MODERN ASPECTS OF PHOTODYNAMIC THERAPY OF ACTINIC KERATOSES

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Abstract

Currently, photodynamic therapy (PDT) remains the most effective treatment for actinic keratosis (AK). With the increase in the incidence of AK, mainly due to the popularization of recreation in countries with increased insolation, there is an increasing interest in developing new methods of diagnostics and treatment and improving the existing ones. Studies that are aimed at determining the final efficacy of PDT, taking into account the resulting adverse reactions and long-term cosmetic results, are becoming increasingly popular. The nature of the light needed to excite a photosensitizer (PS) opens up new possibilities in the field of experimental studies that are aimed at reducing adverse reactions with similar efficacy of the applied therapy.

In the review article, we presented the results of our own and foreign studies on the diagnosis and treatment of AK for 2017–2019, namely: we determined the possibilities of using sources with natural and short-wave radiation at different depths of skin lesions; presented a classification of the growth of AK in the basal layer of the epidermis, which increases the possibility of predicting the outcomes of the disease; showed the prevailing efficiency of fluorescent diagnostics compared with traditional diagnostic methods; evaluated the advantages of PDT using natural light and artificial sources of radiation; described the possibility of using a combination of drugs to increase the effectiveness of PDT in difficult to treat areas and in AK foci with a high degree of damage to the basal layer of the epidermis.

Key words: actinic keratosis, keratinocytic intraepidermal neoplasia, squamous cell carcinoma in situ, photodynamic therapy, fluorescence diagnostics, photosensitizer, natural light, fotoditazin, aminolevulinic acid, cryosurgery.

For citations: Reshetov I.V., Fatyanova A.C., Babaeva Yu.V., Gafarov M.M., Ogdanskaya K.V., Suhova T.E., Korenev S.V., Denisenko M.V., Romanko Yu.S. Modern aspects of photodynamic therapy of actinic keratoses, *Biomedical photonics*, 2019, vol. 8, no. 2, pp. 25–30. (in Russian) doi: 10.24931/2413–9432–2019–8–2–25–30

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СОВРЕМЕННЫЕ АСПЕКТЫ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ АКТИНИЧЕСКОГО КЕРАТОЗА

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Резюме

В настоящее время фотодинамическая терапия (ФДТ) является одним из наиболее эффективных методов лечения актинического кератоза (АК). По мере роста показателей заболеваемости АК, главным образом, из-за популяризации отдыха в странах с повышенной инсоляцией, возрастает интерес к разработке новых и усовершенствованию существующих методов диагностики и лечения. Всё более востребованными становятся исследования, которые направлены на определение конечной эффективности ФДТ с учётом возникших побочных реакций и отдалённых косметических результатов. Природа света, необходимого для возбуждения фотосенсибилизатора (ФС), открывает новые возможности в области экспериментальных исследований, которые направлены на

снижение частоты и степени выраженности побочных реакций при аналогичной эффективности применяемой терапии.
В обзорной статье приводятся результаты собственных и зарубежных исследований по диагностике и лечению АК за 2017–2019 гг.: определены возможности применения источников с естественным и коротковолновым излучением при различной глубине поражения кожи; представлена классификация роста очагов АК в базальном слое эпидермиса, увеличивающая возможность прогнозирования исходов заболевания; показана превалирующая значимость флуоресцентной диагностики (ФД) по сравнению с традиционными методами обследования; оценены преимущества применения ФДТ с использованием естественного света и искусственных источников облучения; описана возможность использования комбинации препаратов для повышения эффективности ФДТ на участках, плохо поддающихсялечению, и в очагах АК при высокой степени поражения базального слоя эпидермиса.

Ключевые слова: актинический кератоз, интраэпидермальная неоплазия кератиноцитов, плоскоклеточный рак кожи *in situ*, фотодинамическая терапия, флуоресцентная диагностика, фотосенсибилизатор, естественный свет, фотодитазин, аминолевулиновая кислота, криохирургия.

Для цитирования: Решетов И.В., Фатьянова А.С., Бабаева Ю.В., Гафаров М.М., Огданская К.В., Сухова Т.Е., Коренев С.В., Денисенко М.В., Романко Ю.С. Современные аспекты фотодинамической терапии актинического кератоза // Biomedical photonics. – 2019. – Т. 8, № 2. – С. 25–30. doi: 10.24931/2413–9432–2019–8–2–25–30

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Actinic keratosis (AK) is a precancerous disease of skin epidermal layer that arises from chronic exposure to ultraviolet radiation. The prevalence of AK is up to 8%, on average, in people over 40 years and tends to increase with age. It is known that in people with Fitzpatrick skin type I and type II, the risk of AK developing increases up to 40% [1-3]. Actinic keratosis is accompanied by atypical keratinocyte proliferation in the epidermis basal layer [4].

The relevance of the selected problem is determined by the risk of AK foci malignancy in squamous cell skin cancer. It is advisable to add the popularization of recreation in countries with high insolation, as well as such global problems of the modern population as obesity and alcohol consumption [5, 6] to existing AK risk factors. It is worth noting that in some cases, keratinocyte intraepidermal neoplasia is prone to spontaneous regression.

Obviously, a correctly chosen method of therapy and an assessment of the disease prognosis are the key to successful outcome of treatment. According to the researchers from the Ruhr University in Germany, the generally accepted histological classification (KINI – KINIII) does not determine the risks of malignancy of AK, so they worked to determine the depth of skin lesion that arises from keratinocyte intraepidermal neoplasia. According to the results of the completed study, it was proposed to identify the following types of AK foci growth:

– PRO I (crowding), characterized by the crowding of atypical keratinocytes in the epidermis basal layer;

– PRO II (budding) – budding of atypical keratinocytes in the upper papillary layer;

– PRO III (papillary sprouting) – atypical papillary keratinocytes sprouting in the upper dermis [8–9].

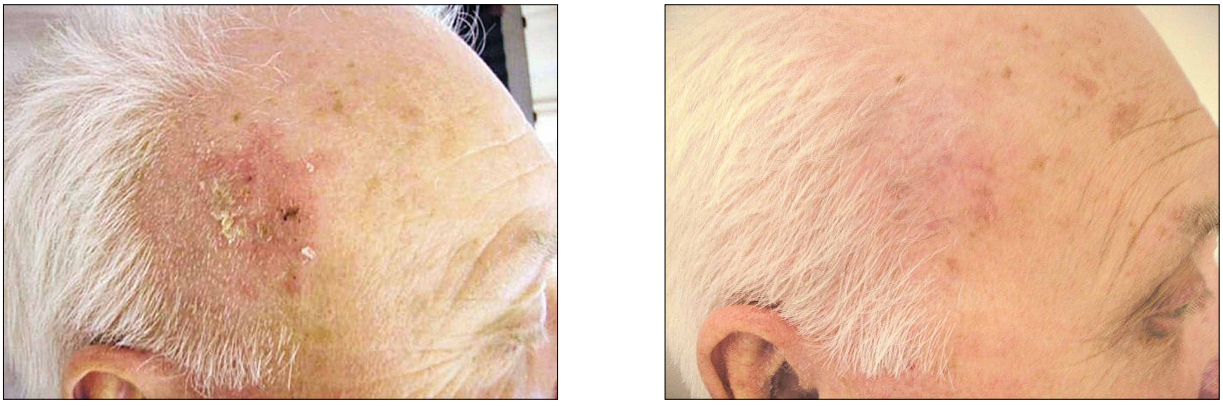
In the work of L. Schmitz and colleagues, it was proved that the risk of SCRC (squamous cell skin cancer) development depends on the AK foci growth pattern in epithelium basal layer [10]. The malignant potential of squamous carcinoma in situ involves early diagnosis and treatment to reduce disability and mortality. There are cases when it is difficult to carry out clinical and dermatoscopic assessment of skin lesions. The article describes 2 clinical cases of SCRC, uncertainly estimated as AK. The lack of the results of the therapy determined the conducting of supportive study of the areas by fluorescent diagnostics (FD) method, and the correct interpretation led to the accurate diagnosis verification. The findings of FD coincided with the results of a control histological study. The authors recommend using a non-invasive technique of confocal microscopy in the diagnosis of doubtful areas, as well as in the case of progression of neoplasia or in the absence of the response to the therapy [10].

G. Pellacani and co-authors from the University of Modena and Reggio Emilia arrived at similar conclusions after analyzing the results of AK treatment using confocal fluorescence microscopy after 5-fluorouracil injection. According to the researchers opinion, FD is a noninvasive alternative to the histological standard [12].

The objective of the authors' research, carried out in 2018, was to study the safety and response to local application of fotoditazin in AK photodynamic therapy (PDT). The study involved 80 patients with AK, represented by two experimental groups: treatment and control. The first group consisted of 40 patients with 151 AK foci (average age is 72 years). Figure 1 presents treatment response by the method of application of fotoditazin when exposed to PDT in given group of patients with AK.

The control group included 40 patients (average age is 65 years) with 64 AK foci treated with liquid nitrogen cryolysis, the results are shown in Fig. 2.

During PDT, the laser apparatus "LAMI" (OOO Novyye Khirurgicheskiye Tekhnologii, Russia) was used. 0.5% fotoditazin gel (VETA-GRAND, Russia) was used as a PS, having an absorption peak at 662 nm. Patients



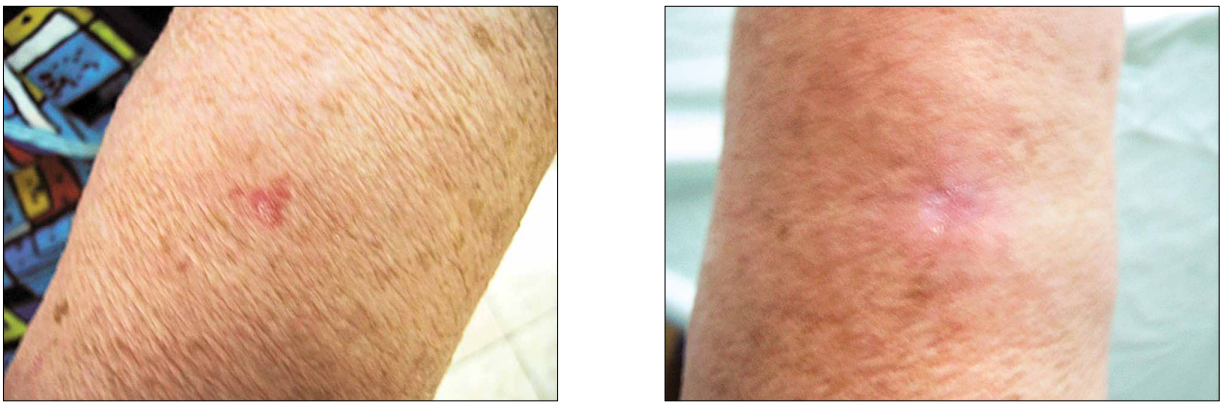
а б

Рис. 1. Очаг актинического кератоза:
а – до лечения;
б – через 3 мес после ФДТ
Fig. 1. Case of actynic keratoses:
а – before treatment;
б – 3 months after PDT

from treatment group received one PDT session after two-hour application of fotoditazin gel with the following irradiation parameters: light dose – 200 J/cm^2, power density – 0.14–0.48 W/cm^2. Patients from control group underwent AK foci cryolysis with liquid nitrogen using cryoprobe.

Two-year relapse-free survival in treatment group was 92.5%, and 85% in control group. Assessment of cosmetic results and adverse reactions of therapy was carried out after 24 months by the presence and severity of such reactions as: hyperemia, exudation, scarring, atrophy and indurations. For this, a visual analogue scale (VAS) was used, in which the value of 0 mm was rated as "very bad" and 100 mm – "very good". Cosmetic results were significantly higher after PDT ($p<0.05$) (Fig. 3), and the frequency and severity of adverse reactions from treatment were not statistically different.

In modern medicine, the qualitative and quantitative characteristics of factors aimed at reducing adverse reactions and improving the cosmetic results of therapeutic correction are of strategic importance. To this end, PDT AK studies are conducted abroad using various light sources. In most foreign studies, aminolevulinic acid (ALA) is used as a PS.



а б

Рис. 2. Очаг актинического кератоза:
а – до лечения;
б – через 3 мес после криодеструкции
Fig. 2. Case of actynic keratoses:
а – before treatment;
б – 3 months after cryosurgery

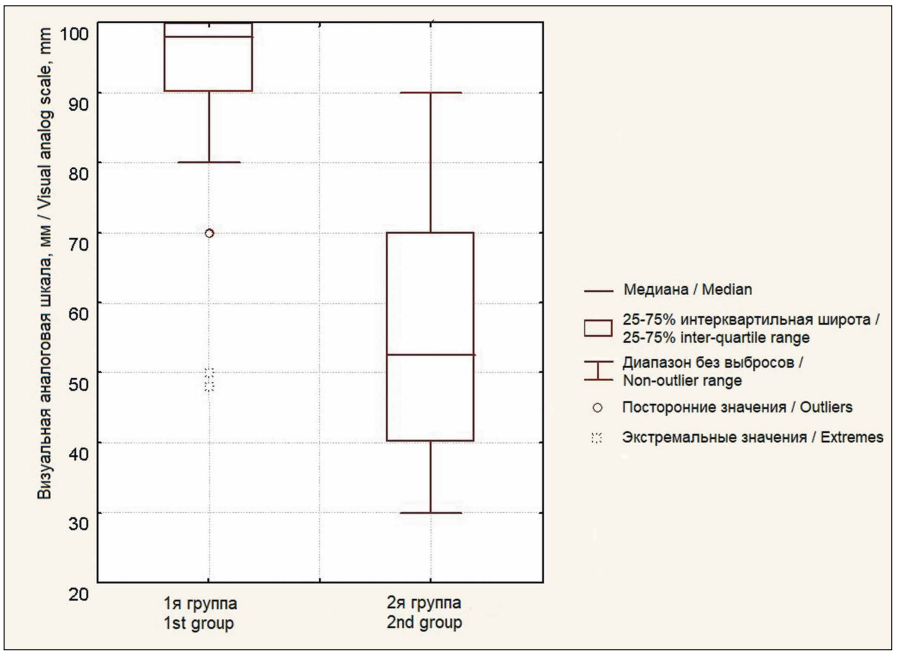


Рис. 3. Оценка косметических результатов в основной и контрольных группах через 24 мес после лечения
Fig. 3. Evaluation of cosmetic results in the main and control groups 24 months after the treatment

E. Kohl and colleagues carried out a research at the university hospital of Regensburg in Germany, which studied the response to cryolysis and PDT with 5-ALA when irradiated with natural light in the treatment of AK foci. Researchers believe that PDT with 5-ALA has a number of advantages over cryolysis, and the results of their work can be used in the treatment and prevention of AK [13].

A study on PDT with 5-ALA AK was published at Wroclaw Medical University, where PS excitation was performed with light of different wavelengths. The results of the study were evaluated after 9 months, the response to PDT with 5-ALA using red and green light was 92% and 87%, respectively. According to the authors, PDT with green light has the same response as AK foci irradiation with red light, but has lower frequency and pain severity [14].

The research work by P. Gholam and colleagues (Germany) presented the use of red and blue light sources. The authors determined response, tolerability, frequency of adverse reactions and cosmetic results of treatment with the most preferred sources of irradiation. PDT with 5-ALA AK was successful in 84% and 85% of cases, the intensity of pain assessed by VAS was 6.1 and 5.4 mm, respectively. According to the author's group, both sources of radiation demonstrate good results and can be used in PDT with 5-ALA AK [14].

Recently, more and more foreign researchers prefer the use of natural light in PDT with 5-ALA AK. For example, at the Aristotle University (Greece), therapeutic AK correction was performed by means of PDT with 5-ALA using natural and artificial irradiation sources. The results evaluated after 12 months after the treatment indicated no significant difference in response to the therapy (72% and 74%, respectively). At the same time, the researchers note that in the course of the treatment, patients prefer irradiation with natural light, due to the smaller number of adverse reactions recorded [16].

At the same time, a work to treat actinic cheilitis with natural light in PDT with 5-ALA was carried out in Rabin Medical Center (Israel). The study completed by scientists was highly valid, and the therapy was successful in 91% of cases [17].

The results of G.N. Galimberti work show high efficiency of PDT with 5-ALA with natural light in the medicinal use of 5-ALA and 5-fluorouracil gels. PS was used in concentrations of 16% and 5%. After 3 months, a regression of 9 affected foci occurred, which amounted up to 80% and 93%, respectively [18].

In the above works, the foci of keratinocyte intraepidermal neoplasia were located in the following areas: face, neck and shoulders. It is known that the treatment of affected areas of such localization has a good therapeutic prognosis, while AK foci located on notal side of the hands are difficult to treat. Scientists from the University of Copenhagen (Denmark) conducted a number of studies in which they used a combination of 5-ALA and 5-fluorouracil medications for the treatment of AK

foci located on hands. The results of exposure to only one 5-ALA showed significant response in 52% of cases, and the use of a combination of two drugs increased the response to the therapy to 63%. At the same time, the intensity of pain and the frequency of occurrence of skin erythema in different groups did not significantly differ [19].

Thus, in the face of increasing time spent by the population in the baking sun, combined with the risk factors for obesity and alcohol consumption, the problem of AK epidemiology is becoming more urgent. Currently, PDT is a global therapeutic vector in the choice of an innovative AK treatment method. To improve the qualitative and quantitative characteristics of the response to the therapy and cosmetic results, high compliance, as well as reduce adverse reactions, both new PS and new PDT techniques are being developed.

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