SKIN

Clinical Management Recommendations

The Role of Field Cancerization in Selecting Therapies for Actinic Keratosis: An Expert Consensus Panel

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ABSTRACT

Background: Actinic keratosis is a very common disease that affects over 40 million people in the United States. In addition to the clinically visible lesion, patients may present with surrounding field cancerization based on their history of ultraviolet exposure. While lesion-directed therapy such as cryosurgery can effectively treat individual actinic keratoses it does not treat subclinical lesions or field cancerization.
Objective: To create consensus recommendations on the role of field cancerization in selecting appropriate therapy for actinic keratoses.
Methods: A comprehensive literature search of PubMed, Google Scholar, and Embase was conducted using the keywords “actinic keratos*,” “treatment,” and “field cancerization” for English-language original research articles without date restrictions. Articles were included that either discussed the role of FC in treating AKs or compared various AK field therapies. The relevant articles were then distributed to a panel of nine dermatologists with significant expertise in managing AKs. Each panelist reviewed the articles and assigned them a level of evidence based on Strength of Recommendation Taxonomy (SORT) criteria. The panel then convened on to discuss the studies and develop consensus statements on the role of FC in selecting AK therapy. The panel utilized a modified Delphi process to approve the adoption of each statement and gave each one a strength of recommendation based on SORT criteria.
Results: The initial literature search produced 243 articles that met search criteria. After a thorough screening of these articles for relevance to the research question, 21 articles were chosen to be reviewed by the panel and assigned a level of evidence. Of the 21 articles that were reviewed, the panel assigned level 1 evidence to three articles, level 2 evidence to six articles, and level 3 evidence to twelve articles. The panel created seven consensus statements related to AK management and FC. All seven statements received a unanimous (9/9) vote for adoption. Each of the statements was given a strength of recommendation according to sort criteria.

Conclusion: Field cancerization due to chronic ultraviolet exposure leads to subclinical AK lesions in addition to lesions that are clinically apparent. In order to address these lesions, field therapy is an important component of an adequate regimen and can be used in conjunction with lesion-directed therapy for optimal results.

INTRODUCTION

Actinic keratoses (AKs) are growths of epidermal keratinocytic dysplasia caused by chronic sun exposure.[1] AKs are very common, with an estimated prevalence of 40 million in the US and an estimated worldwide incidence of 1,928 per 100,000 person-years.[1,2] They have the potential to progress to invasive cutaneous squamous cell carcinoma (cSCC), which is the second most common skin cancer and caused approximately 9,000 deaths in the US in 2012 alone.[3,4] While the exact rate of progression from AK to invasive cSCC is unclear, there are studies that cite the lifetime risk to be as high as 16%.[5-7] Conversely, approximately 26% of AKs may spontaneously regress.[8] However, it is impossible to predict which lesions will regress and which will undergo malignant transformation. Therefore, it is important to treat AKs, especially those with high-risk features or in high-risk patients.[8-10]

Treatment for AKs is typically categorized as lesion-directed therapy or field-directed therapy. Lesion-directed therapy targets destruction of a single AK and includes modalities such as cryosurgery, laser therapy, curettage with electrodessication, and shave excision.[11] Field treatment targets widespread lesions and includes tirbanibulin, 5-fluorouracil (5-FU), imiquimod, diclofenac, and photodynamic therapy (PDT).[11] When creating a treatment plan for a patient with AKs, there are several important considerations in choosing the right therapy or combination of therapies. One important consideration is the concept of field cancerization (FC), which has been defined as multifocal clinical atypia characterized by AKs or cSCC in situ with or without invasive disease in a field exposed to chronic ultraviolet radiation (UVR).[12] The concept of FC was first described in 1953 after pathologic atypia was found in clinically normal tissue surrounding oropharyngeal carcinomas.[13] Since then, this concept has become widely accepted to occur in other tumors, including breast cancer, colon cancer, vulvar, cancer, and skin cancer.[12,14] In fact, cutaneous tissue is particularly susceptible to FC due to the chronic UVR exposure in sun-exposed areas.[12] However, FC is not a distinct diagnosis from AK and the consequences of not treating the field have not been widely described. The purpose of this study was for a panel of experts in AK management to review literature on FC and its role in AK pathogenesis and create consensus statements and recommendations on selecting optimal AK treatments to address this phenomenon.

METHODS

Literature Search and Study Selection

A comprehensive literature search of PubMed, Google Scholar, and Embase was conducted on January 15, 2024, using the keywords “actinic keratos*,” “treatment,” and “field cancerization” for English-language original research articles without date restrictions. Articles were included that either discussed the role of FC in treating AKs or compared various AK field therapies. The relevant articles were then distributed to a

panel of nine dermatologists with significant expertise in managing AKs. Each panelist reviewed the articles and assigned them a level of evidence based on Strength of Recommendation Taxonomy (SORT) criteria.[15] These levels include level 1 (good-quality patient-oriented evidence), level 2 (limited-quality patient-oriented evidence), or level 3 (other evidence such as consensus guidelines, usual practice, opinion, or disease-oriented evidence).[15]

Development of Consensus Statements

The panel then convened on February 15, 2024, to discuss the studies and develop consensus statements on the role of FC in selecting AK therapy. The panel utilized a modified Delphi process to approve the adoption of each statement.[16] This process requires a supermajority vote to adopt a statement via multiple rounds of real-time voting and has been frequently utilized to create expert recommendations in dermatology.[17-20] Of note, a level 2 or 3 designation does not necessarily indicate a poor study but is requisite for retrospective studies or review articles.

RESULTS

Literature Search and Study Selection

The initial literature search produced 243 articles that met search criteria. A thorough screening of these articles for relevance to the research question, 21 articles were chosen to be reviewed by the panel and assigned a level of evidence.

Levels of Evidence Designation

Of the 21 articles that were reviewed, the panel assigned level 1 evidence to three articles[21-23], level 2 evidence to six articles[24-29], and level 3 evidence to twelve articles[12,30-40] (**Table 1**).

Consensus Statements

The panel created seven consensus statements related to AK management and FC. All seven statements received a unanimous (9/9) vote for adoption. Each of the statements was given a strength of recommendation according to sort criteria (**Table 2**).

Statement 1: *When discussing actinic keratoses with patients, the concept of field cancerization and the associated risk of skin cancer should be presented. (SORT Level A)*

It is difficult to quantify the exact risk of an individual AK progressing to invasive cSCC, but it has been estimated to be 0.025% per year.[7] Extrapolation studies estimate the lifetime risk of a person with AKs developing an invasive cSCC to be as high as 16%.[7] One review of 165 cSCC cases found that 80% were contiguous with or arose in close proximity to AKs.[41] Furthermore, molecular data on AK development suggests that many of the cellular changes present within AKs are also seen in cSCCs, further supporting the association.[32] In order to underscore the importance of treating AKs, clinicians should discuss with patients this associated risk of invasice skin cancer. Even in patients that initially present with one or two visible AKs, there may be surrounding photodamage that can progress to AKs or cSCC. The risk factors for FC are similar to those for AK and cSCC, including fair skin, UV exposure, older age, male sex, and immunosuppression.[9] By discussing the concept of FC, patients can better understand the spectrum of keratinocyte carcinogenesis that includes photodamage, AKs, and cSCC. This concept will also help explain why new AKs are likely

Table 1. SORT criteria level of evidence for reviewed articles.

Article	Level of Evidence
Blauvelt A, Kempers S, Lain E, et al. Phase 3 Trials of Tirbanibulin Ointment for Actinic Keratosis. N Engl J Med. 2021;384(6):512-520.	1
Gupta AK, Paquet M. Network meta-analysis of the outcome 'participant complete clearance' in nonimmunosuppressed participants of eight interventions for actinic keratosis: a follow-up on a Cochrane review. Br J Dermatol. 2013;169(2):250-259.	1
Piacquadio D, Houlihan A, Ferdon MB, Berg JE, Marcus SL. A Randomized Trial of Broad Area ALA-PDT for Field Cancerization Mitigation in High-Risk Patients. J Drugs Dermatol. 2020;19(5):452-458.	1
Jansen MHE, Kessels JPHM, Nelemans PJ, et al. Randomized Trial of Four Treatment Approaches for Actinic Keratosis. N Engl J Med. 2019;380(10):935-946.	2
Lampley N 3rd, Rigo R, Schlesinger T, Rossi AM. Field Therapy for Actinic Keratosis: A Structured Review of the Literature on Efficacy, Cost, and Adherence. Dermatol Surg. 2023;49(2):124-129.	2
Micali G, Verzì AE, Barresi S, Dirschka T, Lacarrubba F. Field cancerization in clinically solitary actinic keratosis: A pilot study. Dermatol Ther. 2021;34(1):e14607.	2
Rajkumar JR, Armstrong AW, Kircik LH. INDIVIDUAL ARTICLE: Safety and Tolerability of Topical Agents for Actinic Keratosis: A Systematic Review of Phase 3 Clinical Trials. J Drugs Dermatol. 2021;20(10):s4s4-s14. doi:10.36849/JDD.M1021	2
Schlesinger, T., Kircik, L., Del Rosso, J., Rigel, D., Lebwohl, M., Berman, B., Armstrong, A., Bhatia, N., Patel, V. A., Narayanan, S., Koscielny, V., & Kasujee, I. (2023). Clinician- and Patient-Reported Outcomes with Tirbanibulin 1% Treatment for Actinic Keratosis in Routine Clinical Practice Across the U.S. (PROAK Study). SKIN The Journal of Cutaneous Medicine, 7(3), 771–787.	2
Worley B, Harikumar V, Reynolds K, et al. Treatment of actinic keratosis: a systematic review. Arch Dermatol Res. 2023;315(5):1099-1108.	2
Willenbrink TJ, Ruiz ES, Cornejo CM, Schmults CD, Arron ST, Jambusaria-Pahlajani A. Field cancerization: Definition, epidemiology, risk factors, and outcomes. J Am Acad Dermatol. 2020;83(3):709-717.	3
Cornejo CM, Jambusaria-Pahlajani A, Willenbrink TJ, Schmults CD, Arron ST, Ruiz ES. Field cancerization: Treatment. J Am Acad Dermatol. 2020;83(3):719-730.	3
Dirschka T, Gupta G, Micali G, et al. Real-world approach to actinic keratosis management: practical treatment algorithm for office-based dermatology. J Dermatolog Treat. 2017;28(5):431-442.	3
Eisen DB, Asgari MM, Bennett DD, et al. Guidelines of care for the management of actinic keratosis. J Am Acad Dermatol. 2021;85(4):e209-e233.	3
Eisen DB, Dellavalle RP, Frazer-Green L, Schlesinger TE, Shive M, Wu PA. Focused update: Guidelines of care for the management of actinic keratosis. J Am Acad Dermatol. 2022;87(2):373-374.e5.	3
Goldenberg G. Treatment considerations in actinic keratosis. J Eur Acad Dermatol Venereol. 2017;31 Suppl 2:12-16.	3
Han, H., & Berman, B. (2022). Clinical Management of Actinic Keratosis: Review and Update. SKIN The Journal of Cutaneous Medicine, 6(4), 274–285.	3
Figueras Nart I, Cerio R, Dirschka T, et al. Defining the actinic keratosis field: a literature review and discussion. J Eur Acad Dermatol Venereol. 2018;32(4):544-563.	3
Pariser DM. Approaches to Field Therapy for Actinic Keratoses: Relating Clinical Trial Results to Real-world Practice-A Commentary. J Clin Aesthet Dermatol. 2022;15(4):40-43.	3
Sinclair R, Baker C, Spelman L, Supranowicz M, MacMahon B. A review of actinic keratosis, skin field cancerisation and the efficacy of topical therapies. Australas J Dermatol. 2021;62(2):119-123.	3
Stockfleth E. The importance of treating the field in actinic keratosis. J Eur Acad Dermatol Venereol. 2017;31 Suppl 2:8-11.	3
Zakria, D., Armstrong, A., Berman, B., Del Rosso, J., Lebwohl, M., Schlesinger, T., & Rigel, D. (2023). The Importance of Medication Adherence in the Treatment of Actinic Keratosis: An Expert Consensus Panel. SKIN The Journal of Cutaneous Medicine, 7(3), 752–763.	3

Table 2. Consensus statements adopted by the panel.

Statement	Strength of Recommendation	Consensus Vote
When discussing actinic keratoses with patients, the concept of field cancerization and the associated risk of skin cancer should be presented.	A	9/9
Patients with actinic keratosis may require ongoing prevention and treatment.	A	9/9
Clinicians should consider treating both clinically apparent actinic keratoses and subclinical lesions that are likely present in surrounding skin.	C	9/9
When multiple actinic keratoses are present, both lesion-directed and field-directed therapy should be considered. There is no specific treatment order when using both, but the patient presentation, skin cancer history, and medical history should be considered.	C	9/9
Field-directed therapy could be considered first line for treating diffuse actinic keratoses, severe photodamage, areas at risk for scarring or dyschromia with lesion-directed therapy, or high-risk patients.	C	9/9
Patient preferences for appropriate therapy should be considered when choosing the optimal actinic keratosis regimen.	B	9/9
When assessing the overall efficacy of treatments for actinic keratosis, tolerability is an important consideration.	B	9/9

to appear in the future, especially after lesion-directed therapy is used.

Statement 2: *Patients with actinic keratosis may require ongoing prevention and treatment. (SORT Level A)*

AKs are a chronic disease that often recur.[31] A systematic review found that after spontaneous regression, lesions had a 15-53% recurrence rate.[42] Even with treatment, recurrence rates can be material and necessitate multiple rounds of therapy.[24] Additionally, patients that have had high amounts of UV exposure are likely to have several AKs emerge over a period of years, even after risk factors are mitigated. In one study of ten patients seeking to quantify field cancerization, 7/10 patients developed new, subclinical lesions two weeks after treatment with imiquimod and 9/10 patients developed new lesions within 4 weeks of treatment.[26] In a randomized clinical trial of 932 veterans at high risk for keratinocyte carcinoma, a 2- to 4-week course of topical 5-FU applied twice daily to the face and ears reduced the risk for 1 year of cSCC requiring surgery at those sites by 75%.[43] However, no effect was seen over the course of 4 years, suggesting that there may be a role for annual therapy in high-risk groups. The emergence of new AKs is an important component of counseling patients and further reinforces the concept of FC. Understanding that the formation of new lesions may not represent treatment failure and is often a part of the natural history of AKs can help patients become more committed to AK management.

Statement 3: *Clinicians should consider treating both clinically apparent actinic keratoses and subclinical lesions that are likely present in surrounding skin. (SORT Level C)*

The panel emphasized the value of treating both visible AKs and subclinical lesions that are present in surrounding photodamaged skin. The literature also states that treating the field reduces AK burden as well as the number of new cSCCs.[43-45] Data suggests that field-directed therapy is able to effectively reduce subclinical damage, as identified by reflectance confocal microscopy.[46,47] Since, even a single AK can be a marker of FC, there may be benefits in treating the entire field in any patient that presents with AK.[34] However, the benefit and convenience of field therapy certainly increases in patients with multiple AKs.

Statement 4: *When multiple actinic keratoses are present, both lesion-directed and field-directed therapy should be considered. There is no specific treatment order when using both, but the patient presentation, skin cancer history, and medical history should be considered. (SORT Level C)*

The benefit of field-directed therapy increases when multiple AKs are present. However, the panel emphasized that field-directed therapy and lesion-directed therapy should not be considered in isolation. A combination of the two types of treatment can be the optimal choice when patients present with multiple lesions. Cryosurgery is the mainstay of lesion-directed therapy but can be associated with adverse effects such as erythema, pain, blistering, and hypochromia.[11] For patients that present with multiple AKs, cryosurgery may be inconvenient and difficult to tolerate. In these situations, a combination of cryosurgery and field-directed therapy would be beneficial. Efficacy can also improve by using a combination of treatments. Studies have reported a percent clearance of AKs of 73.6% at 6-12 months after treatment with cryosurgery alone.[29] However, adjunctive treatment with 0.5% 5-FU for 7 days increased the efficacy of cryosurgery by a mean of 13.3 +/- 8.8%.[29] Additionally, one study found that recurrence rates after 12 months were lower after combination treatment with ingenol mebutate and cryosurgery compared to cryosurgery alone (38.9% vs 69.%).[48] This data supports the benefit of combining lesion-directed therapy with field-directed therapy.

While there is a benefit to using both field-directed and lesion-directed therapy, there is no consensus on a specific order. Some members of the panel noted that they prefer to use cryosurgery on clinically apparent, hyperkeratotic AKs and then use field therapy to eradicate remaining lesions and treat subclinical damage. Others use this strategy and then perform an additional round of cryosurgery on any remaining visible lesions after field treatment. A few others stated that the regimen they choose depends on the presentation of the patient. Several studies in the literature support these approaches but ultimately leave it to the discretion of the clinician.[29,31,34]

Statement 5: *Field-directed therapy could be considered first line for treating diffuse actinic keratoses, severe photodamage, areas at risk for scarring or dyschromia with lesion-directed therapy, or high-risk patients. (SORT Level C)*

There are a few scenarios where field-directed therapy can be considered first line. When there are numerous diffuse AKs, lesion-directed therapy can be cumbersome. Additionally, the presence of diffuse AKs

significantly increases the probability of FC, making field-treatment much more effective for reducing the risk of developing cSCC. Additionally, if a patient presents with a few solitary AKs but they have a history of significant UV exposure and evidence of severe photodamage, field therapy may be more appropriate than lesion-directed therapy alone. Patients who have a high risk of developing keratinocyte carcinomas should also be considered for field therapy. This includes patients with a prior history of skin cancer, immunosuppressed patients, and older patients.[9] Additionally, lesion-directed therapy such as cryosurgery can cause dyschromia and scarring, especially in skin of color.[35] In cosmetically sensitive areas, field-directed therapy may be preferred to avoid this risk.

Statement 6: *Patient preferences for appropriate therapy should be considered when choosing the optimal actinic keratosis regimen. (SORT Level B)*

In addition to the clinical presentation, patient preferences are an important consideration when selecting an optimal AK regimen. Each AK therapy varies in the duration of treatment, local skin reactions (LSRs), and tolerability. Additionally, patients may have experience with prior treatments. These points should all be discussed with the patient so that a shared decision can be made. For example, if a patient with diffuse AKs on the face presents a week before they have an important social event, they likely will not want to use 5-FU given the likelihood of severe erythema that can result. On the other hand, if a patient only has a few solitary AKs but previously was unable to tolerate cryosurgery, suggesting this option may be inappropriate.

Statement 7: *When assessing the overall efficacy of treatments for actinic keratosis, tolerability is an important consideration. (SORT Level B)*

An important component of treatment efficacy in the management of AKs is compliance.[40] Patients who cannot tolerate the LSRs that come with a given therapy are unlikely to be adherent. Poor adherence consequently decreases the efficacy of AK treatments and increases the risk of cSCC development. Each field treatment is associated with certain LSRs. The most common LSRs caused by 5-FU are erythema, blistering, and erosions.[35] The most common LSRs seen with imiquimod are erythema, ulceration, blistering, erosion, and edema.[49] In the clinical trials for tirbanibulin, the most common adverse effects were mild treatment site pain and pruritus, which were reported to regress spontaneously.[21] Several real-world studies have demonstrated the tolerability of tirbanibulin. A multi-center observational study of 250 patients that were treated with tirbanibulin for 5 days found that only 7 (2.8%) patients had grade 4 adverse events. In another study of clinician- and patient-reported outcomes, 73.9% of patients and 89.2% of clinicians felt that tirbanibulin had a shorter duration of skin reactions than previous field treatments.[28] Additionally, 91% of clinicians and 76.6% of patients reported that tirbanibulin had milder skin reaction severity than prior field treatments.[28] The tolerability of tirbanibulin makes it more likely that patients will be compliant with therapy and effectively eradicate their AKs.

CONCLUSION

Actinic keratoses are a common neoplasm encountered in the dermatology clinic and adequate treatment is essential to reduce the subsequent development of invasive keratinocyte carcinomas. While both lesion-directed therapy and field-directed therapy

can be very effective, only field-directed therapy is able to treat subclinical lesions and reduce FC. A combination of lesion-directed therapy and field-directed therapy may be necessary for certain patients, and clinicians should consider the risk of FC as well as duration of treatment, LSRs, tolerability, lesion characteristics, medical history, and patient preferences when selecting the optimal treatment.

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