Continuing Medical Education

Field cancerization: a review article

Campo cancerizável: artigo de revisão

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ABSTRACT

Solar or actinic keratosis is a frequent pre-malignant lesion that often occurs in areas exposed to sunlight, and has a 6-10% relative risk of developing into squamous cell carcinoma. Patients with actinic keratosis have multiple and confluent subclinical lesions, leading to the characterization of the condition as being of the field cancerization type. They are multifocal areas with genetic mutations that may become the site of new primary tumors and local recurrence. In recent years, there has been increasing interest in the development of non-invasive diagnostic tests and treatment for these subclinical lesions, with an aim at preventing squamous cell carcinoma.

Keywords: keratosis, actinic; carcinoma, squamous cell; phototherapy.

RESUMO

A queratose solar ou actínica é lesão pré-maligna frequente que ocorre em áreas expostas à luz solar com risco relativo de seis a 10% de desenvolver carcinoma espinocelular. Pacientes com queratoses actínicas apresentam lesões subclínicas múltiplas e confluentes que caracterizam o conceito de campo de cancerização. São áreas multifocais com mutações genéticas que poderão constituir a sede de novos tumores primários e de recorrência local. Nos últimos anos, tem aumentado o interesse para desenvolver exames de diagnóstico não invasivos e tratamento dessas lesões subclínicas para prevenção do carcinoma espinocelular.

Palavras-chave: *ceratose actínica; carcinoma de células escamosas; fototerapia.*

INTRODUCTION

Solar or actinic keratosis (AK) is a common premalignant lesion that affects areas exposed to sunlight.[1,2] It occurs mainly in adults and the elderly due to chronic exposure to ultraviolet radiation.[3] In Australia it affects approximately 40-50% of individuals over the age of 40, due to the large proportion of individuals in the population with skin phototypes I and II. In the northern hemisphere, the prevalence range is 11-25% in the 40 years and older population.[4] It is estimated that the relative risk of an individual bearer of AK developing squamous cell carcinoma (SCC) is 6-10%.[4] The risk of AK progressing to an invasive SCC is calculated at 0.025%-20% per year (calculation based on population rather than on a single individual).[1,4] The groups at highest for development of SCC are: fair-skinned individuals with excessive exposure to sunlight (occupational or recreational), immunosuppressed patients, and the elderly.[4]

In some patients it is possible to observe multiple AK lesions and, in these cases, the concept of field cancerization can be used. Field cancerization is a region containing subclinical and multifocal precancerous abnormalities with genetic mutations that may become sites of new primary tumors and local recurrence.[5,6] Field cancerization has been the subject of some studies. It can be found in most clinically healthy skin areas around AK lesions and presents characteristic AK alterations in the histology.[7] In recent years there has been increasing interest in the development of noninvasive diagnostic tests to confirm not only clinically suspected AK lesions, but also to detect and define subclinical lesions.[5,6] Field cancerization should be treated, and new therapeutic strategies have been developed for this purpose.

Clinical picture

The clinical appearance of AK is that of a maculopapular lesion covered with dry, hard scales with a rough surface and variable in color (from yellow to dark brown), measuring from 0.5 to 1.0 cm. It can also converge and form plaques. Typically, AK lesions are located in areas exposed to sunlight such as the face, ears, neck, in the "V" of the neckline area, forearms, back of hands, legs, and in the scalp of bald individuals. The appearance of an erythematous halo or infiltration of the lesion, the presence of lesions more than 1 cm in diameter, fast growth, bleeding, erythema and ulceration may indicate progression to SCC.[3,4] In 2007 there was a proposal for the clinical classification of AKs into three subtypes: Grade 1 - lesions are slightly palpable, but not very visible; Grade 2 - lesions are in the shape of erythematous scaly plaques, easily palpable and visible; Grade 3 - hyperkeratotic lesions. There is controversy in the literature regarding how to differentiate a Grade 3 AK and an initial CEC.[8]

Patients with significant photodamage and AKs often have subclinical lesions that may be multiple, confluent, and become more apparent with time, a picture that is aligned with the field cancerization concept.[3] The number of sub-clinical lesions in a field cancerization area can be ten times higher than the number of clinically visible AKs. The high recurrence after treatment of AKs is due to the absence of treatment of these lesions. The diagnosis and treatment of AKs and subclinical lesions is key to preventing SCC.[4]

Actinic keratosis is currently considered an incipient *in situ* SCC that develops in a process involving several stages, where UV radiation leads to the formation of an AK field cancerization, culminating in the onset of SCC.[9] The SCC and the AK are often contiguous lesions. In a study evaluating more than 1,000 SCCs located in areas exposed to sunlight, almost 100% of the lesions showed histological alterations consistent with AKs in the periphery of the lesions.[4]

Diagnosis

A) Histopathological examination

The diagnosis of AK is based on the clinical picture, however the most frequently used test for its determination is a histology test. During the biopsy collection it is necessary that the dermis be included in order to exclude invasive SCC.[4]

The initial histologic picture for AK is characterized by the presence of atypical keratinocytes in the basal layer of the epidermis. In its progression it affects other layers of the epidermis. The maturation of the keratinocytes in the epidermis is poor, resulting in hyperkeratosis and parakeratosis. The epithelial tissue around the glands is spared, keeping their normal appearance and keratinization, with an orthokeratotic stratum corneum in the region over these annexes. Actinic keratosis often presents with a dermal solar elastosis and often has lymphocyte infiltration. Therefore, the AK has the following histologic characteristics: parakeratosis, cellular and nuclear pleomorphism, disorder in the epidermal architecture, dyskeratosis and cellular atypia in part of the epidermis, without involvement of the epithelial tissue of the cutaneous appendages. The histological picture of field cancerization's subclinical lesions is similar to that of the AK.[3,7,10-12]

Nevertheless, while histology remains the gold standard regarding AK and non-melanoma skin cancer, biopsies are not always a good approach for the diagnosis and treatment of these lesions. Therefore, noninvasive diagnostic tests represent a good alternative for more accurate diagnosis and monitoring of these lesions. Due to the fact that AK has a potential for progression into carcinoma *in situ* and invasive SCC, it should also be diagnosed and treated as swiftly as possible. The new noninvasive technologies that have helped in the diagnosis of these skin lesions are dermoscopic examination and, more recently, the *in vivo* confocal microscopy examination. Thus, these tests are important not only to detect clinically suspicious lesions of AKs or SCC, but also to detect and define subclinical lesions of field cancerization.

B) Dermoscopy

This technique consists of the use of an optical device that allows 10 to 70 times the image magnification. The basic physical principle of dermoscopy is the improvement of the light's refractive index when it passes through the stratum corneum. It makes it possible to view structures in the epidermis, dermal-epidermal junction, papillary dermis, and even reticular dermis. The dermoscopic evaluation is based on the identification of colors and structures having a well-established correlation with the histologic characteristics of the cutaneous lesions, allowing the noninvasive diagnosis of many skin lesions.[13]

There are few studies describing the dermoscopic standards of AK. According to Zalaudek et al. the most frequently described characteristic in the initial AK lesion is the red pigmentary pseudo network pattern ("strawberry vascular pattern").[14] As the lesion progresses into an intraepidermal carcinoma (IEC) a pattern called red starburst develops, in addition to the appearance of yellow-opaque diffuse scales. As the lesion gradually turns into an SCC, there is an increase in neovascularization, and dotted or glomerular grouped vessels develop, with the appearance of linear and irregular vessels later on. In addition, the scales become thicker, and ulcerations are often described.[15] Dermoscopy is also useful for the differential diagnosis between pigmented AK, lentigo maligna, and pigmented basal cell carcinoma.[7]

C) *In vivo* confocal microscopy (RCM)

In vivo confocal microscopy emerged as a potential resource to study epidermal cutaneous alterations. This is because it allows viewing the superficial skin layers *in vivo* and noninvasively, from images prepared by different reflexing rates of light from skin structures, with microscopic resolution similar to that of conventional histology.[12,16] In this manner, confocal microscopy (CM) can also be used for AK diagnosis with a sensitivity and specificity of 98%.[7] It can currently be considered a noninvasive method for the diagnosis of AK and field cancerization.[7] The findings of AK lesions under MC include irregular hyperkeratosis with parakeratosis, an architectural disarrangement and an increased nuclei of epidermal cells with pleomorphism. The architectural disarrangement pattern does not involve the thickness of the entire epidermis in cases of AK. The AK images may also have thick refractional bands in the dermis, corresponding to the solar elastosis.[3,11,17]

In addition to RCM, the identification of subclinical lesions can be carried out by evaluating the fluorescence under ultraviolet lamp after the application of 5-aminolevulinic acid and the erythema after topical treatment with imiquimod or 5-fluorouracil (5-FU).[3,18]

Field cancerization – the role of gene p53

In 1953, Slaughter et al. defined the expression *field cancerization* for the first time in a histology study on carcinomas in the oral cavity and their local recurrences. The authors described the appearance of carcinomas in multifocal areas, coalescing from premalignant lesions.[5] Field cancerization can be defined molecularly as the presence of mutated cells that can progress to cancerous cells. Molecular analysis of the tissue adjacent to the tumor (even when considered clinically "normal"), as well as of the post-excisional resection margins of tumors, have been carried out in order to allow for a better understanding of this phenomenon.[5,8]

The gene p53 is correlated to tumor suppression. Mutation of this gene occurs in 50% of all tumors and in most skin cancers.[19] Studies performed with molecular technologies showed mutations in the gene p53 in histologically normal tissues.[5]

The analysis of p53 gene mutations have established a clear link between exposure to UV rays, changes in DNA, and skin carcinogenesis. UVB radiation causes very specific changes in the DNA, producing cyclobutane and pyrimidone type pyrimidine dimers.[19] Flaws in DNA repair and replication induce mutations in the genome. The accumulation of these mutations in genes due to chronic exposure to sunlight results in the development of skin cancer.[19]

The mutation frequency of the p53 gene varies in different studies. Ziegler et al. showed a 66% rate of mutations in this gene in AK and 40% in Bowen's disease. Mutation studies in basal cell carcinoma (BCC) and SCC showed a mutation presence of 66% in BCC, 38% in non-aggressive BCC, 35% in aggressive SCC, 50% in non-aggressive SCC, and 10% in skin exposed to sunlight. UVA radiation leads to mutation in the SCC's basal layer, and UVB radiation in the suprabasal layer.[19]

Mutations in p53 arise in skin with apparently normal sun exposure levels. Recent studies in mice have shown that UV, in addition to inducing mutation, induces apoptosis of normal cells, creating an environment that is conducive to cell repopulation. This is the ideal environment for repopulation by clonal expansion of mutated cells.[19]

The results of these studies support the carcinogenesis model in which there is development of a contiguous field genetically altered with clonal alterations and development of multiple neoplasic lesions. The genetically modified stem cell forms a clonal unit of daughter cells, leading to an expanded field. Ultimately, a proliferating field gradually invades the normal epithelium. The clonal deviation can lead to the development of skin cancer in a contiguous field of pre-malignant cells.[9]

This concept has important clinical consequences for it explains the existence of several areas of pre-malignant disease, multiple sites of synchronous primary tumors and the presence of distant tumors. A genetically altered field increases the probability of development of the tumor's local recurrence and/or the appearance of a second tumor in the field. This finding has been described in esophageal, oropharynx, stomach, lung, colon, anus, bladder, cervix, and skin tumors.[9]

Thus, environmental carcinogenic influences, such as the role that tobacco and alcohol play in oropharyngeal tumors, explain the actinic damage caused to skin by ultraviolet radiation (UV), which leads to simultaneous alterations in a large proportion of epithelial cells. This also contributes to the development of premalignant lesions in areas exposed to sunlight.[9]

This model explains carcinoma recurrence after surgery and new cancers in the operated area. This concept and its clinical consequences are important for prevention, diagnosis, and treatment strategies in cases of non-melanoma skin cancer.[9]

The molecular biology analysis performed in locations adjacent to the tumor in the study of surgical margins without histological alterations shows changes in the microsatellite, chromosome instability and alterations of the p53 gene, all demonstrated by DNA amplification, immunohistochemistry, and *in situ* hybridization techniques.[5]

The recognition of field cancerization as an area of genetic alteration of cells with risk for SCC development leads to a new paradigm in the definition of the term used for local recurrence and in the importance of treating this field. The definition of local recurrence should be reconsidered, as this lesion may originate from remaining tumor cells, such as the cells present in field cancerization.[5]

Thus, high levels of p53 (evidenced by immunohistochemistry) due to mutations and increased gene expression can be considered biological markers of actinic damage and of field cancerization. Aligned with this concept, clinically normal areas present early alterations linked to clonal expansion of genetically modified neoplastic cells.

Treatment

A) Objectives of the treatment

The treatment of AK aims to prevent the risk of progres-

sion into SCC. There are several options to consider. In addition to selecting a technique, other factors to take into account are the number, location, and extent of the AK, as well as the patient's age, comorbidities, immunosuppression (transplants), previous history of skin cancer, continuous exposure to sunlight (rural workers, athletes), and cost and conditions for performing the treatment.[3,20]

In addition to treatment, patients should also be advised to avoid exposure to the sun by using sunscreens and wearing adequate clothing, staying in the shade as much as possible and avoiding artificial sources of UV radiation, such as tanning beds.[3]

There are randomized studies showing that low-fat diets decrease the incidence of AK. The use of fish oil and the practice of drinking red wine – due to the presence of resveratrol – can also act as chemopreventive agents in the development of AKs.[3] The use of nonsteroidal anti-inflammatory drugs has in some studies also shown chemopreventive action in the development of AK and SCC.[3]

The use of retinoids in chemoprevention of SCC is indicated in renal transplant patients (20 mg/day acitretin). The drug has an immunomodulatory effect, increasing the number of Langerhans cells after 12 months, both in covered areas and in those exposed to sunlight.[21]

The treatment of field cancerization is performed in multiple areas of AK, visible or palpable, or throughout the area injured by exposure to UV. The treatment of the field is also indicated for new and recurrent lesions, and those that have been treated up to one year before.[3]

The treatment of the field can be accomplished through the self-administered application of topical substances by the patient, photodynamic therapy performed at the clinic, and resurfacing techniques with ablative and non-ablative lasers, dermabrasion, and medium and deep chemical peels.[3]

The various treatment modalities show different advantages and disadvantages in terms of efficacy and tolerability, duration of treatment, discomfort, recovery, patient adhesion and outcome. There is no formal guideline for the treatment of field cancerization. It is recommended that AKs be treated in order to prevent progression into CEC[3] and that field cancerization be treated so as to avoid recurrence and new lesions. In 2007, the British Academy of Dermatology recommended the use of photodynamic therapy for the treatment of multiple and confluent AKs.[2]

B) Conventional AK therapy

There are several treatment modalities for treating AKs, including ablative procedures such as curettage, surgery, laser, and cryotherapy – usually aimed at treating individual lesions – and topical treatments, such as photodynamic therapy, imiquimod, 5-fluorouracil (5-FU) and diclofenac – used to treat individual lesions and field cancerization. Field cancerization areas are also important due to the fact that they are related to morbidity and mortality in patients who underwent organ transplantation, being also relevant in preventing progression into SCC. The treatment of individual lesions does not prevent this progression.[3,22]

B) 1. Destructive methods

I. Cryotherapy

Cryotherapy is the most common treatment for AK. The complete response rate is 67.2%, with 39.0% of responses with freezing times shorter than 5 seconds, 69.0% of responses with freezing times longer than 5 seconds and 83.0% with freezing times in excess of 20 seconds. It is usually well tolerated but can cause discomfort in the application and secondary dischromia.[1]

II. Surgery, curettage, and electrocoagulation

This is the method of choice when aiming at collecting material for pathological examination. It has the disadvantage of needing local anesthesia and can result in scar formation. It can be used in combination with photodynamic therapy. These two destructive methods treat only localized AKs.[1] Surgical excision is not indicated routinely and is used when there is suspicion of invasive SCC.[22]

III. Resurfacing procedures

Procedures such as CO_2 and erbium:YAG lasers can be used to treat AK with a 90.0% response level, in periods of up to 42 months (evidence level C, III). Possible side effects are hyper/hypopigmentation, scarring, and infection and acne, in addition to prolonged healing time. Dermabrasion and microdermabrasion can also be used with the same potential side effects (evidence level C, III). Chemical peels cause necrosis in different layers of the epidermis, depending on the application's concentration, agent, and duration. The most common agent is trichloroacetic acid, which at 35% provides medium peeling and at 50% provides deep peeling. Other agents, such as phenol, can also be used to treat AK. The effectiveness of the chemical peels may reach 75%, with a 35% recurrence level (evidence level C, III).[23]

B) 2. Topical therapy

The most frequently used drugs in topical therapy are 5-FU, 5% and 3.75% imiquimod cream and 3% diclofenac sodium gel. The response to the treatment with such drugs reaches 50% of complete responses and 70% of partial responses. A patient's adherence is often compromised due to the degree of irritation caused, leading to early dropout. Short-term therapies may enhance adherence to the treatment. The latest drug in the treatment of AK is ingenol mebutate, which has the advantage of being used for only two or three days, depending on location, increasing treatment adherence.[1,3]

I. 5-fluorouracil (5-FU)

This therapy has been used for about 40 years.[24] The 5-FU is a topical chemotherapeutic drug used in AKs of the head and neck, and is considered the gold standard in regards to other topical treatments.[3] It is an antimetabolic drug because it inhibits the synthesis of DNA. Its commercial applications are 0.5%, 1.0%, 2.0%, and 5.0%, in different vehicles.[23] The British Association of Dermatology's 2007 guidance recommends using 5-FU twice a day for up to six weeks with efficacy of up to 12 months (evidence level A, I).[2] The response is noticeable 1 to 2

months after the end of the treatment. Studies show that the response for localized disease occurs in 50% of cases, with recurrence in 55% of cases.[23,25,26] Side effects take the form of irritation at the application site, such as dry, erythematous and ulcerated skin, with pain and edema. Adverse events can lead to the discontinuation of treatment.[3] Less aggressive treatment regimens exist, such as pulse therapy (evidence level B, III, 3b).[27]

There are studies on the association of 0.5% 5-FU to 10% salicylic acid in a gel vehicle applied once or twice a day for the treatment of AK, with an aim of strengthening the keratolytic effect.[28]

When comparing cryotherapy with topical use of 5-FU and imiquimod for the treatment of AK, it was possible to observe that 68% of patients treated with cryosurgery, 96% of patients treated with 5-FU, and 85% of patients treated with imiquimod showed clinical improvement. Histologic response was 32% to cryosurgery, 67% to 5-FU, and 73% to the treatment with imiquimod. The 12-month follow-up of these patients' field cancerization treatment observed a 4% response to cryotherapy, 33% to 5-FU and 73% to the treatment with imiquimod. The patients in the imiquimod group were considered to have had the best aesthetic outcomes ($p = 0.0001$).[23]

II. Imiquimod

Imiquimod is a topical immunomodulating drug, agonist of the toll-like receptor, which stimulates local immunity.[29] The drug stimulates the expression of genes of adaptive cellular immunity by activating macrophages, dendritic cells, cytotoxic T-cells and natural killer cells. As a consequence, it leads to the destruction of the lesion by immune-mediated apoptosis.[29] More recently, it has been found that imiquimod also has a direct antineoplastic action on the mitochondria.[1] It is commercially available in 3.75% and 5.0% concentrations.[2]

The British Association of Dermatology's 2007 guidance recommends using imiquimod for up to 16 weeks (evidence level B, I). The remission rate is 84% while the rate of recurrence is 10% in one year and 20% in two years (evidence level B, II). This topical therapy can treat subclinical lesions (field cancerization) and hardly generates scars.[2,27] The US FDA has approved the use of this drug once a day, twice a week for 16 weeks in the topical treatment of non-hypertrophic keratoses.[1] It is, however, a long treatment and may decrease a patient's adherence. It presents cutaneous reactions such as erythema, pruritus, burning sensation, pain, erosions and ulcerations, which can impact a patient's adherence and final outcome. In many cases there is a need to reduce the frequency of applications in order to prevent the interruption of the treatment.[30]

In a comparative study of AK treatment with imiquimod, 5-FU and cryosurgery, the initial effectiveness was 85%, 96%, and 68%, respectively. The recurrence after one year of treatment was 73%, 33%, and 4%, respectively – therefore the results were superior to the imiquimod's.[23]

III. Diclofenac

Diclofenac is a non-steroidal anti-inflammatory that blocks cyclooxygenase-2 (COX-2). Actinic keratosis and non-melanoma skin cancers have increased activity of COX-2. [1] It had a 50% efficacy in a study at 3% concentration in 96 patients with 5 or more AKs in an application area of 5cm2 for 90 days.[1] Another paper describes a 70% efficacy after 60 days of use.[1] The treatment is well tolerated with a low rate of side effects (erythema, pruritus, paresthesia, exanthema, dry skin, and contact dermatitis). The treatment is long and there are no signs of improvement within 30 days of its completion.[3]

IV. Tretinoin

The use of tretinoin has demonstrated good response in 55% of patients using a concentration of 0.3% and in 35% of patients at a concentration of 0.1% twice a day for 16 weeks. According to Misiewicz et al., the use of topical tretinoin can be beneficial in patients with AK.[31]

V. Ingenol

The latest drug in the treatment of AK is 0.05% ingenol mebutate applied once a day for two consecutive days (except for on facial skin), with a complete response in 71% of patients.[3] The 0.015% ingenol mebutate applied on facial skin once a day for three consecutive days showed a complete response in 50% of patients, with partial responses in 85% of patients.[3]

The ingenol mebutate is a diterpene ester derived from Euphorphia peplus. Its mechanism of action is not fully understood, but *in vivo* and *in vitro* models showed a dual mechanism of action: the induction of local cellular death by disrupting the mitochondria of the plasma membrane and tumor cells, and the production of pro-inflammatory cytokines and mass infiltration of neutrophils and other inflammatory cells which give rise to the immune response.[3]

VI. Resiquimod

Resiquimod is a non-specific immunity modulating imidazoquinoline amine. It has a higher potency in inducing cytokine expression than that of imiquimod.[3] In a European phase 2 study of the drug, the rate of complete cure after one therapy course was 40%, with the gel at 0.01%. That rate was 74.2% at a 0.03% concentration; 56.3% at a 0.06% concentration and 70.6% at a 0.1% concentration.[3] The discontinuation rate due to local and systemic cutaneous reactions after the first course of treatment with each resiquimod gel concentration was 0%, 13%, 31%, and 38%, respectively. The authors concluded that the efficacy in the treatment of AK was similar among the tested concentrations, however the gel at 0.01% and 0.03% was better tolerated than it was at higher concentrations.[3]

C) Photodynamic therapy

Photodynamic therapy (PDT) is effective in the treatment of AK.[2] The PDT concept is based on the induction of the proliferative cells' cytotoxicity by using a light source.[32] The treatment begins with the application of 5-aminolevulinic acid (ALA) or methyl aminolevulinic acid (MAL), which are photosynthetizing agents.

These topical substances are converted into protopor-

phyrin IX, which generates reactive oxygen in dysplastic keratinocytes under exposure to light with adequate wavelength (blue light, 14 - 18 hours after ALA application, and red light, 3 hours after the application of MAL).[2] The production of reactive types of oxygen destroys dysplastic keratinocytes that constitute the AKs. The treatment can cause pain of varying degrees. Photodynamic therapy is mainly used for non-hyperkeratotic lesions of the face and scalp, and can be particularly useful in cases of multiple or confluent AK lesions (field cancerization area), or those showing a poor response to therapy. Photodynamic therapy is generally well tolerated, however there are cases with more susceptibility to pain. Several factors, such as location, extent and type of lesion, fluence, light source, number of sessions and skin phototype, were described.[2,33] It produces excellent aesthetic results, with regression of more than 90% of the lesions.[2]

The British Photodermatology Group published a guidance for the use of photodynamic therapy in 2002, with instructions to remove keratin crusts by means of light curettage prior to the application of the drug, which must be occluded for three hours before irradiation. According to the Group, the treatment can cause pain, nevertheless it is safe.[34] In general, the treatment is well tolerated and yields good results with response in more than 90% of lesions.[3] There are studies showing response rates of 69-91% when used to treat facial and scalp AKs with two treatment cycles.[1,23,35]

The clinical and histological improvement in the field cancerization after several MAL-PDT sessions is proven. There is a reduction in the severity and extent of the keratinocyte atypia, associated with a decreased expression of the p53 gene.[36]

Recent studies have shown that photodynamic therapy can be performed outdoors and works with protoporphyrin IX activation by daylight, allowing for the treatment of AK lesions at home. Wiegell et al. have compared the effects of MAL-PDT application illuminated by red LED after a three-hour incubation period with the MAL-PDT illuminated by daylight for 2.5 hours after a thirty-minute incubation period for the treatment of the face and scalp AK. Continuous activation of protoporphyrin IX with PDT light has proven as effective as conventional MAL-PDT and was associated with post-treatment erythema and crusting, however with less pain. The authors concluded that PDT with daylight could provide faster treatment, more convenience and greater cost effectiveness.[37]

D) Combined treatment of injury and treatment field

In patients with many AKs, the combined treatment of the lesion and field would be effective in reducing lesions in multiple foci and subclinical lesions in areas exposed to sunlight.[3] Potential benefits include the total whitening of the lesions with minimal skin reaction and better cosmetic results.[23] There are studies that show that in AKs, the combination of cryotherapy and imiquimod in subclinical lesions was superior to the use of cryotherapy combined with a placebo in a three-month period (imiquimod group's response = 58% versus placebo group's response = 34%).[23] The use of 5-FU after cryotherapy for treatment of residual facial AK proved superior to the use of cryotherapy combined with placebo cream for six months (5-FU group's response = 67%, placebo group's response = 45%).[23]

In a pharmacological study, Gold examined the use of imiquimod, diclofenac, 5-FU or PDT combined with cryotherapy for the treatment of AK. The treatment with imiquimod was the most expensive, followed by 5-FU and diclofenac. PDT was the most cost effective treatment.[23]

E) Other modalities

There are studies featuring several other drugs, however they are small and little discussed in the related literature. Polyphenols (green tea) have been shown to inhibit the growth of cancer cell lineages and suppress the phosphorylation of the receptor's growth factor.[23] Betulinic acid is a natural pentacyclic triterpenoid that has potential antitumor properties as a result of its inhibition of topoisomerase.[23]

Piroxicam is a nonsteroidal anti-inflammatory drug that blocks cyclooxygenase-1 and cyclooxygenase-2. A 2010 Italian study evaluated the efficacy and safety of 1% piroxicam gel applied twice daily for 12 weeks for the treatment of 31 AK lesions, with the complete regression of 50% of the lesions. Adverse effects included erythema, mild pruritus, dry skin, and more rarely, cutaneous eruption.[23]

6. Prevention and chemoprevention

Prevention of SCC development is an important part of the management and treatment of AK.[38] The first step is to educate the patient about the risks of UV radiation and measures of solar protection that present evidence level AI according to the European Guidance 2011. Several studies show that the use of sunscreen is effective in the prevention and reduction of AKs. Controlled studies show that regular application of sunscreen resulted in a positive impact in patients who underwent organ transplantation.[39-42]

In dermatology, the term *chemoprevention* refers to the use of topical or systemic drugs that have the ability to inhibit or reverse a progression into skin cancer. These drugs include retinoids, T4 endonuclease V, polyphenolic antioxidants (such as the epigallocatechin gallate, found in green tea and grape seed extract), silymarin, isoflavone, genistein, nonsteroidal anti-inflammatories, curcumin, lycopene, vitamin E, beta carotene, selenium among others.[43]

CONCLUSION

The proper diagnosis and treatment of AK are crucial to the prevention of invasive SCC. The targeted field therapy is mainly used for multiple visible or palpable lesions in contiguous areas of skin, for subclinical lesions, and for all sun-damaged skin in areas at risk for subclinical lesions. The treatment of field cancerization is important for preventing recurrence and the emergence of new neoplastic and pre-neoplastic lesions. Currently available topical agents require prolonged treatment courses, often causing skin irritation, and are associated with the early interruption of the treatment, impairing results.[3] As a con-

sequence, new drugs are being studied.

The combination of the targeted treatment of the lesion and the treatment of field cancerization offers greater efficiency.[23] Further studies are necessary to determine the best combination therapies and their standardization.

With the field therapy's reduced duration of treatment and decreased severity of adverse events – consequently leading to better adherence to treatment – comes an increase the patient's satisfaction, a decrease in the risk of recurrence, and a reduction in costs.[23]

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