



Photodynamic therapy of virus-associated precancer and early stages cancer of cervix uteri

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Summary We have analyzed the results of photodynamic therapy using light-sensitizing agent “Photogem” in 72 patients – 56 women with pre-cancerous lesions of cervix and 16 women with early cervical cancer (group 1); Photosens in 47 patients – 35 women with pre-cancerous lesions (CIN III), 12 women with non-invasive cervical cancer (carcinoma in situ) (group 2); and Alasens in 22 patients – 8 women with virus-associated pre-cancerous lesions (high-grade CIN III), 14 with virus-associated early cervical cancer (carcinoma in situ, cervical cancer 1A1) (group 3). The results were as follows: group 1 – complete regression of CIN III and non-invasive cervical cancer (carcinoma in situ) was achieved in 50 (89.2%) and 11 (68.8%) cases, significant regression was achieved in 2 cases (3.6%) and in 2 cases (12.5%), stabilization was achieved in 2 cases (3.6%) and in 2 cases (12.5%), progression was achieved in 2 cases (3.6%) and in 1 case (6.2%) accordingly. In the group of patients after PDT using Photosens complete regression of CIN III and non-invasive cervical cancer (carcinoma in situ) was achieved in 33 cases (94.2%) and in 10 cases (83.4%) cases, significant regression was achieved in 1 case (2.9%) and in 1 case (8.3%), stabilization was achieved in 1 cases (2.9%) and in 1 cases (8.3%). In the group of women after surgical treatment anti-viral efficacy was assessed. It is necessary to note that not a single relapse was observed. Anti-viral effect was registered in 49 (90.4%) cases. The longest HPV-free period that we observed was 5 years. 12 women with CIN III and 4 women with carcinoma in situ became pregnant.

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Introduction

In spite of certain success achieved in the sphere of diagnostics and treatment, cervical cancer is still holding one of the leading places in the oncological morbidity of female sexual sphere [1].

Due to the importance of this problem there appeared a primary necessity in the solution of a difficult, but feasible task is to achieve the minimum of cervical cancer morbidity by regular investigation of factors leading to malignant tumors of uterine cervix and the improvement of treatment methods of cervical intraepithelial neoplasia (CIN) at the early stages of the development avoiding thus pre-cancerous cervical lesions and invasive cervical cancer [2].

One of the reasons of CIN and cervical cancer is human papilloma virus (HPV) which is found in 95–100% cases of cervical cancer [3].

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Table 1 Location of tumor-associated changes of cervix.

Groups of patients	Exocervix		Endocervix		Exo-endocervix		Total
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
CIN III	28	50	10	17.9	18	32.1	56
Cr in situ	8	50	—	—	8	50	16

Taking into account the confirmed etiologic role of high-risk human papillomavirus types in the carcinogenesis of the uterine cervix (World Health Organization, 1996), contagiousity and high specific gravity of latent form course of HPV, prevalence of virus-positive cervical cancer among women of a young age, a very high risk of reinfection after treatment there is a necessity of searching drugs for simultaneous anti-tumor and target anti-viral effects aimed at both tumor process and the source of constant infection by HPV of epithelial layers.

Is it possible to achieve anti-tumor and anti-viral effects, preserving anatomical and functional integrity of the organ, menstrual and reproductive functions, to get higher indexes of eradication, lower indexes of reinfection, to improve prognosis factors relating to the clinical course of precancer and early stages of cervical cancer and completely rehabilitation a woman in medical and social aspects?

In view of the above mentioned the priority tendency of science development nowadays is the search of new treatment methods of malignant neoplasm's based on the use of the latest medical technological achievements in chemistry, biology, quantum physics. One of the promising trends in the solution of these problems is the development of photodynamic therapy (PDT) of malignant tumors based on the use of natural and synthetic light-sensitizing substances.

The research objectives are the following: the development of PDT method for the treatment of virus-associated precancer and early cervical cancer using of the Russian photosensitizers, estimation of anticancer and antiviral efficiency of the Russian photosensitizers, possible side effects and complications, assessment of indexes and future prospects of an organ-preserving treatment of oncogynecological patients.

Materials and methods

Our research was based on the clinicomorphological data during the period of 2002–2007, received after PDT of the cervix uterine performed on 141 women aged 22–63 years, 2/3 of them being at reproductive age.

Clinical investigation included colposcopic, cytological, endoscopic, cervicoscopic, ultrasonic and morphological examination, fluorescent diagnostic, tissue typing of DNA (deoxyribonucleic acid) of HPV, using polymerase-chain reaction (PCR). Terms of observation were from 6 months to 5 years.

PDT of uterine cervix of 56 women with pre-cancerous lesions (CIN III), 16 women with non-invasive cervical cancer (cr in situ) was performed using the Russian photosensitizer Photogem (hematoporphyrin derivate). Photogem was administered intravenously in a semi-lit room 48 h prior to tumor irradiation at a dose of 2.5–3.0 mg/kg.

PDT of uterine cervix of 35 women with pre-cancerous lesions (CIN III), 12 women with non-invasive cervical cancer (carcinoma in situ) were treated using the Russian photosensitizer Photosens (sulfonated aluminum phthalocyanine). Photosens was administered intravenously in a semi-lit room 24 h prior to tumor irradiation at a dose of 0.3 mg/kg.

PDT of carcinoma of cervical stump using the Russian photosensitizer Alasens (5-aminolaevulinic acid hydrochloride) in a form of 5 g application of 20% ointment 4 h prior to tumor irradiation was applied in 22 cases after surgical conization of cervix, 8 women with virus-associated pre-cancerous lesions (high-grade CIN III), 14 with virus-associated early cervical cancer (carcinoma in situ, cervical cancer 1A1).

The most frequent pathological changes in cervical epithelial lesions in both groups of patients were located in the other exocervix, the least were in endocervix. In clinical observations both exo – and endocervix were effected simultaneously (Table 1). Cervicoscopy was used to diagnose localization of pre-cancerous lesion focus and carcinoma in situ in the lower third of cervical canal and in the area of transitional epithelium.

All women were tested for the presence of DNA of HPV, using polymerase-chain reaction (PCR). In 127 (90%) clinical cases genotypes of high cancer risk of DNA of HPV were identified (16, 18, 31, 33, 35, 58). In 95% of cervical samples DNA of HPV 16/18 were found.

PDT of cervix uteri was performed using diode laser of small size apparatus ALDH/2.5-0.1-Kristall (made in Russia) wavelength 630 (Photogem) 675 nm (Photosens), of cervical stump – 635 nm (Alasens).

Laser irradiation of the cervical canal was performed using quartz light tube with cylindrical diffuser 1–3 cm long, vaginal portion of the cervix uteri and the cervical stump by microlens with a spot light diameter ranging 1.0–2.0 cm (from 1.0 to 2.0 cm). The energy density of laser irradiation was 150–200 J/cm², power density was 150–250 mW/cm². There were no pain complaints after PDT procedures regardless of field size or irradiation density.

The assessment of effectiveness of anti-tumor and anti-viral activity of the Russian photosensitizers was based on diagnostic algorithm. During the first year of observation colposcopic, cytological and virological investigations were carried out every 3 months. All patients irrespective of the results of clinical examination one year after cervicoscopic with endocervical curettage was performed, biopsy of cervix uterine was performed if needed.

It should be noted that this diagnostic procedure in case of any pathological changes of cervical epithelium was carried out at earlier periods after treatment. Further examination periods were decreased, patients were examined twice or once a year.

Table 2 Efficacy of PDT according to standard criteria (WHO).

Groups of patients	Complete regression		Significant regression		Stabilization		Progression	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Photogem								
CIN III	50	89.2	2	3.6	2	3.6	2	3.6
Cr in situ	11	68.8	2	12.5	2	12.5	1	6.2
Photosens								
CIN III	33	94.2	1	2.9	1	2.9	—	—
Cr in situ	10	83.4	1	8.3	1	8.3	—	—

Results and discussion

Efficacy of treatment was assessed using standard criteria (WHO) which take into account dynamic changes of tumor size with pathological control (complete or significant regression, stabilization, progression), as well as partial or complete eradication of HPV. Nowadays the terms of observation in the first 2 groups were from 6 months to 5 years, in the third group were from 3 months to 2 years.

In the group of patients after PDT using Photogem complete regression of CIN III and non-invasive cervical cancer (carcinoma in situ) was achieved in 50 (89.2%) and 11 (68.8%) cases, significant regression was achieved in 2 cases (3.6%) and in 2 cases (12.5%), stabilization was achieved in 2 cases (3.6%) and in 2 cases (12.5%), progression was achieved in 2 cases (3.6%) and in 1 case (6.2%) accordingly.

In the group of patients after PDT using Photosens complete regression of CIN III and non-invasive cervical cancer (carcinoma in situ) was achieved in 33 cases (94.2%) and in 10 cases (83.4%) cases, significant regression was achieved in 1 case (2.9%) and in 1 case (8.3%), stabilization was achieved in 1 cases (2.9%) and in 1 cases (8.3%) (Table 2).

In the group of women after surgical treatment anti-viral efficacy was assessed. It is necessary to note that not a single relapse was observed.

In all clinical observations with significant regression the repeated course of PDT will positive results was carried out. All patients with a stable process and in 2 cases of progression till carcinoma in situ and micro invasive cancer surgical conization of cervix uteri with extirpation of 2/3 of organ was performed being the next step of an organ preserving treatment.

Special attention should be paid to high indexes of complete eradication of HPV according to several virological investigations. Complete eradication of HPV was achieved in 120 cases (94.4%) out of 127 cases. The maximum term of complete eradication of HPV was 5 years.

The absence of complete eradication of HPV was achieved in 7 cases (5.6%) with long-lasting HPV hence the second course of PDT with further curing in half cases was performed. The received data present a great interest in view of the confirmed etiological role of HPV in the development of cervical cancer. The given statement is defended by the author's invention certificate.

PDT allows to achieve complete eradication of HPV almost in every clinical observation with severe dysplasia and carcinoma in situ.

After PDT all patients preserved menstrual cycle invariable. To prevent impregnation of women used hormonal contraception and protection methods for 1.5–2 years.

The most important criteria of efficacy of an organ preserving method is a reproductive function of cured patients.

12 women with CIN III and 4 women with carcinoma in situ became pregnant as they planned without any complications. According to obstetrical statements (uterine scar, powerless labor, big fetus, complete placental presentation, high degree myopia) 6 pregnant women were performed a caesarean section. Two women delivered a vaginal birth. Nowadays 6 pregnant women are being observed. In the next 2 cases there was an artificial abortion as the women wished. Children have no important abnormalities in their physical growth. Terms of observation are from 1 month to 3 years.

Summing it up PDT of precancerous lesions and early cervical cancer with the Russian agents is a "minimal type" of organ preserving treatment with preservation of anatomical and functional integrity of an organ, it is very important for women planning labor.

The results of 5 year monitoring of patients with CIN III and carcinoma in situ of cervix uteri testify to the fact that PDT method and modes of laser operation and light dose are appropriate.

The higher indexes of eradication of oncogenic types of HPV as compared to therapeutic, surgical and physical methods to effect HPV and absence of reinfection for a long observation period most probably point to sanitation of basal layer of squamoses integument where replication of virus occurs, they also point to the destruction of cells with integrated form of HPV when antiviral drugs become ineffective.

PDT improves the factors of prognostic for a clinical course of precancerous legions and early cervical cancer.

The received results of antiviral efficacy demonstrate PDT effect the aim of which is to prevent a disease relapse.

Preservation of menstrual and reproductive functions gives a woman an opportunity to fulfill her reproductive function in future.

To sum it up, PDT is an alternative treatment mode of organ preserving treatment that effects not only pathological epithelium, but etiological factors of carcinogenesis of cervical cancer that allows not only to cure a patient but leads to complete medical and social realization of a woman.

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