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MINIREVIEWS

Actinic keratosis and field cancerization

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Abstract

While actinic keratoses (AKs) have been considered precancerous until recently for being able to turn into squamous cell carcinomas (SCCs), it is now agreed that it would be more appropriate to call them cancerous. Although not all AKs turn into SCC and some of them may even have a spontaneous regression, there is an obvious association between SCC and AK. Approximately 90% of SCs have been reported to develop from AKs and AKs are the preinvasive form of SCCs. The presence of two or more AKs on a photodamaged skin is an indicator of field cancerization and represents an increased risk of invasive SCC. All lesions should be treated since it cannot be foreseen which of the lesions will regress and which will progress to SCC. AK can be a single lesion or it can involve multiple lesions in a field of cancerization; thus, AK treatment is grouped under two headings: (1) Lesion-specific treatment; and (2) Field-targeted treatment. Lesion-specific treatments are practicable in patients with a small number of clinically visible and isolated lesions. These treatments including cryotherapy, surgical excision, shave excision, curettage and laser are based on physical destruction of the visible lesions. Field-targeted treatments are effective in the treatment of visible lesions, subclinical lesions and keratinocyte changes in the areas surrounding the visible lesions. Field targeted treatment options are topical imiquimod cream, 5% 5-fluorouracil cream, ingenol mebutate, diclofenac gel, resimiquimod and photodynamic therapy.

Key words: Actinic keratosis; Squamous cell carcinoma *in situ*; Field cancerization

Core tip: While actinic keratoses (AKs) have been considered precancerous until recently for being able to turn into squamous cell carcinomas (SCCs), it is now agreed that it would be more appropriate to call them cancerous. The presence of two or more AKs on a photodamaged skin is an indicator of field cancerization and represents an increased risk of invasive SCC. All lesions should be treated since it cannot be foreseen which of the lesions will regress and which will progress to SCC. In this review, epidemiology, ethiopathogenesis, diagnostic approach and treatment options for AK and field cancerization have been evaluated in light of recent literature.

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INTRODUCTION

Actinic keratoses (AKs) are epidermal lesions characterized by skin-colored, red or red-brown crusty and squamous spots, patches or nodules with a potential to progress to squamous cell carcinoma (SCC). Being an indicator of cumulative ultraviolet (UV) exposure, AK lesions typically appear on the areas with chronic sun exposure such as the face, chest, hairless scalp, auricles, hands and dorsal regions of arms[1]. It has been reported that one of every 10 AKs progresses to invasive SCC in time. People with more than five AKs have a relatively increased risk of SCC. While AKs have been considered precancerous until recently for being able to turn into SCCs, it is now agreed that it would be more appropriate to call them cancerous. The term keratinocyte intraepithelial neoplasia (KIN) has been proposed for these lesions[2].

Although not all AKs turn into SCC and some of them may even have a spontaneous regression, there is an obvious association between SCC and AK. Approximately 90% of SCs have been reported to develop from AKs and AKs are the preinvasive form of SCCs[1]. About 20%-25% of the lesions regress in a year. In a similar period of time, 15% of the lesions will reemerge. It is very difficult to predict if any regression is permanent.

All lesions should be treated since it cannot be foreseen which of the lesions will regress and which will progress to SCC. It should be noted that subclinical lesions may also transform into SCC[3]. The histopathology of subclinical lesions is the same as that of clinically observable AKs. The number of subclinical spots in an area is more than 10 times that of visible AKs[1,3]. The risk factors of transformation from AK into SCC have been enumerated as endurance, bleeding, larger lesion diameter, fast growth, erythema and ulceration with minor risks including pain, palpability, hyperkeratosis, itching and pigmentation[4].

EPIDEMIOLOGY

The real incidence of AK is not known. The risk of having AK in a lifetime is estimated to be 50%. The World Health Organization has reported that the prevalence of AK is clearly associated with the location of the place of living. In smaller latitudes, both the prevalence of AK is high and multiple AKs are seen more frequently[5].

The rate of prevalence is reported to be 40%-60% on the average in Australia and between 11% and 25% in the northern hemisphere. They are seen more in males than females[6]. A study has reported the prevalence as 15.4% in men and 5.9% in women in the United Kingdom. These rates go up to 34.1% in men and 18.2% in women after 70 years of age[7]. In Australia, the prevalence was found to be 22% in men and 8% in women and 83% and 64% between the ages 60 and 69, respectively[8].

FIELD CANCERIZATION

Multiple AKs are usually seen in areas exposed to the sun and dysplastic keratinocytes or preclinical lesions can be seen histologically on the clinically lesion-free skin surrounding the AKs. Even if the keratinocytes on these areas appear to be normal histologically, they are candidates for a future tumor growth. This process is defined as field cancerization[1,9]. The presence of two or more AKs on a photodamaged skin is an indicator of field cancerization and represents an increased risk of invasive SCC. Photodamage is the earliest finding of the process progressing from AK to finally SCC[1]. The term field cancerization is defined as the presence of one or more areas created by genetically altered epithelial cells that lead to the prognosis of epithelial carcinogenesis. The effect of field cancerization is well-documented in squamous cell tumors[10].

The definition of field cancerization was first used by Slaughter *et al*[2] in 1953. Such areas are probably associated with exposure to carcinogens[2]. Multiple cancers that are associated with gene aberrations induced by carcinogens, that do not occur due to metastasis of tumor cells and that appear as tumors independent of, and in different distances from, each other are associated with field cancerization[11]. A cutaneous field cancerization refers to the histologically altered areas on the lesion-free skin tissues surrounding the non-melanocytic skin tumors on a chronically photodamaged skin[3].

ETIOPATHOGENESIS

UV

UV radiation seems to be the major player responsible for the process starting from photodamaging of the skin and progressing to actinic keratosis and SCC. The leading risks are intensive or cumulative UV exposure, open area activities, tanning efforts and longevity. The DNA lesions induced by UV are either repaired or if the damage is severe the cell enters apoptosis to protect itself from mutation. In case the cell cannot be fully repaired but it remains alive, the damaged nucleotides result in permanent somatic mutations and accumulation of such mutations may end up in cancer[6].

Gene mutations

In normal cellular growth, the p53 expression is suppressed. Its expression is activated during severe stresses in which the cell is caught between apoptosis and survival in the case of cytotoxic or mutagenic agents for instance. The gene that undergoes mutation most frequently in humans during AK is p53 (37%) and there is a strong relationship between TP53 mutations

and AK/SCC. Both the UVA and UVB wavelengths are among the causes of carcinogenesis in TP53 DNA mutations. The mutations of this gene appear at the early stages of carcinogenesis and also play a role in the progression of cancer[12]. The UV radiation induced TP53 mutation has been found in more than 90% of SCCs developing from AKs[7]. The clonal patches consisting of cells with TP53 mutations can also be found on normal skin. Jonason *et al*[13] have reported that these cell clones are 10 times more in number and are larger on a skin exposed to the sun than on a skin not exposed to sun. Brennan *et al*[14] have shown that tumor recurrence is significantly higher in the presence of mutations in peritumoral areas. No recurrence has been seen in the neighboring areas without any mutations[14]. In CDKN2A mutation, the risk of progression from AK to SCC increases significantly[6]. The other mutations associated with the progression of skin cancers are NOTCH1, NOTCH2 and SMO. Hu *et al*[15] have shown that the Notch/CLS signal is suppressed in the stromal area neighboring premalignant AK lesions. They have also shown that tissue changes such as stromal atrophy and inflammation occur when the Notch/CLS signal is eliminated. This is a potent stimulus for epithelial tumors[15].

Immune suppression

While the rate of progression from AKs to SCCs is 10% in immunocompetent persons, this rate is 50% in immunosuppressed people. Patients who underwent organ transplantations have 100-250 times increased risk of cutaneous SCC. UV and immunosuppressive drugs are effective in the occurrence of skin cancer. Because the immunosuppressive therapy used for transplant patients reduces peritumoral inflammation, the invasion of skin tumors can easily go unnoticed in clinical practice[16]. Trans-urocanic acid (UCA), which is a UVB chromophore, is expressed in stratum corneum in ample amounts. It is rapidly isomerized into a cis form by the effect of UVB. CisUCA is a potent immunosuppressant[6]. Another target of UV radiation is DNA. The keratinocyte and langerhans cells are also direct targets of UV for being located in the upper layers of the skin. Due to UV radiation, not only DNA is damaged but also the antigen presenting functions of LH are suppressed. At the same time, secretion of immunosuppressive inflammatory cytokines such as PG E2 and PAF becomes effective. In the end, UV acts in two ways in skin cancers, by causing genetic damage and by suppressing anti-tumor immunity. Both of these processes are important in the progression of preneoplastic AKs to SCCs[17].

Others

The risk is higher especially in persons whose Fitzpatrick skin type is Ⅰ or Ⅱ (easily having sunburn and hardly having any tan). The presence of freckles on the face, even if only a few, increases the risk significantly[1]. The HPV infections may play a role in the pathogenesis of non-melanoma skin tumors. HPV 38 has been found more frequently in AK lesions than in SCC lesions[18]. Chronic inflammation is an important indicator of tissue changes progressing to carcinogenesis. Cyclooxygenase-2 (COX-2) inhibiting anti-inflammatory drugs can reportedly prevent tumorogenesis, but cannot reverse tumorogenesis that has already started[19].

Mucin 1 (MUC 1), a transmembrane glicoprotein plays a critical role in human cancer. MUC 1 is not expressed by the normal epidermis in human skin. It is expressed by keratinocytes in some premalignant and malign lesions such as epidermolysis bullosa, Paget's disease, Bowen's disease, and Merkel's carcinoma. Arciniegas *et al*[20] found that MUC 1 was localised at the apical surface of some atypical keratinocytes of AKs, but was not detected in the epidermis of normal skin. This findings suggest that the expression of MUC 1 in AK may contribute to the progression of AK to SCC.

UVA in particular causes DNA mutations that are characterized by photo-oxidative stress. Longevity increases the risk due to factors such as increased cumulative UV exposure and decreased immune resistance. The prevalence of AK is higher in males. The rate of working in open areas being higher in men and AGA are risk factors for scalp AKs. The use of photosynthesizing medication and genetic diseases such as xeroderma pigmentozum are also risk increasing factors for AK development[1,2].

HISTOPATHOLOGIC CHARACTERISTICS

AK is characterized by atypia and dysplasia of the keratioctyes in the basal layer of epidermis. The atypical and dysplastic clusters grow in time and advance to upper layers. Alternating areas of parakeratosis and hyperkeratosis are present in the corneum layer[11]. The atypical changes in the epidermal keratinocytes may be in different sizes and shapes and involve nuclear pleomorphism. The neoplastic keratinocyte proliferation in AK is limited to the epidermis[2]. There are signs of lymphocytic inflammatory infiltration and solar elastosis in dermis. From epidermal changes, AK and SCC cannot be distinguished histologically. Molecular changes associated with cancer are present in both AK and SCC. Padilla *et al*[21] have shown that the genetic characteristics of AK and SCC lesions are closely associated with each other. This finding supports the fact that AK is of malign nature from the very beginning. Its lichenoid, hypertrophic, bowenoid, pagetoid and pigmented types have been defined histologically[3,10].

CLINICAL SIGNS

It is most frequently seen in the areas which are mostly affected by DNA damage caused by UV radiation including the head, face, ears, lower lip, dorsal region of hands, lower legs, décolleté region, neck and upper back. AK is the most widely seen skin cancer on a sun-damaged skin[1,22]. It appears as squamous, skin-

colored, pink or red-brown papules, macules or plaques with vague margins. It can be a single lesion, but more commonly there are multiple lesions on a photodamaged skin. A classical aspect of AK is the rough surfaces of lesions feeling like sandpaper[1]. The size of lesions can range from a few millimeters to 3-4 cm and larger. When the lower lip is affected, it appears as a dry, scaled and atrophic lesion, which is called actinic cheilitis[15]. Depending on its clinical appearance, AK may be of classical, hypertrophic, atrophic or pigmented type, or appear as cornu cutaneum or actinic cheilitis. The severity of AK was divided into 3 phases within itself: (1) Lesions not so visible, vaguely felt with palpation; (2) Lesions are of medium thickness, easily palpated and seen; and (3) Hyperkeratotic and thick lesions[23].

DIAGNOSIS

A typical AK lesion does not require any histopathologic analysis. The clinical and subclinical changes of AK and field cancerization on the skin can be diagnosed by way of examination. Alongside multiple AK presence, those areas of the skin with a chronic UV damage such as solar lentigines, pigmentation disorders, altered skin tissue, deep and superficial lines, telangiectasias, xerosis and solar elastosis are considered as a field of cancerization[3]. However, biopsies are required in patients suspected of having invasive SCC lesions including hyperkeratotic and hypertrophic lesions with a diameter larger than 1 cm, which involve induration, bleeding, inflammation, ulceration, fast growth, pain upon palpation, no response despite appropriate treatment or relapses in periods as short as 2-3 mo[24].

DERMOSCOPY

Dermoscopy is a very useful method in diagnosing AK with 98.7% sensitivity and 95% specificity[25]. The value of dermoscopy depends on the physician's experience and the AK's dermoscopic characteristics, of which superficial scurf/scales are the most common one. Sometimes, underlying structures cannot be discerned due to such scurf. The second most widely seen pattern is the red, artificial network structure, which is described by a strawberry appearance. The other dermoscopic signs include targetoid-like appearance, rosette sign, absent fissures/ridges, crypts and milia-like cysts[26].

TREATMENT

The goal of AK treatment is to treat the field of cancerization and prevent formation of new lesions rather than to ameliorate the clinical appearance of AK lesions. Although the evidences showing that this approach is useful are very few, treatment is a requirement when the clinical and histological characteristics of AK are taken into consideration[1]. The need for treatment also involves continuous monitoring of AKs with respect to patient complaints, AK's effect on quality of life and transformation into SCC[24].

AK can be a single lesion or it can involve multiple lesions in a field of cancerization; thus, AK treatment is grouped under two headings: (1) Lesion-specific treatment; and (2) Field-targeted treatment[2].

Lesion-targeted treatments

These are practicable in patients with a small number of clinically visible and isolated lesions. They are based on physical destruction of the visible lesions.

Cryotherapy: This is the first-choice treatment method when the lesions are few or isolated. It is a fast and cheap method. There is no standard protocol about the application time, frequency or cycle intervals of cryotherapy. The success of treatment depends on the experience of the applying person. The correct application method is to create an ice ball that freezes the epidermis. Afterwards, a bulla should occur indicating that the basal membrane is separated from the dermis. This method has been shown to be successful in 90% of thin lesions[2]. Applying it in two freeze-thaw cycles including an area of 1mm around the lesion is generally preferred. The rates of clearance with one or two applications have been reported to be between 68% and 75% at the end of a 3-mo period[24].

Oliveira *et al*[27] experimented the effect of cryotherapy on two lesions of similar character from 13 patients with multiple AKs. They applied a liquid nitrogen cryotherapy to one of the lesions in a single session for 10 s and 30 d later they compared the biopsies taken from the lesions that was and was not administered cryotherapy. They found distinct decreases in keratinocyte atypia, epithelial thickness, and lymphocyte infiltration in the corneum layer and dermis in the lesion which underwent cryotherapy. Thai *et al*[28] administered their cryotherapy in a way to exceed the lesion margin by 1 mm using different freeze times. A full response was obtained in 39% of those that were administered less than 5 s of cryotherapy, in 69% of those that had longer than 5 s and in 83% of those that had longer than 20 s. They reported that they had full response in 94% of the lesions and the cosmetic results were good to excellent.

The side effects are pain during application, development of bullas and scars, hypopigmentation and hyperpigmentation. Hypopigmentation is seen in 29% of the cleared lesions and hyperpigmentation in 6% of them[1,2].

Surgical excision, shave excision and curettage: Surgical methods are not the first-choice in AK treatment. They should be preferred in hyperkeratotic, treatment-resistant and invasive SCC suspected lesions[2]. Through curettage and shave excision, atypical cells are removed mechanically. Both of these two methods are usually completed with an electrodesiccation. In this way, both the remaining abnormal tissues are destroyed and bleeding is controlled. Their disadvantages include the necessity of local anesthesia and their applicability to

a few and only hyperkeratotic lesions. These methods are not useful in the treatment of subclinical lesions and broadly damaged areas. Their possible side effects are scars, wound site infections, dyspigmentation and anesthesia-related complications[29].

Laser treatments: Ablative ultrapulse Er:YAG and CO_2 lasers are indicated in isolated and a limited number of lesions. However, their effects have not been evidenced with double-blind randomized studies. Sherry *et al*[30] have reported that long-term efficacy continues in AK patients who were administered ablative CO_2 laser and the lesion-free period is 27.4 mo on the average. Their side effects include erythema, pain, irritation, itching, and secondary infection.

Non-ablative fractioned lasers (ER:YAG and CO_2) are able to improve skin quality, but they do not achieve a significant decrease in the number of AK lesions[24]. Although a decrease has been achieved in the number of facial AK lesions that had been treated using the fractioned photothermolysis method, it has been reported that the histological aspects of AK and/or SCC continue to exist in histopathological examinations[31]. Their disadvantages are higher cost than cryotherapy and the requirement for specially trained staff.

Field-targeted treatments

They are effective in the treatment of visible lesions, subclinical lesions and keratinocyte changes in the areas surrounding the visible lesions.

5-Fluorouracil cream: It is a pyrimidine analogue that was approved by the FDA in 1970. It impairs DNA formation by stopping conversion from deoxyuradilic acid to timidilic acid through inhibition of thymidilate synthetase. It disrupts cell proliferation, particularly in the fast reproducing cells of basal layer and AK, resulting in cell deaths. It is used in 5% cream form for 2-4 wk, applied once or twice daily[3]. The area of application should not exceed 500 cm^2 at a time. Erythema, burning, itching, pain, hyperpigmentation, wound site infection, bullas and ulceration may occur for about 4-6 wk after the treatment. Its photosensitivity effect limits its use in summer.

The long-term effects of 5% 5-fluorouracil (5-FU) cream applied for 4 wk, twice a day have been explored in a large-scale study published recently. The rates of being cleaned from AK of the patients who were checked every 6 mo in 2.6 years were found higher than the placebo group. Moreover, their spot treatment needs were found significantly less than the placebo group[32].

The 5-FU cream with a lower concentration of 0.5% is approved by FDA, but is not available in Europe. A 12-wk use applied once daily is recommended. The effect of 0.5% formulation has been found similar to that of 5% cream form, but the side effects were less and patient satisfaction was better[33]. The penetration of 5-FU, the biological active substance, is increased by combining low-dose 5-FU with salicylic acid (SA), taking advantage of the keratolitic effect of SA. The combined preparation is approved in Switzerland. Although the 0.5% FU and SA combination seems more effective with fewer side effects, there is a need for long-term studies[3].

The effectiveness of the combination of low-dose 5-FU with 10% SA has been compared to that of diclofenac gel and carrier base. The 5-FU and SA combination was found significantly more effective than diclofenac gel and carrier base with 72% histological cleaning and 55.4% complete cleaning. The application area reactions were seen more in the 5-FU and SA combination and the side effects were found mild and moderate[34]. In a prospective randomized study where it was compared to a two-session cryotherapy application, the 0.5% 5-FU and SA combination was found superior to cryotherapy[35]. In a meta-analysis, the 5% and 0.5% 5-FU formulations were rated superior to other field-targeted treatments[36].

Disadvantages of 5-FU cream include long treatment period, itching, prolonged erythema, pain, ulceration, erosion, secondary infection and depigmentation. It is teratogenic for impairing the DNA synthesis in fast dividing cells. It may have a systemic toxicity risk when used excessively and particularly when used for the areas with impaired barrier function[22].

Imiquimod: Imiquimod is an immune response regulator from the imidazoquinolone group. It is a Toll-like receptor agonist showing its effect on cytokine-producing cells such as monocytes, macrophages and dendritic cells[2,3,22]. It stimulates cytokine secretion by the TLR-7 induction, which improves cellular immunity. It is effective on both natural and acquired immune response, showing indirect antiviral and antineoplastic effect.

It was first approved by FDA in 2004 for the treatment of AK keratosis[37]. Imiquimod 5% cream and 3.75% cream forms are available. The 5% cream form is approved to be used on a hairless scalp and on areas up to 25 cm^2 in the face twice a week for 4 wk followed by a 4-wk resting period. The purpose of such alternating treatment is to reduce local skin reactions. The 3.75% cream form was approved in 2010 to be used every night in a 2-wk period followed by a 2-wk resting period. It can be applied to larger areas on the face and scalp and has a shorter treatment period compared to the 5% cream[2].

In both forms, subclinical lesions emerge together with inflammatory reactions at the beginning of the treatment, leading to an increase in the number of lesions. The rate of cleaning AKs is higher in people with severe local reactions. This supports the fact that inflammation is part of the action mechanism in AK[38]. Pruritus, burning, erythema, edema, pain, dryness, desquamation, erosion and ulceration may be seen locally. Systemic reactions such as myalgia, nausea and weakness are less frequent. Fewer reactions are seen during the second treatment cycle. It should be used carefully if there is an ongoing immunosuppressive

therapy in immunodeficient patients who had organ transplantation[24].

The effect of 3.75% imiquimod on the maximum number of lesions has been assessed in a placebo-controlled, double-blind study made with 319 patients and more than 90% decrease has been found in the number of lesions after 2 treatment cycles of 2 wk. The average and complete decrease in the number of lesions has been found significantly higher than placebo group[39].

Resiquimod: Resiquimod is an immune modulator structured as an imidazoquinoline amin whose phase 3 studies still continue in Switzerland. It is a TLR-7 and 8 agonist and stimulates cytokine secretion (IL-12 and TNF-α) more strongly than imiquimod. Its total cure rates have been found as 74.2% with 0.01% gel and 90.3% with 0.03% gel in patients who were given one more cycle of treatment after the phase 2 study using it 3 d a week, once a day for 4 wk followed by a no treatment period of 8 wk. Most frequently seen side effects are irritation at the application site[1,3].

Diclofenac: Diclofenac gel includes 3% diclofenac sodium in 2.5% hyaluronic acid carrier is a nonsteroidal anti-inflammatory drug which COX-2 inhibitor. UVB is known to induce COX-2 expression in human skin[22]. The production of prostaglandins from arachidonic acid plays a role in the skin cancer induced by UVB. The COX-2 inhibition with diclofenac probably shows its effect in AK treatment by impairing this cascade[2]. Diclofenac gel also plays a role in AK treatment by inducing apoptosis and inhibiting angiogenesis[1]. It is recommended to use it twice a day for 90 d. Side effects include itching, erythema and dryness. Diclofenac gel may rarely lead to photosensitivity in some patients. It is suggested to use it in combination with cryotherapy in hypertrophic lesions.

It was reported at the end of an analysis of 17 studies made with 3% diclofenac gel that there was 58% complete clearing of lesions a month after a 3-mo treatment, its efficacy continued at the end of one year and its effect was comparable to those of 5% imiquimod and 5% 5-FU. It has also been evidenced that it is safe in immunosuppressive patients, suitable to be used following cryotherapy and FDT, and more tolerable than the other treatment agents[40].

Ingenol mebutate (PEP005): Ingenol mebutate is a traditional treatment agent derived from the plant called euphorbia peplus. It was first approved by FDA in January 2012 for the treatment of AKs on the face, scalp, trunk and extremities in adult patients. It still has approvals in Europe, Australia and Canada[1,41]. It is an effective option in the topical treatment of AKs that are not hyperkeratotic. Ingenol mebutate shows its effect through two mechanisms: (1) Causing death of keratinocytes that underwent transformation; and (2) Causing death of remaining cancerous cells by increasing inflammatory reaction[41].

The mechanism of action primarily involves cell necrosis as a result of impaired structures of cell plasma membranes and mitochondria. This action takes place in 1-2 h after its application. In the following days, the remaining tumor cells are eliminated through neutrophile-antibody dependent cellular cytotoxicity[41].

It is recommended to apply its 0.015% gel formation on the face and scalp once a day for 3 consecutive days and its 0.05% gel formation on the trunk and extremities for 2 consecutive days. It can be washed away after keeping it at least 6 h on the application site[42]. Its major side effect is that the local skin reaction makes a peak on the 4th day at the application site, but then dies away after the 8th day. Its other side effects, pain, itching and irritation, are less frequent and milder[43].

The results obtained from the patient group that participated in the phase 3 study and received treatment with ingenol mebutate were assessed in terms of quality of life, patient satisfaction and clinical outcomes. Quality of life and treatment satisfaction were observed to improve significantly in the patients both in the face-scalp group and trunk-extremity group[44]. The advantages of ingenol mebutate therapy are that it is cheaper than other topical treatments, it is used for a short period of time and it does not cause photosensitivity[41,45].

The safety and tolerability of 5% 5-FU cream and 0.015% ingenol mebutate have been compared and the maximum local skin reactions have been found similar. Although the time of experiencing skin reactions has been found longer in the 5-FU group, both therapies have been found safe and tolerable in general[46]. Ingenol mebutate gel applied after cryotherapy increases the effect of cryotherapy alone. A classical dose has been applied to the patients who had at least 10 recurrent and hyperkeratotic lesions 2 wk after cryotherapy and cleaning at a rate between 50% and 100% has been reported[47].

Photodynamic therapy: Photodynamic therapy (PDT) is an effective treatment option for AKs, field cancerization and non-melanoma skin tumors. The most frequently used photosensitizing agents are 5-aminolevulinic acid (5-ALA) and its methyl ester methyl aminolevulinate (MAL), which are the precursors of protoporphyrin IX (Pp IX)[1,2,41]. Pp IX increases mostly in hyperproliferative cells. It absorbs light and causes formation of cytotoxic free oxygen radicals as a result of a photochemical reaction. These radicals lead to cellular necrosis and apoptosis[48]. Cleaning the sloughs and scales with curettage or keratolitic creams before the treatment increases the effect. The photosensitizing cream is applied with occlusion at least 3 h before the procedure. The incubation times, treatment protocols and light sources vary to a large extent. There are efforts to establish the optimal standards for treatment.

The treatment is administered once to thin AKs and AKs of medium thickness. If the effect is not satisfactory 3 mo later, the procedure is repeated once more. The

procedure is performed in 2 sessions with a 1-wk interval in hyperkeratotic AKs if severe atypia is present histopathologically, and in immunosuppressive patients. The most frequent side effects are local reactions in the application site and pain in the irradiation site. Rare side effects include nausea, weakness, paresthesia and headache. ALA-PDT is more effective in severe scalp lesions. MAL-PDT's disadvantage is that it is more expensive than ALA-PDT[48].

PDT produces better cosmetic outcomes than cryosurgery and enables treatment of broader areas with a single session procedure, but cryotherapy has been found superior to PDT in the face and scalp, and in thicker lesions. Local side effects are also milder in cryotherapy[1].

The effect of PDT applied in 3 sessions with monthly intervals was investigated in a study. The lesion biopsy values taken at baseline and at the end of the 3rd month were assessed and the rate of cleaning in AKs was found as 89.5%. The effect at the end of the 2nd treatment was found similar to that of the 3rd session. A significant decrease was found histologically in keratinocyte atypia and the extent of atypia, as well as significant improvements in collagen storage and healing of solar elastosis[49]. Recently, a new nanoformulation of 5-ALA (nano-ALA) PDT was compared with MALT PDT in a pilot study. Passos *et al*[50] found that the efficacy of nano-ALA is 10% higher than of MAL in treating skin field cancerization.

In a meta-analysis involving 25 studies on AK and field cancerization and including 5562 patients, all active treatment methods were found superior to placebo, and the most effective treatment method in terms of total cleaning obtained was found to be ALA-PDT (SUCRA score 90.8%), followed by 4-wk 5% imiquimod (71.7%) and 0.5% 5-FU cream (64.1%)[51].

Piroxicam: Piroxicam (PXM), is a nonsteroidal anti-inflammatory drug which is nonspecific COX-1 and COX-2 inhibitor. Campione *et al*[52] reported that local use of piroxicam was eligible, safe, effective, and well tolerated option for the treatment of AKs and field cancerization (PXM). It was used its 1% gel formation applied twice daily for 12 wk. But its use in AKs is still off-label.

COMBINATION TREATMENTS

Combination treatments are required in patients who have treatment-resistant, multiple lesions at different stages. Although there is no standard guideline on treatment combinations, lesion-targeted and field-targeted treatments may be combined to increase efficacy. Three point seven five percent imiquimod therapy following cryotherapy has been found useful and safe. The complete cleaning rates obtained from a 90-d diclofenac gel therapy following cryotherapy have been found twice as much compared to cryotherapy alone (64% *vs* 32%). Significant increases in the effect have also been achieved in post-cryotherapy 5-FU and post-cryotherapy ingenol mebutate therapies. It has also been shown that more success can be achieved with PDT applied after 5% imiquimod cream, 5% 5-FU or diclofenac gel therapies compared to the success achieved in each therapy alone[1,53].

AK TREATMENT IN ORGAN TRANSPLANT RECIPIENTS

Organ transplant recipients (OTR) are at high risk for NMSTs. Lesion-targeted treatments, cryotherapies, electrocautery, curettages and CO_2 lasers can be safely used in these patients. Diclofenac gel has been compared to placebo in 32 OTR patients in a 16-wk treatment. While the complete cleaning of AKs was 41% in the diclofenac group, it was found to be 0% in the placebo group. No patients were reported to develop invasive SCCs at the end of a 24-mo follow-up period[54].

Ingham *et al*[55] have been applied 5% 5-FU cream to AK lesions on eight renal transplant recipients face twice daily for 3 wk. They reported that 5-FU effective and safe treatment in renal transplant recipients. Imiquimod 5% cream has been found safe in heart, liver and kidney transplant patients if used 3 times a week not more than 2 sachets at a time on areas not exceeding 100 cm^2[56]. It was shown that PDT prevent new AKs formation in renal transplant recipients[57]. But PDT is less effective in immunosuppressed patients compared to the immunocompetent people in the AKs treatment[58].

PROTECTION

Childhood and adolescence are the really important periods for sun protection. The protection from the sun behavior acquired in these periods plays a key role in both prevention of excessive sun exposure and sunburns in childhood and acquisition of protection from the sun protection habit that will continue lifelong[1]. Sunscreens may be useful in high-risk groups. Ulrich *et al*[59] have investigated the effect of sunscreens on protection from NMST in OTR. They reported at the end of the 24-mo study that there was a decrease in the number of basal lesions in the group using sunscreens and they had fewer lesions than the control group. Therefore, protection from the sun is advisable for all patients with field cancerization. Patients should also be trained on the correct use of sunscreens.

It was shown that daily use of 30 mg acitretin for a period of 6 mo in renal transplant patients with multiple AKs resulted in a decrease in the number of AKs and it was effective in preventing the development of SCCs[60].

The chemopreventive effect of nonsteroidal anti-inflammatory drugs such as diclofenac gel on nonmelanoma skin cancers has been demonstrated[52].

FOLLOW-UP

If there are no special risk factors, patients are recommended to examine themselves every 3 mo. New

lesions are recorded, if any, and in the presence of suspicious lesions examination by a clinician is required[1]. Through professional examinations and follow-up, formation of new lesions and occurrence of any changes can be detected at an early stage, other cancers such as melanoma can be identified and patients can be educated and informed about their diseases.

The oral mucosa, palmar regions, scalp and genital regions should also be assessed during examinations and in the presence of an invasive ca risk lymphatic glands should also be examined. Self-examination by the patients themself is as important as clinical assessments and the patient should be trained for self-examination. Patients who have been subject to long-term immune suppression as in OTR require special monitoring for invasive NMSTs. Such patients should undergo annual dermatologic examinations and monthly self-examinations. OTR patients should be examined for NMSTs before the transplantation.

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