PHOTODYNAMIC THERAPY OF CUTANEOUS SQUAMOUS CELL CARCINOMA

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Abstract

Photodynamic therapy has traditionally been used and approved in many countries for the treatment of intraepithelial forms of cutaneous squamous cell carcinoma and precancer - actinic keratosis and Bowen's disease. However, recently a number of studies have been conducted that suggest a possible expansion of the boundaries of photodynamic therapy for cutaneous squamous cell carcinoma. Several authors have suggested a therapeutic effect of photodynamic therapy for superficial, microinvasive and well-differentiated cutaneous squamous cell carcinoma. We reviewed publications on the website https://pubmed.ncbi.nlm.nih.gov devoted to this problem. Analysis of the research results shows that photodynamic therapy can achieve high efficiency and good cosmetic results in patients with microinvasive cutaneous squamous cell carcinoma, and in some cases even with an invasive form, and can be considered as an alternative to surgical treatment in patients with contraindications to surgery.

Keywords: photodynamic therapy, cutaneous squamous cell carcinoma, 5-aminolevulinic acid, 5-aminolevulinic acid methyl ester, chlorin e6.

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ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ БОЛЬНЫХ ПЛОСКОКЛЕТОЧНЫМ РАКОМ КОЖИ

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Резюме

Фотодинамическая терапия традиционно применяется и одобрена во многих странах для лечения внутриэпителиальных форм плоскоклеточного рака и предрака – актинического кератоза и болезни Боуэна. Однако в последнее время был проведен ряд исследований, позволяющих сделать предположение о возможном расширении границ применения фотодинамической терапии при плоскоклеточном раке кожи. Несколькими авторами было высказано предположение о терапевтическом эффекте фотодинамической терапии при поверхностном, микроинвазивном и хорошо дифференцированном плоскоклеточном раке кожи. Мы провели обзор публикаций на сайте https://pubmed.ncbi.nlm.nih.gov, посвященных этой проблеме. Анализ результатов исследований показывает, что фотодинамическая терапия может позволить достичь высокой эффективности и хороших косметических результатов у пациентов с микроинвазивным плоскоклеточным раком кожи, а в ряде случаев – даже с инвазивной формой, и может быть рассмотрена, как альтернатива хирургическому лечению у пациентов с противопоказаниями к оперативному вмешательству.

Ключевые слова: фотодинамическая терапия, плоскоклеточный рак кожи, 5-аминолевулиновая кислота, метиловый эфир 5-аминолевулиновой кислоты, хлорин е6.

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Introduction

Cutaneous squamous cell carcinoma (cSCC) is the second most common non-melanocytic skin tumor after basal cell carcinoma. In the Russian Federation (as in many countries around the world), when analyzing cancer statistics, cSCC is not taken into account separately from other non-melanocytic skin tumors, however, according to some data, cSCC accounts for up to 15-20% of all skin cancer cases [1]. In 2023, the incidence of non-melanocytic malignant skin neoplasms in Russia was 305.5 cases per 100 thousand population [2]. Thus, according to indirect estimates, the incidence of cSCC is about 60 cases per 100 thousand population.

Clinical manifestations

The lesions of cSCC most often have a dense structure with a smooth surface or look like a hyperkeratotic papule or plaque, in the center of which an ulcer may be located. In some cases, the lesion of cSCC may look like a non-healing ulcerated wound that bleeds with minimal trauma [3].

Stages of dissemination

The main precursor of cSCC is actinic keratosis (AK). These two pathologies can be considered as different stages of development of one pathological process with transformation of epidermal keratinocytes [4]. The main ways of development and dissemination of cSCC are local infiltration and proliferation. In some cases, dissemination can occur along nerves and blood and lymphatic vessels. cSCC is characterized by a fairly high frequency of metastasis to the lymph nodes – an average of 3% [5,6]. Most authors note that the risk of metastasis in patients with weakened immunity is higher than with normal functioning of the immune system [7].

The frequency of degeneration of AK foci into cSCC varies significantly from one study to another. On average, it is believed that in about 60% of cases, cSCC develops in the area of AK foci, and there is a clear relationship between the number of actinic keratosis formations and the risk of malignant transformation. However, although AK is considered a risk factor and a possible marker for subsequent invasive cSCC, it should be noted that a number of authors provide data that up to half of AK lesions disappear on their own within 1 year [8].

Non-invasive forms of cSCC (in situ) include Bowen's disease and erythroplasia of Queyrat. When the invasion of the papillary dermis occurs, it is called microinvasive cSCC; when the tumor spreads further into the skin, cSCC is considered invasive [9,10].

Diagnosis

There are several biopsy techniques for taking samples of lesions that may be skin cancer. Initial tissue sampling is usually done by curettage if the lesion is raised, or by punch biopsy of the most abnormal areas of the skin [3].

Therapy

The standard treatment for invasive cSCC is surgical removal of the tumor lesion. However, for some patients, the possibility of surgical removal of the cSCC lesion may be limited due to age, general health, concomitant anticoagulant or immunosuppressive therapy, and allergy to local anesthetics. For such patients, the development of other treatment methods is relevant. According to some guidelines, if surgical removal of the cSCC lesion is not possible, there is a possibility of treating low-risk tumors with radiation therapy. However, as many studies show, radiation therapy is not effective enough for cSCC. In addition, post-radiation skin syndrome may worsen over time, and radiation therapy is usually not prescribed to patients under 55 years of age [3,8,9]. Treatment with cryotherapy, imiquimod, and 5-fluorouracil is associated with poor outcome and a high recurrence rate [11].

Another alternative treatment for cSCC is photodynamic therapy (PDT). PDT demonstrates high efficiency and is approved in Russia and abroad for the treatment of many tumor and precancerous skin diseases [12-15]. In particular, our recent review showed that PDT can be considered as one of the first-line treatment options for in situ cSCC. An analysis of articles devoted to PDT in monotherapy in patients with Bowen's disease demonstrated that PDT is more effective and safer than 5-fluorouracil and cryotherapy and is well tolerated by patients with minimal side effects and an excellent cosmetic result, which is important for patients with non-invasive cSCC lesions on the face and exposed skin areas [16].

However, at present, there is insufficient evidence from large randomized multicenter studies regarding the efficacy of PDT as a treatment for invasive cSCC [17] and there is insufficient evidence to support the routine use of local PDT in cSCC [18]. There are only a few studies evaluating the efficacy and tolerability of PDT for microinvasive and invasive cSCC. According to some authors, although local PDT is quite effective for superficial lesions of cSCC, it is less effective for thicker tumors, mainly due to inefficient absorption of 5-aminolevulinic acid (5-ALA) and its derivatives, uneven distribution of photoactive protoporphyrin IX, and limited penetration of light into deeper tumor tissues [18].

The table provides summary data on the effectiveness of PDT in patients with microinvasive and invasive cSCC. The articles were searched on the website https://pubmed.ncbi.nlm.nih.gov for the period 1995-2024 using the keywords "invasive OR minimally invasive OR microinvasive" AND "cutaneous squamous cell carcinoma" AND "photodynamic therapy".

In a randomized clinical study by Choi S.H. et al., 24 patients with microinvasive cSCC underwent 2 courses of

Таблица
Сводные данные результативности применения фотодинамической терапии у пациентов с микроинвазивным и инвазивным плоскоклеточным раком кожи

Table
Summary of the effectiveness of photodynamic therapy of microinvasive and invasive cutaneous squamous cell carcinoma

Авторы Authors	Число пациентов / количество очагов / No. of patients/ No. of lesions		Фотосенсибилизатор Photosensitizer	Режим облучения Light wavelength	Количество курсов ФДТ Number of PDT courses	Эффективность ФДТ PDT efficiency	Нежелательные реакции Adverse reactions
Calzavara-Pinton P.G. et al., 2008 [10]	71 очаг 71 lesions	Микроинвазивный и инвазивный ПКРК Microinvasive and invasive cSCC	МЭ-АЛК за 3 ч до облучения MAL 3 hours before irradiation	37 Дж/см^2 37 J/cm^2	2 курса с интервалом 1 нед. 2 courses with an interval of 1 week	Полная регрессия очагов через 3 мес: микроинвазивного ПКРК 80,0%, инвазивного ПКРК – 45,2%. Полная регрессия очагов через 24 мес: микроинвазивного ПКРК 57,5%, инвазивного ПКРК – 25,8%. Complete regression of foci after 3 months: microinvasive cSCC 80.0%, invasive cSCC – 45.2%. Complete regression of foci after 24 months: microinvasive cSCC 57.5%, invasive cSCC – 25.8%	Эритрема, отек, слабые болевые ощущения во время светового воздействия Erythema, swelling, mild pain during light exposure
Choi S. H. et al., 2017 [19]	24 пациента 24 patients	Микроинвазивный ПКРК Microinvasive cSCC	МЭ-АЛК за 3 ч до облучения MAL 3 hours before irradiation	37 Дж/см^2 37 J/cm^2	2 курса с интервалом 1 нед. 2 courses with an interval of 1 week	Полная регрессия очагов микроинвазивного ПКРК через 3 месяца 52,4%. Число рецидивов через 24 месяца – 63,6% Complete regression of microinvasive cSCC after 3 months 52.4%. The number of relapses after 24 months is 63.6%	Нет данных No data
Kubler A.C. et al., 2001 [20]	25 пациентов 25 patients	ПКРК губы Tis, T1, T2/N0/M0 cSCC of lips Tis, T1, T2/N0/M0	Темопорфин 0,15 мг/кг за 96 ч до облучения Temoporfin 0.15 mg/kg 96 hours before irradiation	20 Дж/см^2 20 J/cm^2	1 курс 1 course	Полная регрессия очагов ПКРК через 3 месяца 96%. Рецидивы через 4 (1 пациент) и 18 мес (1 пациент) Complete regression of cSCC foci after 3 months 96%. Relapses after 4 (1 patient) and 18 months (1 patient)	Нет данных No data
Капинус В.Н. и соавт. Kapinus V.N. et al., 2014 [21]	51 пациент 51 patients	ПКРК T1-3 cSCC T1-3	Фотолон (хлорин е6) 1,1-1,6 мг/кг внутривенно Photolon (chlorin e6) 1.1-1.6 mg/kg intravenously	100-600 Дж/см^2 100-600 J/cm^2	1-2 курса 1-2 courses	Полная регрессия у 91,7% пациентов, частичная регрессия – у 8,3%. При сроке наблюдения от 6 мес до 5 лет рецидивы были диагностированы у 31,2% пациентов Complete regression in 91.7% of patients, partial regression – in 8.3%. With an observation period of 6 months to 5 years, relapses were diagnosed in 31.2% of patients	Нет данных No data

Fargnole M.C. et al., 2015 [22]	1 пациент 1 patient	Микроинвазивный ПКРК губы Microinvasive cSCC of lips	МЭ-АЛК за 3 ч до облучения MAL 3 hours before irradiation	37 Дж/см^2 37 J/cm^2	2 курса 2 courses	Полная регрессия. 24 мес наблюдения без рецидива Complete regression. 24 months of observation without relapse	Нет данных No data
Sotiriou E. et al., 2010 [23]	1 пациент 1 patient	Инфильтративный ПКРК щеки Infiltrative cSCC of the cheek	5-АЛК за 4 ч до облучения, внутриочаговое введение 5-ALA 4 hours before irradiation, intralesional administration	100 Дж/см^2 100 J/cm^2	1 курс 1 course	Полная регрессия. 16 мес наблюдения без рецидива Complete regression. 16 months of observation without relapse	Нет данных No data
Li Q. et al., 2010 [24]	1 пациент 1 patient	Инвазивный ПКРК головы (толщина опухоли 5,5 мм) Invasive cSCC of the head (tumor thickness 5.5 mm)	Местно 5-АЛК за 6 ч до облучения Locally 5-ALA 6 hours before irradiation	100 Дж/см^2 100 J/cm^2	7 курсов 7 courses	Полная регрессия, наблюдение без рецидива 12 мес Complete regression, 12 months of observation without relapse	Нет данных No data
Rossi R. et al., 2004 [25]	1 пациент 1 patient	ПКРК века cSCC of the eyelid	Местно 5-АЛК за 4 ч до облучения Locally 5-ALA 4 hours before irradiation	80 Дж/см^2 80 J/cm^2	1 курс 1 course	Полная регрессия, наблюдение без рецидива 6 мес Complete regression, 6 months of observation without relapse	Нет данных No data
Струнки Д.Н. и соавт. Strunkin D.N. et al., 2017 [26]	1 пациент 1 patient	ПКРК щеки 4х4 см (прорастание в кожу, инфильтрация подкожной сетчатки) cSCC of the cheek 4x4 cm (ingrowth into the skin, infiltration of the subcutaneous retina)	Внутривенно 0,8 мг/кг фотодитазина (хлорин е6) за 2,5 ч до облучения Intravenously 0.8 mg/kg photoditazine (chlorin e6) 2.5 hours before irradiation	300-350 Дж/см^2 300-350 J/cm^2	1 курс 1 course	Частичная регрессия через 2 мес Partial regression after 2 months	Нет данных No data

*ПКРК – плоскоклеточный рак кожи, 5-АЛК – 5-аминолевулиновая кислота, МЭ-АЛК – метиловый эфир 5-аминолевулиновой кислоты
*cSCC – cutaneous squamous cell carcinoma, 5-ALA – 5-aminolevulinic acid, MAL – 5-aminolevulinic acid methyl ester

PDT with 5-ALA [19]. The study also included 21 patients who underwent 1 course of PDT with preliminary treatment of the cSCC lesion with an ablative fractional laser. The overall complete response rate 3 months after 2 courses of PDT was 52.4%. It should be noted that the use of an ablative laser increased this figure to 84.2%. However, both treatment approaches did not have significant differences in terms of cosmetic results, side effects, or pain intensity.

Calzavara-Pinton P.G. et al. reported the efficacy of PDT with 5-ALA in the treatment of cSCC depending on the depth of invasion [10]. The authors of the article staged cSCC taking into account the level of invasion according to Clark, which shows to what layer of the skin the tumor has spread. The authors assigned level I to cSCC in situ (Bowen's disease), level II (invasion into the papillary dermis) to microinvasive cSCC, and levels III-V to invasive cSCC. The results of the study confirmed the higher efficacy of PDT in relation to microinvasive cSCC (level II according to Clark, invasion into the papillary dermis) compared to invasive variants of cSCC (level III and IV according to Clark). Complete regression 3 months after 2 courses of PDT was achieved in 80.0% of cases of microinvasive cSCC and only in 45.2% of cases of invasive cSCC (Clark levels III and IV). For comparison, when using PDT in patients with cSCC in situ (Bowen's disease), the frequency of complete regressions was slightly higher than in the case of the microinvasive form of the tumor – 87.8%. With long-term observation, the effect in patients with the microinvasive form of cSCC was significantly more stable than in patients with invasive cSCC: after 24 months, complete regression was preserved in 57.5% of cases of microinvasive cSCC and in 25.8% of cases of the invasive form of the disease.

One of the largest studies of the effectiveness of PDT in cSCC (51 patients) was conducted in Russia [21]. Patients underwent PDT after intravenous administration of photolon, a photosensitizer based on chlorin e6. In 24 patients (47.1%), the diagnosis was made for the first time, 27 patients (52.9%) were treated for continued growth or relapse of cSCC after radiation therapy, surgery, cryodestruction, and combined treatment. Among patients with primary cSCC, T1 was established in 7 (29.2%), T2 in 16 (66.7%), and T3 in 1 (4.2%) people. Among these patients, complete regression of tumor foci was achieved in 91.7% of patients and partial in 8.3%. Among patients with recurrent cSCC, the tumor sizes ranged from 2.0 to 5.0 cm in 40.7%, and 5.0 cm or more in 59.3%. Among these patients, complete regression was achieved only in 59.3% of cases, partial regression in 33.3%, and no effect in 7.4%. With an observation period of 6 months to 5 years, recurrent CCRC were diagnosed in 31.2% of patients.

Another large study involving 25 patients from 5 centers in 3 countries was published by Kubler et al. [20]. This was a prospective, open-label, multicenter study conducted on patients with early-stage lip cSCC. The authors used temoporfin (0.15 mg/kg intravenously) as a photosensitizer. The interval between the administration of the photosensitizer and irradiation (20 J/cm^2) was 4 days. The complete response rate at 3 months after treatment was 96%. During the dynamic observation, relapse of cSCC was registered in 2 patients: 4 and 18 months after treatment.

The remaining publications we found were reports of individual clinical observations in which PDT demonstrated high efficacy against microinvasive cSCC (Table).

Discussion

As is known, the method of choice in the treatment of patients with cSCC is surgical removal of tumor foci [3,5,9]. However, for a significant cohort of patients, there are limitations in performing surgical intervention. This may be due to the age of the patients, somatic status, or concomitant therapy. For this cohort of patients, the development of non-invasive methods for influencing cSCC foci is relevant. The use of iquimod and 5-fluorouracil often does not achieve acceptable efficiency [11,16]. Superficial ablative techniques such as electrodissection and curettage, cryotherapy, and the use of CO_2 laser have not shown high efficiency and, thus, the validity of their use for the treatment of invasive cSCC is highly questionable [11]. The use of chemotherapy and radiation therapy are associated with multiple side effects. PDT in the treatment of non-invasive cSCC has a number of advantages, which include relatively less invasiveness, high selectivity for tumor tissue, no serious side effects, good cosmetic results, low recurrence rates, and relative safety for elderly patients and patients with comorbid conditions for which surgical intervention is inappropriate [10,19-26]. Despite all these advantages, PDT still requires some modifications to be successfully used in invasive cSCC [10]. The main reason for the low efficiency of local PDT in invasive cSCC may be insufficient penetration of the topically applied photosensitizer through tumor tissue or insufficient local bioavailability and, as a result, decreased cellular absorption. Studies to increase the efficiency of photosensitizers in relation to cSCC are mainly aimed at developing methods to increase drug penetration and achieve the desired concentration of the photosensitizer in the tumor lesion. To increase the delivery of photosensitizer to tumor cells, a combination of PDT with various methods of physical action and optimization of medicinal forms of photosensitizers is used, facilitating the penetration of the photosensitizer deep into the tissue [11].

For example, in the study by Sotiriou E. et al., intralesional administration of the photosensitizer was used to achieve the maximum concentration of the drug in the tumor focus [20]. This approach allowed achieving

complete regression of the infiltrative cSCC focus after just 1 course of PDT with 5-aminolevulinic acid methyl ester, and the relapse-free observation period was 16 months. Another promising direction is the use of nanoforms for encapsulation of the photosensitizer [27,28].

A number of studies have attempted to increase the efficacy of PDT for invasive cSCC by combining it with other physical or chemotherapeutic modalities. As discussed earlier, Choi S.H. et al. [16] showed that pretreatment of cSCC lesions with an ablative laser resulted in complete regression in more cases than PDT monotherapy, although no significant differences were observed in both cases in terms of cosmetic outcomes, adverse events, or pain intensity. Another study showed in cell culture experiments that metformin pretreatment could inhibit metabolic changes in cSCC cells during PDT treatment and reduce tumor cell survival, and this effect was confirmed in *in vivo* experiments where metformin pretreatment increased the efficacy of PDT with intratumoral administration of MAL [29]. Anand F. et al. demonstrated increased accumulation of photoactive protoporphyrin IX in cSCC cells after 3-day pretreatment of tumor lesions with 5-fluorouracil [30], which resulted in greater tumor cell death. Another mechanism, according to the authors, may be related to the fact that exposure to 5-fluorouracil could cause changes in the expression of key enzymes of protoporphyrin IX metabolism, including coproporphyrinogen oxidase and ferrochelatase.

Regarding the efficacy of various photosensitizers used for PDT of invasive cSCC, the number of studies in this area is not large enough to speak of a statistically significant difference, but there is an obvious trend towards higher efficacy when using photosensitizers based on chlorin e6 [10,19-21].

Conclusion

Photodynamic therapy can achieve high efficiency and good cosmetic results in patients with microinvasive cSCC, and in some cases even with the invasive form, and can be considered as an alternative to surgical treatment in patients with contraindications to surgery. In invasive cSCC, the use of photosensitizers based on chlorin e6 is preferable, as they demonstrate higher efficiency.

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