ORIGINAL ARTICLES

PHOTODYNAMIC THERAPY FOR VULVAR LEUKOPLAKIA

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Abstract

The aim of study is to evaluate the tolerability and effectiveness of photodynamic therapy as an organ-preserving treatment in patients with vulvar leukoplakia. 50 patients with a verified diagnosis of «vulvar leukoplakia» were included in the study. The age varied from 27 to 74 years. The method of treatment assumed the use of the photosensitizer photolon (RUE «Belmedpreparaty», Belarus) administered intravenously in doses of 1.8–2.5 mg/kg. Photoirradiation of pathological foci was carried out 2.5–3 hours after intravenous injection of photolon® using a semiconductor laser «UPL PDT» (LEMT, Belarus, λ=661 nm) at exposure doses from 30 to 100 J/cm^2 with a power density of 100–170 mW/cm^2. The treatment was performed under medical anesthesia. The results of treatment were evaluated using clinical data. Adverse reactions and complications after the introduction of the photosensitizer and photoirradiation have not been observed. Complete clinical regression of the treated pathological foci was noted in 100% of cases with a follow-up observation 1 month after the treatment. At follow-up after 3 months, local recurrences of the disease were detected in 4 cases, which were successfully treated with repeated photodynamic therapy sessions. The percentage of complete regressions was 92%, partial – 8%. The obtained results allow judging on the possibility of using photodynamic therapy in the treatment of patients with vulvar leukoplakia, which allows to preserve the organ and obtain a satisfactory functional and cosmetic result.
Key words: photodynamic therapy, photosensitizer, photolon, vulvar leukoplakia.

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ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ ПРИ ЛЕЙКОПЛАКИИ ВУЛЬВЫ

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Резюме

Целью данной работы была оценка переносимости и эффективности фотодинамической терапии как органосохраняющего метода лечения у пациенток с лейкоплакией вульвы. В исследование было включено 50 пациенток с верифицированным диагнозом лейкоплакия вульвы. Возраст женщин варьировал от 27 до 74 лет. Метод лечения предполагал использование фотосенсибилизатора фотолон (РУП «Белмедпрепараты», Беларусь), который вводили внутривенно в дозах 1,8-2,5 мг/кг. Облучение патологических очагов осуществляли через 2,5–3 ч после внутривенного введения фотолона с помощью полупроводникового лазера «УПЛ ФДТ» («LEMT», Беларусь, λ=661 нм) в дозах от 30 до 100 Дж/см^2 с плотностью мощности излучения 100–170 мВт/см^2. Лечение осуществляли под медикаментозным обезболиванием. Результаты лечения оценивали по клиническим данным. Нежелательных реакций после введения фотосенсибилизатора и дальнейшего облучения зарегистрировано не было. Полная клиническая регрессия пролеченных патологических очагов отмечена в 100% случаев при контрольном наблюдении через 1 мес после проведенного лечения. При контрольном наблюдении через 3 мес у 4 пациенток выявлены локальные очаги продолженного роста опухоли, которые были успешно пролечены с помощью повторного курса фотодинамической терапии. Частота полных регрессий составила 92%, частичных – 8%. Полученные результаты позволяют судить о возможности применения фотодинамической терапии в лечении пациенток с лейкоплакией вульвы с сохранением целостности органа при получении удовлетворительного функционального и косметического результата.

Ключевые слова: фотодинамическая терапия, фотосенсибилизатор, фотолон, лейкоплакия вульвы.

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Introduction

In the last decade, an increasing number of patients with dystrophic diseases of the vulva (DDV) has been observed, occupying from 1% to 10% in the structure of gynecological pathology [1]. These diseases defined as «neurodystrophic diseases» include lichen sclerosus (lichen, kraurosis), squamous hyperplasia (leukoplakia) and vulvar intraepithelial neoplasia (VIN) of the vulva) [2]. Leukoplakia of the vulva (LV) is a main manifestation of the squamous hyperplasia, which is a DDV involving non-keratinized stratified squamous epithelium. In the epidemiological structure of benign lesions of the vulva, over 50% of cases are squamous hyperplasia, 25% of cases are lichen sclerosus, and remaining 25% of cases include their association [3]. This group of diseases is also characterised by a high risk of malignancy: in the setting of kraurosis, the risk of malignancy is 9%; in the setting of VIN, it is from 6% to 18%; and when both processes are combined, the risk is 60% [4]. Thus, given the duration and severity of the disease course as well as the high probability of malignancy, the search for effective methods of treating this pathology is an urgent problem of modern medicine [5].

The main method of treating patients with DDV is a surgery. In most cases, the excision of nidi is performed; when the disease extent is significant, the vulvectomy is used. The advantage of this treatment method is a possibility of histological verification in tissues of removed nidi to estimate the risk of malignancy; the disadvantages include injuries, the risk of postoperative complications and, in some cases, poor cosmetic results. In addition, according to the literature, the rate of local recurrence after vulva surgeries is from 30% to 46% [7].

The key non-surgical methods of treating DDV are laser CO_2 coagulation and vaporization of pathological areas of the vulva with a radiation intensity of over 1,000 W/cm^2. Unlike surgical treatment, these therapeutic modalities provide a good cosmetic result, but, like surgical treatment, they do not affect etiopathogenetic mechanisms of diseases, which is the reason for the development of local recurrence in the early posttreatment period. The rate of local recurrence after laser CO_2 coagulation and vaporization ranges from 15% to 48% [8, 9].

A relevant research direction is the use of high-intensity focused ultrasound, which is characterized by high tolerability, a high rate of histologically proven complete regressions (up to 88.9%) and a long period of the remission (up to 6 months) [10].

The imiquimod immunomodulator has certain therapeutic opportunities [11]. During its use, the local recurrence rate is over 40% [12]. The use of application forms of 5-fluorouracil in the treatment of DDV features a low rate of complete regressions (up to 34%) and adverse events (burns of the 1st and 2nd degree, painful ulcers) [13].

The main reasons for the search for new methods of treating DDV are the frequent recurrence of the process, the long and persistent course of the disease, the unreasonable and ineffective use of drugs, which lead to the development of various psychosomatic disorders in patients that have an adverse effect on their body state and the deterioration in women's quality of life. The existing non-surgical therapies relieve the main symptom, itching of external genital organs, but they do not fully eliminate local morphological manifestations of the disease, do not provide durable remissions and require the long period of treatment. In addition, the long-term non-surgical treatment does not prevent malignancy of the disease.

One of the most promising directions for the treatment of DDV is photodynamic therapy (PDT). This treatment method is based on the use of a special substance – a photosensitizer (PS) – whose cytotoxicity is manifested when it is exposed to laser irradiation with a specific wavelength. The results of pre-sensitized tissue irradiation are apoptosis, autophagy and ischemic necrosis of the irradiated tissues [14].

The main PSs used for PDT of DDV are 5-aminolevulinic acid (5-ALA), chlorine derivatives and dyes [15–17]. The main researches are aimed at studying the efficiency of PDT of DDV with topical application of photosensitizing agents. However, the efficiency of treatment with topical application of the chlorine based PS is low compared to traditional methods (there is no effect in more than 30–40% of cases) [18].

The majority of published abroad clinical studies, which confirm the PDT efficiency, are devoted to the use of application forms of 5-ALA as a PS.

According to P. Hillemanns et al., PDT (with laser irradiation energy density of 100 J/cm^2, $\lambda = 635$ nm) with topical application of a 20% solution of 5-ALA in 25 patients with VIN of the 1st to 3rd degrees allowed to achieve a high rate of complete regressions (CR): for VIN of the 1st degree and monofocal and bifocal lesions of the 2nd and 3rd degrees, this value was 100%; for a multifocal form of the disease, it was 27% [15].

M. K. Fehr reported on 66% of clinical CRs and 57% of histologically proven CRs for PDT (with laser irradiation energy density of 80–125 J/cm^2, $\lambda = 635$ nm) with application of a 10% gel form of 5-ALA in 22 patients with VIN of the 2nd and 3rd degrees [19]. A. Zawislak et al. presented the experience of treating 23 patients with VIN of the 2nd and 3rd degrees using PDT (with laser irradiation energy density of 100 J/cm^2, $\lambda = 635$ nm) with a 20% solution of 5-ALA. The authors reported on 52% of clinical CRs and 38% of histological CRs [20].

The CIS countries have a considerable experience in application of PDT with chlorine based PSs (fotodi-

tazine, photolon, radahlorin) in the treatment of patients with DDV. For example, O. B. Otdelnova reported on the outcomes of treatment of 6 patients with benign vulvar diseases (lichen sclerosus of the vulva, squamous hyperplasia of the vulva). The authors used the fotoditazine as a PS (intravenous infusion at a dose of 1 mg/kg + application of 1 ml of 0.5% penetrator gel). Irradiation was performed using an «Atkus-2 » semiconductor laser with laser irradiation energy density of 100–200 J/cm^2 under topical anesthesia with a 2% lidocaine solution. The efficiency assessment was based on physical examination data and the presence of clinical symptoms of the disease (itching). During follow-up after 3 months, the therapeutic effect persisted. Itching relief was observed in 3 out of 4 patients with lichen sclerosus; data of cytological examination of scraping and vulvoscopy showed the complete cure in all patients with squamous hyperplasia. A good cosmetic result was reported in all cases. However, such an adverse event as a severe pain syndrome was observed in all patients during photoradiation, which limited the application of a therapeutic dose of irratiation to the nidi [18].

E. A. Chulkova reported on outcomes of PDT with a 20% ointment of 5-ALA in 90 patients with dystrophic and premalignant diseases of the vulva. The average radiation power was 1.5 W in the spectral range of 630±10 nm. The authors noted that PDT with the 20% ointment of 5-ALA proved to be an effective method that minimally injures the healthy vulvar tissue, which is very important for young and middle-aged patients [21].

O. V. Makarov presented the experience of treating 97 patients with DDV: lichen sclerosus of the vulva was verified in 75 (77.3%) patients, squamous hyperplasia of the vulva was verified in 18 (18.6%) patients, and mixed dystrophy was verified in 4 (4.1%) patients. PDT was performed with the fotoditazine: the PS was administered via IV infusion at a dose of 1 mg/kg (n=64) or applied topically as a 0.5% penetrator gel (n=33). Irradiation was carried out in a continuous or fractional mode with laser irradiation energy density of 100–250 J/cm^2 (λ=630 nm). The authors observed a high rate (90.6%) of CRs for intravenous administration of the PS and 78.8% of CRs for topical application. One year after the PDT session, the recurrence rate was 9.1% in the 1st group and 22.6% in the 2nd group [22].

A. Z. Khashukoeva performed PDT of 50 patients with DDV (lichen sclerosus, squamous hyperplasia, mixed dystrophy) using the fotoditazine (1mg/kg). The author reports a 94% of CRs (clinical) when using laser irradiation energy density of 100–250 J/cm^2 (λ=662 nm) [23].

The purpose of this work is to assess the efficiency, safety and cosmetic results in patients with DDV treated with PDT with the photolon PS.

Materials and methods

The study included 50 patients with the morphologically verified diagnosis of leukoplakia of the vulva. The patients were from 27 to 74 years old.

The clinical diagnosis was made on the basis of complaints, history and examination of patients, vulvoscopy and the results of the morphological (histological and/or cytological) examination of the pathologically changed tissues of the vulva.

The criteria for patient enrollment in the study of PDT were histological and cytological validation of the diagnosis, the absence of the severe comorbidity and a written consent to treatment. The treatment was carried out on an outpatient basis.

The PS was Photolon (RUE «Belmedpreparaty», Belarus), which is a complex of trisodium salt of chlorin e_6 with polyvinylpyrrolidone. The PS was dissolved in 200 ml of physiological saline and was administered via IV infusion at doses of 1.8–2.5 mg/kg-BM of the patient in a darkened room.

A PDT session was conducted 2.5–3 hours after the PS administration using a «UPL PDT» semiconductor laser («Lemt», Belarus, λ=661 nm). The radiation was supplied using a light cable equipped with a microlens («Biospec» LLC, Russia), which has a homogeneous distribution of the irradiation energy over the light spot.

The size of irradiation fields varied from 1.5 to 2 cm; the number of fields ranged from 1 to 4; the power density was from 0.1 to 0.17 W/cm^2; the light dose was from 40 to 100 J/cm^2. The duration of a PDT session varied from 10 to 30 minutes depending on the number of irradiation fields. The irradiated area always included 3–5 mm of normal tissues from the edges of the afflicted zone.

Due to particular sensitivity of the treated area, premedication with non-narcotic analgesics (Ketorolac, intramuscularly, 4 ml) was carried out 15–20 minutes before the session for the pain management.

The nidus response to the treatment was evaluated immediately after the PDT session and after 1, 7 and 30 days.

The tolerance of the treatment was estimated based on the frequency and severity of adverse events using the analysis of CTCAE criteria (version 4.0).

Antitumour effects of the PDT with photolon were assessed based on visual observation of changes in the area of treated nidi and information on the presence or absence of clinical symptoms of the disease (itching in the vulva for leukoplakia) 1 and 3 months after the treatment (WHO criteria):

- a complete regression (CR) is the absence of all signs of the disease after 100% resorption of nidi 1 month after the PDT, confirmed 3 months after the treatment;
- a partial regression (PR) is a decrease in the total size of the nidi by 50% or more with subsequent stabi-

lization established after 1 month and confirmed 3 months after the PDT session;
- lack of effect is a decrease in the total size of the nidi by less than 50%, a condition without a decrease or increase in the affected area.

Results and discussion

All patients that observed the light regime for 3–4 days after the treatment had no adverse events associated with skin phototoxicity (superficial skin burns, hypopigmentation and hyperpigmentation, face soft tissues oedema).

During the infusion of the photosensitizer, the condition of the patients was satisfactory, no adverse events were observed. No allergic reactions accompanied by major organs dysfunction (drop of blood pressure, bronchospasm, generalised urticaria, etc.) and requiring to stop infusion were recorded.

Oedema and hyperthermia of irradiated areas with nidi were observed in all patients immediately after the PDT session. A brown or black photochemical necrotic scab clearly separated from normal tissues was formed within 2-4 days. Complete epithelialization of the irradiated area was observed 4–8 weeks after the PDT.

PDT sessions were accompanied by moderate pain, which was managed with drugs (2% Ketorolac, intramuscularly, 4 ml) or by a decrease in a laser irradiation power density with an unchanged light dose. In 15 patients (30% of cases), the pain persisted for 3–7 days after the treatment (CTCAE, version 4.0; 1st and 2nd degrees). 5 patients (10% of cases) showed a slight increase in body temperature (up to +37.3–37.5°C).

Clinical signs of the complete regression were observed in all patients with leukoplakia of the vulva during the follow-up after 1 month. The CR rate was 100%. The second PDT courses were conducted due to an extensive nidi area and impossibility of their simultaneous irradiation because of the moderate pain.

Local nidi of the continued tumour growth were detected in 4 cases out of 50 (8%) during the follow-up after 3 months, which were successfully treated using another PDT course. The CR rate at this time point after the treatment was 92%, and the PR rate was 8%.

In the follow-up period of 6 months, a sustained remission of the clinical symptoms of the disease (itching in the vulva) in the treated nidi was observed, including 8% of cases where the second PDT course was conducted after the PR achievement.

As a result of the study, the following indications for PDT in patients with leukoplakia of the vulva were determined:

1. a morphologically verified diagnosis;
2. primary and recurrent forms of the disease;
3. resistance to traditional (non-surgical) methods of treatment;
4. a patient's refusal to be treated with traditional methods;
5. multiple lesions.

The main advantages of PDT are:

1. minimal toxicity for normal tissues located close to nidi;
2. the minimal risk of severe pain and other adverse events;
3. the lack of treatment resistance;
4. the possibility of repeated treatment sessions;
5. the possibility of combination with traditional methods of treatment;
6. the possibility of application when the process is advanced;
7. good cosmetic results;
8. the possibility of organ preservation treatment;
9. the relatively low price and availability of treatment.

The outcomes of the PDT with photolon are confirmed by the following clinical example.

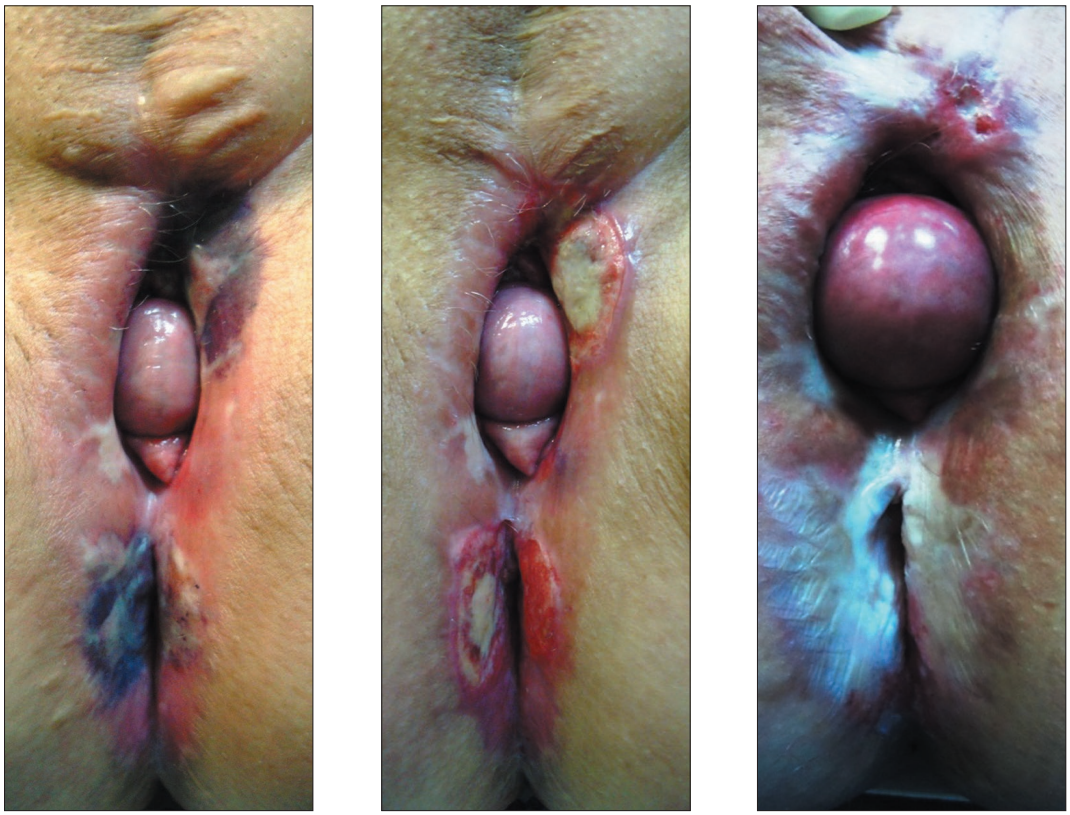
Clinical example

Patient Ya. (outpatient card No. 5747/06), 62 years old. She was followed up with complaints of severe itching in the vulva since 2006. Leukoplakia of the vulva was diagnosed. In 2008–2010, surgeries were performed due to the main disease. The progression in the treatment area was observed since 2011. Non-surgical methods of treatment were ineffective.

The patient was referred for consultation and treatment to the Republican Research and Practice Centre of Oncology and Medical Radiology named after N. N. Aleksandrov. After the consultation with specialists and histological examination, the diagnosis was made: leukoplakia of the vulva, recurrent form. Treatment with PDT was recommended. Treatment: on November 21, 2012, the patient was given a PDT course with photolon administered intravenously at a dose of 2.5 mg/kg (200 mg) in hospital environment. Nidi in the vulva and perianal area were irradiated using a «UPL PDT» semiconductor laser (λ=661 nm) in a darkened room 3 hours after the PS administration. 3 fields of 2 cm diameter were irradiated with a light cable equipped with a microlens at a laser irradiation energy density of 50 J/cm^2, a power density of 0.1 W/cm^2 and a radiation power of 0.3 W for 9 minutes per field. The effect in the form of growing necrosis was observed by the end of the first week after the treatment.

After the release from the hospital, the woman performed non-specific therapy of the irradiated area. The completion of the epithelialization processes was recorded by the 6th week.

On February 21, 2013 (after 3 months), the significant improvement in the treatment zone and the lack of complaints were noted during the follow-up clinical examination (Fig. *c*).



a b c

Рис. Лейкоплакия вульвы, состояние после ФДТ с фотолоном в дозе 2,5 мг/кг (плотность энергии лазерного облучения 50 Дж/см^2):
a – состояние через 24 ч после ФДТ;
b – полная регрессия через 1 мес после проведенного лечения;
c – полная регрессия через 3 мес после проведенного лечения

Fig. Vulvar leukoplakia. The state after PDT with photolon at a dose of 2.5 mg/kg and exposure dose of photoirradiation of 50 J/cm^2:
a – 24 hours after PDT
b – complete regression 1 month after the treatment;
c – complete regression 3 months after the treatment.

Conclusion

The outcomes of the clinical use of the PDT with photolon in the treatment of patients with background and premalignant diseases of the vulva presented in this study indicate its high therapeutic efficacy, minimum adverse events and good cosmetic results. During the follow-up, the complete regression of the nidi was observed in all patients. Local recurrence of the disease was detected in 8% of cases 3 months after the PDT, which was successfully treated with the second course.

It can therefore be concluded that PDT is easy to use, well tolerated, efficient and can be recommended for the treatment of dystrophic diseases and the prevention of vulvar cancer.

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