Preliminary Analysis of Cervical Cancer Immunotherapy

Zhen Ma, MSc, Xinxin Zou, MSc, Zhaohua Yan, Caiyun Chen, Yumei Chen,
and Aizhen Fu, PhD

Abstract: Cervical cancer is one of the most common gynecologically malignancies worldwide. Although vaccine and cervical cancer screening including human papillomavirus testing, cytology testing, and colposcopy have developed rapidly in recent years, effectively reducing cervical cancer mortality, cervical cancer remains a malignancy with higher female fatality rates worldwide and has a high risk for socioeconomically disadvantaged groups. The combination of platinum-paclitaxel and chemotherapy, possibly with the addition of bevacizumab, is currently the treatment of choice for advanced cervical cancer, but it only has remission purposes. Therefore, new therapeutic strategies are needed for both locally advanced and metastatic cervical cancer. Here, we make a preliminary analysis of cervical cancer immunotherapy.

Key Words: cervical cancer, immune checkpoint, vaccine, immune checkpoint inhibitors

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BACKGROUND

Cervical cancer is one of the most common gynecologically malignancies worldwide, with nearly 570,000 new cervical cancer cases and more than 300,000 deaths every year. In 2018, there were about 570,000 new cases and about 310,000 deaths per year worldwide, an increase from 2012.[1] Although vaccine and cervical cancer screening, including human papillomavirus (HPV) testing, cytology testing, and colposcopy, have developed rapidly in recent years, effectively reducing cervical cancer mortality, cervical cancer remains a malignancy with higher female fatality rates worldwide and has a high risk for socioeconomically disadvantaged groups. Advanced disease has a poor prognosis.[2] Currently, the treatment of cervical cancer depends on the stage of the disease. According to The International Federation of Gynecology and Obstetrics stage, the treatment of cancers confined to the uterus is based on surgery (from tization to hysterectomy), and radiotherapy/chemotherapy is the standard of treatment for locally advanced cancer, and the recurrence rate of locally advanced tumors with chemotherapy and radiotherapy still reaches 20%.[3] The combination of platinum-paclitaxel and chemotherapy, possibly with the addition of bevacizumab, is currently the treatment of choice for advanced cervical cancer, but it only has remission purposes.[4–6] Therefore, new therapeutic strategies are needed for both locally advanced and metastatic cervical cancer.

Immune Checkpoint

Currently, many immunomodulatory therapies are being investigated in various clinical trials with different potential targets, including programmed cell death-1 (PD-1), CTLA-4, T-cell immunoglobulin mucin molecule-3 (Tim-3), and induced costimulatory molecules, 4-1BB, and OX-40, etc. Among these targets, induced costimulatory molecules, 4-1BB, and OX-40 are costimulatory receptor.[7–9] However, PD-1, CTLA-4, and Tim-3 are the inhibitory receptors for T-cell immunity. In addition, the newly discovered inhibitory receptors, including T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain protein (TIGIT), killer cell lectin-like receptor G1, and 2B4, have also gradually attracted public attention.

PD

The programmed death-ligand 1 (PD-L1)/PD-1 axis is a key determinant of physiological immune homeostasis and pathologic immune destabilization. In the context of chronic antigen continuous stimulation and presence, T cells gradually lose their effector-killing function, and eventually develop a state of effector (or dysfunctional) depletion. It was recently shown that high PD-1 expression is one of the features of effector killing of depleted T cells.[10] PD-1 plays a role in causing an immune-dysfunctional state in depleted T cells. In cancer, a significant enrichment of PD-1-positive T cells in the tumor tissue and peripheral blood was detected.[11,12] Tumor cells in the tumor microenvironment (TME) are subjected to immune surveillance from both innate and adaptive immunity. Many inflammatory cytokines are present in this region and coordinate the balance of antitumor immunity. However, cancer cells can also hijack inflammatory pathways to create favorable conditions for tumor progression by suppressing antitumor immunity. TME induces PD-L1 expression by increasing proinflammatory cytokines (eg, interferon [IFN], tumor necrosis factor, and interleukin [IL-6]), weakens the activation of immune cells, defends against T-cell attack, and further enhances the immune escape of cancer cells.[13] IFN is a proinflammatory cytokine produced by T cells and natural killer (NK) cells that promotes the presentation of neoantigens on tumor cells by enhancing major histocompatibility complex expression. Binding of the IFN to its receptor results in the activation of the classical JAK-STAT signaling pathway that induces an increased expression of a range of transcription factors.[14,15] By controlling the IFN/JAK/STAT1 pathway, PD-L1 expressed by cancer cells can inactivate CTLs and attenuate immune surveillance in the TME. Lipopolysaccharide also leads to increased PD-L1 expression. Lipopolysaccharide activates NF-κB and induces, via TLR4, the secretion of type I IFN.[16]

Many oncogenic signaling pathways may promote tumor growth by driving the expression of PD-L1, thus leading to immune escape. Overexpression of the MYC oncogene occurs in ~70% of all cancers. MYC gene knockdown or

pharmacological inhibition inhibited PD-L1 expression, and MYC was able to directly bind to the PD-L1 promoter, suggesting that PD-L1 can be directly regulated by MYC at the transcriptional level.[17] Binding to the PD-L1 promoter suggests that PD-L1 can be directly regulated in by MYC at the transcriptional level. Another driver of PD-L1 upregulation is anaplastic lymphoma kinase (ALK), which promotes PD-L1 expression through STAT3 after hyperactivation of ALK signaling caused by NPM-ALK gene fusion.[18] In addition to MYC and ALK, HIF1/2 also binds to the hypoxia response element of the PD-L1 promoter region, resulting in increased PD-L1 transcript expression.[19,20] Posttranslational modifications of PD-L1 have become an important regulatory mechanism for regulating immune suppression in cancer. Posttranslational modifications including glycosylation, phosphorylation, and ubiquitination play an important role in the regulation of the protein stability, translocation, and protein-protein interactions of PD-L1. In the study of epidermal growth factor/epidermal growth factor receptor signaling, the B3GNT3-mediated poly-N-acetyl lactosamine glycosylation at both PD-L1 N192 and N200 is required for the PD-L1/PD-1 interaction.[21] These findings support an important role for PD-L1 glycosylation in suppressing antitumor immunity in T cells.

CTLA-4

CTLA-4, also known as CD152, is one of the important costimulatory molecules on the T-cell surface. The CTLA-4 gene is located at the location of 2 on band 33 (2q33) of chromosome long, which belongs to the same family as CD28 molecules, can be combined with B7 receptor molecules on the surface of antigen-presenting cells (APCs).[22] However, CTLA-4 has a strong binding force with B7 molecules and can competitively bind B7 molecules with CD28 molecules, blocking the signaling pathway produced by CD28 and B7 molecules, and play a role in negatively regulating the proliferation and differentiation of T cells. Meanwhile, the binding of CTLA-4 to B7 molecule inhibited cytokine secretion and cell cycle progression. At present, scholars have done a lot of research on the polymorphism of CTLA-4 gene.[23] The polymorphisms of CTLA-4-318, CT60, and + 49 AA genes were related to the development of cervical cancer and affected the differentiated function of T cells. Another study showed that the ratio of regulatory T cells (Tregs) to CD4 + T cells and CTLA-4 expression on the Tregs cell surface showed significantly higher expression rates in advanced non–small cell lung cancer patients than in adjacent tissues.[24] In view of the above studies, to effectively help patients with antitumor immunotherapy, some scholars will fuse the T-cell antigen CTLA-4 with HPV16 E7 and E6 into a fusion therapy DNA vaccine (pctla4-e7e6), further verified in mice, with high antitumor specificity and relatively strong specific CTL response, the development of the vaccine may provide a new idea for cervical cancer patients.[25] A recent clinical trial reported the safety and antitumor activity of anti-CTLA-4 monoclonal antibody Ipilimumab in recurrent cervical cancer showed that Ipilimumab could be tolerated in the population and can mediate anti-CTLA-4-specific immune response, but the promotion of this drug requires extensive and long-term clinical observation.[26]

TIM-3

The Tim gene family was discovered in 2001 by Mcintire and colleagues and was named Tim for its containing immunoglobulin IgV-like and mucin domains,[27] Tim-3 is mainly expressed on the differentiating mature Th1 surface and, which, upon binding to its corresponding ligand, acts as a negative regulator and negatively regulates the immune response. The presence of Tim-3 with these coexpressing cells can affect the cell cycle and cell proliferation, as well as the secretion of cytokines such as IL2, tumor necrosis factor- and IFN, induced incompetence, or depletion of CD8 + T cells. Tim-3 was upregulated in hepatocellular carcinoma immune microenvironment and further promoted hepatocellular carcinoma cell proliferation.[28] In cervical cancer patients, Tim-3 is in a high expression state, and the degree of its expression is related to cancer progression and metastasis. The multivariate analysis shows that Tim-3 expression is an independent factor in predicting cervical cancer prognosis, and it is closely related to the metastasis of cervical cancer.[29] Related studies have found that, CD8 + T cells Tim-3 can restore secretory cytokine function and effectively control the tumor growth after blocking the Tim-3/PD-1 signaling pathway in tumor patients.[28] Tim-3 is also highly expressed on the surface of tumor-infiltrating dendritic cells (DCs), and Tim-3 can reduce the entry of nucleic acid from tumor dead cells into the DCs by interacting with B1 protein, and subsequently inhibit the antitumor immune response caused by nucleic acid.[30] Alternatively, promoting the production of Tregs during tumor progression further influences the tumor patient prognosis, a process that is correlated with Tim-3–mediated downregulation of NK cells.[31] On the basis of the above mechanistic studies, the Tim-3 blocker Ipilimumab has been studied in tumor patients in recent years, and the results show that some patients benefit from it.

TIGIT

However, in recent years, another type is specifically expressed in activated T cells, regulatory T cells, and NK cells. The inhibitory receptor TIGIT on the surface of immune cells has received much attention.[32] TIGIT is a T-cell immunoglobulin and ITIM domain protein, also known as Vsig9, Vstm3, or WUCAM. TIGIT is a type I transmembrane protein containing both Ig and ITIM domains, including the IgV extracellular segment and the immunoglobulin tyrosine tail-like phosphorylated fragment. TIGIT binds to the adhesion molecules, CD155, and CD122 and is essential for T cells, as well as for NK cell-mediated cytotoxic anti-tumor resistance,[33] CD155 and CD122 also associate with other ligands, including CD226, the costimulatory molecule of TIGIT, which interacts with LFA-1 to positively regulate the immune function of T cells.[34] CD155 and CD122 are important in the antitumor T-cell–mediated and NK cell–mediated cytotoxic effects. CD155 is the type I transmembrane glycoprotein of the immunoglobulin superfamily and is expressed on the surface of epithelial cells, endothelial cells, T cells, platelets, dendritic cells, and activated T cells.[35] CD155 is a ligand for the NK cell–activating receptor CD226, and CD226 is one of the main activated receptors that initiate NK cells to kill tumor cells. However, some recent studies have shown that CD155 overexpression, which can cause tumor immune escape.[36] In Lozano et al,[37] in DCs, TIGIT enhances IL-10 levels by binding to CD155, thereby inhibiting the proliferation, differentiation, and function of CD4 + T lymphocytes. Additional studies have shown that TIGIT suppresses T-cell function through competitive effects with CD226. Moreover, studies have shown that tumor-infiltrating T lymphocytes have high surface expression of TIGIT in non–small cell lung cancer, colon cancer tissues, which is associated with the inactivation of PD-1-expressing tumor antigen-specific CTLs.[38] CD122 is a cytokine receptor subunit that binds to CD132 to form a low-affinity IL-2 receptor; CD25 (IL-2R) and CD132 to form a high-affinity IL-2 receptor; and IL-2 to promote lymphocytes. Proliferation, differentiation, and participation in the regulation of peripheral immune tolerance.[39]

Immune Checkpoint Inhibitors

Since 2015, relevant clinical trials of cervical cancer treatment have been conducted against various ICIs. KEY-NOTE-028 is a phase I study of pembrolizumab in advanced solid tumors, where the CC cohort contained 24 patients with stage IVB or recurrent cervical cancer with PD-L1 expression > 1%, all had previous systemic chemotherapy, 63% had 2 or more regimens, and 42% had previous bevacizumab treatment. The enrolled patients were treated with 10 mg/kg of PD-1 antibody pembrolizumab every 2 weeks for 24 months. The results showed an overall objective response rate (ORR) of 17% (4/24), a case fatality rate of 12.5% (3/24), a 6-month progression-free survival (PFS) of 13%, and an overall survival rate of 66.7%.[40] More interesting is the KEYNOTE-158 phase II clinical study, also for previously treated patients with advanced cervical cancer, unlike KEYNOTE-028, where the enrolled patients no longer limit their PD-L1 status.[41] Preliminary results from the first 47 patients showed an ORR of 17%. Although the ORR was not associated with PD-L1 status, 87% of the patients were PD-L1 positive (> 1%). As 91% of patients were effective and responded for > 6 months, the US Food and Drug Administration has accelerated the approval of apolizumab for the treatment of recurrent or metastatic cervical cancer. Like pembrolizumab, nivolumab is also an antibody directed against PD-1 and was first used for the treatment of CC patients in the NRG-GY002 II study. All patients in this study received 1 chemotherapy in relapse, and 77% of patients expressed PD-L1. Of the 25 evaluable responses, although only 1 patient had a PR, the right rate was 4%. But the median survival period in this group was 14.5 months (95% CI, 8.3 to 26.8). Checkmate 358 is a single-arm clinical trial evaluating Nivolumab in HPV-positive recurrent or metastatic cervical, vulvar, or vaginal cancer, enrolling 24 patients with 19 cervical and 5 exceptional vaginal or vaginal cancers. The treatment regimen is 240 mg intravenous infusion every 2 weeks with a median follow-up of 31 weeks. The results showed an objective response rate of 26.3% and was not associated with PD-L1 or HPV status.[42] A clinical trial evaluating the efficacy and safety of the CTLA-4 inhibitor Ipilimumab enrolled 42 subjects with metastatic or recurrent cervical cancer with an intravenous dose of Ipilimumab at 10 mg/kg every 3 weeks, and 1 course every 12 weeks thereafter. One out of 34 patients that could be used for efficacy assessment had a partial remission, 10 were stable, and 23 progressed, with a right rate of only 3%. The patient had a median PFS of 2.5 months, and the median overall survival was 8.5 months.[43] Several other checkpoint inhibitors are currently under development. The targets of these antibodies include TIM-3, LAG-3, killer cell lectin-like receptor G1, and TIGIT. It remains to be determined whether they are more active than the currently available cervical cancer drugs.

Vaccine

Vaccines With Bacteria as Carriers

Listeria monocytogenes is the bacterial carrier that has attracted the most attention. The vaccine Lm-LLO-E7 (a therapeutic HPV vaccine based on a listeria vector) produces an immune response against the E7 oncoprotein by expressing the HPV 16 E7 antigen.[44]

Vaccines With the Virus as a Vector

The natural property of viruses is to transduce their own genetic information into the host cells for replication, so viruses are a good tool for developing therapeutic vaccines. Existing viral vectors include adenovirus and its associated viruses, alphaviruses, lentiviruses, and poxviruses. Oncolytic adenovirus can selectively replicate and lyse cancer cells in cancer cells, and its role in IFN exposes the tumor antigens in the immune environment, thus transforming the immunosuppressive TME into the TME of the tumor immune response, and then stimulating the host immune response to the cancer cells. Its preclinical studies have shown strong antitumor efficacy, and clinical trials of oncolytic adenovirus for HPV-related diseases are currently underway.[45] Vaccinia virus, a coated double-stranded DNA virus belonging to the poxvirus (Poxvirus) family, has been widely used as an immunogen because of its large, highly infectious genome and the small possibility that exogenous DNA is not integrated into its genome without regulation. In patients with advanced cervical cancer, a single treatment with TA-HPV (a recombinant vaccinia virus expressing the HPV 16 and HPV 18E6 and E7 genes) showed an HPV-specific cytotoxic T lymphocytes (cytotoxic T lymphocyte, CTL) response in 1 of 3 patients and an HPV-specific antibody response in 3 of 8 patients.[46]

Peptide-based Vaccines

Peptide-based vaccines are stable, safe, and easy to produce. Long overlapping peptide (SLP) regimen containing E6/E7 peptide synthesis has been shown to be effective in some preclinical models, can increase the innate immunity and adaptive immunity, to 20 advanced or recurrent cervical cancer patients vaccinated by E6 and E7 overlapping peptide and 51 HPV16 synthetic 5 peptide adjuvant (Montanite ISA-51), 9 cases of HPV16-specific T-cell response.[47] In addition, the long peptide vaccine (ISA101/ISA101b), consisting of the E6 and E7 genes of HPV 16, is in phase II clinical trials to evaluate the safety and efficacy of its combination with paclitaxel and carboplatin (plus or without bevacizumab) for advanced or recurrent cervical cancer.

Protein-based Vaccines

E6/E7 or HPV fusion proteins have been used as a source of antigen in early therapeutic vaccines with the advantage of including many CD4 + and CD8 + T epitopes and therefore not restricted by major histocompatibility complex; however, the potential disadvantage of protein vaccines is that they may induce antibody responses rather than CTL responses, antigen targeting of fusion proteins of DC, and the use of adjuvants can enhance immunogenicity. TA-CIN, a fusion protein subunit vaccine consisting of HPV 16 L2, E6, and E7, showed 63% of patients with increased CD4 + and CD8 + T cells in phase II trials (VIN2-3) 1 year after TA-CIN vaccination, and vaginal intraepithelial neoplasia completely subsided.[48]

Nucleic Acid Vaccine

DNA vaccines are mostly bacterial-derived plasmids engineered genetically to encode immunogens under the control of promoters, thereby promoting stable DNA expression in cells and inducing adaptive immunity. Despite the advantages of DNA vaccines, easy production, and reproducible administration of DNA vaccines, they lack relative immunogenicity, and the delivery of vaccines such as electroporation, encapsulation, gene guns, or laser therapy has been identified as methods to enhance immunogenicity. At present, DC is a key element in DNA vaccine development, because DC is an important APC capable of initiating naive T cells. RNA-based vaccines are derived from RNA replicon systems of positive and negative single-stranded RNA viruses. The obvious advantage of RNA replicon vaccines is that their ability to self-replicate in a variety of cells and can help maintain cellular

antigen expression, allowing them to produce more target proteins than conventional DNA vaccines, but they are limited by poor stability and poor cell-to-cell diffusion.

Cell Immunotherapy

The DC-based HPV vaccine has emerged as a potential therapeutic vaccine against HPV-related malignancies because of it. Not only are they the main APCs, but they can also serve as natural adjuvants to enhance the effectiveness of antigen-specific immunotherapies against cancer. Although can use small interference with proapoptotic molecules of RNA (small interfering RNA), DC, there are still because of technical requirements lead to mass production, effective route of vaccine drug delivery is not certain, need patients to provide enough autologous DC, low transduction efficiency, terminal differentiation DC cannot in vitro amplification and DC life is limited.[49] Adoptive cell therapy (ACT) or T-cell therapy based on T cells has made a breakthrough in the era of precision medicine. ACT is a highly personalized approach to specifically kill tumor cells by using autologous or allogeneic tumor-specific T cells after mass in vitro expansion or modified and amplified by genetic engineering techniques. They mainly include tumor-infiltrating lymphocytes (TILs), chimeric antigen receptor T cells (CAR-T), and T-cell receptor-modified T cells (TCR-T). TILs are a heterogeneous group of lymphocytes that infiltrate primary tumors, metastatic tissues, and lymph nodes bearing tumors to control tumor growth. A higher proportion of tumor-specific T cells of TILs compared with peripheral lymphocytes. It has been shown that IL-7 and IL-15 can maximize tumor-reactive TIL amplification in vitro as compared with IL-2. Studies have found that the infusion of TIL (mainly CD8 +) can transport, infiltrate, and destroy tumor cells, leading to most patients with cancer regression and produce tumor antigen-specific memory T cells, and can circulate in patients and play a sustained role in cancer, thus confirming the feasibility of ACT therapy in patients with advanced cervical cancer treatment.[50]

CONCLUSIONS

With the development of immunotherapy in cancer, which has shown strong clinical efficacy in many malignancies, including prolonged patient PFS or overall survival in many cancer patients, whereas targeting monoclonal antibodies against immune checkpoint proteins have been successful. However, most patients initially fail to respond to therapy or have limited efficacy, so they need to further enhance the clinical benefits of single immunotherapy by combining relevant traditional therapies or developing drugs with synergistic mechanisms, thus making immunotherapy more widely available for common malignancies. The combination of immunotherapy and chemotherapy has a high response rate in triple-negative breast cancer and HPV-positive head and neck squamous cell carcinoma patients compared with previous treatments, including immunotherapy combined with radiotherapy in advanced lung cancer treatment and nanoscale drugs in enhanced immunotherapy. Collaborative combination of immunotherapy agents and new tricombinations of immunotherapy and targeted therapy are being studied, all of which will enhance the potential for the clinical success of immunotherapy. Although cancer immunotherapy has been successfully used in a variety of human cancers, relevant evidence-based medical evidence suggests that only a few patients with advanced tumors achieve durable survival in these therapies, that cancer presents differently in different patients, and that specific human tumors may differ. All of these indicate the complexity and predictability of the interaction between the human immune system and cancer, meaning that cancer immunotherapy still faces many challenges.

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