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MODERN CONSERVATIVE ETIOPATHOGENETIC TREATMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA (LITERATURE REVIEW)

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Annotation. *We used PubMed, Cochrane Library, Google Scholar databases, mostly referring to publications from the last five years (2016-2020). The long-term persistence of oncogenic types of human papilloma virus is the main etiological factor for cervical intraepithelial neoplasia (CIN). Prolonged persistence of herpes infection can also have a transformative effect on cervical epithelium. Since this pathology is most often diagnosed in women of reproductive age, the maximum preservation of reproductive function, prevention of perinatal complications requires the search for new conservative CIN treatments aimed at the complete elimination of viruses and neoplastic cells. The effectiveness of conservative antiviral therapy of CIN I, II without the use of surgical methods has been proved, especially in women who have not fulfilled their reproductive plans. In addition, antiviral therapy during pre- and postoperative periods contributes to the reduction of complications and relapses in women with severe cervical neoplasia.*
Keywords: *papilloma virus, herpes simplex virus, cervical intraepithelial neoplasia, treatment.*

High incidence of human papillomavirus (HPV) infection and virus persistence in women of reproductive age, opportunistic cervical screening in Ukraine as well as the lack of primary prevention at the state level are accompanied by the high incidence of cervical neoplasia (CIN) and cervical cancer. The etiological role of viruses in the development of neoplastic transformations of the cervical epithelium from mild to malignant transformation has been proved.

Viruses are the cause of 90 % of acute infectious and exacerbated chronic diseases. Viruses that induce tumors are particularly noteworthy [1, 8] as an etiological factor in the pathology development which can have a negative impact on women's reproductive function.

The aim of our work is to analyze literature sources for the existence of possible conservative treatments for CIN based on the influence on etiological factors and the main pathogenetic mechanisms of neoplasia of the cervical epithelium.

In the mid-seventies of the 20th century, Harald zur Hausen from the German Cancer Research Center in Heidelberg found that women with cervical cancer were 100 % infected with HPV. In 1983 he managed to detect papillomavirus DNA in cervical cancer biopsy specimens. Therefore, this event could be considered a discovery of oncogenic HPV - 16. A year later, he cloned HPV-16 and HPV-18 DNA of patients with cervical cancer. Cells infected with such viruses sooner or later become cancerous in 100 %. In addition, a malignant tumor develops from them [8].

Other HPV strains belonging to two important phylogenetically related families: related to HPV-16 (strains 31, 33, 35, 52, and 58) and related to HPV-18 (strains 39, 45, 59 and 68) has become known to lead to the development of cervical cancer (CC)) [1, 8, 21].

Papillomaviridae family representatives cause damage to the cover epithelium and mucous membranes in humans and other mammals. According to modern classification, the family Papillomaviridae includes viruses of 16 genera, which were previously united in a single genus Papillomavirus [1, 8, 21].

Nowadays, papillomavirus infection in women of reproductive age is most commonly associated with the development of cervical epithelial pathology. Although, the etiological role of human papilloma virus in the development of oropharyngeal malignancies, respiratory tract, external genitalia, adenocarcinoma of the anal region, skin and even breast is well known and confirmed by many sources [1, 8, 19, 21].

More and more attention is being paid at herpetic infection as an etiological factor of epithelial dysplasia. Herpes simplex virus (HSV) persists in the body for a long time and has transformative properties. The ability of HSV-2 to induce neoplastic transformation of cells in vitro has been established, indicating the risk of virus-induced tumors. Some researchers have linked this fact to the possibility of HSV to induce cervical cancer. HSV is known to be a potent co-factor in papillomavirus infection. The combination of HSV and HPV is accompanied by an increase in the incidence of cervical neoplasia 2-fold [1, 2, 8, 14].

The uniqueness of carcinogenesis associated with viral infection is due to the constant persistence in tumor cells of viral DNA which has a pronounced transforming potential [8, 10, 11, 12, 13, 19].

The development of epithelial neoplasia begins with the penetration of the virus into the basal layers of the epithelium due to the action of the damaging factor (infection, inflammation, trauma, etc.) [1, 3, 11, 13, 16, 19].

Virus propagation begins in basal cells, though, virions mature in superficial layers after the cells are keratinized.

After the infection with HPV, epithelial cells disrupt the normal process of division and differentiation. This is especially true for cells in the intermediate layer, where a clonal expansion of infected HPV cells of the basal layer which have undergone only the primary stage of differentiation (clonal expansion is associated with their transformation and subsequent malignancy) takes place. In this case, the deformation of the inner layers of the epidermis and its overall thickening, the loss of the normal layer structure is observed. At the stage of advanced infection, cells of the parabasal layer of the epidermis during the transition to the intermediate (granular) layer are most active in the synthesis of viral DNA. As a result, the granular layer of the epidermis is severely affected. It should be noted that the expression of late genes (L1 and L2) is absent at this stage. It is observed only at the final stage of differentiation of the superficial layer of the flat epithelium, where an active accumulation of mature viral particles (productive stage of infection), their separation from the destroyed peeled epitheliocytes take place, indicating the completed life cycle of HPV and high elimination probability [1, 3, 12, 13, 21].

Neoplastic cell transformation in response to the penetration of the virus causes an integrative type of viral infection in which the viral genome partially or fully integrates with the host cell genome. It replicates and functions together with the host cell genome. In transformed cells and tumor cells papillomavirus DNA is integrated into the cell genome. In cervical carcinomas, papillomavirus DNA is present in the integrated state [1, 11, 12, 18].

The transforming effect of HPV and their oncogenic properties is the result of the expression of early virus-specific genes (E5, E6 and E7 oncoproteins) and their interaction with the products of specific cellular genes (p53, pRB) [1, 11, 19].

E6 attaches to p53 (tumor suppressor protein) and leads to its degradation, thus blocking the apoptosis of transformed cells and E7 interacts with the cellular protein pRB (retinoblastoma protein) and other related proteins to enhance their proliferation. Therefore, expression of E6 and E7 oncoproteins of highly oncogenic human papilloma virus types provides unrestricted division of transformed cells. The interaction of viral oncoproteins with cellular cyclin-dependent kinase inhibitors (p16, p21, p27) is also an important event in the process of immortalization. E7 and E6 modulate DNA methylation which affects the expression of p16 protein. P16 overexpression is one of the main features of HPV activity in the cell. One of the consequences of overexpression of E7 and E6 is genomic instability of the cell which contributes to the further accumulation of aberrations in the genes of the host cell and its malignant transformation [1, 11, 12, 13, 19].

The role of oncoprotein E5 in the realization of the transforming and immunosuppressive effects of HPV, as well as mutagenic effects on the cell genome have been highlighted in scientific publications [8, 12, 19]. Studies show that E5, E6, and E7 oncoproteins modulate the expression of proteins that control mitogenic activity, cell differentiation and evasion of the immune surveillance. Expression of E5 oncoprotein provides transforming activity of E6 and E7, induces atypical cell mitogenesis and influences epithelial cell differentiation and growth processes. The fact that expression of E5 oncoprotein is characterized mainly by highly oncogenic types of HPV is really important, whereas for viruses with low oncogenicity E5 expression is not determined or its polymorphism is observed. Therefore, the oncogenicity of HPV can be associated with E5 oncoprotein [8, 19]. However, the statement of E5 activity at the integrative stage of infection remains doubtful. While some researchers believe that its activity disappears after integration of viral DNA into the cell genome, some others claim to determine the expression of HPV 16 E5 mRNA in the biopsy of patients with severe dysplasia and cancer. Since E5 is expressed in the early stages of the viral process, the impact on its activity and effects may possibly be the subject of the study of treatment programs aimed at stopping the progression of transformation processes and their reverse development [19].

The transforming effect of tumor-inducing viruses on the epithelium is ensured by their long-term persistence. The main mechanisms and factors of HPV and HSV persistence are the integrative relationships between viruses and host cells. Viruses avoid the immune attack of a macroorganism using the following mechanisms:

- latent unproductive infection of non-permisive cells - the virus replicates in cells of one type however latency is established in other parts of the body (for example, herpes viruses in the latent state are found in the nerve ganglia or B-lymphocytes but productively multiply and cause acute lesions in the epithelial cells of the mucous membranes);
- consecutive stages of virus replication occur in cells at different stages of differentiation (papillomaviruses infect basal epithelial cells at the beginning of differentiation, but form infectious virions only in differentiated keratinocytes);
- special localization of viruses in the body protects them from the action of immunocytes and antibodies: the spread of the virus in the body without the stage of its leaving the cell (migration of herpes virus by intercellular bridges and penetration of HPV into daughter cells during division);
- interference with cellular immunity by inhibiting the presentation of viral peptides as well as inhibiting the activity of natural killer cells;
- inhibition of cytokine expression as well as apoptosis of infected cells [1, 8, 19].

Human HPV avoids the body's immune attack by expressing E5, E6 and E7 oncoproteins [19]. E5 oncoprotein is believed to play a key role in this process.

The cell-mediated immunity is the main controlling immune response to HPV. T-lymphocyte activation is a key one to regressing and eliminating transforming viral infection [8, 19]; these immune cells have cytolytic properties and synthesize a large number of mediators to support antigen-specific memory of B cells; they also perform lysis of the

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infected and tumor cells. Cytotoxic T lymphocytes recognize the antigens E6/E7 of HPV introduced by antigen-presenting cells (APC) and destroy virus-infected cells. E5 oncoprotein disrupts the presentation of viral antigen [8, 19]. However, E5 oncoprotein impairs T-lymphocytes recognition of E6/E7 antigens. As a consequence, there is a decrease in the number and activity of Langerhans cells, the balance of T-helper/T-suppressors with suppressor dominance is impaired, the production of γ-interferon by T-helpers is decreased, the activation of specific cytotoxic T lymphocytes is impaired [19].

Interferons (IFNs) are the key components of the body's antiviral defense [5, 18]. In the first stage of infection, locally (at sites of infection) IFN-α and IFN-β have the following effect:

- intracellular inhibition of virus reproduction;
- elimination of infected material by NK cells and cytotoxic lymphocytes;
- protection against possible damage to other uninfected cells [5].

IFNs are classified due to their types:

I (α, β),

II (γ),

III (more known as interleukins 28A, 28B and 29; having similar type I and II properties, but without systemic effect, capable of activating immune cells - macrophages, NK cells) [18]. All IFNs have antiviral, antitumor and immunomodulatory activity [5, 18].

High-oncogenic types of HPV avoid natural immunity because due to expressing the E5, E6 and E7 oncoproteins, they inhibit the production of type 1 interferons in cells, reduce the entry of macrophages into the foci of infection, inhibit the production of anti-inflammatory cytokines by activating anti-inflammatory cytokines. Thus, the immunosuppressive effect makes the virus invisible to the immune system [1, 12, 18].

Keratinocytes in response to viral infection should correspond to high levels of type I IFNs that have antiviral and antitumor properties. However, it doesn't happen in case of infection with highly cancerous HPV types. Instead, such activation of the interferon system occurs while infecting with low-carcinogenic types of HPV. This may explain the contradictory data on the effectiveness of interferon therapy of neoplasia of the cervix. IFNs also stimulate the apoptosis of infected, neoplastic cells, and, therefore, have antitumor effect as well as carry out antiviral protection of healthy cells [5, 7]. E5 affects IFN synthesis thereby promoting carcinogenesis. All these facts explain the conflicting data on the effectiveness of interferon therapy of neoplasia of the cervical epithelium. The success of the treatment will depend on the correct timing and conditions of its use. The use of type I interferons may have a good result at the episomal stage of infection, leading to apoptosis of infected cells, whereas in the integrative form of HPV infection their use will be ineffective. Some studies show that in this case the prescription of γ-IFN is more effective. The use of IFN type III is not accompanied by systemic effects on the body, so their therapeutic use is considered the most promising area for research and introduction into the treatment process [18].

Modern IFN drugs are divided into natural, recombinant, consensus and pegylated. The efficacy of the natural and recombinant IFNs is the most clinically researched [7].

IFN inducers have a number of advantages over pure IFN drugs. In case of papillomavirus and genital herpesvirus infections, IFN drugs increase the content of α-IFN only in patients' blood and have low immunomodulatory activity; IFN inducers have a pronounced immunomodulatory effect, stimulate the production of α, β, γ-IFN, restore the balance of proinflammatory (interleukin-2, tumor necrosis factor-α) and anti-inflammatory (interleukin-10) cytokines [13].

There have been reports on the success of conservative therapy for tumor-inducing viral infections, i.e, HPV and HSV - alloferon [12]. Alloferon is an effective inducer of the synthesis of endogenous and γ-IFNs and an activator of the natural killer system. The agent stimulates the recognition and lysis of defective cells by cytotoxic lymphocytes. Alloferon interacts with immunocompetent cells after penetration into the systemic circulation. An increase in IFN is observed 2 hours after drug administration and is maintained at a high level (2 - 2.5 times above normal background) for 6 - 8 hours. The return to the original values occurs by the end of the day. Increased functional activity of natural killer cells is observed within 7 days after drug administration. In addition to IFN induction, alloferon has the potential to induce the activity of natural killer cells, which is reduced by the oncoprotein E5, E6 and E7, in terms of the effective treatment of cervical epithelial dysplasia viruses. Thus, this drug has a pathogenetically based therapeutic effect, as it restores immune surveillance and promotes the destruction of the immune system of neoplastic cells [12, 19].

The main purpose of cervical epithelial dysplasia treatment of viral etiology is the elimination of transformed cells with integrated viral DNA. The impact on the major pathogenesis and the etiological factor of dysplastic transformation of the epithelium is the most effective in achieving this goal. Along with surgical treatment for cervical neoplasia, conservative therapy can be effective in mild degrees of dysplastic processes of the cervical epithelium, CIN II, which will help to avoid surgery itself or reduce its volume and prevent recurrence. This is especially true for women who have reproductive plans.

The elimination of the risk factors for cervical disease is effective to prevent the development of persistence and to ensure the elimination of HPV. These include the treatment of concomitant genital infections and inflammatory diseases of the genital organs, restoration of the genital ecosystem [2, 3, 14, 15, 16], abandonment of bad habits, especially smoking [3], rational storage to ensure a sufficient level of activity of the immune system [15].

It is important for the successful treatment of non-plastic transformations of the cervical epithelium to eliminate hormonal background disorders. It is known that

hyperestrogenemia on the background of relative or absolute hypoprogesteronemia leads to increased proliferative activity of cells under the influence of viral infection [3, 10]. Therefore, the treatment of dyshormonal disorders and their clinical manifestations is one of the factors that can prevent the transforming effect of viruses on the cervical epithelium.

Numerous clinical and experimental studies show that substances of natural origin (indole-3-carbinol and epigallocatechin-3-gallate) have a pathogenetically substantiated prophylactic effect on the development of precancerous and cancerous conditions of the cervix. In particular, it has been proven that in vitro and in vivo indole-3-carbinol negates the estradiol-dependent induction of E6 and E7 oncogenes, normalizes estradiol metabolism in cells infected with HPV, induces apoptosis processes of HPV-infected cells [21, 23].

The flavonoid epigallocatechin-3-gallate is an effective inhibitor of the DNA-methyltransferase enzyme, which directly regulates the activity of tumor suppressor genes responsible for the body's antitumor protection. It has been proved that the use of indole-3-carbinol in combination with antiviral therapy for genital papillomavirus infection allows to achieve high intensity of antiviral immunity and to ensure a minimum number of relapses. The use of epigallocatechin-3-gallate in patients after surgical treatment enhances reparative processes and reduces the risk of pathological scarring. The combination of indole-3-carbinol and epigallocatechin-3-gallate simultaneously has multiple directional effects on the pathogenetic links of cervical epithelial dysplasia associated with viral infection. It suppresses inflammation, tumor cell growth, tumor neoangiogenesis, stimulates apoptosis of transformed cells as well as increases immune function. Therefore, its use for the treatment of manifestations of viral infections that cause tumors is pathogenetically substantiated and confirmed by experimental and clinical experience [3, 10, 23].

Success in the treatment of papillomavirus infection requires elimination of the virus, restoration of the physiological level of cellular immunity, synthesis of interferons and regression of hyperplastic processes. The search, development, and clinical investigation of agents which therapeutic effect is directed simultaneously to all pathogenetic mechanisms of the virus-induced neoplastic processes make up an important and promising area of the research.

Therefore, the main points of the etiopathogenetic treatment of neoplastic cervical processes caused by viral infection are:

- elimination of an infectious agent (virus),
- inhibition (inhibition) of cell proliferation,
- induction of cell differentiation,
- induction of neoplastic cells apoptosis,
- influence on mechanisms of induction of immunosuppression - restoration of physiological level of antiviral immunity (restoration of immune surveillance).

These requirements meet the natural flavonoids of proteflazide (obtained from a mixture of Herba Deschampsia caespitosa L. and Herba Calamagrostis epigeios L.), which are both immunomodulators, they activate apoptosis and perform antiproliferative action on cells as well as directly affect the activity of DNA- and RNA-polymerase specific virus enzymes. Inhibition of these enzymes results in the cessation of virus DNA replication which makes it impossible to multiply. Thus, natural flavonoids have a pronounced direct virostatic effect on viruses of DNA and RNA groups [21, 23].

The confirmed antiviral (virostatic) effect against human papillomavirus is a valid argument for the use of Proteflazid for the treatment of HPV-associated cervical epithelial dysplasia. The results of 230 clinical and experimental studies in the period from 2000 to 2017 have been published in Ukrainian and foreign literature. That, have actually, demonstrated the pharmacological effects of Proteflazid in the treatment of viral infections, including HPV infection [20, 22].

The ability to use Proteflazid locally is particularly noteworthy. This maximizes the immediate direct effect of the drug on the altered cells and thus increases the therapeutic effect. The results of clinical studies demonstrate the regression of neoplastic changes in the cervical epithelium and the restoration of healthy epithelium after topical application of Proteflazid in the form of vaginal suppositories. The simultaneous complex and local application of natural flavonoids is the most effective way for successful treatment of CIN I and CIN II without surgery [20, 22].

Nowadays, it is possible to determine the risk of malignant progression of HPV-induced neoplasia and, therefore, the pathogenetic stage of the infectious process. Conservative tactics without the surgical stage of treatment are possible provided that they are infected with low oncogenic types of HPV and are at the reproductive stage of the infectious process. The conclusion is based on the results of the capsid test and the expression of the protein p16, Ki67 [9, 17]. Positive capsid test L1 and inactive expression of p16, Ki67, even in the presence of clinical and subclinical manifestations of papillomavirus infection, is the basis for conservative therapy of papillomavirus infection with subsequent dynamic monitoring once every 6 months [1, 9, 17].

Conclusions and prospects for further development

1. Treatment with CIN I and CIN II, confirmed by a positive capsid L1 test and low expression of p16 and Ki67 protein, can be conservative using interferon therapy, systemic and local treatment with a complex of natural flavonoids of Proteflazid. It is mandatory to eliminate the factors that contribute to the persistence of HPV. The direct antiviral (virostatic) effect of Proteflazid against human

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papillomaviruses may be a priority in the choice of a conservative treatment for CIN.

2. The therapeutic effect of alloferon, a combination of indole-3-carbinol and epigallocatechin-3-gallate is pathogenetically justified.

Thus, the etiologically and pathogenetically directed conservative therapy of virus-induced cervical dysplasia is effective and promising for further improvement as it allows to preserve a woman's reproductive health, to avoid and reduce the incidence of perinatal complications, to avoid or reduce the volume of surgery, the incidence of recurrence after destructive CIN treatments.

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СУЧАСНЕ КОНСЕРВАТИВНЕ ЕТІОПАТОГЕНЕТИЧНЕ ЛІКУВАННЯ ЦЕРВІКАЛЬНИХ ІНТРАЕПІТЕЛІАЛЬНИХ НЕОПЛАЗІЙ (ОГЛЯД ЛІТЕРАТУРИ)

Герич О. Х., Горбатюк О. Г., Григоренко А.П., Дудікова Л.В., Кондратюк А.Л., Шатковська А.С., Біньковська А.М., Гарбузюк В.В.

Анотація. *Ми використовували бази даних PubMed, Cochrane Library, Google Scholar, посилаючись в переважній більшості на публікації останніх п'яти років (2016-2020). Основним етіологічним фактором цервікальних інтраепітеліальних неоплазій (CIN) є тривала персистенція онкогенних типів вірусу папіломи людини. Тривала персистенція герпетичної інфекції також може мати трансформуючий вплив на епітелій шийки матки. Оскільки ця патологія найчастіше діагностується у жінок репродуктивного віку, максимальне збереження репродуктивної функції, профілактика перинатальних ускладнень вимагають пошуку нових консервативних методів лікування CIN, спрямованих на повну елімінацію вірусів та неопластичних клітин. Доведено ефективність консервативної противірусної терапії CIN I, II без використання хірургічних методів, особливо у жінок, які не реалізували свої репродуктивні плани. Крім того, противірусна терапія в до- та післяопераційному періоді сприяє зменшенню кількості ускладнень та рецидивів у жінок з важким ступенем цервікальних неоплазій.*

Ключові слова: *папілома вірус, вірус простого герпесу, цервікальна інтраепітеліальна неоплазія, лікування.*

СОВРЕМЕННОЕ КОНСЕРВАТИВНОЕ ЭТИОПАТОГЕНЕТИЧЕСКОЕ ЛЕЧЕНИЕ ЦЕРВИКАЛЬНЫХ ИНТРАЭПИТЕЛИАЛЬНЫХ НЕОПЛАЗИЙ (ОБЗОР ЛИТЕРАТУРЫ)

Герич Е. Ф., Горбатюк О. Г., Григоренко А. П., Дудикова Л. В., Кондратюк А. Л., Шатковская А. С., Биньковская А. Н., Гарбузюк В. В.

Аннотация. *Мы использовали базы данных PubMed, Cochrane Library, Google Scholar, ссылаясь в подавляющем большинстве на публикации последних пяти лет (2016-2020). Основным этиологическим фактором цервикальных интраэпителиальных неоплазий (CIN) является длительная персистенция онкогенных типов вируса папилломы человека. Длительная персистенция герпетической инфекции также может иметь трансформирующее влияние на эпителий шейки матки. Поскольку эта патология чаще всего диагностируется у женщин репродуктивного возраста, максимальное сохранение репродуктивной функции, профилактика перинатальных осложнений требуют поиска новых консервативных методов лечения CIN, направленных на полную элиминацию вирусов и неопластических клеток. Доказана эффективность консервативной противовирусной терапии CIN I, II без использования хирургических методов, особенно у женщин, не реализовавших своих репродуктивных планов. Кроме того, противовирусная терапия в до- и послеоперационном периоде способствует уменьшению количества осложнений и рецидивов у женщин с тяжелой степенью цервикальных неоплазий.*

Ключевые слова: *папиллома вирус, вирус простого герпеса, цервикальная интраэпителиальная неоплазия, лечение.*