Actinic Keratosis: A Practical Overview

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Introduction

Actinic keratosis (AK) is a prevalent skin condition that warrants 5.2 million office visits in the US each year.1 Strongly associated with ultraviolet (UV) exposure, AK is widely regarded as a premalignant condition that can progress to squamous cell carcinoma (SCC).2-8 Data regarding the risk of progression to malignant disease ranges from 0.025% to 16% per year.7 Prevalence of AK has been reported to be as high as 38% and 46% in certain Dutch and Australian communities respectively.9,10 Given the prevalence and risk of progression to invasive disease, general consensus is that treatment and prevention11-14 of AK in a timely manner is important in reducing the incidence of non-melanoma skin cancer. Studies have shown that a large proportion of SCC lesions arise from pre-existing AK.4,5,15

Presentation & Diagnosis of AK

• AK is characterized by abnormal proliferation of keratinocytes that have large and variably shaped nuclei, found in the basal cell layer of the epidermis.12
• It typically presents as pink-red dry, rough, scaly papules or plaques measuring a few millimetres in diameter to no larger than 1 cm.12,16
• Lesions can sometimes be sensitive.
• AK is found more commonly on areas of the body exposed to the sun, such as the face, upper chest, and dorsal surface of the arms and hands.12
• Diagnosis is typically made on a clinical basis but one study demonstrated high sensitivity and specificity (95.6% and 95% respectively) with use of dermoscopy.11
• The differential diagnosis for AK includes SCC, Bowen's disease, basal cell carcinoma (BCC), and lentigo maligna melanoma.12
• Many risk factors have been linked to the development of AK, most notably sun exposure, fair skin, male gender, and older age.9,17-19
• UV radiation from the sun is damaging to skin DNA and has been directly implicated in the pathogenesis of AK.
• UV radiation hampers the natural immune response and increases immunosuppression, ultimately increasing the risk of SCC.20 Therefore, sunscreen use as well as clothing, hats and sunglasses have long been encouraged as a preventative measure against AK.14

Overview of Treatment Options

Treatment for AK can be divided into two categories:
1. Targeted (local) therapy
2. Field therapy
Common side effects of imiquimod therapy include hypopigmentation, erythema, crusting, and ulceration. Although many of the field therapies have been shown to be efficacious and tolerable, the range of clearance rates varies significantly (39-100%). A number of recent studies have demonstrated good clearance with a temperature of -5°C. However, more recent studies have demonstrated variable clearance rates. One study demonstrated that imiquimod has demonstrated good clearance with a temperature of -5°C.

Curettage and electrodessication involve the scraping down of an AK lesion followed by electrocautery. However, more recent studies have demonstrated good clearance with a temperature of -5°C. For example, one study demonstrated that curettage and electrodessication are highly efficacious, targeted therapy (specifically cryosurgery) continues to be the mainstay first-line treatment for AK. There is a growing literature to show that a combination of targeted and field therapy has an advantage over either of the therapies as standalone.

Targeted Therapy

- Examples of targeted treatment include cryotherapy with liquid nitrogen and curettage with electrodessication.
- One limitation is that only a small number of lesions can be treated at once.
- Additionally, because subclinical changes can occur to the DNA of skin (also known as field cancerization), targeted therapy is not ideal for extensive UV-damaged skin.

Field Therapy

- Field therapy can address both clinically apparent as well as occult disease.
- It encompasses topical treatments such as 5-fluorouracil, imiquimod, ingenol mebutate, and diclofenac sodium gel.
- Although many of the field therapies have been shown to be highly efficacious, targeted therapy (specifically cryosurgery) continues to be the mainstay first-line treatment for AK.
- There is a growing literature to show that a combination of targeted and field therapy has an advantage over either of the therapies as standalone.

Local Treatments

Cryotherapy Treatment Regimen:

1. One freeze-thaw cycle, 5-15 seconds, and 1mm margin.

Overview

- Cryotherapy is a widely used treatment option that involves cold temperature to physically destroy cells of skin lesions.
- It is one of the most commonly used treatments for AK.
- Liquid nitrogen is sprayed onto the lesion, bringing the skin to a temperature where cell death occurs. Early studies suggested that temperatures of -30°C to -40°C were needed to kill keratinocytes. However, more recent studies have demonstrated good clearance with a temperature of -5°C.
- Cryotherapy has been shown to be both highly efficacious and tolerable but the range of clearance rates varies significantly (39-100%). Another study demonstrated a complete clearance rate of 75% at 3 months.
- The duration of freezing likely has an effect on the response to treatment.
- Side effects include hypopigmentation, erythema, crusting, blistering, and ulceration.
- As a stand-alone therapy, cryotherapy is better suited for disease that involves only a small number of lesions. When combined sequentially with a field-directed treatment, AK lesion clearance increases and recurrence diminishes.

Curettage with Electrodesiccation

- Curettage and electrodessication involve the scraping down of an AK lesion followed by electrocautery.
- This procedure is often reserved for hypertrophic AK and has the potential for scarring.
- Curettage can also be performed on hypertrophic lesions prior to administration of a field-therapy such as photodynamic therapy, which is better suited for superficial lesions.

Field-Directed Treatments

Imiquimod Treatment Regimens:

1. Imiquimod 5% cream (Aldara®): Treatment should be limited to areas ≤25 cm²; apply twice weekly for 16 weeks. Apply at bed-time and leave on skin for approximately 8 hours, then remove with soap and water.
2. Imiquimod 3.75% cream (Zyclara®): Treatment is indicated for a surface area of up to 200 cm². Apply once daily for 2 weeks, then 2 weeks off, then daily for 2 more weeks. Apply at bed-time and leave on skin for approximately 8 hours, then remove with soap and water. Treatment holidays of several days are possible with this formulation, allowing for the management of any possible skin reactions.
3. Imiquimod 3.75% solution is also available in a pump formulation for easier dispensing and improved adherence.

Overview

- Imiquimod is an immunomodulator that has been shown to stimulate immune function by inducing cytokine expression, particularly interferon-α (IFN-α), interleukin-6 (IL-6), and tumour necrosis factor-α (TNF-α). Consequently, this topical agent exhibits both antitumor and antiviral effects.
- Imiquimod 5% cream was initially approved for use in human papillomavirus genital warts in Canada in 1999, and was approved for treatment of AK in 2004.
- Numerous studies have shown that imiquimod is both efficacious and tolerable.
- Results from two randomized control trials demonstrated a mean initial reduction of AK lesions of 83%.
- Because AK lesions have a high recurrence rate, researchers have also performed longitudinal studies to look at sustained clearance rates. One study demonstrated that imiquimod has both a high initial clearance rate (85%) as well as sustained clearance rate at 1 year (73%).
- Several studies also show added benefit when imiquimod is combined with another therapy. When preceded by phototherapy, better clinical as well as histological outcomes are achieved.
- Additionally, imiquimod combined with cryotherapy is more effective in treating hypertrophic AK compared to cryotherapy alone.
- Common side effects of imiquimod therapy include erythema, crusting and dryness.
- Patients receiving imiquimod are generally satisfied with the outcome.

5-Fluorouracil Treatment Regimens:

1. Efudex®: apply to lesions twice daily for 2-4 weeks; complete healing may not be evident for 1-2 months following treatment.
2. Fluoroplex®: apply to lesions twice daily for 2-6 weeks.

Overview

- 5-fluorouracil (5FU) is an antimetabolite drug used as chemotherapy for treatment of colorectal cancer.
- 5FU is taken up by cells as if it were uracil. Its active metabolites are subsequently incorporated into DNA and RNA, thereby disrupting replication and causing cell destruction.
• Besides its role in cancer treatment, 5FU has been used for many years in treating dermatological conditions, including AK, warts, keratoacanthoma, and SCC. 40
• 5FU has been shown to significantly reduce AK lesions initially but is less effective in long-term clearance. One study found that 5FU resulted in a reduction of AK lesions by 83% and a sustained clearance rate of 53% after one month. 41 Another study showed a very high initial clearance rate (96%) but much lower sustained clearance rate (54%) at one year follow-up. 42
• Like other field therapies, 5FU is more effective and results in lower recurrence rates when combined with targeted therapy such as cryotherapy. 27
• Common nuisance side effects include erythema, burning, and eye irritation. 43 Despite these side effects, discontinuation rates are low. 42

**Ingenol Mebutate Treatment Regimens:** 42
1. Ingenol mebutate gel (Picato®) 0.015% for face and scalp: apply to affected area once daily for 3 consecutive days.
2. Ingenol mebutate gel (Picato®) 0.05% for trunk and extremities: apply to affected area once daily for 2 consecutive days.

**Overview**
• Ingenol mebutate is indicated for a 25 cm² contiguous field. 17
• Ingenol mebutate is the naturally occurring active substance found in the sap of *Euphorbia peplus*. This plant has been used for many decades in Australia as a natural remedy for AK, and early subjective reports on its use indicate good outcomes. 44
• Ingenol mebutate is the newest field therapy. The short duration of application lasting 2 or 3 days is appealing, however patient response can be brisk and may last for 2 weeks, although it typically peaks at day 4. 44, 46
• The quick action of ingenol mebutate is thought to arise because of two simultaneous mechanisms of action: direct cytotoxicity leading to cell death and activation of a neutrophil-mediated inflammatory response. 46
• Results of two phase II and III trials have demonstrated promise. 45, 47, 48 Pooled analysis of the two phase III trials show a complete clearance of 42% on the face and scalp and 34% on the trunk and extremities. In a long-term follow-up study at 1 year, lesion clearance rates were approximately 87% for the face, scalp, trunk or extremities. 49 Further lesions either developed or recurred in the treated field in 53.9% of patients. Skin reactions of up to 2 weeks were generally mild to moderate, and the most common side effects were erythema, dryness, and flaking. 47

**Diclofenac Sodium 3% Gel Treatment Regimen:**
1. Diclofenac sodium 3% (Solaraze® gel): apply to affected area twice daily for 60-90 days.

**Overview**
• Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) widely used for its analgesic properties.
• It is a non-selective cyclooxygenase (COX) inhibitor which also exhibits antitumor effects, given that COX-2 has been implicated in keratinocyte proliferation. 50, 51
• Diclofenac has also been shown to induce apoptosis via death receptor signalling. 52
• A number of studies have demonstrated that diclofenac is a well-tolerated and effective field therapy for AK. 53-55
• One study showed no difference in efficacy between topical diclofenac 3% sodium and imiquimod 5%. 53
• Another study comparing diclofenac with imiquimod demonstrated similar clearance rates between the two drugs but recurrence occurred quicker following diclofenac treatment. 54
• As is the case with other field therapy options, diclofenac used sequentially with cryotherapy increases clearance rates as well as decreases recurrence rates. 29, 30
• Side effects are usually tolerable and may include dryness, itchiness and erythema. 53, 55

**Photodynamic Therapy (PDT)**

**Treatment procedure:**
1. Prior to PDT: curettage of hypertrophic AK or acetone scrubs or microdermabrasion.
2. Apply methyl-aminolevulinate (MAL) (Metvix®) or 5-aminolevulinic acid (ALA), 1mm thick, 10-15mm margins.
3. Allow 1-3 hours for MAL/ALA to penetrate.
4. Remove MAL/ALA.
5. Illuminate with blue or red light emitting diode, or use other laser/light sources or even daylight activation for MAL.

**Overview**
• PDT uses a combination of a topical photosensitizer, such as ALA or MAL, and a light source to treat AK lesions. These photosensitizers are converted to protoporphyrin IX (PpIX), which then induce apoptosis and necrosis. 56, 57
• PDT has been shown to be similar in efficacy to cryotherapy. 58
• One of the drawbacks of PDT is that its use is limited to superficial lesions and is less effective in hypertrophic AK. 59
• The most common side effects are erythema, edema and crusting. 60
• The procedure can be painful for patients, but spraying cold water on the treatment site has been shown to improve tolerability. 56 Otherwise, PDT is quite well tolerated and results in good cosmetic outcome with minimal downtime.

**Conclusion**
AK is a premalignant skin condition that should be identified and treated promptly. Untreated AKs can lead to SCC. There are many treatment options that all have comparable efficacy. Cryosurgery is often first-line therapy for disease with a small number of lesions. Field-directed therapy is recommended when the skin is extensively photodamaged or there are many AK lesions or frequent AK recurrences. Combining a local treatment such as cryotherapy with a topical agent has been shown to be more effective than either therapy alone.
References