ACTINIC KERATOSIS (review of literature)

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Abstract

Actinic keratosis is an important medical and social problem, the correct diagnosis and treatment of which will help to avoid the development of invasive forms of cutaneous squamous cell carcinoma. With the further development of the early diagnosis of cancer, including skin cancer, the increase in human life expectancy, and the popularization of travel to exotic countries, the number of cases of actinic keratosis among the population will continue to grow. In this regard, it is important to discuss the causes and pathogenesis of the disease, the varied clinical picture of the disease, methods of non-invasive diagnostics, as well as methods of treatment, of which there are a great many in the treatment of actinic keratosis today. However, each of the methods has both advantages and disadvantages, and in the global trend towards a personalized approach to treatment, it is important to choose from the standpoint of evidence-based medicine the most suitable for each individual patient. Moreover, after treatment of actinic keratosis, relapses often occur, which are the result of insufficient diagnosis and the development of incorrect treatment tactics. The review article provides the clinical picture of actinic keratosis, diagnostic and therapeutic methods, and their comparison with each other in terms of efficacy and safety.

Key words: actinic keratosis, cutaneous squamous cell carcinoma in situ, photodynamic therapy.

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АКТИНИЧЕСКИЙ КЕРАТОЗ (обзор литературы)

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Резюме

Актинический кератоз (АК) рассматривается как предраковое состояние, ассоциированное с повышенным, в случаях отсутствия лечения до 20%, риском развития плоскоклеточного рака кожи. По мере дальнейшего развития технологий ранней диагностики онкологических заболеваний, в том числе и рака кожи, увеличения продолжительности жизни людей и популяризации путешествий в экзотические страны, число случаев АК среди населения будет возрастать. В этой связи информирование медицинского сообщества о причинах и патогенезе заболевания, разнообразии клинической картины АК, методах неинвазивной диагностики и лечения представляется важной медико-социальной задачей. Каждый из диагностических и терапевтических методов имеет свои преимущества и недостатки, поэтому, руководствуясь данными доказательной медицины, важно персонифицировать подходы к диагностике и лечению для каждого конкретного пациента. Более того, после лечения АК часто возникают рецидивы, которые являются следствием недостаточной диагностики и выработки неправильной тактики лечения. В обзорной статье приводятся клиническая картина АК, сравнительная характеристика диагностических и лечебных методов с позиций эффективности и безопасности применения у пациентов с АК.

Ключевые слова: актинический кератоз, плоскоклеточный рак кожи in situ, фотодинамическая терапия.

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Introduction

The global trend of increasing life expectancy and aging of the population, along with the improvement of early diagnosis of malignant neoplasms, contribute to the growth of cancer incidence. Technological progress, the development of air transport and the popularization of travel to exotic countries lead to the fact that more and more people with fair skin find themselves in geographic areas with excessive insolation. Long-term exposure to ultraviolet radiation is a major cause of melanoma and non-melanocytic skin cancers (NMSCs), such as squamous cell skin cancer (SCSC), basal cell skin cancer (BCSC), Merkel cell carcinoma, and other rarer skin cancers. Most malignant skin neoplasms develop against the background of diseases classified as "precancerous skin lesions". Actinic keratosis (AK), also known as solar keratosis or senile keratosis, is a premalignant skin lesion composed of proliferating atypical epidermal keratinocytes that can progress to invasive squamous cell carcinoma [1].

Etiology and pathogenesis

AK was described by Dubreuil in 1826 [2]. Freudenthal later proposed the term "senile keratoma", and in 1958 Pinkus renamed these lesions AK [3]. Some authors suggest considering them as in situ neoplasms, since they originate from clonal DNA modifications in keratinocytes [3]. A number of authors consider AK as a dermatosis with signs of malignancy from the moment of their occurrence. In terms of cytological changes, they are epidermal keratinocytes similar to those seen in SCSC, including loss of polarity, nuclear pleomorphism, maturation dysregulation, and increased mitosis; from the molecular point of view, they are identical mutations in the p53 protein [4]. According to the classification of skin neoplasms of the World Health Organization (WHO), AK is classified as skin precancer [5].

Excessive exposure to UV radiation is the main factor acting as a complete carcinogen, causing and promoting tumor growth [6]. UV radiation activates molecular signaling cascades that lead to changes in regulatory cytokine levels, immunosuppressive effects, abnormal cell differentiation, and apoptosis. UV radiation is divided into UV-A, UV-B and UV-C radiation. About 94-97% of the total UV radiation that reaches the Earth's surface consists of UV-A rays. UV-B rays are partially filtered by the ozone layer of the atmosphere and make up 3-6%, UV-C rays are almost completely absorbed by the atmosphere and only their minimum levels reach the Earth's surface.

UV-A radiation (wavelength 320-400 nm) penetrates deep into the skin and stimulates the production of reactive oxygen species that damage cell membranes, nuclei and protein molecules [6], promotes mutational substitutions of guanine (G) for thymine (T) in DNA [7]. As a result, signal transduction and cellular interaction pathways are affected, which contributes to abnormal cell proliferation [6].

UV-B radiation (290-320 nm) is absorbed by cellular DNA, causing errors in the repair of cyclobutane-pyrimidine dimers and the formation of pyrimidine photoproducts, as well as characteristic cytosine-thymine (C-T) DNA substitutions [6]. These effects lead to mutations in the p53 protein, which regulates the cell cycle and repairs damaged DNA, mutations in the telomerase gene, and increased production of pro-inflammatory cytokines [4, 6].

The mechanisms involved in the occurrence of AK include inflammation, oxidative stress, immunosuppression, impaired apoptosis, cell cycle deregulation and cell proliferation, and tissue remodeling [6]. The inflammatory process is mediated by the metabolic breakdown of arachidonic acid through the production of pro-inflammatory cytokines, mast cell activation, and macrophage migration inhibition factor. As a result of the activation of these mediators, lipid peroxidation, an increase in intralesional levels of T-lymphocytes and Langerhans cells, an increase in p53 and Bcl-2, and a decrease in Fas (cd95) and Fas-ligand, which are important initial factors in the process of apoptosis of UV-mutated cells, are turned on. An association between inflammation and the development of AK is seen in lesions progressing to SCSC. This is supported by the fact that anti-inflammatory therapies are effective in the treatment of AK [6]. Oxidative stress is also involved in the process of carcinogenesis as a result of excessive exposure to UV radiation, which leads to the production of reactive oxygen species and ends with lipid peroxidation and cell destruction with damage to genomic and mitochondrial DNA [6]. Altered cell signal transduction pathways result from membrane tyrosine kinase phosphorylation, changes in epidermal growth factor in Ras and RAF, and in the dissociation of nuclear factor B from inhibitory complex B [6]. These events lead to the production of cytokines, including interleukin-1 (IL-1), tumor necrosis factor and IL-6, as well as activation of the metabolic breakdown of arachidonic acid. The end result is signal transduction of transcription factors into cell nuclei with modifications in gene expression [4].

The difficulty in establishing unambiguous criteria for determining when an AK undergoes transformation into SCSC supports this hypothesis. According to Ackerman, there is no clear threshold between AK and initial SCSC, and AK is considered part of the evolutionary spectrum of SCSC, described as "embryonic" SCSC. Therefore, the proposed nomenclature to replace the term "actinic keratosis" would include keratinocytic intraepidermal neoplasia and intraepidermal solar keratotic SCSC [3]. AK is formed as a result of the proliferation of keratinocytes with varying degrees of dysplasia in the epidermis, moreover, they have the potential

for malignant transformation, especially in the case of SCSC, lesions occur predominantly in areas exposed to the sun [2].

The likelihood and rate of transition from AK to SCSC is individual, highly variable and unpredictable. A systematic review noted a high rate of progression of 0.53% per lesion per year in patients with a history of SCSC or other SCC. Solitary AK has been found to have a high regression rate of 15 to 53% per year, as well as a long-term recurrence rate of over 50%. In the review article, this trend was partly explained by the methodological shortcomings of published studies: the lack of data on the treatment and prevention of AK using sunscreens, and a high percentage of patients dropping out of the study. However, literature data and clinical experience do show that AK and light-induced skin damage are a dynamic rather than a static pathological process [8].

The cumulative dose of UV exposure is a major risk factor for the development of AK and SCSC. If a patient has six or more lesions of AK, SCSC, or an area of skin with "field cancerization" (the so-called field of cancerization or tumor field) with an area of \u200b\u200bat least 4 cm^2 that is exposed to UV radiation due to the patient's work activity, the presence of possible occupational disease.

Epidemiology

AK ranks third in frequency of dermatological consultations, second only to acne and dermatitis [9]. With the overall population aging, a gradual increase in the incidence of AK is expected. With regard to the prevalence of AK, according to WHO estimates, the highest levels are observed in representatives of the Caucasian race living near the equator [10]. The prevalence of AK increases with increasing age of patients: in Caucasians, from less than 10% at the age of 20-29 years to 80% in the group of people 60-69 years old [4].

In the Russian Federation, skin cancer ranks first or second in the overall (both sexes) structure of the incidence of malignant neoplasms after breast cancer. According to statistics, the incidence of non-melanoma skin cancer (NMSC) is steadily increasing: from 236.5 cases per 100,000 population in 2009 to 310.4 cases in 2019. In 2019, 73,150 patients were registered with a diagnosis of skin cancer (except melanoma) for the first time in their lives [11]. Given the increase in the incidence of skin cancer in the population, timely diagnosis, treatment and prevention of AK is an urgent problem.

Clinical and histological picture

AK appears as erythematous macules, papules, or plaques, usually with poorly defined borders, which may be covered with dry pells. Sometimes they are better identified by palpation than by visual inspection, they can represent hyperkeratosis of varying degrees [2, 12]. Lesions may be solitary or multiple, and the color may vary from pink to erythematous or brownish in the case of pigmented AK [13, 14]. The degree of infiltration also varies depending on the intensity and degree of dysplasia or associated inflammation. In most cases, AK occurs without additional symptoms, although some patients experience discomfort, burning, pain, bleeding, and itching [2, 12, 19]. AK predominantly occurs on areas of the skin that are chronically exposed to light, such as the face, bald scalp, neck, shoulders, forearms, and back of the hands [4]. In both sexes, lesions most often occur on the upper extremities, as well as on the face and scalp. These areas, especially the head, neck, and forearms, are responsible for 75% of reported lesions. AK can manifest itself in various forms and existing clinical variants, such as hyperkeratotic AK, atrophic, pigmental lichenoid actinic keratosis, cutaneous horn and actinic cheilitis [14].

The gold standard of the AK assessment system in clinical practice has not yet been defined. It is important to emphasize that the degree of agreement between clinical and histological gradation is low, which confirms the need to treat all AK foci, regardless of their severity [15]. In a number of literary sources, based on histological examination, AK is divided into seven subtypes: hypertrophic, atrophic, bowenoid, acantholytic, epidermolytic, lichenoid, and pigmental [2, 4, 16]. All histological subtypes can be seen in a single lesion [4].

Diagnosis

AK in most cases is diagnosed clinically. Lesions that are identified during the physical examination and confirmed by the history can be recognized and do not require additional examination. Dermoscopy has been shown to be extremely important in increasing the level of certainty and accuracy in questionable lesions. Other non-invasive imaging modalities such as confocal microscopy (CM) may also be useful in certain situations where available. In questionable cases, histological examination is required to confirm the diagnosis.

Treatment

Given that AK is potentially associated with malignancy and it is impossible to predict which lesions will transform and which will regress, all lesions should be treated [2, 17]. When managing patients with AK, it is necessary to regularly examine the skin of the whole body with an assessment of the presence of tumor fields and the therapeutic effect on them, the use of ablative treatment methods for hyperkeratotic lesions, informing patients about the chronic course of the disease, the need for photoprotection and periodic repetition of treatment procedures, and regular self-examination of the skin by the patient [18]. The

impact on AK foci includes several methods. Basically, they can be divided into ablative or surgical methods and topical therapy by non-surgical methods (see Table) [19].

The use of these methods in combination or sequentially in the management of such patients is a common practice [20]. It is noteworthy that from 25 to 75% of treated patients need re-treatment within 12 months due to the appearance of new lesions, which indicates a chronic course of AK, even if the tumor fields were treated [21]. Most often, relapses are observed in patients who have undergone only cryotherapy, less often in those who have received treatment with an effect on tumor fields [22]. A large systematic review analyzing various treatments for AK concluded that 5-fluorouracil (5-FU), diclofenac, imiquimod, and ingenol mebutate (IM) may have similar efficacy [23].

The choice of treatment varies depending on the clinical picture, the location of AK foci, their number and severity of the lesion; therefore, treatment should be selected individually in accordance with the individualities of each patient. Techniques aimed at the lesion focus, as a rule, can be applied quickly, do not require long-term rehabilitation, but they are effective only with lesions limited in area. The application of methods aimed at the tumor field requires long-term treatment from several days to months and, therefore, requires high discipline and commitment from the patient.

Таблица
Абляционно-хирургические и нехирургические методы лечения актинического кератоза
Table
Ablative-surgical and non-surgical treatments for AK

Варианты хирургического лечения Surgical treatment options	Местные и пероральные методы лечения Topical and oral treatments
Криохирургия (уровень убедительности рекомендаций А, уровень достоверности доказательств 1 ++) [20] Cryosurgery (recommendation strength level A, level of evidence 1++) [20]	5-Фторурацил (уровень убедительности рекомендаций А, уровень достоверности доказательств 1 ++) [20] 5-Fluorouracil (recommendation grade A, evidence level 1++) [20]
CO_2-лазер (уровень убедительности рекомендаций В, уровень достоверности доказательств 1+) [20] CO_2 laser (recommendation grade B, evidence level 1+) [20]	Имиквимод (уровень убедительности рекомендаций А, уровень достоверности доказательств 1 ++) [20] Imiquimod (recommendation level A, level of evidence 1++) [20]
Кюретаж и электрокоагуляция (уровень убедительности рекомендаций D, уровень достоверности доказательств 4) Curettage and electrodesication (grade of recommendation D, level of evidence 4)	Мебутат ингенола (уровень убедительности рекомендаций А, уровень достоверности доказательств 1+) [20] Ingenol mebutate (recommendation level A, evidence level 1+) [20]
Хирургическое лечение (уровень убедительности рекомендаций D, уровень достоверности доказательств 4) Surgical exeresis (grade of recommendation D, level of evidence 4)	Фотодинамическая терапия (уровень убедительности рекомендаций А, уровень достоверности доказательств 1+) [20] Photodynamic therapy (recommendation grade A, evidence level 1+) [20]
	Диклофенак (уровень убедительности рекомендаций А, уровень достоверности доказательств 1+) [20] Diclofenac (recommendation level A, evidence level 1+) [20]
	Ретиноиды для местного применения (уровень убедительности рекомендаций В, уровень достоверности доказательств 1+) [20] Topical retinoids (recommendation level B, evidence level 1+) [20]
	Системная терапия (уровень убедительности рекомендаций С, уровень достоверности доказательств 2+) [20] Systemic therapy (recommendation grade C, level of evidence 2+) [20]

Increasingly, combinations of several methods are being considered, for example, after treating a local focus, the treatment of the tumor field is resorted to. Before PDT, laser ablation can be performed to remove foci of volumetric hyperkeratotic lesions, thereby making the skin surface more permeable for applying the cream. Other studies have shown that the combination of imiquimod and PDT results in significantly higher healing rates than imiquimod monotherapy [24, 25].

Operative therapy

Curettage

The use of curettage under local anesthesia can be performed alone or in combination with electrocoagulation, which appears to increase devitalization of potentially remaining dysplastic cells, and to achieve hemostasis. An alternative to electrocoagulation is cryotherapy [19]. As monotherapy, curettage is especially indicated in patients with solitary lesions, especially those with hyperkeratotic AK. The lack of randomized clinical trials to evaluate the effectiveness of the method leads to a low degree of recommendation of the procedure for the treatment of AK [26].

Cryotherapy

Cryotherapy is a destructive method used for the isolated treatment of AK, which uses liquid nitrogen to achieve the processes of freezing and thawing of tissues leading to their destruction [26]. Cryotherapy is indicated for the treatment of patients with single or small lesions without tumor fields. Despite widespread use in dermatological practice, persistent complete remission after cryotherapy in patients with isolated lesions at 12 months of follow-up is lower (28%) than in patients treated with 5-FU (54%) and imiquimod (73%). This is precisely because some patients have preclinical changes in the immediate vicinity of the treated lesions [22]. The advantages of this treatment method are low cost, easy accessibility and satisfactory patient compliance. The disadvantages include the fact that the method does not allow to treat tumor fields, causes discomfort during application and has a long rehabilitation time. Cryotherapy has received a sufficient level of persuasiveness of recommendations for the treatment of localized lesions in patients without immunosuppression, while at the same time in patients with immunosuppression, the effect is limited [26].

CO_2 laser

Lasers cause coagulative necrosis, ablation and hyperthermia, which leads to the destruction of the lesion. One session of non-fractional CO_2 laser can be used to remove superficial lesions of the epidermis, including AK. A non-fractional CO_2 laser with a wavelength of 10,600 nm is absorbed by water, resulting in non-specific tissue destruction. Thus, a non-fractional CO_2 laser can be used to destroy localized lesions. The results of the full therapeutic effect in the first months are similar to those obtained with cryotherapy (72.8% in the laser group versus 78% in the cryotherapy group). However, on long-term follow-up, lesions treated with CO_2 laser have a lower objective response rate: no recurrence was found in 37% of patients treated with laser compared to 66.8% of patients treated with cryotherapy [27]. Due to the increased risk of infection in immunosuppressed patients, CO_2 laser is not recommended for the treatment of tumor fields and should only be used for localized lesions [26]. Although the use of CO_2 laser can be considered as a treatment option for AK, the degree of recommendation for its use in patients with a normal immune response is not conclusive [28].

Non-surgical treatment

5-fluorouracil

5-Fluorouracil (5-FU) is used in AK at concentrations ranging from 0.5% to 5%. 5-FU prevents DNA synthesis due to irreversible inactivation of thymidylate synthase; the end result is apoptosis of highly proliferating cells such as keratinocytes in AK lesions [29].

Imichimod

Imichimod is a synthetic compound from the imidazoquinoline family that acts as an immunomodulator. The drug acts as an instrumental receptor in the expression of mRNA of immunomodulatory genes that induce the production of cytokines; as a result, the innate and acquired immune response with increased antitumor and antiviral activity is stimulated [30].

The strength of recommendation for the treatment of tumor fields with imichimod 3.75% is high, while for imichimod 5% the strength of recommendation is low; this difference is due to the methodological quality of the studies [26].

Ingenol mebutate

Ingenol mebutate (IM) is derived from the plant Euphorbia peplus. Recommended for the treatment of AK of the scalp and face at a concentration of 0.015% for three consecutive days (one vial per day); for use outside the face at a concentration of 0.05% for two consecutive days. IM has two mechanisms of action mediated by neutrophils - cytotoxic and immunomodulatory [31].

Diclofenac

The use of 3% diclofenac gel in combination with 2.5% hyaluronic acid, used to optimize the penetration of diclofenac into the epidermis, is recommended for the treatment of AK twice a day for a minimum period of 60–90 days [32]. The therapy action mechanism is the inhibition of cyclooxygenase-2 (COX-2), which leads to a decrease in prostaglandin synthesis and inhibition of cell differentiation and angiogenesis, induction of apoptosis and changes in cell proliferative activity [32]. Diclofenac also activates hormone receptors in the cell nucleus involved in cell differentiation and apoptosis [32].

Photodynamic therapy

The PDT technique consists of using a photosensitizing agent (PS) and a light source of a certain wavelength to generate reactive oxygen species, which then destroy dysplastic cells through a photochemical reaction [33]. This reaction is achieved by the use of 5-ALA or MAL, which are precursors to the photoactive metabolites of PPIX. These metabolites accumulate in neoplastic cells and, when activated by visible light, lead to the formation of singlet oxygen [33]. They initiate a biochemical cascade of events that cause death of the target cell as a result of apoptosis or necrosis and immunomodulatory action [34]. The photochemical reaction for each PS occurs after irradiation with a light source of a certain wavelength in the visible light spectrum [35]. The spectrum has four porphyrin absorption peaks, the largest of which is in the blue light spectrum at 410 nm, with smaller peaks at 540 nm, 580 nm, and 635 nm [36]. Red light (625–740 nm) penetrates deeper than blue light and is therefore preferred in the treatment of larger lesions. The blue light spectrum (440–485 nm) due to absorption by hemoglobin reaches a depth of 1–2 mm and is commonly used to treat superficial lesions [36]. Light emitting diode (LED) devices are the most commonly used light sources for PDT and are considered the gold standard [37]. Superficial curettage of lesions is recommended prior to application of PS to the treated area [36]. In addition, techniques that increase the depth of PS penetration can be used: microneedling, ablative fractional laser, the use of calcipotriol [36, 38]. According to the Cochrane review of AK treatment, PDT with 5-ALA or MAL using both red and blue LED light has similar efficacy [22].

PDT with 5-ALA was approved by the FDA for AK therapy back in 1999 [39]. Since then, it has been widely used for the treatment of AK foci and tumor fields with the same efficacy demonstrated in controlled clinical trials [40, 41]. In 2016, a clinical consensus guideline stated that PDT for AK is highly effective for head and neck lesions and is similar or superior to other FDA-approved therapies. The cosmetic results of PDT are superior to those of cryotherapy [42]. New recommendations for the treatment of AK from the American Academy of Dermatology (AAD) were released in 2021 [43]. The International League of Dermatological Societies, in collaboration with the European Dermatology Forum, recommend PDT for patients with tumor fields [44]. The British Association of Dermatologists guidelines for the treatment of patients with AK state that PDT is an effective treatment for confluent AK lesions in the absence of invasive disease. Otherwise, confluent AK lesions in areas such as the scalp are difficult to treat or not treatable at all. The British Association of Dermatologists also notes that PDT has a low potential for scarring and reduces the risk of poor healing compared to other therapies in certain areas, such as the lower leg [45]. The British Association of Dermatologists has provided guidance on the use of PDT for the treatment of AK, focusing on drugs and light sources, and recommends this treatment (level A recommendation, quality of evidence 1) [46].

In the conventional MAL PDT protocol, a thin layer of product 1 mm thick should be applied to the treated area, which is closed for 3 hours, then the area should be cleaned and irradiated with the selected light source. The main randomized controlled trials evaluating the complete response rate 3 months after PDT with ALA showed that 69-91% of treated patients achieved complete resolution of the lesions. In a meta-analysis that included 641 participants with 2,174 cryo-treated AK lesions and 2,170 PDT-treated AK lesions, participants achieved 14% more complete responses in the PDT group. Complete remission with PDT with MAL after 3 months was achieved in 90% of cases [47], excellent cosmetic results were noted in 91-98% of treated patients [48].

The results of controlled clinical trials also confirm the effectiveness of PDT as the main therapy for patients with AK [49]. An analysis of comparative clinical studies has also shown that PDT is no less effective than other approaches to tumor field therapy, including imiquimod [50], chemical skin peels [51], diclofenac [32] and 5-FU [52]. A clinical study in Europe evaluated the efficacy of 5-FU (4–8 weeks), imiquimod (4–8 weeks), ingenol mebutate (3–6 days), and MAL-PDT (1–2 sessions). It was found that 12 months after completion of treatment, the probability of avoiding therapy failure (clearance > 75%) was significantly higher in patients treated with 5-FU compared with other compared methods [53]. PDT has also demonstrated rejuvenating effects in actinic degeneration and other signs of aging from sun damage [54].

PDT has a high level of persuasiveness of recommendations for the treatment of AKs and tumor fields [44], so the method is most suitable for patients with multiple AKs. Generally, the benefits of PDT include few long-term side effects, reproducible outpatient efficacy, non-invasiveness of the procedure, patient compliance, and the ability to address subclinical lesions. Potential risks include increased skin sensitivity to light for 24 to 48 hours after treatment and possible side effects at the PDT site for about two weeks, including short-term skin swelling, sloughing, scabs, blisters, itching, burning, and (rarely) skin infections. [55]. About 20% of patients complain of severe pain (pain grade over 6 on a scale of 0 to 10) during LED irradiation and remain with intense erythema and scaling for up to 21 days [56]. Physicians should consider possible contraindications to PDT before prescribing treatment, including hypersensitivity to porphyrins or

any component of the 5-ALA gel (often 10%), porphyria, or photodermatoses. Before starting PDT, a physical examination should be performed to assess the presence of skin cancer in the proposed treatment area. In addition to grade I–III AK, PDT can treat patients with morphologically confirmed in situ SCSC or superficial BCSC. Lesions suspected of melanoma, invasive SCSC, or BCSC should be biopsied and treated with other methods. The presence or absence of a history of herpes simplex should be confirmed, and patients with a positive history should be given valaciclovir or famciclovir prior to PDT. The use of PDT is also limited in pigmented lesions, which reduce the efficiency of the photochemical reaction, since the melanin pigment competes with PPIX in absorbing light, reducing the desired photodynamic effect [57].

In recent years, daylight PDT has been described as having the same response rate as classical PDT, but with fewer radiation-related side effects [58]. The PDT method using daylight consists in applying MAL cream to the focus, then, after 30 min, placing the patient in daylight for about 2 hours in order to activate MAL with visible light in the wavelength range from 380 to 740 nm [59]. Daylight PDT is mainly recommended for the treatment of non-pigmented AKs [60]. Studies comparing conventional PDT and daylight PDT have demonstrated the same efficacy and safety of both AK treatments on the face and scalp [61]. Both 5-ALA PDT and MAL PDT are highly recommended for the treatment of multiple lesions and tumor fields.

PDT was effectively combined with other topical drugs in the treatment of tumor fields [62, 63]. A meta-analysis including the results of 10 randomized controlled trials in which PDT was combined with imiquimod, 5-FU, ingenol mebutate, tazarotene, or calcipotriol showed that the use of a combination of methods improved overall response rates compared with the separate use of PDT or topical agents [24].

PDT has also been used to prevent AK and NMSC in organ transplant recipients. In a small pilot study, 12 high-risk patients received cyclic 5-ALA-PDT at intervals of 4 to 8 weeks for two years. The median reduction in the incidence of SCSC after 12 and 24 months was 79% and 95%, respectively [64]. Repeated use of PDT was a primary method of skin dysplasia prevention in kidney transplant recipients. In a randomized trial involving 25 patients with clinically normal skin who received MAL-PDT at 6-month intervals for five years, a 63% reduction in the formation of new AKs in previously treated skin areas was observed [65]. Sequential daylight PDT has been shown to be effective in preventing the appearance of new AK and NMSC lesions in organ transplant patients. The treatment of tumor fields was also accompanied by a significantly lower appearance of new lesions in dynamics, higher adherence of patients to treatment compared with the control group, which used cryotherapy [66]. A systematic review published in 2020 and a meta-analysis of 12 studies involving organ transplant patients favored the use of PDT as an effective preventive measure for the development of AK and SCSC [67].

Conclusion

One of the problems of AK treatment is a high percentage of relapses in tumor fields. Therefore, treatment should cover not only AK foci, but also visually unchanged tissues, which limits the use of surgical techniques due to the volume of intervention and the severity of the surgical injury, which affect the cosmetic results of treatment and the duration of rehabilitation.

If the patient has tumor fields, it is necessary to consider the possibilities of other methods of therapy, that allow, with satisfactory tolerability, to carry out treatment on a wide area of AK lesion. However, as systematic reviews have shown, the better the tolerability of a particular non-surgical method, the lower its effectiveness [68, 69].

If it is necessary to treat large tumor fields, PDT can become an ideal method of treatment, during which it is possible to achieve both high therapeutic efficacy - up to 90% complete regressions, and good cosmetic results in 91-98% of patients [57, 66].

The main side effect of PDT is pain during treatment, which is described as a burning and tingling sensation localized to the area of treatment. Currently, research is being carried out aimed at modifying PDT techniques to achieve better treatment tolerance without reducing its effectiveness. The European-approved PDT technology with daylight activation is as effective as the classical version, but is better tolerated and almost painless [61]. Unfortunately, daylight-activated PDT is weather dependent and cannot be performed in rainy, windy, or cold weather [70]. Moreover, due to the varying intensity of daylight depending on weather conditions and location, it is not possible to control the light dose. New PDT protocols, including the Flexitheralight protocol [71], can significantly reduce the level of pain when using PDT technology with daylight activation without loss of efficiency, expand the conditions for its use: regardless of the season and weather conditions, with a known dose of light, corresponding in this respect to the classical PDT protocol [33].

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