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The Evolving Management of Actinic Keratoses

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Abstract Dermatologists agree that due to the risk of progression to non-melanoma skin cancer, the treatment of actinic keratoses is warranted, however no consensus exists on a preferred treatment modality. While cryotherapy is the most widely utilized treatment for actinic keratoses, the increasing understanding of field cancerization has revealed that this approach misses the forest for the trees so to speak. The pathophysiology and treatment of actinic keratoses (AK), from lesion-directed to field-directed, was expertly discussed in two continuing education webinars available at the *Journal of Drugs in Dermatology* online. The recorded sessions entitled, *Actinic Keratosis: Current Understanding of Pathophysiology and Therapeutic Targets* by Dr. Brian Berman, as well as *Actinic Keratosis: Therapeutic Options and Evolving Considerations* by Dr. James Q. Del Rosso stress the importance of increased utilization of topical field therapies to treat both clinically evident and subclinical AKs present in the adjacent regional skin. AK treatment commonly results in anticipated sequelae, depending on the modality used, including erythema, crusting, vesiculation, pustulation, and erosion, so emphasis should be placed on minimizing the magnitude and duration of adverse events while maximizing efficacy. Attention was paid to the newest addition to the topical field therapy armamentarium, tirbanibulin, a tubulin and Src kinase inhibitor, and its efficacy and safety were reviewed.

Introduction

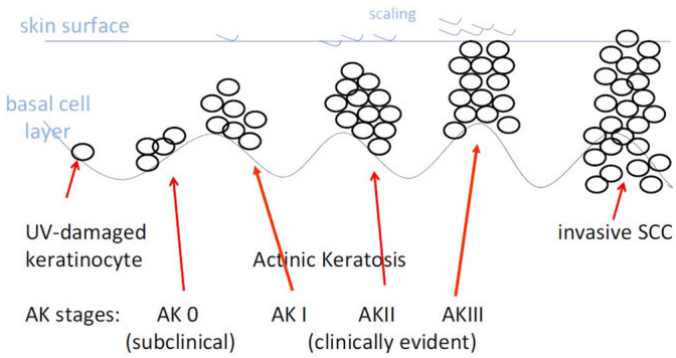
Playing whack-a-mole triggers a transient dopamine surge every time a participant hammers down one of the rodents, but no matter how much effort, the goal of clearing the board always seems to appear just out of reach—by design. Dermatologic practitioners have unwillingly found themselves playing a similar form of this game with actinic keratoses (AKs) when using lesion-directed therapies, especially in lighter skin patients with chronic sun exposure. AKs are rough erythematous papules resulting from significant ultraviolet radiation (UV) exposure and are associated with increased risk for development of non-melanoma skin cancer (NMSC), most notably squamous cell carcinoma (SCC). Prevalence of AKs in the US is 1.77% for patients between 50 and 59, 4.61% for patients between 60 and 69, 9.38% for patients between 70 and 79, and 14.57% for patients ≥80.[1]

The current understanding and therapies for AKs were skillfully discussed by Dr. Brian Berman, Co-Director of the Center for Clinical and Cosmetic Research and voluntary faculty of the Department of Dermatology and Cutaneous Surgery at the University of Miami during his continuing education webinar, *Actinic Keratosis: Current Understanding of Pathophysiology and Therapeutic Targets* available through the JDD online. Dr. Berman noted that the number of AKs a patient has is correlated with the risk of developing SCC such that someone with one-to-five AKs has a RR of 1.7 (0.4, 6.5), and someone with over twenty AKs has a RR of 11.0 (2.6, 46.6). One study examined a population of veterans to monitor what would happen if an AK was left without treatment and one year later 0.6% progressed to SCC compared to 2.57% after four years.[2,3] Few new entrants to the AK treatment arsenal have been approved in the past decade as Dr. James Q. Del Rosso, Research Director of JDR Dermatology Research in Las Vegas, Nevada and Senior Vice President of Clinical Research and Strategic Development at Advanced Dermatology and Cutaneous Surgery in Maitland, Florida, conveyed in his continuing education webinar, *Actinic Keratosis: Therapeutic Options and Evolving Considerations.* Drs. Berman and Del Rosso both reviewed tirbanibulin as the newest and possibly the most tolerable treatment for AKs.

Historically, clinicians only treated what they could see, also known as lesion-directed therapy, but more recently there has been a shift to a more comprehensive approach to address the entire area of actinic damage with field-directed therapies.[4]

To highlight the importance of this point, Dr. Berman referenced a study in which normal appearing skin between two clinically apparent AKs demonstrates histologic evidence of AK and therefore argued that, although not clinically evident, microscopic disease is present and could pose malignant potential.[5,6] Dr. Berman also cited a study that compared the incidence of various classifications of AKs in proximity to an SCC; intuitively one might consider that more clinically apparent AKs would be identified in perilesional biopsies of SCCs, however the authors determined that lower grade AK1s are found overlaying an SCC 63.8% of the time, compared to 17.9% for AK2s and 18.4% for AK3s (Figure 1).[7,8] Although a larger, scalier, and more eye catching AK may appear higher risk, these studies together argue that lower grade AKs and perilesional skin must not be forgotten during treatment.

Figure 1. The spectrum of AKs to SCC. AKs are graded histologically into three categories with AK3s most closely resembling SCCs. *Reprinted with permission from Dermatologic Therapy, by D. Kopera, 2020, p. 2. Copyright 2020 by Wiley.*



Drs. Berman and Del Rosso conveyed that data on field cancerization supports that perilesional skin of an AK is comparably at risk for mutations and dysplastic cells even if no clinical evidence is apparent visibly, even with a dermatoscope. Clinicians have for some time utilized field therapy with numerous and chronic AKs, often combining with lesion directed therapy.[3,5] The combination of lesion-directed and field therapies together has shown to provide more efficacious treatment of AKs and therefore prevention of SCCs.[9,10] However, the shift toward field therapy is happening far too slowly, in fact, one study found that from 2009–2016 50.8% office visits for AKs resulted in treatment with cryotherapy, and field therapy accounting for only 3.2%.[11] There is a need to increase awareness and utilization of field therapy for AKs in an effort to improve the standard of care and benefit to patients.

Pathophysiology of AKs

DNA repair mechanisms aim to prevent aberrant cells from proliferating and causing local tissue damage or even death. However, those mechanisms can falter with cumulative UV

exposure to keratinocytes throughout one's lifetime. Dr. Berman explained the pathophysiology of AKs and their transformation to SCC by describing that UV exposure increases oxidative stress, which initially causes a reversible mutation in the p53 tumor suppressor gene. Additional UV exposure then reversibly mutates the RAS proto-oncogene, which is crucial for cell growth, differentiation, and development. At this stage, a clinically apparent AK is likely present. Further UV exposure irreversibly mutates the p16 tumor suppressor gene, which is then characteristic of SCCs. This spectrum is correlated with disorganized hyperproliferation of keratinocytes and invasive SCC as a result. Many additional variables go into whether one is at risk for AKs including genetics, exposure, skin type, and those with existing defects in DNA repair enzymes, but mutations in p53, RAS, and p16 are among the most common and traceable along the progression to SCC[12,13] Drs. Berman and Del Rosso stressed the chronic nature of AKs and highlighted that effective treatment often requires repeated use of one or more therapies and that continued surveillance for malignancy is always warranted.

Therapeutic Options for AKs

Treatment for AKs includes photoprotective measures, chemopreventative supplements, as well as lesion-directed treatment and field therapy. Photoprotective measures include sensible avoidance, sunscreen, and protective attire. Polypodium leucotomas extract is a natural supplement with published safety data and appears to show some evidence of reducing UV induced damage, however, supplements in the US are not regulated by the FDA, so independent research is recommended for products containing polypodium leucotomas extract which are supported by recognized scientific data published in peer-reviewed literature.[14]

Drs. Berman and Del Rosso both emphasized that higher risk patients with prior skin cancers can benefit from chemoprevention with Vitamin B3, nicotinamide (NAM), 500mg twice daily. One study found NAM was associated with a 13% reduction in AKs, 23% reduction in NMSC, and 30% reduction in SCC as compared to the placebo group after one year. NAM works by replenishing NAD+ stores in the cell as well as inhibiting PARP-1 and sirtuins, which normally act to suppress p53 tumor suppressor gene. The study found a significant causal relationship between NAM and reducing skin cancer in those who have had one previously, but theoretically the mechanism would be similar in someone who is yet to have an AK or NMSC.[15,16]

Lesion-directed therapy is recommended for patients with few AKs and consists of cryotherapy, photodynamic therapy (PDT), and much less commonly, intralesional 5-fluourouracil (5-FU).

Cryotherapy rapidly freezes the exposed cells to subzero temperatures, usually with liquid nitrogen, which forms ice crystals in the cells and extracellular matrix effectively lysing the cells. Upon thawing, rapid shift in ions like calcium and potassium further damage the surviving and some adjacent cells.[17] While many assume cryotherapy is effective, one study found that AKs are 72% likely to recur in the same spot compared to 54% for topical 5-FU, and 73% for imiquimod.[18] Cryotherapy also poses the risk of dyspigmentation and scarring, especially in darker skin types.[19]

Dr. Berman mentioned that PDT is FDA approved as a lesion-directed therapy of AKs, but in practice, methyl aminolevulinic acid (MLA) or aminolevulinic acid (ALA) are generally applied to a field like the face or scalp. Dysplastic cells will selectively convert MLA or ALA into photoporphryin IX in their mitochondria during a brief incubation time. A blue or red light is then shined on the affected area for sixteen minutes and forty seconds and the photons are selectively absorbed by photoporphryin IX in the dysplastic cells that later undergo apoptosis.[19] LSRs from one large study with PDT include erythema in 89% of patients, crusting in 9% and pustules in 6%.[20,21]

5-FU is a thymidylate synthase inhibitor that acts as an antimetabolite stopping the growth of rapidly proliferating cells and is also directly cellular toxic. Intralesional 5-FU is effective against AKs and SCC, but due to its cellular toxicity 5-FU can cause marked pain, erythema, scaling, pruritus, and even necrosis. 5-FU is more commonly applied topically than intralesional due to the difficulty in treating the remaining field as well as the significantly associated adverse events associated with intralesional 5-FU including erythema, pustulation, and necrosis.[22]

Drs. Berman and Del Rosso agree that if that lesion-directed or field therapy do not resolve an AK, a biopsy should be considered as any lesion that has been treated with a less invasive modality multiple times without resolution has an increased risk for SCC. Benefits of a biopsy include diagnosing a possible SCC, regression of a remaining AK, or even revealing a different unexpected diagnosis.

Field therapy is recommended for patients who have numerous AKs such that lesion-directed therapy would be too numerous, painful, and not cost effective. Field cancerization argues that patients with one AK would benefit from topical field therapies, which consist of 5-FU, imiquimod, diclofenac, and now tirbanibulin. Each field therapy interestingly has a unique mechanism of action and therefore requires varying application durations, and subsequently varying intensity of adverse events. Some clinicians have reported success with chemical peeling agents and ablative lasers to treat and prevent AKs however these have not been FDA approved for this indication.[8]

5-FU, as discussed previously, is a toxic antimetabolite that stops growth of rapidly proliferating cells and must be applied once or twice daily for two-to-four weeks for full effect. The topical form has been approved in 0.5%, 0.1%, as well as 5% in creams and solutions. A recent study comparing four field therapies found that 5-FU performed the best at reducing total AKs such that 74.7% of patients achieved 75% reduction in AKs one year following treatment.[23] One study found that 0.5% 5-FU cream once daily was as effective as 5% 5-FU cream twice daily

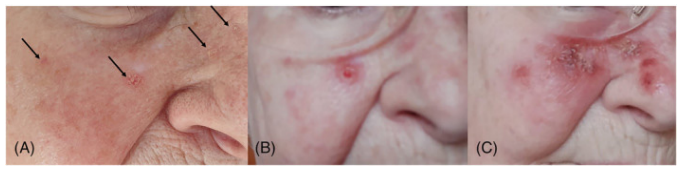
in percent reduction and total clearance of AKs. The same study found the lower concentration was more effective than the 5% cream in reducing AKs from baseline and suggested patients prefer the lower concentration.[24]

Ingenol mebutate induces a rapid influx of calcium followed by downstream effects of modulating protein kinase C in dysplastic cells. Ingenol mebutate was available in a gel vehicle as 0.015% and 0.05% concentrations and indicated to apply for 2–3 days. Phase 3 trials showed that after eight weeks 21.4% of patients were completely clear and 59.4% had a 75% reduction in AKs. One study compared the tolerability of 5% 5-FU against 0.015% ingenol mebutate, 5-FU applied twice weekly for four weeks and ingenol mebutate applied daily for three days and found comparable results. Ingenol mebutate commonly caused pain, erythema, scale, crusting, and pustulation among patients that peaked one week into treatment and resolved after two weeks on average. LSRs graded out of 24 peaked at a mean of 10.85 (+-3.12) and on day four, which resolved by day 15 on average. The local skin responses (LSRs) of ingenol mebutate was comparable to 5-FU, which scored 10.86 (+-3.55). However, LSR from 5-FU peaked on day 29, and resolved by day 36. This study should be assumed to have a lesser LSR than one in which 5-FU was applied more frequently as usually directed. However, ingenol mebutate was recently removed from most markets, including the United States, due to a variety of factors including concerns regarding increased risk of SCC. The European Medicine Agency, equivalent to the FDA, found in a three-year study of 484 patients, that 3.3% of developed SCC in the Ingenol Mebutate group versus 0.4% in the imiquimod group.[25,26,27]

Imiquimod is a toll-like receptor-7 agonist that amplifies the host immune response and stimulates apoptosis of dysplastic cells. Imiquimod is more selective for dysplasia rather than proliferating cells like 5-FU. This selectivity allows imiquimod to be more tolerable overall for most patients compared to 5-FU, however the adverse events are similar. Imiquimod is approved in 3.75% and 2.5% creams and phase 3 trials showed a 100% clearance in AKs among 35.6% and 30.6% of patients, respectively. 75% reduction in AKs was achieved by 59.4% and 48.1% of patients in the 3.75% and 2.5% concentration groups. LSRs were observed in almost all the patients during treatment course that consisted of once daily applications for two-week treatment intervals broken up by a two-week break. Erythema, crusting, and pustulation were observed most frequently by up to 25.2% and 13.8% of the stronger concentration and 14.4% and 9.4% of patients in the weaker concentration.[28,29] Figure 2 provides an example of AKs before and during treatment with imiquimod 3.75%.[8]

Diclofenac 3% gel is a nonsteroidal anti-inflammatory that inhibits cyclooxygenase-2, effectively reducing prostaglandin E2 and Bcl-2, which normally prevent apoptosis in dysplastic cells. In a phase 4 study, 41% of patients achieved 100% clearance of AKs and 78% achieved 75% reduction in AKs after 90 days. Adverse events were limited to mild application site reactions, itching, erythema, dry skin, exfoliation, localized edema, photosensitivity, and paresthesia. Diclofenac has the most tolerable side effect profile due to the slow extended duration of use but poses a compliance risk as it must be applied twice daily for sixty to ninety days.[30]

Figure 2. Example of LSRs to 3.75% imiquimod cream. (A) Eighty-seven-year-old female showing small erythematous scaly lesions on her right cheek (arrows). (B) Inflammatory reaction starting from day 3 of treatment with topical imiquimod 3.75% cream. (C) Day 14, end of treatment phase, showing field cancerization. *Reprinted with permission from Dermatologic Therapy, by D. Kopera, 2020, p. 2. Copyright 2020 by Wiley.*



The most recent FDA-approved topical therapy for AK treatments, tirbanibulin 1% ointment, inhibits tubulin polymerization and halts the cell cycle selectively in proliferating cells, resulting in augmented apoptosis of dysplastic cells that form AK lesions. Tirbanibulin also disrupts Src kinase, which is crucial for cellular growth, division, and proliferation. These mechanisms allow tirbanibulin to act as a potent anti-proliferative and pro-apoptotic agent without any direct cellular toxicity that intensifies inflammation through marked cytokine release (such as observed with 5-FU application). Most importantly, clinical trial data supports use of tirbanibulin over a short five-day course of application with demonstration of efficacy on follow-up. The LSRs associated with tirbanibulin use were shown to exhibit a low magnitude and relatively short duration of erythema, crusting, erosion, and discomfort, especially when considering LSRs observed with other topical field therapies. LSRs for tirbanibulin were measured on an 18-point scale, rather than the 24-point scale in references above. In the pivotal trials with tirbanibulin, LSRs peaked at day 8, decreased through day 15, and resolved by day 28 in the majority of cases. Compared to other field therapies, the onset of LSRs appears less intense and more manageable for patients. Drs. Berman and Del Rosso presented phase 3 studies that revealed 100% complete clearance of AKs in 44–54% of patients 57 days following treatment with tirbanibulin. 68–76% of patients achieved ≥ 75% reduction in AKs. The pooled median percent reduction in lesion count was 87.5%. In patients with complete clearance, presence of AKs in the treatment field were noted in 47% of patients at one year, showing that a single 5-day course of topical tirbanibulin sustained suppression of AKs in the treatment in a large number of patients without use of any other topical or field-directed AK therapy. The short 5-day duration of treatment combined with both efficacy and favorable tolerability are likely to attract increasing numbers of clinicians and patients to the use of tirbanibulin, which was echoed by both presenters.[31]

Dr. Berman discussed future directions in treating AKs and presented a study combining calcipotriol with 5-FU that enhanced the efficacy in treating AKs by inducing thymic stromal lymphopoietin and recruiting local CD4+ T cells to the region.[32]

Treating AKs satisfactorily necessitates a multifaceted approach and patient-applied topical field therapies that require fewer applications and pose fewer risks are invaluable. With the addition of tirbanibulin to the arsenal of AK therapies, clinicians can reduce the multiple adverse sequelae that AKs cause including progression to skin cancer.

Disclosure

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