PHOTODYNAMIC THERAPY OF LEUKOPLAKIA OF THE ORAL MUCOSA: EXPERIENCE OF USING THE METHOD IN 223 PATIENTS

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Abstract

The aim of this study was to analyze the immediate and long-term results of using photodynamic therapy (PDT) in patients with leukoplakia of the oral mucosa. The retrospective study included 223 patients with morphologically verified leukoplakia of the oral mucosa. Patients received treatment at the hyperthermia and photodynamic therapy department from 2013 to 2023. The average age was 51.9±8.9 years. Clinically, 211 patients (94.6%) had a flat form of the disease, 12 patients (5.4%) had a verrucous form. The photosensitizer (PS), based on chlorin e6, was administered intravenously once in doses of 1.7 to 2.5 mg/kg body weight. Irradiation of pathologically changed lesions was carried out 2-2.5 hours after the end of its infusion, using a semiconductor laser device "UPL PDT", with a wavelength λ=665±5 nm. The laser radiation dose density varied from 25 to 100 J/cm^2, the power density from 0.07 to 0.32 W/cm^2, the duration of one irradiation field - from 2 to 13.5 minutes, depending on its linear dimensions. The severity of adverse reactions was assessed on days 1-30 after treatment using the CTCAE 4.03 scale. The immediate results of treatment were assessed up to 3 months after PDT, with morphological confirmation of the response to treatment. No serious adverse reactions were observed during PS infusion and irradiation. No symptoms of dermal phototoxicity were reported. During control examinations, up to 3 months after irradiation in patients with flat and verrucous forms, the frequency of complete regressions was 97.1% (n=205) and 58.3% (n=6) cases, partial regressions - 2,9% (n=7) and 25% (n=3) of cases, respectively. Objective response rates were observed at 100% and 83.3%, respectively. The period of observation of patients varies from 3 to 120 months. (average 66 months). The frequency of disease relapses during this period was 9%. Patients with partial regression and identified relapse were treated with repeated PDT sessions. PDT is a well-tolerated and effective treatment method for patients with leukoplakia of the oral mucosa, which has significant advantages over traditional methods of treating this precancerous pathology. These include minimal toxicity to the normal tissues surrounding the pathological foci due to the selective accumulation of PS in leukoplakia tissues, a slight risk of serious adverse reactions, the possibility of an outpatient session, the possibility of repeated treatment over a large area of damage and good cosmetic results).

Key words: photodynamic therapy, photolon, patients, leukoplakia of the oral mucosa, precancer.

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ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ ЛЕЙКОПЛАКИИ СЛИЗИСТОЙ ПОЛОСТА РТА: ОПЫТ ПРИМЕНЕНИЯ МЕТОДА У 223 ПАЦИЕНТОВ

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Резюме

Целью настоящего исследования было изучение непосредственных и отдаленных результатов применения метода фотодинамической терапии (ФДТ) у пациентов с лейкоплакией слизистой оболочки полости рта (СОР). В ретроспективное исследование включено 223 пациента с морфологически верифицированной лейкоплакией слизистой оболочки полости рта. Пациенты получали лечение на базе отделения гипертермии и фотодинамической терапии в период с 2013 г. по 2023 г. Средний возраст составил 51,9±8,9 года. Клинически у 211 пациентов (94,6%) была плоская форма заболевания, у 12 пациентов (5,4%) – веррукозная. В качестве фотосенсибилизатора (ФС) использовался препарат фотолон, на основе хлорина е6, который вводился однократно внутривенно в дозах от 1,7 до 2,5 мг/кг массы тела. Облучение патологически измененных очагов осуществлялось через 2-2,5 ч после окончания его инфузии, с помощью полупроводникового лазерного устройства «УПЛ ФДТ» с λ=665±5 нм. Плотность дозы лазерного излучения варьировала от 25 до 100 Дж/см^2, плотность мощности от 0,07 до 0,32 Вт/см^2, продолжительность одного поля облучения – от 2 до 13,5 мин в зависимости от его линейных размеров. Степень выраженности нежелательных реакций оценивали на 1-30 сут после лечения по шкале

CTCAE 4.03. Непосредственные результаты лечения оценивались в сроки до 3 мес после ФДТ, с морфологическим подтверждением ответа на лечение. Серьезных нежелательных реакций при инфузии ФС и облучении не отмечено. Симптомов кожной фототоксичности не было зарегистрировано. При контрольных обследованиях, в сроки до 3 мес после облучения у пациентов с плоской и верукозной формами частота полных регрессий составила 97,1% (n=205) и 58,3% (n=6), частичных регрессий – 2,9% (n=7) и 25% (n=3) соответственно. Частота объективных ответов наблюдалась в 100% и 83,3% случаев соответственно. Период наблюдения за пациентами варьирует от 3 до 120 мес (в среднем 66 мес). Частота рецидивов заболевания за указанный период составила 9%. Пациенты с частичной регрессией и выявленным рецидивом получали лечение в объеме повторных курсов ФДТ. ФДТ является хорошо переносимым и эффективным методом лечения пациентов с лейкоплакией СОР и обладает весомыми преимуществами перед традиционными методами лечения данной предопухолевой патологии. К таковым можно отнести минимальную токсичность для окружающих патологические очаги нормальных тканей, незначительный риск возникновения серьезных нежелательных реакций, возможность амбулаторного проведения лечения, возможность многократного проведения лечения при большой площади поражения и хорошие косметические результаты.

Ключевые слова: фотодинамическая терапия, фотолон, пациенты, лейкоплакия слизистой полости рта, предрак.

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Introduction

In recent years, there has been a steady increase in the incidence of patients with precancerous diseases of various locations. One of the most common nosological forms of this pathology is leukoplakia, which is a chronic lesion of the mucous membranes, characterized by varying degrees of keratinization of the integumentary epithelium. Particular attention is paid to leukoplakia of the oral mucosa. According to S. Zhang et al., who analyzed 69 studies conducted in 28 countries, including a total of 1,263,028 potentially healthy people, leukoplakia in these locations was detected on average in 1.39% of cases (from 0.12% to 33. 33%) [1]. According to Y. Huang et al., the incidence of leukoplakia of the oral mucosa in the world is 4.1% [2].

This disease can be caused by exogenous and endogenous factors. Exogenous factors include smoking, eating spicy or sour foods, excessively hot food. alcoholic beverages; chronic mechanical damage to the oral cavity, etc. Endogenous factors include gastrointestinal diseases; hypovitaminosis A; diseases associated with metabolic disorders; chronic inflammatory processes in the oral cavity; neurodystrophic changes in mucous membranes [3].

According to A.L. Mashkilleison's classification, a distinction is made between flat, verrucous, erosive-ulcerative, mild leukoplakia and Tappeiner's leukoplakia (nicotine stomatitis), which have different malignancy potentials. According to H.M. Chen et al., the frequency of malignancy of the flat form varies from 1% to 7%, while for the verrucous form this figure increases significantly and averages 18-47% [4]. Based on an analysis of data on 16,604 patients, J. M. Aguirre-Urizar et al. report that this indicator, depending on the form of the disease, decreases from 1.1% to 40.8% [5].

Treatment of the oral mucosa leukoplakia depends on the clinical form of the disease, area of damage and a number of other reasons [6]. Thus, for a flat form, mainly conservative treatment is used, leading to regression of pathological foci. In this case, the termination of irritating factors is a prerequisite. Local treatment includes sanitation of the oral cavity, reasonable and competent provision of dental care. It is recommended to prescribe multivitamin complexes of vitamins A and E in the form of solutions taken orally and application. At the same time, the incidence of incurable diseases remains high, which requires the search for new treatment approaches based on fundamentally different mechanisms of action on pathological foci of leukoplakia.

One of the most relevant and effective methods of treating patients with precancerous diseases of the oral cavity is photodynamic therapy (PDT), which is a method of local activation of a special drug, a photosensitizer (PS), selectively accumulated in pathologically altered tissue, with visible red light. Subsequently, in the presence of tissue oxygen, photochemical reactions are initiated with the formation of reactive oxygen species (singlet oxygen, superoxide anion, etc.), initiating oxidative stress syndrome in tissues that have accumulated PS, and their subsequent death through apoptosis, necrosis, autophagy and paraptosis depending on a number of factors [9, 10, 11]. In the case of PS accumulation in the endothelium of blood vessels, subsequent exposure to laser radiation leads to the formation of blood clots, vasoconstriction, vascular stasis and, consequently, the development of ischemic necrosis [12, 13]. An important role in tissue photodamage is played by the activation of the immune system, which manifests itself in the infiltration of pathologically altered tissues by neutrophils and macrophages in response to irradiation and is accompanied by the release of cytokines and inflammatory mediators. Activation of T lymphocytes leads to the destruction of the remaining pathologically altered cells [12, 13].

In recent years, the world has gained experience in using PDT with application and injection forms of various PS (5-aminolevulinic acid (5-ALA), chlorins, etc.) for patients with leukoplakia SOP. The results of both pilot studies on small samples of patients and systematic reviews of the literature involving hundreds of patients have been published. The use of PDT shows good tolerability, fairly high rates of complete regressions (from 22.58% to 100%) with a relapse rate (from 0% to 60%) [14, 15, 16].

All of the above makes further research in the field of application of laser technologies in the treatment of precancerous diseases of the oral mucosa relevant and promising.

The purpose of this research was to study the tolerability and effectiveness of the PDT method with chlorine PS photolon for patients with leukoplakia of the oral mucosa.

Materials and Methods

Patients

The retrospective study included 223 patients with a morphologically verified diagnosis of «Leukoplakia of the oral mucosa», who received treatment at the department of hyperthermia and photodynamic therapy (N.N. Alexandrov National Cancer Center pf Belarus, Republic of Belarus) from 2013 to 2023. According to clinical forms, the flat form predominated – 211 (94.6%) patients; verrucous form – 12 (5.4%) patients. Men made up 151 observations (67.7%) of the total cohort, women – 72 (32.3%). Age ranged from 28 to 76 years, average – 51.9±8.9 years.

The criteria for inclusion of patients in the study were:

- age 18 or more;
- clinically and morphologically verified diagnosis of «leukoplakia»;
- informed consent of the patient to undergo treatment using the PDT method.

Exclusion criteria were:

- morphologically verified cancer of the oral cavity;
- presence of contraindications for intravenous administration of PS;
- absence of severe concomitant pathology of the cardiovascular system, liver and kidneys in the stage of decompensation;
- patient's refusal to undergo PDT treatment.

The diagnosis was established on the basis of clinical and instrumental examination and morphological verification. When verifying the process, cytological or histological examination of pathologically altered tissues was used.

Ethical aspects

The study was designed in accordance with the Declaration of Helsinki (1975, revised 64th WMA General Assembly, Fortaleza, Brazil, 2013). All patients were informed about the PDT method used by the PS, possible adverse reactions, the need to adhere to the light regime in the first 3-4 days after treatment, the timing of follow-up visits for recovery, alternative treatment options, and gave written consent to the use of this treatment method.

Taking into account the fact that the treatment of patients with leukoplakia of the oral mucosa is not included in the National standards for the treatment of this pathology in the Republic of Belarus and in section 4.1 «Indications for use» of the General characteristics of the drug photolon (Order of the Ministry of Health of the Republic of Belarus dated November 28, 2022 № 1659), inclusion of patients in this study was carried out on the basis of the Instructions for Use «Photodynamic (fluorescent) diagnosis and therapy of cancer and precancerous diseases of the mucous membrane of the oropharyngeal zone» (Developer institution – N.N. Alexandrov National Cancer Center of Belarus, authors: Istomin Yu.P., Chalov V.N., Yaskevich L.S., Neiman O.I.), approved by the Ministry of Health of the Republic of Belarus, dated December 23, 2011, № 112-1111).

Photosensitizer

In the study, chlorin e6 was used as a pharmaceutical substance produced (RUE «Belmedpreparaty», Republic of Belarus, registration certificate № 16/11/886 dated November 8, 2016), which is a complex of trisodium salt of chlorine e6 with povidone with a K-value of 17. The drug diluted in 200 ml of 0.9% sodium chloride solution and administered intravenously over 30 minutes at a dosage of 1.7 to 2.5 mg/kg body weight, in a darkened room.

Photodynamic therapy

Before and after every PDT session, the radiation power at the output of the light guide was controlled using a production device («Solar», Republic of Belarus). The PDT session was carried out 2-2.5 hours after the end of the PS infusion using a semiconductor laser device «UPL PDT», produced («Lemt BelOMO», Republic of Belarus) with $\lambda = 665\pm5$ nm. To supply radiation, a fiber-optic light guide with a lens diffuser for external irradiation was used. The laser radiation dose density varied from 25 to 100 J/cm^2, the laser radiation power density varied from 0.07 to 0.32 W/cm^2, and the duration of one irradiation field varied from 2 to 13.5 minutes, depending on its linear dimensions. The number of irradiation sessions ranged from 1 to 6 depending on the area of pathological foci.

Depending on the location, area and clinical form of the disease, two types of radiation were used: in the first case, if the size of the pathological focus did not exceed 1 cm, the distal end of the light guide was brought into direct contact with the surface of the oral cavity; in the second case, if the size of the pathological lesion exceeded 1 cm, the radiation was applied remotely, perpendicular to its surface, and, if necessary, the entire surface of the formation was irradiated with several fields. The irradiation zone included pathologically altered tissues and an area of visually normal tissues at a distance of at

least 3-5 mm from the border of the pathology. Screening of surrounding intact tissue was not performed [17]. For pain relief, 15-20 minutes before the start of treatment, all patients were intramuscularly injected with ketorolac (4 ml); in some cases, local anesthesia was performed with lidocaine 2% in the form of a spray – 2-5 ml [3, 18].

Tolerability of treatment

The frequency and severity of adverse events when using PDT were assessed within 1-30 days after treatment using the CTCAE scale (version 4.03, dated 2010).

Treatment effectiveness

Control examinations were carried out after 7 days; 1, 3 and 6 months after treatment. The immediate results of treatment of patients with leukoplakia of the oral mucosa were assessed based on WHO criteria [3]:

- complete regression (CR) – complete disappearance of all manifestations of the disease, established both visually and by palpation and confirmed by negative results of a morphological study within 1-3 months after treatment;
- partial regression (PR) – a decrease in the pathological focus (or formations) by 50% or more, or when, in the clinically complete absence of pathology, tumor cells are revealed during a morphological study;
- tumor reduction by less than 50% or no change in tumor size was regarded as no effect (NE).

Results

No serious adverse reactions (anaphylactic shock, bronchospasm, drop in blood pressure, etc.) corresponding to CTCAE (grades III-IV) associated with PS infusion were recorded. There were also no symptoms of cutaneous phototoxicity (skin itching, hyperemia, conjunctivitis). In isolated cases, in the early post-procedural period (1-5 days after the administration of PS and the PDT session) a low-grade fever (+37.0-37.7°C) was noted, which corresponds to CTCAE (grades I-II). On days 1-3 after treatment, the formation of photo-induced hemorrhagic necrosis with exudation and swelling of surrounding tissues, followed by the formation of fibrinous deposits, was noted at the irradiation site. In a number of observations, patients experienced swelling of the soft tissues of the face of varying severity, which disappeared on its own after 1-5 days.

Within 2-8 days after treatment, patients noted moderate pain in the affected area, which was well relieved by the administration of non-narcotic analgesics and sedatives (CTCAE, grade I-II).

During control examinations up to 3 months after irradiation, the frequency of complete regressions in the general cohort of patients was 95.4% of observations (213 patients), partial regressions – 3.4% of observations (8 patients). An objective response rate of 98.8% was observed. In 1.2% of observations (2 patients), there was no effect on the treatment.

The distribution of PDT effects depending on the clinical form of the disease is presented in Table 1.

The period of observation of patients varies from 3 to 120 months (average 66 months). The frequency of disease relapses during this period was 9%.

Patients with partial regression and identified relapse of the disease were treated with repeated PDT sessions.

In connection with the development of necrosis of irradiated tissues, in order to prevent purulent-septic complications, it is necessary to constantly treat the COP with solutions of antiseptic drugs (furacilin, anti-inflammatory herbal preparations, etc.). Starting from 3-4 days after the PDT session, patients underwent applications with solcoseryl, Metrogyl Denta gel, and sea buckthorn oil in order to stimulate regenerative processes. Final epithelization of wound defects occurred, on average, 3-6 weeks after photoirradiation. In the overwhelming majority of observations, good

Таблица 1
Эффективность ФДТ с хлорином е6 у больных с различными клиническими формами лейкоплакии слизистой оболочки полости рта

Table 1
Efficacy of PDT with chlorin e6 in patients with various clinical forms of leukoplakia of the oral mucosa

Клиническая форма лейкоплакии Clinical form of leukoplakia	Полная регрессия, число пациентов и % Full regression, number of patients and %		Частичная регрессия, число пациентов и % Partial regression, number of patients and %		Отсутствие эффекта, число пациентов и % No effect, number of patients and %		Объективный ответ*, число пациентов и % Objective answer*, number of patients and %	
Плоская Flat	205	97,1	6	2,9	0	0	211	100
Веррукозная Verrucous	7	58,3	3	25	2	16,7	10	83,3

*Объективный ответ включает полные и частичные регрессии заболевания
*Objective response includes complete and partial regression of the disease

cosmetic results were achieved: the wound surface was epithelialized with minimal formation of scar tissue.

The results obtained in the study are illustrated by the following clinical examples (Fig. 1, 2, 3, 4 and 5).

Discussion

Leukoplakia of the oral mucosa is a precancerous disease, the treatment of which directly depends on a number of factors: the clinical form of the disease, the area and extent of pathologically altered tissues, the nature of previous treatment. In the treatment of a flat form, a conservative approach is relevant, namely, sanitation of the oral cavity, rational and competent provision of dental care. It is recommended to prescribe multivitamin complexes of vitamins A and E in the form of solutions taken orally and application. In the case of verrucous and erosive-ulcerative forms, surgical tactics predominate: pathologically altered foci are removed

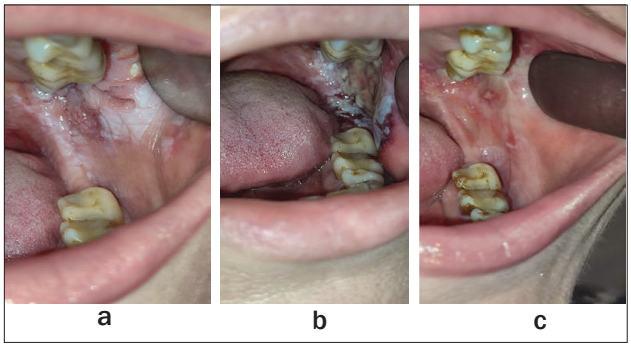

Рис. 3. Лейкоплакия щеки, плоская форма
a – состояние до ФДТ;
b – локальный статус через 3 сут после ФДТ (экспозиционная доза – 100 Дж/см^2);
c – локальный статус через 3 мес после ФДТ (достигнута полная регрессия)
Fig. 3. Leukoplakia cheeks, flat shape
a – state before PDT;
b – local status 3 days after PDT (exposure dose – 100 J/cm^2);
c – local status 3 months after PDT (full regression achieved).

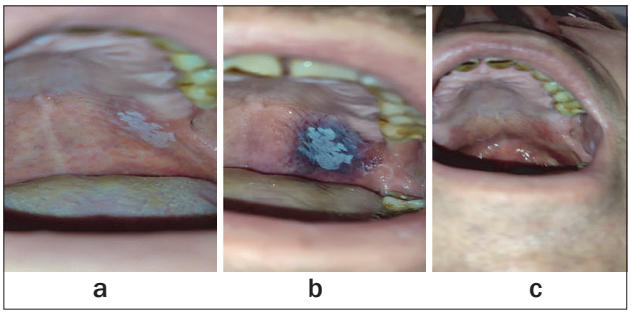

Рис. 1. Лейкоплакия мягкого неба, плоская форма
a – состояние до ФДТ;
b – локальный статус через 7 сут после ФДТ (экспозиционная доза – 100 Дж/см^2);
c – локальный статус через 3 мес после ФДТ (достигнута полная регрессия).
Fig. 1. Leukoplakia of the soft palate, flat form
a – state before PDT;
b – local status 7 days after PDT (exposure dose – 100 J/cm^2);
c – local status 3 months after PDT (complete regression achieved).

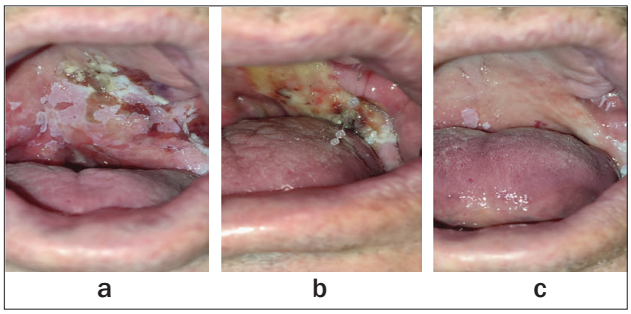

Рис. 4. Лейкоплакия мягкого неба, плоская форма
a – состояние до ФДТ;
b – локальный статус через 7 сут после ФДТ (экспозиционная доза – 100 Дж/см^2);
c – локальный статус через 3 мес после ФДТ (достигнута частичная регрессия; пациент продолжает лечение методом ФДТ).
Fig. 4. Leukoplakia of the soft palate, flat form
a – state before PDT;
b – local status 7 days after PDT (exposure dose – 100 J/cm^2);
c – local status 3 months after PDT (partial regression has been achieved; the patient continues treatment with PDT).

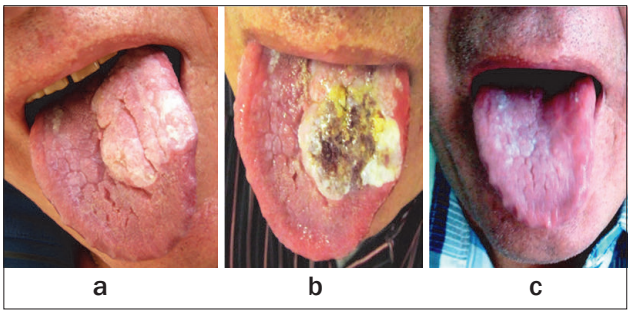

Рис. 2. Лейкоплакия тела языка, веррукозная форма
a – состояние до ФДТ;
b – локальный статус через 7 сут после ФДТ (экспозиционная доза – 100 Дж/см^2);
c – локальный статус через 3 мес после 3 сеансов ФДТ (достигнута полная регрессия)
Fig. 2. Leukoplakia of the body of the tongue, verrucous form
a – state before PDT;
b – local status 7 days after PDT (exposure dose – 100 J/cm^2);
c – local status 3 months after 3 PDT sessions (full regression achieved).

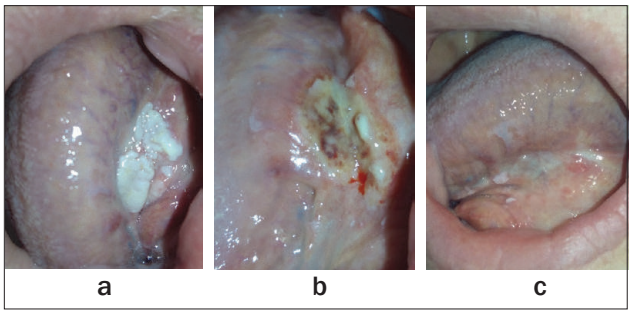

Рис. 5. Лейкоплакия языка, плоская форма
a – состояние до ФДТ;
b – локальный статус через 5 сут после ФДТ (экспозиционная доза – 100 Дж/см^2);
c – локальный статус через 3 мес после ФДТ (достигнута полная регрессия).
Fig. 5. Leukoplakia of the tongue, flat shape
a – state before PDT;
b – local status 5 days after PDT (exposure dose – 100 J/cm^2);
c – local status 3 months after PDT (complete regression achieved).

using laser Nd:YAG or CO_2 ablation of tissues affected by leukoplakia. Despite the variety of ways to treat this disease, the incidence of recurrence of the disease remains high. For example, in a study by J.M. White et al. (1998) in a comparative aspect, the long-term results of the use of Nd:YAG and CO2 in the treatment of 39 patients with oral leukoplakia were studied. According to the authors, the recurrence rate of the disease with the use of these therapeutic options was 27% and 24%, respectively [19]. W. Gushiken de Campos et al. (2022) presented the results of the use of CO_2 laser therapy in 37 patients with oral leukoplakia, who had an average follow-up period of 38.2 months in 35.1% of cases with a recurrence of the disease [20]. The presumed reasons for the high percentage of recurrences in patients with this pathology using conservative approaches, surgical tactics and laser methods are exclusively mechanical impact on leukoplakia, multiple nature of the lesion and possible presence of clinically undetectable foci of the disease. All of the above requires the search for new approaches to treatment based on fundamentally different mechanisms of influence on pathological foci of leukoplakia of the oral mucosa.

One of these methods is the PDT method, which has proven to be a well-tolerated and effective option for the therapeutic treatment of precancerous diseases of the oral mucosa. The effectiveness of the method directly depends on the clinical form of the disease, the nature of the lesion (single or multiple foci), previous treatment, etc. In our retrospective study based on the analysis of the treatment results of 223 patients with primary oral mucosal leukoplakia, the frequency of complete and partial regressions for flat and verrucose forms was 97.1% and 58.3%, as well as 2.9% and 25%, respectively. The recurrence rate of the disease for the follow-up period from 3 to 120 months was 9%. In our opinion, the different efficacy of PDT in patients with flat and verrucous forms of leukoplakia is associated with both the peculiarities of PS accumulation in pathologically altered tissues (a high concentration of the drug in the flat form) and, potentially, a more pronounced exophytic component in the verrucous form, which does not allow laser radiation to penetrate sufficiently to the entire depth of the focus leukoplakia. Thus, the depth of penetration of laser radiation with λ=660±5 nm, specific for chlorin e6, into biological tissues is on average 7 mm.

In recent years, the world has accumulated experience in the use of PDT with application and injection forms of various PS (5-ALA, chlorines, etc.) in several thousand patients with leukoplakia of the oral mucosa. Various teams of authors from large research centers and clinics in Europe, Southeast Asia, and the USA have published both the results of pilot studies on small samples of patients and systematic literature reviews involving hundreds of patients. In the publications presented below, a lower percentage of objective responses to treatment with PDT was primarily associated with the use of application forms of PS (5-ALA), the local application of which to pathological foci did not allow achieving a higher concentration of PS compared to intravenous administration, which affected the effectiveness of PDT. It is also worth mentioning the fact that the distribution of PS, as a rule, is not homogeneous during application due to the anatomical features of the structure of the oral mucosa. This is due to the presence of crypts, folds, various vascularization, keratinization of the epithelium or its absence. And, of course, an important aspect is λ=630 nm, which makes it possible to activate 5-ALA, which has accumulated in pathologically altered tissues. In this case, active photodynamic exposure is possible to a depth of 1 to 1.5-2 mm, which significantly reduces the therapeutic possibilities of PDT with this PS.

In the case of photofrin II or its analogues (λ=629-635 nm), this indicator is, on average, 2-3 mm. These PS are used for PDT for oral mucosal leukoplakia in injectable forms. Nevertheless, it is the insignificant depth of effective photodynamic impact that leads, in some cases, to an increase in the frequency of local recurrences of the disease and partial regressions.

Selected results of the use of PDT in the treatment of precancerous diseases of the oral mucosa with various PS, published as part of systematic reviews of the literature, are presented in Table 2.

As the results of numerous foreign studies show, the PDT method is an effective option for organ-preserving treatment of patients with leukoplakia of the oral mucosa, which is confirmed by a fairly high frequency of objective responses (according to various data, from 22.58% to 100%) to the treatment [14, 15, 16, 21, 22]. However, despite the optimistic immediate the frequency of registered recurrences of the disease remains high (up to 60%), which requires the search for new and further optimization of existing treatment regimens for this category of patients using the most effective PDT parameters. For this purpose, it is advisable to conduct multicenter randomized clinical trials on large samples of patients.

Conclusion

It is a well-known fact that the main advantages of PDT in comparison with traditional methods of treatment of precancerous diseases of the oral mucosa are minimal toxicity to normal tissues surrounding pathological foci due to the selective accumulation of PS in the tissues of leukoplakia, a low risk of serious adverse reactions, the possibility of an outpatient session, the possibility of repeated treatment in case of large area of lesion, good cosmetic results [23, 24]. These positive aspects of PDT make it possible not only to ensure the effective use of the method, but also to significantly improve the quality of life of the treated patients.

Таблица 2
Эффективность ФДТ у больных с предраковыми заболеваниями слизистой оболочки полости рта
Table 2
The effectiveness of PDT in patients with precancerous diseases of the oral mucosa

Авторы, год, страна, ссылка Authors, year, country, link	Число исследований, число пациентов Number of studies, number of patients	Клинические диагнозы Clinical diagnosis	ФС PS	Параметры ФДТ PDT parameters	Частота ПР, ЧР и ОЭ, % Frequency of CR, PR and NR, %	Частота рецидивов, % Relapse rate, %
Vohra F., 2015, США, [14] Vohra F., 2015, USA, [14]	13 5-147 13 5-147	Лейкоплакия, эритроплакия, эритро-лейкоплакия, веррукозная гиперплазия Leukoplakia, erythroplakia, erythro-leukoplakia, verrucous hyperplasia	5-АЛК, хлорин е6, фоскан, фотофрин II 5-ALA, chlorine e6, foscan, photofrin II	λ=585-660 нм 0,1-0,15 Вт/см^2 1-16,5 мин. λ=585-660 nm 0.1-0.15 W/cm^2 1-16.5 min.	27-100 5-50 0-25 27-100 5-50 0-25	>36 >36
Gondivkar S.M., 2018, Индия, [15] Gondivkar S.M., 2018, India, [15]	26 2-147 26 2-147	Лейкоплакия, эритроплакия, эритро-лейкоплакия, веррукозная дисплазия Leukoplakia, erythroplakia, erythro-leukoplakia, verrucous dysplasia	5-АЛК, хлорин е6, фотосан, гемато-порфирин, фотофрин II 5-ALA, chlorine e6, photosan, hemato-porphirin, photofrin II	λ=585-652 нм 0,05-0,5 Вт/см^2 1-143 мин. λ=585-652 nm 0.05-0.5 W/cm^2 1-143 min.	22,58-100 4-66 0-38,7 22.58-100 4-66 0-38.7	- -
Li Y., 2019, Китай, [16] Li Y., 2019, China, [16]	16 352 16 352	Лейкоплакия, Дисплазия Leukoplakia, dysplasia	5-АЛК, метиленовый синий, хлорин е6 5-ALA, methylene blue, chlorine e6	λ=420-660 нм 0,1-0,15 Вт/см^2 1-16,5 мин. λ=420-660 nm 0.1-0.15 W/cm^2 1-16.5 min.	32,9 43,2 - 32.9 43.2 -	0-60 0-60

*ФС – фотосенсибилизатор, ФДТ – фотодинамическая терапия, ПР – полная регрессия, ЧР – частичная регрессия, ОЭ – отсутствие эффекта
*PS – photosensitizer, PDT – photodynamic therapy, CR – complete regression, PR – partial regression, NR – no response

As a result, summarizing our own data, demonstrating that the method is well tolerated (no serious adverse reactions of III-IV degree and minimal risk of developing stage I-II reactions according to the CTCAE classification), a high frequency of objective responses to the treatment (100% for the flat form and 83.3% for the verrucous form) and a low risk of disease recurrence (9%), PDT with chlorin e6 can be recommended as a highly effective alternative standard methods of treatment of patients with leukoplakia of the oral mucosa, as well as a way to prevent the development of malignant neoplasms of this localization.

REFERENCES

1. Zhang C., Li B., Zeng X., et al. The global prevalence of oral leukoplakia: a systematic review and meta-analysis from 1996 to 2022. *BMC Oral Health*, 2023, Vol. 23(1), pp. 645. doi: 10.1186/s12903-023-03342-y.
2. Huang Y., Zhang Q., Guo Z. Potential noninvasive biomarkers for the malignant transformation of oral leukoplakia: A systematic review and meta-analysis. *Cancer Med*, 2023, Vol. 12(13), pp. 14718-14730. doi: 10.1002/cam4.6095.
3. Yu.P. Istomin, Artsemyeva T.P., Tzerkovsky D.A. Photodynamic therapy with photosensitizer photolon for oral leukoplakia. *Biomedical Photonics*, 2016, Vol. 5(2), pp. 13-20. doi:10.24931/2413-9432-2016-5-2-13-20.

ЛИТЕРАТУРА

1. Zhang C., Li B., Zeng X., et al. The global prevalence of oral leukoplakia: a systematic review and meta-analysis from 1996 to 2022 // BMC Oral Health. – 2023. – Vol. 23(1). – P. 645. doi: 10.1186/s12903-023-03342-y.
2. Huang Y., Zhang Q., Guo Z. Potential noninvasive biomarkers for the malignant transformation of oral leukoplakia: A systematic review and meta-analysis // Cancer Med. – 2023. – Vol. 12(13). – P. 14718-14730. doi: 10.1002/cam4.6095.
3. Istomin Yu.P., Artsemyeva T.P., Tzerkovsky D.A. Photodynamic therapy with photosensitizer photolon for oral leukoplakia // Biomedical Photonics. – 2016. – Vol. 5(2). – P. 13-20. (in Russ.). doi:10.24931/2413-9432-2016-5-2-13-20.

4. Chen H.M., Yu C.H., Tsai T., et al. Topical 5-aminolevulinic acidmediated photodynamic therapy for oral verrucous hyperplasia, oral leukoplakia and oral erythroleukoplakia. *Photodiagnosis Photodyn Ther*, 2007, Vol. 4, pp. 44-52. doi: 10.1016/j.pdpdt.2006.11.003.
5. Aguirre-Uzizar J.M., Lafuente-Ibanez de Mendoza I., Warnakulasuriva S. Malignant transformation of oral leukoplakia: Systematic review and meta-analysis of the last 5 years. *Oral Dis*, 2021, Vol. 27(8), pp. 1881-1895. doi: 10.1111/odi.13810.
6. Lodi G., Franchini R., Warnakulasuriva S., et al. Interventions for treating oral leukoplakia to prevent oral cancer. *Cochrane Database Syst Rev*, 2016, Vol. 7(7), CD001829. doi: 10.1002/14651858.CD001829.pub4.
7. Van der Wall I. Oral leukoplakia, the ongoing discussion on definition and terminology. *Med Oral Patol Oral Cir Bucal*, 2015, Vol. 20(6), pp. 685-692. doi: 10.4317/medoral.21007.
8. Proano-Haro A., Bagan J.V., Bagan J.V. Recurrences following treatment of proliferative verrucous leukoplakia: A systematic review and meta-analysis. *J Oral Pathol Med*, 2021, Vol. 50(8), pp. 820-828. doi: 10.1111/jop.13178.
9. Kessel D. Photodynamic therapy: apoptosis, paraptosis and beyond. *Apoptosis*, 2020, Vol. 25(9-10), pp. 611–615. doi: 10.1007/s10495-020-01634-0.
10. Niculescu A.G., Grumezescu A.M. Photodynamic therapy – an up-to-date review. *Appl Sci*, 2021, Vol. 11, e3626. doi: 10.3390/app11083626.
11. Reshetov I.V., Korenev S.V., Romanko Yu.S. Forms of cell death and targets at photodynamic therapy. *Siberian J Oncol*, 2022, Vol. 21(5), pp. 149-154. (In Russ.) doi:10.21294/1814-4861-2022-21-5-149-154.
12. Uzdensky, A.B. Cellular and molecular mechanisms of photodynamic therapy / A.B. Uzdensky. – Saint-Petersburg : Science, 2010. – 327 p. (in Russ.).
13. Abdel-Kader, M. H. Photodynamic therapy. From theory to application / M. H. Abdel-Kader. – Verlag, Berlin, Heidelberg : Springer, 2014. – P. 312.
14. Vohra F., Al-Kheraif A.A., Qadri T., et al. Efficacy of photodynamic therapy in the management of oral premalignant lesions. A systematic review. *Photodiagnosis Photodyn Ther*, 2015, Vol. 12(1), pp. 150-159. doi: 10.1016/j.pdpdt.2014.10.001.
15. Gondiykar S.M., Ramchandra Gadbail A., Choudhary M.C., et al. Photodynamic treatment outcomes of potentially-malignant lesions and malignancies of the head and neck region: A systematic review. *J Investig Clin Dent*, 2018, Vol. 9(1), e12270. doi: 10.1111/jicd.12270.
16. Li Y., Wang B., Zheng S., et al. Photodynamic therapy in the treatment of oral leukoplakia: A systematic review. *Photodiagnosis Photodyn Ther*, 2019, Vol. 25, pp. 17-22. doi: 10.1016/j.pdpdt.2018.10.023.
17. Neiman O., Yaskevich L., Istomin Y., et al. Photodynamic therapy with photolon at the treatment of pretumour diseases of the oral-pharungeal zone: results of treatments. *Oncol. J*, 2011, Vol. 5(1), pp. 77-80 (in Russ.).
18. Tserkovsky D.A., Artsemyeva T.P. Photodynamic therapy for oral mucous membrane idiopathic leukoplakia. *Healthcare*, 2019, Vol. 11, pp. 36-40 (in Russ.).
19. White J.M., Chaundhry S.I., Kudler J.J., et al. Nd:YAG and CO2 laser therapy of oral mucosal lesions. *J Clin Laser Med Surg*, 1998, Vol. 19, pp. 299-304. doi: 10.1089/clm.1998.16.299.
20. Gushiken de Campos W., Esteves C.V., de Barros Gallo C., et al. Treatment of oral leukoplakia with CO2 laser (10,600 nm): analysis of 37 cases. *Braz Oral Res*, 2022, Vol. 36, e014. doi: 10.1590/1807-3107bor-2022.vol36.0014.
21. Jing Y., Shu R., Wu T., et al. Clinical efficacy of photodynamic therapy of oral potentially malignant disorder. *Photodiagnosis Photodyn Ther*, 2024, Vol. 46, pp. 104026. doi: 10.1016/j.pdpdt.2024.104026.
22. Wang Y., Tang H., Wang K., et al. Clinical evaluation of photodynamic therapy for oral leukoplakia: a retrospective study of 50 patients. *BMC Oral Health*, 2024, Vol. 24(1), pp. 9. doi: 10.1186/s12903-023-03791-5.
23. Filonenko E.V. Clinical implementation and scientific development of photodynamic therapy in Russia in 2010-2020. *Biomedical Photonics*, 2021, Vol. 10(4), pp. 4-22 (in Russ.) https://doi.org/10.24931/2413-9432-2021-9-4-4-22.
24. Panaseykin Y.A., Kapinus V.N., Filonenko E.V., et al. Photodynamic therapy treatment of oral cavity cancer in patients with comorbidities. *Biomedical Photonics*, 2022, Vol. 11(4), pp. 19-24 (in Russ.). https://doi.org/10.24931/2413-9432-2022-11-4-19-24.

4. Chen H.M., Yu C.H., Tsai T., et al. Topical 5-aminolevulinic acidmediated photodynamic therapy for oral verrucous hyperplasia, oral leukoplakia and oral erythroleukoplakia // Photodiagnosis Photodyn Ther. – 2007. – Vol. 4. – P. 44-52. doi: 10.1016/j.pdpdt.2006.11.003.
5. Aguirre-Uzizar J.M., Lafuente-Ibanez de Mendoza I., Warnakulasuriva S. Malignant transformation of oral leukoplakia: Systematic review and meta-analysis of the last 5 years // Oral Dis. – 2021. – Vol. 27(8). – P. 1881-1895. doi: 10.1111/odi.13810.
6. Lodi G., Franchini R., Warnakulasuriva S., et al. Interventions for treating oral leukoplakia to prevent oral cancer // Cochrane Database Syst Rev. – 2016. – Vol. 7(7). – CD001829. doi: 10.1002/14651858.CD001829.pub4.
7. Van der Wall I. Oral leukoplakia, the ongoing discussion on definition and terminology // Med Oral Patol Oral Cir Bucal. – 2015. – Vol. 20(6). – P. 685-692. doi: 10.4317/medoral.21007.
8. Proano-Haro A., Bagan J.V., Bagan J.V. Recurrences following treatment of proliferative verrucous leukoplakia: A systematic review and meta-analysis // J Oral Pathol Med. – 2021. – Vol. 50(8). – P. 820-828. doi: 10.1111/jop.13178.
9. Kessel D. Photodynamic therapy: apoptosis, paraptosis and beyond // Apoptosis. – 2020. – Vol. 25(9-10). – P. 611-615. doi: 10.1007/s10495-020-01634-0.
10. Niculescu A.G., Grumezescu A.M. Photodynamic therapy – an up-to-date review // Appl Sci. – 2021. – Vol. 11. – e3626. doi: 10.3390/app11083626.
11. Reshetov I.V., Korenev S.V., Romanko Yu.S. Forms of cell death and targets at photodynamic therapy // Siberian J Oncol. – 2022. – Vol. 21(5). – P. 149-154. (In Russ.) doi:10.21294/1814-4861-2022-21-5-149-154.
12. Узденский, А.Б. Клеточно-молекулярные механизмы фотодинамической терапии / А.Б. Узденский. – Санкт-Петербург : Наука, 2010. – 327 с.
13. Abdel-Kader, M. H. Photodynamic therapy. From theory to application / M. H. Abdel-Kader. – Verlag, Berlin, Heidelberg : Springer, 2014. – P. 312.
14. Vohra F., Al-Kheraif A.A., Qadri T., et al. Efficacy of photodynamic therapy in the management of oral premalignant lesions. A systematic review // Photodiagnosis Photodyn Ther. – 2015. – Vol. 12(1). – P. 150-159. doi: 10.1016/j.pdpdt.2014.10.001.
15. Gondiykar S.M., Ramchandra Gadbail A., Choudhary M.C., et al. Photodynamic treatment outcomes of potentially-malignant lesions and malignancies of the head and neck region: A systematic review // J Investig Clin Dent. – 2018. – Vol. 9(1). – e12270. doi: 10.1111/jicd.12270.
16. Li Y., Wang B., Zheng S., et al. Photodynamic therapy in the treatment of oral leukoplakia: A systematic review // Photodiagnosis Photodyn Ther. – 2019. – Vol. 25. – P. 17-22. doi: 10.1016/j.pdpdt.2018.10.023.
17. Нейман О.И., Яськевич Л.С., Истомин Ю.П., и др. Фотодинамическая терапия с фотолоном предраковых заболеваний слизистой оболочки орофарингеальной зоны: результаты лечения // Онкол журн. – 2011. – Т. 5, №. 1. – С. 77-80.
18. Церковский Д.А., Артемьева Т.П. Фотодинамическая терапия идиопатической формы лейкоплакии слизистой оболочки полости рта // Здравоохранение. – 2019. – № 11. – С. 36-40.
19. White J.M., Chaundhry S.I., Kudler J.J., et al. Nd:YAG and CO_2 laser therapy of oral mucosal lesions // J Clin Laser Med Surg. – 1998. – Vol. 19. – P. 299-304. doi: 10.1089/clm.1998.16.299.
20. Gushiken de Campos W., Esteves C.V., de Barros Gallo C., et al. Treatment of oral leukoplakia with CO2 laser (10,600 nm): analysis of 37 cases // Braz Oral Res. – 2022. – Vol. 36. – e014. doi: 10.1590/1807-3107bor-2022.vol36.0014.
21. Jing Y., Shu R., Wu T., et al. Clinical efficacy of photodynamic therapy of oral potentially malignant disorder // Photodiagnosis Photodyn Ther. – 2024. – Vol. 46. – P. 104026. doi: 10.1016/j.pdpdt.2024.104026.
22. Wang Y., Tang H., Wang K., et al. Clinical evaluation of photodynamic therapy for oral leukoplakia: a retrospective study of 50 patients // BMC Oral Health. – 2024. – Vol. 24(1). – P. 9. doi: 10.1186/s12903-023-03791-5.
23. Filonenko E.V. Clinical implementation and scientific development of photodynamic therapy in Russia in 2010-2020 // Biomedical Photonics. – 2021. – Vol. 10(4). – P. 4-22 (in Russ.) https://doi.org/10.24931/2413-9432-2021-9-4-4-22.
24. Panaseykin Y.A., Kapinus V.N., Filonenko E.V., et al. Photodynamic therapy treatment of oral cavity cancer in patients with comorbidities // Biomedical Photonics. – 2022. – Vol. 11(4). – P. 19-24. https://doi.org/10.24931/2413-9432-2022-11-4-19-24.