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Treatment of cutaneous field cancerization

Tratamento do campo de cancerização cutâneo

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ABSTRACT

The cutaneous field cancerization corresponds to an area of skin chronically exposed to the sun. It contains actinic keratoses and other skin signs of photodamage caused by ultraviolet radiation. This field comprises the genetic alterations that form the basis of the process of cutaneous carcinogenesis. Actinic keratoses have the potential to be stable for years, to regress spontaneously or to become invasive carcinomas. There is a consensus in the literature that the treatment of the entire field cancerization is more effective than treating just isolated lesions since it is not possible to predict which of these lesions will evolve to invasive cancer. It is also effective in the prophylaxis and treatment of the existing clinically imperceptible incipient lesions. There are several therapeutic options for individualized actinic keratoses and the field cancerization, from self-applied topical drug therapies to interventional and surgical therapies.

Keywords: Actinic keratoses; Skin cancerization field; cutaneous carcinogenesis; squamous cell carcinoma

RESUMO

O campo cutâneo de cancerização corresponde a uma área de pele cronicamente exposta ao sol. Nela, são encontradas as queratoses actínicas e outros sinais cutâneos de fotodano causados pela radiação ultravioleta. Nesse campo, estão as alterações genéticas que constituem as bases do processo da carcinogênese cutânea. As queratoses actínicas têm potencial para ficarem estáveis por anos, regredirem espontaneamente ou se tornarem carcinomas invasivos. Há um consenso na literatura de que é mais eficaz o tratamento de todo o campo de cancerização do que apenas o das lesões isoladas, uma vez que, além de não se poder prever qual dessas lesões irá evoluir para câncer invasivo, também será feita a profilaxia e tratamento das lesões incipientes clinicamente imperceptíveis já existentes. Existem diversas opções terapêuticas para as queratoses actínicas individualizadas e para o campo de cancerização, desde terapias medicamentosas tópicas autoaplicadas até intervencionistas e cirúrgicas.

Palavras-Chave: *Queratoses actínicas; Campo de cancerização cutâneo; Carcinogênese cutânea; Carcinoma espinocelular*

Review Articles

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INTRODUCTION

The term "field cancerization" was first used by Slaughter in 1953 based on histopathological studies of oral mucosa neoplasms. It was observed that these lesions appeared in multifocal areas, with precancerous changes, and that the tissue around the primary tumor was histologically altered. It was also found that neoplasias, although multifocal, could coalesce, and that persistence of adjacent abnormal tissue following surgical excision of the primary lesion could explain recurrences and the appearance of new cancerous lesions in previously treated areas.[1] In addition to the oral mucosa, other organs may present a field cancerization, including the skin. Paul Unna made the first correlation between ultraviolet radiation and skin cancer in the late 19th century, describing the development of these lesions in chronically sun-exposed places in sailors.

Therefore, by definition, the skin field cancerization (SFC) is a chronically photoexposed skin area, damaged by the exposure to ultraviolet (UV) rays, that presents multiple actinic keratoses (AKs) and other signs of photodamage. The term "keratosis" refers to the thickening of the stratum corneum, and the term "actinic" refers to the origin by sun exposure. Currently, it is well established that the genetic alterations of these fields form the basis of the carcinogenesis process.[2]

ACTINIC KERATOSES

SFC is a group of alterations found in the areas chronically exposed to solar radiation, which determine the appearance of several foci of non-melanocytic neoplasms resulting from DNA damage, the AKs.[3] It occurs due to the cumulative doses of ultraviolet (UV) radiation absorbed over a lifetime. The AKs manifest as discrete intraepidermal lesions, typically presenting as rough, scaly, and sometimes keratotic papules or plaques. They can be found in all races and genders, but are much more common in men, light-skinned (Fitzpatrick phototype skin I and II), middle-aged or older individuals. More than 80% occur in the head (ears, frontal region, supraorbital prominence, nasal dorsum, malar region, and scalp of bald individuals), neck, and upper extremities (back of the hands and extensor surfaces of the forearms). They may present as a single lesion, but most often they are multiple lesions.[4]

In addition to the classic forms described above, there are some clinical variants of AK: hyperkeratotic AK, which manifests as a firm and infiltrated papule, covered by keratosic scale and rough on palpation; pigmented AK, which closely resembles solar lentigo; ant cutaneous horn, in which a conical projection is formed over the lesion, giving it a peculiar clinical aspect. Actinic cheilitis is the term used for AKs that appear on the lips, especially in the lower lip, resulting from the confluence of the lesions.[5]

Historically, AKs have been considered the most common premalignant skin lesions. However, some researchers prefer to classify them as in situ squamous cell carcinoma (SCC), as evidence has shown that they have histopathological criteria, genetic tumor markers, and p53 gene mutations identical to the SCC. Although 25% of AKs are estimated to have spontaneous regression, the risk of progression to invasive SCC ranges from 0.025% to 20% per year.[6,7] In recent decades, the incidence of AK has been increasing. The approximate prevalence in the 60 to 69 age group is 79% in men and 68% in women.[8] Recent studies show that AKs with atypical cells present only in the basal layer of the epidermis are the most common precursors of invasive SCC.[5]

SKIN FIELD CANCERIZATION

The SFC concept suggests that healthy skin around areas of AK supports the basis for clonal expansion of genetically altered neoplastic cells.[2] In clinical practice, defining SFC requires three factors: a determined skin region, multiple AKs, and at least one SCC within that region.[9] Histopathology of biopsies and optical coherence tomography (OCT) of skin areas suspected of SFC confirm that 79% of apparently healthy skin has evidence of dysplasia or occult carcinoma.[10] The SFC paradigm has two critical implications for the treatment of SCC. First, because SCC originates from multifocal areas with precancerous changes, and the presence of at least one SCC increases the risk of subsequent tumors by 42% within five years. Second, a clinical relapse of a completely surgically excised SCC may, in fact, represent not a relapse but the development of a new primary cancer.[11]

Despite all the advances in diagnostic methods, it cannot yet be predetermined which AKs will regress or which will evolve into a deep invasion. Because there are subclinical lesions, treatment must be performed on the isolated lesion and also on the entire field cancerization, considering that it is compromised with genetically altered cells.[12]

THERAPEUTIC OPTIONS

There are multiple options available for treating AK and SFC. The choice must be made taking into consideration:

1. The location, number, duration and clinical course of lesions;
2. The history of skin cancer, age, whether or not there is immunosuppression, and comorbidities;
3. The frequency and duration of sun exposure;
4. The physician's experience;
5. The treatment cost;
6. The patient's preference.[2,13]

Therapeutic measures are indicated both for the treatment of isolated lesions and for the field cancerization. The treatment of isolated lesions is based on the destruction of clinically apparent lesions and it is best suited for patients who have a small number of lesions and who have low-risk characteristics for invasive SCC.

Treatments for isolated AKs include cryosurgery with liquid nitrogen, curettage and electrocoagulation, dermabrasion, caustic application, and several types of lasers. All of these methods are effective, have variable costs and different adverse events such as pain, blistering, slow healing by secondary intention, and residual hypochromia. SFC therapy is directed to both clinically apparent and preclinical lesions and is, therefore, the

most recommended option for most patients.

Patients with multiple lesions may benefit from combined therapies, the destruction of isolated lesions, and concomitant treatment of SFC. Whatever the option, long-term monitoring is required to verify the healing or if new subclinical lesions have emerged.[2]

FIELD CANCERIZATION TREATMENT

The first step in controlling patients with multiple AKs and SFC is strict sun protection. Ultraviolet (UV) radiation is the initiator and promoter of tumor growth. Studies show that there is a reduction in the appearance of precursor lesions when UV radiation exposure is interrupted.[14]

The ultimate goal of SFC treatment is to remove all lesions, whether clinically apparent or subclinical, and to reduce the potential risk of SCC.[7,10] Topical drugs, photodynamic therapy (PDT), daylight PDT, and ablative procedures such as dermabrasion, lasers, and chemical peels are available. The advantages of topical therapies are that they are proven effective and can be self-administered, although they have the disadvantages of being generally long-term treatments with significant adverse events, which would decrease treatment adherence and increase the risk of relapse. On the other hand, PDT and ablative options are more expensive and need more post-procedure care because of the higher risk of complications (infections, hypopigmentations, unsightly scars, and relapses, among others).[2]

PHOTOPROTECTION

Several studies have shown that the regular use of photoprotection (sunscreen) is effective in preventing the progression of AK to invasive SCC and the emergence of new lesions. Thompson *et al.* conducted a randomized, placebo-controlled study involving 588 patients analyzing the remission rates of AK lesions after daily use of broad-spectrum sunscreen. The group that used sunscreens presented a higher rate of remission than the control group (OR = 1.53; 95% CI, 1.29–1.80) and a lower rate of new lesions emergence.15 There is a large number of sunscreen options on the market today, most of them with good quality, allowing the dermatologist to make a suitable, almost individualized choice for each patient. In addition to chemical photoprotection, patients subjected to constant or intermittent sun exposure, due to work or leisure, should be advised to use physical photoprotection, such as hats, clothing, umbrella, and others.

5-FLUOROURACIL (5-FU)

5-FU is a topical chemotherapy drug classified as a pyrimidine analog used as an antineoplastic agent. Its primary mechanism of action is the reduction of atypical cell proliferation and the induction of apoptosis by interfering with DNA and RNA synthesis in mutated cells. The drug causes intense inflammation, enhancing its antitumor effect .[3] 5-FU has been used in the clinical practice for over five decades and has the great advantage of its low cost. In Brazil, it is marketed as cream 5%, but it can be handled in other concentrations (0.5%, 1%, and 2%) and in vehicle lotion. According to a consensus published in 2007, 5-FU should be used twice a day for six weeks, reaching cure rates of 70% to 80%. But the same consensus reported recurrence rates of approximately 55%.[7]

It has important adverse events such as pruritus, prolonged erythema, ulceration, pain, and secondary pigmentation, making it difficult for patients to adhere to treatment. Also, prolonged use is another limiting factor.[11] The area to be treated should not exceed 500cm^2. When it is necessary to treat larger areas, it is advisable to do so in a staggered manner. It has a good indication for SFC treatment because it can show, through erythema and eczematization, apparently healthy areas, but with the onset of neoplasia.

In 2010, a pilot study was published in Germany using the combination of 5-FU 0.5% and salicylic acid 10% three times a week for four weeks in 15 patients with a mean of 66 AK lesions each. After 12 weeks, there was a complete response in 77% of patients, partial response in 21%, and no response in 2%. The authors concluded that the treatment was effective and very well tolerated.[7] Other publications support this therapy in other European countries.[3] Another study compared the results of the treatment of AKs located on the back of the hands with 5-FU 5% alone and in combination with tretinoin. This study concluded that the association with tretinoin was more effective than 5-FU alone.[7] A randomized, placebo-controlled study, published in 2015 by Pomerantz *et al.*, conducted a long-term follow-up of patients receiving a one-time field cancerization treatment with 5-FU 5% cream. The authors observed that there was a lightening of the precursor lesions of SCC that lasted for more than three years.[16] In another recent study, published in 2018, a randomized, double-blind clinical trial was conducted in 932 patients with a history of skin cancer (39% presenting a history of previous SCC). After a year, the authors identified a 75% reduction in SCC incidence after a single course of treatment with topical 5-FU 5% (5 patients with SCC in the 5-FU group *versus* 20 patients in the placebo group). They concluded that a single field cancerization treatment with 5-FU 5% cream could significantly reduce the incidence of SCC for at least one year. Further clinical trials are needed to support the use of this treatment, notably the SFC treatment repetition interval for high-risk patients.[14]

In another recent study, published in March 2019, Abby *et al.* conducted a prospective, randomized, double-blind, cohort trial. In this study, participants underwent therapy for face and scalp AKs with 5-FU 5% combined with calcipotriol 0.005%, while the control group received 5-FU 5% associated with vaseline. The treatment lasted four days. The incidence of squamous and basal cell carcinoma was evaluated for one, two, and three years. The authors concluded that there was a significant increase in erythema, a marked improvement in cellular immunity, and an induction of tissue-resident memory T cells against actinic keratoses, as well as a significant reduction in the risk of developing squamous cell carcinoma after three years of treatment.[17] Another low cost and effective option for the treatment of multiple AKs and SFC, especially in the forearms, is peels combining Jessner's solution and 5-FU 5% in propylene glycol. The application begins with one to three layers of Jessner's solution and then

a layer of 5-FU 5%. The patient is advised to wash the sites after 24 hours and completely avoid sun exposure by physical methods during this period. Six to eight applications are conducted, with biweekly or monthly intervals, depending on the patient's tolerability. Thus, it is concluded that, despite being an ancient drug, 5-FU remains one of the protagonists in the treatment of AKs and SCF.

RETINOIDS

For over 35 years, topical retinoids, especially tretinoin, have been used for various dermatoses, including acne, melasma, photoaging, and AK.[3] Tretinoin, or retinoic acid, is a molecule derived from vitamin A and the nuclear retinoid receptor mediates its mechanism of action.[18] The first use of tretinoin for AK was in 1962 by Stuttgen, and then several studies have shown generally low variable efficacy with this drug, both in the treatment of AS and in the prevention of skin cancer. Therefore, its use in the treatment of AK and SFC remains controversial, being more indicated for the treatment of photoaging than for SFC.[2]

DICLOFENAC SODIUM 3% IN HYALURONIC ACID

Diclofenac is a non-hormonal anti-inflammatory cyclooxygenase 2 (COX-2) inhibitor[10], an enzyme that, when activated, has been implicated in the carcinogenesis of tumors induced by UV radiation by promoting tumor growth, increasing cell proliferation, stimulating angiogenesis, and inhibiting apoptosis. The inhibition of this enzyme results in decreased prostaglandin production.[20] It has been used to treat AK and SFC at a concentration of 3% in a hyaluronic acid gel vehicle twice a day for a period of 60 to 90 days. There is slight or moderate irritation at the application site. The mechanism of action is by apoptosis induction. Several phases 3 and 4 studies have shown the efficacy of complete lesion resolution of 33% to 50% between 60 and 90 days of treatment.[21-24] One of them, a meta-analysis of three randomized trials comprising 364 patients, found a cure rate of 40%. In 2010, Ulrich *et al.* published a randomized, placebo-controlled study evaluating topical diclofenac 3% in transplant patients with multiple AKs. The authors observed a complete response in 41% of the AKs, a decrease in the number of lesions, and, despite being a high-risk group, they identified no patients with invasive SCC at 24 months of follow-up. The authors concluded that the treatment is effective and well-tolerated.[25] Nevertheless, this therapeutic option requires proper patient compliance due to the long duration of use. According to the British Association of Dermatologists Therapy Guidelines, the level of recommendation for diclofenac gel in the treatment of SFC and AK is B, and the quality of evidence is I.[2]

PIROXICAM

Piroxicam is a nonsteroidal anti-inflammatory drug (NSAID) with a mechanism of action similar to diclofenac. It is a potent inhibitor of cyclooxygenase 1 (COX-1) and suppressor of proteinases related to tumor growth.[26] Babino *et al.* used this drug at a concentration of 0.8% incorporated into photoprotection products applied twice a day for six months and found a clear improvement in AKs.[27]

DOBESILATE

Dobesilate is used for the secondary prevention and progression stabilization of mild to moderate nonproliferative diabetic retinopathy. It also improves the clinical manifestations of chronic venous insufficiency (CVI) of the lower limbs. Its mechanism of action is to inhibit the vascular endothelial growth factors (VEGF) and fibroblast growth factors (FGF). Studies with this drug are still in preliminary stages. It has been used at 2.5% and 5% concentrations in cream for AK and basal cell carcinoma and has been showing to be effective, safe, and well-tolerated.[28,3]

IMIQUIMOD

Imiquimod is considered a nonspecific immunomodulator that acts as a toll-like receptor 7 agonist. These receptors are located on the surface of dendritic cells, monocytes, macrophages, and Langerhans cells. When imiquimod activates them, they induce apoptosis and lead to the release of cytokines and chemokines, including tumor necrosis factor-alpha (TNF–α), interferon c (INF-c), and interleukins. This release determines an influx of inflammatory cells within the lesions and, consequently, their cell-mediated destruction of the innate immune response.[3] Although its mechanism of action is not yet fully elucidated, it has a recognized antiviral and antitumor action. It is a well-studied drug in the treatment of AKs, notably in non-hyperkeratotic or hypertrophic lesions located on the face and bald area. It is marketed in Brazil in 5% cream. The application should be three times per week for 16 weeks over an area of up to 25cm^2, and determine cure rates ranging from 45% to 84%, according to several well-conducted placebo-controlled studies.[29, 30, 31] In these studies, recurrence rates were approximately 10% in the first year and 20% in the second year. The FDA has approved other concentrations, such as 3.75% and 2.5%, but they are not sold in Brazil. These lower doses were also effective, with shorter use time and fewer adverse events.[32] Its drawbacks are the long treatment duration and important local adverse events such as erosion, ulceration, blistering, pain, and residual hypochromia. When applied to large areas, even systemic symptoms (malaise, headache, and fever) may occur. For these reasons, adherence to treatment is more difficult and should be very clear to patients.[2,3]

RESIQUIMOD

It is an emerging therapy that also acts as an immunomodulator by the toll-like receptor 7 and 8 agonist mechanism. It induces a more intense response of myeloid dendritic cells and a higher expression of TNF-α and interleukin 12 than imiquimod.[4] It was used in a European gel vehicle study with four different concentrations (0.01%, 0.03%, 0.06%, and 0.1%) once a day, three times a week for four weeks in a 25cm2 area on the face and/or bald area. High cure rates were observed at all concentrations (ranging from 40% to 74.6%), with the highest rates at the highest concentrations. The authors concluded that all concentrations are effective, but the lowest (0.01% and 0.03%) were better tolerated.[33]

INGENOL MEBUTATE

Ingenol mebutate is the most recently introduced substance for the treatment of SFC. FDA approved it in January 2012. It is a macrocyclic diterpene ester taken from *Euphorbia peplus*, a plant native to most of Europe, northeast Africa, northwestern Asia, Australia, New Zealand, North America, and temperate regions. The mechanism of action, although not yet fully elucidated, seems to be due to two mechanisms: rapid lesion necrosis within a few hours, direct cytotoxic effect on keratinocytes, followed by the production of inflammatory cytokines and induction of dense inflammatory infiltrate consisting of neutrophils and eosinophils. What sets it apart from the other therapeutic agents mentioned is the short duration of treatment, which is two to three days, contributing to higher patient compliance.

It is commercially available in two gel vehicle concentrations: 150mcg/g and 500mcg/g formulated in propyl alcohol-based gel. The former is given once daily for three consecutive days on the face and/or scalp, and the latter is administered once daily for two consecutive days on the trunk and/or extremities. It can be used to treat localized lesions and/or SFC. After topical application, it crosses the stratum corneum and exerts its action on the dermis and hypodermis with minimal systemic absorption. Each single-dose package is sufficient to treat an area of 25cm^2. Phases 2 and 3 studies showed higher efficacy than placebo, in which the number of lesions on the face and scalp reduced a mean 83% and on the back and limbs, a mean 75%.[34,35] High sensitivity pharmacokinetic studies did not detect systemic absorption of ingenol mebutate, and its metabolites do no affect cytochrome P450.[36]

The main adverse events are erythema, edema, pruritus, erosion, and blistering, with varying intensities. These events usually disappear spontaneously within two days on the face and bald area, and within four days on the body and extremities.[37] In early May 2019, the laboratory responsible for marketing the product in Brazil announced its discontinuation to the Brazilian Society of Dermatology.

PHOTODYNAMIC THERAPY (PDT)

Photodynamic therapy (PDT) is a therapeutic option for SFC already well established in the literature. It is based on the photoactivation of protoporphyrin IX. It acts through the interaction between a photosensitizing agent and a light source, which produces reactive oxygen species (ROS). The most commonly used photosensitizing agents are 5-aminolevulinic acid (ALA) and methyl aminolevulinate (MAL), which preferentially accumulate within AK cells where they become protoporphyrin IX. They are applied topically to the skin at intervals ranging from 1 to 18 hours before being exposed to a visible light source. They absorb this light and generate reactive oxygen species that determine microvascular damage, inducing a local inflammatory reaction and cell death. Because the conversion of prodrugs to protoporphyrin IX is increased in malignant and premalignant cells, treatment is relatively selective for SCC precursors.[3]

Several published studies show good results in the treatment of AKs, SFC, and superficial basal cell carcinomas (BCC), mainly in less hyperkeratotic lesions. The association with the previous curettage seems to increase the efficacy. Pain at the time of application is the most commonly reported adverse event, followed by photosensitization. According to a European guideline, published in 2013, with evidence B and quality I, PDT in the treatment of the field cancerization in transplant patients can prevent the emergence of new AKs and their transformation into invasive SCC. They also reported that in immunocompetent patients, this therapy showed a significant delay, on average six months, in the appearance of new lesions. According to these guidelines, this prophylactic effect is because PDT decreases the p53 expression, a marker of skin cancer.[38] Szeimies *et al.*, in a study published in 2012, concluded that MAL-PDT treatment decreases the carcinogenic potential in the skin field cancerization and partially reverses the intrinsic and extrinsic signs of skin aging due to dermal collagen deposition.[39] In a randomized controlled trial, the results of the treatment of multiple AKs on the face and scalp with ALA-PDT versus TCA 35% peel in 28 patients were compared using new and pre-existing lesions count as assessment base. Patients were examined at one, three, six, and 12-month intervals. They found that PDT was significantly more effective than TCA 35% peel, with a cure rate of 73.7% *versus* 48.8%. The cosmetic result was similar in both treatments.[40]

More recently, an alternative form of PDT has been developed using the MAL photosensitizer. Instead of using an artificial light source, single two-hour exposure to indirect sunlight activates MAL. There is higher tolerability, shorter treatment duration, and the cost is lower because it does not require an artificial light source. There are studies showing the same efficacy as conventional therapy with fewer adverse events.[41,42,43] Neither PDT, and probably any other therapeutic option, can eliminate the precursors of skin cancer. Therefore, like the others, repeated treatments are necessary to prevent the onset of SCC.[11] A limiting factor is the treatment cost. Currently, in Brazil, there are problems with the supply and acquisition of photosensitizers, which has hindered its use.

CRYOTHERAPY

The cryotherapy is a destructive technique that uses direct application of liquid nitrogen (or more rarely other cryogens) to freeze skin lesions. Keratinocyte is destroyed at -40 °C to -50 °C, and liquid nitrogen reaches -196 °C, making it a very effective agent. It is best indicated for the treatment of individualized and discrete AK since the effect is smaller in larger and thicker lesions.[44,45] The application time varies from five to 15 seconds but may reach up to 30 seconds in thicker lesions. The procedure must be performed inside and around the lesion and must reach a freezing range of 2mm to 4mm to destroy it.[3] Despite being a widely used treatment, few studies determine its real efficacy, application frequency, duration, intensity, and appropriate temperature. This lack of uniformity leads to different results.[46] One of the cryotherapy advantages is that, in general, only one application is required. Cure rates range from 75% to 99%.[43,47] In 2008, Kaufmann *et al.* published a randomized, multicenter, comparative study on the safety and efficacy of PDT with MAL *versus* cryotherapy in the treatment of AK on

the extremity in 121 patients. Complete response with cryotherapy after 24 weeks was 88%.48 Some studies show increased efficacy of this technique when combined with other topical treatments, such as imiquimod, diclofenac, and ingenol mebutate. Adverse events may arise during treatment, such as erythema, pain, blistering, and scabbing of varying intensity, as well as the possibility of residual hypopigmentation.

SYSTEMIC RETINOIDS

Patients with SFC and a high risk of developing SCC may benefit from systemic treatment with acitretin. Studies in animal models have shown that this drug can suppress proliferation, promote keratinocyte differentiation, and induce tumor regression. In humans, acitretin was used in 30 mg/day in renal transplant patients for six months, and there was an 88% reduction in the incidence of SCC. However, there was an increased incidence in both acitretin and placebo control groups with therapy discontinuation.49 Therefore, this drug was not able to eliminate SCC precursors, and thus therapy should be administered over a long time, with all known adverse events (xerosis, mucositis, hepato-toxicity, hyperlipidemia, and others) and teratogenicity.[50]

SURGERY AND LASER

Surgical treatment is restricted to isolated and/or localized lesions. It is indicated for individuals at high risk or for those who have already undergone malignant transformation. The most commonly used techniques are curettage and electrocoagulation, as well as surgical excision. Ablative and non-ablative lasers are being investigated as monotherapy and in combination with other SFC therapies, and they have shown promising results.[51,52] A limiting factor of laser therapy is its high costs.

CONCLUSIONS

We can draw some practical conclusions from all that have been described to contribute to the daily conduct of dermatologists.

1. The concept of skin field cancerization (SFC) is well-grounded in the literature.

2. Although some clinical and histopathological data suggest some AKs to have a higher or lower potential to become invasive carcinoma, it is not yet possible to predict which one will evolve.

3. As a result, it is necessary to perform the treatment in all areas where there are lesions likely to transform and not only in individualized lesions.

4. There are numerous therapeutic options available, with evidence of varying favorable outcomes. It is up to the dermatologist to choose the most appropriate for each case, considering several factors, such as effectiveness, time of use, adverse events, comorbidities, and costs.●

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