PHOTODYNAMIC THERAPY IN THE TREATMENT OF INTRAEPITHELIAL NEOPLASIA OF THE CERVIX, VULVA AND VAGINA

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Abstract

In the present review the authors analyzed the effectiveness of treatment of intraepithelial neoplasia I-II-III of the cervix (CIN), vulva (VIN) and vagina (VaIN) using photodynamic therapy (PDT). PDT is a method based on exposure to light after preliminary introduction of a photosensitizer into the body with the formation of singlet oxygen, which has a cytotoxic effect. The results of research on the use of PDT with various photosensitizers in the complex of therapeutic measures in patients with CIN, VIN, VaIN are presented. These data on the effectiveness and safety of PDT, ease of use allow this medical technology to be attributed to one of the most promising areas in the treatment of pathological intraepithelial changes of the cervix, vulva and vagina. The presented information allows focusing the attention on the PDT method and informing doctors and researchers about the broad prospects for applying this treatment method in clinical practice.

Keywords: photodynamic therapy, photosensitizer, cervical intraepithelial neoplasia, vaginal intraepithelial neoplasia, vulvar intraepithelial neoplasia.

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ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ В ЛЕЧЕНИИ ИНТРАЭПИТЕЛИАЛЬНЫХ НЕОПЛАЗИЙ ШЕЙКИ МАТКИ, ВУЛЬВЫ И ВЛАГАЛИЩА

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Резюме

В обзоре литературы представлен анализ эффективности лечения интраэпителиальной неоплазии I-II-III степени шейки матки (CIN), вульвы (VIN) и влагалища (VaIN) с использованием фотодинамической терапии (ФДТ). ФДТ – метод, основанный на воздействии светом после предварительного введения в организм фотосенсибилизатора с образованием синглетного кислорода, оказывающего цитотоксический эффект. Представлены результаты исследований по использованию ФДТ с различными фотосенсибилизаторами в комплексе лечебных мероприятий у больных с CIN, VIN, VaIN. Приведенные данные об эффективности и безопасности ФДТ, простота применения позволяют данную медицинскую технологию отнести к числу наиболее перспективных направлений в лечении различ-

ной степени выраженности интраэпителиальных изменений шейки матки, вульвы и влагалища. Представленная информация позволит акцентировать внимание на ФДТ и информировать врачей и научных сотрудников о широких перспективах применения данного метода в клинической практике.

Ключевые слова: фотодинамическая терапия, фотосенсибилизатор, цервикальная интраэпителиальная неоплазия, влагалищная интраэпителиальная неоплазия, вульварная интраэпителиальная неоплазия.

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As doctors are trying to deal with the difficult, but solvable task of reducing cancer morbidity and mortality, the requirements for the selection of modern optimal methods of patient treatment are becoming more rigorous. The achievements in photochemistry, photobiology, and quantum physics have made possible the advances in this direction that provide alternatives to the traditional methods of treatment; a method worth focusing on among the new ones is photodynamic therapy (PDT).

The PDT mechanism is based on the ability of some photosensitizers (PSs) to accumulate in the tumor tissue and, when interacting with light radiation of a certain wavelength, initiate the formation of singlet oxygen through a series of photochemical processes, which has a destructive effect on the vital structures of tumor cells, leading to their death.- The damaging mechanism of photodynamic effects on tumor tissues is mainly determined by the average intracellular concentration of PS, its localization in the cell, and its photochemical activity: the quantum yield of singlet oxygen or free radicals generation [1, 2, 3, 4].

In addition to the direct phototoxic effect on tumor cells, an important role in the destruction mechanism is played by impaired blood circulation in the tumor tissue due to damage to blood vessels endothelium [5], a hyperthermic effect associated with active light absorption by tumor cells, as well as cytokine reactions caused by stimulation of the tumor necrosis factor and activation of macrophages, leukocytes, and lymphocytes [6, 7].

The increased interest in PDT is caused by the wide possibilities of using light radiation in oncology and PDT's advantages over other methods of treatment, such as low invasiveness; selectivity of destruction of malignant tumors and pathological areas; minimal damage to healthy tissue; the possibility of repeated use, as no resistance develops after repeated cycles; the absence of toxic and immunosuppressive reactions [8].

In oncogynecology, the method can be used for both radical and palliative treatment, which determines its use in women with precancerous and neoplastic diseases of genital organs [9].

The increasing attention of gynecologists and oncogynecologists to PDT is associated with the need to expand the range of organ preservation treatment options, which is extremely important in connection with the steady increase in the incidence of cervical, vulvar, and vaginal cancer in young women over the past two decades [10]. This method meets the main characteristics of an organ-preserving treatment, i.e., high effectiveness against the pathology, low frequency of relapses after treatment, tolerability (minimal number of side effects), and ease of administration of the treatment [11]. However, with the advent of the viral concept of cervical cancer, and with frequent detection of human papillomavirus (HPV) in cervical intraepithelial neoplasia (CIN) cases in direct proportional to the severity of the changes (CIN I: 25%, CIN II: 80%, CIN III: 88–100%) [12], the identification of the viral genome in intraepithelial neoplasias of the vagina (VaIN) and vulva (VIN), respectively, in 80% and 20% of cases [13], etiopathogenetic therapy becomes the center of attention, as it is aimed not only at the pathological process itself, but also at HPV eradication.

To date, there are no clear recommendations in the world for the treatment of HPV-associated intraepithelial pathology of the cervix, vulva, and vagina, which may have various degrees of severity. It has become possible to revise the traditional treatment approaches, taking into account the need for eradication of papillomavirus infection (PVI), thanks to the accumulated experience and modern developments in the field of medical technologies.

The specifics of the HPV life cycle are one of the determining factors of the antiviral treatment effectiveness. In the episomal form of HPV, physical methods of treatment aimed at destroying the primary lesion or immunotherapy are successfully used, provided that the duration of PVI is not more than one year and no virus persistence is present [14]. When HPV is integrated into

the genome of the host cell, interferon therapy is powerless, since the infected cells contain no virus as such in the traditional sense of the word, and, therefore, treatment methods aimed at destroying viral heterotopias are necessary [15].

PDT and CIN

The methods of treatment of CIN I–II–III and microinvasive cervical cancer (1A1 st.) based on ablation (diathermic and radiocoagulation, cryodestruction, laser vaporization) and removal (laser, electric, radio, knife excision/conization) of the primary lesion as a monotherapy are not effective enough for the elimination of HPV, as the effect is directed only on clinical lesions without affecting multifocal areas with latent or subclinical form of PVI, insufficient depth of destruction of the epithelial layer to the basal layer, where the reservoir of papillomaviruses is located, the absence of targeted destruction of papillomaviruses and irradiation of the transition zone and the cervical canal, which together lead to the persistence of the viral genome [16, 17, 18, 19]. The expression of HPV DNA at the sites of cervical primary lesions, the necrosis zone, the mucous membranes adjacent to the edge of destruction or resection, and the reactivation of the viral genome together provoke a high risk of CIN relapses in a fairly short period of time (from 12 to 36 months), the progression of the tumor process to preinvasive or eventually to microinvasive cancer (from 15 to 50%) and low effectiveness of treatment (45– 97%) [19, 20].

The potential of PDT in the treatment of cervical cancer pathology has been studied since the 1990s. In oncogynecology, the choice of the cervix as the first model for clinical research is explained by the relevance of the outcomes, and the development and implementation of new approaches to the prevention and treatment of cervical cancer. The incidence of the disease has been growing in a number of countries over the past two decades. Another reason is the availability of visual and non-invasive research methods. Some studies examined the issues related to the pharmacokinetics of exogenous and endogenous PS chemicals, the development of scientifically based methodological approaches to PDT with the use of Russian-made pharmaceuticals of various groups in achieving the antitumor and antiviral effect, depending on the severity of intraepithelial cervical changes: laser irradiation modes; the choice of PS and methods of administration (local, systemic); calculation of the light dose and the method of radiation delivery to abnormal tissues [21, 22].

The results of the use of PDT in the treatment of cervical tumor pathology were first published in 1996. In the study, attempts were made to optimize PDT regimens in the treatment of non-invasive cervical cancer with intravenous administration of photofrin in order to achieve complete regression. A positive effect was registered in 62% of clinical observations at a light dose of 100–140 J/cm$^{2.}$ PDT of the cervix with non-invasive tumor changes is decribed as an organ-sparing treatment method [23].

Promising results of PDT in the treatment of CIN I–II–III were obtained with topical application of aminolevulinic acid hexyl ether (HAL) and the use of a light dose of 100 J/cm^2 and a laser wavelength of 633 nm. The studies related to the pharmacokinetics and selectivity of porphyrins established the optimal concentration of the drug (10 mmol/l) and the exposure time (5–9 h). This methodological approach made it possible to achieve a complete regression in 63% cases, with the best treatment results obtained in cases with minimal cervical changes: 100% for CIN I, 50% for CIN II, and 43% for CIN III [24].

PDT with photohem at a dose of 2 mg per kg of body weight with intravenous administration, a light dose of 100–150 J/cm^2, and exposure time of 24 h led to complete regression of CIN II–III in 93% of cases, which indicates the method's high effectiveness in antitumor treatment. Photoreduction with photohem is proposed as a fertility-preserving method, an alternative to destructive treatment of the cervix [25].

The prospects of PDT in the treatment of CIN II–III in comparison with traditional methods were demonstrated with photolon (0.5% aqueous solution), leading to complete regression of cervical pathology in 65% of women, with intravenous administration of the drug, an exposure time of 2.5 hours, laser radiation wavelength of 662 nm and radiation power density of 100–300 W/cm$^{2.}$ The authors found that errors in the calculation of the light dose, which is particularly important in achieving maximum photodynamic destruction, can lead to a lack of response to treatment, or, on the contrary, to pronounced destructive changes in the tissues in the PDT area, which in turn leads to prolonged wound healing, rough scarring, and longer rehabilitation periods [26].

Another study conducted in the framework of phase III clinical trials of radachlorin, a photosensitizer produced in the Russian Federation, describes the results of PDT in patients with precancerous conditions and initial cervical cancer. The study included 30 patients: 4 with cervical ectopia, 5 with CIN II, 13 with CIN III, 4 with carcinoma in situ, and 4 with stage Ia cervical cancer. The PDT session involved irradiation of the entire cervical canal and the vaginal portion of the cervix. In the groups diagnosed with cervical ectopia, CIN II, and carcinoma in situ, complete regression was registered in all cases. In the group with CIN III, complete regression was obtained in 77% of cases, partial regression, in 23%; in the group with a diagnosis of stage Ia cervical cancer, in 75% and 25%, respectively. All patients with partial regression underwent a second course of PDT, which had a full effect [27].

The ability of PDT to provide not only a pronounced antitumor effect but also antiviral effect as an independent method of treatment has recently attracted significant attention to the method. One of the first publications on this subject was a study performed on a large clinical material in women with HPV-associated precancerous and initial tumor changes in the cervix; treatment was performed with photohem (intravenous administration, dose: 3.0 mg per kilo of body weight, exposure time: 48 h, wavelength: 630 nm, energy density: 150–200 J/cm^2, power: 150–250 MW/cm^2) and photosense (intravenous administration, dose: 0.3 mg per kg of body weight, exposure time: 24 h, wavelength: 675 nm, energy density: 100–150 J/cm^2, power: 150–250 MW/cm^2) [28]. The difference between the developed PDT technique and other variants of photodynamic destruction of the cervix is the use of polypositional irradiation of the cervical canal throughout the entire area of the vaginal portion of the cervix. The authors believe that this approach makes it possible to selectively destroy the foci of precancerous and initial tumor pathology in 90–92.5% and 77.7–80.7%, respectively, and to achieve an antiviral effect due to the destruction of clinical, latent and subclinical forms of PVI in 94.2% of cases. Based on the results of the study, it is possible to see PDT as the minimalistic option of organ-sparing treatment, which is of great interest in the light of the proven etiological role of HPV in the development of cervical cancer.

The antiviral effect of PDT has created a new direction towards solving the urgent problem of preventing relapses of HPV-associated CIN and cervical cancer. The treatment method that consists of local application of a Russian-made pharmaceutical product based on 5-aminolevulinic acid (5-ALA), an inducer of the synthesis of protoporphyrin IX, an endogenous photosensitizer (dose: 0.1 mg/cm^2, exposure time: 6 h, wavelength: 635 nm, energy density: 150 J/cm^2, power density: 150–250 MW/cm^2), allows achieving complete eradication of PVI after primary organ-preserving treatment in 96% of cases. HPV elimination is caused by irradiation of the remaining part of the cervical canal and the vaginal portion of the cervical stump after conization with the polypositional effect of light energy on the resection zone, the exposure involving the vaginal arches. PDT is recommended for antiviral purposes at the second stage of treatment after knife amputation, laser, electric and radiowave cone excision/conization of the cervix, as well as as an alternative to diathermal and radiocoagulation, cryodestruction, and laser vaporization in the treatment of cervical PVI [29].

A number of studies in subsequent years evaluated the antitumor and antiviral efficacy of PDT in the treatment of CIN I–II–III with photosensitizers of various groups.

M. C. Choi et al. (2013), in their study where they used photohem as a PS in patients with HPV+ CIN II–III (intravenous administration, dose: 3.0 mg per kg of body weight, exposure time: 48 h, wavelength: 630 nm, energy density: 150 J/cm^2), complete regression was observed in 98.1%, and HPV eradication in 89.8% of the cases [30].

P. Hillemanns et al. (2014), in PDT of CIN II, used hexyl aminolevulinate in various concentrations (5%, 1%, and 0.2%) as an ointment application on ectocervix (exposure time 5 h, radiation wavelength 629 nm, energy density 100 J/cm^2). To assess the antitumor effect of treatment, a cervical biopsy was performed 3 and 6 months after the treatment. The best results in terms of CIN II complete regression were found in observations with a 5% concentration of the drug (95%), in other cases, this indicator was 79% and did not depend on the concentration. The best results in terms of complete eradication of HPV were registered in cases of 5% ointment application (83%), with the use of lower concentrations of the product (1% and 0.1%), complete eradication of HPV was noted only in 48% and 42% of cases, respectively. Thus, the antiviral effectiveness of hexyl aminolevulinate is directly dependent on the concentration of the product. The index of viral elimination is less high in comparison with the data published by other researchers, which may well be due to the absence of photo-radiation of the cervical canal [31].

Y. K. Park et al. (2016) also indicate high antitumor and antiviral efficacy of PDT with photofrin (intravenous administration, dose: 2 mg per kg of body weight, exposure time: 5 h, radiation wavelength: 629 nm, energy density: 100 J/cm^2) in the treatment of CIN II–III. Photodestruction was performed on both exocervix and endocervix. Complete regression of intraepithelial pathologic changes and HPV elimination were achieved in 95 and 90.9%, respectively [32].

H. Cai et al. (2020) report a complete regression of CIN I–II–III in 100% of cases, while HPV eradication was observed in 83.3% of cases after 4–7 PDT sessions with 5-ALA in the form of 20% ointment application on exocervix (exposure time: 3 h, radiation wavelength: 635 nm, energy density: 100 J/cm^2, power density: 80 MW/cm^2). The effect of the treatment was evaluated after 6–7 months by a loop electrosurgical excision. The results of the study indicate the need for endocervix irradiation in order to achieve a pronounced antiviral effect [33].

PDT and VIN

Publications in the Russian and foreign literature devoted to PDT in background diseases, precancerous conditions, and initial vulvar cancer are few and limited to a small number of clinical observations. Early detection and treatment of diseases of this localization is still one of the most pressing issues of gynecology and oncogynecology. The possibilities to prevent the development of a tu-

mor and cure pre-cancerous changes in the tissues exist, which urges active research for new effective treatment methods and their further development. In the past, vulvar intraepithelial neoplasia (VIN) was considered a pathology of women aged over 40, but in recent years, the condition is increasingly more often diagnosed in younger women (aged 25–40). A direct correlation was established between the presence of types 16 and 18 HPV in vulvar tissues and VIN in young women [34, 35].

Treatment options for dystrophic diseases of the vulva are extremely diverse, which is explained by their low effectiveness, as well as by the recurrent nature of the disease. The methods of treatment include conservative and surgical ones. The first treatment option includes hormone therapy, but it should be noted that it does not actually cure but only eliminates the symptoms of the disease and promotes a temporary remission. Surgical methods include cryodestruction, laser vaporization, and surgical excision of lesions. Unfortunately, the relapse rate after such treatment is high, as well as scar tissue deformity, which forces doctors to look for new therapies that combine the optimal therapeutic effect and the absence of complications [36]. One of the latest approaches to the vulvar pathology treatment is PDT. The potential of the method in the treatment of VIN is due to its non-invasive nature and its wide applicability [37, 38].

In one of the first studies that evaluated the effectiveness of PDT in the treatment of background and precancerous diseases of the vulva with the use of 5-ALA in the form of 20% ointment application, the following treatment modes were used: exposure time: 6 h, radiation wavelength: 629 nm, energy density: 100 J/cm^2 power density: 100–200 MW/cm$^{2.}$ Patients with dystrophic changes of the vulva (lichen sclerosis, squamous cell hyperplasia) were administered two courses of PDT with an interval of 30 days, while patients with VIN I–III had 2– 3 courses of treatment. In the group of women with lichen sclerosis, the positive effect of treatment, established on the basis of the disappearance of itching and dryness, and the achievement of more elasticity and softness of the skin on the labia majora, was noted in 85% of patients. Complete regression of hyperplastic processes of the vulva was diagnosed in 100% of cases, the outcome of treatment remained after 1, 3 and 6 months. High efficiency of PDT was observed in the vulva irradiation with VIN I–II–III phenomena. Control histological examinations performed after 1 month in all cases with VIN I–II did not reveal epithelial atypia, whereas in 60% of women with VIN III, the condition regressed to VIN I–II, which was regarded as an indication for another course of PDT; such course then demonstrated complete effectiveness. No relapses of the disease during one year after the treatment were noted, and a good cosmetic effect was achieved, which is of great importance for young and middle-aged patients [39].

In another study, in which 50 patients with vulvar leukoplakia underwent PDT with photolon (intravenous administration, dose 1,8–2.5 mg per kg of body weight, exposure time: 2.5–3 h, radiation wavelength: 661 nm, energy density: 30–100 J/cm^2, radiation power density: 100–170 MW/cm^2) a high cure rate, 92%, was established after 3 months. The results of the study allow us to make conclusions on the possibility of the use of this methodological approach in the treatment of background diseases of the vulva to achieve satisfactory functional and cosmetic results [40].

A similar satisfactory effect from treatment was registered after 3 courses of PDT with 5-ALA (20% ointment, exposure time: 3 h, radiation wavelength: 633 nm, energy density: 120 J/cm^2 power density: 100 MW/cm^2) in the treatment of VIN III. Complete regression for 12 months was established in 94%, and a good cosmetic result was observed in 71% of cases. A significant improvement in the quality of life and mental health was observed in all patients [41].

The lower effectiveness of PDT with 5-ALA in the treatment of VIN II–III is indicated in three studies. In two of them, when applied topically, as 10 g of ointment (exposure time: 2.6 h, radiation wavelength: 635 nm, energy density: 116 J/cm^2 (+/- 16 J/cm^2), power density: 100 MW/cm^2 (88 +/-17 MW/cm^2) and 10 ml of 20% ointment (exposure time: 3 h, radiation wavelength: 635 nm, energy density: 100 J/cm^2 power density: 100 MW/cm^2). complete regression over a short observation period of 8 weeks and 12 weeks, respectively, was established, in 57% [42], and 52% of cases [43]. In the third study, when 5-ALA was used in the form of a patch (38 mg/cm^2, exposure time: 20–28 minutes, radiation wavelength: 630 nm, energy density: 100 J/cm^2), a positive effect of PDT was registered in 38% of observations [44].

PDT and VaIN

The PDT method in the treatment of VaIN is in its initial stage, and, therefore, there are no clear recommendations for its widespread implementation in clinical practice. At the moment, there are only a few studies describing this technique, but the sample of patients is too small for the results to be convincing [45].

In a combined study aimed at evaluating the effectiveness of PDT in the treatment of VIN II–III and VIN II–III with the use of photohem at a dose of 2 mg per kg of body weight (exposure time: 48 h, radiation wavelength: 630 nm, energy density: 150 J/cm^2), complete regression was established in 3 out of 5 patients after 3 months. In 2 patients, a partial effect was observed, in connection with which one patient underwent a vulvectomy, and the other underwent a second course of PDT with 5-ALA in the form of ointment application. In two cases with complete regression, there was a relapse of VIN III and VIN II one year after the treatment. Cutaneous phototoxicity

and facial edema, which was regarded as a side effect of treatment, were observed in one patient. The authors concluded that PDT is effective as an alternative method of treating precancerous lesions of the lower parts of the female genital organs, with normal anatomy and sexual function of the organs maintained [46].

Another study published in 2020 compared the effectiveness of combined treatment (CO2 laser + PDT) and CO2 laser monotherapy in the treatment of 40 patients with HPV-associated VAIN I. In the first group (n=20), treatment was carried out with one course of CO2 laser and three courses of PDT with 5-ALA (topical 20% gel, exposure time: 3 h, laser wavelength: 635 nm, energy density: 100–150 J/cm^2, interval: 1 week). In the second group (n=20), 3 procedures were performed with a CO2 laser. In the group of patients who received combined treatment, complete regression was 85%, the frequency of complete eradication of HPV was – 95%, whereas in the second group it was – 65% and 25%, respectively. The data obtained suggest that the inclusion of PDT in the treatment of HPV-associated VaIN I improves the outcome in terms of complete regression and eradication of the viral genome. The method is safe and well-tolerated by the patients [47].

Thus, the analysis of the presented PDT results showed their high practical significance. It is important to emphasize the following facts.

PDT for precancers and primary cancers of the cervix, vulva, and vagina is the minimalist option of organ-sparing treatment, an alternative to surgical methods with the preservation of the anatomical and functional integrity of the organs, which is important for the implementation of reproductive function.

The results of the antiviral efficacy of PDT are of great interest in connection with the proven etiological role of HPV in cervical carcinogenesis and the frequency of PVI presence in female genital organs. The relationship between the complete regression of the tumor process and the eradication of PVI is obvious, which indicates the preventive value of photodynamic radiation against the development of relapses of the disease. A plausible explanation of higher rates of eradication of oncogenic HPV types in comparison with other methods of treatment, and the absence of reinfection over a long period of observation, can be based on selective accumulation of photosensitizer in infected cells, their direct phototoxic destruction, as well as point-like effects on clinical, latent, and subclinical foci of multifocal viral damage. This approach leads to a significant reduction in the likelihood of HPV-associated relapses, reducing the duration of antiviral therapy in comparison with standard therapeutic methods of treatment.

The reasons for the ineffectiveness of PDT are noncompliance with the developed and approved PDT methods for each nosological form of the disease.

PDT provides full-fledged medical and social rehabilitation of patients, and the economic significance of the method comes from the fact that no labor rehabilitation is required after the treatment.

PDT can be considered as a secondary method for prevention of HPV$^+$ CC, HPV$^+$ vulvar cancer, HPV$^+$ vaginal cancer, but PDT can also be used as an independent treatment method, which opens up broad prospects for its use in gynecology and oncogynecology.

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