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Antiviral therapy efficacy evaluation in the treatment of precancerous diseases of cervix

Relevance: *Cervical diseases associated with human papillomavirus (HPV) shall be diagnosed and treated since HPV can lead to malignancy.*

The purpose of the study *was to evaluate the clinical efficacy of Panavir and Epigen intimate spray after destructive cervix uteri treatment methods.*

Results: *The efficacy of Panavir and Epigen intimate spray was evaluated by PCR control in 60 women with HPV types 16, 18, 31, and 33. The efficacy of Panavir and Epigen intimate spray has amounted to 85.2% three and six months after the start of treatment. 84.7% of patients who received Panavir and Epigen intimate spray by local administration had a remission of the disease. Two patients co-infected by HPV and cytomegalovirus (CMV) plus the history of early miscarriages became pregnant after six months. Dynamic PCR control, cytology, and colposcopy showed the absence of HPV and CMV after three months. In 2 cases, clinically significant HPV concentrations were detected (5 lg per 105 cells), with a normal colposcopy picture, and CIN III during cytological analysis. These cases required additional treatment.*

All patients had good tolerability of Panavir and Epigen intimate spray; no side effects, individual intolerance, or adverse events were recorded.

Conclusion: *The use of antiviral therapy has prevented the recurrence of cervical diseases caused by papillomavirus.*

Keywords: *cervical cancer, human papillomavirus, antiviral treatment, Panavir, Epigen intimate spray.*

Introduction: Almost nothing is known about the spread of human papillomavirus (HPV) genotypes in the general female population of Kazakhstan [1]. Data on HPV prevalence in the Republic of Kazakhstan is limited to three studies. At the conference of the Ministry of Healthcare of the Republic of Kazakhstan in 2010, N. Mahmutov reported on examining 17,000 women of screening age in South Kazakhstan region using the "double hybrid capture" method (HybrydCapture 2). High-risk HPV (HR HPV) was detected in 11% of cases [2]. Unfortunately, the detailed results of that survey have not been published to cover the knowledge gap on HR HPV prevalence in Kazakhstan.

In 2013-2014, Bekmuhambetov et al. have conducted a retrospective analysis of data from the laboratories of the West Kazakhstan region on HR HPV prevalence among 1,661 men and women. The overall prevalence of HR HPV was 26% (95% CI). Type 16 HPV was prevailing (10.9%), followed by type 39 (5.83%), type 51 (5.27%), and type 31 (4.85%). Most of HR HPV-infected women were aged 16 to 29 years, with significant domination of type 16 HPV (59.7%, $p<0.05$) [3].

In the study by L. Niyazmetova et al., covering 140 women in Nur-Sultan, HR HPV was detected in 43.6% (61/140). Among 12 types of HR HPV found in the study, the most frequent were type 16 (18.44%), and type 18 (22%). Oncocytology showed a positive correlation between HR HPV infection and cervical abnormalities (12%), as well as between HR HPV infection and precancerous cervical pathology [4].

The incidence of cervical cancer (CC) in the Republic of Kazakhstan has increased from 15.3‰ of the female population in 2007 to 19.1% in 2016, i.e., the growth over ten years was 20%. During that period, the peak of incidence has shifted from the age of 50-54 years to the age of 40-44 years.

The CC mortality rate remains stably high and amounted to 7.1‰ in 2016. The highest incidence was registered in Almaty (20.5±1.46‰, $p<0.05$), the lowest incidence rate – in East Kazakhstan region (13.76±0.3‰, $p<0.05$) [5].

Diagnostics and treatment of HPV-associated cervical diseases is an urgent task since this pathogen can cause malignant pathology [6-9]. The HPV infection is the main etiological factor for CC [10, 11]. This virus's life strategy is based on blocking the innate and adaptive antiviral immunity mechanisms. Suppressing the activity of immunocompetent cells, HPV protects the infected epithelial cells from their destruction by T-lymphocytes and natural killers, ensures unhindered replication of the viral genome, and the infection of new host cells [9-11]. HR HPV-infected women are 30-times more subjected to CC compared to the population without HPV [12-14]. The patterns of reproductive behavior are most often mentioned as risk factors for HPV infection [14]. At the same time, there are no specific drugs to suppress HPV infection. Despite the growing portfolio of antiviral medications, the treatment of HPV infection remains a challenge [10-16]. Recently, there is an increasing interest in the use of herbal preparations, such as Panavir. Panavir is a high molecular polysaccharide from the class of hexose glycosides. It is an antiviral and immunomodulating agent that increases the nonspecific resistance of the body to various infections and promotes the

induction of interferon. Another effective medicine is Epigen intimate spray, which is a local immunomodulator of herbal origin with a pronounced antiviral effect.

The purpose of the study was to evaluate the effectiveness of Panavir and Epigen intimate spray for women with precancerous diseases and HPV-associated cervical infection.

Materials and Methods: 60 women with cervical diseases underwent a complete physical examination at the Kazakh Institute of Oncology and Radiology (KazIOR) which included the collection of anamnestic data, cytological, colposcopic, histological examination, diagnostics for sexually transmitted infections (STIs), and the determination of the type of HPV infection (16, 18, 31, 33, 35. 39, 45, 51, 56, 59) by Polymerase Chain Reaction (PCR). The patients with types 16, 18, 31, or 33 HPV in combination with subclinical and clinical manifestations of cervical HPV infection received antiviral therapy with Panavir by intravenous administration and Epigen intimate spray by the local administration. Panavir was administered as a 0.004% isotonic solution, 5.0 ml, in 5 intravenous injections every 48 hours. The antiviral efficacy of Panavir and Epigen intimal spray was evaluated based on PCR control after 3 and 6 months.

At the first stage, all patients underwent destructive treatment with the account of their age, anamnesis, and identified diseases of the cervix. In the second stage, the patients were treated with Panavir according to the a.m. scheme. Epigen intimate spray was applied in parallel daily within 10 days.

Since HPV belongs to STIs, both partners were screened and treated. The partners received intravenous injections of Panavir according to the same scheme.

The patients with CIN III, cancer in situ, underwent diathermoconization of the cervix with diagnostic curettage of the cervical canal and uterine cavity. The treatment was administered, taking into account the cytological, histological, and molecular evidence of HPV infection. In the study group, 64.4% of women underwent diathermoconization, and 36.6% underwent laser vaporization against the background of Panavir therapy.

Results and Discussion: The study included 60 patients with cytologically and histologically verified grade 1-3 epithelial dysplasia of the cervix (CIN I, II, III) or Ca in situ. PCR diagnostics revealed the following HPV genotypes: genotype 16 (50.8% cases), genotype 18 (11.9%), genotype 33 (15.3%), genotype 31 (10.2%), genotype 31+33 (10.2%), and genotype 45 (1.6%) (Figure 1). The average age of the patients was 23.4±4.1 years (from 19 to 43 years). In the study group, 52.5% of women were nulliparous, 20.3% had a burdened history (abortion, miscarriage). The age of sexual debut was 17.8±2.1 years (15 to 27 years). 14 (23.7%) women had sex before the age of 16.

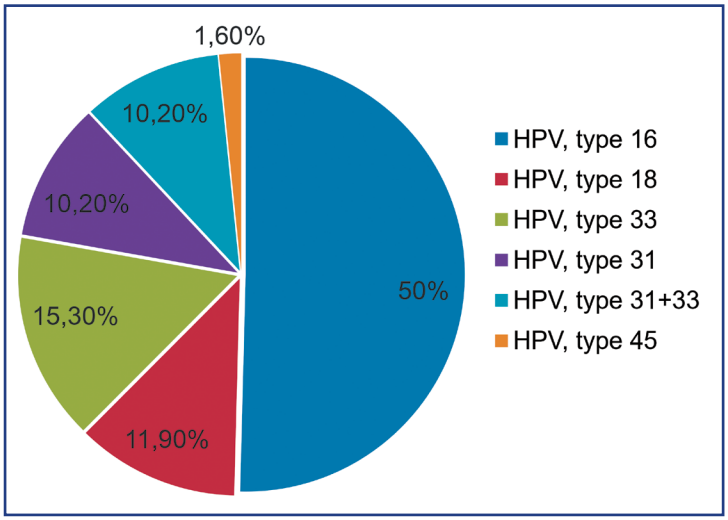

Figure 1 – HPV types detected in the study group (n=60)

The prevalence of HPV is highest among young women (15–25 years old) and decreases with age. Young women were found to have a faster spontaneous cleansing of HPV and regression of the existing pathology than elder women [8, 11]. The time interval between the first sexual contact and the time of examination for HPV is considered to be a significant risk factor for CC [8].

In patients whose sexual experience did not exceed four years, HPV was nine times more common compared to those who had sexual relations for more than ten years. The data obtained demonstrated a gradual formation of specific immunity in HPV-infected women.

The women in the study group were using oral hormonal contraceptives (47/5%), barrier methods of contraception (23.7%), barrier and oral hormonal contraceptives (13.5%), coitus interruptus (6.8%), intrauterine contraception (1.7%), or no contraceptives (6.8%) (Table 1).

Table 1 - Methods of contraception in the study group (n=60)

Contraceptive methods	Number in percentage
Oral Hormonal Contraceptives	47.5%
Barrier methods of contraception	23.7%
Barrier Method and Oral Hormonal Contraceptives	13.5%
Rejected sexual intercourse	6.8%
Intrauterine contraception	1.7%
Did not use contraceptives	6.8%

Background and precancerous processes on the vesical cervix are known to have no clear clinical symptoms [5]. The patients in the study group mainly reported itching (30.5%), burning in the externalia (45.8%), moderate whitish vaginal discharge (86.4%), or had no complaints (13.6%) (Figure 2).

All patients were examined for STIs and non-specific diseases of infectious pathology and underwent sanation at detection. The detected diseases included chlamydia (6.8%), candidiasis (37.3%), ureamycoplasmosis (23.8%), and mixed infection (5.1%). Thus, 72.9% of patients in the study group had STIs and non-specific diseases of infectious pathology.

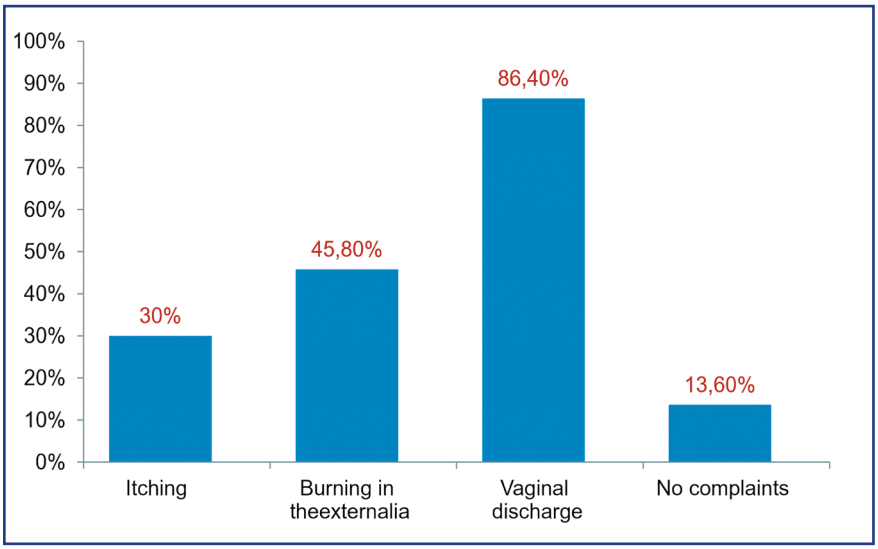

Figure 2 - Main clinical symptoms in the study group (n=60)

All patients received the appropriate anti-inflammatory therapy based on the examination results. Colposcopy revealed abnormal colposcopic patterns in the form of the acanthoid arm of the epithelium, mosaic, punctuation, iodine-negative zones, and atypical vessels in 81.3% of women who later underwent biopsy with colposcopic control.

The extended colposcopy allows determining the transformation zone on the vesical cervix that is the target of HPV infection. The virus enters the basal cells of the epithelium through microtrauma resulting from sexual contact. The viral DNA which stays in the basal layer in a small number of copies is not detected by colposcopy, cytology, or histology. A further expression of the virus results in a subclinical and then clinical stage of the disease [14-16].

Twenty-one (35.6%) out of 60 women in the study group had externalia condylomatosis together with cervical diseases.

Currently, any treatment for cervical pathology should be combined with antiviral therapy, as the persistence of HPV infection is a key factor for the occurrence of cervical cancer. At the same time, antiviral drugs alone are powerless to stop the process of tumor transformation, since infected cells contain a "modified" virus. Therefore these cells must be removed by any of the known methods: electrocoagulation, cryodestruction, laser vaporization, or cervical electroconization [17]. Women who underwent such treatment shall be tested for HPV and shall receive antiviral treatment if the virus persists [16, 17].

84.7% of patients who received Panavir for 3, 6 months had a remission. Two patients (n=2) with cytomegalovirus (CMV) and the history of early miscarriages in addition to HPV became pregnant after 6 months. After 3 months of dynamic monitoring, PCR control showed the absence of HPV and CMV; cytology and colposcopy confirmed the clinical cure. In 2 cases, HPV infection was detected in clinically significant concentrations (5 lg per 105 cells); the colposcopic picture was normal; the cytology showed CIN III that required additional treatment.

Therefore, an increase in HPV concentration during the dynamic monitoring requires to examine the sexual partner for the presence of HPV infection and the treatment of both sexual partners.

The therapy with Panavir and Epigen intimate spray was well tolerable by all patients. No side effects, individual intolerance, or adverse events were recorded.

Conclusions:

1. The incidence of cervical cancer (CC) in the Republic of Kazakhstan has increased from 15.3‰ of the female population in 2007 to 19.1% in 2016, i.e., the growth over ten years was 20%. During that period, the peak of incidence has shifted from the age of 50-54 years to the age of 40-44 years. The CC mortality rate remains stably high and amounted to 7.1‰ in 2016. The highest incidence was registered in Almaty (20.5±1.46‰, $p<0.05$), the lowest incidence rate – in East Kazakhstan region (13.76±0.3‰, $p<0.05$) [5].

2. In early diagnostics for CC up to the age of 34, the Papanicolaou test is required; women over 35 years shall be tested for high-risk HPV and shall undergo cytological and colposcopic assessment for HPV manifestations.

3. Systemic antiviral treatment of background and precancerous diseases of the vesical cervix with Panavir and the Epigen intimate spray by local administration has an efficacy of 84.7%.

4. Cervical pathology requires a differentiated approach to treatment (diathermy surgical treatment). Grade 2 and 3 dysplasia, cancer in situ, microinvasive cancer of the vesical cervix require surgical treatment followed by antiviral treatment under dynamic observation.

References:

1. Kaidarova D.P., Kairbaev M.P., Bolatbekova P.O. Epidemiologiya raka sheyki matki v Respublike Kazakhstan za 10 let (2007-2016gg) (Epidemiology of cervical cancer in the Republic of Kazakhstan for 10 years (2007-2016)) // Vopr. Onkol. – 2017. – №63 (4). – P. 572–579 [in Russian];

2. Makhmutov N. MOH Conference: Cervical cancer prevention. Looking into the future. Abstract book. – Astana, 2010. – 88 p;

3. Bekmukhambetov Y., Balmagambetova S., Jarkenov T., Nurtayeva S., Mukashev T. Distribution of High-Risk Human Papillomavirus Types in Western Kazakhstan - Retrospective Analysis of PCR Data // Asian Pac J Cancer Prev. – 2016. – №17(5). – P. 2667-2672.

4. Niyazmetova L., Aimagambetova G.,Stambekova N., Abugalieva Z., Seksembayeva K., Ali S., AzizanA. Application of molecular genotyping to determine prevalence of HPV strains in Pap smears of Kazakhstan women // Int J Infect Dis. – 2017. – Vol. 54. – P. 85–88;

5. Dinamika pokazateley zabolevayemosti i smertnosti ot raka sheyki matki posle vvedeniya skriningovoy programmy v Respublike Kazakhstan (Dynamics of morbidity and mortality from cervical cancer after the introduction of a screening program in the Republic of Kazakhstan) // Materialy XII Mezhdunarodnoy (XXI) Vserossiyskoy Pirogovskoy nauchnoy meditsinskoy konferentsii (Materials of the XII International (XXI) All-Russian Pirogov Scientific Medical Conference of Students and Young Scientists). – 2017. – P. 28 [in Russian];

6. Ashrafyan L.A., Kiselev V.I. Sovremennyye vozmozhnosti profilaktiki i ranney diagnostiki predraka i raka reproduktivnykh organov (Modern opportunities for the prevention and early diagnosis of precancer and cancer of the reproductive organs) // Akusherstvo i ginekologiya (Obstetrics and gynecology).– 2009. – № 4. – P. 24–29 [in Russian];

7. Golovanova V.A., Novik V.I., Gurkin YU.A. Chastota i faktory riska papillomavirusnoy infektsii i displazii epiteliya sheyki matki u seksual'no aktivnykh devushek-podrostkov (Frequency and risk factors for human papillomavirus infection and cervical epithelium dysplasia in sexually active teenage girls) // Vopr. onkol.– 1999. – T. 45. – № 6. – P. 623–626 [in Russian];

8. Prilepskaya V.N., Rogovskaya S.I., Bebneva T.N., Mezhevitinova Ye.A., Golubenko A.I., Lebedeva M.I., Shamarakova M.V. Lecheniye ploskokletochnykh intraepitelial'nykh porazheniy sheyki matki nizkoy stepeni (Treatment of squamous intraepithelial lesions of the cervix of the low degree) // Akusherstvo i ginekologiya (Obstetrics and gynecology). – 2009. – № 2. – P. 48–53 [in Russian];

9. Franco E.L., Rohan T.E., Villa L.L. Epidemiologic evidence and human papillomavirus infection as a necessary cause of cervical cancer // J. Nat. Cancer Inst. – 1999. – Vol. 91. – P. 506–511;

10. Khleif S.N. Molecular mechanisms of human papillomavirus-induced carcinogenesis: insights on potential targets for prevention // Orlando, ASCO. – 2005. – Educational book. – P. 407–410;

11. Kraus I., Molden T., Holm R. et al. Presence of E6 and E7 mRNA from human papillomavirus types 16, 18, 31, 33 and 45 in the majority of cervical carcinomas // Am. Clin. Microbiol. – 2006. – Vol. 44. – № 40. – P. 1307–1310;

12. Muderspach L., Wilczynski S., Roman. A phase I trial of a human papillomavirus (HPV) peptide vaccine for women with high-grade cervical and vulvar intraepithelial neoplasia who are HPV 16 positive // Clin. Cancer Res. – 2000. – № 6. – P. 3406–3416;

13. Zelinski G.D., Rozendaal L., Voorhorst F.J. et al. HPV testing can reduce the number of follow-up visits in women treated for cervical intraepithe1ia1 neop1asia grade 3 // Gynecol. Oncol. – 2003. – Vol. 91. – P. 67–73;

14. Rogovskaya S.I., Shabalova I.P., Mikheeva I.V, Minkina G.N., Podzolkova N.M., Shipulina O.Y., Poljak M. Human papillomavirus prevalence and type-distribution, cervical cancer screening practices and current status of vaccination implementation in Russian Federation, the Western countries of the former Soviet Union, Caucasus region and Central Asia // Vaccine. – 2013. – Vol. 31(7). – P. 46–58;

15. Kaidarova D., Kairbayev M., Kim H., Han B.-D., Ismailov S., Shibanova A., Kukubassov E., Shalbayeva R., Yeleubayeva Z., Bolatbekova R., Jeong P.H., Jeong K.H. Prevalence of high-risk human papillomaviruses and abnormal PAP smears among women visiting gynecological outpatient units in Kazakhstan: A cross sectional study // J ClinOncol. – 2018. – №36. – P. 13596;

16. Bolatbekova R., Kairbayev M., Shalbayeva R., Kaidarova D., Oštrbenk A., Šterbenc A., Hošnjak L., Poljak M. Distribution of high-risk HPVtypes in women with invasive cervical carcinoma in Kazakhstan // Eurogin.– 2017. – Free Communications. – P. 3–5;

17. Kaidarova D.R., Serikov S.M., Kairbayev M.R., Bolatbekova R.O. Burden of cervical cancer in Kazakhstan // Annals of Oncology. – 2017. – Vol. 28(10). – P. 303.