



COMMENTARY

Management of Actinic Keratoses

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Actinic keratoses (AKs) are premalignant lesions which affect people who have had chronic exposure to sun. The prevalence significantly increases with age, primarily targeting those 40-years-old and older [1]. Clinically, actinic keratoses can either regress, stabilize, or transform into squamous cell carcinoma [2]. Although most AKs do not undergo malignant transformation, most invasive squamous cell carcinomas develop from pre-existing AKs [3]. Thus, adequate and timely treatment of AKs is crucial in preventing the development of invasive skin cancer. However, if left untreated, diagnosing this development of squamous cell carcinoma in Medicare patients alone has been estimated to cost over 500 million US healthcare dollars annually [4].

Chronic sun exposure causes the development and progression of AKs. This is due to the cumulative ultraviolet (UV) radiation from the sun which causes neoplastic effects in keratinocytes. Ultraviolet radiation exists in three wavelengths: UVA at 315-400 nm, UVB at 280-315 nm, and UVC at 100-280 nm. Generally, only UVA and UVB make it through the ozone layer. The long wavelength of UVA allows it to penetrate the skin as deep as the basal layer. This causes melanocytes within the basal layer to react and produce more melanin, indicative of skin damage [5]. Ultraviolet-A also stimulates free radicals to form and cause oxidative damage. When radiation by UVB occurs, an inflammatory cytokine cascade causes the skin to demonstrate signs of sunburn. Ultraviolet-B also forms DNA photolesions, such as thymine dimers. At increased levels of UVB, keratinocyte apoptosis is induced. Following sunburn, keratinocytes will proliferate and cause epidermal thickening in attempt to prevent further damage from UV penetration

Table 1: Treatment modalities for actinic keratoses.

First Line Therapies	Second Line Therapies
Liquid Nitrogen Cryotherapy	IngenolMebutate gel
5-Fluorouracil cream	Diclofenac gel
Imiquimod cream	Retinoids
Photodynamic Therapy	Dermabrasion
Daylight Photodynamic Therapy	Chemical Peels
Sequential Therapy	Resurfacing Lasers

[6]. Evidently, UV radiations can cause tumorigenesis through multiple mechanisms. After chronic, excessive UV exposure, the skin begins to become red, rough, and scaly in sun-exposed areas, forming AKs. Common locations for AKs include the back of the hands, face, and scalp. Patients often present with numerous lesions and develop new lesions over time [2].

While there are many treatment options for AKs their efficacy is variable (Table 1). Treatment options range from targeted in office procedures such as cryotherapy with liquid nitrogen to topical therapies that are applied by the patient. Additionally, each therapy, not surprisingly, has its own unintended side effects ranging from a stinging sensation on the skin to therapy induced fevers. When choosing an appropriate therapy for each patient some considerations include skin type, disease burden and patient reliability.

The first line and most accessible treatment of AKs is considered to be freezing with liquid nitrogen, or cryotherapy. In this modality, liquid nitrogen is targeted at each AK lesion in repetitive cycles of freezing and thawing. Many practitioners prefer treating AKs with

cryotherapy, however, this may not be the most optimal treatment for every patient. Additionally, studies have shown that liquid nitrogen cryotherapy only has a 32-85% response rate when treating AKs [7,8]. This variation in results is due to the administration variation when using this treatment modality. Differences in freeze-thaw cycles, freeze duration, and cryostat distance all play a role in the efficacy of this treatment. Furthermore, cryotherapy may cause side effects such as hypopigmentation of treated skin, blurring of the vermillion border, scarring, nail matrix injury, blistering, and cold urticaria.

Given their accessibility and convenience, practitioners should keep topical therapies in mind when considering treatment therapies for their patient. With topical agents, patients do not need to make an office visit and can apply the medication themselves at a time that best fits their schedule. Many patients appreciate having the autonomy and comfort of treating their own lesions at home. Generally, topical medications are less painful compared to destructive therapy. Furthermore, topical therapies allow for treatment of greater areas. When patients have multiple AKs, treating each individual lesion with cryotherapy may not be practical. However, topical agents allow for what is known as field therapy. By easily applying a topical agent over the affected areas, more skin can be treated in a single treatment session.

Diclofenac is a topical nonsteroidal anti-inflammatory drug that is formulated in a gel vehicle. Diclofenac exerts its effects by blocking COX1 and COX2, thereby decreasing prostaglandin production. Since COX2 is activated by stimuli such as UV light, sun exposure can increase COX2 expression and prostaglandin E2 which participate in the formation of tumorigenesis through angiogenesis and cell proliferation. Diclofenac therefore reduces UVB-induced skin cancer pathogenesis by inducing cell death, inhibiting angiogenesis, and halting cell proliferation [9,10]. The proper dosage and duration are diclofenac 3% in 2.5% hyaluronan gel applied twice daily for two to three months. Studies reviewing the effectiveness of Diclofenac in reducing AKs found about 40% clearance of AKs [11]. However, studies with Diclofenac in treatment of AKs have only been sufficiently conducted on the face; therefore, its efficacy may be lower when treating other areas such as the chest or scalp. Adverse reactions include erythema at the site of application, as well as dry or itchy skin.

Another easily accessible topical remedy is prescription retinoids. Retinoids have anti-proliferative properties and help regulate gene expression [12]. However, the efficacy of retinoid treatment of AKs is poorly studied and does not seem to show a correlative relationship in AK clearance and retinoid strength. For example, one study was able to demonstrate that the application 0.3% adapalene gel decreased the total number of AKs

in study participants. However, another study showed that tretinoin 0.1% cream, which is considered a stronger retinoid therapy than 0.3% adapalene, did not effectively reduce the number of AKs in study participants. Thus, we do not currently recommend topical retinoid therapy as a mainstay treatment of AKs until further studies are conducted.

Ingenolmebutate gel, derived from the *Euphorbia peplus* plant, is another topical therapy used in the treatment of AKs. This agent works by causing cell membrane and mitochondrial dysfunction followed by antibody-dependent cellular cytotoxicity through induction of neutrophils. This gel is often used for two to three days and is found in a 0.015% gel for the face and scalp and 0.05% gel for the trunk and extremities. There's been reported clearance rates' ranging from 28.5% to 40% of AKs. However, some studies have surprisingly demonstrated a potential increased risk of developing cutaneous squamous cell carcinoma after use of ingenolmebutate gel. This finding limits its efficacy in field directed therapies, but may be useful treatment for patients with few AK lesions. Adverse effects of this therapy include pain, pruritis, erythema, and ulceration. Additionally, severe herpes zoster and anaphylaxis have been reported. Patients should also be cautioned to thoroughly wash their hands after applications as the gel may cause severe ocular injury if accidentally transferred to the eye.

Another, more efficacious, topical therapy is 5-fluorouracil cream. 5-fluorouracil works by inhibiting thymidylate synthetase which ultimately causes cell death. Additionally, it causes an inflammatory reaction which aids in its necrotic abilities. This inflammatory cascade causes the skin to become red and necrotic which finally causes the desired erosion. This erosion indicates that the precancer is gone and the cream is discontinued to allow for skin healing. 5-fluorouracil cream comes in a 5% formulation for body AKs and 0.5% cream for facial AKs. The cream is used daily until superficial erosion occurs or for up to 4 weeks. Patients often complain of discomfort throughout the inflammatory stages and a topical steroid in conjunction with treatment may increase patient compliance. Many studies implicate that 5-fluorouracil is the most successful topical remedy for treating AKs.

Imiquimod cream is another topical agent used to treat AKs. It is a toll-like receptor-7 agonist and acts as a modulator of the immune system. It induces cytokines which activate natural killer cells and T-helper cells. This inflammatory reaction acts similarly to that of 5-fluorouracil in the treatment of AKs. Imiquimod comes in a 5%, 3.75%, and 2.5% cream. The higher strengths cause more inflammatory side effects, but show greater success in treating AKs. The 5% cream should not be applied to the face or scalp. The treatment cycle is for 16 weeks. However, when treating sensitive areas like the

face, imiquimod is used for 2 consecutive weeks and then discontinued for 2 consecutive weeks, repeating for 16 weeks total. Some notable adverse events associated with this cream include fever, chills, and myalgia. Taking an antipyretic prior to treatment might help mitigate these unwanted effects.

As an alternative to topical therapies, light therapy can be used in the treatment of AKs. Light therapy may be utilized when patients can't apply topical therapies on their own, have a hard time remembering to reapply them, or simply have a history of noncompliance. There is also added benefit in that laser photodynamic therapy has more cosmetically acceptable outcomes compared to some topical therapies or cryotherapy. Additionally, treatment course can be shorter when using a destructive therapy like lasers rather than topical therapies. Light therapy which involves daylight can also be used as a field therapy.

One type of laser therapy is photodynamic light therapy which utilizes photosensitizing agents, such as methyl aminolevulinate or aminolaevulinic acid, in addition to visible light illumination. These photosensitizing agents convert to protoporphyrin IX (PpIX) in the skin so that when the AK is exposed to a light which is absorbed at the same wavelength as PpIX, a tissue-specific photochemical reaction can occur to form reactive oxygen species which subsequently attacks the tumor cells [13]. Studies have shown incredible efficacy with this therapy with upwards of 95% clearance. In addition, using an alternative light source such as an ablative laser has shown increased efficacy compared to non-ablative lasers. Furthermore, leaving the photosensitizing agent on for four hours has shown increased AK clearance compared to just one to two hours. A similar treatment plan utilizes daylight as the light source. A sunscreen without minerals is applied prior to the photosensitizer. After thirty minutes of application of the photosensitizer, the patient goes into the outdoors for two hours. This treatment is great because it is affordable, painless, and can theoretically treat the entire body. Efficacy is similar to that of photodynamic light therapy with a laser light source. Increased cosmetic outcomes have been reported in patients undergoing photodynamic light therapy rather than topical agents such as 5-fluorouracil and destructive remedies such as liquid nitrogen.

For resistant lesions, sequential therapies may be necessary. Sequential therapy involves treating an AK with either photodynamic light therapy or cryotherapy followed by, or preceded by, a topical agent such as 5-fluorouracil or imiquimod. Studies have shown that combining two treatment modalities have more impactful results compared to cryotherapy alone. Other treatment modalities for AKs include dermabrasion, chemical peels, and laser resurfacing. Furthermore, a shave biopsy and electrodesiccation and curettage may be necessary to definitively rule out squamous cell carcinoma

of the skin. In these difficult cases, a dermatologist should be consulted.

Dermabrasion is a field ablation treatment which works by retexturizing the skin through removal of the entire stratum corneum. It is extremely painful and requires analgesia. Its efficacy reduces over time, but more studies should be done to explore this treatment option. Trichloroacetic acid chemical peels induce the wound healing process and have shown approximately 40-50% clearance of AKs. Similarly, laser resurfacing has shown variable efficacy. It is a destructive therapy ideal for isolated, thickened AKs. One study showed that after 4 treatments with the fractionated, non-ablative lithium laser, the six-month follow up demonstrated a reduction of 87% of AKs. More studies need to be performed in order to understand the accurate efficacy of these treatment modalities.

Some key points should be kept in mind when treating AKs. When a patient presents with numerous lesions, topical therapies may be most practical. For hyperkeratotic, thick lesions, sequential therapies have been shown to be the most effective. Photodynamic light therapy may have better cosmetic outcomes than cryotherapy, and when combined with topical treatments, may be just as effective. However, there is a serious lacking in the number of clinical trials exploring alternative treatment modalities of AKs. More research needs to be conducted regarding the use of lasers, light therapy, and destructive therapies so healthcare providers can provide the best care to address the individual needs of their patients.

Authors Declaration

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