

Existing Therapeutic Vaccine Approaches for Cervical Cancer

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Abstract. As the level of modern medical treatment gradually advances and improves with the development, therapeutic vaccines are gradually being researched and applied in clinical treatment, but there are still some areas that require further research and improvement. This article summarizes the research progress, market development, awareness and popularity of cervical cancer therapeutic vaccines in recent years and treatment scope. The study found that the clinical basis for therapeutic vaccines and their popularity and awareness in remote and low-income developing countries are low, and people in these areas also have misunderstandings about cervical cancer. In addition, the cervical cancer therapeutic vaccine mainly targets HPV16 and HPV18, two subtypes that are the main factors causing cervical cancer. Therefore, there is basically no progress in the research of therapeutic vaccines for cervical cancer except for these two subtypes. The development of therapeutic vaccines for cervical cancer has gradually progressed, but in some places, there are still shortcomings compared with vaccines that are already on the market and are used proficiently.

Keywords: cervical cancer; vaccines; treatment.

1. Introduction

Cervical cancer causes a gradual increase in the number of deaths, which make the Global Women and Health Organization focus on cervical cancer's social question due to the effects of cervical cancer on women's health security and cancer mortality [1]. The pathogeny of cervical cancer is persistent HPV infection due to sex activities. Moreover, symptoms after contracting cervical cancer usually manifest as menstrual bleeding or clots during menopause or pregnancy, other manifestations include soreness in the back, legs, and other places of the body, fatigue, swelling, vaginal discomfort, and abnormal vaginal discharge [1]. However, under the existing research and treatment, cervical cancer already got both efficient prevention and treatment modalities.

In order to control and eliminate the increase in cervical cancer cases, WHO has published a "90-70-90" goal, which is about 90% of girls will be injected with HPV at 15 years old, 70% of women will be finishing their high-performance test and review between age 35-45, and 90% of cervical cancer patient could be treated [1]. According to relevant information, the global number of cervical cancer cases in 2018 was 568847 cases within 311365 cases of death, which mainly happened and focused in South Africa and other countries with low human development index and high capacity for alcohol [2]. In addition, the morbidity of cervical cancer in young people group was increasing especially in Cyprus, Sweden, and Norway. After that, cervical cancer cases increased to 604127 with 341813 cases of death, which mainly happened in Malawi, Africa, Zambia and Bolivia [3]. In general, the number of cervical cancer cases decreasing with HDI increase also means the proportion between HDI and case decreases. However, in countries that have a high income, the number of cases is stable at a lower level. By comparison, not only the global number of cervical cancer cases from 2018 and 2022 are increasing, but also the ratio between cases and death cases is slowly increasing. The number of cervical cancer case is still increasing with the death case and effect in woman's healthcare and sanitary safety therefore is essential to research and develop the way of expectant treatment such as therapeutic vaccine.

In the current research and development of cervical cancer's therapeutic vaccine, the DNA vaccine has been becoming the research emphasis, which has been shown to have certain efficacy in phase 1 and phase 2 clinical treatment trials without excessive side effects. Despite this, cervical cancer's



therapeutic vaccine is still in the testing and researching phase which hasn't reached the stage of listing and popularization. Therefore, people usually choose preventive vaccines in the prevention stage, and chemotherapy for treatment after infecting the cervical cancer. In order to completely prevent cervical cancer and effectively implement and complete the 90-70-90 goal, the development of vaccines is crucial. The research and development of therapeutic vaccines for cervical cancer can provide safer and more stable treatment options for developing and developing countries so that more patients with cervical cancer can be spared from the pain and death caused by cervical cancer. Therefore, the research and development of cervical cancer vaccines is particularly important and meaningful.

2. Application of therapeutic vaccine for cervical cancer

According to statistics, the types of therapeutic vaccines that have made some research progresses are tumor cell vaccines, live virus vector vaccines, live bacterial vector vaccines, peptide vaccines, dendritic cell vaccines and DNA vaccines. These different types of vaccines have different production methods and operating systems and ultimately achieve the purpose of treating cervical cancer. A few types of therapeutic vaccines have been marketed, such as GX-188E and Vvax001 in DNA vaccines, and some regulators or inhibitors such as Perbrolizumb, Balsilimab, and Zalifrelimab. In addition, although the therapeutic vaccines currently on the market can have corresponding therapeutic vaccines or drugs from the early stage to the late stage. The limitations on the types and subtypes of cervical cancer will be much greater, because the current therapeutic vaccines focus on two subtypes of HPV-16 and HPV-18. When necessary, the therapeutic vaccine for cervical cancer needs to be combined with other drugs or treatment methods to achieve the desired or better therapeutic effect.

The existing therapeutic vaccines, whether on the market or not, are concentrated on the two subtypes of HPV-16 and HPV-18, which means the opportunities for other cervical cancer subtypes to be cured by therapeutic vaccines will be reduced. Therefore, in remote countries, the treatment rate of some cervical cancer subtypes will decrease, and the mortality rate will increase. Most clinical HPV therapeutic vaccines focus on HPV-16 and HPV-18 subtypes. Cervical vaccines are divided into different types of vaccines, such as viral vector vaccine, peptide and protein-based vaccine and DNA-based Vaccine. While mainly focused on antigens, all therapeutic vaccine has been shown in only HPV-16 and HPV 18. In detail, 18 out of 26 are targeted only at HPV-16. Moreover, 8 out of 26 vaccines are targeted to both HPV-16 and HPV-18 even though there are no vaccines only targeted to HPV-18. Throughout the data in the table, whether the status of the vaccine is completed, terminated, recruiting, or active, no data and evidence showing that nowadays development is trying and focusing on other subtypes such as HPV-31, 33, 35, 39, and so on for other 9 high-risk types. Although HPV-16 and HPV-18 caused 70% of cervical cancer, the developer is more focused on making a therapeutic vaccine that targets HPV-16 and HPV-18. However, there are 200 kinds of HPV in nowadays world, therefore if scientists only focus on HPV-16 and HPV-18, there are other kinds of subtypes that cause cancer, which won't easily be treated by therapeutic vaccine. In remote or developing countries, when the living standards of the people and the medical level of the country are not particularly developed and advanced, only the therapeutic vaccines for two subtypes of HPV-16 and HPV-18 will make people infected with other high-risk subtypes cancer patients cannot be treated conservatively, which increases the mortality rate of cervical cancer to a certain extent.

Except for the therapeutic vaccine research that is too focused on HPV-16 and HPV-18, most of the therapeutic vaccines currently being developed and researched lack sufficient clinical trials and reliability to support their vaccine development and marketing. According to research on different therapeutic vaccines, most of the therapeutic vaccines for cervical cancer on the market need further research and trials to prove that their efficacy, stability and safety have reached the level of marketing and use. Among them, there is a case of using liposomal formulations of poly-leucine-antigen to make a therapeutic vaccine, but its effect has only been verified and effective in experimental mice, and there is no clinical trial and data yet. As a promising and promising therapeutic vaccine strategy, the CRISPR/Cas genome needs further testing and optimization for its safety and specificity before it can enter clinical application. Another example is the ADXS11-001 therapeutic vaccine, which is

currently in clinical trials, but the clinical trials have not yet been completed and sufficient effective data has been collected. In terms of safety, some vaccines that have been marketed and have clinical trials show that a small number of patients will die or be forced to stop treatment due to adverse reactions (7.7%), which is reflected in the clinical trials of Balstilimab and Zalifrelimab [4]. In addition, the research on Pembrolizumab (MK-3475) Plus Platinum and Gemcitabine as a treatment has not reached the final procedure to obtain accurate results [5]. Based on the above information, on the premise that therapeutic vaccines against cervical cancer have been developed, some vaccines cannot be clinically tested and effective clinical data cannot be obtained due to facilities, technical, or resource reasons. This has led to the inability of vaccines to be marketed without clinical data, which means that the scope and methods of current therapeutic vaccines are limited. Besides, in the case of insufficient clinical data, factors such as the safety, specificity, and stability of the vaccine itself cannot be guaranteed. As a result, in addition to fewer choices of therapeutic vaccines, the size and probability of adverse reactions in patients after vaccination will gradually increase with the instability of the vaccine itself, which increases the probability of treatment failure. This increases the chances of being approved to stop treatment.

Apart from the research mechanism and safety of the vaccine itself, its sustainability and accessibility are also problematic [6]. Because the vaccine production process is relatively cumbersome, and the state of many developed vaccines is very unstable, it is very easy to be interfered with by the outside world it will cause changes or destroy some functions, resulting in vaccine failure. Except for the vaccines under development, there is still a supply problem in remote areas of the therapeutic vaccines against cervical cancer that have been marketed. Due to the lack of infrastructure and vaccine facilities in remote areas, coupled with the high cost of vaccine production, people living in remote areas cannot easily obtain vaccination services [7]. Because the popularity of cervical cancer disease and vaccines is not in place in remote areas, people in remote areas have certain prejudices and misunderstandings about cervical cancer and HPV, which leads to the lack of attention to cervical cancer therapeutic vaccines in remote areas. There are also great obstacles to universal vaccination [7]. According to relevant data, $M: I$, which can be used to replace the mortality rate, can be obtained by dividing the mortality rate by the incidence rate [8]. The information lists different countries, regions with different incomes, and the world's average death rate. From the perspective of high- and low-income areas, the mortality rate of cervical cancer will gradually decrease when income increases. The cervical cancer mortality rate in developed countries and regions is even lower than the global average. In contrast, cervical cancer mortality rates in developing countries and territories exceed the global mortality rate. Among them, the lowest death rate is in the high-income area, and the data shows that it is about 0.3, while the second-lowest middle-income area is about 0.5 [8]. This is followed by the global average mortality rate of about 0.56, and finally by the low-income population of approximately 0.6 and low-income regions of approximately 0.7 [8]. In general, vaccine coverage and vaccination services in remote and low-income areas are much lower than in developing and high-income countries, so the corresponding cervical cancer mortality rate in low-income and remote areas will be higher.

To sum up, to achieve the goal of eradicating cervical cancer issued by WHO and to research and promote therapeutic vaccines for cervical cancer, the three main problems mentioned above need to be improved. In this way, a safer, lower-cost, and more diverse therapeutic vaccine against cervical cancer can be developed to a greater extent and further.

On the first big issue, most cervical cancer therapeutic vaccines focus on two subtypes, HPV-16 and HPV-18. To achieve the goal of therapeutic vaccine diversity, the scientists' study could be expanded to include other high-risk subtypes of cervical cancer. Its related research on other high-level subspecies of cervical cancer such as HPV31 shows that the area under the curve of HPV31 is the highest at 0.81, so HPV31 may cause a variety of infections [9]. The genome-wide methylation pattern of HPV3 has a significant increase in multiple CpG sites in regions such as E2, L2, and L1, and methylation can show which parts can cause cancer [9], as shown in Fig. 1. Therefore, in addition to HPV16 and HPV18, the development of vaccines for other high-risk subspecies is also very

necessary, so that the deaths caused by cervical cancer can be avoided and eliminated to the greatest extent. At the same time, clinical research on vaccines is also very important. Only sufficient data can fully prove and ensure the efficacy, safety, specificity, etc. of vaccines. Related studies have shown that the current strategy for the cervical cancer recurrence therapy is limited to the combination therapy of pembrolizumab with chemotherapy and bevacizumab [10]. For this reason, cervical cancer vaccines development still needs a large number of clinical trials and data to prove the safety, feasibility, and efficacy of therapeutic vaccines. Therefore, adjustments to vaccines that have already shown efficacy can be accelerated to achieve faster clinical trial results. In this way, when the clinical trials are completed, researchers can adjust the final adjuvant and vaccine formula more quickly and speed up the progress of marketing. Finally, there is the issue of vaccine cost and therapeutic popularization of vaccines in remote areas. In addition to needing the help of the state and the government to increase the income of the people in the area and the level of service and medical care in the country, such areas also need formal and frequent dissemination of disease and physiological knowledge. Letting the disease of cervical cancer not suffer from prejudice and misperception can help promote the popularization of therapeutic vaccines.

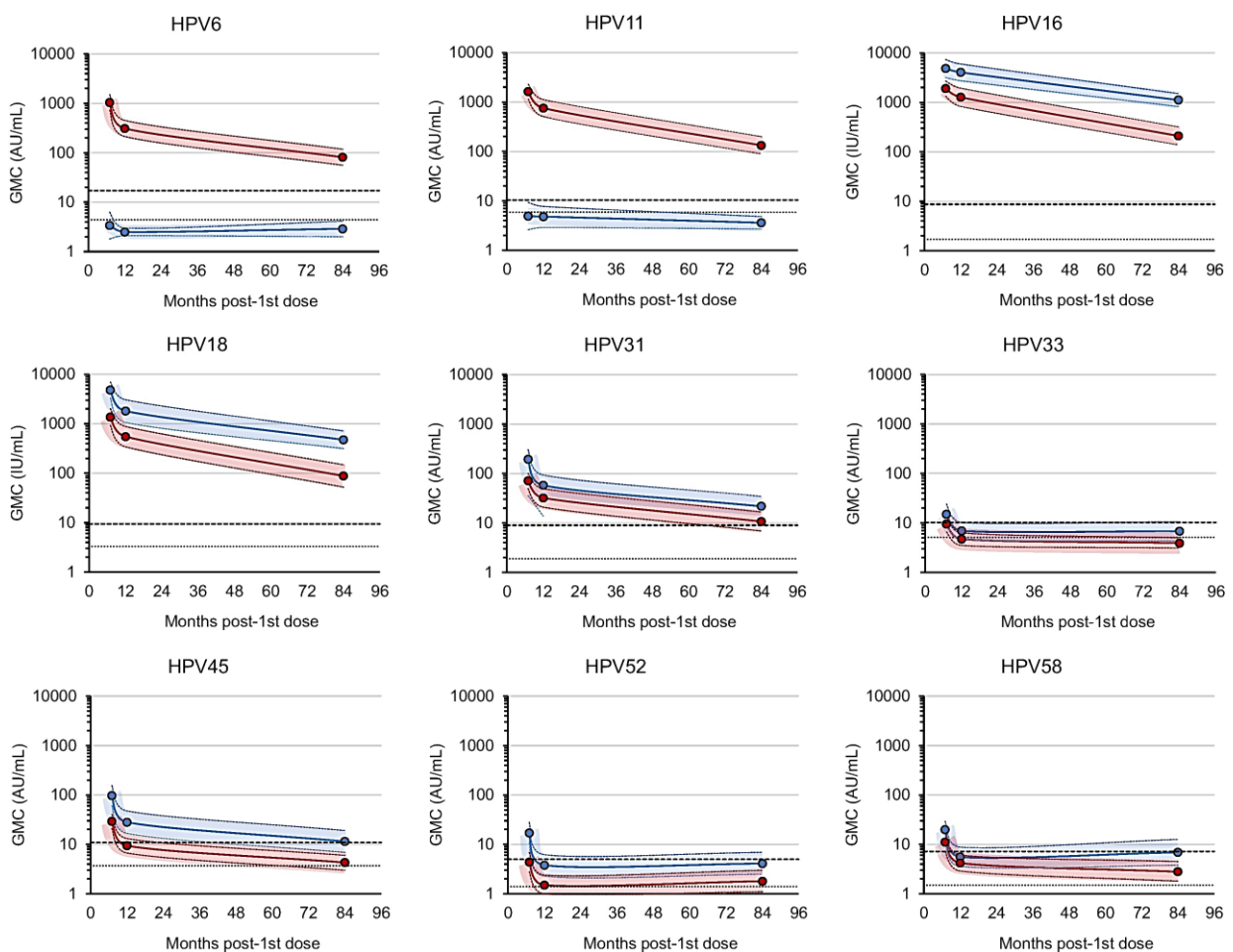


Figure 1. Binding to different antibody levels over time [9].

3. Conclusion

This study found that therapeutic vaccines are very helpful for the cervical cancer treatment. However, the mechanism of current vaccine, data, and popularity are not mature enough and require further research and development. Especially in remote and developing areas, due to the low popularity and high cost of cervical cancer and cervical cancer vaccines, the probability and possibility of treating the disease through therapeutic cervical cancer vaccines will be greatly reduced. In response to this result, corresponding suggestions and solutions are also mentioned above, such as conducting more effective clinical trials for some vaccines, and carrying out science popularization and introduction

activities related to cervical cancer in remote areas to increase the popularity and the cervical cancer awareness. Regarding the scarcity of cervical cancer vaccine types and subtypes, HPV16 and HPV18 currently cover most of the causes of cervical cancer, so therapeutic vaccines targeting these two antigens and subtypes also cover a larger therapeutic range. Research on other subtypes is not particularly urgent compared to several other issues. As a result, therapeutic vaccines for cervical cancer have made great progress in modern medicine, and the development of some vaccines has reached standards for use and treatment, but there is still a lack of popularization and science. The development of therapeutic vaccines has added another conservative treatment option to the treatment of cervical cancer, filling the gap where chemotherapy and other treatments are expensive and dangerous. The development mechanism of cervical cancer therapeutic vaccines can provide an effective reference for subsequent therapeutic vaccines for more cancers and different subtypes of cervical cancer. This article mainly summarizes the progress and shortcomings of cervical cancer therapeutic vaccines, which is helpful for researchers and related scholars to summarize more conveniently. Future research can further study and improve based on the gaps in therapeutic vaccines summarized in this study.

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