A GP's guide to actinic keratosis

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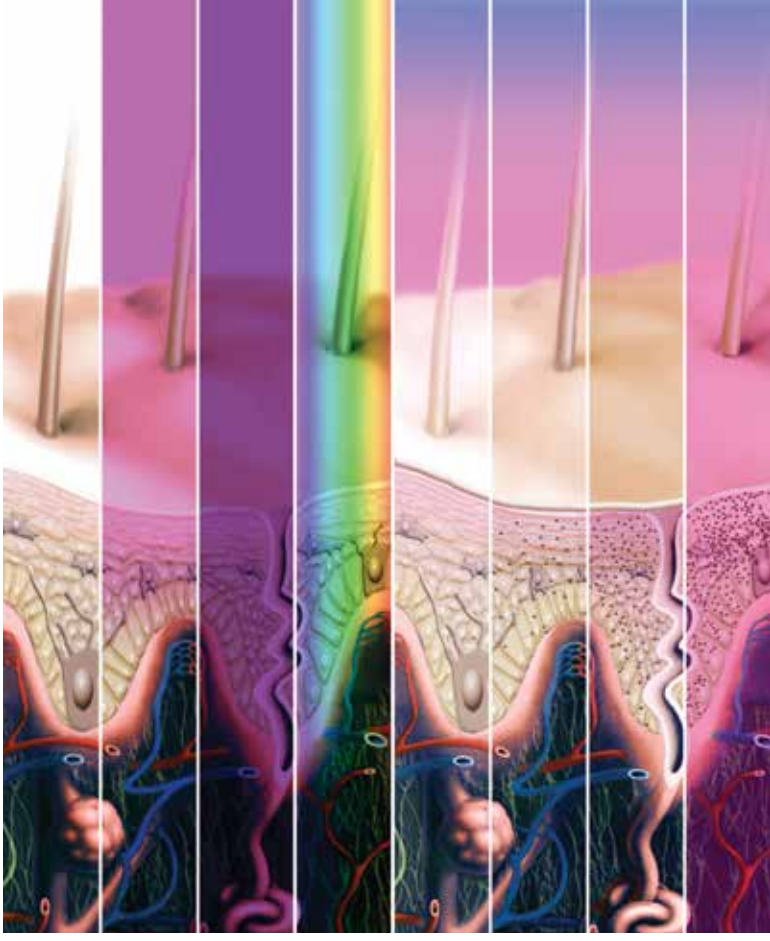
Australia has the highest prevalence of actinic keratoses in the world. Due to the risk of transformation into invasive squamous cell carcinomas, actinic keratoses are routinely treated with an array of methods to prevent progression to invasive disease.



KEY POINTS

- Actinic keratoses (AKs) are premalignant lesions that have the potential to transform into in situ or invasive squamous cell carcinoma (SCC).
- The main cause of AKs is chronic ultraviolet radiation-induced skin damage.
- The diagnosis of AKs is a clinical one, although dermoscopy is a useful adjunct to diagnosis.
- The use of high sun protection factor sunscreen and sun protection measures is the most important preventive measure for AKs.
- Other treatment modalities for AK can be broadly divided into lesion-directed and field-directed.
- Dermatologist referral is recommended for patients with lesions suspicious of SCC, extensive photodamage or immunosuppression and those at increased risk of developing SCC due to pre-existing medical conditions.

Actinic keratoses (AKs) are superficial, discrete, erythematous and scaly skin lesions. They are also known as solar keratoses or 'sunspots'. AKs are found predominantly on sun-exposed areas such as the scalp, face and forearms.[1] Globally, Australians have the highest rate of AK development, resulting in a prevalence of 40 to 60% among the Caucasian population above the age of 40 years.[1,2] Not surprisingly, the treatment of AK often falls under the responsibility of GPs so it is important to be aware of the full range of available treatment options.

Pathogenesis and natural history

AKs arise from chronic ultraviolet (UV) radiation-induced damage to keratinocytes – epithelial cells that produce keratin. In response to UV radiation, a cascade of pathological cellular processes leads to downstream mutagenesis and, ultimately, carcinogenesis of keratinocytes.[1] In AK, the cellular atypia is limited to the epidermis.

The natural history of untreated AKs is:

- regression – spontaneous remission
- no change – stable, without progression, or
- progression – squamous cell carcinoma (SCC) in situ (i.e. Bowen's disease) or invasive SCC.[3]

According to a recent systematic review, the rate of regression of single AK lesions ranges from 15 to 63% per year, with recurrence rates of 15 to 53%.[3] Meanwhile, up to 0.53% of single AKs progress to SCCs each year.[3] SCCs may cross the epidermal basement membrane, invade the dermis and metastasise, causing significant morbidity and mortality.[1] AKs can be regarded as part of a continuum and, in some cases, result in skin cancer development.[4]

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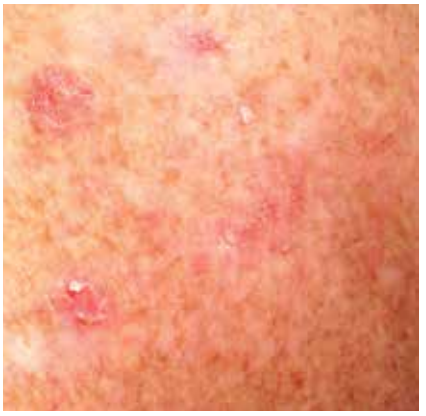


Figure 1. Thin actinic keratosis (clinical grade I).

Although the rates of spontaneous remission and malignant transformation of AKs cannot be definitively elucidated, clinicians should regard and treat all AKs as premalignant lesions.[5]

Another important concept is field damage or 'field cancerisation'. Despite often appearing clinically normal, the skin surrounding AKs, Bowen's disease and SCCs often houses precancerous cells as a result of chronic UV damage.[6] Additionally, AKs, Bowen's disease and SCCs may develop within this area if left untreated. This finding leads to the important consideration of field treatment.

Importance of treatment

AKs are regarded as the precursor of Bowen's disease and SCCs but there is currently no universally accepted definition of AK, which makes reliable identification of these lesions difficult.[7] Nonetheless, clinicians agree that AKs are premalignant lesions and that early identification and treatment are essential in reducing a patient's overall carcinogenic risk.[7,8] This is supported by histology reports showing that 60 to 80% of SCCs arise from AK lesions.[8]

Studies have shown that it takes about two years for previously confirmed AKs to transform into invasive SCCs.[8] Correspondingly, this window presents a golden opportunity for GPs to intervene and treat AKs to reduce the risk of SCC development.

Evaluation in the general practice setting

The diagnosis of AK is predominantly a clinical one. An optimal skin examination requires adequate consultation time, and good lighting and magnification by using hand-held or head-mounted loupes.

Clinically, AKs can be classified according to three grades (Box, Figures 1 to 3a to c):[9]

- I – slightly palpable
- II – moderately thick
- III – very thick and hyperkeratotic.

In reality, grading systems tend to be reserved for teaching purposes and clinical trials. In practice, dermatologists talk about thin, thick or hyperkeratotic AKs, which may remain as discrete lesions or form confluent patches. Variants include pigmented AKs and cutaneous horns. Although usually asymptomatic apart from their cosmetic appearance, AKs can become itchy, or burn and sting.

As an adjunct to diagnosing AK via the clinical grading system, dermoscopy is a useful noninvasive diagnostic technique.[10] The three clinical grades for AKs correspond well with three dermoscopic patterns (Box, Figures 4a to c):[9]

- red pseudonetwork
- 'strawberry' pattern
- 'yellow-white keratin'.

Clinical and dermoscopic identification of SCC

Clinical and dermoscopic grading systems can help delineate grades I and II AKs from SCC, because SCCs are more likely to display the vascular patterns that are absent in low grade (I and II) AKs. The usefulness of these grading systems fall short when attempting to differentiate grade III AK from SCC. Clinically, you would be suspicious of SCC rather than AK if there was:

- bleeding or ulceration
- recent growth
- tenderness or inflammation
- a nodular appearance
- a lesion that is refractory to treatment.

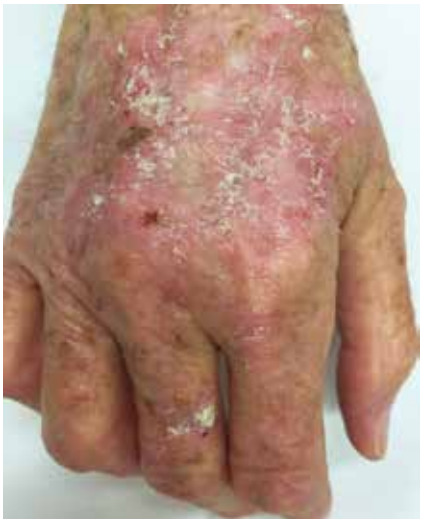


Figure 2. Clinically obvious hyperkeratotic actinic keratosis with field damage (clinical grade III).

Indications for referral to a dermatologist

Although GPs are able to manage most AKs in the primary care setting, referral to a dermatologist is advised for the following:

- patients with lesions that are suspicious for SCC based on clinical and dermoscopic features
- patients with widespread and severe actinic damage
- immunocompromised patients
- young patients with increased risks of developing SCC due to pre-existing medical conditions (e.g. xeroderma pigmentosum).

Treatment options

The treatment modalities for AK are many and varied. Choosing the most appropriate therapy depends on several factors including the number and distribution of lesions, the patient's tolerance to pain, desired cosmetic outcomes, patient adherence to treatment and treatment side effects and costs. It is essential to consider field treatment for prophylaxis in patients with widespread actinic damage or who are immunocompromised. Multimodal or sequential therapy is often required in these patients.

A simplified approach to treatment is

provided in Table 2 (modified from the 2015 European Dermatology Forum guidelines).[11] Treatment of AKs can be broadly divided into lesion-directed treatment and field-directed therapy. Lesion-directed treatments such as cryotherapy and curettage are suitable for treatment of discrete AKs. On the other hand, when there are multiple AKs in an area, and lesion-directed treatment is inappropriate, topical agents such as 5-fluorouracil (5-FU), imiquimod, ingenol mebutate and diclofenac or conventional or daylight photodynamic therapy (PDT) can be used.

As highlighted from a multinational survey, the consensus is that topical field therapy is the most beneficial treatment for AKs and is preferred over lesion-directed treatment because of the potential to target both clinically visible and subclinical (non-obvious) lesions.[12] However, for field-directed treatments, nonadherence due to local skin reactions is a significant limiting factor.

When prescribing field-directed treatment, agents with the shortest treatment duration are generally preferred, which has led to the development of newer agents such as ingenol mebutate.[12] Table 3 summarises the various treatment modalities, protocols and indications used for AKs.

Treatment options

Emollients and keratolytics

Regular application of emollients (with or without keratolytics such as 2 to 5% salicylic acid) reduces scaling in AKs. It is important to use before applying therapeutic modalities because it reduces keratin, allowing therapy to reach the atypical keratinocytes.

Sunscreen and sun protection

The most important preventive measure for AK is the regular use of high sun protection factor (SPF) sunscreen and sun protection, such as protective clothing, and avoiding excessive sun exposure. Sunscreen has been shown to both reduce UV-induced skin mutations and decrease the immunosuppressive effects of UV radiation.[5] Studies have shown that high SPF sunscreen can also reduce the development of new AKs vvand increase the rates of remission of existing AKs.[1]

A practical tool that GPs can introduce to their patients is a mobile app called SunSmart (www.sunsmart.com.au/tools/interactive-tools/free-sunsmart-app). This app has useful features such as the ability to set alerts for sun protection, daily reminders for times when interval UV levels are damaging and two-hourly reminders to re-apply sunscreen.

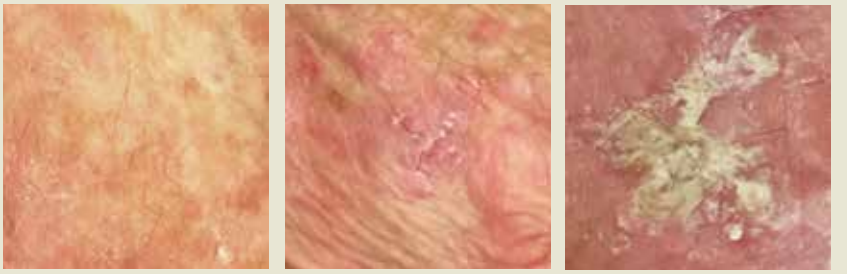
Cryotherapy

Cryotherapy with liquid nitrogen is a

CLINICAL AND DERMOSCOPIC GRADING OF ACTINIC KERATOSIS[9]

Clinical grades

I – slightly palpable **II – moderately thick** **III – hyperkeratotic**



Figures 3a to c. Clinical grades of actinic keratosis.

Dermoscopic grades

I – red pseudonetwork **II – 'strawberry pattern'** **III – 'yellow-white keratin'**

Figures 4a to c. Dermoscopic grades of actinic keratosis.

TABLE 1. CLINICAL AND DERMOSCOPIC FEATURES OF ACTINIC KERATOSIS

Grade	Clinical features	Dermoscopic features
I	Slightly palpable – better felt than seen Flat, pink maculae without hyperkeratosis	Red pseudonetwork pattern and discrete white scales
II	Moderately thick – easily felt and seen Moderately thick hyperkeratosis on the background of erythema	'Strawberry pattern' Background erythema intermixed with whitish-yellow, keratotic and enlarged follicular openings
III	Hyperkeratotic – clinically obvious Very thick scale More difficult to differentiate from SCC Background erythema	Structureless, 'yellow-white keratin' Enlarged follicular openings filled with keratotic plugs over a scaly yellow-white background or marked hyperkeratosis

TABLE 2. TREATMENT OPTIONS FOR ACTINIC KERATOSIS[11]

Treatment	Condition		
	Single or few (<6) distinct AK lesions in the affected area	**Multiple (≥6) distinct AK lesions or widespread actinic damage in the affected area**	**Widespread actinic damage or AK in patients with immunosuppression**
General	Sun protection (broad spectrum SPF 30+)		
First line	Lesion-directed therapy: • Cryotherapy	Field-directed therapy: • 5-FU • Imiquimod • Ingenol mebutate • Conventional or daylight PDT	Lesion-directed therapy: • Cryotherapy • Curettage and cautery Field-directed therapy: • 5-FU • Imiquimod • Conventional or daylight PDT
Second line	Lesion-directed therapy: • Curettage and cautery	Lesion-directed therapy: • Cryotherapy • Diclofenac	Field-directed and systemic therapy: • Nicotinamide (patients at high risk of nonmelanoma skin cancers) • Acitretin (immunosuppressed patients)

Abbreviations: AK = actinic keratosis; 5-FU = 5-fluorouracil; PDT = photodynamic therapy; SPF = sun protection factor.

mainstay of AK treatment and is most effective for thin, less keratotic lesions. Treatment involves a single freeze–thaw cycle with the freezing time lasting for three to seven seconds depending upon the site and lesion thickness. This method is effective in removing about 70% of all AKs.[13] This popular method is cost efficient, widely available and effective. Limiting factors include pain, risk of wound infection and potential for hypopigmentation.

5-Fluorouracil

5-FU is a topical cytotoxic agent used in 5% concentration to treat discrete or multiple AKs (including field changes), particularly involving the head and neck. It targets atypical keratinocytes in preference to normal skin. The 5-FU cream is usually applied once to twice daily for two to four weeks. A meta-analysis showed clearance and partial response rates of 87.8% and 62.5%, respectively, following one treatment cycle.[14]

5-FU acts by interfering with DNA and RNA synthesis of dysplastic keratinocytes. The most common (and expected) side effect is localised skin inflammation that

TABLE 3. TREATMENT MODALITIES AND INDICATIONS FOR ACTINIC KERATOSIS

Treatment	Protocol	Indications
Cryotherapy	Freeze lesion for about 3 to 7 seconds	Single or few (<6) distinct AK lesions in the affected area
Curettage and electrodessication	Shave lesion superficially followed by curettage (requires local anaesthetic)	Single or few (<6) distinct AK lesions in the affected area
5% Fluorouracil cream	Apply once or twice daily for 3 to 6 weeks depending upon site	Multiple (≥6) distinct AK lesions in an area or treatment of field
5% Imiquimod cream	Apply 3 times a week for 4 weeks. Follow this with a 4-week break from treatment, then treat again, applying again 3 times weekly for 4 weeks	Multiple (≥6) distinct AK lesions in an area or treatment of field
3% Diclofenac in 2.5% hyaluronic acid gel	Apply twice daily for 60 to 90 days	Multiple (≥6) distinct AK lesions in an area or treatment of field
0.015% Ingenol mebutate (150 µg/g) gel – face and scalp	Apply once daily for 3 consecutive days	Multiple (≥6) distinct AK lesions in an area or treatment of field
0.05% Ingenol mebutate (500 µg/g) gel – trunk and extremities	Apply once daily for 2 consecutive days	Multiple (≥6) distinct AK lesions in an area or treatment of field
Conventional photodynamic therapy	Apply photosensitiser cream (methyl aminolevulinate [MAL] 160 mg/g) and cover area from light for 3 hours before light treatment	Multiple (≥6) distinct AK lesions in an area or treatment of field
Daylight photodynamic therapy	Apply photosensitiser (MAL, 160 mg/g) and expose to daylight (outdoors) for 2 hours, then remove cream and protect from daylight for the remainder of day	Multiple (≥6) distinct AK lesions in an area or treatment of field
0.05% Topical tretinoin cream	Apply once daily	Multiple (≥6) distinct AK lesions in an area or treatment of field
Systemic acitretin	10 to 25 mg orally daily	Immunosuppressed patients
1% Topical nicotinamide	Apply twice daily	Patients at high risk of developing nonmelanoma skin cancer
Systemic nicotinamide	500 mg orally twice daily	Patients at high risk of developing nonmelanoma skin cancer
Chemical peels	Jessner's solution and 35% trichloroacetic acid applied by experienced operators	Multiple (≥6) distinct AK lesions in an area or treatment of field
Laser resurfacing	Ablative laser such as carbon dioxide and erbium:YAG (yttrium aluminium garnet) performed by experienced operators	Multiple (≥6) distinct AK lesions in an area or treatment of field

lasts for two to three weeks (Figure 5). The enzyme required to metabolise 5-FU, dihydropyrimidine dehydrogenase (DPD), is absent in about 5% of the population and mutated in another 3 to 5%. Individuals with deficient or mutated DPD may develop florid skin and even systemic reactions following topical 5-FU use.[15,16] Thus, it is essential to inform patients not only of the expected reactions but also the potential for exaggerated reactions to 5-FU, and instruct them to seek medical attention if unexpected reactions occur.

Currently, it is recommended that the maximum treatment surface area with 5-FU on skin is 500 cm^2 at one time.[15] However, off-label field treatment of widespread AKs on the limbs with topical 5-FU under occlusion (chemowraps) has gained traction in recent years.

In two studies (one with treatment over four to eight weeks and the other, 12 to 14 weeks), topical 5-FU applied to sun-damaged limbs under a zinc-containing occlusive dressing (chemowrap) and reviewed weekly was associated with substantial clinical improvement.[15,16] 5-FU

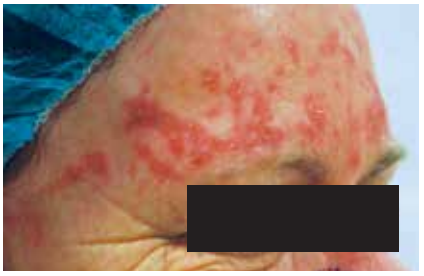


Figure 5. Common self-limiting localised skin inflammation associated with 5-fluorouracil.

chemowraps have been reported to be accepted by patients due to convenience and a low side effect profile.[15,16]

Imiquimod

Imiquimod is an immune-response modifier. This topical agent activates toll-like receptor 7, resulting in inflammation and subsequent clearance of dysplastic keratinocytes. In Australia, the 5% concentration cream is available and is applied three times weekly for four weeks. Then, after a four-week treatment-free period, the same treatment regimen for another four weeks is undertaken as tolerated.

In a multicentre randomised double-blinded study, imiquimod use was associated with complete and partial AK clearance rates of 45.1% and 59.1%, respectively.[17] Limiting factors for the use of imiquimod include cost (it is not PBS-listed for AK treatment), reduced adherence due to the long duration of treatment, and adverse effects such as severe inflammatory reactions, locally and systemically (Figure 6).

Diclofenac

Diclofenac decreases the levels of prostaglandin in skin cells. Although 3% diclofenac is an effective agent for thin AKs, patients are required to apply the agent twice daily for up to 90 days. This long duration of therapy can adversely affect treatment adherence. In a study where diclofenac was applied twice daily for 90 days, complete clearance of target lesions occurred in 50% of AKs, as compared with 20% using placebo.[18] Cost is a limiting factor because diclofenac is not PBS-listed for AK treatment.

Ingenol mebutate

Ingenol mebutate (0.015% or 0.05%, depending on the site) is one of the newest agents on the market used to treat AKs. It preferentially targets dysplastic cells by promoting apoptosis and induces neutrophil-mediated immunostimulatory effects.[19] This agent is applied once daily for two or three consecutive days, depending on the site. One study reported 35% complete and 53% partial response rates.[20] Due to the short treatment period, ingenol mebutate is associated with high patient satisfaction.[19,21] In practice, however, severe irritant reactions have occurred without achieving sustained clearance. A limitation of treatment is cost, as ingenol mebutate is not PBS-listed, and the small packaging size is single use for up to 25 cm^2, about the size of the dorsum of the hand.[19]

Curettage and electrodessication

Curettage and electrodessication (or cautery) is a modality well known to dermatologists, particularly for hyperkeratotic AK. This technique involves a superficial shave of the lesion, followed by curettage using a sharp-edged spoon curette (disposable or autoclavable). Ballpoint cautery or electrodessication of the superficial dermis follows. This procedure requires the use of local anaesthetic.

Light curettage is often used to debride hyperkeratotic lesions before cryotherapy or photodynamic therapy (PDT). The drawbacks to curettage include the need for local anaesthesia and the potential for hypopigmented scarring and wound infection.

Photodynamic therapy

Over the past three decades, conventional PDT has increased in popularity. Although it is more commonly used in the treatment of nonmelanoma skin cancers such as Bowen's disease and basal cell carcinoma (BCC), it has been adopted by some to treat large or hyperkeratotic AKs or as field treatment. Lesion treatment comprises gentle curettage of surface scale, followed by application of the photosensitiser cream, methyl aminolevulinate (MAL) 160 mg/g. This area is protected from light for three hours, during

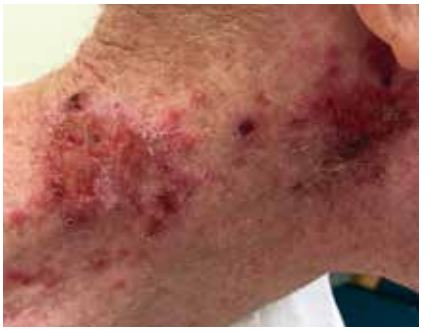


Figure 6. Local reaction to imiquimod.

which time the abnormal cells preferentially accumulate the MAL. The area is then illuminated with a red light source at a dose of 37 J/cm^2 at a distance of 5 to 8 cm. Depending upon the lamp, it can take 8 to 15 minutes to deliver this energy. A photodynamic reaction between the chemical MAL and light occurs, known as the photodynamic reaction, creating free oxygen radicals which destroy the cancerous cells. The efficacy rates are between 80% and 85%.[13] Limiting factors include cost, because it is not PBS-subsidised, and pain during treatment often requiring local anaesthesia.

Daylight photodynamic therapy

As for PDT, the MAL photosensitiser cream is applied but instead of covering the cream, the patient is advised to sit outdoors in daylight (the light source). Prior to this, the area has been gently debrided and a chemical sunscreen has been applied to the exposed skin. Immediately after application of the MAL cream, patients should be exposed to daylight for two hours, after which the excess MAL cream is removed. Patients must subsequently avoid outdoor light for the remainder of the day.[22]

Many patients prefer daylight PDT over conventional PDT because it is less painful and associated with a lower incidence of post-treatment inflammation. Generally, this treatment can be performed all year round in Australia; however, treatment is limited by the location of the AKs and if they are in an area usually covered by clothes. The Australian consensus supports use of daylight PDT to treat extensive chronic

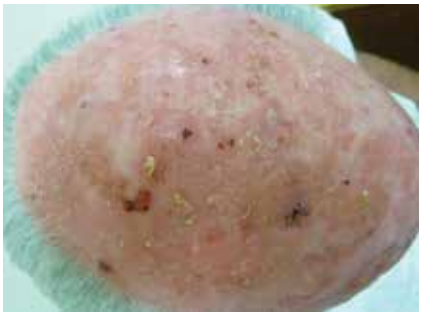


Figure 7. Actinic field damage on the scalp, suitable for treatment by daylight PDT.

actinic damage that can be exposed easily to daylight, particularly grade I and II AK on the face and scalp (Figure 7).[23]

Weather conditions can render the treatment less effective or necessitate the use of a greenhouse as an alternative to daylight illumination.[22] Currently, indoor 'daylight PDT' using artificial light sources are being trialled.[22]

Retinoids – topical and oral

Topical retinoids interact with nuclear retinoic acid receptors and promote cellular differentiation, therefore reducing dysplasia in AKs and promoting new collagen formation. The treatment duration of topical retinoid therapy, such as 0.05% tretinoin, is once daily for variable time periods, depending upon tolerability. As a pretreatment before 5-FU treatment, it is used up to four weeks beforehand. As maintenance therapy, it is used daily in an ongoing manner.

Oral retinoids are used in the management of widespread AKs, especially in the immunosuppressed population. Low-dose systemic retinoids, such as acitretin at a dose of 10 to 25 mg daily, have been shown to be effective in the secondary prevention of AKs in patients who have undergone renal transplantation. The low dose is generally well tolerated by patients, with a reasonable side effect profile. Refer to a dermatologist for prescription of oral retinoids in this setting.

Nicotinamide – topical and oral

It has been established that topical and oral nicotinamide (vitamin B3) are safe and inexpensive treatment options to reduce AKs because of the photoprotective effects of nicotinamide against carcinogenesis and immune suppression in keratinocytes.[24] In a randomised, double-blinded, placebo-controlled study, the topical application of 1% nicotinamide resulted in a significant reduction in AKs within the first six months of treatment, suggesting that nicotinamide may accelerate the natural seasonal resolution of AKs by reducing

UV-induced immunosuppression.[25]

Furthermore, 500 mg of oral nicotinamide twice daily resulted in a 13% reduction of AKs in patients using nicotinamide compared with matched placebo in a study after 12 months.[26] Oral nicotinamide has been shown to be beneficial for patients with extensive AKs or at high-risk of developing nonmelanoma skin cancer; however, it has not been shown to be of value in patients without a significant history of skin cancer nor is it recommended for children.[27]

Oral nicotinamide has also been suggested as an effective and safe chemopreventive agent in transplant patients according to a recent phase 2 clinical trial.[28] The routine use of nicotinamide is however not currently recommended until a phase 3 clinical trial is performed to ensure safety in this patient population.

It is important to note that oral chemoprevention (with retinoids and/or nicotinamide) does not negate the need for sun protection measures and regular cutaneous surveillance, commensurate with an individual's skin cancer risk profile.

Chemical peels

Superficial, medium and deep chemical peels have been used for decades to reduce field epidermal dysplasia. A common medium depth peel is a combination of Jessner's solution and 35% trichloroacetic acid, but the procedure needs to be performed by an experienced operator because irreversible scarring may occur.

Laser resurfacing

Ablative laser treatments such as carbon dioxide and erbium:YAG (yttrium aluminium garnet) have water as their chromophore and emit wavelengths that are able to penetrate the epidermis to varying depths. In the 1980s and 1990s, full resurfacing was used to remove field actinic damage but it was fraught with loss of pigment and demarcation lines at the jaw line. Fractionated systems now exist but as they leave columns of cells to repopulate, AK recurrence is not uncommon. Lasers are best used in conjunction with other modalities.

Other treatments

A variety of other agents, predominantly with antioxidant properties, have been proposed as potential AK treatments, including beta-carotene, vitamin E, lycopene and green tea extracts. However, the evidence is not strong to support their use.

Conclusion

AKs are cutaneous, premalignant lesions found on sun-exposed areas that have the potential to transform into SCCs. Therefore, early identification and treatment of AKs are essential to prevent the progression to invasive disease.

The most important and often forgotten measure to treat AKs is sun protection with high SPF sunscreen, protective clothing and reduced sun exposure. In addition, a number of treatment modalities, divided into lesion-direct or field-directed treatments, can be used. Given the spectrum of AK, a patient may require multimodal or sequential therapies.

Follow up is essential to ensure that clearance of AK has occurred and, more importantly, to detect recurrence or progression to malignancy. MT

References

A list of references is included in the website version of this article (www.medicinetoday.com.au).

COMPETING INTERESTS: None.

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