PHOTODYNAMIC THERAPY FOR PRECANCER DISEASES AND CERVICAL CANCER (REVIEW OF LITERATURE)

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Abstract

The paper presents the results of literature data analysis on the main directions of precancerous diseases of the cervix uteri and cervical cancer treatment. Side effects following surgery or radiation treatment can lead to structural deformities, scarring, hyperpigmentation, systemic side effects, and destruction of normal tissue. In addition, the use of traditional methods of treatment can cause multidrug resistance, which will lead to ineffective treatment and the development of a relapse of the disease. To avoid toxicity and reduce side effects, alternative treatment strategies have been proposed. Photodynamic therapy (PDT) is a promising organ-preserving highly selective method for treating cervical neoplasia, which includes two stages: the introduction of a photosensitizer and local exposure to directed light radiation. A number of studies have demonstrated the high clinical efficacy of this method in the treatment of patients with cervical neoplasia and carriage of human papillomavirus infection without adverse consequences for fertility. The use of PDT contributes to the successful outcome of the treatment of pathological foci on the mucous membrane of the cervix, the effectiveness and safety of the method is ensured by the selective effect on tissues. In the course of treatment, normal surrounding tissues are not damaged, there is no gross scarring and stenosis of the cervical canal, thereby PDT allows maintaining the normal anatomical and functional characteristics of the cervix.

Key words: cervical cancer, cervical dysplasia, human papillomavirus, photodynamic therapy, photosensitizers..

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ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ ПРЕДРАКОВЫХ ЗАБОЛЕВАНИЙ И РАКА ШЕЙКИ МАТКИ (ОБЗОР ЛИТЕРАТУРЫ)

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Резюме

Представлены результаты анализа данных литературы об основных направлениях лечения предраковых заболеваний шейки матки и рака шейки матки. Побочные эффекты после хирургического или лучевого лечения могут привести к структурным деформациям, рубцам, гиперпигментации, системным побочным эффектам и разрушению нормальных тканей. Использование традиционных методов лечения может вызвать множественную лекарственную устойчивость, что приведет к неэффективности лечения и развитию рецидива заболевания. Чтобы избежать токсичности и уменьшить побочные эффекты были предложены альтернативные стратегии лечения. Перспективным органосохраняющим высокоселективным методом лечения неоплазии шейки матки является фотодинамическая терапия (ФДТ), которая включает два этапа: введение фотосенсибилизатора и локальное воздействие направленного светового излучения. В ряде исследований продемонстрирована высокая клиническая эффективность этого метода в лечении пациенток с цервикальной неоплазией и носительством инфекции вируса папилломы человека без неблагоприятных последствий для фертильности. Использование ФДТ способствует успешному результату лечения патологических очагов на слизистой оболочке шейки матки, эффективность и безопасность метода обеспечивается избирательностью воздействия на ткани. В процессе лечения не повреждаются нормальные окружающие ткани, не происходит грубого рубцевания и стеноза цервикального канала, тем самым ФДТ позволяет сохранить нормальные анатомо-функциональные характеристики шейки матки.

Ключевые слова: рак шейки матки, дисплазия шейки матки, вирус папилломы человека, фотодинамическая терапия, фотосенсибилизатор.

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Introduction

Currently, cervical cancer (CC) is one of the most common oncological diseases and is a serious public health problem. In most countries, this disease is the main cause of death for women [1]. According to the International Agency for Research on Cancer, in 2020, 603,863 new cases of cervical cancer were registered in the world, of which 341,680 were fatal. In the structure of oncological mortality in women, cervical cancer is 7.7% [2]. The 5-year survival rate of patients with cervical cancer in 2020 varied in different countries from 37% to 77% [3]. The proposed approaches to the treatment of this disease largely depend on the stage of the disease, the presence of relapses and tumor metastases [4].

Intraepithelial neoplasia of the cervix are precancerous forms of CC. The risk of developing a malignant tumor in patients with squamous intraepithelial neoplasia is 20 times higher than in healthy women [5]. Therefore, timely treatment of cervical intraepithelial neoplasia (CIN) in the early stages is an extremely important task to prevent the development of cervical cancer.

In the vast majority of cases, the human papillomavirus (HPV) acts as the leading etiological factor in the development of squamous intraepithelial lesions of cervical cancer and squamous cervical cancer [6].

Conventional anticancer therapy for cervical cancer includes surgery, radiation therapy, and chemotherapy. However, these methods have obvious disadvantages [7].

Side effects after surgery or radiation treatment can lead to structural deformities, scarring, hyperpigmentation, systemic side effects, and destruction of normal tissues. In addition, the use of traditional therapies can cause multidrug resistance, leading to treatment failure and disease recurrence. Alternative treatment strategies have been proposed to avoid toxicity and reduce side effects. Photodynamic therapy (PDT) is one of the least invasive methods, in which non-toxic photosensitizers (PS) are administered systemically or applied locally, followed by their activation by light of a certain wavelength in the presence of cellular oxygen. PDT is successfully used in clinical practice, in particular, in the treatment of oncological diseases [8, 9, 10]. PDT makes it possible to achieve positive results, avoid the appearance of rough cicatricial tissues, and preserve the patients' quality of life, including in cases where the use of other methods of antitumor therapy was ineffective [11, 12, 13]. Fluorescent diagnostics, also based on the use of PS, is successfully used for the purpose of early diagnosis of neoplasms, as well as to clarify the boundaries of an already detected tumor focus and identify additional foci during surgical treatment in order to more radically remove the tumor and reduce the likelihood of recurrences [14, 15].

After a certain time (from several minutes to several days), the tumor is irradiated with red or near infra-

red light, which excites the PS with the formation of a long-lived triplet state. PS reacts with ambient oxygen to form reactive oxygen species and/or hydroxyl radicals, which kill tumor cells, destroy tumor blood vessels, and lead to tumor regression and necrosis [16].

The aim of the work was to analyze the literature on the effectiveness of PDT for precancerous diseases of the cervix and cervical cancer.

The effectiveness of PDT depends primarily on the accumulation of PS in the affected tissue, as well as on local light delivery. At the same time, the physicochemical properties of PS have a great influence on their effectiveness, pharmacodynamics, and pharmacokinetics [17]. Porphyrins, chlorins, bacteriochlorins, and phthalocyanins have been extensively studied for use in PDT. Several compounds have received clinical approval [18, 19]. For the treatment of large or deep-seated tumors, bacteriochlorophyll a derivatives with intense absorption in the long-wavelength region of the spectrum have recently been studied [20]. Numerous experimental works studying the mechanisms of action, tissue and cellular targets of PS have been performed abroad [21] and in Russia [22, 23].

Results of experimental studies of the effectiveness of PDT

In 2019, Guo W. et al. [7] investigated *in vitro* the antitumor activity of curcumin-containing liposomes against three different cancer cell lines: HeLa, UD-SCC-2, and VX2. Cancer cells in the concentration range from 0 to 100 μmol/l were incubated with liposomes for 4 h, then irradiated with LEDs at a wavelength of 457 nm and an energy density of 1, 3, and 5 J/cm^2. The results showed increased cytotoxicity at a light energy density of 3 J/cm^2, a decrease in the rate of colony formation, cell proliferation and migration. Curcumin-containing liposomes have been proposed as an effective treatment for HPV-associated cancers.

Microencapsulation and targeted delivery of cytotoxic and antibacterial agents during PDT improve the results of cancer treatment. In many cases, loss of potency, poor encapsulation efficiency, and inadequate drug dosing hinder the success of this technology. Therefore, the development of new and reliable microencapsulated dosage forms that provide high therapeutic efficacy is of paramount importance. In the study of Ermakov A.V. et al. [24] a delivery using biodegradable microcapsules assembled from dextran sulfate (DS) and poly-1-arginine (PArg), a choline derivative of zinc phthalocyanine (holosens), a water-soluble cationic preparation for PDT was carried out *in vitro*. The capsules were tested using cervical adenocarcinoma (HeLa) cell lines, normal human diploid fibroblasts (NHDF), and two bacterial strains: Gram-positive Staphylococcus aureus and Gram-negative Escherichia coli. The results of the study provided strong evidence that the encapsulated forms of holosens are effective as PDT preparations. The authors believe that polymer multilayer capsules obtained by sequential self-assembly on the surface of additional naturally occurring biocompatible polyions will outperform the vast majority of nanomaterials in cancer treatment due to their stable structure and safety.

A study of the effect of 5-aminolevulinic acid PDT (5-ALA-PDT) on the endoplasmic reticulum and associated mechanisms of infection with high-risk HPV types showed that 5-ALA-PDT suppressed the viability of HeLa cells *in vitro* and induced autophagy in HeLa cells via the pathway Ca^{2+}-CamKKβ-AMPK. At the same time, 5-ALA-PDT induced apoptosis via activation of caspase 12 [25].

The same authors investigated the effectiveness of combined treatment of HPV infection with 5-ALA-PDT and dihydroartemisinin (DHA). DHA is a derivative of artemisinin, which has an inhibitory effect on cancer cells. HeLa cells were treated with 5-ALA and/or DHA and PDT was performed. Cell viability, proliferation duration, production of reactive oxygen species (ROS), and apoptosis activity were assessed. It was found that the use of DHA can enhance the effect of 5-ALA-PDT on the duration of cell proliferation and viability, the level of ROS production, and apoptosis in HeLa cells. According to the authors, the use of 5-ALA and DHA during PDT is very promising, since DHA enhances the effect of 5-ALA-PDT in the presence of HPV [26].

In the work of J.H. Ha and Y.J. Kim [27] the possibility of using capsules with pheophorbide A (an epitopic analogue of oncoprotein E7, EAE7) as part of polymeric nanoparticles in the combined treatment of HPV infection using PDT and cold plasma treatment of cervical cancer cells was evaluated. The results of *in vitro* analysis of PDT efficiency demonstrated that the use of nanoparticles increases the activity of the method in relation to CaSki cells, which is due to an increase in the targeted effect of radiation. The combined effect, causing increased intracellular formation of reactive oxygen species and apoptotic death of tumor cells, more effectively inhibited the growth of cervical cancer cells.

M. Pola et al. [28] studied the role of oxygen during photodynamic treatment of CC cells of the HeLa line. The effect of PDT was evaluated by adding disulfonated zinc phthalocyanine ($ZnPcS_2$) and tetrasulfonated zinc tetraphenylporphyrin ($ZnTPPS_4$) to the cell culture. Analysis of phototoxicity at various levels of oxygen partial pressure showed dose-dependent cellular responses during PDT. The efficiency of using $ZnPcS_2$ as a PS at the minimum level of oxygen in the atmosphere was noted. It was found that hyperbaric

oxygen therapy did not result in higher PDT efficacy with any of the PSs used in the study. At the same time, both PS can cause a significant decrease in the potential of the mitochondrial membrane, and $ZnPcS_2$ has a more pronounced effect on mitochondrial respiration, which is completely blocked after two short sessions of PDT. In general, the results of the study showed that PDT can be effective even under hypoxic conditions with the selection of the appropriate PS, for example, $ZnPcS_2$.

Z. Li et al. studied the action mechanism of a new PS (TBZPy) and the possibility of its potential use in the treatment of HPV-associated diseases with a high carcinogenic risk. HeLa cells infected with HPV type 18 were subjected to PDT using TBZPy. PDT contributed to the loss of the mitochondrial membrane potential, led to suppression of the expression of anti-apoptotic proteins, increased the expression of pro-apoptotic proteins, stimulated the production of reactive oxygen species, the release of lactate dehydrogenase and apoptosis of HeLa cells *in vitro*, and suppressed cell viability. Photodynamic exposure also suppressed the expression of HPV E6 and E7 proteins, which indicated the possibility of using the new PS in the treatment of diseases etiologically associated with human papillomavirus infection [29].

Results of clinical studies of the effectiveness of PDT of precancerous lesions of cervix and cervical cancer

In clinical trials, PDT has proven to be a promising organ-preserving highly selective treatment for intraepithelial neoplasia of cervical cancer and early invasive cervical cancer. According to the data given in the work of Park Y.K. et al. [30], the frequency of complete remission during PDT of cervical intraepithelial neoplasia was noted in 95% of cases. The authors showed that PDT can be recommended as a new method for the treatment of patients with pre-malignant lesions, as well as carcinoma in situ and early invasive cervical cancer. In the case of more advanced stages of invasive cervical cancer, combined chemo-photodynamic therapy is necessary.

J. Xie et al. [31] assessed the HPV viral load before and after PDT with 5-ALA during a dynamic examination of 111 patients with genital warts. In condyloma cells, induction of the expression of the regulatory proteins LC3II and p62 was observed along with an increase in the regulatory activity of caspase-3. This approach contributed to the inhibition of HeLa cell proliferation in a dose-dependent manner and effectively reduced the HPV viral load by influencing autophagy, apoptosis, Ras/Raf/MEK/ERK and PI3K/AKT/mTOR signaling cascades.

The high clinical efficacy of the PDT method has been demonstrated in the treatment of patients with CIN and carriers of cervical HPV infection without adverse effects on fertility [32].

The effectiveness of PDT with 5-ALA in the treatment of foci of vaginal intraepithelial neoplasia has been shown. H. Cai et al. [33] evaluated the effectiveness of PDT in 6 women aged 49-54 years with a diagnosis of HPV-induced vaginal intraepithelial neoplasia. Treatment included 4 to 8 procedures. Irradiation was carried out 3 h after the introduction of 5-ALA, the power density was 80 mW/cm^2. In 4 out of 6 women, the result of testing for HPV was negative 3-4 months after the end of PDT. There were no signs of relapse during this follow-up period.

The efficacy and safety of PDT in the treatment of cervix neoplasms have also been substantiated in a number of other studies. Tissue selectivity and high safety of the method compared to traditional methods have contributed to the fact that PDT is increasingly being used as an effective alternative approach to the treatment of HPV-associated CIN and preinvasive cancer, especially in young women planning reproductive function [34, 35].

Several types of PS are currently in use, but it should be noted that there are no clinical trial data comparing the efficacy of these PS in the treatment of CIN or cervical HPV infection.

The high efficiency of PDT with the use of PS based on chlorin e6 in the treatment of women with severe squamous intraepithelial damage to cervical cancer (HSIL) [36, 37]. The advantages of these PS are the selectivity of accumulation in tissues, which leads to mild phototoxicity and a low incidence of side effects. The high rate of distribution of water-soluble PS derivatives of chlorin e6 in tumor tissues makes it possible to shorten the interval between drug administration and irradiation. The action mechanism of these PSs is largely based on the accumulation of the drug in the vascular network that feeds the neoplasm, which justifies the effectiveness of PDT [38].

Resistant persistence of HPV is also due to the presence of the virus in the vaginal mucosa, as a result of which re-infection with cervical cancer is possible [39]. Therefore, the actual problem remains the development of treatment methods that allow to achieve the elimination of the virus from all mucous membranes of the genital tract, to which HPV is tropic. Based on this, it is impossible to carry out the destruction and/or ablation of relatively large areas on the surface of the cervix, vagina and vulva at the same time, given the possibility of infection of these anatomical areas. The advantage of PDT is the possibility of influencing all localizations in order to eradicate HPV.

A systematic review and meta-analysis of 168 randomized clinical trials by M.C. Choi et al. demonstrated the effectiveness of PDT in patients with CIN

grades I, II, and III [40]. According to the pooled data, 82% (804 of 980) of patients achieved primary complete remission at the end of the 3-month follow-up period, which was confirmed by cytological and histological data. None of the patients was pregnant at the time of PDT, 6 women became pregnant within 3 months after the end of treatment and gave birth to full-term healthy babies. These results indicate the effectiveness of the method for the treatment of patients with HPV-associated squamous intraepithelial lesions of cervical cancer without any serious adverse effect on fertility.

In another study [36], 15 patients with CIN were able to become pregnant after PDT treatment. Of these, 6 women gave birth to full-term children, 2 required delivery by caesarean section, 1 patient had a dead fetus, 4 who became pregnant within 3 months after PDT had inevitable miscarriage in the early stages of gestation.

In the study of E.V. Grebenkina et al. [41] the experience of PDT treatment of 12 patients diagnosed with CIN II–III and cancer in situ was described. The chlorin PS photolon was administered intravenously at a dose of 0.75–1.15 mg/kg of body weight, after 1.5–2 hours an irradiation session was performed using a polypositional laser exposure technique (the energy density of laser radiation was 150 J/cm^2, the power density – 400–500 mW/cm^2). 30 days after treatment, cervical conization was performed with endocervical curettage. According to the results of the histological study of postoperative material, the effect of treatment in 4 patients was assessed as complete regression, 7 patients had small CIN I foci, and 1 had CIN II foci. In 8 out of 10 HPV-positive patients, complete eradication of HPV was obtained after treatment. No serious adverse events were reported during the irradiation procedure. The authors concluded that the pronounced therapeutic effect, high antiviral activity, and good tolerability make it possible to consider PDT as an alternative organ-preserving treatment for early cervical cancer and precancer.

In the study [42], the purpose of which was to optimize the parameters of PDT with the PS photoditazine in patients with tumor and precancerous pathology of cervical cancer, 52 patients were included, of which 34 were diagnosed with precancerous cervical disease, 11 with cervical cancer, and 7 with chronic cervicitis. PS in the form of a 0.5% gel was applied to the CM in a volume of 1 ml. The results of the study showed that photoditazine accumulates well in pathological tissues. The maximum accumulation of the drug was noted after 30 min, persisted for about 15 min, then the PS level gradually decreased. It was found that the minimum light dose required to activate photochemical reactions is 100 J/cm^2, while the optimal dose that destroys all atypical cells is 250 J/cm^2.

E. V. Filonenko et al. [43] presented the results of a clinical study of the effectiveness of PDT with radachlorin in 30 patients with precancerous and neoplastic cervical pathology. PS was administered once intravenously by means of a 30-minute infusion at a dose of 1.0 mg/kg of body weight 3 hours before irradiation at a power density of 300–350 J/cm^2. The result of treatment in 26 (86.7%) patients was qualified as a complete regression of the tumor, in 4 (13.3%) – as a partial regression. In groups with a clinical diagnosis of cervical erosion, II st. dysplasia and carcinoma in situ complete regression was observed in all cases. After the first course of PDT in the group of patients with stage III dysplasia, complete regression was achieved in 77%, with a diagnosis of cervical cancer Ia. stage – in 75% of observations. Patients with partial regression of the pathological process 3–6 months after the end of the first course of treatment underwent a second course of PDT, which resulted in complete regression. During treatment and during follow-up, no adverse reactions associated with the use of radachlorin or PDT were recorded. The PDT method using radachlorin showed high efficiency in the treatment of cervical cancer pathology.

M.C. Choi et al. [44] reported the frequency of adverse events during PDT at the level of only 13.6%. Adverse reactions were manifested only by a burning sensation and vaginal discharge from mild to moderate severity.

T.G. Ahn and S.J. Han [45] in cervical cancer 1B1 and 1B2 st. in women of childbearing age who wished to preserve fertility, simultaneous chemo-photodynamic therapy (CPDT) was used. 16 months after the cessation of CPDT, 2 out of 3 patients gave birth to full-term babies by caesarean section. 45 months after 1 patient gave birth to twins by caesarean section. Observation for 60 months revealed no cases of recurrence of the disease.

In general, the currently available information on the effectiveness and safety of PDT, as well as the convenience and ease of use of the method, allow us to consider this medical technology as the most promising direction in the treatment of varying degrees of severity of intraepithelial lesions of the cervix, vulva, and vagina [46].

The effectiveness of PDT in the treatment of patients with CIN depends on the PS chemical structure and the method of its administration. At the same time, the maximum efficiency is achieved with systemic (intravenous) administration of PS, while the use of 5-ALA application forms (solutions, gels and ointments) does not lead to high efficiency in the treatment of CIN. The results of studies by various authors confirm the wide possibilities of using PDT in the treatment of patients with CIN, which is

possible due to the presence of a number of advantages of this method compared to existing standard methods of treatment. The main advantages of PDT include minimal toxicity to surrounding normal tissues due to the selective accumulation of PS in pathological tissues, a low risk of a pronounced pain syndrome, minor systemic effects, the absence of mechanisms of primary and acquired resistance, the possibility of an outpatient treatment session, the possibility of combination with other methods of therapeutic exposure, the absence of limiting cumulative doses of PS and light exposure, the possibility of repeating the procedure many times, good cosmetic results, the possibility of implementing an organ-preserving approach [9, 15, 47].

Conclusion

Due to the fact that CC occupies a leading position among malignant tumors in women aged 15 to 39 years, there is a need for adequate timely treatment of precancerous CC and early invasive CC while maintaining the reproductive capabilities of patients. CC is one of the most successfully treatable forms of cancer when the disease is detected at an early stage. Therefore, the development of effective alternative methods for the treatment of HPV-associated squamous intraepithelial lesions of cervical cancer and preinvasive cervical cancer without compromising the patient's fertility is of high relevance.

An analysis of literature data indicates that the use of PDT contributes to the successful treatment of pathological foci on the cervical mucosa. The effectiveness of the method is ensured by the selectivity of the effect of light radiation on pathologically altered tissue areas in this area. When implementing the method, an impact is carried out that does not cause damage to normal surrounding tissues, rough scarring and stenosis of the cervical canal, thereby PDT allows to save the normal anatomical and functional characteristics of the cervix.

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