Actinic keratoses

Actinic keratoses (AK) commonly occur in the caucasian population living in environments of high levels of sun exposure, and are considered to be a marker for chronic sun damage. This article reviews the epidemiology, pathogenesis, and current debate on AK as precancerous lesions. The various treatment options for AK, including combination therapy, are also discussed.

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Actinic keratoses (AK), or solar keratoses commonly occur in the caucasian population living in environments with high levels of sun exposure. They overwhelmingly occur on sun exposed areas of fair skinned individuals and are a marker for chronic sun damage.

Epidemiology

Cumulative sun exposure is the single most important cause of AK.[1] The prevalence of AK in the Australian caucasian population over 40 years of age is 40–50%.[2] The incidence of AK rises with age, increasing from less than 10% in the third decade of life to more than 80% in the seventh decade.[3,4] The most important factor determining susceptibility to ultraviolet (UV) radiation damage is the skin phenotype. Individuals with fair skin who sunburn easily (Fitzpatrick type I and II) and have difficulty tanning, are most at risk.

An Australian population based survey has demonstrated that individuals with AK have on average 6–8 lesions.[2] The upper limbs and head/neck region account for more than 80% of all AK, with the back of the hands and forearm being the most commonly affected.

Pathogenesis

Ultraviolet radiation damages the DNA of keratinocytes with repeated exposure. It has been suggested that AK will more likely progress to invasive squamous cell carcinoma (SCC) if mutations occur in p16(INK4a).[5] Ultraviolet radiation also gives rise to AK through interference of the skin's immune system.[6,7] A decrease in cellular immunity allows some DNA damaged keratinocytes to escape apoptosis, which may lead to the growth of atypical clones. These molecular changes are part of a multistep process that leads to the development of AK and SCCs. This process may be accelerated in immunocompromised patients.

Relationship with SCC

Actinic keratoses can progress to, but are by no means an obligate precursor of, SCC. The risk of progression is estimated as 0.075–0.096% per lesion per year, or around 1% over 10 years,[8] with some estimates as high as 10% over 10 years.[9] Conversely, AK may regress spontaneously or remain stable.[10] The relative risk for SCC increases for those with more than five AK.[11]

Actinic keratoses have historically been considered premalignant, but recent publications have advocated that AK be considered 'cancerous'.[12,13] Actinic keratoses share many similar molecular and histological features with SCC and it can sometimes be difficult to distinguish between the two clinically. Some clinicians[14] are concerned about the ramifications of a 'cancer' diagnosis for the patient and the health care system. These include the patient's emotional distress associated with the diagnosis of 'cancer' and also increased health care costs. AK may be regarded as an early clinical manifestation on a biological spectrum that has invasive SCC at the other end. Actinic keratoses are nevertheless considered a relatively late event on the carcinogenesis pathway as it requires substantial UV damage to the skin for AK to occur.

Treatment

Treatment of AK needs to be discussed with patients for several reasons. Patients should realise that there is a low rate of transformation of AK to SCC. Despite this, the presence of AK indicates that they have a higher risk for skin cancers compared to the general population, and would therefore need to be screened and checked on a regular basis. Ultimately, most patients want their AK treated, either for their malignant potential, or other reasons such as cosmesis and symptomatic relief. The discussion should also include advice on reducing or preventing further sun damage by ensuring appropriate outdoor clothing and the use of sunscreens. It has been shown that regular use of sunscreen not only prevents the development of AK, but also hastens the remission of existing AK.[15]

Lesion specific therapy

Lesion specific therapies, such as cryotherapy, are widely considered the most practical and effective

treatment options for AK. Other lesion specific options include curettage (alone or with electrodessication/cautery) and shave excision. Adverse reactions include pigment changes (usually hypopigmentation), scarring, poor wound healing and rarely, nerve damage. Hence, they may not be as useful in cosmetically sensitive areas or in regions with large numbers of AK.

Cryotherapy using liquid nitrogen is most commonly used to treat AK. This method destroys the keratinocytes through freezing, while mostly preserving important dermal structures such as blood vessels, nerves and collagen due to their higher resistance to cold. This ranges from the 83% reported for freezing times longer than 20 seconds, to 39% for 5 seconds or less of freezing.[16] Hypopigmentation is a recognised sequelae with cryotherapy because the melanocytes in the epidermis are also susceptible to freezing injury.

Curettage is another lesion specific technique for AK that is quick and convenient to perform but requires local anaesthesia. Bleeding can be controlled by aluminium chloride, silver nitrate, or electrodessication. Another advantage of curettage over cryotherapy is the availability of tissue for histological examination, particularly when SCC is suspected. Scarring occurs more commonly than with cryotherapy.

Field therapy

Field therapy is treatment of an entire field (eg. forehead, cheek) that is marked by the presence of visible AK. It is increasingly accepted as another modality of treatment as it treats not only visible AK but the expanded clones of dysplastic cells at the subclinical and cellular level in that region of UV damaged skin.[17] Most field therapy agents used these days have good tolerability and efficacy, and excellent cosmetic outcome. These include 5-fluorouracil (5-FU), diclofenac, PDT/ALA, and imiquimod.

5-fluorouracil

Topical 5-FU has been an established treatment for AK for several decades.[18] It interferes with DNA synthesis by blocking the conversion of deoxyuradilic acid to thymidylic acid.[19] 5-fluorouracil has generally been viewed as effective for AK and it's efficacy is dependent on the degree of inflammation, erosion and ulceration elicited during treatment. Noncompliance is an issue with this treatment because of the significant side effects such as erythema, itching, burning and crusting. Although temporary, the side effects can be unpleasant and may cause discomfort and short term disfigurement. Side effects usually begin after the first week and can persist for up to 2 weeks following the treatment period. Pulsed 5-FU therapy has been advocated by some as a way of obtaining the same efficacy but with reduced AR.[20] This has yet to be universally accepted in clinical practice, and therefore pulsed 5-FU therapy is not commonly used as a treatment for AK in Australia.

Diclofenac

Diclofenac is a nonsteroidal anti-inflammatory drug that can be suspended in hyaluronic acid gel for topical treatment of AK. The exact mechanism of the drug is not established but is likely to be related to the inhibition of the COX-2 enzyme[21] leading to decreased levels of prostaglandins and prostacyclines, mediators that are involved in carcinogenesis. Diclofenac achieved a 100% AK clearance in 50% of the patients after 3 months of twice per day application compared to placebo gel.[22] This relatively long treatment duration is a disadvantage and reduces compliance, but a shorter treatment period is reported to have lower efficacy, probably due to the delayed onset of action.[22] The advantage of diclofenac treatment is its higher tolerability due to limited local inflammation and irritation. Side effects and local reactions may include contact dermatitis, dry skin, pruritus and rash.[23]

PDT

This treatment modality involves the application of a pre-photosensitiser to the area of the skin being treated. An incubation period (1–3 hours) is necessary for it to be preferentially accumulated in dysplastic and malignant cells, where it is converted enzymatically to the potent photosensitiser protoporphyrin IX. The area is then exposed to a light source, leading to preferential tumour cell death. This is due to the generation of reactive oxygen species resulting in oxidative cell damage. Methyl 5-aminolevulinate (Metvix) is the most commonly applied agent as it has better penetration capabilities and higher selectivity for abnormal cells compared to other commercially available PDT sensitisers.[24] PDT with Metvix has been reported to achieve 100% clearance in up to 82% of patients and an efficacy of 90% for individual AK lesions.[25] The phototoxic reactions also cause adverse events such as erythema, stinging, itching, oedema and exudation. The pain associated with such reactions may be severe enough to require local anaesthesia, especially during the illumination process. Healing time is often less than 10 days. Patient satisfaction levels are high with regards to the cosmetic outcome.[25]

Imiquimod

Imiquimod is an immune response modifier that targets both innate and acquired immunity. It acts largely by triggering the expression of a range of cytokines including interferon alpha, gamma and interleukin.[12] Imiquimod has the ability to induce apoptosis in tumour cells and thus decrease tumour development.[26]

Five precent imiquimod was found to be effective and well tolerated for the treatment of multiple AK when used twice per week for a total of 16 weeks as reported in a recent pivotal phase III study.[27] More than 41% of imiquimod treated patients achieved complete clearance, while the median percent reduction in AK numbers was 83%. A three times per week treatment regimen for 16 weeks has also been shown to be effective (48–57% complete clearance).[28,29] With the aim of decreasing local skin reactions, which can be quite variable in severity, smaller studies of cycle therapy have been performed.[30,31] In these studies, imiquimod was applied 2–3 times a week for 3–4 weeks and this was repeated after a rest period of 4 weeks in those with residual lesions. A complete clearance rate was achieved in up to 82% of treatment sites. The rest period also allows the physician to assess the need for another 'cycle' of treatment as the therapeutic effect continues while inflammation subsides.

Combining therapies

The different therapies mentioned above can often be combined. These benefits include higher efficacy with limited local side effects and better cosmetic results. The published evidence supporting the use of combination therapy is scant. Despite this, the wider availability of

different classes of therapy for AK will likely prompt an increase in clinicians combining the benefits of various treatments. One example would be the use of a field therapy combined with cryotherapy. Field therapies may treat subclinical lesions not treated by cryotherapy, while cryotherapy or curettage can treat hyperkeratotic lesions that may not respond well to field therapy.

The number, location and character (eg. hypertrophic, lichenoid) of AK will influence the choice of therapy. Multiple AK on diffusely sun damaged skin may benefit from field therapy while lesion specific therapy might suffice for fewer or solitary lesions. The accessibility to clinic visits and anticipated compliance would be additional considerations. Cosmetic outcome may influence choice of treatment, particularly in younger patients.

Immunocompromised patient

Immunocompromised patients are at an increased risk of developing AK. These include organ transplant recipients who are on immunosuppressive therapy. Transplant recipients are up to 250 times more likely to develop AK.[32] Imiquimod and other field therapies have been used in these immunocompromised patients with good results.[33] Imiquimod is generally thought to be safe in immunocompromised patients.[33]

Other treatments

Other treatments less commonly used to treat AK include chemical peels, laser resurfacing and dermabrasion. Medium depth peels are used either alone or as an adjunct for the treatment of AK, especially in the head and neck areas. Chemical agents used for peels include glycolic acid, trichloroacetic acid, and salicylic acid. Laser resurfacing and dermabrasion are techniques that work by physical destruction of AK and removes outer epidermal layers. They generally have a good cosmetic outcome. A novel therapy being trialled at present is the use of 3-ingenyl angelate (extract of Euphorbia peplus plant) to treat AK.[34]

Conclusion

Actinic keratosis is a common dermatological problem in caucasian populations that live, or holiday, in climates with high levels of sun exposure. Although there is ongoing debate about whether AK are malignant or premalignant, the rate of transformation to SCC is low. Nevertheless, AK remains a useful marker for SCC risk. Field and lesion targeted therapies serve different clinical scenarios but are increasingly combined for optimal management of both immunocompetent and immunosuppressed patients. Established and newer field treatment methods are additionally useful for subclinical lesions with the added benefit of a potentially superior cosmetic outcome.

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