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

O.I. Trushina PhD*, E.G. Novikova, V.V. Sokolov, E.V. Filonenko, V.I. Chissov, G.N. Vorozhtsov

P.A. Hertzen, Moscow Research Oncological Institute, Russian Federation
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KEYWORDS
Photodynamic therapy; Photogem; Photosens; Alasens; Pre-cancerous lesions; Early cervical cancer; Human papilloma virus (HPV) infection

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 2 cases (3.6%) and in 2 cases (12.5%), 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 s 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].
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.


### 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, cervoscopical, ultrasonic and morphological examination, fluorescent diagnostic, tissue typing of DNA (desoxyribonucleic 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 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 uterai was performed using diode laser of small size apparatus ALDH/2.5-0.1-Krstall (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 microlos 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 1 Location of tumor-associated changes of cervix.

<table>
<thead>
<tr>
<th>Groups of patients</th>
<th>Exocervix</th>
<th>Endocervix</th>
<th>Exo-endocervix</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>CIN III</td>
<td>28</td>
<td>50</td>
<td>10</td>
<td>17.9</td>
</tr>
<tr>
<td>Cr in situ</td>
<td>8</td>
<td>50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Total  | 36 |     | 28 |     | 36 |     |

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

PDT of cervix uterine 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 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.

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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 as compared to therapeutic, surgical and physical methods to effect HPV and absence of reinfection for a long observation period most probably point to sanation 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 coarse 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.

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

<table>
<thead>
<tr>
<th>Groups of patients</th>
<th>Complete regression</th>
<th>Significant regression</th>
<th>Stabilization</th>
<th>Progression</th>
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<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
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<td>Photogem</td>
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<td>CIN III</td>
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<td>3.6</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>CIN III</td>
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<td>1</td>
<td>2.9</td>
</tr>
<tr>
<td>Cr in situ</td>
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<td>83.4</td>
<td>1</td>
<td>8.3</td>
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References

