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Clinical Evidence. Practical Advice

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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 prevention[11-14] 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

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[20]), targeted therapy is not ideal for extensive UV-damaged skin.[2]

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.[12]

Local Treatments

Cryotherapy Treatment Regimen:

1. One freeze-thaw cycle, 5-15 seconds, and 1mm margin.[21]

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.[22,23]
- 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.[21] However, more recent studies have demonstrated good clearance with a temperature of -5°C.[24]
- Cryotherapy has been shown to be both highly efficacious and tolerable but the range of clearance rates varies significantly (39-100%[24,25]). Another study demonstrated a complete clearance rate of 75% at 3 months.[26]
- The duration of freezing likely has an effect on the response to treatment.[25]
- Side effects include hypopigmentation, erythema, crusting, blistering, and ulceration.[24]
- 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.[27-30]

Curettage with Electrodessication

- 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.[31]
- 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 cm^2; 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 cm^2.[32] 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).[33] 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.[34-37]
- Results from two randomized control trials demonstrated a mean initial reduction of AK lesions of 83%.[37]
- 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%).[36]
- 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.[36]
- Additionally, imiquimod combined with cryotherapy is more effective in treating hypertrophic AK compared to cryotherapy alone.[28]
- Common side effects of imiquimod therapy include erythema, crusting and dryness.[37]
- Patients receiving imiquimod are generally satisfied with the outcome.[35]

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.[39]
- 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.[38]
- 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.[41] 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 cm^2 contiguous field.[47]
- 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.

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