for patients is to compare how dermatologists examine for AKs the same way dentists search for dental caries, with the mindset that one cavity today could be the sign that there will be ten cavities later. In the same assessment, a dentist filling cavities is like freezing the AKs: it is a bandage not a remedy of the process without incorporating some treatment for the entire disease and more importantly, a strategy for prevention. The same patient needs to consider that they did not just brush one tooth, all of them were brushed, and should that same approach be considered for treating actinic keratoses. Finally, by the same analogy, is sunscreen similar to toothpaste for the skin? Dental patients are instructed to brush their teeth twice a day and after every meal, so the same should go for applying sunscreen routinely at breakfast and lunch and while outdoors. Excessive sun exposure could even be the same as eating too many sweets. In the end, dermatologists not only treat but also provide methods to prevent consequences from cumulative UV exposure; similarly to brushing our teeth every day is meant to prevent dental problems [7].

Epidemiology

The destiny of an actinic keratosis is often under debate, for as often as it is considered to be "pre-cancerous"; there is also the possibility that they may spontaneously regress and will therefore not require treatment. Although one single study has not been done to prove the destiny of an actinic keratosis, several articles have been published looking at patterns of not only lesion behaviors but also trends in their treatment. One of the earliest studies published in 1988 involved 1689 Australian patients aged 40 years and over who were diagnosed with at least one actinic keratosis. These patients were followed for over a 5-year period to determine the incidence of malignant transformation of solar keratoses and examined in consecutive years. The authors reported that a total of 21,905 solar keratoses were documented on the first visit, and a squamous cell carcinoma was documented within 1 year on 28 of the 4267 patient visits. Where accurate mapping of both SCCs and pre-existing solar keratoses was available, it was found that 10/17 (60%) SCCs arose from a lesion diagnosed clinically as a solar keratosis in the previous year and the other seven (40%) SCCs on what had been clinically normal skin 12 months previously. The risk of malignant transformation of a solar keratosis to SCC within 1 year was less than 0.001%. The cost-effectiveness of treating all solar keratoses to prevent the development of SCC is questionable [8].

An analysis of five published studies over a 10-year span was reviewed, examining the risk of progression of actinic keratoses to invasive SCC. The range of progression varied from 0.025 to 16% per year which suggested an average rate of risk of approximately 8% given the statistical rates published in the studies reviewed. The eventual decision to treat AKs in this analysis would involve the other factors that present in the clinic with each individual patient, such as duration of persistence, patient age, extent of photodamage, and history of skin cancer [9]. Another study examined the length of time for an AK to progress to an SCC by evaluating the records and history of patients diagnosed with a biopsy-proven SCC over a 2-year span. Approximately 6691 patient records were reviewed, and of these, 91 had a diagnosis of an AK confirmed by biopsy to be at the original location as the subsequent SCC that was diagnosed. It was determined that the length of time of the estimated 10% of AKs that will develop into an SCC for an AK to progress to an SCC was around 24 months, although the authors suggested that a non-retrospective study would be needed to substantiate this time frame [10]. Finally, a smaller study involving 239 transplant recipients evaluated the risk of SCC with increasing total numbers of incident AKs. Analysis of the data showed that the risk of SCC was significantly increased only in participants with 20 or more incident AKs, when compared with those with less than three incident AKs and no independent association between AK regression and SCC was observed. In addition, showed patients that developed more than ten AKs were significantly more likely to develop SCC compared to those with fewer than ten AKs. The authors concluded that among organ transplant patients, there exists a net variation in the progression of AKs during a 1-year span which is associated with a significant increase in skin cancer [11••].

The issue of treating subclinical actinic keratoses is important to treating the consequences of photodamage. Whether with the eyes, dermoscopy, confocal microscopy, or fluorescence, the presence of "evolving AKs" indicates that there are still AKs in the field of treatment, whether we see them or feel them. Therefore, to reduce the risk of skin cancer, the new paradigm dictates that dermatologists treat what is coming and not just what is seen today [12, 13].

Optimizing Management and Patient Satisfaction

What have been the obstacles for successful treatment of actinic keratoses? Some of the reasons seem simple yet difficult to overcome: Patients with AKs are no longer just the Medicare patients; 30–40-year-old patients develop them also as a result of early use of tanning beds and lack of solar protection; generic medications do not have coupon cards or samples that accompany branded therapies, yet patients still ask for both; finally, dermatologists are sometimes fixated on reactions and not on outcomes, which is important for managing patient expectations and strategies (Table 1). Compliance can often be enhanced by education of the patient

Table 1 Word association [14]

Side effects
•Application site reactions
•Expected or adverse responses at application site
•Patient should be made aware
•Local skin reactions
•Adverse unanticipated variable reactions
•Potentially dose limiting
•Anticipated responses
•Expected reactions based on the MOA of the active ingredient
•Should not be classified as negative and patient should be counseled

using words and phrases they can understand. In the new era of compliance, combination therapies of topical treatments and destruction modalities are never promoted off-label by pharmaceutical companies, and neither are the strategies to managing reactions [14, 15] (Table 1).

So what should dermatologists be doing better when it comes to management of actinic keratoses? Several simple strategies should be incorporated, such as repetitive counseling of the patients on anticipated responses, avoid misdiagnosing and labeling drug allergies in charts or in patient messages, and having patients return more frequently during treatment milestones to avoid phone calls and noncompliance. Photos to demonstrate anticipated responses should also be taken whenever possible so patients know to expect and not run to the urgent care clinic with what they believe is an allergic reaction [14–16]. Starting long-term management with imiquimod cream, diclofenac gel, and topical 5-fluorouracil slowly and building up frequency with appropriate adjunctive emollients and photoprotection will lead to sustained adherence. Screening for any history of HSV labialis is essential to avoid reactivation of disease, as is waiting at least a week after cryotherapy, photodynamic therapy, or other facial procedure to minimize any exuberant response. In today's practice environment, patients should be instructed to fill prescriptions between Monday to Thursday so that it is less likely to be switched to another therapy compared to those filled on Fridays or weekends, and, most importantly, patients should start treatments on Sundays so that reactions occur in the middle of the week rather than on weekends allowing for unscheduled assessments in the office [14–16]. The strategy will be different using ingenol mebutate gel as the reaction patterns are underway with the application of therapy, so strategic follow-up during the milestones of reactions during the first 15 days will prove to be both supportive and reassuring to patients (Table 2).

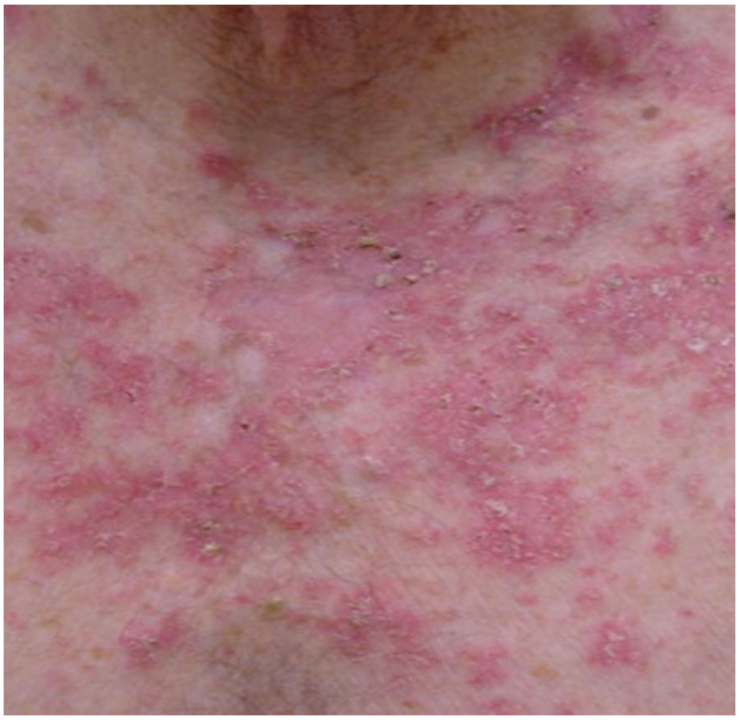
New Medical Therapies

Can the treatment of AKs be simple yet still complete when the concerns for subclinical disease are not met? Attempts to address this question came from the Veterans Affairs Keratinocyte Carcinoma Chemoprevention (VAKCC) trial, performed at 12 VA medical centers recruited from 2009 to 2011 involving 932 veterans with two or more AKs that were followed up until 2013. The conclusion after patients were treated with a single course of 5% fluorouracil cream was that there was effective reduction of AK counts and the impact from spot treatments lasted for longer than 2 years [19]. However, the concern for spot treatment as an acceptable method in the era of field therapy was also measured. Subjects were divided between the group treated with 5% FU cream (n = 468) or with vehicle cream (n = 464) to the face and ears twice a day for 4 weeks. Assessments at 6 months, the 5-FU-treated group demonstrated fewer AKs compared with the control group (3.0 vs 8.1, $P < 0.001$) and higher complete AK clearance rates (38 vs 17% at 6 months) with fewer spot treatments at 6-month intervals, at and in between study visits during the trial ($P < 0.01$ for all) [19].

The paradox of spot treatment was addressed in a comparison study performed in Europe involving a similar course of 5% FU cream to the affected areas bid for 4 weeks, versus another group treated with imiquimod 5% cream daily but for only 4 weeks instead of the requisite 12 weeks with that frequency, and a third group treated with cryotherapy for 20–40 s per lesion [20]. Although the comparison of clinical clearance independent of cutaneous reactions favored the subjects in the 5-FU arm, there were significant differences in both the histological clearance, field clearance, and the cosmetic outcomes measured in a subjective assessment, bringing into focus the need to consider long-term outcomes when incorporating topical management [20].

Aside from the previously mentioned ingenol disoxate gel, several other new topical agents and approaches to treating actinic keratoses are either in trials or released (Table 3) with unique mechanisms of action as well as delivery systems meant to treat the entire disease process as well as maximize compliance. Most recently in 2016 was the launch of a 4% 5-fluorouracil in an aqueous cream that contains peanut oil that is applied once daily for 30 days. A 4-week comparison study against 5% 5-FU applied bid (n = 841) was performed to compare both efficacy and tolerability, especially important in the current generic marketplace where the use of 5% 5-FU more often than not was used without a clear regimen or endpoint by prescribers of various specialties. All subjects in the 4% FU in peanut oil arm achieved 75% clearance and 80% of these were 100% clear, compared to 75% subjects for 5% 5-FU gel achieving this endpoint, which was nearly similar [21]. However, only 30% of the subjects

Table 2 Anticipated reactions to ingenol mebutate 0.05% gel on chest at milestones days 4 and 15



Ingenol mebutate topical gel is thought to work by induction of keratinocyte necrosis in conjunction with protein kinase C-mediated immune responses such as neutrophil activation and antibody-dependent cellular cytotoxicity. This dual mechanism of action may help explain its rapid efficacy in AK, achieved after only a relatively short application period measured in days rather than weeks, as for other therapies. Certain milestones for the anticipated cutaneous reactions, especially from day 1 to day 15, have been delineated [17]. Ingenol disoxate 0.018 and 0.037% gel compounds are waiting for FDA approval and are currently still in trial phases for treating full face, scalp, and chest. A modified ester of ingenol has been suspected to have more potent activation of protein kinase C and more exuberant bursts of neutrophils [18].

experienced irritation in the 4% 5-FU cream in peanut oil arm compared to 60% in 5% 5-FU arm, which is important for considerations of compliance, adjunctive symptomatic relief, and repeat therapeutic courses as needed [21]. In addition, the investigators concluded that the superior results comparing stinging, crusting, and itching by the subjects treated with the addition of peanut oil were from the moisturizing effects and, most important, was safe to use in patients with peanut sensitivity [21] (Table 3).

Table 3 Potential and future therapeutic options for actinic keratoses (https://www.clinicaltrials.gov)

- •KX2-391 ointment: inhibit T cell migration and endothelial tubule, lymphocyte infiltration, and angiogenesis
- •VDA-1102 Ointment: anti-neoplastic agent; selective modulation of VDAC/HK2, unique to glycolysis, and mitochondrial; and trigger of apoptosis in atypical cells
- •SR-T100 gel—antiproliferative; *Solanum lycocarpum* alkaloidic extract and constituents, solamargine and solasonine
- •Actikerall (LAS41005): 0.5% 5-fluorouracil (5-FU) and 10% salicylic acid in film-forming base

Photodynamic Therapy and the Future

Optimizing photodynamic therapy for treating AKs starts with simple assessments:

1. Picking the right patient…one who knows the role of therapy, reads the pamphlets and consent forms, and reviews potential outcomes. In addition, the schedules cooperate so that there are not any upcoming social events, photo sessions, or vacations, and there has been a thorough review any oral medications or using any topical prescription or non-prescription products on their face or scalp.
2. Prepare the staff…there should be periodic refreshers and reminders on the basic training to apply the treating agent, operate the light, follow the patient through the procedure, and manage any potential adverse events. There should be adequate time for treatment on everyone's schedule to dedicate hands on care to the patient to avoid discontinuation midstream, to discuss pre- and post-treatment expectations, provide patient education, and for some

"talkesthesia" during the first 6 min which is when the treatment can be not only the most painful but the least expected for the patient.

3. Prepare the clinic space for regular patient flow…aside from the insurance approval issues, consent forms, and before and after instructions for patients; there should be a designated space for storage of the medications, adequate space for patient and light to avoiding claustrophobia, and easy access to the stop button as well as the patient's face. A chair, mayo stand for arms, towels, fans, water mist, wraps for occlusion, and goggles are only a few of the essentials for optimizing outcomes and efficiency [22].

On the treatment day itself, independent of incubation times for the chosen protocol, patients should be reminded to bring books, music, or work to use the time wisely, as well as a wide-brimmed hat to shield the treated lesions from ambient light. The clinic staff could also provide a "care package" that includes appropriate cleansers, moisturizers, and sunscreens. Finally, there does not appear to be a rationale for stopping medications such as antibiotics, diuretics, and anti-hypertensives that are potentially photosensitizing in the UV spectrum (290–400 nm) since blue light(410–417 nm) and red light (635 nm). However, any apprehension or concern for photosensitivity should lead to having patients hold these drugs on the day before and the day of treatment [22, 23].

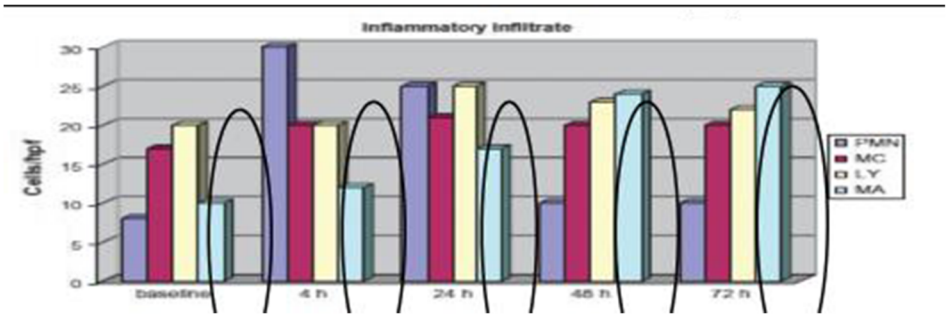
The rationale for instituting non-sedating antihistamines has been studied and is gaining interest as a treatment adjunct. As the primary anticipated responses to ALA PDT, erythema, pruritus, pain, and edema are influenced somewhat by mast cell degranulation from start to 72 h later; it has been suggested that non-sedating antihistamines could potentially reduce these and provide some inherent symptomatic relief (Table 4). In addition, alternatives to application of steroids for these interventions could be considered more opportune (for more than safety reasons) as the mast cell effects over 72 h are more elevated than those of lymphocytes or other mediators otherwise responsive to corticosteroids. Currently these regimens are under further study for dosage protocols using both blue and red light [24] (Table 4).

Several other pre-treatment and combination regimens for blue light PDT have been investigated. A small case series involved ten patients with AKs on the upper extremities treated for 60 min incubations of 20% ALA. In all ten subjects, one extremity was pre-treated with tazarotene 0.1% gel twice a day for 1 week, whereas the other extremity was occluded during incubation. The author concluded that the pre-treatment provided enhanced therapeutic effect based on lesion count between baseline and 8 weeks, without significant elevation in adverse events [25].

Another investigator blinded randomized study of 30 patients compared with efficacy of ALA/PDT alone vs 5% 5-FU alone vs ALA/PDT with 5% 5-FU pretreatment, using identification of subclinical lesions as a secondary endpoint. Group 1 was pretreated for 6–7 days with 5-FU BID, incubated with ALA using a wet gauze for 2 h then with blue light PDT, whereas Group 2 was treated with 5-FU BID for 6–7 days alone but not PDT, and Group 3 was not given pre-treatment but underwent treatment with ALA wet gauze for 2 h then blue light PDT. Of note, all subjects were then given a re-challenge course of 5-FU for 6 days and reassessed at screening/baseline, treatment for ALA/PDT, 24 h post-treatment, 1-week, 1-month, and 3-month post-treatment. The observations of the investigators were that all three routines appeared equally efficacious in treating visible

Table 4 Inflammatory responses to PDT

As suggested by the graphs measured over time, the initial spike in neutrophils observed at 4 h then reduces at 48 h. By contrast, the percentage of lymphocytes and macrophages steadily rises and there is a gradual increases in mast cell proliferation over 72 h post-treatment. From this trend, it is hypothesized that anti-histamines could reduce edema and symptoms although timing of dosage has not been determined.



Graph adapted from Brooke, CC R, Sinha, A, Watson, REB et al. "Histamine is released following aminolevulinic acid dose-related immediate inflammatory response" *J Inv. Derm* (2006) 126, 2296–2301

AKs but a synergistic role of 5-FU with ALA/PDT was demonstrated over ALA/PDT or 5-FU alone. In addition, although treatment of subclinical lesions could possibly result in a longer remission, they suggested that the re-challenge with 5-FU could be useful to judge the efficacy of the initial course of treatment [26]. Smaller and similar comparative studies using imiquimod 5% cream and ingenol mebutate 0.015% gel in combination with blue light PDT gave mixed results and further studies with more subjects would be necessary to make definitive conclusions on efficacy of these regimens [27, 28].

Although a standardization for PDT in general practice has yet to be agreed upon, there exists more evidence that incubation for at least 2 h with aminolevulinic acid followed by sequential treatment over a 2-month period will result in superior clearance of actinic keratoses [29]. Chemoprevention strategies have not been formally incorporated using PDT, but to date adequate trials to support the reduction of skin cancer produced in high-risk patients has been limited to the transplant community [30]. A study done by Willey et al. demonstrated that sequential treatment every other month for two consecutive years resulted in 95% reduction in the incidence of SCC in comparison to an untreated arm, suggesting that a routine of treatments for high-risk patients might have an impact on the development of new skin cancer over time, especially when the risk is augmented by immunosuppression [30].

Advances in photoprotection have also served utility with incorporating PDT. Photoprotection using daily sunscreen can reduce the development of progression of actinic keratosis, but there are now new preparations that contain UV filters and liposomes with exogenous photolyases for use in photoprotection as well as bringing to the forefront a potential role as chemoprevention of actinic keratoses [31]. Observations were reported from a 9-month long study from Europe involving 30 patients with photodamaged skin treated with photodynamic therapy on the scalp, 15 of which were also using sunscreen containing photolyases. After one PDT treatment, these subjects all experienced longer remission time of AKs and were not given additional PDT treatments, unlike 10 of the 15 subjects in the untreated group that did require a second treatment (Fig. 1) [32].

A larger study involved 35 patients with AKs on the scalp, 19 of which underwent treatment with photolyases in sunscreen [33]. The subjects were all treated with red light MAL-PDT and underwent serial punch biopsies at different point on the scalp 1 month prior to PDT, 1 month and 1 year later for capturing biomarker levels. The findings included a decrease in the expression of p53 and Ki67 in the 19 subjects treated with sunscreen containing photolyases daily, suggesting that the combination with this and PDT improves restoration of epidermal differentiation markers, enhanced antigen presentation, and overall improvement of antitumor immune responses in the attempt to manage the field of actinic damage [33, 34].

Many other adjunctive procedures and interventions are being studied. The use of thermal energy devices to heat the skin has become more commonly accepted given the increased conversion of protoporphyrin IX at higher temperatures in the skin [35••]. Microneedling procedures prior to the application of ALA have been shown to increase tolerability

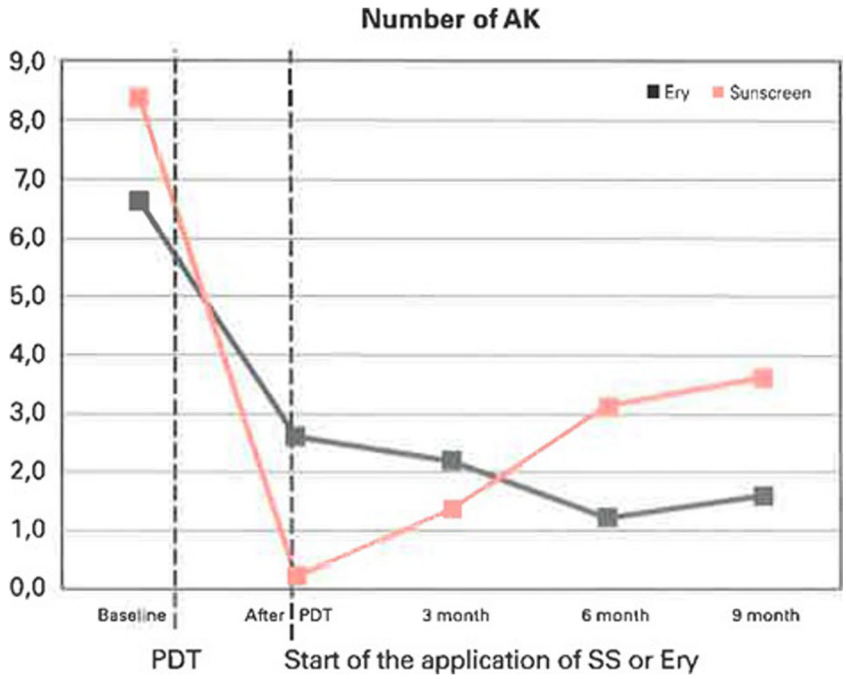


Fig. 1 Evidence of sustained remission of previously treated AKs and preventative effects of photolyases compared to conventional sunscreens in patients treated once with photodynamic therapy. All patients that were treated with sunscreens containing photolyases avoided a second PDT treatment, while 10 of 15 subjects in the non-photolyases sunscreen group required a second treatment to maintain clearance [31, 32]

and cosmetic outcomes when studied with 1-h incubation [36]. Other studies with microneedling have shown similar tolerability measures with objective measures supporting conversion of porphyrins [37]. Other studies are in various phases measuring lesion counts and long-term efficacy (https://www.clinicaltrials.gov).

Finally, a 10% ALA in nanoemulsion gel with activation in the red light spectrum around 630 nm optimizes the transport of 5-ALA through the stratum corneum with no PpIX induction below the basal membrane [38]. A Phase III pivotal trial involved 570 patients with skin type I–II and four to eight AKs. The 10% gel was studied against MAL 21.3% and placebo, and of the patients activated with narrow emission LED lamps (630 nm), only 54% patients in the active group required a second treatment to meet study endpoints. By comparison, almost 90% of lesions cleared compared to 80% in the MAL group and 37% in the placebo group with similar or less pain or other adverse events [38]. In a similar study, using a dedicated red light system, over 94% lesion reduction was reported in comparison to 33% for placebo, with the treated group reporting good cosmetic outcomes [39•].

Chemoprevention

Although there currently is not an FDA-approved modality, drug or device that is indicated for skin cancer prevention, many of the available medical treatments as well as PDT regimens have had expanded potential for not only reducing recurrence potential of AKs in a treatment field but also reducing risk of SCC development [40]. There are many factors to indicate when to consider chemoprevention for NMSC, starting with reduction of any source of immunosuppression such as therapeutic management for solid organ transplant patients, reducing risks to oncology patients on chemotherapy or with hematopoietic malignancies, or control of diabetes mellitus.

Intervention to reduce tumorigenesis, agents such as retinoids, NSAIDs, phytoparticles, antimetabolites, immunomodulators, and PDT have been used in practice, but a balance has to be found between the morbidity and inconvenience of surgery and risk of progression vs adverse effects of systemic therapy. In short, in high-risk patients, the benefits of systemic chemoprevention must outweigh the risks and potential for adverse effects.

The off-label use of systemic retinoids, historically acitretin, has been well-documented, and pearls for their use have been shared within the dermatology community. Several small but controlled studies suggested that to maximize tolerability dosage should start acitretin slowly at 10 mg daily and increase as tolerated to 25 mg qod then qd, titrating up and down to manage side effects. In addition, in the less common scenario of considering women of childbearing age, it might be easier to use isotretinoin due to its shorter half-life despite its off-label application [41, 42]. Risks will rebound with discontinuation so treating with a routine to balance dryness, labs, and risks of alopecia, and neurological effects will require dose modification, hence increasing recurrence risks. In addition, physicians and patients alike have to monitor the expenses as there is no endpoint for treatment.

The potential role of nicotinamide 1000 mg daily in skin cancer prevention was assessed in a Phase 3 study known as ONTRAC ($N = 386$ patients) evaluated the risk of skin cancer developing in subjects aged 30–91 years with a history of two or more NMSC occurring over past 5 years. Overall, the investigators reported a reduced incidence of new skin CA by 23% vs. placebo after 1 year among high-risk patients. In addition, there was a reduction of new AKs by 11% at 3 months and 15% after 12 months. The proposed mechanism of action for this supplement in the role as possible chemopreventative agent included prevention of UV-induced ATP depletion, glycolytic blockade leading to enhance DNA repair, reduction of UV-induced immunosuppression. There were no reported vasodilatory side effects such as headache, flushing, itching, or measurable hypotension. Although not FDA approved for this indication, as an inexpensive option, nicotinamide may become an adjunct in long-term management strategies [43••].

Other similar compounds have been evaluated in uncontrolled trials. The role of oral vitamin D was summarized from 63 observational studies in relation to visceral cancer risk (30 colon, 13 breast, 26 prostate, and 7 ovarian cancer) and reviewed the association of vitamin D receptor genotype with increased potential for carcinogenesis. The correlation between cancer risk and a protective relationship was based on reported decreases in glutathione peroxidase and promotion of early UV-induced increases in superoxide dismutase and catalase [44]. In other reports involving the role of selenium, a causal linkage of low-plasma selenium levels to increased risk of NMSC in humans was observed primarily in a study of hairless mice examined the dietary selenium level and carcinogenesis. When exposed to UV doses of 90 mJ/cm^2, 3×/week for 20 weeks, all groups developed skin CA. However, a notable decrease in the incidence of tumors was observed for mice on 0.5 mg/kg of dietary Selenium. These studies have yet to be conducted in humans despite the reported benefits [45].

One of the more pivotal studies demonstrating the chemoprevention potential of PDT was conducted at the University of Minnesota. A group of 12 solid organ transplant patients at high risk for developing SCC was treated with ALA-PDT either monthly or every other month for 2 years with assays at 12 months and 24 months and measured in comparison with the number of SCCs that developed 1 year prior to initiation of the treatment cycle rather than against a placebo. The investigators found that after 12 months of treatment, there was a

79% reduction in SCC counts and 95% reduction after 24 months of this treatment cycle, suggesting a method for reducing the risk of tumor development with this or similar regimens [46]. A similar study was performed on immunocompetent patients evaluating development of AKs on the face and scalp, evaluating treatment with 20% ALA-PDT compared to PDT alone. Patients were treated on either side of a split face or scalp with either modality with two treatments 1 week apart then assessed for lesion counts at 3, 6, and 9 months as well as at the end in 1 year. At 1 year, there was an average amount of 30 new AKs counted on the patients treated with PDT alone compared to the ALA-PDT patients developing on average 14 AKs. The authors concluded that treatment suggests a possible preventative effect against NMSC formation in this high-risk group [47].

Conclusions

The considerations for treatment of actinic keratoses start with answers to some of the fundamental questions facing both patients and clinicians: Will they turn into SCC? Will they leave scars? Is it the disease or a symptom of a bigger disease of photodamage? And most importantly, is the treatment worse than the disease? These answers will help drive treatment options and long-term management strategies.

Compliance with Ethical Standards

Conflict of Interest Dr. Bhatia reports being a consultant and/or investigator for Actavis, Allergan, Anacor, Aqua, Bayer, Biofrontera, BiopharmX, Dermira, Dusa, Exeltis, Ferndale, Foamix, Galderma, Intraderm, ISDIN, LaRoche-Posay, Leo, Novan, Novartis, PharmaDerm, Promius, Regeneron, Sanofi, SunPharma, and Valeant.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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