Journal of Clinical and Cellular Immunology
ISSN: 2155-9899
OPEN ACCESS Freely available online
Mini Review

Combination Therapies for HPV-Associated Malignancies

Claire Smalley Rumfield, Jeffrey Schlom*, Caroline Jochems

Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

ABSTRACT

Human papillomavirus (HPV)-associated malignancies cause almost all cases of cervical cancer in women, and a significant percentage of head and neck cancer, together totaling almost 5% of the global cancer burden, and representing an important public health issue. The approval and use of two prophylactic HPV vaccines, Gardasil® and Cervarix®, have significantly decreased infections with HPV, but unfortunately, prophylactic vaccination does not treat established infections or malignancies resulting from HPV. Therefore, therapies for HPV-associated malignancies are necessary to improve the quality of life and survival in patients with these diseases. This review will detail new combinations of therapies in clinical development for HPV-associated malignancies.

Keywords: Human papillomavirus (HPV); Therapeutic vaccine; Cervical cancer; Head and neck squamous cell carcinoma (HNSCC); Combination immunotherapies; HPV vaccine

INTRODUCTION

Human papillomavirus (HPV)-associated malignancies account for approximately 4.5% of all cancer, or about 600,000 cases of cancer worldwide each year [1]. This group of cancers includes cervical cancer, and squamous cell carcinoma of the oropharynx, anus, rectum, penis, and vagina. HPV is a double-stranded DNA virus that includes over 200 known types that are divided into low-risk and high-risk subtypes: HPV6 and HPV11 are low risk and result in benign neoplastic disorders such as anogenital condyloma and recurrent respiratory papillomatosis (RRP), whereas HPV16 and HPV18 are high risk and account for about 75% of HPV-associated malignancies [2-4]. HPV encodes several early (E) proteins that drive the virus life cycle and integration into the host genome. The E6 and E7 oncoproteins interfere with the p53 and Rb proteins that regulate the normal cell cycle, and are therefore responsible for driving uncontrolled cell growth, resulting in the development of pre-malignancies. If left untreated, these can progress to invasive cancer [5,6].

Infection with HPV can be prevented by vaccination with a prophylactic HPV vaccine, marketed as Gardasil (Merck, Kenilworth, NJ, USA) and Cervarix (GlaxoSmithKline, Brentford, UK). These vaccines are based on virus-like particles (VLP) that stimulate an antibody response to the L1 protein on the surface of HPV virions. These antibodies bind to HPV, preventing it from binding to epithelial cells and causing infection [7]. Prophylactic vaccines, however, will not clear an ongoing infection, and do not result in the generation of the antigen-specific CD4+ and CD8+ T cells that are necessary to combat precancerous and cancerous lesions.

Immunotherapeutics for HPV-positive malignancies have increasingly been the subject of clinical trials for this group of solid tumors within the last 10 years. There are currently over 20 clinical trials using checkpoint inhibitors with radiation, chemotherapy, surgery, other checkpoint inhibitors, or a mixture of these treatment options for HPV-associated malignancies (NCT03811015, NCT03107182, NCT03618134, NCT03623646, NCT03829722, NCT02827838, NCT03452332, among others).

Aside from checkpoint inhibitors, other promising immunotherapies for HPV-associated malignancies are therapeutic HPV vaccines. These vaccines target the HPV oncoproteins E6 and E7, which are constitutively expressed on tumor cells, making them an attractive non-self-target for vaccine development [8]. Therapeutic vaccines have been developed on a wide variety of platforms, including viral vectors, DNA vectors, mRNA vectors, and bacterial vectors, all of which have demonstrated efficacy in clinical trials in generating antigen-specific T cells in patients with HPV-associated premalignancies and malignancies. These vaccines have been reviewed in great detail elsewhere [9-11].

Recently, multiple combinations of vaccines and checkpoint inhibitors, as well as traditional therapies, such as chemotherapy and radiation, have been initiated in clinical studies. A long-standing issue in therapeutic cancer vaccine development has been the attempt to modulate the immunosuppressive microenvironment in order to allow antigen-specific T cells close enough to kill tumor cells, to decrease T-cell anergy, and to decrease immunosuppressive elements such as regulatory T cells

Correspondence to: Jeffrey Schlom, Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute, 10 Center Drive, Room 8B09, Bethesda, MD 20892, USA, Tel: 240-858-3463; Fax: 240-541-4558; E-mail: schlomj@mail.nih.gov

Received: December 07, 2020; **Accepted:** December 21, 2020; **Published:** December 28, 2020

Citation: Smalley Rumfield C, Schlom J, Jochems C (2021) Combination Therapies for HPV-Associated Malignancies. J Clin Cell Immunol. 12:608.

and myeloid-derived suppressor cells (MDSC). The synchronized addition of multiple immunotherapeutics or other treatments may be useful to potentiate the efficacy of a therapeutic vaccine.

RATIONALE FOR COMBINATION TREATMENTS WITH VACCINES AND OTHER MODALITIES

One of the most well-known inhibitory pathways effector cells find in the tumor microenvironment (TME) is the programmed cell death protein-1 (PD1)/programmed cell death protein-1 ligand (PDL1) axis. PDL1 is expressed on tumor cells, and when this ligand binds to the PD1 expressed on the surface of effector T-cells, "brakes" are put on the responding T cells, leading to T-cell anergy and an immunosuppressive TME. Multiple monoclonal antibody therapies to inhibit this axis have been approved by the Food and Drug Administration, leading to a revolution in immunotherapeutic treatments. Another important checkpoint pathway is the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitory pathway, which has been similarly targeted with monoclonal antibodies as therapeutics. CTLA-4 is upregulated on T cells after activation [12]. The ligation of CTLA-4 with B7 prevents CD28 from interacting with B7. Otherwise, CD28-B7 interaction inhibits costimulation to increase T-cell activation. An additional co-receptor involved in the CTLA-4 pathway is 41BB, which can activate both T cells and antigen-presenting cells. Activation of this receptor has been shown to increase the production of the inflammatory cytokines IL-12 and IL-6 [13].

PRECLINICAL STUDIES

Multiple recent studies have confirmed a link between HPV E6/E7 expression and expression of the checkpoints PDL1 and CTLA-4. One preclinical study showed that overexpression of E7 in an HPV-negative cell line led to increased PDL1 expression, while the silencing of E7 in an HPV-positive cell line led to decreased PDL1 expression [14]. Increases in PDL1 expression are associated with evasion of immunosurveillance [12], and were found to correlate with a decreased rate of overall survival in head and neck squamous cell carcinoma (HNSCC) patients [15]. Preclinically, there is significant evidence for combining PDL1 checkpoint inhibitors with therapeutic HPV vaccines: many murine models have shown increased survival with the combination compared to monotherapies [16,17].

Similar to PDL1 expression, CTLA-4 expression has also been associated with HPV E7 expression. Transfection of HPV-negative tumor cell lines with HPV E7 led to increases in CTLA-4 expression, and the overexpression of HPV E7 in HPV-positive cell lines also led to significant increases in CTLA-4 expression [18]. In preclinical studies, HPV E6/E7 vaccine in combination with anti-CTLA-4 monoclonal antibodies produced significant tumor regression. Furthermore, 41BB stimulation by an agonist was shown to induce highly cytotoxic CD4+ and CD8+ T cells as well as tumor regression in combination with vaccine [19]. An additional preclinical study showed that agonistic anti-41BB treatment in combination with recombinant IL-2 (rIL-2) and an HPV E7 DNA vaccine resulted in a significantly higher tumor cure rate in tumor-bearing mice than treatment without the 41BB stimulator in control mice [20]. This preclinical data emphasizes the rationale behind combining checkpoint inhibitors with therapeutic vaccination targeting the early HPV proteins.

CLINICAL STUDIES

Clinically, there is a robust pipeline of therapeutic HPV vaccines in combination with checkpoint inhibitors. One of the landmark studies using this combination is the ISA101 synthetic long peptide vaccine combined with the anti-PD1 checkpoint inhibitor nivolumab (Bristol-Myers Squibb, New York, NY, USA) (NCT02426892) [21]. The combination of the vaccine and the checkpoint inhibitor led to an overall response rate of 33%, with a median duration of response of 10.3 months in patients with advanced cervical cancer. In previous studies, ISA101 had an excellent response rate when used as a single agent in Cervical Intraepithelial Neoplasia (CIN), but when used in the advanced cervical cancer setting it failed to induce tumor regression. Nivolumab, as a single agent, has a response rate of about 20% in a similar patient population. The increased efficacy of using the combination of the two immunotherapies over either monotherapy is an exciting step for the treatment of advanced malignancies.

Another combination study using the DNA vaccine GX188E with pembrolizumab, an anti-PD1 checkpoint inhibitor (Merck, NCT03444376), showed an increase in efficacy over either vaccine or checkpoint inhibitor alone [22]. There are multiple ongoing clinical trials investigating the combination of therapeutic HPV vaccines with anti-PD1/PDL1 checkpoint inhibitors (NCT03439085, NCT03946358, NCT03618953, NCT04001413, NCT04084951, NCT04260126, NCT02291055, NCT03260023, NTC03669718, NCT04369937, NCT04534205). The combination of vaccine, ISA101b, with a 41BB checkpoint inhibitor, utomilumab (Pfizer, New York, NY, USA), is also being investigated in advanced oropharyngeal cancer patients in an ongoing clinical trial (NCT03258008).

Anecdotal data from the MEDI0457 trial (NCT02163057), which included a DNA vaccine against HPV 16/18 E6 and E7 combined with an IL-12 plasmid, describes a patient with a complete response (CR) and a significant induction of antigen-specific T cells after four treatments with MEDI0457. Nivolumab was added to the treatment after the patient had progressed, resulting in a durable CR [23], suggesting that the combination of vaccine and checkpoint allows for both an increase in antigen-specific T cells and releasing the brakes imposed on the T cells by the immunosuppressive TME.

COMBINATIONS OF MULTIPLE THERAPEUTIC MODALITIES

Several new trials combining multiple immunotherapeutic agents have been initiated. One such trial, NCT04287868, combines the therapeutic HPV vaccine PDS0101, bintrafusp alfa (EMD Serono, Billerica, MA, USA, and Pfizer, New York, NY, USA), and NHS-IL12 (EMD Serono). Bintrafusp alfa is a bifunctional anti-PDL1 antibody with a TGFβ "trap" that sequesters TGFβ in the TME [24,25]. NHS-IL12 binds to necrotic tumor tissue and contains IL-12 to enhance T-cell responses in the TME [26,27] and PDS0101 is a liposomal nanoparticle-based therapeutic HPV16 vaccine. This phase II trial is based on a preclinical study showing enhanced anti-tumor efficacy when all three agents were combined compared to double combinations and single agents alone [28].

A phase I/II neoadjuvant trial combining a novel HPV16/18 vaccine on a gorilla adenovirus platform, PRGN-2009, with bintrafusp alfa before planned definitive therapy with chemoradiation or surgery in HPV-positive oropharyngeal cancer is also ongoing (NCT04432597). In the phase II part of the trial, patients will be

evaluated for increases in T-cell infiltration of the tumor post- vs. pre-treatment with vaccine alone or in combination with bintrafusp alfa.

COMBINATIONS OF VACCINE WITH STANDARD-OF-CARE THERAPEUTICS

Combination therapies that include the current standard of care, like carboplatin, paclitaxel, or bevacizumab, are currently being evaluated with therapeutic HPV vaccines. Currently, ISA101/101b is being tested with these standard-of-care options in patients with advanced or recurrent cervical cancer (NCT02128126). Results from this trial indicate that after patients received three doses of vaccine (2 weeks after each dose of standard chemotherapy), increased IFNγ+ T-cell responses were associated with overall survival [29]. This study highlights the potential value of adding therapeutic vaccine to the standard of care in order to increase overall survival in advanced patient populations.

An additional therapeutic HPV-based peptide vaccine, P16_37-63, was also combined with cisplatin-based chemotherapy in a phase I clinical trial (NCT02526316), but an update on the progress of this trial has not yet been provided. Furthermore, ADXS11-001, a therapeutic HPV vaccine on a listeria-based platform, was given before robotic surgery for HPV-positive oropharyngeal cancer to evaluate the HPV-specific response rate (NCT02002182).

COMBINATIONS OF HPV VACCINES WITH OTHER THERAPIES

Novel combination therapies are being introduced for the eventual treatment of HPV-associated malignancies. One such combination is that of the new drug fimaporfin, a photosensitizer drug that enhances the internalization of antigen in a site-specific, light-directed manner, in combination with HPV E7 peptides in healthy volunteers (NCT02947854). This study aimed to assess the safety and tolerability of fimaporfin. The combination, which also included Hiltonol® (Oncovir, Washington, DC, USA), a poly-ICLC TLR3 agonist, was found to be safe and enhanced the antigen-specific T-cell response [30].

Multiple ongoing clinical trials combine new drugs with checkpoint inhibitors, radiation, or both. One clinical trial using a novel agent with checkpoint inhibitor is a phase I study using CUE-101 and prembrolizumab (Keytruda®, Merck), a well-known anti-PDL1 inhibitor, in HPV-positive HNSCC (NCT03978689). CUE-101 is a novel fusion protein that consists of a human IgG1 Fc region, an HPV16 E7 epitope, an HLA complex, and reduced affinity IL-2 molecules [31]. Preclinical data demonstrated that CUE-101 could bind, activate, and expand HPV-specific T cells in peripheral blood mononuclear cells (PBMC), as well as induce anti-tumor efficacy in a tumor-bearing mouse model. This effect was enhanced by combination with anti-PDL1 [31].

An additional phase I/II clinical trial (NCT04555837) combines a novel drug, alisertib, with pembrolizumab in patients with Rb-deficient HNSCC, which includes HPV-positive HNSCC. Alisertib is an Aurora A kinase (AAK) inhibitor that has been shown to be safe and increase progression-free survival in combination with chemotherapy in patients with advanced breast cancer or recurrent ovarian cancer [32].

Phase I clinical trial NCT04533750 focuses on using radiation in combination with the novel drug peposertib (M3814) in patients with advanced HNSCC. Peposertib is a selective DNA protein kinase (DNA-PK) inhibitor that inhibits the ability of DNA-PK to repair DNA damage induced by chemotherapy or radiation [33]. Peposertib was well-tolerated and demonstrated moderate efficacy as monotherapy in patients with advanced solid tumors (NCT02316197) [25].

The final phase I study (NCT04576091) focuses on the combination of pembrolizumab, radiation, and the novel drug BAY1895344 in patients with advanced HNSCC. BAY1895344 is an ataxia telangiectasia and Rad3-related (ATR) kinase inhibitor that interferes with the ability of ATR to repair DNA damage resulting from chemotherapy or radiation. BAY1895344 demonstrated an effect as a monotherapy in xenograft models with DNA damage repair deficiencies, and showed increased anti-tumor efficacy in combination with other agents [34].

CONCLUSION

Combination strategies for treating advanced cases of HPV-associated malignancies have significantly increased in the past several years. Multiple clinical trials are exploring the combination of anti-PD1/PDL1 checkpoint inhibitors with HPV therapeutic vaccines, and recent data suggest this is an effective strategy. Other combinations, including therapeutic HPV vaccine with standard-of-care chemotherapy and radiation, as well as combinations containing multiple immunotherapeutic agents, are also being evaluated. These combinations may enhance the effectiveness of therapeutic vaccines by modulating the TME to decrease the inhibition of antigen-specific T cells, decrease immunosuppressive entities such as MDSC, reduce levels of regulatory T cells and macrophages, and/or increase pro-inflammatory cytokine production.

AUTHOR CONTRIBUTIONS

Jeffrey Schlom and Caroline Jochems contributed equally.

COMPETING INTERESTS

The authors declare that they have no competing interests.

ORCID IDs

Jeffrey Schlom: 0000-0001-7932-4072

Caroline Jochems: 0000-0002-9000-9855

ACKNOWLEDGMENTS

This work was supported by the Intramural Research Program of the Center for Cancer Research, National Cancer Institute, National Institutes of Health, ZIA BC 010944.

The authors thank Debra Weingarten for her assistance in the preparation of this manuscript.

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