CLINICAL MANAGEMENT RECOMMENDATION

Considerations in the Management of Actinic Keratosis: The Importance of Adherence and Persistence to Therapy

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ABSTRACT

Background: Actinic keratosis (AK) is a pre-malignant lesion with a poorly defined risk of progression to invasive squamous cell carcinoma (SCC). AKs are also associated with increased future risk of invasive SCC. However, there are many barriers to therapy adherence that may affect long-term treatment efficacy.

Objective: To review the current literature reporting known known factors of AK treatment non-adherence intrinsic to patient behavior and treatment regimens and re-examine how dermatologists can navigate these challenges.

Methods: A Medline literature search was performed to identify existing evidence regarding barriers to adherence with AK treatment regimens intrinsic to patient behavior, patient counseling, and treatment regimens pertinent for review.

Results & Discussion: Factors intrinsic to prescribed patient-applied therapy that can exacerbate non-adherence include: 1) length of treatment duration, 2) frequency of application, 3) complexity of treatment regimen, 4) duration and 5) severity of local skin reactions (LSR) and adverse reactions. Novel mechanisms of action that induce cellular apoptosis (as opposed to necrosis) via inhibition of tubulin polymerization and cell cycle arrest, may promote treatment regimen adherence and long-term outcomes. Dermatologists should also be conscious of how they counsel patients as insufficient counseling may also lead to poor adherence.

Conclusion: Dermatologists must understand the value of shorter course therapies and their positive impact on adherence and be well-versed in the mechanisms, efficacy and adverse events associated with treatment options. By doing so, dermatologists may best counsel and educate patients and devise regimens that address individualized patient concerns.

INTRODUCTION

Adherence can defined as how closely a patient follows and executes a prescribed treatment regimen.[1,2] This includes (but is not limited to) factors such as obtaining the medication, completing the entirety of a treatment course (persistence), utilizing the medication at the appropriate frequency and dose, and properly implementing the route/location of administration.[1-4] Even after successfully obtaining a medication, adherence can be compromised by the

length of treatment, the complexity of a regimen, perceived (relative) lack of improvement, as well as duration and severity of adverse events, such as local skin reactions.[3,4] Unfortunately, in a real-world setting, a patient's adherence to therapy is as important, if not more so, than the efficacy and mechanism of action of the chosen regimen in achieving optimal long-term outcomes. These barriers can be amplified when managing chronic dermatoses as patients must adhere to repeated, regular treatments over the course of months or years. Furthermore, future repeat cycles of therapy may be negatively impacted by current severe local skin reactions. These negative experiences may color patients' perceptions of AK management and affect their risk-benefit analyses future therapy.

Actinic keratoses (AK) are likely one of the most prevalent skin diseases treated by dermatologists, accounting for over 14% of all dermatology visits and upwards of $3.1 billion in annual healthcare expenditures.[5,6] These pre-malignant lesions arise from decades of actinic and ultraviolet damage leading to field cancerization. The presence of a single AK therefore likely suggests the presence of many subclinical actinic keratoses in evolution. AKs are also known to have the potential to progress into invasive cutaneous squamous cell carcinoma (cSCC).[7-11] Unfortunately, there are no universally accepted clinical factors and few histopathological signs to indicate which AK has the 0.025-16%[12] risk of progression to invasive SCC and therefore all AKs require medical evaluation and management.

Because of the chronic nature of AK pathophysiology as well as the need for their treatment, long-term efficacy of therapy relies not only on mechanism of action but also the adherence to the prescribed treatment regimen.

METHODS

A review of the literature pertaining to the epidemiology, natural history, prognosis, management of AK as well as the mechanism of action of and adherence to current and impending patient-applied AK therapy was conducted. The goal of this search was to evaluate the literature for barriers to adherence intrinsic to patient behavior, patient counseling, and treatment regimens. The Medline database was queried for all relevant articles published between 1980 and 2021 using exploded MeSH terms and keywords pertaining to the following themes: diagnosis, prognosis, and epidemiology, risk factors, squamous cell carcinoma, therapy. The Boolean term "AND" was used to find the intersection of these themes with the term "actinic keratosis."

RESULTS & DISCUSSION

The State of Patient-applied Field Therapy for Actinic Keratoses

Aside from prevention and sun-protective measures, there are two overarching principles for treating AKs: lesion-directed therapy and field therapy.[13] Lesion-directed therapy are office-based, dermatologist-administered treatments such as cryosurgery, surgery, chemical peel, or laser that primarily target single, clinically visible AKs.[14,15] These treatments are often complemented and augmented by field therapy such as photodynamic therapy (PDT) or at-home, patient-applied therapies that treat both clinically-visible and subclinical AKs.[3,4,14-16] Field therapy is important in managing AKs between office visits given the likelihood of subclinical

lesions in the setting of field cancerization and chronic nature of AKs and actinic damage.[17-20]

Current field-therapies rely on either disrupting cell signaling, halting cellular division or stimulating the immune system to detect and destroy atypical cells.[21] While there are multiple pathways that these therapies utilize, they function by either primarily or secondarily stimulating local (and in the case of imiquimod, also systemic) inflammation.[14,21] Agents such as 5-fluorouracil(5-FU), which interferes with DNA replication, applied over 2-6 weeks, can induce significant inflammation, leading to cellular necrosis, to treat AKs.[14,22,23] In a less severe fashion, imiquimod, which augments the immune system to induce inflammation, applied over 4-16 weeks, can lead to a less robust inflammatory response that also utilizes necrosis in subacute and chronic AK management.[14,22,23] However, these mechanisms that utilize necrosis can induce moderate to severe local skin reactions (LSR), including varying degrees of painful erythema, crusting, and erosions in up to 90% of patients that may last several weeks.[3,24,25] Conversely, agents that are thought to treat AKs by promoting apoptosis, such as diclofenac (which inhibits epidermal COX-2 expression) lead to negligible LSRs, with the caveat that treatment requires 60-90 days of continual twice daily application.[3,22,26,27]

Barriers to Effective Field Therapy For AK

While there are few head-to-head definitive trials to assess the relative (real-world) efficacy of various field therapies, recent meta-analyses have suggested there is a hierarchy of AK treatment efficacy.[3,14,22] Therapeutic agents that induce more inflammation (and LSRs) tend to have greater efficacy. Unfortunately, prior studies have also demonstrated that patients are more than willing to tolerate increased risk of developing skin cancer and potential improvements in the appearance of their skin if it means minimizing the inconvenience of treatment by reducing the 1) severity of local skin reactions, 2) length/frequency of treatment, and 3) eliminating systemic symptoms.[28] Given current available patient-applied home therapies, selecting an optimal agent requires balancing ideal efficacy with potential patient non-adherence with treatment application.

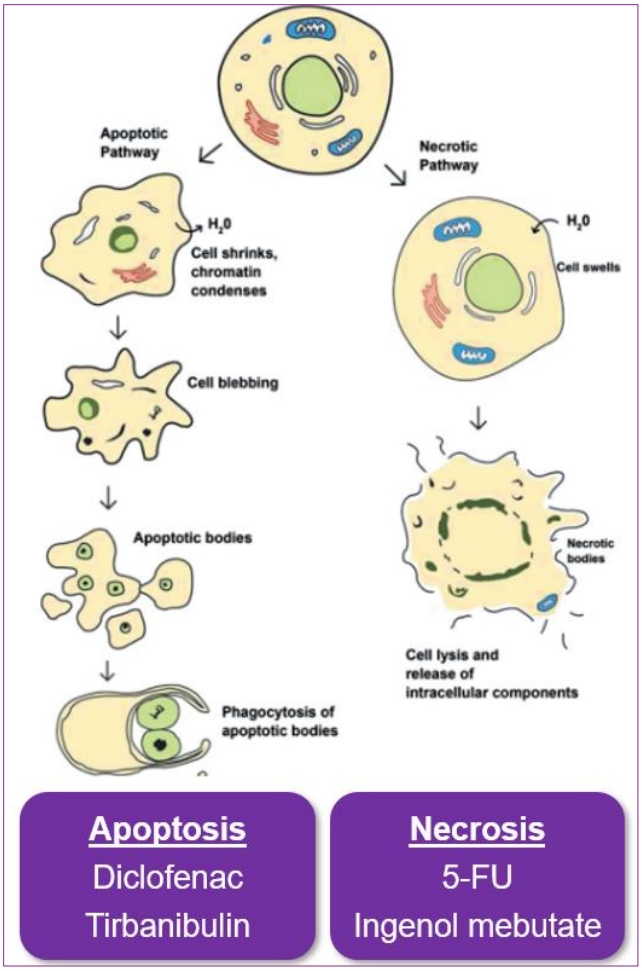

Figure 1. Apoptosis versus necrosis. Agents such as diclofenac and tirbanibulin induce apoptosis which minimize inflammation and local skin reactions relative to necrosis-induced inflammation from 5-fluorouracil or ingenol mebutate.

Choosing a regimen is further complicated when considering the chronic nature of actinic damage and AKs. Given the accumulated chronic actinic damage will only produce more AKs (and other skin cancers) with time demanding prolonged recurrent (and necessary) treatment, dermatologists must also consider how a patient's experience with treatment will affect their adherence to future therapies, and therefore the overall, long-term outcomes associated with each regimen.

Advancements in Patient-Applied Treatment for Actinic Keratoses

Studies suggest that shorter course therapies[16] that are less cumbersome[29] may be more practical for patients and result in improved adherence, and therefore, improved real-world efficacy. Studies have attempted to combine available therapies in hopes of synergistically improving efficacy and reducing duration/frequency of application.[30] However, combinations such as 5-FU and calcipotriene, though potentially more efficacious than 5-FU alone based on the limited data available, also lead to increased rates of intolerable, dose-limiting LSRs.[30]

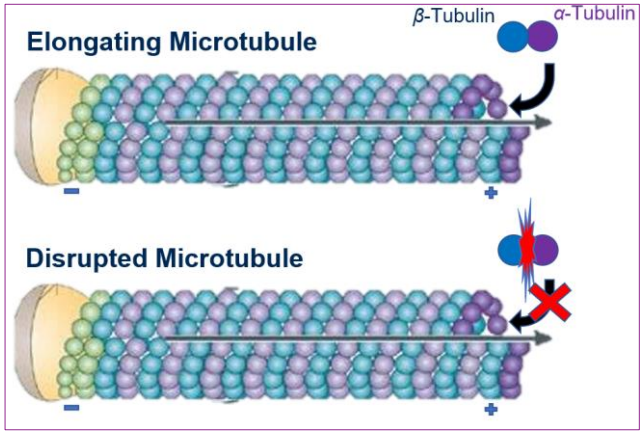

Figure 2. Tirbanibulin's mechanism of action. Microtubule polymerization requires α-tubulin and β-tubulin dimerization. Tirbanibulin inhibits tubulin dimerization thereby leading to cell-cycle arrest and apoptosis.

Advances in our understanding of keratinocyte dysplasia have yielded new small molecules capable of inducing apoptosis with minimal inflammation.[31,32] In vitro studies have demonstrated that KX2-391 (tirbanibulin) specifically targets rapidly dividing cells and, by reversible-binding of microtubules essential to cellular division, prevents polymerization of tubulin thereby leading to cell-cycle arrest and apoptosis.[31,32] Tirbanibulin may also exert anti-tumor activity by disrupting a non-receptor tyrosine kinase, the proto-oncogene Src kinase.[31]

Clinical trials have shown after only 5 consecutive days of daily tirbanibulin application to the face and scalp, participants noticed continued AK clearance through day 57 with 40-50% with 100% clearance.[33-35] At 12-month follow up, not only were there no notable adverse effects, but 42% of participants had no recurrence of originally treated AKs.[34,35] Perhaps more importantly from an adherence standpoint, studies have shown that LSRs were mild-moderate, peaked within 8 days of first application and resolved entirely within 15-29 days.[33-35] Taken together these data suggest inhibition of tubulin polymerization provides an efficacious way to treat AKs that also mitigates unpleasant adverse effects of contemporary AK treatments and its shorter course may also further improve adherence to therapy.

The Importance of Actinic Keratosis Therapy and Patient Counseling

Studies have also demonstrated the importance of the semantics and wording used during patient counseling had a significant effect in patients' decision-making regarding AK treatment.[36] A significantly larger proportion of participants opted for treatment when told "AKs are precancers" or had the potential for malignant

transformation compared to when were more optimistically counseled by highlighting the chance of regression.[36]

More recent meta-analyses of field therapies have determined there may in fact be a hierarchy of efficacy.[3,14] It is important that physicians are aware of both the efficacy of treatment and severity of local skin reactions and other adverse events so that they can provide focused counseling for patients. Dermatologists may consider off-label modifications and adjunctive therapies (such as steroidal and non-steroidal anti-inflammatory agents, moisturizers and emollients, topical antibiotics, and anti-pruritic agents) to mitigate LSRs with the caveat that there is limited evidence for their use.[37] By being able to combine evidenced-based regimens with patient-centered values, dermatologists may potentially maximize long-term compliance and therefore achieve (near-)ideal outcomes regarding AK care.[38]

CONCLUSION

AKs are a chronic condition with a still poorly defined potential for progression into invasive SCC. Because of the overall chronic nature of AKs and actinic damage, adequate treatment requires a combination of recurrent Dermatologist-administered office treatment and continual patient-applied home therapies. To achieve ideal outcomes, Dermatologists must understand the value of shorter course therapies and their positive impact on adherence and be well-versed in the mechanisms, efficacy and adverse events associated with treatment options so they may best counsel and educate patients as well as devise regimens that address individualized patient concerns. In this way, Dermatologists can potentially maximize adherence to therapy and improve long-term patient outcomes.

Conflict of Interest Disclosures: JWM has no relevant disclosures. **JDR** serves as a research investigator, speaker, and consultant for Almirall, Bausch Health (Ortho Dermatology), and Sun Pharma and a consultant for Biofrontera. **NB** has affiliations with Abbvie, Almirall, Biofrontera, BMS, BI, EPI Health, Ferndale, Foamix, Galderma, InCyte, ISDIN, J&J, LaRoche-Posay, Leo, Lilly, Ortho, Pfizer, P&G, Regeneron, Sanofi, SunPharma, Vyne, and Vyome. **DSR** served as an advisory board member for Almirall, Inc.

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