

PHOTODYNAMIC THERAPY WITH PHOTSENSITIZER PHOTOLON FOR ORAL LEUKOPLAKIA

Istomin Yu.P., Artemyeva T.P., Tzerkovsky D.A.

N.N. Alexandrov National Cancer Centre of Belarus, Lesnoy, Republic of Belarus

Abstract

The objective – to assess tolerability, safety and immediate results of treatment of patients with oral leukoplakia using photodynamic therapy (PDT) with a photosensitizer photolon. The study included 40 patients (7 men, 33 women) with morphologically verified leukoplakia of the oral mucosa. The average age – 55 ± 14 years. Number of treated foci – 109 (1 to 8). Photolon was administered intravenously at doses of 1.7-2.5 mg/kg. Photoirradiation («UPL PDT», Belarus, $\lambda = 660 \pm 5$ nm) was performed 2.5-3 h after administration: light exposure dose varied from 25 to 100 J/cm², power density of 0.07 to 0.32 W/cm², the duration of one field photoirradiation – from 2 to 13.5 min and according to its linear dimensions. The effectiveness of treatment was assessed 1-2 months after PDT by clinical data. Complete regression of foci recorded in 95% of cases (n=38), partial – in 5% (n=2). The follow-up period varied from 1 to 30 months. Full-epithelialization of the wound defect occurred within the period of 3-6 weeks after treatment. Photodynamic therapy may be recommended for patients with circumscribed or widespread oral leukoplakia as a simple, well-tolerated and effective option.

Keywords: photodynamic therapy, photolon, oral leukoplakia.

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Contacts: Tzerkovsky D.A., e-mail: tzerkovsky@mail.ru

Introduction

Leukoplakia is a chronic mucous membrane lesion characterized by keratinization of the surface epithelium with varying severity [1].

The main reasons for the development of oral mucosa leukoplakia are exogenous stimuli:

- smoking, having both chemical and thermal effect;
- spices, spicy and sour dishes, too hot food, alcoholic beverages;
- side effects of the drugs;
- continuous mechanical trauma to the mucous membrane of the mouth with a sharp edge of the tooth, unpolished filling, or poor-quality orthopedic prosthesis;
- galvanism of fillings, dentures, and other metal structures in the oral cavity.

Endogenous risk factors include:

- gastrointestinal disease;
- vitamin deficiencies (vitamin A deficiency);
- diseases associated with metabolic disorders (diabetes);
- anemia;
- chronic inflammatory processes in the oral cavity;
- neurodystrophic mucous alterations (upon stomatitis, gingivitis);
- HIV infection;
- genetic predisposition to dyskeratosis.

The development of this pathology is typical for older persons and refers to precancerous diseases with varying degrees of potential malignancy, depending on the disease form and process location from 6-7% to 15-20% [2].

The following clinical forms of leukoplakia are distinguished [4]:

- flat;
- verrucous (warty and patchy);
- erosive and ulcerative;
- Tappeiner leukoplakia (nicotine stomatitis);
- soft (white spongy Pashkov nevus).

Flat leukoplakia is the most common form of the disease. According to H.M. Chen, the frequency of the flat form malignancy is 1-7% [3]. The clinical course of this form is characterized by the absence of objective sensations. The sense of tightness and burning of mucous membranes, as well as taste impairment in the event of large foci on the tongue, are noted.

The verrucous form is developed against the background of flat leukoplakia and occurs in two clinical forms, plaque and warty. The main clinical sign of the first one is pearl-white plaque, towering over the mucosal surface, with clear jagged borders and rough surface, causing the patient's discomfort, and sometimes biting. The warty form is characterized by the appearance of hilly gray-white formations. According to H.M. Chen, the frequency of verrucous form malignancy is 18-47% [3].

The erosive-ulcerative form is accompanied by the appearance of pain, especially when eating. Erosion can be single and multiple in the background of hyperkeratosis. This form is commonly malignant.

Tappeiner smokers leukoplakia is characterized by clouding of the hard and soft palate mucosa, mostly pronounced along the edge of the gums. Against this background, in the back of the hard palate, small red nodules appear with the output duct point of the minor salivary gland in the center.

Soft leukoplakia is manifested by epithelial dysplasia and is inherited in an autosomal dominant manner. Its occurrence is possible immediately after birth, followed by the development until puberty. Subjective feelings are not marked. Commonly, the mucosa of the cheek with the development of a diffuse haze and the rise of mucosa in the form of a white band is affected. The lesions are soft, loose, swollen, without clear boundaries. When the lesions are extensive, the speech function is disrupted, and eating becomes difficult.

The flat form of the oral mucosa leukoplakia is primarily treated conservatively with lesion regression after termination of the irritating effect. The topical treatment includes dental health, reasonable and competent provision of dental care. The prescription of multivitamin complexes of A and E vitamins in the form of solutions for oral administration and topical application is recommended. When the patient's leukoplakia was transformed into a verrucous or erosive ulcerous form, the surgical removal of the affected area (excision, electro- or cryocautery) is performed with mandatory histological examination [1,2,4]. However, the incidence of uncured disease remains high, requiring a search for new approaches to the treatment based on fundamentally different mechanisms of influence on the pathological lesions of leukoplakia.

In recent years, an increase of interest in the use of the laser technology in treatment of various forms of leukoplakia is noted [5]. According to several authors [6-8], one of the possible ways of solving this problem is photodynamic therapy (PDT).

In recent years, there has been particular interest in the application of this technique in patients with this disease. The vast amount of research is dedicated to the use of 5-aminolevulinic acid (5-ALA) and its derivatives as application drugs. The results of the major research are presented in Table 1.

Table 1
 Efficiency of PDT in patients with oral leukoplakia (reported by literature)

Authors	Diagnosis/ patients, n	Photosensitizers, mg/kg	Characteristics of photoirradiation	Efficiency
Sieron A. 2003 [10]	leukoplakia/n=8	5-ALA 10% solution	$\lambda=635$ nm 100 J/cm ²	CR was in 10 of 12 patients.
Chen H.M. 2004 [11]	verrucous leukoplakia/n=5	5-ALA 20% gel	$\lambda=635\pm 5$ nm 100 J/cm ² 3 fractions	CR was 3 months later in all patients. At 3–11 months of follow-up there were no local recurrences.
Chen H.M. 2005 [12]	verrucous hyperplasia/n=8 leukoplakia/n=8	5-ALA 20% gel	$\lambda=635\pm 5$ nm 100 J/cm ² 5 fractions	<u>Verrucous hyperplasia:</u> CR after 2–5 sessions in all patients, at 5–14 months of follow-up there were no local recurrences. <u>Leukoplakia:</u> 24 foci – 2 sessions of PDT, CR (n=8: local recurrence was 9 and 11 months later), PR (n=16).
Agha- hosseini F. 2006 [13]	leukoplakia/n=13	methylene blue 5% solution	$\lambda=632$ nm 120 J/cm ²	Decrease of pathologic area by 44.3%.
Jerjes W. 2011 [14]	leukoplakia/n=128	5-ALA 60 mg/kg foscan 0,1 mg/kg	$\lambda=630$ nm 100 J/cm ² $\lambda=652$ nm 100–200 J/cm ²	CR rate – 81%, PR rate – 8.2%. Recurrences were detected in 11.6% of cases.
Jajarm H.H. 2015 [15]	leukoplakia/n=25 group 1 – PDT group 2 – dexamethasone + nystatin	toluidine blue	$\lambda=630$ nm 1,5 J/cm ²	There was decrease of lesion area (p<0.005). Over follow-up duration there were no local recurrences in PDT group.

PDT – photodynamic therapy; CR – complete regression; PR – partial regression

The aim of our study is to evaluate the tolerability, safety and immediate results of treatment of patients with oral mucosa leukoplakia by PDT with photolon.

Material and methods

The aim of our study is to evaluate the tolerability, safety and immediate results of treatment of patients with oral mucosa leukoplakia by PDT with photolon.

PDT with photolon was conducted to 40 patients with histologically verified leukoplakia of the oral mucosa. The number of treated lesions was 109 (1 to 8 in each patient). The number of PDT sessions was 66 (1 to 6). All patients were treated on an outpatient basis, after signing of an informed consent for PDT treatment. More information about the patients included in the study is presented in Table 2.

Photolon was administered intravenously at the dose of 1.7-2.5 mg/kg of body weight in a darkened room. The injection solution was prepared ex tempore at the rate of 100 mg of photolon per 100 ml of saline. No adverse reaction during the drug administration was observed.

In order to optimize the photodynamic treatment modes, the fluorescence spectrophotometry was used. This additional method ensures correction of the clinical data of PDT efficacy, allows tracking the dynamics of photosensitizer accumulation in pathologic tissue and its elimination from the body (control of cutaneous photosensitivity). It was used to determine the optimal time of the laser action, indications for repeated sessions of irradiation and timing. The degree of photosensitizer accumulation was assessed by the local fluorescence spectroscopy using the fiber-optic spectrum analyzer LESA-6 (BIOSPEC CJSC, Russia). The signal from normal and pathologic mucosa was recorded consistently. To avoid the influence of inhomogeneous distribution of the photosensitizer in the tissue, the registration was carried out in at least 10 different points of each area. The measurements were conducted on the radius of the pathological focus. The diagnostic parameter of the photosensitizer accumulation intensity in tissue is the fluorescence signal intensity in the spectrum maximum (relative units). The PDT session was planned according to clinical data and results of fluorescence diagnosis. The specific-

Table 2
Characteristics of patients included into the study

Characteristics of patients	Number of patients, n (%)
pre-treated leukoplakia	
yes	5 (12,5%)
no	35 (87,5%)
sex	
males	7 (17,5%)
females	33 (82,5%)
age, years	
30-39	5 (12,5%)
40-49	5 (12,5%)
50-59	16 (40%)
60-69	7 (17,5%)
70-79	7 (17,5%)
average age, years	55±14
site of leukoplakia	
buccal mucosa	17 (42,5%)
tongue	15 (37,5%)
gingiva	5 (12,5%)
oral floor	3 (7,5%)
clinical type of leukoplakia*	
flat	36 (90%)
verrucous	4 (10%)
size of the lesion	
<1,5 cm	26 (65%)
>1,5 cm	14 (35%)
etiologic factor	
smoking	
yes	4 (10%)
no	36 (90%)
alcohol	
yes	0 (0%)
no	40 (100%)
dental defects	
yes	17 (42,5%)
no	23 (57,5%)

*there were no patients with erosive and ulcerative type, leukoplakia mollis and Tappeiner's leukoplakia in the study

ity and sensitivity of the method were determined using the R-system package for scientific statistical calculations (version 2.10.1). To evaluate the specificity and sensitivity of fluorescence diagnosis, the criterion of signal strength in the fluorescence peak at the wavelength of 660 ± 5 nm [9].

The irradiation session was conducted 2,5-3 hours after drug injection using UPL PDT semiconductor laser apparatus (LEMT, Belarus, $\lambda=660\pm 5$ nm). To supply the radiation, the fiber optic catheter for PDT with lens diffuser for external exposure was used. The density of the laser radiation dose varied from 25 to 100 J/cm², the laser radiation power density varied from 0,07 to 0,13 W/cm² (while the light spot diameter was 1 cm – from 0,25 to 0,32 W/cm²), and one irradiation field duration varied from 2 to 13,5 minutes, depending on its linear dimensions. The number of radiation sessions ranged from 1 to 3, depending on the size of the affected area.

During the session, all patients reported a burning sensation, tingling, and pain in the affected area, the intensity of which depended on the pathological

focus location. For the purpose of anesthesia, 15-20 minutes before the treatment start, all patients were administered ketorolac 4 ml intramuscular, and in some cases the local anesthesia with lidocaine 2,0% in the form of a spray, 2-5 ml, was carried out.

The follow-up examinations were carried out 7 days; 1, 3 and 6 months after treatment. The immediate results of treatment of patients with the oral mucosa leukoplakia were assessed, guided by the WHO criteria:

- complete regression (CR), a complete disappearance of all symptoms of the disease, established both visually and by palpation and confirmed by negative results of the morphological study 1-2 months after the treatment;
- partial regression (PR), a reduction of the pathological focus (or formations) by 50% or more, or when the morphological study revealed the tumor cells in the background of clinically complete absence of pathology;
- tumor reduction by less than 50% or no change in the tumor size was determined as no effect (NE).

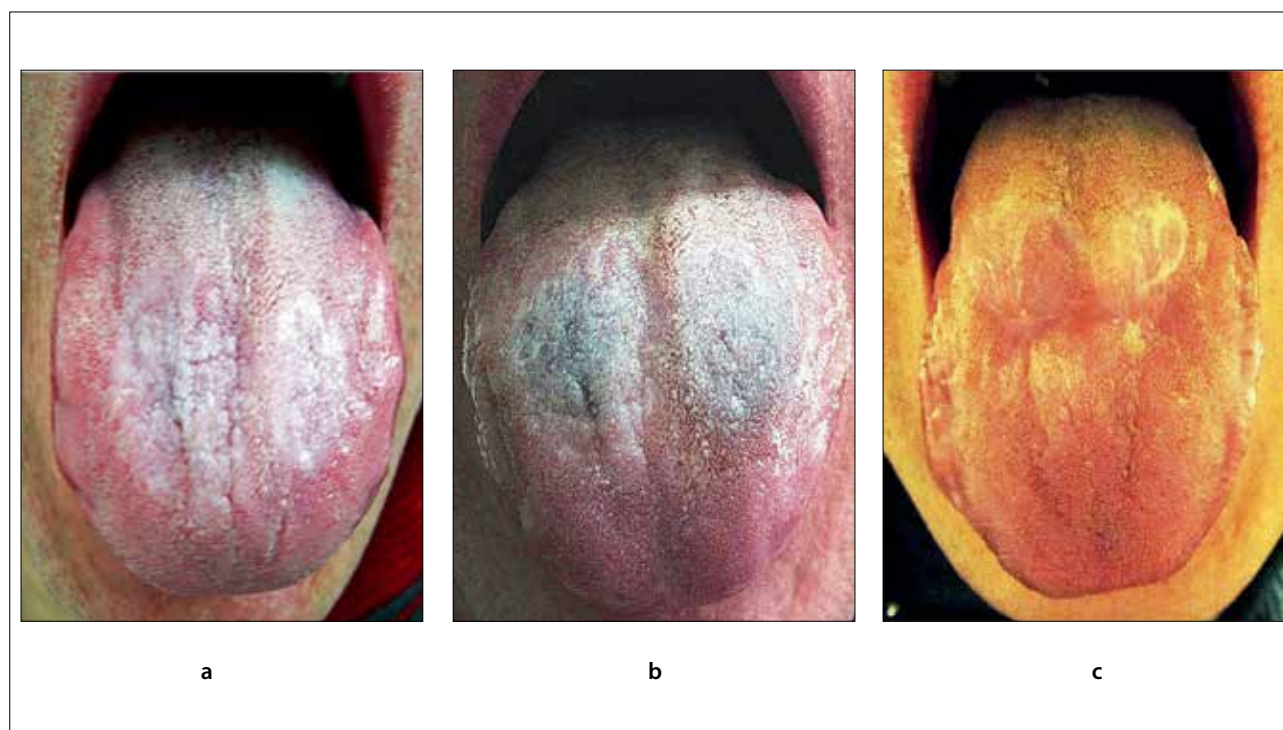


Fig. Patient B., 1972 year of birth, diagnosis: leukoplakia of the mucosa of tongue's body, flat type, light dose – 100 J/cm²; a – before PDT; b – 7 days after PDT; c – 1 month after PDT

Table 3
Efficiency of PDT of oral leukoplakia

Patient	Site	Clinical type	Number of PDT sessions, n	Dose of photolon, mg/kg	Laser irradiation dose, J/cm ²	Effects
1	buccal mucosa	verrucous	2	1,7	80; 100	CR
2	buccal mucosa	flat	1	1,7	100	CR
3	lip	flat	3	1,8	40; 40; 70	CR
4	tongue	verrucous	3	2	100; 50; 40	PR
5	tongue	flat	1	2	70	CR
6	buccal mucosa	flat	1	2	50	CR
7	tongue	verrucous	2	2	50; 100	PR
8	gingiva	flat	3	2	30; 40; 50	CR
9	buccal mucosa	flat	1	2	50	CR
10	lip	flat	1	2	40	CR
11	tongue	flat	2	2	50; 50	CR
12	buccal mucosa	flat	1	2	50	CR
13	tongue	flat	1	2	40	CR
14	tongue	flat	1	2	40	CR
15	buccal mucosa	flat	2	2	40; 50	CR
16	tongue	flat	2	2	40; 40	CR
17	tongue	flat	2	2	30; 40	CR
18	gingiva	flat	2	2	25; 40	CR
19	tongue	flat	1	2	30	CR
20	tongue	flat	1	2	40	CR
21	buccal mucosa	flat	1	2,5	40	CR
22	buccal mucosa	flat	1	2	40	CR
23	tongue	flat	3	2	30; 40; 40	CR
24	gingiva	flat	3	2	25; 30; 40	CR
25	buccal mucosa	flat	1	2	30	CR
26	buccal mucosa	flat	1	2	50	CR
27	tongue	flat	1	2	40	CR
28	buccal mucosa	flat	1	2	40	CR
29	buccal mucosa	flat	3	2,5	40; 40; 40	CR
30	tongue	flat	3	2	40; 40; 30	CR
31	buccal mucosa	flat	1	2,5	40	CR
32	buccal mucosa	flat	1	2	40	CR
33	buccal mucosa	flat	1	2	50	CR
34	tongue	verrucous	1	2	60	CR
35	gingiva	flat	1	2	30	CR
36	buccal mucosa	flat	1	2	30	CR
37	tongue	flat	1	2	30	CR
38	tongue	flat	1	2	30	CR
39	buccal mucosa	flat	1	2	40	CR
40	gingiva	flat	1	2	30	CR

PDT – photodynamic therapy; CR – complete regression; PR – partial regression

Results and discussion

No complications associated with photolon administration were observed. In the early period after treatment (on day 2-6) the hemorrhagic necrosis was observed with a marked exudation and edema of the surrounding tissue, accompanied by violation of the integrity of the mucous membrane, with subsequent formation of fibrinous overlay in the treated area. In some cases, the patients had soft tissue swelling of the face with varying degrees of severity, which disappears after 1-5 days. Within 3-7 days after treatment, the patients reported pain of varying severity in the treated area, stopped well by prescription of non-narcotic analgesics and sedatives.

For vast majority of patients, the fluorescence signal in the focus of leukoplakia was 2,5-3 times higher than that for the intact oral mucosa after 3 hours. This phenomenon was maintained for 24 hours. In 4 patients, the pathological focus fluorescence boundaries exceeded the visible ones by 0,5-1,0 cm. The PD sensitivity for oral mucosa leukoplakia was 66,5%; and the specificity was 73,5%.

38 of 40 patients showed a complete regression of lesions exposed to PDT during the follow-up examination 1-2 months after treatment. 2 patients with verrucous form of leukoplakia and marked exophytic component showed a partial regression (Table 3).

In connection with the development of necrosis foci and appearance of fibrinous overlaps in the treated area, the need for continuous oral cavity treatment with antiseptic solutions (anti-inflammatory herbal, furatsilin) appeared. Since the third day, solkoseril, metrogil denta gel, and sea buckthorn oil was used for applications to accelerate the rejection fibrinous overlaps and areas of necrosis, stimulate the healing and epithelialization [9]. Against the background of the said measures, a complete epi-

thelialization of the wound defect occurred within 3-6 weeks, depending on location, clinical form of the growth and size of the pathological focus and PDT parameters.

The features of the blood supply to the oropharyngeal mucosa and high suction capacity of the oral mucosa have contributed to the development of auto-intoxication phenomena associated with the resorption of degradation products as a result of tissue necrosis. These phenomena were stopped by prescription of abundant alkaline drinking (mineral water), vitamins, and antihistamines [9].

Of note, PDT with photolon has good functional and cosmetic results registered in 100% of patients. A delicate whitish scar was formed in the place of the resorbed pathological tissue (Fig.).

Patients with partial regression (Table. 3) have been re-treated by PDT (1 and 2 sessions of irradiation). The treatment effectiveness was estimated as a complete regression after 1-2 months.

One patient noted the appearance of new lesions of the oral mucosa leukoplakia in the area of previous treatment by PDT 4 months after treatment. The patient passed the second course of PDT with the achievement of complete regression during the follow-up examination 3 months later.

All patients are followed up. The follow-up period varies from 1 to 30 months.

Conclusion

Based on the analysis of our research findings, the PDT method may be recommended to patients with localized and widespread leukoplakia of the oral mucosa as a simple, well-tolerated (minimal risk of complications and adverse reactions) and effective method, which does not require hospitalization of patients, and allows reducing the treatment cost significantly.

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