Current management of actinic keratosis in primary care

Tony Downs FRCP

The incidence of actinic keratosis is increasing and it is a risk factor for developing basal and squamous cell carcinoma. Here, the author discusses its management and the available treatment options.

Figure 1. AKs are associated with excessive sun exposure and treatment should include a general examination for skin cancer

Actinic keratoses (AKs), also known as solar keratoses, appear on chronic sun-exposed skin as a result of accumulated (rather than intermittent) ultraviolet B exposure. The face, lips, ears, forearms, back of the hands, neck and anterior chest are the commonest sites, and the whole area or ‘field’ is damaged. Rough, sand-papery, dry, flat or slightly raised localised lesions are easily identifiable (see Figure 1). The changes can be more diffuse on a background of dyspigmentation, telangiectasia and thinned and wrinkled skin (solar elastosis).

Lesions can be flesh, pink, grey or red macules, or up to 1 cm in diameter. They can flake white scale or be hard, wart-like and firmly adherent – bleeding when picked or scratched. Patients may complain of itching, burning and skin sensitivity.1,2

The incidence of AKs is increasing. Males are more commonly affected, as are older patients and those with low immunity, excessive recreational and occupational sun exposure and fair skin.1 In the UK, approximately 19–23 per cent of those over 60 have AKs.3

What is the clinical significance of actinic keratosis?

AKs are a marker for sun damage and highly associated with the risk of developing basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). If AKs are observed then an examination of the sun-exposed skin (including the lower legs and upper back) looking for unrecognised skin cancer is obligatory.

In the long term, AK will transform into SCC. The relative risk will depend on lesion thickness, grade of inflammation, degree of surrounding photo damage, previous SCC and immune status (immunosuppressed or old). The quoted transformation rates range from 0.1 to 15 per cent.1,2

Spontaneous regression rates for individual lesions have been quoted as 26 per cent, but this is in a dynamic field with newly developing lesions conferring only a 4 per cent overall percentage decrease in 12 months of clinically observable lesions in patients not receiving treatment (other than reducing their sun exposure).4

Within an AK field there will be a high-risk population of subclinical invisible disease, multiple primary tumours, recurrences and premalignant change. If only the individual lesions are targeted for treatment then, over time, multiple treatments with increasing morbidity will be required.1,5

It is impossible to predict which AKs will progress into SCC. Assessing AK
severity is not always that straightforward. Statistically, lip and ear AKs are more likely to transform. Lesions that have changed by becoming inflamed, thicker, rapidly enlarged, ulcerated, greater than 1cm in diameter or painful are all associated with SCC transformation and should be referred to secondary or intermediate care for assessment as per NICE skin cancer guidelines.6,7

How should actinic keratoses be treated?
Some but not all AKs require treatment, and most can be safely treated in primary care. Patients may seek treatment because lesions are unsightly and symptomatic, while physicians may choose to treat AKs to prevent disease progression and reduce long-term SCC risk.

Treatment of AK must include a general examination for skin cancer, patient education on the use of all-year-round sun block and reduced sun exposure, advice on self-monitoring for changing lesions and an agreed follow-up plan (see Table 1).

For mild AKs, this treatment may be sufficient. If a topical treatment is prescribed it is important to discuss this in detail as many have temporary unpleasant side-effects.

Suggested field-directed treatment is outlined in Table 2 and lesion-directed treatment in Table 3.

The dorsum of the hands responds less well to topical treatment.

Organ transplant patients with AKs or skin cancer should be managed in dedicated secondary-care clinics.5,6

Treatment options
A comparison of the field treatments is made in Table 4.

Diclofenac/hyaluronic acid gel
Diclofenac 3 per cent/hyaluronic acid 2.5 per cent gel (Solaraze) induces selective skin tumour cell apoptosis (death). Some AKs will clear with twice-daily treatment for 60 days, but maximum benefit is at 90 days. The treated area should be reassessed one month after treatment cessation. Meta-analysis shows 40 per cent complete clearance with 30 per cent recurrence at 12 months.

Adverse effects are mild to moderate (itching, redness, dryness and occasional photoallergic or contact dermatitis). Sun exposure should be avoided but the simultaneous use of sunscreens on efficacy is not known.

Systemic absorption is negligible but a theoretical warning exists regarding avoidance in patients who would otherwise avoid oral NSAIDs.

With a maximum dose of 8g per day large areas can be treated.8,9

5-fluorouracil cream
5-fluorouracil (5FU) inhibits DNA synthesis in fast-growing cells leading to cell death. Inflammation is required to produce a therapeutic effect. Available as a 5 per cent cream (Efudix) applied twice a day for three weeks it causes extensive erosions; less frequent application reduces the therapeutic effect. Maximum inflammation is at the end of the treatment period and worse in skin folds such as the nasolabial fold.

Itching, pain, tenderness, dyspigmentation, ulceration and photosensitivity are also common side-effects. It can take up to six weeks after treatment for the skin to heal (and longer on the arms or legs). Persistent redness and skin sensitivity usually fades over several weeks or occasionally months.

Co-prescribing a topical steroid is popular but in reality shows no evidence for reducing side-effects or accelerating healing. Avoid occlusive dressings and prolonged sunlight exposure. Mucosal application is not recommended but out of licence use on the lips for actinic cheilitis can be very effective.

Initial clearance rates of 50 per cent and a later recurrence rate of 55 per cent have been reported. However, many patients discontinue treatment because of the inflammation, thereby reducing overall efficacy in routine clinical practice.

Large areas can be treated but it is usually applied in a ‘piecemeal’ fashion over time, allowing one area to recover before treating another.2,10

Ingenol mebutate gel
Ingenol mebutate gel (Picato) is supplied as a box of either three single-use only tubes (0.015 per cent) applied for three consecutive days over a 25cm² area of the face or scalp, or two tubes (0.05 per cent) applied for two days on the limbs or torso. The gel must be refrigerated by the patient once dispensed. It should be allowed to dry on for 15 minutes and patients advised not to touch the treated area to avoid gel transference to elsewhere. Periorbital skin should be avoided because of oedema; this may also be observed around the mouth.

It probably selectively targets p53-mutated skin cells causing rapid cell necrosis and a secondary delayed anti-tumour immune response.

Local inflammatory reactions (crusting, flaking, shallow erosions, redness, oedema, pustulation) peak on day 4 and are mostly settled by day 14. Inflammation is confined to the epidermis so dyspigmentation or scarring is not a feature. Selective targeting of p53-damaged skin means little or no gel reaction on nonphotodamaged skin.

Approximately one-third of patients will experience a marked inflammatory response. Clearance rates of 40–54 per cent sustained at 12 months with only 13 per cent recurrence have been reported.11

<table>
<thead>
<tr>
<th>Table 1. Stepwise treatment approach to AK</th>
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<tbody>
<tr>
<td><strong>Step 1</strong> Patient education and examine for unrecognised skin cancers.</td>
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<tr>
<td><strong>Step 2</strong> Treat the field.</td>
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<tr>
<td><strong>Step 3</strong> Reassess at 6 weeks post field treatment and treat any residual lesions with lesion-directed therapy. If field changes still present, choose an alternative field treatment and reassess again.</td>
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<tr>
<td><strong>Step 4</strong> Reassess at 6 weeks post lesion treatment. If clear arrange follow-up 6–12 months, or sooner if recurrences occur. If lesions persist then curette for histology or refer to intermediate or secondary care.</td>
</tr>
</tbody>
</table>

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Table 2. Suggested field-directed treatment

**Imiquimod cream**

*Imiquimod 5 per cent cream (Aldara)* Imiquimod is a Toll-like receptor agonist that induces an enhanced antitumour cellular immunity. The 5 per cent cream is dispensed as one box of 12 sachets to treat a 25cm² area. It is recommended to discard each sachet once opened, but it is common practice to refrigerate opened sachets and reuse within seven days.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td><strong>First line</strong></td>
<td></td>
</tr>
<tr>
<td>5FU cream</td>
<td>cost effective</td>
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<tr>
<td><strong>Second line</strong></td>
<td></td>
</tr>
<tr>
<td>ingenol mebutate gel</td>
<td>high adherence, good efficacy and cosmesis, well tolerated, very low recurrence rate well tolerated, good cosmesis, low recurrence rate</td>
</tr>
<tr>
<td>3% diclofenac gel</td>
<td></td>
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<tr>
<td><strong>Third line</strong></td>
<td></td>
</tr>
<tr>
<td>photodynamic therapy</td>
<td>high efficacy, low recurrence, well tolerated, good cosmesis and adherence 5% shows good efficacy</td>
</tr>
<tr>
<td>imiquimod</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Suggested lesion-directed treatment

**Imiquimod 3.75 per cent cream (Zyclara)** is also prescribed as sachets for up to an area of 100cm². It is to be applied twice a week for two weeks and repeated after two weeks. Clinical evidence and therefore recommended use is limited to the face and balding scalp only.

Side-effects are similar to imiquimod 5 per cent but with a less severe inflammatory reaction (but this is unpredictable) and a shorter recovery period (approximately two weeks).

Initial average clear or nearly-clear rates of 36 per cent are reported with 60 per cent recurrence at 12 months. 13

**Photodynamic therapy**

This is usually in combination with methyl aminolevulinic acid (Metvix) 16 per cent cream applied for three hours under occlusion and photo activated. It is highly selective and causes cell death with minimal inflammation and quick healing. This is an excellent treatment for delicate skin at risk of ulceration or poor wound healing such as the lower legs or inflamed scalps. A sustained clearance rate of 50 per cent with one treatment and 70–90 per cent with two treatments have been reported.

This therapy is only available in secondary or intermediate care. While onward referral and perceived high cost have limited widespread use, it is recommended in NICE guidance 7 and an economic evaluation of AK treatments (sponsored by the manufacturer) shows it is in fact a more cost-effective treatment than imiquimod cream. 14,15

A 78mg per g gel formulation of 5-aminolevulinic acid (Ameluz) is now also available.

**5-fluorouracil/salicylic acid**

5FU 0.5 per cent/salicylic acid 10 per cent solution (Actikerall) is applied daily for 12 weeks to moderately thick hyperkeratotic lesions. Up to 10 lesions within each 5cm² area can be treated. Remove the dried-on film before each application.

A sustained clinical clearance of 85 per cent has been reported at 12 months. A variable amount of inflammation is anticipated.

Recurrences within the treatment field have not been formally assessed, but would be expected to be a common occurrence. 16

**Cryotherapy with liquid nitrogen**

This treatment for individual lesions is extremely user dependent. Clearance rates of 83 per cent have been reported with a 20-second freeze-thaw cycle and 39 per cent clearance with a five-second cycle.
Actinic keratosis

Expect multiple recurrences over time within the cryotherapy treatment field. In addition, skin freezing over 15 seconds risks permanent hypopigmentation. Short-term side-effects include pain, blistering and oedema. Nevertheless, where available it is liked for its speed of treatment and convenience.

Hyperkeratotic lesions are unlikely to respond without initial debridement.1–6

Combination treatments
Increased efficacy has been observed by initially treating the field with imiquimod or 5FU cream followed by cryotherapy. It is likely that this would also be seen with diclofenac gel, ingenol mebutate or photodynamic therapy followed by cryotherapy or 5FU/salicylic acid solution.1,2

Conclusion
When treating AKs consider the extent, patient age/co-morbidity factors, tolerability to previous treatments, treatment side-effects, product familiarity, patient preference, cosmetic outcome and cost. Treatment efficacy and adherence are both important and inter-related.

Unless a few clearly isolated lesions are all there are, field-directed therapy should be chosen first (see Table 2) and lesion-directed therapy for any untreated/unresponsive lesions that remain (see Table 3).1–6

References
7. NICE. Improving outcomes for people with skin tumours including melanoma. May 2010.

Declaration of interests
Dr Downs has received payments to attend educational meetings from Almirall, LEO Pharma, Galderma and 3M. He has also been involved in recruiting patients for commercial trials for LEO Pharma and Galderma.

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Letters

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Table 4. Comparison of AK field-treatment characteristics

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Ingenol</th>
<th>5FU cream</th>
<th>Diclofenac gel</th>
<th>2.5% imiquimod</th>
<th>5% imiquimod</th>
<th>PDT</th>
</tr>
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<tbody>
<tr>
<td>Adherence</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+++</td>
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<tr>
<td>Tolerability</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
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<tr>
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<td>+++</td>
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<td>+++</td>
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<tr>
<td>Sustained response*</td>
<td>+++</td>
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<td>+++</td>
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</table>

*observed low recurrence in clinical trial

PDT = photodynamic therapy

Table 4.

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