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REVIEW

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Progress in therapeutic HPV vaccines: observations from clinical trials

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Abstract

Human papillomavirus (HPV)-related cancer accounts for a large number of new-onset malignant tumors caused by infection annually. Exogenous genes integrated into the tumors, mainly HPV E6 and E7, are ideal targets for therapeutic vaccines. Although there are no officially approved therapeutic HPV vaccines, several breakthroughs have been made in peptide-based, vector and DNA vaccines against HPV-related tumors and precancerous lesions. Therapeutic HPV vaccines alone showed limited clinical efficacy against HPV-related tumors, but preliminary results with combination treatments have been encouraging. Thus, more studies should focus on the role of HPV in tumorigenesis and tumor microenvironment to overcome therapy resistance and improve clinical efficacy.

Keywords

HPV; Peptide-based vaccine; Vector vaccine; DNA vaccine

1. Introduction

The World Health Organization estimates that about 15.4% of the annual new-onset malignant tumors are caused by infections, of which 9.9% are related to viruses [1]. There are about 700,000 HPV-related malignant tumors every year, of which cervical cancer is the most prevalent virus-related tumor, accounting for 570,000 cases [2]. The number of HPV-positive oropharyngeal cancer patients have surpassed their HPV-negative counterpart in the United States [3]. Besides, HPV is also responsible for anal, penis and vulvar cancers [4]. Thus, the U.S. Food and Drug Administration (FDA) has approved the listing of prophylactic HPV vaccines as early as 2006 to prevent cervical cancer. However, HPV-related malignant tumors still account for a large part of infection-related tumors, possibly related to the high cost of these vaccines in developing countries and insufficient vaccination coverage in developed countries [5, 6]. Therefore, more emphasis should be laid on the importance of therapeutic vaccines to handle the existed infection-related tumors.

HPV is a double-stranded DNA virus with a genome size of 8 kb, encoding six "early" proteins (E1, E2, E4, E5, E6 and E7) and two "late" proteins (L1 and L2). Virus-like particles (VLP) of capsid protein HPV L1 from high-risk HPV subtypes are used in prophylactic vaccines to generate HPV-neutralizing antibodies to prevent the initial infection [5]. However, HPV-associated malignancies or precancerous lesions are related to carcinogenic proteins HPV E6 and E7, which are beyond the scope of prophylactic vaccines and are the target of various therapeutic vaccines [7]. Although therapeutic HPV vaccines such as peptide-based, vector and DNA vaccines have made encouraging progress in clinical research, with some even entering phase 3 clinical trial stages, there is still no officially approved therapeutic vaccine to combat HPV-related cancers [8]. In this paper, we reviewed current clinical research on therapeutic HPV vaccines and provided insights and suggestions for future studies in this area. (Table 1).

2. Peptide-based vaccine

Peptide-based therapeutic HPV vaccine uses short or long peptides encoded by HPV oncogenes to induce immune responses. Its main merit is stability during storage and transport and convenience to obtain, while its primary drawbacks are low immunogenicity *in vivo* and poor stability *in vitro* [9]. The key points for peptide vaccines are improving their immunogenicity and overcoming major histocompatibility complex (MHC) restrictions. Therefore, effective adjuvant and appropriate epitopes based on HPV carcinogenic protein could be considered as options.

Many peptide-based vaccines have adopted the E7 epitope due to its high affinity with retinoblastoma protein (pRB), which can effectively control the early life cycle of HPV to eliminate immortalization tumors, leading to a more effective cellular immune response than the E6 epitope [9]. The combined use of E6 and E7 epitopes is also a common strategy to overcome MHC restriction and boost immune responses [9].

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TABLE 1. clinical trials of therapeutic HPV vaccines.

Vaccine used	Patient group	No. of subjects	Outcome	Antigen used	Year of publication/Reference
Peptide-based vaccine					
HPV16 SLP	intraepithelial neoplasia 3	20 (19 evaluable patients)	79% (15/19) had clinical responses, 47% (9/19) showed complete responses at 12 months	HPV-16 E6/E7	2009/[10]
ISA101	HPV16+ highgrade VIN/VaIN	43 (29 evaluable patients)	52% (15/29) had clinical response at 12 months	HPV-16 E6/E7	2016/[11]
PepCan	high-grade squamous intraepithelial lesion	31	complete histological regression rate reached 47% at 12 months	HPV16 E6	2016/[12]
GL-0810	recurrent or metastatic head and neck cancer	9	no significant clinical benefit	HPV16	2016/[13]
ISA101 combined with PD-1 antibody	incurable HPV16+ tumor	24	overall response rate was 33%, median overall survival 17.5 months	/	2019/[14]
ISA101 combined with carboplatin/paclitaxel	advanced, recurrent or metastatic cervical cancer	79 (72 evaluable patients)	tumor regressions were observed in 43% of 72 evaluable patients	/	2020/[15]
Vector vaccines					
TA-HPV	cervical cancer	8	no significant clinical effects	HPV16/18 E6 E7	1996/[17]
Tipapkinogen Sovacivec	CIN2/3	192	complete resolution in the vaccine group *vs.* placebo (24% *vs.* 10%)	HPV16 E6 E7	2019/[18]
ADXS11-001 combined with/or without cisplatin	advanced cervical cancer	109	OS rate in the combination group *vs.* the ADXS11-001 group (34.9% *vs.* 24.8%)	HPV-16 E7	2018/[19]
ADXS11-001 combined with mitomycin, fluorouracil and radiation	locally advanced anal cancer	10 (9 evaluable patients)	89% (8/9) had no progress at a median follow-up of 42 months	/	2018/[21]
ADXS-HPV	advanced cervical carcinoma	54 (50 evaluable patients)	12-month OS was 38% (19/50). Median OS was 6.1 months	HPV-16 E7	2020/[22]
DNA vaccines					
VGX-3100	intraepithelial neoplasia 2/3	167 (143 evaluable patients)	histopathological regression in VGX-3100 recipients *vs.* placebo recipients (49.5% (53/107) *vs.* 30.6% (11/36))	HPV16/18 E6/ E7	2015/[27]
MEDI0457	locally advanced, p16+ head and neck cancer	22 (21 evaluable patients)	85.71% (18/21) patients showed elevated antigen specific T cell activity	IL12 + HPV16/18 E6/ E7	2019/[29]

TABLE 1. Continued.

Vaccine used	Patient group	No. of subjects	Outcome	Antigen used	Year of publication/Reference
GX-188E	CIN3	9	7 showed complete regression of CIN and virus clearance at 36 weeks	HPV E6/E7	2014/[30]
GX-188E	CIN3	72	67% presented histopathological regression at 36 weeks	/	2020/[31]
Pembrolizumab plus GX-188E	HPV16+/18+ advanced cervical cancer	36 (26 evaluable patients for interim activity assessment)	overall response at 24 weeks 42% (11/26), 15% (4/26) had a complete response, 27% (7/26) had a partial response	/	2020/[32]
DNA tattoo vaccine	HPV16+ VIN	14	43% (6/14) had clinical responses, 14% (2/14) showed complete responses at 12 months	HPV-16 E6/E7	2021/[33]

HPV: Human papillomavirus; PD: Programmed cell death; VIN: vulvar intraepithelial neoplasia; OS: overall survival. SLP: synthetic long peptide; CIN: cervical intraepithelial neoplasia; VaIN: vaginal intraepithelial neoplasia.

Kenter *et al.* [10] used nine HPV-16 E6 and four HPV-16 E7 synthetic peptides (HPV16 synthetic long peptide (SLP)) emulsified with incomplete Freund's adjuvant (IFA; Montanide ISA 51) to treat patients with grade 3 intraepithelial neoplasia. During the 12-month follow-up, 79% (15/29) of the patients demonstrated clinical responses, with 47% (9/19) showing a complete response, which was maintained at 24 months of follow-up. All patients had vaccine-induced T cell response, and those with complete response had stronger INF-γ (Interferon-gamma) related proliferative CD (cluster of differentiation) 4+ T cell response and broader CD8+ T cell response than patients without complete response. Immune monitoring showed that the response of CD8+ T cells was weaker than that of CD4+ T cells after vaccination with HPV16 SLP vaccine. The reaction was mainly induced by the E6 oncoprotein. To overcome this obstacle, researchers divided the synthetic peptide vaccine into two parts to form a new ISA101 vaccine, one consisting of seven E6 synthetic peptides, while the other contained two E6 and four E7 synthetic peptides, which were injected into the left and right arms, respectively [11].

Poelgeest *et al.* [11] conducted a multicenter, open, randomized controlled trial to investigate the efficacy of ISA101 alone or in combination with imiquimod to treat high-grade HPV16-positive patients with vulvar or vaginal intraepithelial neoplasia. The intensity of immune responses of HPV16-specific CD8+ T cells and their relationship with clinical responses (lesion size, histology and virology) were evaluated, and the results showed a clinical response was 52% (15/29) at 12 months after the last vaccination in which 8 patients had complete histological response. Of those cases with complete histological responses, only one had complete virus clearance. Vaccine-induced T cell immune response was observed in all patients, and those with better clinical responses demonstrated stronger immune responses. The investigators also observed that the topical use of imiquimod did not improve the vaccine's efficacy. Thus, the study confirmed that the long peptide vaccine ISA101 could induce HPV16-specific T cell immune response and could be an effective treatment for high-grade vulvar or vaginal intraepithelial neoplasia induced by HPV16.

Coleman *et al.* [12] developed a therapeutic HPV vaccine named PepCan, which contains four synthetic peptides covering the HPV16 E6 protein, using Candin®, a colorless extract from Candida albicans, as the adjuvant. In a phase I clinical trial for high-grade intraepithelial neoplasia, the rate of complete histological regression was 47% at 12 months, with no recurrence observed at 24 months [12]. The virus load of all the patients with histological regression decreased significantly. Immune profiling showed that the level of regulatory T cells in responders (determined *via* histology) was significantly lower than in non-responders.

Zandbergetal *et al.* [13] designed an HPV16-based therapeutic vaccine called GL-0810. It contained a "penetrating protein" sequence (RKKRRQRRR) derived from human immunodeficiency virus -transactivator (HIV-TAT) that promoted the direct transport of antigen peptides to the endoplasmic reticulum and Golgi apparatus through the cell membrane to form a polypeptide-human leukocyte antigen complex. Montanide ISA 51 and granulocyte-macrophage colony-stimulating factor (GM-CSF) were used to enhance antigen presentation and promote the migration of dendritic cells (DC) to the vaccination site. The results showed obvious anti-tumor effects in animal experiments. However, in a phase I clinical trial for recurrent or metastatic head and neck cancers, no significant clinical benefit was observed, although 80% of the HPV16 positive patients showed T cell and antibody responses [13]. Thus, these findings showed that therapeutic vaccines alone might not be as effective in treating HPV-related tumors, and combination therapy might be an alternative option.

Massarelli *et al.* [14] conducted a phase II single-arm and single-center clinical trial, in which the HPV long peptide vaccine ISA101 was combined with anti-programmed cell death 1 (PD-1) antibodies (Nivolumab) to treat patients with incurable HPV-16 positive tumors. The results showed that the median survival time of the patients treated with the combined therapy was twice as long as those treated with Nivolumab alone. Despite the study being a small-scale trial with a non-randomized design, it shed new light on the feasibility of combined therapy with vaccines. Further analysis revealed that CD8+ cytotoxic T cells played a critical role in targeting tumors and were the key to immunotherapy [14]. They also found a higher ratio of PD-1+ T cells, PD-1+ cytotoxic T cells and an enriched environment with resting M0-macrophages significantly associated with treatment response. ISA101 may stimulate active and infiltrating E6/E7-specific T cells and pro-inflammatory cytokines to promote the phenotypic transformation of macrophages to pro-inflammatory M1, which is beneficial to tumor destruction.

Melief *et al.* [15] conducted a clinical trial using carboplatin/paclitaxel standard chemotherapy combined with ISA101 in patients with advanced, recurrent or metastatic cervical cancer. They observed tumor regression in 43% of the 72 assessable patients. Those with higher than median vaccine-induced immune responses had better survival benefits, with a flat long tail effect on the survival curve. The investigators suggested that the results might be associated with the consumption of suppressive myeloid immune cells in the tumor microenvironment by chemotherapeutic drugs, where partial relief tumor immunosuppression paved the way for ISA101 to induce a robust T cell immune response. However, this effect could not be proved because pre- and post-vaccination tumor materials were not collected in the trial. In addition, there was a lack of control group using chemotherapeutic drugs alone. Although the response rate of the trial was higher than that of standard carboplatin/paclitaxel chemotherapy, the conclusion should be validated and compared with a control group.

3. Vector vaccines

Vector vaccines use attenuated or inactivated bacteria or viruses as vectors to express target antigens and induce specific immune responses [16]. Such vaccines can induce strong innate and adaptive responses and can be easy to edit and generate. However, it also has the risk of causing secondary infections, which is more common in live attenuated vaccines [16].

Vaccinia virus is a commonly used vector virus. The chance

of exogenous DNA aberrant integration into host cells is small because the virus infection is lytic. The insertion sequences can use vaccinia-specific promoters to continuously generate cytotoxic T lymphocytes [17]. As early as 1996, Borysiewicz *et al*. [17] conducted an open phase I/II clinical trial to treat advanced cervical cancer patients with vaccinia virus vector vaccines expressing HPV16 and 18 carcinogenic proteins E6 and E7 (TA-HPV). A total of eight patients with cervical cancer were enrolled in the trial, of whom three expressed HPV-specific antibodies and one expressed HPV-specific cytotoxic T cells. It was the first clinical study using attenuated vaccinia vector vaccine in patients with cervical cancer and preliminarily explored the safety and efficacy of such vaccine.

Tipapkinogen Sovacivec (TS) is another attenuated vaccinia vector vaccine that uses the modified vaccinia virus Ankara (MVA) as a vector and inserts genes encoding three proteins: human cytokine IL (interleukin) -2, and the modified forms of non-oncogenic HPV16 E6 and E7 proteins [18]. After subcutaneous injection of TS, the expressed HPV16 E6 and E7 proteins were processed by DC and presented to naive T cells in draining lymph nodes, resulting in a targeted cell-mediated immune response. In a clinical trial of TS in cervical intraepithelial neoplasia (CIN) 2/3 patients, the complete or partial remission rate and viral DNA clearance rate in the vaccine group were found to be higher than those in the control group, regardless of baseline HPV infection [18]. No significant adverse reactions were observed at 30 months of follow-up. However, the complete remission/partial response rate (36%) in the study group was lower than 60%, which was the clinically acceptable extinction threshold.

ADXS11-001 is a therapeutic vaccine using Listeria monocytogenes as a live vector [19]. The vaccine introduces a foreign gene through the listeria plasmid vector, with the fusion protein composing of bacterial toxin protein LLO (Listeria monocytogenes (Lm)-listeriolysin O) and HPV E7 protein. An effective immune response was observed in a pre-clinical trial, and antigen-specific CD8+ T cells were identified as key to inducing tumor regression in a cervical cancer mouse model [20]. In a phase II clinical trial, ADXS11-001 was combined with or without cisplatin in advanced cervical cancer patients [19]. The combined median overall survival (OS) rate in the combination group and the ADXS11-001 group was 34.9% and 24.8%, respectively. Although adverse events in the combination group were more common, most were mild to moderate in severity and well-tolerated. Safran *et al*. [21] conducted a clinical trial of ADXS11-001 combined with mitomycin, fluorouracil and radiation for locally advanced anal cancer, with 10 patients enrolled in the trial. They reported grade 3 toxicity in 2 patients after the first ADXS11-001 injection, characterized by shivering, back pain and hyponatremia. One patient died the next day after using fluorouracil, but no autopsy was performed. Nine patients showed clinical reactions, of whom 8 (89%) had no progress at a median follow-up of 42 months. This trial initially planned to recruit 25 patients but was partially suspended by the US FDA because one patient developed systemic Listeria monocytogenes infection on a cooperative group study. The study preliminarily confirmed the safety and efficacy of ADXS11-001 combined with standard radiotherapy and chemotherapy in the treatment of anal cancer. However, the small cohort and lack of a control group were the main drawbacks of the trial. Huh *et al*. [22] conducted a phase II clinical trial with ADXS11-001 for advanced cervical carcinoma. The patients enrolled in the trial had undergone at least one treatment and their disease had progressed. In the first stage, the patients received 3 doses of ADXS-HPV once every 28 days, and in the second stage, the treatment continued until progression, intolerable adverse events (AEs), or voluntary withdrawal of consent. Among the 50 evaluable patients, the observed 12-month OS was 38%, and the median OS and progression-free survival were 6.1 months and 2.8 months, respectively. Most of the adverse reactions were grade 1 or 2 and were relieved by symptomatic treatment. This trial demonstrated that ADXS11-001 was more effective than previous studies (the 12-month OS, 21%) but was limited by its small sample size and lack of a control group. A larger, randomized, double-blind, controlled phase 3 clinical trial is ongoing using ADXS11-001 combined with radiotherapy and chemotherapy for advanced cervical cancer (NCT02853604). An exploratory clinical trial using the ADXS11-001 vaccine as a neo-adjuvant therapy for HPV-positive oropharyngeal cancer is also ongoing (NCT02002182).

Besides, several potential candidate vectors, including adenovirus, oncolytic virus and SFV (Semliki Forest virus) virus, have been used to develop vaccines to counter HPV+ malignant tumors [23–25], with some even showing promising results in both animal experiments and phase I clinical trials [23–25]. Further clinical trials in humans are anticipated.

4. DNA vaccines

DNA vaccines are constructed by integrating an Ag-encoding gene into bacterial plasmid DNA. The bacterial plasmid contains unmethylated CpG motifs, which act as adjuvants to trigger a strong TLR (Toll-like receptors) 9-dependent immune response mediated by DC [8]. Animal experiments confirmed that DNA vaccines could trigger strong innate immunity and adaptive immune responses [8]. However, a limited immune response was observed in humans [26]. Electroporation is often used in clinical trials to increase cell transfection and improve the immunogenicity of DNA vaccines.

VGX-3100 is a synthetic plasmid DNA vaccine transmitted by electroporation to confront HPV16 and HPV18 carcinogenic proteins. Trimble *et al*. [27] conducted a randomized, double-blind, placebo-controlled trial using VGX-3100 for cervical intraepithelial neoplasia (CIN) 2/3. They observed that complete histopathological regression in the treatment group (49.5%) was significantly higher than in the placebo group (30.6%) at 36 weeks. About 80% of recipients with histopathological regression also had viral clearance. No serious adverse events were reported in the study. Further analysis revealed that the therapeutic effect of the VGX-3100 vaccine was closely related to the perforin secreted by HPV-specific CD8+ CD137+ T lymphocytes [28].

MEDI0457 is a DNA therapeutic vaccine based on VGX-3100. It contains exogenous genes that encode IL12 protein to enhance the cellular immune responses induced by this vaccine. Aggarwal *et al*. [29] performed a phase Ib/II clinical trial using MEDI0457 in advanced head and neck cancer. Of

their 21 evaluable patients, 18 showed an increased antigen-specific T cell activity, and one developed tumor metastasis and showed rapid and sustained complete remission with PD1 inhibitors. This phenomenon suggested that the vaccine enhanced the anti-tumor effect of PD1 inhibitors. The subjects only had mild reactions at the injection site, and no grade 3–5 adverse reactions were reported. Thus, this trial not only verified the safety of MEDI0457 but also suggested that the vaccine could induce long-lasting HPV16/18 antigen-specific peripheral anti-tumor immune responses. An open trial of MEDI0457 combined with durvalumab (anti-PD-L1 antibody) (NCT03162224) is underway to determine whether this combination would improve the efficiency of immune checkpoint inhibitors in patients with recurrent or metastatic oropharyngeal cancer.

GX-188E is another therapeutic DNA vaccine that has been well studied. The vaccine expressed HPVE6/E7 antigen and fms-like tyrosine kinase-3 (FLT3) ligand recombinant protein, which promoted the processing and presentation of HPVE6/E7 antigen by DC and enhanced the immunogenicity of the vaccine by electroporation. Kim *et al*. [30] performed a clinical trial of GX-188E in grade 3 CIN or carcinoma *in situ*. They recruited 9 subjects and were followed up for 36 weeks to determine the vaccine's efficacy. The results showed that 8 patients had increased HPV-specific CD8+ T cells. Seven showed complete regression of CIN and virus clearance, and no serious adverse events were observed in the study. A prospective, randomized, multicenter phase II clinical trial enrolling 72 patients was then conducted to validate the efficacy of GX-188E in treating grade 3 CIN [31]. The percentage of patients with histopathological regression at 20- and 36-week follow-ups were 52% and 67%, and their corresponding HPV clearances were 73% and 77%, respectively [31]. Compared with those without histopathological regression, INF-γ showed a significant increase in patients with histopathological regression. This trial further validated the effectiveness of GX-188E in grade 3 CIN, but its main limitation was the absence of a double-blind design. An open-label, single-arm phase II clinical trial recruited 36 patients with advanced cervical cancer [32], and its 24-week mid-term analysis showed that the overall response rate of the assessable patients was 42%, with 15% showing a complete response and 27% partial response. The overall response rate in the combination treatment group was significantly higher than that of Pembrolizumab alone (14.3%). Though the incidence of adverse events was 44%, no treatment-related deaths were recorded in the combination treatment group. The increased total response rate was reported to be related to the increase in tumor-infiltrating lymphocytes and the expression of PD-L1 in the tumor by GX-188E. This trial suggested that the therapeutic DNA vaccine combined with immune checkpoint inhibitors could become one of the standard treatments for patients with advanced cervical cancer in the future. Further large-scale, randomized, double-blind, controlled clinical trials are thus urgently needed to provide more high-level evidence.

Unlike GX-188E, the DNA tattoo vaccine uses a polymer multilayer structure to wrap the plasmid DNA, then stabs the vaccine into the skin like a tattoo, gradually releasing it with slow degradation of the polymer resulting in vaccine-specific T-cell responses [33]. Bakker *et al*. [34] conducted a phase I/II clinical trial using a DNA tattoo vaccine for HPV16+ vulvar intraepithelial neoplasia (VIN) and observed that 43% (6/14) of patients responded to the vaccine, and HPV-specific T lymphocytes were detected among 5 responders. No serious adverse reactions were recorded. The study preliminarily verified the safety and efficacy of the DNA tattoo vaccine and showed that HPV-specific T lymphocytes were related to the reaction.

5. A cocktail with multi-drug therapy

Although many HPV therapeutic vaccines are currently being investigated in clinical trials, vaccine-alone treatment failed to show promising clinical responses. Strauss *et al*. [35] used a combination of multi-drug therapy for HPV-positive malignant tumors. They evaluated a cocktail of three therapies in HPV-positive malignant tumors, including a peptide vaccine, a tumor-specific immune cytokine, and an immune checkpoint inhibitor. The phase 2 clinical trial included 25 patients with anal, vulvar, cervical, and oropharyngeal cancer, of whom 18 were HPV16 positive. They observed an overall response rate of 55.6% among the HPV16 positive patients. Further, 6 patients who had previously not used immune checkpoint inhibitors demonstrated a total response rate of 83.3%. After a median follow-up of 8 months, of the 12 patients who previously used immune checkpoint inhibitors, the total response rate was 41.7%, and 10 patients were still alive at the 8-month follow-up. These results showed a significant improvement in survival compared with the historical median OS of 3–4 months.

6. Lessons learned from clinical trials

Though the E2 gene is not integrated into tumor DNA, many studies demonstrated HPV E2 antibodies in HPV-related tumors, suggesting that the HPV E2 gene may be involved in the formation of tumors [36–38]. The therapeutic vaccine targeting HPV E2 protein, MVA E2, showing promising clinical effects against intraepithelial lesions [39]. HPV E2 protein may become the target of therapeutic HPV Vaccines in the future. It is well established that HPV-positive tumors have a better prognosis than their HPV-negative counterparts [40, 41]. Studies have shown that HPV infection may make tumor cells sensitive to chemotherapy by increasing protein kinase R (PKR)-Like Endoplasmic Reticulum Kinase (PERK)-mediated ROS (reactive oxygen species) production [42]. These promising findings suggest that the role of HPV in tumorigenesis and prognosis needs to be further explored.

Increasing evidence indicated that the tumor microenvironment (TME), formed by noncancerous cells surrounding the tumor and extracellular matrix (ECM) proteins and enriched with chemokines, cytokines, and immune modulators that are secreted by both the tumor and stromal cells, played a critical role in HPV-related tumorigenesis and made them resistant to therapy [42–45]. For example, cytotoxic T cells and NK cells have been shown to have tumor inhibition abilities. In contrast, Tregs and myeloid-derived suppressor cells are immunosuppressive cells that promote tumorigenesis. Therefore, under-

standing the complexity of the tumor microenvironment may pave the way to developing individualized, targeted therapeutic vaccines for HPV+ malignant tumors in the future. Immune molecular subgroups in tumors also provide implications for immunotherapy [46]. Studies have shown that the response of immune-hot HPV tumors to therapeutic HPV vaccines was significantly higher than that of immune-cold tumors [47]. Thus, modifying the tumor immune status to make them more sensitive to treatment remains the focus of future studies.

7. Conclusion

HPV-related tumors rank first among virus-related tumors, and there is an urgent demand for HPV therapeutic vaccines in clinics. However, although previous studies using anti-cancer vaccines showed no serious adverse events, the clinical benefits were still far from satisfaction. Recent breakthroughs have been made in this field, with some vaccines showing improved efficacies, especially when combined with other drugs and have entered phase 3 clinical trials. The preliminary results of HPV therapeutic vaccines combined with immune checkpoint inhibitors and/or other tumor-targeted cytokine drugs are encouraging, but further large-scale, randomized, double-blind, controlled clinical trials are expected. The immune mechanism of tumors is complex, and understanding the complexity of tumorigenesis may pave the way for developing individualized, targeted therapeutic vaccines for HPV-positive malignant tumors.

AUTHOR CONTRIBUTIONS

JHW—designed the research. TZ and RL—wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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