ORIGINAL ARTICLES

PHOTODYNAMIC THERAPY IN THE PREVENTION OF HPV-INDUCED RECURRENCES OF PRECANCER AND INITIAL CANCER OF THE CERVIX

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Abstract

Photodynamic therapy (PDT) has antiviral activity and is an effective method for preventing cervical HPV-associated relapses. In our study, we assessed the effectiveness of prophylactic anti-relapse PDT of the cervical stump at the second stage after high amputation of the cervix in 65 patients with a clinical diagnosis of carcinoma in situ and 35 with a diagnosis of cervical cancer stage 1A1. As a photosensitizer, a drug based on 5-aminolevulinic acid (5-ALA) in the form of a 12% gel at a dose of 0.1 mg/cm^2 was used. Irradiation was performed after 4 hours (light dose – 150 J/cm^2). Complete eradication of HPV DNA was achieved in 94% of patients. In the remaining 6% of observations, the antiviral effect was registered as eradication of one or two types in case of multiple HPV infection with dominance of strains 16 and 18, or a significant decrease in the viral load. The observation periods ranged from 3 to 10 years. A persistent antiviral effect was maintained throughout the observation period in 93 (93%) women. Thus, PDT of the cervical stump with 5-ALA provides a pronounced antiviral effect at the second stage of treatment of precancerous and initial tumor pathology of the cervix due to the selective accumulation of the photosensitizer in infected cells with their subsequent direct phototoxic and photochemical destruction to the basal and parabasal layers of the epithelium, in which virus replication occurs.

Key words: cervical cancer, photodynamic therapy, human papillomavirus, 5-aminolevulinic acid.

For citations: Trushina O.I., Filonenko E.V., Novikova E.G., Mukhtarulina S.V. Photodynamic therapy in the prevention of HPV-induced recurrences of precancer and initial cancer of the cervix, *Biomedical Photonics*, 2024, vol. 13, no. 3, pp. 42–46. doi: 10.24931/2413–9432–2024–13–3 –42–46

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ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ В ПРОФИЛАКТИКЕ ВПЧ-ИНДУЦИРОВАННЫХ РЕЦИДИВОВ ПРЕДРАКА И НАЧАЛЬНОГО РАКА ШЕЙКИ МАТКИ

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Резюме

Фотодинамическая терапия (ФДТ) обладает противовирусной активностью и является эффективным методом профилактики цервикальных ВПЧ-ассоциированных рецидивов. В нашем исследовании была оценена эффективность профилактической противорецидивной ФДТ культи шейки матки на втором этапе после высокой ампутации шейки матки у 65 пациенток с клиническим диагнозом carcinoma in situ и 35 – с диагнозом РШМ 1А1 ст. В качестве фотосенсибилизатора использовали аппликационно препарат на основе 5-аминолевулиновой кислоты (5-АЛК) в виде 12%-го геля в дозе 0,1 мг/см^2. Облучение проводили через 4 ч (световая доза – 150 Дж/см^2). Полная эрадикация ДНК ВПЧ была достигнута у 94% пациенток. В остальных 6% наблюдениях противовирусный эффект зарегистрирован в виде эрадикации одного или двух типов при множественном инфицировании ВПЧ с доминированием 16 и 18 штаммов, или значительном снижении вирусной нагрузки. Сроки наблюдения составили от 3 до 10 лет. Стойкий противовирусный эффект в течение всего периода наблюдения сохранялся у 93 (93%) женщин. Таким образом, ФДТ культи шейки матки с 5-АЛК обеспечивает выраженный противовирусный эффект на втором этапе лечения предопухолевой и начальной опухолевой патологии шейки матки за счет селективного накопления фотосенсибилизатора в инфицированных клетках с последующим их прямым фототоксическим и фотохимическим разрушением до базальных и парабазальных слоев эпителия, в которых происходит репликация вируса.

Ключевые слова: рак шейки матки, фотодинамическая терапия, вирус папилломы человека, 5-аминолевулиновая кислота.

Для цитирования: Трушина О.И, Филоненко Е.В., Новикова Е.Г., Мухтарулина С.В. Фотодинамическая терапия в профилактике ВПЧ-индуцированных рецидивов предрака и начального рака шейки матки // Biomedical Photonics. – 2024. – Т. 13, № 3. – С. 42–46. doi: 10.24931/2413–9432–2024–13–3–42–46

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Introduction

The problem of cervical cancer (CC) has been the focus of attention of leading oncologists from all over the world for many decades. The steady increase in the number of women with malignant neoplasms of the cervix and the pronounced trend towards "rejuvenation" of the disease undoubtedly indicate the relevance of the search, development and implementation of new approaches to the prevention, diagnosis and treatment of cervical precancerous and tumor pathology. In the successful implementation of these tasks, an important role is given to the etiological factor of cervical carcinogenesis – the human papillomavirus (HPV). The DNA of this viral agent has a high oncogenic potential and is found in 99.7% of CC [1,2].

Over the past two decades, much attention has been paid to the issues of progression of papillomavirus infection (PVI) to invasive CC, while an equally important direction in the prevention of relapses of the disease after organ-preserving treatment of initial cervical oncopathology remains poorly studied. Recurrence of the tumor process in the cervix indicates to a greater extent the persistence of HPV, the leading factor in stimulating epithelial proliferation [3,4]. This viral agent is capable of initiating relapses of cervical intraepithelial neoplasia II-III (CIN) and initial CC (carcinoma in situ, CC stage 1A1) during the first three years after electrosurgical conization, the frequency of which, according to a number of authors, is variable and amounts to 15-75% [5,6]. Relapses of the disease in women under 40 years are more common (57.9%) than at an older age [7]. The frequency of relapses increases with involvement of the cervical canal in the process or in the case of mixed localization of the process, especially at the age of 30-39 years – 83.3% [8].

The causes of recurrence of precancer and initial cervical cancer of the uterine in the presence of a negative morphological resection margin are: preservation and persistence of latent and subclinical forms of HPV in unchanged tissues at the border with resection or destruction, necrosis zone, multifocal lesions; deposition of HPV DNA along with smoke on the mucous membranes of the cervix and vagina; the presence of additional foci of HPV infection in the vagina and perineum in every fourth woman with cervical neoplasia; reinfection; the inability to prevent the expression of papillomaviruses in the surrounding tissues [9,10,11,12,13].

The ineffectiveness of antiviral drug therapy aimed at regulating and normalizing the immune system is due to the effect only on episomal forms of HPV activity without destroying the virus strains integrated into the cellular genome [14,15]. Ablation methods (radiofrequency, electro-cryo-laser, argon-plasma) do not ensure HPV eradication due to insufficient destruction depth, when only the superficial epithelium is destroyed without sanitizing the actively multiplying viral strains located in the basal layer [16]. Physical treatment methods also do not have the ability to precisely destroy papillomaviruses and do not affect the squamous-cylindrical junction of the epithelia and foci of metaplasia in the cervical canal [17,18]. In addition, the persistence of HPV leads to reactivation of latent infection to subclinical and clinical forms. Patients with a latent form of infection represent a risk group for the development of cervical relapses [19].

Thus, antitumor treatment measures do not have a targeted pathogenetically determined effect on HPV, since they do not take into account the features of the life cycle and physical status of the viral genome, respectively, and the risk of HPV-associated relapses of CIN and initial CC remains quite high.

The viral concept of cervical cancer dictates the need to revise traditional approaches to improving the results of treatment of precancerous and initial tumor pathology of the cervix, to search for new effective pathogenetically substantiated methods of influencing the risk factors of malignant progression of PVI, which will significantly reduce the risk of cervical relapses.

Materials and Methods

One of the promising methods of antiviral therapy and, accordingly, prevention of cervical HPV-associated relapses is photodynamic therapy (PDT). The method is based on the selective accumulation of a photosensitizer (PS) in virus-containing cells and the interaction of this drug with light radiation of a certain wavelength, which initiates a series of photophysical processes leading to the destruction of these cells that have accumulated the drug [20]. In connection with the above-described mechanism, it is advisable to supplement surgical treatment of virus-associated precancer and early cervical cancer with one or more courses of antiviral PDT.

PDT of the cervical stump was performed at the second stage after high amputation of the cervix in 65 patients with a clinical diagnosis of carcinoma in situ and 35 with a diagnosis of CC stage 1A1. The average age of the women was 35.6 ± 3.7 years. A drug based on 5-aminolevulinic acid (5-ALA) was used as a photosensitizer. The risk factors for HPV infection included young age, onset of sexual activity before the age of 16 (40%), more than 5 sexual partners (53.5%), infection with bacterial and other viral flora (18.2%), long-term use of oral contraceptives (5%), smoking and unprotected sex (50%).

Identification and differentiation of HPV DNA in all studies were performed using qualitative (PCR) and quantitative (RT PCR, Hybrid Capture II, competitive PCR) methods of detecting the viral genome. The

qualitative method identified virus-positive women, established the frequency of various types of PVI, determined the number of observations with mono- and mixed infection, identified age-related changes, and was also used to assess the antiviral efficacy of PDT. Quantitative research methods were performed to study the activity of the viral genome in stimulating epithelial proliferation, comparing the values of virus concentration with the severity of morphological changes, assessing and monitoring the antiviral efficacy of PDT depending on the genotype, mono- or mixed infection.

The unit of measurement for PCR RT was the logarithm of HPV DNA copies per 10^5 epithelial cells (lg/10^5 cells), Hybrid Capture II – exceeding the clinically significant threshold level (this threshold was estimated as a concentration of 100 thousand genocopies/ml or 1 mg/ml), competitive PCR – the viral load of the 16th type of HPV in various concentrations from 101 to 106 copies per test tube.

A diagnostic test for HPV DNA identification was performed before surgical treatment by collecting not only cervical scrapings, but also material from the mucous membranes of the dome and vaginal walls, in which HPV, a powerful carcinogen and a key factor in disease recurrence, can also persist.

Infection with highly oncogenic HPV genotypes was an indication for PDT of the cervical stump after organ-preserving treatment with 5-ALA, an inducer of endogenous protoporphyrin IX (PPIX) synthesis. Treatment was performed on the 6th-8th day of the menstrual cycle. The time interval between the surgical stage of treatment and PDT was 3-4 weeks and depended on the timing of epithelialization in the treatment area.

Testing for HPV DNA was performed during the first year of observation 3-6-12 months after PDT, the second year – 6-12 months and in subsequent years (upon achieving complete eradication) – once every 3 years.

The antiviral efficacy of PDT was assessed by the following criteria:

- complete effect – complete eradication of HPV DNA, absence of viral load;
- no effect – absence of eradication of all types of HPV DNA and/or decrease in viral load values.

When developing the technique of antiviral PDT of the cervical stump, the need for irradiation of not only the integumentary epithelium of the cervical stump, but also the remaining part of the cervical canal, as well as the vaults and walls of the vagina was taken into account. This approach ensures an effect not only on the resection zone, but also on externally unchanged adjacent tissues.

5-ALA in the form of a 12% gel at a dose of 0.1 mg/cm^2 was applied topically to the cervical stump, capturing the vaults and the upper third of the vagina, 4 hours before irradiation. Light regime is not required with this technology.

The diode laser "LFT-630-01-BIOSPEC" (Russia) was used as a source of light radiation. The radiation wavelength was 635 nm, the energy density was 150 J/cm^2.

PDT of the cervical canal was performed using a flexible mono-fiber quartz light guide with a cylindrical diffuser providing a 360^0 light matrix and a length corresponding to the length of the endocervix (from 1 to 2 cm). Photodynamic exposure to the vaginal portion of the cervical stump was performed remotely using a light guide with a lens and a light spot diameter of 2-3.5 cm. Irradiation was performed from one position.

The reaction of the cervical epithelium in the photodynamic exposure zone was minor edema and mild tissue hyperemia with the development of film necrosis on days 2-3 without a significant increase in these phenomena in the following days. Epithelialization processes were completed by the 12th-13th day of treatment.

Local administration of 5-ALA gel did not cause adverse or local allergic reactions in any clinical observation; the tolerability of the pharmaceutical was satisfactory. Cutaneous phototoxicity in the form of photodermatosis did not occur in any observation.

Results

A study of the overall prevalence of HPV types, which consists of the sum of the frequency of occurrence of the virus as a monotype and its association with other types, revealed a significant proportion of women (58.9%) infected with type 16 ($p<0.05$). The remaining types were distributed by frequency of prevalence as follows: 18 – 12.8%, 31 – 10%, 45 – 7%, 33 – 4.5%, 35 – 3.8%, 56 – 2.6%, 58 – 0.2%. In a small number of cases, types 39, 48, 51, 52 were identified (0.1%). The data obtained coincide with large-scale epidemiological studies, which established the leading role in the development of cervical cancer of highly oncogenic HPV genotypes, among which types 16 and 18 are found in 70% of cases.

The number of patients infected with two or more HPV types was significantly higher (62.8%) than with one type (37.2%) ($p=0.000006$), while the frequency of multiple types of the viral genome did not depend on the severity of pathological changes in the cervix ($p<0.01$).

In the age category up to 40 years, there were more patients infected with several HPV types (75.6%) than in the group of older women (24.4%). This fact can be associated with higher sexual activity in reproductive age. The frequency of HPV type 16 was almost identical in the group of women of reproductive, premenopausal and postmenopausal ages in 88.2%, 86.7% and 86.3% of observations, respectively, which indicates the leading

etiologic role of HPV type 16 in inducing malignant transformation in the cervical epithelium, regardless of age characteristics.

The antiviral efficacy of PDT of the cervical stump was assessed in all clinical observations (n=100). Complete eradication of HPV DNA was achieved in 94% of patients. In the remaining 6% of observations, the antiviral effect was recorded as eradication of one or two types in case of multiple HPV infection with the dominance of strains 16 and 18, or a significant decrease in the viral load.

The observation periods ranged from 3 to 10 years. Complete eradication of HPV DNA after PDT of the cervical stump was established in 94 (94%) women. A persistent antiviral effect was maintained throughout the observation period in 93 women (93%).

In all clinical observations where there was no complete eradication of HPVt, a 2nd course of PDT was performed with a positive treatment result.

Relapse of the disease was recorded in only one patient (1%) 2 years after completion of treatment for preinvasive cervical cancer, where there was reinfection with HPV type 16 from a sexual partner.

Thus, PDT of the cervical stump with 5-ALA provides a pronounced antiviral effect at the second stage of treatment of precancerous and initial tumor pathology of the cervix due to the selective accumulation of the photosensitizer in infected cells with their subsequent direct phototoxic and photochemical destruction to the basal and parabasal layers of the epithelium, in which virus replication occurs. Higher rates of eradication of oncogenic HPV types in comparison with methods of therapeutic, surgical and physical effects on the viral genome, the absence of reactivation of infection over a long observation period can be associated with the accumulation of endogenous PPIX by HPV-infected cells with subsequent photodynamic destruction of not only clinical and subclinical, but also latent forms of PVI activity. Targeted "point" destruction of multifocal foci of viral infection, irradiation of not only the vaginal portion of the cervical stump, but also the transition zone with the cervical canal along its entire length, destruction of cells with an integrated form of HPV when antiviral drugs are ineffective, impact on the physical status of the virus and viral load, also minimize the risk of activation of the viral process, which predetermines the success of treatment.

The obtained data on the antiviral effectiveness of PDT are of great interest in light of the proven etiological role of HPV in the development of cervical cancer.

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