Management of actinic keratosis

There are many different treatments available for patients with actinic keratosis. Choosing the correct treatment regimen and being aware of its limitations can reduce the burden of disease and help to prevent squamous cell carcinoma.

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Actinic keratosis often occurs during and after the midlife stage and is primarily caused by prolonged exposure to ultraviolet radiation. Clinical features of this condition include lesional hyperkeratoses, often with underlying inflammation and occasional hyperpigmentation. Actinic keratoses often vary in size (from a few millimetres to over a centimetre in diameter) and can be found adjacent to one another. They are most likely to appear on sun exposed areas, such as the face, ears, bald scalp, neck, backs of hands, forearms and lips.

Actinic keratoses are well recognised potential precursors of squamous cell carcinomas. The proportion of actinic keratoses that develop into squamous cell carcinomas is estimated to be as high as 16% during a 10-year period, although in practice it is much less.[1] It can be difficult to identify early squamous cell carcinomas in patients with extensive keratoses. Clearing of background actinic keratoses enables easier visualisation of invasive skin malignancy.

Treatment

There are many different treatments available for patients with actinic keratosis; however, the appropriate treatment depends on a number of factors, which are listed in Table 1. Treatments can be grouped according to the thickness and number of actinic keratoses on an individual (Table 2). Many topical applications, such as imiquimod (Aldara) and 5-fluorouracil (Efudix), can clear both the visible and the nonvisible lesions; these latter lesions can become inflamed during treatment.

Patients with actinic keratosis are often treated over a period of time because lesions can continue to erupt, depending on the level of exposure to ultraviolet radiation. Some patients with severe actinic keratosis require cryotherapy treatments as frequently as every six weeks, particularly if they have not had any treatment for some time. Other patients require treatment at 12-monthly intervals, or sometimes even longer. It is possible to increase

IN SUMMARY

- **Actinic keratosis often occurs during and after the midlife stage and is primarily caused by prolonged exposure to ultraviolet radiation. Clinical features of this condition include lesional hyperkeratoses, often with underlying inflammation and occasional hyperpigmentation.**
- **Actinic keratoses are well recognised potential precursors of squamous cell carcinomas.**
- **There are many different treatments available for patients with actinic keratosis. These include topical retinoids and keratolytics, topical 5-fluorouracil, imiquimod and diclofenac sodium 3% gel, cryotherapy, photodynamic therapy, chemical peels, curettage and electrodessication, facial resurfacing and radiotherapy.**
- **Referral of patients to a dermatologist should be considered if a decision on the most appropriate treatment is difficult to make, a treatment that is indicated is unavailable to the GP or a patient does not respond to therapy.**

the interval between treatment schedules by treating the preclinical lesions.

In general practice, mild actinic keratosis (Figure 1) is easy to manage. Referral of patients to a dermatologist should be considered if a decision on the most appropriate treatment is difficult to make, a treatment that is indicated is unavailable to the GP or a patient does not respond to therapy.

Table 1. Factors that influence choice of treatment

- Nature of the keratoses (e.g. mild or severe disease)
- Site of the keratoses
- Extent of the keratoses
- Density of the keratoses
- Patient immunosuppression
- Medical comorbidities
- Age of the patient
- Patient pain tolerance
- Cosmetic considerations
- Presence of carcinomas

Avoidance of and protection from the sun

Treatment begins with avoidance of and protection from the sun. The difference that avoidance of exposure to ultraviolet radiation can make is often underestimated. Adequate photoprotection can prevent new actinic keratoses from occurring and prolong clinical remission in patients with existing lesions.[2]

It is useful to inform patients that light shade is equivalent to an SPF of only 2 and that the sun should be avoided between the hours of 10.00 a.m. and 3.00 p.m. Clothing (e.g. lycra surf shirts) is more effective than sunscreens at protecting the skin from the sun. (The more opaque the clothing is when held up to the light, the better the protection.)

Actinic keratoses can resolve naturally, and this is enhanced by complete avoidance of exposure to ultraviolet radiation. Ultraviolet radiation can induce immunosuppression. Susceptibility to immunosuppression has been shown to be associated with skin that is sensitive to sunburn. Patients are often unaware of the importance of indirect radiation.

Topical keratolytics and retinoids

A number of topical keratolytics have been used to treat patients with actinic keratosis for many years. These include 3 to 6% salicylic acid, 10% urea cream, 50% propylene glycol preparations and various alpha hydroxy acid preparations. Keratolytics often clear mild keratoses and enable visualisation of underlying neoplasia. Twice daily applications are more efficacious than once daily applications. Keratolytics have the advantage of high patient acceptance; however, complete clearance does not often occur and there can be recurrence of the keratoses after treatment cessation. Treatment with keratolytics is suitable for patients with mild actinic keratosis or for older patients who cannot tolerate the more aggressive therapies.

Topical retinoids can be use to treat individuals with actinic keratosis but are probably not optimal as monotherapy. They should be applied at night. If scaling is reported, the number of applications should be reduced. Patients with a high number of hyperkeratotic lesions tend to be less responsive to topical retinoid treatment.

Topical 5-fluorouracil

Topical 5-fluorouracil is efficacious in treating patients with actinic keratosis. The cream is applied to the face twice a day for two to three weeks, and the endpoint of treatment is erosion of the lesions.

Patients can become extremely uncomfortable when the lesions erode, particularly if they have a large number of them

Table 2. Actinic keratoses treatments according to lesion size and number

Thin lesions (0 to 1 mm) and a low number (<5 per 100 cm^2)

Gentle cryotherapy (freeze–thaw time of five to 10 seconds)
Topical retinoids and keratolytics (e.g. 3 to 6% salicylic acid, 10% urea cream, 50% propylene glycol preparations and various alpha hydroxy acid preparations)
Topical diclofenac sodium 3% gel
Topical 5-fluorouracil
Topical imiquimod

Thicker lesions (1 to 4 mm) or a high number of lesions (>5 per 100 cm^2)

Moderate cryotherapy (freeze–thaw time of 10 to 15 seconds)
Photodynamic therapy
Chemical peels
Topical 5-fluorouracil
Topical imiquimod

Thick lesions (>5 mm)

Aggressive cryotherapy (freeze–thaw time of 15 to 30 seconds)
Curettage with or without electrosurgery
Dermabrasion
Laser resurfacing
Adjunctive oral retinoids (for extensive disease)
Excisional surgery

(over 100) on the face. However, this can be managed by treating small regions at a time. Exposure to sunlight should be minimised because it can cause intense pain and discomfort to patients in the areas that are being treated. Flexures near the nose, mouth or eyes are often irritated and best avoided. Application of topical 5-fluorouracil can worsen other cutaneous conditions, such as melasma or rosacea. Allergy to the drug or its delivery vehicle can be quite severe and is identified by erythema in all regions that the cream has been applied rather than only in the areas of keratoses (Figure 2).

If allergy to 5-fluorouracil occurs, the application of 1% hydrocortisone cream twice daily for one week is appropriate. This will also speed the resolution of the erythema.

The effect of two to three weeks' treatment with 5-fluorouracil can last for up to five years before application needs to be repeated. The duration of treatment should be increased to four weeks when treating the arms of patients as the keratoses in this region are slower to respond.

Topical imiquimod

Topical imiquimod is a useful agent to treat either a region of actinic keratoses or individual lesions. In cosmetically sensitive areas, particularly on the face, the cosmetic outcome is excellent in most patients. Lesional inflammation is to be expected with current protocols. Of the various treatment regimens proposed, the protocol of two or three applications per week for six weeks seems to be most effective. Treatment is then reviewed after the cycle and repeated if necessary for one further cycle. There is no benefit from further cycles if the keratoses are resistant to treatment.

Imiquimod binds to the toll-like receptor 7, which is a natural ligand for influenza RNA. This induces secretion of proinflammatory cytokines, predominantly interferon-alpha, tumour necrosis factor-alpha and interleukin-12. In the setting of marked involvement of a region with actinic keratoses more inflammation is expected. Excessive release of interferon-alpha can give symptoms of a flu-like illness. Although this is uncommon, it can be disabling and generally precludes further treatment.

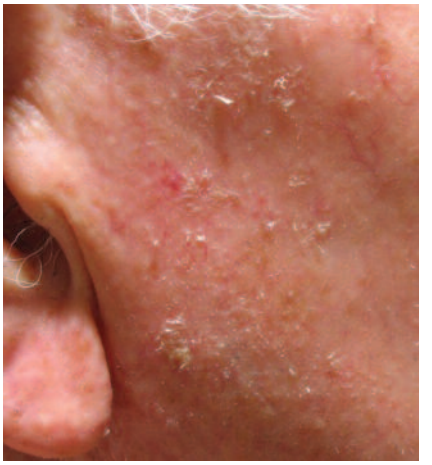


Figure 1. A patient with mild actinic keratosis.

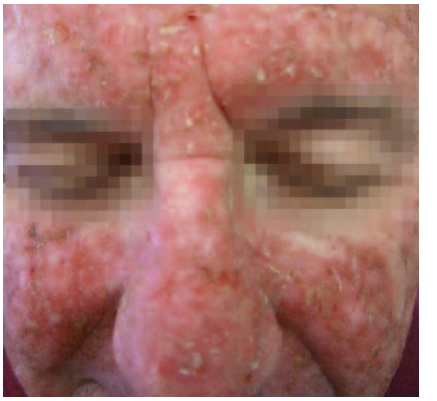


Figure 2. An irritant reaction to treatment with topical 5-fluorouracil in a patient with actinic keratosis.

If significant inflammation occurs on the skin, a reduction in the number of applications or a rest from treatment for a week will most likely be necessary. This does not affect efficacy provided that some inflammation is maintained. When complete clearance of actinic keratoses is achieved, remission periods of two to three years can be expected.

Topical diclofenac sodium 3% gel

Diclofenac gel (Solaraze) has recently been approved by the TGA for management of actinic keratosis. The gel is well tolerated in patients, however, there is a long duration of therapy of 90 days and it is not as effective as topical 5-flourouracil. Diclofenac gel could be a preferred starting option for patients with public obligations because there is less inflammation compared with other topical agents.

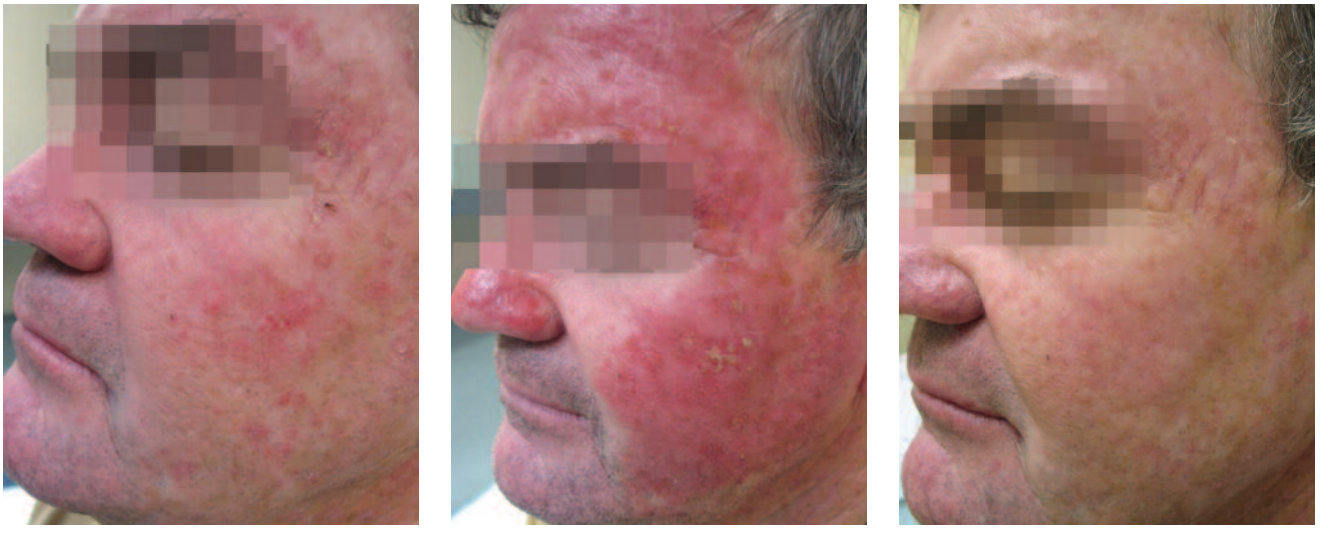
Cryotherapy

Cryotherapy remains the current standard technique to manage patients with actinic keratosis. Cure rates of up to 98.8% have been reported.[3] Treatment with liquid nitrogen achieves a skin temperature of -50°C.

A recent multicentre study of 90 patients with untreated actinic keratoses greater than 5 mm in diameter on the face and scalp investigated a single freeze–thaw cycle of cryotherapy.[4] The results showed that with a freeze–thaw time of less than five seconds, the complete response rate of the treated lesions was 39%. A freeze–thaw time of longer than 10 seconds gave a complete response rate of at least 80%. A freeze–thaw time longer than 10 seconds but less than 15 seconds produced the optimal balance between maximisation of efficacy and minimisation of long term undesirable effects. (The freeze–thaw time is the time from the white ice appearing until the ice has thawed out). The incidence of hypopigmentation increased with longer freeze–thaw times and was present in 29% of lesions that showed a complete response and 6% of lesions that showed an incomplete response.

Cryotherapy is more efficacious with a double freeze–thaw cycle and can be used in patients with hyperkeratotic keratoses. Remission periods are variable and can last between three and 12 months.

Cryotherapy can cause significant pain, particularly on the scalp and forehead



Figures 3a to c. A patient with actinic keratosis before (a, left), two days after (b, centre) and four weeks after (c, right) photodynamic therapy.

regions. Techniques to reduce the discomfort include infiltration with local anaesthesia prior to cryotherapy. Oral pain killers can be taken 30 minutes before treatment and are most useful in decreasing pain after a session of cryotherapy. Various techniques of after care, such as application of weak antiseptics, can help reduce the risk of infection.

Photodynamic therapy

Many dermatologists use photodynamic therapy (PDT) to treat patients with actinic keratosis and superficial basal cell carcinoma (Figures 3a to c). Two sessions of PDT using topical methyl aminolevulinate (Metvix) have been shown to be effective in removing 91% of lesions in patients with actinic keratosis.[5] PDT can be used to treat a region of keratoses, the treatment can be repeated and the cosmetic outcome is superior to that achieved with cryotherapy. PDT may be particularly advantageous in patients with large and/or multiple lesions and if lesions are in sites where disfigurement or poor healing from conventional therapies is a particular risk.[6] Remission periods can last 12 to 24 months.

The disadvantage of PDT is that in approximately 10 to 15% of patients there is significant discomfort associated with the photoactive protoporphyrin. There is an unpredictable interindividual variation in the degree of pain experienced. Pain is less common with methyl aminolevulinate than with aminolevulinic acid because of a reduced uptake by the cutaneous nerves. The use of refrigerated air can reduce pain by up to 60%. Patients with severe pain may require regional local anaesthesia.[7]

Patients with mild actinic cheilitis treated with PDT using methyl aminolevulinate have also shown a dramatic improvement after two treatment sessions, one week apart. Patients experienced a postprocedure inflammatory stage lasting for five to seven days. There was no textural change to the lip as can be seen after treatment with laser resurfacing using carbon dioxide.

Chemical peels

Many different chemical peels have been used to control actinic keratoses. The more aggressive the chemical peeling agent is, the more improvement one can expect. Usually a medium depth peel would be necessary to produce a significant improvement in patients with actinic keratosis.[8] However, patients often experience postoperative swelling and discomfort to achieve the desired results.

Patients will need a week of rest after a medium depth peel. To treat patients using chemical peels, referral to a dermatologist will often be necessary. The improvement after a medium depth peel should last for two to three years. The techniques used for chemical peels are well described elsewhere.[8]

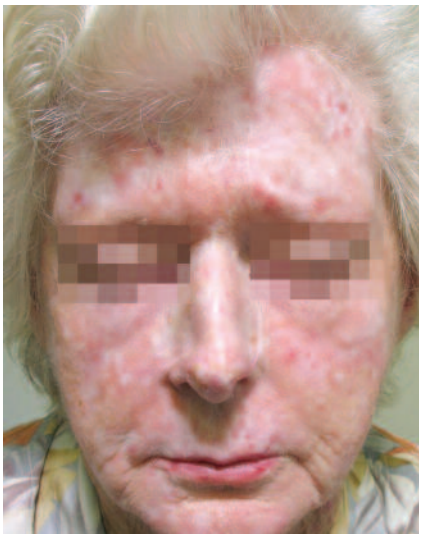


Figure 4. A patient with severe actinic keratosis who is suitable for facial resurfacing.

Curettage and electrodessication

Patients with hyperkeratotic keratoses who do not have squamous cell carcinomas are best treated with curettage and electrodessication. Any induration not due to the keratin may indicate a squamous cell carcinoma. Histological evaluation is often necessary for these hypertrophic lesions. Rarely, excision will be necessary for persisting hypertrophic lesions, particularly if hypopigmentation will cause cosmetic concern and if the scar line can be concealed in a crease.

Facial resurfacing

Full facial resurfacing with either an ablative laser or dermabrasion should be considered in patients with severe sun damage who have a significant number of actinic keratoses and have had multiple excisions for skin tumours. Ongoing ultraviolet exposure is contraindicated because there will be significant postoperative hypopigmentation. Therefore, only patients who are able to avoid ongoing sun exposure should be considered for this more aggressive procedure. Patients who undergo facial resurfacing need to be selected carefully because of significant healing times and risks of scarring (Figure 4).

Counselling patients requiring facial resurfacing is important. It is a major procedure that should be performed by an experienced operator, usually a dermatologist or plastic surgeon with laser training, to avoid unnecessary complications. Patients who undergo the procedure should avoid repeat carbon dioxide resurfacing because the risks, particularly of scarring, are greatly increased.

Radiotherapy

Radiotherapy, although effective, is not recommended because it will preclude future radiotherapy treatment in the region, should it become necessary.

Summary

An increasing array of treatments is available for patients with actinic keratosis. By studying the various techniques and being aware of their limitations the burden of disease can be reduced, helping to prevent squamous cell carcinoma. Referral of patients to a dermatologist is beneficial if a decision on the most appropriate treatment is difficult to make, the treatment that is indicated is not available to the GP (such as PDT) or a patient does not respond to therapy. MT

References

1. Babilas P, Landthaler M, Szeimies RM. Actinic keratoses. Hautarzt 2003; 54: 551-560.
2. Marks R. Epidemiology of non-melanoma skin cancer and solar keratoses in Australia: a tale of self-immolation in Elysian fields. Australas J Dermatol 1997; 38(1 Suppl): S26-29.
3. Lubritz RR, Smolewski SA. Cryosurgery cure rate of actinic keratoses. J Am Acad Dermatol 1982; 7: 631-632.
4. Thai KE. Fergin P, Freeman M, et al. A prospective study of the use of cryosurgery for the treatment of actinic keratoses. Int J Dermatol 2004; 43: 687-692.
5. Freeman M, Vinciullo C, Francis D, et al. A comparison of photodynamic therapy using topical methyl aminolevulinate (Metvix) with single cycle cryotherapy in patients with actinic keratosis: a prospective, randomized study. J Dermatolog Treat 2003; 14: 99-106.
6. Braathen L, Szeimies R, Basset-Seguin N, et al. Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: an international consensus. International Society for Photodynamic Therapy in Dermatology, 2005. J Am Acad Dermatol 2007; 56: 125-143.
7. Pua VS, Barnetson RS. Photodynamic therapy for skin cancers. Med Today 2006; 7(2): 37-40.
8. Otley CC, Roenigk RK. Medium-depth chemical peeling. Semin Cutan Med Surg 1996; 15: 145-154.

DECLARATION OF INTEREST: Dr Freeman has no financial interest. He has performed trials for Photocure on Metvix and for 3M on Aldara.