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Review Article

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Double Prevention of Skin Cancer: Primary and Secondary Forces United Against Actinic Keratosis

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Introduction

Actinic keratoses (AKs) are clinically defined as scaly erythematous plaques that develop on sun-damaged skin after prolonged exposure to ultraviolet (UV) radiation [1]. They are mainly seen on sun-exposed areas including the face, neck, scalp and extremities [2]. The importance of diagnosing AKs lies in their ability to transform to cancer, squamous cell carcinoma (SCC) specifically [3]. Protecting the skin from harmful UV radiation is an incontrovertible fact that has been proven to be effective in preventing AKs by reliable studies [4].

Epidemiology

Those who have skin that burns easily when out in the sun, also known as Fitzpatrick skin type I and II are more susceptible to get AKs. Other risk factors include male gender, having freckles or fair complexion, living closer to the equator and immunosuppression [5]. Age is a key player in the process; AKs are commonly seen in the elderly [6].

In Australia, 40-60% of the population has AKs, on the other hand; the United States' population recorded 11-26% and in Europe; 15% of men and 6% of women have been affected [7-8].

Genetics and Histology

On a molecular level, keratinocytes' DNA is damaged by UVA and UVB radiation resulting in AKs. There have been many genes involved in the process including P14, P15, P16 and P53 [9]. UV radiation causes oxidative damage to nucleic acids, membrane lipids and cell proteins by producing reactive oxygen species (ROSs) that interrupt normal cell proliferation [10]. P53 is a tumor suppressor gene that is rendered dysfunctional by UVB rays; its damage is a main element in the progression of AKs [11].

Histologically, AKs and SCC can look similar, however; AKs are epidermal lesions of the basal layer that may spread to involve the granular and cornified layers. At the farther end of the epidermal involvement spectrum lays squamous cell carcinoma in situ (Bowen's disease) which can be very difficult to differentiate from AKs. Invasive SCC occurs beyond the epidermis through the basement membrane and into the dermis [12].

Management

Approaching AKs differs from one place to another. There are no established guidelines being used to manage those lesions universally, different regions around the world approach it according to their available treatments and the experience physicians have in this field. Mainly, two types of treatments are available, procedural and topical.

Procedural

Cryotherapy is the commonest procedure in this category [13]. Freezing with liquid Nitrogen destroys the epidermal keratinocytes; multiple sessions may be required to fully treat the area. It is an operator dependent procedure, however; a freezing time of 5 to 10 seconds is adequate enough to destroy the lesion without resulting in side effects.

Advantages of cryotherapy [14]

- Fast and easy.
- Low cost.
- Well tolerated.
- Complications are absent with almost all patients.
- It's effective.

Disadvantages of Cryotherapy [13-14]

- Pain or discomfort.
- Temporary erythema.
- Aggressive therapy may cause depigmentation and scarring.
- Hypopigmentation or hyperpigmentation.

Other procedural treatments include curettage and shave excision or conventional excision. These are considered with hyperkeratotic lesions or if invasive SCC is suspected. Laser resurfacing, chemical peels, and dermabrasion are also effective in treating AKs, however; they come with a small risk of infection, and widespread scarring, as a result they are not frequently implemented [15,16].

Topical

Topical treatment is issued when there are multiple AKs involving a larger area of skin, where cryotherapy would not be an ideal candidate for treatment. The current used agents are 5-FU, Diclofenac, Imiquimod, Ingenol mebutate and PDT.

5-FU is a pyrimidine analog that kills abusive cells in AKs by stopping DNA from replicating by stopping the conversion of deoxyuradilic acid to thymidylic acid [17]. It is the most established

topical treatment, and considered gold standard to some physicians worldwide [1]. It is available as 0.5%, 1% and 5% concentrations and as a solution in 2% and 5% concentrations. The regimen prescribed is usually 5% or 0.5% cream twice daily for 2-4 weeks. Side effects are a major point of consideration with this candidate. Inflammation, erosion, and ulceration are essential components to the mechanism of action and that puts patients' compliance at risk. Other side effects include burning, erythema, xerosis, pain and swelling. Tolerability with 5-FU is one factor to keep in mind when using it in the treatment of stubborn AKs as patients may not be using it due to its mentioned side effects; the results however are satisfactory with consistent use [18].

Diclofenac 3% combined with 2.5% hyaluronic acid is another common topical agent used in the treatment of AKs. It acts by inhibiting COX2 pathway and the up regulation of arachidonic acid cascade that are both involved in the proliferation of the insulting cells in AKs [19]. The regimen that is commonly prescribed is twice daily for 90 days. When compared to 5-FU, patients report better tolerance and less side effects in general, however studies have shown that Diclofenac is slightly less effective when used alone, and when combined with cryotherapy it provided better outcomes [20].Side effects included itch, xerosis, and contact dermatitis. Nevertheless it is still a successful option of treatment and the fact that patients tolerate it better puts it at a superior spot when considering their compliance in choosing a topical treatment [21].

Imiquimod is a toll-like receptor-7 agonist that modifies the skin's immune response and results in apoptosis preventing the progression of AKs [22,23]. It was first used for AKs in 2004, and the current appropriate regimen is twice daily for 4 weeks then patients have to take a 4-week rest period and repeat the cycle till satisfactory outcomes are achieved [24]. Imiquimod is available in 3.75% and 5% preparations. Side effects include skin irritation, erythema, and rarely flu-like symptoms and lymphadenopathy [25].

Ingenol mebutate is also a recent topical agent developed in Australia and was officially used for AKs in 2012. It has a dual mechanism of action; first it causes rapid disruption of plasma membrane and mitochondrial swelling leading to rapid cellular necrosis, secondly; it targets the remaining dysplastic epidermal cells through a specific neutrophil mediated, antibody-dependent cellular cytotoxicity [26]. Its rapid destruction indicates a short duration of usage; for 2 to 3 days, and is currently available as 0.015% and 0.05% preparations [27]. Common side effects include erythema, scaling, crusting, depigmentation, swelling, and pruritus. Some studies showed recurrence of lesions [27].

PDT stands for photodynamic therapy that employs a photosensitizing agent; currently either ALA or MAL are used in this procedure [28,29]. The agent is applied on the lesion and after an incubation period the area is illuminated by an appropriate wavelength depending on the photosensitizing agent used [28]. PDT is considered in patients who are having poor compliance with topical treatments, resistant AKs, and in patients who have aesthetic concerns with other modalities [28]. Side effects include erythema, edema, itching, and pain during light exposure. Air-cooling or local anesthetics for pain may be needed if patients are not tolerating the discomfort [30]. The main advantage with PDT is satisfaction from a cosmetic point of view [28]. One session is usually sufficient to destroy the lesion; the reported clearance rates are up to 90% with this procedure [31].

Prevention

Patients have to understand that AKs are a result of chronic UV radiation exposure, treating current lesions is an important step in the therapeutic process, however; sun protection is essential to prevent recurrence and further damage to the skin [4].

The FDA has approved 17 sun-protective ingredients, which are categorized as either UVA or UVB filters, in addition to physical blockers, which act as a physical barrier against sunrays [32]. Wearing a broad-spectrum sunscreen or sunblock with a minimum SPF of 15 is crucial in the prevention of AKs especially during treatment of developed lesions.

Other issues

As mentioned earlier, AKs are seen in a group of population that has multiple needs and frequent health care attendance due to several conditions and co-morbidities. When handling elderly patients, education about their condition is important to keep them oriented with all the needed treatment sessions and their progression, also making sure that their circumstances allow them to be compliant with the chosen regimen depending on how early or late they present with AKs, having said that; compliance includes the medication and prevention. Prevention of AKs is accomplished by assiduous sunscreen use and avoiding prolonged sun exposure as mentioned. Poor compliance in this group of patients is explained by many factors such as side effects of topical medications, dependency and absence of care providers, debilitating conditions that limit their activity, conditions affecting their cognition and memory, and sometimes patients underestimate the consequences of not treating AKs or preventing them, and those are comprehensible justifications from the doctor's point of view, therefore highlighting those factors at the consultation will assist in choosing the right management plan.

Compliance with preventative measures is the challenge here, individuals with AKs automatically give the impression of poor sun protection, when lesions are being treated and prevention is not taken into serious consideration, patients are going to present with recurrent AKs and sometimes it is difficult enough to adhere to treatment to reach full resolution, as a result it is going to be a never-ending cycle of resolving and recurring lesions with the possibility of having undetected SCC in situ or even invasive SCC.

"Primary and Secondary Prevention Combined" Concept

Applying Topical products is a miserable task to many individuals, especially with AKs; patients have to be hardworking with treatment and sunscreen use, which are both topical. Keeping up the motivation to adhere to primary and secondary prevention can be challenging for physicians. If patients were given one product that combined both tasks; treating and preventing AKs, it is expected that their compliance would have a better score, instead of sending patients home with two items to apply on their skin, they can go home with one product that combines the treating agent and sun-filtering or blocking ingredients. This remains a very theoretical idea, and would need several experiments by a specialized compounding laboratory to decide whether this combination is stable or not, will the treating agent be as efficacious as when on its own, and deciding a suitable sun protective ingredient in this blend.

Diclofenac is an appropriate agent to start with, when compared to 5-FU it has fewer side effects and patients tolerate it a lot better, it is

assumed that it will be a friendlier ingredient to add to this mixture. Even though 5-FU scores better outcomes, diclofenac remains a competitive player in this field especially that poor compliance is the main concern that this concept is aiming at. Ingenol mebutate and Imiquimod are recently developed and their efficacy and pharmacodynamics would need further studies to include them in this trial, nevertheless; Diclofenac is not the final candidate, other agents may match better depending on the outcomes of mixing them with UVA and UVB filters. It is difficult to pick a sun-protective ingredient from theory; only ground experiments can answer the question of which one is best suitable for this recipe.

Conclusion

Actinic keratosis is common and seen in elderly patients, as its growth requires chronic sun exposure without protecting the skin. Even though the risk of AKs to grow into SCC is low, it still demands physicians' attention since their growth serves as sun damage marker. The choice of treatment depends on the number of lesions, patient's factors and concerns including compliance with treatment and sun protection and outcomes from a cosmetic point of view as well as the cost of it. Combining therapies is a successful way to approach those lesions and should be addressed to fit patients' needs and concerns and at the same time provide anticipated outcomes. Prevention by wearing sunscreen is the mainstay of avoiding the growth of AKs; especially during and after treatment of existing lesions as relapse and further skin damage is not desirable.

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