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The ways of reducing diagnostic and therapeutic aggression of the patients with HPV-infection in reproductive age

N. N. Voloshina[1], E. D. Zvantseva[2]
[1]Zaporizhzhia Medical Academy of Post-Graduate Education
[2]Zaporizhzhia Regional Clinical Oncology Centre

The problem of early diagnostics and prevention of cervical cancer is pressing in Ukraine. The leading etiologic factor in the genesis of neoplasia of the cervix and a number of other organs is Human papillomavirus (HPV). The human papillomavirus is sexually transmitted and has high contagiousness. Cancer prevention consists in effective screening, early detection and treatment of pathological changes in the cervix. The aggressive treatment of diseases caused by (HPV) has been replaced with a tactic of a differentiated approach, taking into account the age of a woman and her reproductive plans.

***Objective*: was to study the efficacy and tolerance of the combined use of Proteflazid® systemically in drops form and topically in the form of suppositories for 3 months in patients with cervical intraepithelial neoplasia (CIN) of mild and moderate severity (CIN 1 and CIN 2) associated with human papillomavirus (HPV); determination on the basis of the results of the need for further destructive treatment.**

***Materials and methods*. For the period from July 2016 to September 2017, we examined and treated 86 women with morphologically confirmed intraepithelial neoplasia of the cervix associated with HPV infection.**

***Results*. Based on the performed studies, it was found that 6 months after treatment with Proteflazid® systemically and topically for 3 months, regression of CIN was reported in 93% of patients. In all cases, a reduction in viral load of more than 2 Lg HPV/105, which is a marker of the efficiency of antiviral therapy, was observed. Six months after treatment in 84% of patients and 9 months after treatment in 88%, there was complete elimination of HPV or reduced viral load to clinically insignificant values – less than 3 Lg.**

***Conclusion*. Proteflazid® suppositories and drops contribute to the elimination of human papillomavirus (HPV) and other viral-bacterial infections and reduces the risk of cervical neoplasia.**

Key words: *cervical cancer, screening, cervical neoplasia, Human papillomavirus, viral-bacterial infections, Proteflazid®.*

Cervical cancer (CC) is one of the important problems of modern gynaecological oncology. Annually about 5 thousand primary cervical cancer patients are registered in our country. Since 1990, there has been a trend towards an increase in the incidence and mortality from cervical cancer. From 1997 to 2015, according to the cancer registry of Ukraine, there was an increase in the incidence of cervical cancer at a young age: 21-25 years – from 1.7 to 2.9 cases per 100 thousand of the female population, 30-34 years – from 14. 6 to 18.5 cases per 100 thousand of the female population. The median age of patients with cervical cancer *in situ* decreased from 40 to 30 years, it is 10-15 years lower than that in patients with invasive cervical cancer [21, 30].

The problem of early diagnosis and treatment of cervical cancer remains relevant in Ukraine, since cervical cancer is diagnosed in advanced stages in almost 25% of patients. There is a steadily high mortality rate of up to one year, which is an integrated parameter of the quality of diagnosis and treatment of cervical cancer and is up to 20%. It is proved that human papillomavirus (HPV) is the leading etiological factor in the genesis of neoplasia of the cervix and a number of other organs. HPV is transmitted sexually and has high contagiousness [5, 30, 33].

In recent decades, there have been significant changes in the diagnosis, treatment and prevention of diseases caused by papillomaviruses, including cervical cancer [3, 17, 26, 33].

Based on the experience gained, the aggressive treatment of diseases caused by HPV was replaced with tactics of a differentiated approach, taking into account the age of the woman, her reproductive plans, and the clinic ability to conduct an adequate examination and case monitoring.

Papillomaviruses have tropism to the epithelial cells of the skin and mucous membranes. More than 150 HPV types have been identified and described based on the determination of the nucleotide sequence of the L1 genome, which encodes the main capsid protein. These types of viruses are classified into high and low risk groups according to their potential to induce cancer [2, 5, 21, 33]. The International Agency for Research on Cancer (IARC) currently identifies twelve types of high-risk HPV that are associated with human malignant tumors (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59- d), and additional types with limited data on their carcinogenicity (types 68 and 73) [4, 17, 33]. Although infection with the oncogenic type of high-risk HPV causes almost all cases of cervical cancer, these infections do not always cause cancer. Most women infected with high-risk HPV do not develop cancer, because papillomavirus infection (PVI) is short-term. The average time between HPV infection and seroconversion is approximately 8-12 months. Most HPV infections (70-90%) are asymptomatic and stop spontaneously within 1-2 years. In some cases, persistent or recurrent PVI caused by types of high oncogenic risk may progress: precancerous changes develop gradually, up to an invasive carcinoma at the site of lesion. Chronic HPV infection develops in 5-10% of infected women and is determined by the presence of type-specific HPV DNA in the analysis of repeated clinical biological samples within 6-18 months. Long-lasting PVI with involvement of cervical squamous epithelium is classified histopathologically as cervical intraepithelial neoplasia – CIN.

The course of PVI largely depends on the state of immunity.

Considering HPV epitheliotropism, the local immunity factors are of particular importance. Local immunity provides protection of the mucous membranes and skin of the human body from the damaging effect of viruses, bacteria, toxins, allergens, parasites, protozoa and other harmful factors. Mucous membranes are characterized by developed lymphoid tissue and high saturation with immunocompetent cells. Epithelial cells of the mucous membranes are not just a physical barrier against pathogens and infectious agents, but also secrete a wide range of protective factors such as lysozyme, lactoferrin, peroxidase, complement components, as well as cytokines and chemokines that attract and activate immune cells [6, 8, 11, 15, 16].

Secretory IgA (sIgA) is the main type of immunoglobulins (Ig) involved in local immunity, especially in maintaining normal microflora. By binding to microorganisms, it delays their attachment to the surface of cells and, together with nonspecific immunity factors, provides protection of mucous membranes against microorganisms and viruses [13, 16, 24]. Lysozyme is synthesized by neutrophilic granulocytes, it is detected in the vaginal fluid and, in greater concentration, in the mucous plug of the cervix. In addition to the antibacterial effect, lysozyme is able to block infiltration of viruses into the cell and their further replication [1, 6, 8, 15]. Reduced levels of local defense factors is an important element in the pathogenesis of HPV infections, which contributes to the progression of the disease.

At present, risk factors for more aggressive PVI course have been identified. These include:

- HPV type and degree of its oncogenicity;
- the patient's immune status;
- other concomitant sexually transmitted infections (STIs), such as herpes simplex virus (HSV), chlamydia, trichomoniasis and gonorrhea.

Women who have a large number of sexual partners, early childbirth (under 18 years), as well as a large number of births and abortions, smokers, and alcohol abusers fall into the risk group for cervical cancer [21, 29, 33].

The duration of HPV course with progression to invasive cancer is usually up to 10 years or more. Thus, the patient and the doctor have enough time to diagnose, treat and prevent progression of the neoplasia process [1, 2, 5, 21, 32].

The presence of PVI and CIN can be diagnosed using: a panel of tests – a PAP test (cytological examination), HPV testing (detection of HPV DNA); colposcopy; biopsy followed by a histological examination; immune histochemistry; determination of biomarkers.

The information value of these methods depends on a number of subjective factors. Unfortunately, none of the methods can guarantee 100% detection of the disease.

The information value of the PAP test largely depends on the preparation of the patient for the examination, quality of the cytological material taken by the gynecologist or the trained nurse, correct fixation, staining method, as well as competent interpretation of cellular changes by the cytologist. Currently, cytological testing remains the main screening method for cervical cancer in most countries [3, 9, 21, 35].

The use of the modern Bethesda terminological classification (The Bethesda system – TBS, 1988, USA), which was changed and supplemented in 2001, 2006, 2014, allows characterizing the cytological changes associated with PVI [9, 35].

TBS presents a two-level system for assessing squamous intraepithelial lesions of low and high grade (LSIL and HSIL), which reflect the biology of changes occurring when HPV infection occurs. PVI productive (episomal) stage corresponds to LSIL, and integrated stage – to HSIL [21, 35].

Under modern conditions, in most countries using cytological screening, it is recommended to give cytological opinion based on the Bethesda system (2014), in which the following categories of changes are identified to evaluate cervical squamous epithelium:

- NILM (Negative for intraepithelial lesion or malignancy);
- LSIL (Low-grade squamous intraepithelial lesion);
- HSIL (High-grade squamous intraepithelial lesion);
- ASC-US (Atypical squamous cells of undetermined significance);
- ASC-H (Atypical squamous cells cannot exclude HSIL);
- CIS (Carcinoma in situ);
- SCC (Squamous cell carcinoma).

A cytological opinion based on the TBS system standardizes the format of cytological findings around the world, provides an opportunity for sharing experiences on the tactics of managing different types of pathology. Distinguishing ASC-US/ASC-H categories for squamous epithelium increases the diagnostic sensitivity of cytological screening [21, 27, 35].

The WHO classification and CIN-system (1997) are used for the histological study. The informative value of the biopsy depends on the quality and size of the sample, as well as on the number of fragments taken for examination. If the material is not properly sampled for examination (at a depth of less than 6 mm or from sites with a lower severity), severe lesions may not be verified. In such cases, the patient is at risk of destructive exposure without further histological monitoring. This can lead to the progression of the malignant process. An important point is the use of targeted (under the control of a colposcope) multiple biopsy or loop excision. Then, the areas of the most altered epithelium are more likely to be investigated. A diagnosis is established and the tactics of management are determined based on the histological opinion [21, 28, 32].

The HPV test has a high sensitivity, but less specificity. According to international recommendations (2013, 2014), this method is recommended for cervical cancer screening programs in women aged 30 years and above together with the PAP test, as well as for dynamic monitoring of patients with CIN who have undergone some type of treatment. In these cases, it is important to carry out not only HPV testing, but also to determine the type of virus, possibility of its persistence and viral load.

CINs, which are precursors of cervical cancer, occur predominantly in young women of reproductive age. As the majority of the researchers state as well as analyzing our own observations, young women are more often diagnosed with low-grade lesions (LSIL), which spontaneously regress after elimination of papillomavirus [21, 32]. The frequency of cytological and colposcopic changes caused by transient PVI is quite high. A share of cervical cancer development before the age of 21 is minimal and is 0.01% of all cases of cervical cancer.

Quite often, taking into account only colposcopic cervical changes, young patients undergo unreasonable invasive interventions and destructive treatment. In the presence of persistent infection on the background of immature epithelium, most patients have relapses of the disease that cannot be fully treated, and the possibility of repeated surgical manipulations is limited. Therefore, it is very important to correctly interpret colposcopic patterns [21, 28, 29, 33].

The colposcopic classification, approved at the XIV World Congress on Colposcopy and Cervical Pathology (IFCPC) in 2011 in Rio de Janeiro, summarizes new knowledge on CIN development and is convenient for practical application. One of the most important criteria for assessing colposcopic patterns is visualization of the transformation zone (TZ) and evaluation of the colposcopic examination adequacy [28, 33].

By the ratio of exo- and endocervical components, three types of ST are distinguished:

- Type 1 TZ – fully visualized. It is located on exocervix and can be of any size.
- Type 2 TZ – not completely located on the exocervix. Has endocervical component. It is visualized almost completely, can be of any size.
- Type 3 TZ – not fully visualized. Has a large endocervical component. Unsatisfactory CS, a joint in the endocervix is not visible.

One of the important problems is the formation of type 3 TZ in young patients after carrying out destructive treatment on ectocervix. Pathological processes that develop in the presence of persistent PVI in the cervical canal may not be available for examination, are not timely diagnosed, and in the future can lead to the development of endocervical cancer.

The colposcopic pattern of the transformation zone depends on the degree of substitution of the cylindrical epithelium with squamous epithelium and on the nature of metaplasia. TZ metaplastic epithelium remains thin and not saturated with glycogen for a long time. Therefore, on examination and simple colposcopy, it looks red. After treatment with acetic solution, the metaplastic epithelium turns white; a picture of the acetowhite epithelium (AWE) appears. The lower the degree of maturity of the epithelium, the more unfavorable it looks upon colposcopy. AWE is the most important colposcopic sign of pathological changes in the cervix, including a marker of the presence of papillomavirus infection. This feature is pathognomonic for all CIN degrees and allows suspecting the process at the earliest stages of development. The intensity of whitening directly correlates with the severity of the pathological process. An important colposcopic feature is the presence of a zone with coarser changes within the pathologically altered area (presence of the inner margin) [21, 28, 33].

The term “iodine negative zones” (INZs), unlike the terms “leukoplakia”, “keratosis”, characterizes the changes in stratified squamous epithelium (SSE), which can be detected only after treatment with Lugol’s solution. INZs often represent a different degree of SSE keratinization (often after intense coagulation). But it is impossible to predict the condition of tissues under the SSE stratified layer colposcopically. Many authors consider it necessary to conduct a biopsy from INZ sites [27, 33].

The terms “punctuation” or “stippling” correspond to the old terms “stem” or “papillary zone”. Puncture is a manifestation of atypical vascularization of the epithelium. A histological examination of puncture sites shows an epithelium with elongated stromal papillae with vascular loops penetrating the epithelium.

The term “mosaic” corresponds to the old term “field”. A histological examination detects stromal branched outgrowths with vessels inside. Mosaic represents islands of metaplastic or atypical epithelium, surrounded by vascular lines. Punctuation and mosaic are usually not visible with the naked eye. They are clearly outlined on the cervix with advanced colposcopy [21, 28, 29].

As a rule, normal vessels disappear for a short time in acetic acid test. Atypia of the vessels is detected in the form of randomly arranged vessels of irregular shape that do not react to acetic solution.

The variety of pathological colposcopic patterns caused by the presence of immature or metaplastic epithelium against PVI causes oncophobia in the doctor, leading to the appointment of various invasive interventions. Impaired integrity of the cervix and cervical canal affects the subsequent pregnancy and childbirth. These data must be taken into account when planning the treatment of pathological processes on the cervix, especially in women who have reproductive plans [21, 27, 33].

In the world practice, different methods of treatment of patients with CIN have been developed. Most modern treatment regimens are based on the destruction of the affected tissue by electrosurgical excision, laser or cryodestruction. Recently various versions of radio wave treatment, argon-plasma coagulation and photodynamic therapy have been introduced.

Unreasonable aggressive treatment of the cervix in young patients often leads to the development of iatrogenic pathology and in the future to difficulties in implementing reproductive plans. The analysis of histological findings of cervical fragments obtained after excisions showed that this tactic is unreasonable in almost 90% of cases. Before carrying out invasive diagnostic and treatment procedures, it is necessary to identify and eliminate accompanying aggravating factors and apply the most sparing methods in patients of early reproductive age.

Modern tactics of management of patients with cervical pathology should be based on evidence-based medicine and be justified. The management of patients with CIN should take into account a number of factors: the patient’s age, CIN severity, reproductive plans, somatic state, capabilities of the clinic.

With CIN 1, it is preferable to perform case monitoring with cytological and colposcopic control. Active management with CIN 1 is recommended in case of:

- unsatisfactory colposcopy; extensive lesions of the cervix;
- CIN1 duration of more than 18 months;
- woman’s age over 35;
- impossibility of follow up.

With CIN 2 it is necessary to conduct excision therapy with mandatory histopathological examination and a description of the edges of the excised zone.

With CIN 3, the patient should be referred for consultation with the gynecologic oncologist.

The lack of a unified approach to the diagnosis and treatment of PVI and associated diseases allows practitioners to determine the tactics of managing such patients, based on personal preferences. It results in a high percentage of mistakes in the choice of strategy and treatment tactics and, as a result, a high incidence of relapse of the diseases and leads to problems with the realization of the reproductive function.

In this regard, the search for new and improved methods of effective conservative sparing therapy in the treatment of diseases associated with HPV is of particular relevance [13, 19, 20].

Given the etiology of the CIN onset, therapy aimed at eliminating etiologic agents (HPV) is essential for the treatment of this pathology. Elimination of HPV allows the use of sparing methods of treatment. This is especially important for patients of reproductive age who plan pregnancy [18].

One of the promising directions in PVI treatment and secondary prevention is the use of natural flavonoids, which have a direct antiviral effect; systemic and topical immunotropic action; activate

apoptosis and exert an antiproliferative effect on the virus-infected cell [13, 19, 20].

Proteflazid® contains flavonoids derived from a mixture of (1: 1) lime grass (*Herba Deschampsia caespitosa* L.) and bush grass (*Herba Calamagrostis epigeios* L.); is released in a liquid dosage form (extract in the form of drops) and in the form of suppositories. Proteflazid® belongs to the group of direct antiviral agents – it inhibits the synthesis of DNA and RNA viruses in infected cells due to inhibition of the activity of virus-specific enzymes of RNA and DNA polymerases, thymidine kinase, reverse transcriptase. The antiviral action of Proteflazid is enhanced by its immunotropic properties. The product stimulates the synthesis of alpha and gamma interferons without the development of refractivity, allowing its use for a long time. Proteflazid® significantly and steadily increases the content and improves the ratio of parameters of the main factors of local immunity – sIgA, lysozyme and C_3-complement component, which strengthens the anti-infective protection of cervical mucus and mucous membranes of the genitals as a whole in the treatment of diseases caused by PVI, herpes viruses and mixed urogenital infection [9, 13, 17, 19, 23, 38]. Clinical studies have shown that Proteflazid® suppositories restores the protective function of the mucous membrane of the vagina and cervix due to the normalization of local immunity factors (sIgA, lysozyme and C_3 complement components) [13, 23, 26]. With vaginosis, vaginitis and inflammatory diseases of the cervix, it helps to restore local immunity and faster and more effective elimination of the pathogen [17, 20, 22]. The product is a modulator of apoptosis, enhancing the effect of apoptosis inducing factors, contributes to faster elimination of virus-infected cells and primary prevention of the onset of chronic diseases against latent viral infections [14, 23, 26].

In our clinic for more than 10 years, Proteflazid® in the form of drops is widely used to treat herpetic, papillomavirus, mixed infections in patients of all ages, their partners and pregnant women.

Since July 2016, after the release of the new form of Proteflazid® suppositories, we actively use the scheme of concomitant administration of Proteflazid® drops orally and Proteflazid® suppositories intravaginally.

Objective: to study the efficacy and tolerability of the combined use of Proteflazid® systemically in the form of drops and topically in the form of suppositories for 3 months in patients with CIN of mild and moderate severity (CIN 1 and CIN 2) associated with HPV; determination based on the findings, the need for further destructive treatment.

MATERIALS AND METHODS

For the period from July 2016 to September 2017, we examined and treated 86 women with morphologically confirmed intraepithelial neoplasia of the cervix associated with HPV infection. In general, these were patients who were examined at their place of residence in maternity welfare centers or private medical centers. They were referred to us to decide on the need for destructive or conservative treatment. Cytological and histological examinations detected CIN 1 or CIN 2 in all patients. The presence of HPV DNA of high oncological risk was detected by the method of polymerase chain reaction (PCR) in all participants of the study.

A prerequisite was the willingness of patients to comply with the regimen and duration of taking Proteflazid®, and undergo scheduled examinations and studies for 6 months after the end of treatment. To do this, before the beginning of treatment, an individual conversation was conducted with each patient, explaining the purpose and method of treatment. All patients are recommended to stop nicotine smoking and use barrier methods of contraception. As a rule, after such a conversation, the patients follow the doctor's recommendations.

The patients took Proteflazid® drops orally, 15 drops 2 times daily before meals for three months continuously. Concomitantly, Proteflazid® suppositories were administered deep into the vagina, 1 suppository 2 times a day for 15 days after menstruation for three menstrual cycles. Patients with disturbed vaginal biocenosis and the presence of bacterial-fungal-protozoal infections were enrolled in the study after the preparatory standard course of treatment.

After the termination of the course of treatment all patients underwent a control colposcopic, cytological and PCR examination in 3 and 6 months.

Treatment was considered effective if, 6 months after its termination, the viral load was reduced to a clinically insignificant level or the virus was not detected, there was an improvement in the colposcopic pattern, as well as CIN regression was reported, which was confirmed by cytological and morphological examinations.

RESULTS OF THE STUDY AND THEIR DISCUSSION

The age of the subjects is 18-30 years. The average age is 25 ± 3.2 years. In the study of the reproductive history, 18 (21%) women had childbirth, 12 (14%) had childbirth and abortion, and 28 (33%) had only abortions. All patients had reproductive plans, so destructive methods of treatment for them were particularly undesirable. The survey found that 58 (67%) of the patients smoked (2 to 20 cigarettes a day). Barrier methods of contraception were used (irregularly) only 20% of the women surveyed. In the history of gynecological diseases, the first place in terms of frequency was occupied by chronic inflammatory diseases of the pelvic organs – in 48 (56%); various vaginitis – in 45 (52%); bacterial vaginosis – in 22 (26%) patients; an impaired menstrual cycle were reported by 38 (17%) women; uterine myoma was detected in 7 (8%) women.

Before the start of the treatment, the most frequent changes upon colposcopic examination included the presence of SSE areas of varying degrees of density in 72 (64%) patients, iodine negative areas in 24 (28%), mosaic and puncture in 30 (35%), thin leukoplakia – in 12 (14%) women.

In the control colposcopic study, all patients showed a positive dynamics in the form of a decrease or disappearance of foci of leukoplakia, SSE, mosaic and puncture. In 57 (67%), normalization of the colposcopic pattern was observed.

In most patients 3 months after the end of treatment, the colposcopic examination detected type I or type II transformation zones with ectopic areas of the cylindrical epithelium, a vascular network of a correct structure, which reacts well to the acetic acid test.

The dynamics of PAP test results is presented in Table 1.

Table 1

Dynamics of PAP test results according to the Bethesda classification (2014)

Parameter	Before treatment		3 months after the end of treatment	
	Abs. number	%	Abs. number	%
NILM	0	0	68	79
ASC-US	18	21	0	0
LSIL	54	63	13	14
HSIL (CIN 2)	14	16	5	6

Table 2

Dynamics of viral load of HPV before and after treatment

Lg HPV/10^5	Before treatment		6 months after the end of treatment		9 months after the end of treatment	
	Abs. number	%	Abs. number	%	Abs. number	%
Not detected	0	0	22	26%	52	60
Less than 3	0	0	50	58%	24	28
3 to 5	38	44	10	12%	8	9
More than 5	48	56	4	5%	2	2

Cytological findings indicate regress of the pathological process in the majority of patients. As a result of treatment, the control PAP test did not detect atypical cells of undetermined significance (ASC-US) in any of the examined women. In 68 (79%) subjects PAP-test had a picture of NILM (negative for intraepithelial lesion or malignancy). The LSIL regression (CIN 1) and transition of HSIL (CIN 2) to CIN 1 was reported in 59 (87%) of 68 patients.

HPV of high oncogenic risk was detected in all patients upon PCR-based DNA typing in the study group prior to treatment. 16th (21%), 18th (16%), 31st (14%), 33rd (13%), 45th (5%), 52nd (11%) genotype of the HPV prevailed, and one in five (20%) patients had associations from two to four types of HPV.

Viral load was determined before treatment and 6 and 9 months after the end of treatment. The results of the examination are presented in Table 2.

After treatment 6 months later in all patients, regardless of the initial parameters, the viral load decreased by more than 2 Lg HPV/10^5, which is a marker of the efficacy of antiviral therapy. 9 months later, 52 (60%) patients had HPV elimination, and 24 (28%) had a decrease in viral load to clinically low values (less than 3 Lg HPV/10^5). In 2 (2%) patients, the viral load after 9 months decreased, but remained more than 5 Lg. In both patients, the disease was caused by the association of four HPV types. They were recommended to conduct an additional control examination for HPV DNA after 12 months.

The analysis of viral load dynamics showed that its decrease continued throughout the follow up period, which indicates the delayed antiviral effect of Proteflazid. Therefore, in clinical practice, to evaluate the efficacy of therapy, it is advisable to conduct a PCR test not earlier than 6 months after the end of the course of treatment with a control at 12 months.

Patients who had a corresponding PAP test 3 months after the end of treatment (5 women) underwent an excisional cervical biopsy followed by a histological and immunohistochemical study.

Six months after the end of treatment, 80 (93%) patients showed improvement in the colposcopic and cytological pattern. Regression of LSIL (CIN 1) and (CIN 2) was reported in 85% of patients. This allowed a balanced determination of further tactics for managing patients, as well as avoiding excessive medical and invasive aggression.

The tolerability of treatment was assessed by complaints of patients. During the combined use of Proteflazid® drops and Proteflazid® suppositories for 3 months 6 (7%) of patients reported slight itching and burning in the vagina during the first days of administration of suppositories, which did not require drug discontinuation. These symptoms resolved on their own on days 3-4 of treatment. At the beginning of the treatment five (6%) patients complained of incomplete dissolution of the suppository from the moment of administration until insertion of the next suppository. After the recommendation to observe the rule of deep introduction of suppositories, there were no complaints of incomplete dissolution.

The studies have demonstrated that 6 months after treatment with Proteflazid® systemically and topically for 3 months, CIN regress was reported in 93% of patients. In all cases, a decrease in the viral load by more than 2 Lg HPV/10^5 was reported, which is a marker of efficacy of antiviral therapy. Six months after treatment in 84% of patients, and 9 months after treatment in 88% there was complete HPV elimination or a decrease in viral load to clinically insignificant values – less than 3 Lg. The patients tolerated the therapy well; a slight vaginal itching in the first days of administration of suppositories did not require the discontinuation of the product. As a result of the therapeutic treatment with Proteflazid®, 93% of women did not need destructive methods of therapy, which is important given their reproductive plans.

CONCLUSIONS

Based on the above data, it is possible to recommend a scheme of concomitant use of Proteflazid® suppositories and Proteflazid® drops as an effective and safe agent for treatment of patients with cervical intraepithelial neoplasia (CIN) of mild and moderate severity (CIN 1 and CIN 2) associated with HPV.

This treatment regimen makes it possible for a practitioner to reduce unreasonable drug and invasive aggression in the treatment of patients with HPV-associated diseases.

Successful treatment of CIN is the key to preventing subsequent cervical cancer.

The ways of reducing diagnostic and therapeutic aggression of the patients with HPV-infection in reproductive age

N.M. Voloshena, E.D. Zvantseva

The problem of early diagnostics and prevention of cervical cancer is actual in Ukraine. The leading etiologic factor in the genesis of cervical neoplasia and a number of other organs is Human papillomavirus (HPV). The human papillomavirus is sexually transmitted and has high contagiosity. Cancer prevention consists in effective screening, early detection and treatment of pathological changes in the cervix. The aggressive treatment of diseases caused by (HPV) has been replaced by a tactic of a differentiated approach, taking into account to the age of the woman and her reproductive plans.

The objective: was to study the efficacy and tolerability of the combined use of Proteflazid® systemically in drops form and locally in the form of suppositories for 3 months in patients with cervical intraepithelial neoplasia (CIN) of lung and moderate severity (CIN 1 and CIN 2) associated with the human papillomavirus (HPV); determination on the basis of the results of the need for further destructive treatment.

Materials and methods. For the period from July 2016 to September 2017, we examined and treated 86 women with morphologically confirmed intraepithelial neoplasia of the cervix associated with HPV infection.

Results. Based on the performed studies, it was found that 6 months after treatment with Proteplasid® systemically and locally for 3 months, regression of CIN was noted in 93% of patients. In all cases, a reduction in viral load of more than 2 Lg of HPV/105, which is a marker of the effectiveness of antiviral therapy, has been recorded. Six months after treatment in 84% of patients and 9 months in 88%, there was complete elimination of HPV or reduced viral load to clinically insignificant values – less than 3 Lg.

Conclusion. The drug Proteflazid® suppositories and drops contributes to the elimination of human papillomavirus (HPV) and other viral-bacterial infections and reduces the risk of cervical neoplasia.

Key words: *cervical cancer, screening, cervical neoplasia, Human papillomavirus, viral-bacterial infections, Proteflazid®.*

Information about authors

Voloshina Nadezhda Nikolaevna – Department of Oncology, Zaporizhzhia Medical Academy of Post-Graduate Education, Vinter Blvd 20, 69096, Zaporizhzhia. *E-mail: nnvoloshyna@gmail.com*

Zvantseva Elina Dmitrievna – Zaporizhzhia Regional Clinical Oncology Centre, Kulturnaia Street, 177a, 69040, Zaporizhzhia. *E-mail: elinazvantseva@gmail.com*

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