PHOTODYNAMIC THERAPY OF BOWEN'S DISEASE

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Abstract

Bowen's disease is a form of non-invasive (*in situ*) squamous cell skin cancer localized in the non-genital area. Russian and European clinical guidelines include photodynamic therapy (PDT) in the standard of care for patients with Bowen's disease. In the present review, the efficacy and safety profile of different PDT regimens for Bowen's disease are analyzed according to the available literature data. PDT can be used to treat large Bowen's disease lesions localized in areas of the body characterized by severe healing and in cases where surgery is not feasible. Analysis of the results of studies shows that PDT is superior in efficacy and cosmetic results to traditional local treatments such as 5-fluorouracil or cryotherapy. In all analyzed studies in patients with Bowen's disease, PDT achieved a significant clinical effect. Complete regression of pathologic foci was achieved in 67-100% of patients. In studies evaluating the recurrence rate of Bowen's disease after PDT, this value ranged from 2-28% with the range of 6-18% in most of the studies. Most often, 5-aminolevulinic acid and its methyl ester are used for PDT in Bowen's disease. According to some researchers, aminolevulinic acid allows to achieve a more long-term positive clinical effect with a lower incidence of painful reactions during treatment.

Key words: photodynamic therapy, Bowen's disease, 5-aminolevulinic acid, 5-aminolevulinic acid methyl ester.

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ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ ПАЦИЕНТОВ С БОЛЕЗНЬЮ БОУЭНА

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Резюме

Болезнь Боуэна – форма неинвазивного (*in situ*) плоскоклеточного рака кожи, локализованная в негенитальной области. Российские и европейские клинические рекомендации включают фотодинамическую терапию (ФДТ) в стандарты лечения пациентов с болезнью Боуэна. В настоящем обзоре по имеющимся литературным данным проанализированы эффективность и профиль безопасности различных схем применения ФДТ при болезни Боуэна. ФДТ может быть применена для воздействия на очаги болезни Боуэна большого размера, локализованные на участках тела, характеризующихся тяжелым заживлением, а также в случаях, когда хирургическое вмешательство представляется нецелесообразным. Анализ результатов исследований показывает, что ФДТ превосходит по эффективности и косметическим результатам традиционные местные методы лечение, такие как применение 5-фторурацила или криотерапию. Во всех проанализированных исследованиях у пациентов с болезнью Боуэна, ФДТ позволила достичь значимого клинического эффекта. Полная регрессия патологических очагов была достигнута у 67-100% пациентов. В исследованиях, оценивавших частоту рецидивов болезни Боуэна после ФДТ, значение этого показателя составляло 2-28%, в большинстве исследований 6-18%. Чаще всего для ФДТ при болезни Боуэна применяют 5-аминолевулиновую кислоту и ее метиловый эфир. По данным некоторых исследователей аминолевулиновая кислота позволяет достичь более долгосрочного положительного клинического эффекта с меньшей частотой развития болевых реакций в процессе лечения.

Ключевые слова: фотодинамическая терапия, болезнь Боуэна, плоскоклеточный рак кожи in situ, 5-аминолевулиновая кислота, метиловый эфир 5-аминолевулиновой кислоты.

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Introduction

Bowen's disease (first described in 1912) is a form of intraepidermal (*in situ*) squamous cell skin cancer (SCSC). In addition to Bowen's disease, non-invasive forms of SCSC also include Keir's erythroplasia. According to current concepts, Bowen's disease is an *in situ* SCSC for lesions located in non-genital areas [1,2]. In Bowen's disease, if untreated, pathologic foci continue to slowly increase in size and may develop into an invasive form of SCSC after many years [2].

Etiology and pathogenesis

The factors that provoke the development of Bowen's disease include [2]:

- various types of irradiation (ultraviolet radiation, radiation therapy)
- local action of carcinogenic compounds (e.g., arsenic)
- immunosuppressors (in particular, various drugs with immunosuppressive effects)
- viruses (in a systematic review by Namgoong S. et al. human papillomavirus (HPV) was found in 28.3% of 904 extragenital in situ specimens of SCSC, with HPV-16 being the most common, followed by HPV-30 [3])
- chronic trauma
- dermatoses (e.g., common or chronic lupus erythematosus)
- seborrheic keratoses

etc.

Bowen's disease develops slowly, but can progress to invasive SCSC in about 10% of patients if not adequately treated. At the same time, cases of SCSC developed in patients with Bowen's disease are often more aggressive than those arising in actinic keratoses [4].

Clinical manifestations

There are certain difficulties in diagnosing Bowen's disease when differentiating it from various dermatoses. This is due to the fact that Bowen's disease often has no specific clinical manifestations [5].

Pathologic foci in Bowen's disease are usually well-defined, asymptomatic erythematous hyperkeratotic plaques with irregular well-defined borders, with tightly seated dry scales on the surface. Foci appear more often on areas of skin exposed to the sun, usually in light-skinned people. The pigmented variant of Bowen's disease occurs in 1.7-5.5% of cases, mostly in men with darker skin types, on sun-protected areas such as the lower extremities [2].

One of the first signs to suspect Bowen's disease may be the absence of any response to topical anti-inflammatory therapy [1,2].

At the onset of the disease, a small red spot (or several spots) is observed on the skin, the surface of which is covered with scales. The latter are easily removed from the surface of the spot. Under the removed scales, a foci with a moist and red surface is exposed, not accompanied by subjective sensations. With disease progression, the lesion thickens, an infiltrate appears, and in its place a dense plaque with clear even boundaries is formed, which can grow, become voluminous and rise above the skin [2,5].

There are four clinical forms of Bowen's disease [5]:

- anular, in which the plaque forms in the shape of a circle;
- verrucous, in which wart-like growths appear on the surface;
- pigmented in the form of a plaque of dark color (due to the content of a large amount of melanin);
- acral form, accompanied by skin lesions of the nail plate (more often on the lower extremities).

Diagnosis

Dermatoscopic examination is necessary to confirm the diagnosis of Bowen's disease. Bowen's disease usually shows superficial areas of scaling, tortuous vessels ("glomerular" vessels) and/or red clots ("globular" vessels), and small brown dots and globules in the pigmented variant. If there is doubt about the diagnosis or if confirmation is required before a particular treatment, the patient may be scheduled for a punch biopsy to histologically reveal full thickness epidermal dysplasia [1,2].

Therapy

Surgical removal

Standard surgical excision of a focus of Bowen's disease is recommended when there is diagnostic uncertainty regarding the invasiveness of the disease, as well as in the recurrent form of the disease and in immunocompromised patients. When performing surgical removal, it is advisable to remove the pathologic focus with a reserve of 3-5 mm [1,2].

In cases where it is important to preserve healthy tissue as much as possible (e.g., when removing a pathologic focus in the eye area or nail plate), Mohs micrographic surgery is the preferred option for surgical removal [2].

If surgical treatment is not possible (e.g., due to patient refusal of treatment, severe patient condition, or unsatisfactory expected cosmetic results with surgery), one of the local therapy options is recommended: curettage and electrocoagulation, radiation therapy, cryodestruction, photodynamic therapy, or local drugs with antitumor activity [1,2,5,6].

Local drug therapy

In Bowen's disease with small lesions (less than 2 cm), local application of 5% of 5-fluorouracil 1-2 times a day for 3-4 weeks is recommended. This therapy may cause

local side effects in the form of local inflammation, skin ulceration at the sites of application, and scarring at the site of lesions. In some cases, topical application of 5-fluorouracil is possible for larger lesions located in low-risk areas [1,2].

According to the clinical guidelines of the British Association of Dermatologists, local application of 5-fluorouracil cannot be recommended directly, but may be considered as an alternative to other treatments (e.g., if the patient refuses other treatments) in patients with large, localized lesions in areas where healing is usually difficult (e.g., shins in elderly patients) and in immunocompromised patients for the treatment of multiple and recurrent lesions [2,7-10].

Among other topical agents, 5% imiquimod may be recommended in patients with Bowen's disease (usually only if other alternative treatments are not possible) [2].

Cryodestruction

Cryodestruction may be recommended as a first-line treatment option for patients with small (<2 cm) *in situ* SCSC lesions [2,7,9]. One cycle of cryotherapy with freezing for 20-30 s or two cycles of 10-20 s is used to treat lesions in Bowen's disease. According to the British Association of Dermatologists, cryotherapy may be associated with greater discomfort, poorer healing, and more recurrences compared with scraping with cauterization. The use of cryotherapy in patients with Bowen's disease with large lesions or lesions located on the shin (higher probability of non-healing ulcers) and in immunocompromised patients is possible but should be considered on an individual basis [2,9].

Curettage with cauterization

Curettage with cauterization is mainly used to treat patients with small foci of Bowen's disease [2]. After the procedure, ulceration and prolonged healing of postoperative wounds are possible, so the age of the patient, general skin condition, localization and size of the lesion should be taken into account when prescribing this type of therapy. Besides, it is possible to use curettage with cauterization in immunocompromised patients [2].

Laser irradiation

Laser irradiation to target foci of Bowen's disease is used when other treatments have been ineffective or are not appropriate for the patient. The ablative CO_2 laser is considered more effective than the non-ablative neodymium:YAG laser [2].

Radiation therapy

Radiation therapy is performed only in immunocompetent patients with Bowen's disease, usually when the lesion is recurrent or unresponsive to other treatments, or when surgery is inappropriate or of a high risk [2].

Photodynamic therapy

In recent years, the use of non-invasive therapies has attracted increasing attention in the treatment of cancer and precancerous lesions. Photodynamic therapy (PDT) is one such conservative and non-invasive methods. During PDT, antitumor immune responses are triggered by nontoxic photosensitizers selectively accumulated in pathological tissue, which convert oxygen into cytotoxic reactive oxygen species under the action of light of a certain wavelength [11].

Numerous studies have confirmed that PDT demonstrates high efficacy with excellent cosmetic results in the treatment of superficial basal cell skin cancer [12], actinic keratosis [13], SCSC *in situ*, including genital localization [14], extramammary Paget's cancer [15], mycosis fungoides [16], and other tumor and pre-tumor diseases.

The aim of this review is to analyze the efficacy and safety profile of different PDT regimens for Bowen's disease.

The efficacy of PDT for Bowen's disease is considered to be equivalent or superior to local application of 5-fluorouracil and cryotherapy [9,8,10]. The cosmetic outcome with PDT is considered to be better compared to standard therapy. PDT can be used to treat large lesions, lesions localized to areas of the body characterized by severe healing, and in cases where surgery is not feasible [17].

In 2016 the American Society for Dermatologic Surgery approved protocols for the treatment of patients with Bowen's disease by PDT [4]:

- 5-aminolevulinic acid (5-ALA) topically, incubation time 4 h, irradiation with a red light source, light dose >100 J/cm^2;
- 5-ALA methyl ester (MAL) topically, incubation time 3 h, irradiation with red light source, light dose 75-100 J/cm^2.

The performed literature analysis allowed to identify 10 studies of PDT efficacy and safety in patients with Bowen's disease since 2000, in which 20 or more (up to 335) patients have been included (see Table). Studies in which PDT was performed in combination with other therapies were not included in the analysis, as the results of such studies do not allow estimating the contribution to the efficacy of PDT specifically.

In 3 studies out of those included in the analysis 5-ALA was used for PDT, in 6 – MAL, in 1 study – in part of patients 5-ALA, and in other part – MAL. The most frequent light dose in the studies was 37-75 J/cm^2, and 100-105 J/cm^2 in 2 studies. The number of performed PDT courses was usually 1-2, but in some studies it reached 6.

Effectiveness of PDT in Bowen's disease

As can be seen from the Table, in all studies in patients with Bowen's disease, PDT achieved a significant clinical effect. Complete regression of pathologic foci was

Таблица
Сводные данные результативности применения фотодинамической терапии у пациентов с болезнью Боуэна
Table
Summary of the effectiveness of photodynamic therapy in patients with Bowen's desease

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
Varma et al., 2001 [18]	Нет данных/48	5-АЛК 5-ALA	105 Дж/см^2 105 J/cm^2	Нет данных No data	Полный эффект после 2 курсов 88%. Через 12 мес эффект сохранился у 69%. Full effect after 2 courses in 88%. After 12 months, the effect was maintained in 69%.	Нет данных No data
Salim et al., 2003 [8]	20/33	5-АЛК 5-ALA	100 Дж/см^2 100 J/cm^2	1-2 курса с интервалом 6 нед 1-2 courses with an interval of 6 weeks	Полный эффект 66,6% (после 1 курса) и 88% (после 2 курсов). Частота рецидивов 6%. Full effect in 66.6% (after 1 course) and in 88% (after 2 courses). Recurrence rate 6%.	Нет данных No data
Morton et al., 2006 [7]	90/111	МЭ-АЛК MAL	75 Дж/см^2 75 J/cm^2	2 курса с интервалом 1 нед. Повтор лечения через 3 мес в случае частичного эффекта 2 courses with an interval of 1 week. Repeat treatment after 3 months in case of partial effect	Частота клинического ответа 73% после двух курсов, 93% после 4 курсов. Частота рецидивов 15%. Хороший или отличный косметический результат в 97% случаев через 12 мес после лечения. Clinical response rate of 73% after 2 courses, 93% after 4 courses. Relapse rate 15%. Good or excellent cosmetic result in 97% of cases 12 months after treatment.	Нет данных No data
de Haas et al., 2007 [19]	40/50	5-АЛК 5-ALA	Сравнение двух схем облучения: 1) Однократное облучение (75 Дж/см^2) 2) Двукратное облучение (20 + 80 Дж/см^2) с 2-часовым интервалом затемнения Comparison of two irradiation schemes: 1) Single irradiation (75 J/cm^2) 2) Double irradiation (20 + 80 J/cm^2) with a 2-hour darkening interval	Нет данных No data	Полный эффект 80% (для схемы однократного облучения) и 88% (для схемы двукратного облучения). The total effect in 80% (for a single irradiation scheme) and in 88% (for a double irradiation scheme).	В группе с двукратным облучением у 5 пациентов зарегистрированы болевые ощущения во время сеанса облучения. In the group with double irradiation, 5 patients reported pain during the irradiation session.

Calzavara-Pinton et al., 2008 [20]	Нет данных/41 No data/41	МЭ-АЛК MAL	37 Дж/см^2 37 J/cm^2	2 курса с интервалом 1 нед. 2 courses with an interval of 1 week	Полный эффект 87,8%. Частота рецидивов 17,1%. Full effect 87.8%. Recurrence rate 17.1%.	Нет данных No data
Cavicchini et al., 2011 [21]	30/43	МЭ-АЛК MAL	75 Дж/см^2 75 J/cm^2	2 курса с интервалом 1 нед. 2 courses with an interval of 1 week	Полный эффект 100%. Частота рецидивов 16,7%. Full effect 100%. Recurrence rate 16.7%.	Хорошая переносимость, ощущение покалывания и жжения от умеренной до сильной степени во время облучения (93% пациентов) Well tolerated, moderate to severe tingling and burning sensation during radiation (93% of patients)
Truchuelo et al., 2012 [22]	47/51	МЭ-АЛК MAL	38 Дж/см^2 38 J/cm^2	2 курса с интервалом 1 нед. 2 courses with an interval of 1 week	Полный эффект после двух курсов 76%. Частота рецидивов 14,3%. Превосходных косметический результат. The full effect after two courses is 76%. Recurrence rate – 14.3%. Excellent cosmetic results.	Чаще всего из нежелательных явлений – чувство жжения в момент лечения. The most common side effect is a burning sensation during treatment.
Ratour-Bigot et al., 2016 [23]	64/64	МЭ-АЛК MAL	Нет данных No data	1-6 курсов 1-6 courses	Полный эффект 52%. Частота рецидивов не оценена. Full effect 52%. Recurrence rates have not been assessed.	Нет данных No data
Zaar et al., 2017 [24]	335/423	МЭ-АЛК MAL	37 Дж/см^2 37 J/cm^2	1-2	Полный эффект 77,5%. Частота рецидивов 18,3%. Full effect in 77.5%. Recurrence rate – 18.3%.	Образование рубцов – 8,8%, эритема –6%, гипопигментация – 2,4%, гиперпигментация – 2,0% Scar formation – 8.8%, erythema -6%, hypopigmentation – 2.4%, hyperpigmentation – 2.0%
Alique-García et al., 2019 [25]	171/191	5-АЛК (55 очагов), МЭ-АЛК (136 очагов) 5-ALA (55 lesions), MAL (136 lesions)	37 Дж/см^2 37 J/cm^2	2 курса с интервалом 1 нед. Повтор лечения через 3 мес в случае частичного эффекта 2 courses with an interval of 1 week. Repeat treatment after 3 months in case of partial effect	ФДТ с 5-АЛК: полный эффект 87%; частота рецидивов 2%, через 12 мес эффект сохранился у 85%. ФДТ с МЭ-АЛК: полный эффект 76%; частота рецидивов 28%, через 12 мес эффект сохранился у 55%. PDT with 5-ALA: full effect in 87%; recurrence rate – 2%, after 12 months the effect was maintained in 85%. PDT with MAL: full effect in 76%; recurrence rate – 28%, after 12 months the effect was maintained in 55%.	У 5% пациентов, в группе 5-АЛК и у 2% пациентов в группе МЭ-АЛК лечение было прервано из-за сильной боли. Так же в обеих группах примерно у половины пациентов наблюдались эритрема, шелушение и образование поверхностных ран. In 5% of patients in the 5-ALA group and 2% of patients in the MAL group, treatment was interrupted due to severe pain. Also in both groups, approximately half of the patients experienced erythrema, desquamation and the formation of superficial wounds.

achieved in 67-100% of patients. In studies evaluating the recurrence rate, the value was 2-28%, in most studies it was 6-18%.

Interesting comparative data on the efficacy of 5-ALA and MAL were obtained in a study by Alique-García et al. [25]. The authors of the study showed that the efficacy was significantly higher with 5-ALA. Thus, in PDT with 5-ALA, the full effect was obtained in 87% of patients, while in PDT with MAL it was seen only in 76% of patients. The difference in efficacy amounted to 11%. In 12 months after treatment this difference became even greater – 30% (85% vs. 55%). Thus, it can be concluded that the effect after PDT with 5-ALA is maintained longer than after PDT with MAL.

Safety of PDT in Bowen's disease

In most studies, the authors reported painful sensations in patients during irradiation of the pathologic focus [21,22,23]. In rare cases, treatment had to be interrupted due to intolerable pain (from the data by Alique-García et al. [25]: treatment was interrupted in 2-5% of patients). Most authors also point out developing local skin reactions: erythremia, scar formation, hypo- and hyperpigmentation, and desquamation. Most of these adverse events were reversible [24,25].

Number of PDT courses

The number of PDT courses required to achieve a clinically meaningful effect in the treatment of Bowen's disease remains a debated issue. For example, the Scottish PDT Center in Dundee, after performing approximately 5000 PDT treatments in patients with Bowen's disease, estimates incomplete clearance after 4 PDT sessions as a treatment failure. The Center claims that the majority of patients they treated who had complete clearance after PDT achieved it after 2, rarely after 4 sessions [26]. However, there are examples in the literature when patients achieved full recovery after more sessions, for example, 6 [23,27]. Each patient should be individually evaluated on a case-by-case basis when administering PDT [25].

Factors associated with unfavorable prognosis of PDT

In a study by Zaar et al. [24] the following factors associated with poor prognosis in patients with Bowen's disease treated with PDT were identified: large lesion size (> 2 cm) and a single PDT session. In another recent study in which patients with SCSC *in situ* were treated with PDT with 20% 5-ALA solution, it was reported that longer incubation time with 5-ALA, smaller tumor diameter, and facial location were associated with increased efficacy [28]. The dependence of treatment efficacy on the size of the pathologic focus was also confirmed in a study by Morton et al. [7]. Another study showed that severe atypia and older age were associated with an increased risk of treatment failure in PDT of patients with Bowen's disease [29].

Several studies have shown that immunocompromised patients with Bowen's disease had an initial rate of complete effect with PDT was comparable to the main cohort of immunocompetent patients, but a higher rate of recurrence within the first year after treatment was observed in this group [21,30].

Comparative analysis of the efficacy and safety of treatment of Bowen's disease by different methods

An important issue is the comparison of PDT with other treatments for Bowen's disease according to efficacy and safety criteria.

Several direct comparative studies of the efficacy and safety of PDT and other treatments for patients with Bowen's disease have been described in the literature.

A study by Morton et al. [7] showed that cosmetic outcome after 3 months was good or excellent in 94% of patients receiving PDT with MAL, compared with 66% with cryotherapy and 76% with 5-fluorouracil, and was maintained for 12 months.

In the study by Salim et al. [8] it is shown that PDT with 5-ALA in patients with Bowen's disease was accompanied by better clinical results than topical application of 5-fluorouracil: the immediate clinical effect was 88% in the PDT group versus 67% with 5-fluorouracil. After 12 months, complete clinical clearance rates were 82% and 48%, respectively. In addition, PDT demonstrated a better safety profile compared to 5-fluorouracil. With the latter, 7 patients developed severe eczematous reactions, 3 patients developed ulceration and 2 patients developed erosions. No such reactions occurred after PDT.

A meta-analysis performed in 2020 confirmed that PDT is more effective than 5-fluorouracil and cryotherapy for the treatment of Bowen's disease. However, the authors found no significant differences in recurrence rates after treatment with PDT and other treatments (5-fluorouracil and cryotherapy) [9]. In a 2022 meta-analysis of 4 clinical trials involving 292 patients, PDT also showed a higher complete response rate and improved cosmetic results, but also a reduced recurrence rate compared with cryotherapy and 5-fluorouracil [10].

In some studies, the efficacy of PDT was lower than for other topical therapies.

For example, in a study by Park et al. [6] the medical records of 121 patients at Seoul St. Mary's Hospital in Seoul with Bowen's disease were analyzed. The treatment methods were surgical excision, cryotherapy, PDT, and imiquimod. The mean treatment period was longest for cryotherapy, followed by imiquimod, PDT, and surgical excision (119, 88, 68, and 1 day, respectively). The therapeutic efficacy was highest in the surgical removal group (100%) and lowest in the PDT group (62.5%). The recurrence rate was highest in the imiquimod group (33.33%). The authors of the study note that 9% of patients who received cryotherapy developed satellite lesions during the follow-up

period, which requires careful follow-up after treatment of patients with Bowen's disease by cryotherapy [6].

Conclusion

The present data allow us to consider PDT as one of the options for first-line therapy in Bowen's disease. Most studies show that PDT is more effective and safer than 5-fluorouracil and cryotherapy in Bowen's disease [4,5,8,9,10,25]. PDT provides excellent cosmetic results and is generally well tolerated by patients with minimal side effects [17,19,21,22]. The use of PDT is most relevant in patients with Bowen's disease for whom surgery is contraindicated for any reason, patients with multiple lesions [17], foci located on the lower extremities [25] and with recurrent Bowen's disease [17].

Although there are many different PDT protocols for Bowen's disease, most studies perform 2 courses of PDT 7 days apart using red light (≈ 630 nm) at a dose of approximately 37 J/cm^2 after application of 5-ALA or MAL under occlusion for 3-4 h to obtain optimal results [20,22,24,25].

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