Advances in Cervical Cancer Immunotherapy and Prevention Research

Ruichen Ma

Yan'an University, Yan 'a city, Shaanxi Province, China

Keywords: Cervical cancer; immunotherapy; vaccine; research progress.

Abstract: The incidence of cervical cancer ranks first among malignant tumors of the female reproductive system and is a serious threat to women's health, and in recent years, the incidence of cervical cancer is trending younger. Persistent high-risk human papilloma (HPV) infection is the main risk factor for the development of cervical cancer. Meanwhile, early sexual intercourse, multiple sexual partners, frequent deliveries, pathogen infection, smoking and poor hygiene habits can increase the risk of cervical cancer. Early screening can help detect precancerous lesions and cervical cancer in time. The main methods to deal with cervical cancer are prevention before the onset of the disease and treatment after the onset of the disease. For patients who have been diagnosed with cervical cancer, clinical treatment is mainly surgery and radiotherapy, supplemented by chemotherapy, and the specific treatment plan is mainly based on the patient's tumor stage and mostly adopts comprehensive therapy. This article introduces the prevention, screening and treatment methods of cervical cancer, aiming to provide reference for the prevention and treatment of cervical cancer in clinical practice.

1. The process of cervical cancer development

Cervical cancer is a common gynecological malignant tumor, among which squamous carcinoma is the most common, accounting for about 75% of invasive cervical cancer. There are various factors contributing to the development of cervical cancer, including early sexual intercourse, early marriage, early childbirth, multiple births, close births and sexual disorders, but the most important cause is HPV infection [3]. HPV is a small epitheliophilic DNA virus, classified by differences in DNA homology, and there are more than 100 kinds, which can cause tumors in multiple sites, especially reproductive system tumors. According to its effect on the organism HPV is divided into high-risk and low-risk types. hpv-16, hpv-18, hpv-31 and hpv-45 belong to the high-risk types, integrated in the cellular genome and associated with the development of cervical cancer. the process of HPV tumorigenesis is complex, and it involves both the process of HPV tumorigenesis is complex, involving both viral tumorigenic proteins and other co-infecting factors (e.g., sex hormones, smoking, and co-infection with other pathogenic microorganisms), which act together to cause HPV-infected cells to become cancerous. Such latent infections can be abrogated by autoimmunity if the HPV virus is not very aggressive and the body's immunity is functioning well. If the opposite is true, the HPV virus will be replicated and spread, and some HPV-DNA will be integrated into the host chromosome, inducing genetic mutations, activating the oncogene of the virus, causing overexpression of oncoproteins, interfering with the normal cell cycle, inhibiting apoptosis, destroying the body's immunity, causing long-term persistent infection and atypical proliferation of cervical epithelial cells. If the virus continues to develop, cervical cancer will occur.

2. Different methods to deal with different stages of cervical cancer at present

The main methods to deal with cervical cancer are prevention before the onset of the disease and treatment after the onset of the disease. The prevention of cervical cancer includes screening and vaccination. The treatment of cervical cancer includes surgery and concurrent radiotherapy, including cisplatin-based chemotherapy and brachytherapy. Considering the permanent damage to the body and

the low cure rate of surgical treatment for cervical cancer, we should attend annual medical checkups and get HPV vaccine when conditions permit to prevent the occurrence of cervical cancer.

2.1 Vaccination

Cervical cancer vaccines can be divided into preventive and curative vaccines. The rationale behind prophylactic vaccination is to obtain high levels of specific neutralizing antibodies against HPV types, thereby preventing cervical infection. Prophylactic vaccines have been widely used in the United States and the United Kingdom, and are now available in China by appointment, at community hospitals at your own expense. The different types of HPV vaccines and their applicable ages and vaccination procedures are shown in Table 1.

Table: 1 Different types of HPV vaccines

Type of vaccine	Prevention of HPV subtypes	Applicable age (years)	Vaccination procedure
Bivalent vaccine	16. 18type	9~45 years old	1 dose each for 0, 1 and 6 months
Tetravalent vaccine	16, 18 types and types causing genital warts (types 6 and 11)	20~45 years old	1 dose each for 0, 2 and 6 months
9-Valent HPV Vaccine	Type 6, 11, 16, 18, 31, 33, 45, 52 and 58	16~26 years old	1 dose each for 0, 2 and 6 months

The HPV vaccine is not effective for women who are already infected with HPV. Systemic or local adverse reactions such as fever, nausea, dizziness, fatigue, myalgia, headache, redness and swelling can occur after vaccination. Therapeutic vaccines are cervical cancer vaccines with therapeutic effects. For example, VGX-3100 therapeutic vaccine, which consists of two DNA plasmids, is the first effective therapeutic vaccine against HPV-16 and HPV-18-associated CIN2/3, but it is not yet widely used.

2.2 Treatment of cervical precancerous lesions

The main cause of cervical cancer development is HPV infection. From HPV infection to the development of cervical cancer, it will experience cervical precancerous lesions, i.e. CIN, in the state of CIN, cervical cells are in immortalized state, i.e. equivalent to the clinical precancerous stage, which will lead to cervical cancer when there are synergistic factors acting together. The cure rate of precancerous lesions is higher than that of cervical cancer. Early treatment of precancerous cervical lesions is mainly directed to the site of the lesion and there are three methods as shown in Table 2. Since surgical treatment will directly destroy the site of disease, the choice should be critically evaluated, and if it can be cured with pharmacological treatment, try to choose pharmacological treatment.

The current treatment for CIN is somewhat excessive, for example, the standard of care for CIN2/3 is surgical excision, but not all CIN2/3 develop into cervical cancer and surgical excision can lead to long-term reproductive disease, and MATTEW et al. suggested that the VGX-3100 therapeutic vaccine could be used as a non-surgical treatment option for CIN2/3.

Table 2: 3 methods of early treatment of precancerous lesions of the cervix

Treatment method	Treatment
Destructive therapy	Cryo, CO2 laser and electrocoagulation
Excisional therapy	LEEP, cold knife conization and laser conization
Drug treatment	Interferon, povidone-based suppositories and fluorouracil

3. Therapeutic vaccines

Therapeutic vaccines work in two ways: cellular immunity and humoral immunity. There are several major categories of therapeutic vaccines commonly used today.

3.1 Vector vaccines

Viral vectors are effective in presenting HPV proteins. Nowadays, adenoviruses, adeno-associated viruses, alpha viruses, cowpox viruses, etc. are mostly used. Viral vector vaccines can stimulate host cells, induce endogenous synthesis of viruses and recombinant proteins, and promote strong T-cell responses; they can also display surface antigens, thus inducing strong antibody responses, and are often used directly as a gene technology in preclinical vaccine studies; bacterial vectors used to develop HPV therapeutic vaccines include not only Listeria Listeriamonocytogenes, Streptococcus lactis and Lactobacillus plantarum are also used for the development of HPV therapeutic vaccines. In 2009, the first clinical application of Listeria vector vaccine, Lm-LLO-E7, a genetically deficient type of attenuated strain that secretes HPV16E7 with a non-hemolytic LLO fusion protein, was introduced.

3.2 DNA vaccines

DNA vaccines are cloned from genes encoding a specific antigen and expressed in vivo to stimulate humoral and cellular immune responses with antigenic properties for the prevention and treatment of disease. immunogenicity is weak for bare DNA vaccines. The main DNA vaccines in clinical trials with good efficacy are ZYC101a, Sig/E7detox/HSP70 and VGX-31003.

3.3 DC vaccine

Dendritic cells (DCs) are powerful antigen-presenting cells in the body that activate T-lymphocyte activation, and tumors occur when the dendritic cells responsible for antigen presentation are malfunctioning, resulting in immune system suppression or tumor immune escape. DCs can express high levels of MHC class I and II molecules, B7, CD40 and other co-stimulatory molecules, and can initiate CD4+ and CD8+ T cell responses in vivo. However, the disadvantages of DC vaccines are that they are expensive and cumbersome to produce, requiring large scale mass culture; and some patients may have hypersensitivity reactions, so further in-depth research and clinical trials are needed for DC vaccines to be better used in clinical settings.

3.4 Other types of vaccines

In addition to the four types of HPV vaccines mentioned above, RNA replicon vaccines and tumor cell vaccines are also being investigated; RNA replicon vaccines can retain the viral replicase gene, but some studies have found that it may cause apoptosis of surrounding cells, therefore, these vaccines are mostly used in conjunction with anti-apoptotic factors; genes encoding co-stimulatory molecules or cytokines can be transferred to tumor cells by tumor cell vaccines as a way to enhance immunogenicity and thus achieve T-cell activation and post-immunization anti-tumor effects. The genes encoding co-stimulatory molecules or cytokines can be transferred to tumor cells by tumor cell vaccines to enhance immunogenicity and thus achieve T cell activation and post-immunization antitumor effects. Not to be overlooked, experiments by MassaS et al. showed that fusion of both, mutant HPV16E7 sequence and B-1,3-1,4-glucanase (LicKM) from Clostridium thermophilum, induced by instantaneous immunization of mice with E7-specific IgG and cytotoxic T-cell response while fighting against E7 tumor cells; another information has been demonstrated that:HPVE2 protein can inhibit the transcription of E6 and E7, and it is possible that the E2 gene and the oncogenic proteins encoded by E6 and E7 genes hold an inverse effect; BlakajDM et al [31] found that HPVE2 vaccine is promising as a broad-spectrum vaccine for the treatment of cervical cancer. It has also been shown that chloroplast-targeted transient expression in tobacco plants is expected to produce a cheap and effective HPV16L1VLP vaccine, and research is underway to develop a plant VLPs for the production of cervical cancer vaccines. All these findings make us happy to find that there are new discoveries and value in vaccine development for cervical cancer. So far, studies have concluded that vaccines are unlikely to work in patients with pre-existing HPV infection and cervical cancer. The Advisory Committee on Immunization Practices (ACIP) recommended targets are bivalent or quadrivalent vaccine for women at age 11 or 12 years and quadrivalent vaccine for men at the same age; nine-valent vaccine for women between 13 and 26 years of age and for men between 13 and 21 years of age, and delayed until age 26 for male-male contacts and immunocompromised individuals. Prophylactic

vaccines are not recommended during pregnancy, but studies have shown no direct association between cervical cancer vaccine application during pregnancy and adverse pregnancy outcomes such as teratogenicity and mortality. Studies have shown that quadrivalent vaccine has the same immunizing effect in HIV-infected patients and that HIV-infected patients can also benefit from immunization based on its safety and tolerability.

4. Conclusion

With the development of molecular biology and immunology, immunotherapy of cervical cancer has shown initial success, especially in the prevention of cervical cancer. Many clinical trials are underway, and there are also many basic studies providing new ideas. At present, the main directions of clinical trials include the addition of immunotherapy during the same period of standard treatment or after standard treatment for locally progressive cervical cancer, single-agent immunotherapy and combined anti-vascular therapy or multiple immunotherapeutic drugs in advanced, previously ineffective standard treatment and recurrent cervical cancer, and the study of HPV prophylactic vaccine with lower cost and wider protection, etc. We believe that the future development of immunotherapy for cervical cancer will be more promising. The development of cervical cancer immunotherapy will be more extensive. The causes of tumors are complex and heterogeneous. With the rational use of various therapeutic methods such as surgery, chemotherapy, radiotherapy, targeted therapy and immunotherapy, patients with cervical cancer will definitely be able to have more clinical benefits.

References

[1] Aromseree S, Pientong C. Possible contributing role of Epstein-Barr virus (EBV) as a cofactor in human papillomavirus (HPV) -associated cervical carcinogenesis [J]. J Clin Virol, 2015(73): 70-76.

[2] Chen M, Zhang Y, Zheng PS. Tafazzin (TAZ) promotes the tu- morigenicity of cervical cancer cells and inhibits apoptosis [J]. PLoS One, 2017, 12(5): e0177171.

[3] Sun B, Ye X, Li Y, et al. Lgr5 is a potential prognostic marker in patients with cervical carcinoma [J]. Int J Clin Exp Pathol, 2015, 8(2): 1783-1789.

[4] Niu G, Wang D, Pei Y, et al. Systematic identification of key genes and pathways in the development of invasive cervical cancer [J]. Gene, 2017, 618: 28-41.

[5] Miekus K, Pawlowska M. MET receptor is a potential therapeutic target in high grade cervical cancer [J]. Oncotarget, 2015, 6(12) :10086-10101.

[6] Costa S, Sideri M. The predictive value of human papillomavirus testing for the outcome of patients conservatively treated for stage Ia squamous cell cervical carcinoma [J]. J Clin Virol, 2015, (70): 53-57.

[7] Deng T, Feng Y, Zheng J, et al. Low initial human papillomavirus viral load may indicate worse prognosis in patients with cervical carcinoma treated with surgery [J]. J Gynecol Oncol, 2015, 26 (2): 111-117.

[8] Blakaj DM, Fernandez-Fuentes N, Chen Z, et al. Evolutionary and biophysical relationships among the papillomavirus E2 pro- teins [J]. Front Biosci, 2009, 14: 900-917.

[9] Zahin M, Joh J, Khanal S, et al. Scalable production of HPV16 L1 protein and VLPs from tobacco leaves [J]. PLoS One, 2016, 11 (8): e0160995.

[10] Handler MZ, Handler NS, Majewski S, et al. Human papillomavir- us vaccine trials and tribulations clinical perspectives [J]. J Am Acad Dermatol, 2015, 73: 743-758.

[11] Garland SM, Ault KA, Gall SA, et al. Pregnancy and infantout- comes in the clinical trials of a human paplliomavirus type 6 /16 / 18 vaccine: A combined analysisi of five randomized controlled trials [J]. Obstet Gynecol, 2009, 114(6): 1179-1188.

[12] Sewell DA, Pan ZK, Paterson Y. Listeria-based HPV-16 E7 vaccines limit autochthonous tumor growth in a transgenic mouse model for HPV-16 transformed tumors [J]. Vaccine, 2008, 26 (41): 5322-5327