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Prevalence of Oncogenic Human Papillomavirus and its Association with Cervical Neoplasia

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Annotation: Cervical cancer ranks second in the cancer incidence structure in Uzbekistan. In 2024, 1837 new cases were identified, 1000 women died. Cervical cancer is caused by persistence papillomavirus infection, so the main factor in preventing cervical cancer is screening and vaccination against the human papillomavirus. Infection of the epithelial cells of the cervix with HPV is a necessary but insufficient factor for their malignancy. Therefore, if infection has already occurred, it is important to carry out therapeutic measures aimed at eliminating HPV from the body. One of the effective methods of complex conservative therapy is stimulation of cellular immunity using an analogue of natural purines - inosine pranobex as an immunostimulant . The antiviral effect of inosine pranobex is to suppress the replication of DNA and RNA viruses by binding to the ribosome of the cell. The immunomodulatory ability is characterized by stimulation of nonspecific immunity, increased production of interleukins, increased synthesis of antibodies, stimulation of chemotactic and phagocytic activity of monocytes, macrophages and polymorphonuclear cells. The article consolidates data from open and double-blind placebo-controlled studies of inosine pranobex , which confirmed its effectiveness in the treatment of HPV infection.

Keywords: human papillomavirus, HPV, papillomavirus infection, cervical neoplasia, inosine pranobex , immunomodulators.

The relevance of the problem. Treatment and prevention of cervical diseases associated with the human papilloma virus is determined, first of all, by the ability of this pathogen to initiate oncological transformation.

Infection of cervical tissues with high-risk HPV is a key etiologic factor in the development of cervical cancer. In more than half of cases of moderate and severe squamous epithelium dysplasia of the cervix and in 80-90% of women with invasive cervical cancer, high-risk HPV DNA is detected, which is a key etiologic factor in the development of cervical cancer. In more than half of cases of moderate and severe squamous epithelium dysplasia of the cervix and in 80-90% of women with invasive cervical cancer, high-risk HPV DNA is detected, mainly types 16 and 18 [4,11].

cancer accounts for 16% of the total number of malignant tumors of the female reproductive organs and ranks third [11].

The main factor in preventing cervical cancer is effective treatment of precancerous processes. However, a significant part of treatment measures for precancerous processes is surgical methods aimed at removing the organ or part of it affected by the tumor, which is generally justified.

It is important to note that the elimination of the precancerous lesion together with a part of the affected organ does not eliminate the cause of the precancerous transformation itself, which requires complex conservative therapy aimed at the key pathogenetic links of the disease in order to prevent relapse and prevent further progression of the pathological process in the cervix. Despite the high potential danger, HPV is an opportunistic pathogen, i.e., with a normal level of immunity and the absence of additional risk factors, in most cases the body manages to eliminate the papillomavirus infection on its own.

Sherman ME et al. indicate that in the United States, of more than 50 million women with HPV, clinical manifestations of the infection are noted in 10 million, and cervical intraepithelial neoplasia (

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Cervical intraepithelial neoplasia (CIN) of varying degrees and invasive cervical cancer are annually detected in only 2.5 million (CIN I-II), 65 thousand (CIN III) and 14 thousand women (cervical cancer), respectively [15].

Other studies have shown that only 5% of CIN I cases transform into invasive cancer, with CIN II disease progression observed in 10%, and with CIN III – in less than 17% of cases [18].

Infection of cervical epithelial cells with HPV is a necessary but insufficient factor for their malignancy. In this regard, it seems important to consider the stages of development of papillomavirus infection (PVI) and the mechanisms implementing carcinogenesis in HPV.

Currently, two stages of HPV are distinguished. The first (reversible) stage is the stage of reproductive infection. It is characterized by the fact that HPV DNA is in the infected cell in a free (episomal) state. If its outcome is favorable, many HPV-infected patients experience remission. At the first stage, the expression of oncogenes E6 and E7 is regulated by the expression product of the E2 gene, which is a repressor of their transcription [16]. The second stage is the stage of integrative infection. At this stage, the viral DNA is integrated into the genome of infected cells, losing its individuality [9].

Unlike the first stage, the second stage is the initial path to tumor transformation of a cell infected with the human papillomavirus. As a result of the inclusion of viral DNA into the host cell genome, a partial loss of viral genetic material occurs, but with the obligatory preservation of oncogenes E6 and E7. The second stage is characterized by a breakdown of the E2 gene, which is accompanied by hyperexpression of E6 and E7 and leads to the activation of the main biological events mediating carcinogenesis [13].

Viral oncoproteins produced by genes E6 and E7 are key factors in the development of pathological proliferative processes in HPV-infected cells of the cervix. E6 and E7 are capable of playing an important role in the regulation of proliferation, apoptosis and other processes mediating carcinogenesis (neoangiogenesis, invasion, inflammation). Oncoproteins E6 and E7 interact with tumor suppressor genes pRB and p53 with their subsequent inactivation [7,12].

E6 and E7 are characterized by an increased capacity for mutagenic activity and epigenetic disturbances leading to the initiation of tumor transformation [10,18].

It is important to note that HPV oncoproteins E6 and E7 have a pronounced immunosuppressive effect, as a result of which HPV-infected cells bypass immunological control and are not destroyed by programmed cell death (apoptosis) [12]. Thus, oncoproteins E6 and E7 expressed by viral genes can lead to genetic instability with subsequent activation of malignancy processes in HPV-infected cells. Since HPV persists in the epithelial cells of the cervix and the use of destructive methods does not guarantee against relapses, an important factor in terms of complex conservative therapy is stimulation of cellular immunity. In this aspect, one of the effective methods of treating HPV is treatment using an analogue of natural purines, inosine pranobex , as an immunostimulant .

It should be noted that the natural analogue as a purine metabolite is completely excreted through the kidneys, which distinguishes it from synthetic or recombinant cytokines. The antiviral effect of IP is to suppress the replication of DNA and RNA viruses by binding to the cell ribosome. The immunomodulatory ability of IP is characterized by stimulation of nonspecific immunity, increased production of interleukins, increased synthesis of antibodies, stimulation of chemotactic and phagocytic activity of monocytes, macrophages and polymorphonuclear cells.

It should be noted that the use of IP is advisable both as an independent treatment in monotherapy and as an adjuvant therapy against the background of the main treatment by destruction of cervical tissue in HPV-associated pathology. According to A.V. Zabelev et al ., 25% of women who received IP as monotherapy showed regression and disappearance of atypical epithelium in dysplastic processes of the cervix [4].

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According to the results of a clinical laboratory study conducted by L.I. Linas , complete elimination of HPV after immunotherapy in monotherapy with IP was 95%, and with a combined approach – 97% [1].

To evaluate the efficacy of inosine pranobex in the treatment of Tay SK papillomavirus infection , a randomized, double-blind, placebo-controlled study was conducted involving 55 women with vulvar and cervical pathology, 25 of whom received , and 25 patients formed the control group and received placebo. In total, 65.3% of patients taking PI showed HPV elimination during the treatment. In this regard, the authors concluded that PI has significant pharmacological activity in HPV infection of the vulva and cervix and its use can be considered as an alternative to surgical treatment [21].

Mohanty KC and Scott CS analyzed the efficacy of treatment in 165 patients with PVI with and without PIs. The authors found that with PIs, the efficacy of treatment increased from 41% to 94%. Immunological studies in 134 patients with PVI showed an increase in the number of B cells in 21% of peripheral blood samples [15].

A.G. Kedrova, Yu.I. Podistov , V.V. Kuznetsov et al . conducted a study to evaluate the effectiveness of using IP in the complex therapy of patients with CINI–III and preinvasive cervical cancer (Cancer in situ), as well as patients infected with HPV with recurrent CIN or Cancer in situ in the remaining part of the cervix. The researchers found that after one course of therapy, HPV-16 was not detected in 78% of patients and HPV-18 was not detected in 50% of patients. The authors believe that at the first stage of treatment, patients with CIN and Cancer in situ should be subjected to electrocoagulation, cryodestruction , laser vaporization , and electroconization of the cervix, as indicated . At the second stage, antiviral treatment is mandatory, since the persistence of the virus is a key factor for the recurrence of the disease [6].

The results of the study conducted by V.F. Dolgushina et al . indicate that the time of restoration of normal epithelial tissue of the vaginal part of the cervix after cryotherapy using IP was statistically significantly higher compared to the same indicator without the use of IP [3]. It should be noted that the frequency of relapses of dysplasia and Cancer in situ after destructive treatment methods is quite high and depends on the characteristics of the viral infection - while HPV is in the episomal state, benign processes are observed, which determines the implementation of antiviral and immunomodulatory therapy to prevent oncotransformation . In the oncoprophylaxis of cervical cancer, HPV vaccines - Gardasil and Cervarix - have currently taken a strong place [1,5,7].

However, it should be noted that these drugs are intended mainly for prophylactic use, while, according to statistics, about 50% of the sexually active population of the planet is already infected with HPV. It is also important to consider the fact that the HPV family is very numerous and in addition to the dominant types 16 and 18, there are over 150 other types, a significant part of which is a high oncogenic risk group.

In conclusion, it should be noted that a promising direction in successfully solving the issues of therapy of HPV-associated diseases of the cervix is the identification of new links in pathogenesis for the implementation of a pathogenetically substantiated approach to treatment with an impact on the maximum number of key links in the pathogenetic chain, including immune homeostasis.

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