Current therapies for actinic keratosis

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Abstract

Actinic keratosis (AK) is a very common skin disease caused by chronic sun damage, which in 75% of cases arises on chronically sun-exposed areas, such as face, scalp, neck, hands, and forearms. AKs must be considered an early squamous cell carcinoma (SCC) for their probable progression into invasive SCC. For this reason, all AK should be treated, and clinical follow-up is recommended. The aims of treatment are: (i) to clinically eradicate evident and subclinical lesions, (ii) to prevent their evolution into SCC, and (iii) to reduce the number of relapses. Among available treatments, it is possible to distinguish *lesion-directed therapies* and *field-directed therapies*. Lesion-directed treatments include: (i) cryotherapy; (ii) laser therapy; (iii) surgery; and (iv) curettage. Whereas, field-directed treatments are: (i) 5-fluorouracil (5-FU); (ii) diclofenac 3% gel; (iii) chemical peeling; (iv) imiquimod; and (v) photodynamic therapy (PDT). Prevention plays an important role in the treatment of AKs, and it is based on the continuous use of sunscreen and protective clothing. This review shows different types of available treatments and describes the characteristics and benefits of each medication, underlining the best choice.

Introduction

Actinic keratosis (AK) is a very common skin disease caused by chronic sun damage; in fact over 75% of AKs arise on chronically sun-exposed areas such as face, scalp, neck, and back of hands/forearms.[1–3] Rates of malignant transformation vary from 0.025 to 16%,[4] and the risk of progression in SCC increases in patients with multiple AKs (more than five); for example it is 4-fold higher in patients with 6-20 AKs and 11-fold higher in those with more than 20 lesions.[5] AKs are a risk factor for the development of SCC, but it is impossible to predict the risk of evolution of each lesion, therefore their treatment is important. The aims of treatment were: (i) to clinically eradicate evident and subclinical lesions, (ii) to prevent the evolution into SCC, and (iii) to reduce the number of relapses.[6] There are several therapeutic options: (i) cryosurgery, (ii) curettage, (iii) excision surgery, (iv) photodynamic therapy (PDT), and (v) topical treatment. The choice of treatment is determined by the type and number of lesions. This review examines the different types of medical and pharmacological treatments through careful evaluation of previously conducted studies about current therapeutic options and strategies.

Epidemiology and Risk Factors

AK is a highly prevalent skin condition; the American Academy of Dermatology (AAD) diagnose at least one lesion in 60% of predisposed individuals over the age of 40 years. This explains why it is the third most common skin disease treated by dermatologists.[7,8] In the USA, 14.6 million dermatological examinations are performed for evaluation and treatment of AKs.[9] In Australia, 40% of the population over the age of 40 has AKs.[10] In Italy, the prevalence seems to be lower than USA and Australia, probably because AKs are underdiagnosed and undertreated.[11]

Independent risk factors for AK include: age (up to 80% of adults ranging in age from 60-69 years are affected), male gender, fair skin (Fitzpatrick phototypes I-II), ultraviolet (UV) exposure including sunbed, immunosuppression, previous history of AKs or skin cancer, and genetic diseases (xeroderma pigmentosus, Bloom syndrome, or Rothmund-Thomson syndrome).[12] The most important risk factor is chronic sun exposure: the spectrum of UVB irradiation causes the formation of dimers of thymidine into DNA and RNA that produce mutations of the telomerase gene, whereas UVA indirectly induces DNA mutation through photo-oxidative stress.[13] Sun exposure is not the only documented risk

factor for the development of AKs; in fact, recent studies have also shown association between HPV and AK.[14]

AK is not a life threatening disease but it has a high prevalence, and the burden of the disease is significant.[7]

The presence of AK also has a personal impact on quality of life for affected individuals due to associated symptoms such as burning, itching, or bleeding.[15,16]

Diagnosis

Diagnosis of AK is usually clinical, but, if in doubt, dermascopic analysis can be used, especially for differential diagnosis, also for an accurate definition of degree of the lesion.[17,18]

The precision of the clinical diagnosis varies from 74 to 94%.[19–21]

Seborrheic keratosis (SK), Bowen's disease (BD), SCC, basal cell carcinoma (BCC), and discoid lupus erythematosus (DLE) can at times be mistaken for AK.

Clinically, AK could be divided into three degrees: the first, visible and slightly palpable, better felt than seen; the second, visible and palpable, easily felt and seen; and the third, frankly visible and hyperkeratotic.[22]

Dermoscopically, Zalaudek et al[23] recognized three prevalent dermoscopic patterns associated with nonpigmented AK, dividing the lesion into three different degrees: the first exhibits a red pseudonetwork pattern and discrete white scales (Fig1a); the second type is characterized by an erythematous background, the so-called "strawberry pattern" (Fig1b); the third shows enlarged follicular openings that are filled with keratotic plugs over a scaly and white- to yellow-appearing background (Fig1c).

The diagnostic sensitivity and specificity of dermoscopy in the diagnosis of not-pigmented AK has been reported to reach 98 and 95%, respectively.

Treatment

The skin surrounding the AK may visibly seem not involved in the cancerization process, but it may be a subclinical manifestation of a larger area of "field cancerization".[24,25] If left untreated, the 10-year incidence rate of progression of AKs to SCCs is around 10%, with little differences among sexes, leading to metastases and death.[5,26] A research study showed that, assessing 271 lesions, one in every 25 lesions considered clinically as AK, the histological diagnosis was invasive SCC.[27] AK must be considered carcinoma *in situ*[28] and for the probable progression to invasive SCC, they all should be treated[29] and a clinical follow-up is recommended.[30]

There is no standard treatment for AK and one should be careful to consider: (i) density and clinical manifestation of the lesion; (ii) tolerability and cost of the treatment; (iii) age, immune system activity, and compliance of the patient.

The aim of the ideal treatment is to detect and clear both clinical and subclinical lesions across the entire cancerous field.

Among available treatments, we should distinguish lesion-directed and field-directed therapies.[5] Lesion-directed treatment modalities include: (i) cryotherapy; (ii) laser therapy; (iii) surgery (excision or shave biopsy); and (iv) curettage. Whereas, field-directed treatment modalities comprehend: (i) 5-FU; (ii) diclofenac 3% gel; (iii) chemical peeling; (iv) imiquimod; and (v) photodynamic therapy (PDT)[5] (Table 1).

Lesion-directed treatments remove atypical keratinocytes that constitute every single lesion. Field-directed treatment options have the same aim, but their action is extended to atypical keratinocytes within a field of chronic sun damaged skin, the aforementioned "field cancerization".[26]

Lesion-directed therapies

Lesion-directed treatment modalities commonly involve focal ablative procedures[30] (Table 2).

Cryotherapy

Cryosurgery (liquid nitrogen) should be considered the treatment of choice[29–31] for patients with only a few lesions (about 1-6 lesions) or isolated lesions, or for patients who are noncompliant with topical agents.[3,29–31] Liquid nitrogen is usually

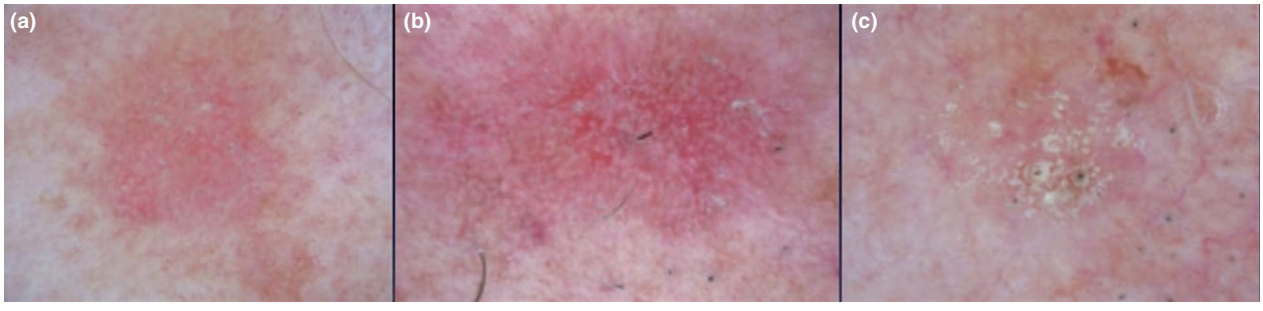

Figure 1 Dermoscopy of nonpigmented actinic keratosis showing (a) first degree, a red pseudo-network pattern and discrete white scales; (b) second degree, erythematous background, the so-called "strawberry pattern"; (c) third degree enlarged follicular openings with keratotic plugs over a scaly and white to yellow-appearing background

Table 1 Scheme of treatments of all the possible therapies (lesion-direct and field-direct treatments) for actinic keratosis

Therapy	Scheme
Cryotherapy	1-2 times[32]
Laser therapy	1 or more times[33]
Surgery	1 time[33]
Curettage	1-2 times[33,35]
5% Fluorouracil (5-FU)	1-2/d for 2-4 weeks[36,43]
5-FU 0.5% in 10% salicylic acid	1x/d for 6-12 weeks[42]
Topical retinoids	1x/d at least 3 months[36]
Diclofenac 3%	2x/d for 90 days[42]
Chemical peeling	1 or more times[35]
Imiquimod 5%	3x/week for 4 weeks[42]
Imiquimod 3.75%	1x/d for 2-0-2 weeks[42]
MAL or ALA-PDT	1 or more times[33]
Ingenol mebutate 0.015%	1x/d for 3 days[42]
Ingenol mebutate 0.05%	1x/d for 2 days[42]

ALA, aminolevulinic acid; MAL, methyl aminolevulinate; PDT, photodynamic therapy.

Table 2 Characteristics of lesion-directed therapies specifying the benefits and drawbacks of each treatment for actinic keratosis

Therapy	Benefits	Drawback
Cryotherapy	Rapid technique	Redness, pain, blistering, bubbles, hypochromia
Laser therapy	Rapid technique	Pain, inflammation, pigment change, delayed healing
Surgery	Rapid technique	Anesthesia, inflammation, scarring
Curettage	Rapid technique	Anesthesia, inflammation, scarring

applied with cotton-tipped applicator or spray during a single freeze-thaw cycle involving also a 1 mm rim of normal skin between 5 and 40 seconds.[32] Cryotherapy is a rapid technique, which does not require anesthesia, ensuring an excellent result. Sometimes side effects can appear such as redness, pain, blistering, bubbles, and areas of hypochromia.[25]

Complete response rate to cryotherapy is around 98%, and the result depends on the duration of the freezing.[24]

The efficacy can be increased by the use of 3% diclofenac gel or 5-FU as pretreatment as reported by some data in the literature.[33,34] Imiquimod 5% post cryotherapy may increase removal and destruction of target, subclinical, and total AKs.[24,35]

Laser therapy

Laser therapy is probably one of the most effective techniques, even if it is more expensive and characterized by a higher learning curve compared to cryotherapy.[33,36] It consists of ablative treatment that allows the physical removal of AKs and full-face skin resurfacing, ensuring long-term effective prophylaxis against new lesions and reducing the incidence of AK-related SCC.[33] Laser therapies available include lasers (Co2 and erbium yttrium aluminum garnet) that remove the superficial layers of the skin ablating epidermis and superficial dermis, or non-ablative fractional laser (erbium glass lasers) systems that evaporate or coagulate tiny columns of skin leaving the surrounding skin undamaged.

The rate of response to treatment is about 90%, whereas the rate of recurrence of lesions at 6 months is about 10-15%.[33]

Possible side effects are pain, inflammation, pigment change, and delayed healing of the skin.[4,33]

Both ablative and fractional lasers can be combined with other therapies, such as local agents in order to improve the effectiveness of the treatment.[37–39]

A randomized trial, comparing cryotherapy and Co2 laser ablation for the treatment of isolated AKs of the face and scalp, demonstrates that after 3 months the results in terms of complete response are similar for the two treatments (71.6% for cryotherapy vs 65.3% for laser ablation). A greater number of patients remain stable in a year with the treatment of cryotherapy (66.8% for cryotherapy vs 37% for laser ablation).[40]

Surgery

Surgical removal of lesions is suggested in front of doubtful lesion (high suspicion of SCC), particularly when the lesions are hyperkeratotic.[33] It requires anesthesia and it can lead to side effects such as inflammation of the skin in the area of excision or residual scarring.[33]

Curettage

Curettage is indicated for hyperkeratotic lesions or refractory to other local treatments.[33]. Curettage may be followed by electrodessication for the definition of the lesion margins and for post-curettage hemostasis. This technique requires anesthesia and carries a high risk of scarring. It allows, as the surgical procedure, to obtain a skin sample for histopathological examination.[35]

Field-directed therapies

Field-direct therapy includes several medications that have the objective to remove not only the visible lesion but also the ones that are not visible. This category includes: (i) 5-fluorouracil (5-FU), (ii) oral retinoids, (iii) diclofenac, (iv) chemical peels, (v) imiquimod, (vi) photodynamic therapy, and (vii) ingenol mebutate (Table 3).

5-Fluorouracil

5-Fluorouracil, a pyrimidine analogue, is a chemotherapeutic anticancer agent, belonging to the family of antimetabolites. The

Table 3 Characteristics of field-directed therapies specifying the benefits and drawbacks of each treatment for actinic keratosis

Therapy	Benefits	Drawback
5-Fluorouracil	Simple to apply	Pain, pruritus, burning, erythema, erosion, inflammation
Retinoids	Prophylactic action	Photosensitivity, erythema, erosion, pruritus, pain
Diclofenac 3%	Few side effects	Long duration
Chemical peeling	Rapid technique	Superinfection, inflammation, abnormal pigmentation, scarring
Imiquimod 3.75%	Best long-term response	Erythema, scabbing, erosion but are easy to manage
Imiquimod 5%	Higher rate of clinical clearance	Erythema, scabbing, erosion
ALA or MAL-PDT	Good cosmetic results	Pain, erythema, inflammation, hypochromia
Ingenol mebutate	Shortest duration	Not modifiable side effects

mechanism of action has been associated with inhibition of thymidylate synthase (TS) and incorporation of 5-FU into RNA and DNA. It represents an appropriate topical agent for the treatment of multiple AKs. In addition, it is simple to apply and is inexpensive even if the patient must be ready to handle the side effects of the treatment as pain, pruritus, burning, erythema, inflammation, and erosions.[29] Various formulations of the drug are available and include 5% fluorouracil cream or solution, 1% fluorouracil cream or solution, 2% solution, and 0.5% fluorouracil cream.[7,41] The historical European preparation of the drug 5% 5-FU, known as *@Efudix*, should be applied twice daily in the skin area to be treated for 4 weeks.[7]

Full adherence to the regimen is crucial to achieving the desired result. In addition, combination with other treatments such as local tretinoin can enhance the effectiveness of the treatment.[3]

Moreover the use of 5-FU one week before treatment with cryotherapy increases the long-term result of the keratoses therapy.[8,36]

In order to obtain effective results, reducing the duration of the treatment, combination therapies have been developed. Further studies are needed to define appropriate therapeutic schemes.[4]

The association of once a day for 12 weeks with 10% salicylic acid (@Actikerall) has been approved in Europe for the local treatment of AKs. The keratolytic action of salicylic acid would enhance the penetration of 5-FU. The treatment should be carried out for 12 weeks by applying the agent once a day on the face and scalp keratosis.[41] Regarding side effects, this association is generally well-tolerated with only local irritation, burning sensation, and inflammation.[41]

Retinoids

Local or oral retinoids play a role in both prevention and treatment of lesions through a mechanism which acts on the pathway of oxidative stress or cell differentiation,[7] although recent studies have shown that retinoids do not have a decisive effect in reducing the evolution of AKs and for this reason, to date, is not used as a first therapeutic choice. [47]

A possible treatment for AKs is guaranteed by topical all-trans-retinoic acid (tretinoin).[36]

Retinaldehyde, a derivate of vitamin A, has a similar action of retinoic acid, in addition it has an antioxidant action, which seems to determine the reduction of damaged cells. Side effects of topically applied retinoids include photosensitivity, erythema, erosions, pruritus, and pain.[7] Oral administration is preferable in patients with multiple lesions (>6) or in high risk patients such as patients with immune or genetic disorders such as transplantation or xeroderma pigmentosum or nevoid basal cell carcinoma syndrome. A questioned result is the prevention of newly developed nonmelanoma skin cancers (NMSC) in transplanted patients through the use of retinoids. Finally, "turbo therapy", which is the association of 20 mg of isotretinoin with two daily applications of 5-FU, offers good prospects of success.[7]

Diclofenac

AKs are characterized by an increased expression of COX-2, an enzyme involved in prostaglandin synthesis. Moreover, prostaglandins potentially increase the risk of developing UV-induced NMSC. Because of these pathogenic mechanisms, diclofenac, a nonsteroidal anti-inflammatory drug, is considered a valuable therapeutic support in the treatment of AKs. It blocks the activity of cyclooxygenase and inhibits UV-induced proinflammatory cytokines.[35] Diclofenac also acts by blocking tumor cell proliferation and angiogenesis and inducing the action of metalloproteinases resulting in increased keratolysis and collagen degradation.[8,41] It is available as a 3% gel in 2.5% hyaluronate sodium (*@Solaraze*) and should be applied daily for a period of 60-90 days with a complete clearance rate of 58% after 30 days.[41] The use of hyaluronic acid as drug vehicle has been developed to ensure a better treatment since in this way the drug penetrates the epidermis and the superficial dermis.[8] More or less, diclofenac is well tolerated even if possible side effects such as pruritus, erythema, and dry scaly skin can appear.[33] It should be avoided in aspirin-sensitive patients.[33]

In addition, diclofenac associated with cryotherapy increases the complete clearance rate of cryotherapy from 32% to 64% and, if it is put in comparison with 5% 5-FU cream, has the same clearance rate but is better tolerated.[41]

Chemical peels

Chemical peels (CP) consist of the application of caustic agents on the skin surface: they cause cell death at specific depths.

CP constitute a valid alternative in the treatment of extensive AKs on face. The most used chemical agents are trichloracetic acid (TCA), alpha hydroxy acids (AHA), zinc chloride, or phenolic acid. The result depends on the agent used and on its concentration, time of application and the thickness of the lesion treated. The effectiveness is about 75%, and the relapse rate is around 25-35% within 1 year after therapy.

The most common side effects include superinfection, inflammation, pain, abnormal pigmentation, and risk of scarring.[35]

Combined treatments were studied by coupling caustic agents to local treatments such as 5-FU or tretinoin. From these studies, it was observed that the combination of 5-FU with Jessner's solution or with 70% buffered glycolic acid solution, carried out for eight weeks, offers higher clearance of the keratosis than just peeling alone.[4]

Imiquimod

Imiquimod is a synthetic drug with immunomodulating action that was approved for the treatment of external genital and perianal warts by FDA in 1999. In 2004 the use of Imiquimod was extended to the treatment of AKs and BCC.[42] It is a toll-like-receptor-7 (TLR-7) agonist, and it works by promoting the immune response stimulating the production and release of cytokines such as tumor necrosis factor-alfa (TNF-α), interferon-gamma (IFN-γ), interferon-alfa (IFN-α), and interleukin-12 (IL-12). It plays an important role in gene modulation that regulates the activation of macrophages, dendritic cells, cytotoxic T-cells, and natural killer cells. Moreover it has an indirect antiviral and antitumoral potency.[26,41]

Imiquimod is a topical treatment used for AKs, especially on the face and scalp. To avoid wasting product in the application, a good strategy would be to apply it to the back of the hand rather than with fingertips: Keenan Hogan et al suggest to use the back of the right hand on the left face and vice-versa. In this way, the back of the hands, and other places of greater occurrence of injuries, can be treated too.[43]

To date, many permeation enhancers have been studied in order to define the one with the highest rate of effectiveness in terms of skin penetration. The best and highest results were obtained in terms of good permeability and deposition of drug with transethosomes.[41,43]

Imiquimod is currently available as 2.5%; 3.75% (*@Zyclara*) and 5% cream (*@Aldara*).[41]

A long treatment regimen is usually associated with adverse skin reactions such as erythema, weeping, crusting, and erosion,[36] and this is the reason shorter duration treatment has been proposed.[4]

Different schemes of therapies have been suggested over the years in order to define the best solution in efficacy and to increase compliance and reduce side effects.

Imiquimod 5% cream is indicated for a limited area of 25 cm^2 on face and balding scalp,[13] applied three times a week for 4 weeks within a duration of 16 weeks. Therapy cycle has shown 85% clinical clearance of AK and a recurrence rate of 10% within 1 year.[41]

The new formulation Imiquimod 3.75% cream (*@Zyclara*) was introduced as a local treatment that can reduce the rate of AKs in a field of cancerization extended on face and scalp,[5] being approved for the treatment of a larger surface area of up to 200 cm^2. Shorter and safer treatment regimens[3] increase patients' compliance and adherence.[41] This formulation should be applied once a day following a 6-week regimen, including two central weeks of rest period (2 weeks on, 2 weeks off, and 2 weeks on). Dirschka et al. proposed a cycle of treatment without a 2-week rest period, applying the cream for four consecutively weeks, with no impact on the efficacy.[44] Imiquimod 3.75% detects and removes both visible clinical and subclinical lesions in a wide area of cancerization. The maximum lesion count (Lmax) during the treatment is the new parameter introduced to evaluate the effectiveness of therapy.[45] This new parameter shows the efficacy of a field-directed therapy against both clinical and subclinical lesions, it is the sum of clinical lesions together with subclinical lesions which become detectable during treatment. Some data showed 92% effectiveness for treatment with this drug starting from an initial level of Lmax until the end of the treatment.[45] Local skin side effects, such as erythema, itching, and erosion, are easy to manage.[46]

Recently, imiquimod 2.5% was approved, as the previous formulas, in the treatment of AKs following a regimen of 6 weeks with daily administration similar to imiquimod 3.5% (2 weeks on, 2 weeks off, and 2 weeks on).[41]

Swanson et al demonstrated, through two placebo-controlled studies, a different but similar complete clinical clearance using imiquimod cream at different concentrations. Particularly, they reported a rate of complete clinical clearance amounting to 45% for imiquimod 5%; 35.6% for imiquimod 3.75% and 30.6% for imiquimod 2.5%.[41,47]

Analyzing the clearance of AK with imiquimod versus cryotherapy, a recent study demonstrated a higher complete clearance using cryotherapy rather than imiquimod 5% cream three times per week for 16 weeks. Unfortunately, the cryotherapy group was characterized by more side effects and poor cosmetic outcomes.[41]

The association of cryotherapy with imiquimod 5% might be a viable choice for the therapeutic removal of isolated hyperkeratotic/hypertrophic lesions occurring within a field of mild/moderate AKs.[32]

Photodynamic therapy

Photodynamic therapy (PDT) is a local treatment based on the interaction between the photosensitizer, appropriate wavelength of light, and oxygen.[48] It is generally used as a photosensitizer topical drug such as 5-aminolevulinic acid (ALA) or derivate as methyl aminolevulinate (MAL) and after more or less than 3 hours, exposure to light.[33] These substances are captured by premalignant tissue and subsequently activated by exposure to

wavelengths that fall in the specific absorption spectrum of the photosensitizer. The irradiation leads to activation of photochemical mechanisms mediated by various prostaglandins and cytokines as PGE-2, IL-1, IL-2, TNF-α, generating reactive oxygen species (ROS). These events stimulate the death of cells, causing necrosis or apoptosis and vascular endothelial damage.

PDT is suitable for multiple lesions in the group of NMSC, especially for AK, extended in a vast "field of cancerization" with satisfactory results on face and scalp rather than on extremities.

In order to increase the effectiveness of treatment, some studies have tried to carry out incubation of ALA at high temperatures for the treatment of keratoses of the extremities (naturally lower in temperature areas of human body), being the temperature closely related to the production process of the porphyrin. Positive results have been reported, with an efficacy rate of 70-90% and a recurrence rate of 20% at 12 months. Efficacy rate is lower in immunosuppressed patients.[33]

Treatment failure, recurrence, or the development of cancerous tumors in the field of cancerization could be linked to immune suppression or to DNA damage, triggered by UV rays or by the same PDT.

In the treatment of AK of the scalp, oral administration of Polypodium leucotomos showed an increase in clearance at 6 months compared to only PDT and a reduction in the rate of recurrence by reducing immunosuppression and damage caused by UV rays. This treatment has the advantage of not leaving scars nor disfigurements, even if post-treatment inflammation or photo-sensitization could at times result.[33]

Daylight photodynamic therapy (DL-PDT) is considered by experts a first-line treatment available in immunocompetent patients with grade I and II AK on face and scalp. MAL or ALA cream should be applied on the affected area and daylight exposure started simultaneously or within 30 minutes to avoid developing excessive pain. Application of a chemical filter during exposure is required to block the action of UV rays and avoid sunburn. After two hours of exposure, the cream should be removed.

Cantisani et al, evaluated the results of MAL DL-PDT with a 3D-camera in a retrospective study, showed good clinical and cosmetic results emphasizing reduction in the production of melanin, change in the disposition of melanin, wrinkle reduction, and an increased skin tone.

Ingenol Mebutate

In January 2012, the FDA approved ingenol mebutate (IM) gel (*@Picato*) for the topical treatment of nonhypertrophic and nonhyperkeratotic AKs.[3,33]

The drug acts through different mechanisms of action: (i) to induce necrosis of abnormal keratinocytes; (ii) to support inflammatory state through the establishment of an inflammatory infiltrate; and (iii) to stimulate the production of tumor-specific antibodies.[3,41]

The action of the drug is rapid, and this requires only 2-3 days of treatment.[3]

The gel formulation is available both at concentrations of 0.015% for the treatment of face and 0.05% for treatment of the body.[3]

It should be performed with a daily application for two consecutive days for the treatment of AKs on the body and a daily application for three consecutive days for the treatment of lesions of the face.[41]

The length of time treatment with IM is shorter than with diclofenac or 5-FU treatment, increasing the compliance rate to therapy (about 98%).[3,41]

Possible side effects are erythema, scabbing, and scaling.[41]

IM is neither a photosensitizer nor phototoxic, so its use can be extended over years.[33]

Pellacani et al, in a randomized trial comparing simultaneous vs sequential application of IM in field-directed therapy of AK on two separate areas of the head and body demonstrated similar results for complete clearance rate in the two groups (52.7% vs 46.9%). Clinicians, in accordance with the patient, choose the best regimen in order to obtain a similar result. In literature, a clearance rate of lesions of about 42% and a reduction rate of about 83% is reported.[33] Applied for three consecutive days, three weeks after the cryosurgery, IM has shown an increase of the therapeutic yield of cryosurgery.[33]

Conclusions

AKs are early tumors that are associated with a possible risk of recurrence and/or of neoplastic transformation into more invasive forms, such as SCC.[48] The treatment of lesions is therefore necessary, considering not only the visible lesions but the so-called "field of cancerization". Our review, analyzing the indications of the single available treatments, underlines the choice of the best therapy that could be made on the basis of the lesion characteristics (number, location, histology) and patient characteristics (age, compliance, immune status). Clinicians, according to the patients, should always remember the important role of sun prevention, modifying their lifestyle with the use of hats, sunglasses, and sunscreen. The aim of current therapies is to detect and clear both clinical and subclinical lesions across the entire cancerous field, but, currently, the best treatment, in terms of results and side effects, still has not been identified.

In our opinion, the optimal choice could be based on the needs of patients and clinical experience of dermatologists.

Further studies are necessary to find a therapy able to obtain the best result on visible lesion and stable results on field of cancerization, with lower side effects and shorter duration to avoid a poor compliance of the patients.

Questions (answers provided after references)

1 True or False: Chronic sun damage is one of the risk factors for actinic keratosis

2 True or False: Actinic keratosis is a highly prevalent skin condition

3 True or False: Actinic keratosis could be diagnosed with clinic and dermoscopic examination

4 True or False: Actinic keratosis could be divided into three degrees

5 True or False: Actinic keratosis could be considered as an "in situ" cancer

6 True or False: The skin surrounding the actinic keratosis could be considered as a subclinical manifestation of a larger area of "field cancerization"

7 True or False: Cryotherapy is one of the lesion-directed therapies

8 True or False: Imiquimod is one of the field-directed therapies

9 True or False: The optimal choice of treatment does not exist

10 True or False: Further studies are necessary to find a therapy able to obtain the best result on visible lesion

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Answers to questions

1 Answer: True. Chronic sun damage is the most relevant risk factor for actinic keratosis in association with age (up to 80% of adults aged 60-69 years are affected), male gender, fair skin (Fitzpatrick phototypes I-II), UV exposure including sunbed, immunosuppression, previous history of AKs or skin cancer and genetic diseases (Xeroderma pigmentosus, Bloom syndrome or Rothmund-Thomson syndrome)

2 Answer: True. Actinic Keratosis is a highly prevalent skin condition; the AAD diagnose at least one lesion in 60% of predisposed individuals over the age of 40 year old

3 Answer: True. Diagnosis of Actinic Keratosis is usually clinical, but, if in doubt, dermatoscopic analysis can be used, especially for differential diagnosis, also for an accurate definition of degree of the lesion

4 Answer: True. Actinic Keratosis could be divided into three degrees: the first, visible and slightly palpable, better felt than seen; the second, visible and palpable, easily felt and seen, the third, frankly visible and hyperkeratotic.

5 Answer: True. Actinic Keratosis must be considered carcinoma in situ and for the probable progression to invasive cutaneous Squamous Cell Carcinoma, they all should be treated and a clinical follow-up is recommended

6 Answe: True. The skin surrounding the Actinic Keratosis may visibly seem not involved in the cancerization process, but it may be a subclinical manifestation of a larger area of “field cancerization”

7 Answer: True. Cryosurgery (liquid nitrogen) should be considered the treatment of choice for patients with only a few lesions (about 1-6 lesions) or isolated lesions, or for patients who are noncompliant with topical agents

8 Answer: True. Imiquimod is a topical treatment used for Actinic Keratosis, especially on the face and scalp.

9 Answer: True. The optimal choice could be based on needs of patients and clinical experience of dermatologists

10 Answer: True. Further studies are necessary to find a therapy able to obtain the best result on visible lesion and stable results on field of cancerization, with lower side effects and shorter duration to avoid a poor compliance of the patients