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Current Status Of Immunotherapy For Cervical Cancer

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Abstract. Cervical cancer is one of the common gynecological malignancies that threaten women's health. Its etiology is complex, among which persistent human papillomavirus (HPV) infection is the main pathogenic factor. Due to the lack of obvious early symptoms, many patients are already in the middle and late stages when diagnosed. Although conventional chemotherapy can alleviate the disease, some patients will still experience recurrence or metastasis, indicating that the existing treatment methods are still limited. In recent years, immunotherapy technology has been continuously improved, especially the application of immune checkpoint inhibitors (ICIs) has provided a new direction for the treatment of cervical cancer. This article systematically reviews the common treatment methods and emerging immunosuppressive treatment strategies for cervical cancer, including chemotherapy, radiotherapy, anti-angiogenic therapy and bispecific immunoconjugates, and discusses their basic principles, mechanisms of action and drug side effects. Although some immunotherapy regimens have shown certain efficacy in clinical practice, existing studies are still insufficient in terms of drug diversity and mechanism interpretation. In the future, more new immunosuppressive drugs and treatment methods need to be further developed to improve the prognosis and survival rate of patients with cervical cancer.

Keywords: Cervical cancer (CC), treatment, immune system.

1. Introduction

Cervical cancer (CC) is one of the most common gynecological malignancies threatening women's health and also one of the main causes of death among female patients with malignant tumors. There are various causes for the occurrence of cervical cancer, among which persistent human papillomavirus (HPV) infection is the main reason. The early symptoms of cervical cancer are not obvious, and most patients do not show obvious clinical symptoms. After the initial traditional chemotherapy, some patients still experience recurrence or metastasis, indicating that the treatment options for cervical cancer are quite limited. With the continuous progress of immunotherapy, new treatment methods for cervical cancer metastasis or recurrence are constantly emerging, such as combination therapies of chemotherapy, radiotherapy, anti-angiogenesis therapy, and bispecific immune conjugate therapy, etc., which are currently under active research.

Cervical cancer cells may affect multiple systems and tissues throughout the body, including but not limited to the liver, skin, endocrine glands, and sometimes even the nervous system, cardiovascular system, and hematological system. Currently, the main treatment principles are: baseline assessment, careful screening, regular monitoring, early identification, and timely intervention. The application of immune checkpoint inhibitors (ICIs) in the treatment of cervical cancer is expected to make progress in the future and improve the survival rate of patients. This article aims to conduct a comprehensive review of the commonly used CC treatment methods and some newer ICIs compositions, basic principles, mechanisms of action, drug side effects, and future prospects and developments. This article partially analyzes and summarizes the immune suppressive therapy for cervical cancer, but there are still some gaps and deficiencies. In the future, more emerging technologies and drugs are needed for the research and development of cervical cancer immune suppressive therapy drugs.

2. ICIs

2.1. PD1/PD-L1

2.1.1. Introduction

The full name of PD-1 is programmed death receptor, an important immunosuppressive molecule. It belongs to the CD28 superfamily and is a type I transmembrane protein composed of 268 amino acids. The PD-L1 protein acts as a ligand for PD-1. When PD-1 binds to PD-L1 in the stroma, T cells lose their ability to attack cancer cells. As a co-inhibitory signal that mediates T cell activation, it suppresses the cytotoxic function of T cells, thereby negatively regulating the human immune response. During the growth of human tumor cells, these cells often exploit this immune-protective mechanism to maintain their survival. After ICI treatment, the prognosis is good; early-stage patients can achieve a 5-year survival rate of 95%, and a 5-year overall survival rate of 70-90%, demonstrating significant therapeutic effects [1,2]. Although immune checkpoint inhibitors enhance the immune system's ability to fight tumor cells, they inevitably cause damage to normal cells and tissues. Adverse events caused by autoimmune-like inflammatory responses triggered by immune checkpoint inhibitors are typically referred to as immune-related adverse events (irAE). Most irAE can be treated by delaying the administration of ICIs or temporarily inducing immunity with drugs such as glucocorticoids or other immunosuppressants [3]. PD-1 is expressed in the tumor stroma of approximately 60.8% of CC patients, while PD-L1 can be observed in about 34.4%-96.0% of CC tissues [4]. Blocking this pathway is necessary because PD-1 and PD-L1 allow tumor infiltration without inhibition.

2.1.2. Principle

In the PD-1 and PD-L1 signaling pathways, T cell activation functions as a dual signaling system. The first signal is the specific binding of T cell receptors to major histocompatibility complex molecules, while the second signal involves the interaction between antigen-presenting cells and co-stimulatory molecules on T cell surfaces. This pathway is subject to negative regulation; co-stimulatory molecules are known as immune checkpoints, primarily preventing overactivation of the immune system. When this pathway is impaired, PD-1 inhibitors and PD-L1 inhibitors become particularly important. PD-1 inhibitors restore T cell activity by blocking the binding of PD-1 to its ligand, enhancing the immune system's ability to attack tumor cells. PD-L1 inhibitors prevent PD-L1 from binding to PD-1, thereby disrupting the immune escape mechanisms of tumor cells.

2.1.3. Drug effects and applications

As of December 3, 2024, seven PD-1 and PD-L1 inhibitors have been approved, including tislelizumab, nivolumab, panitumumab, atezolizumab, durvalimab, avastin, and pembrolizumab. Nivolumab and pembrolizumab are widely used PD-1 inhibitors in clinical practice [5]. And atezolizumab and durvalumab represent typical PD-L1 inhibitors. In terms of drug application, each inhibitor has its own characteristics. The advantage of PD-L1 monoclonal antibodies lies in blocking the PD-1/PD-L1 binding pathway alone, effectively avoiding side effects such as interstitial pneumonia. Additionally, PD-L1 monoclonal antibodies can more comprehensively activate the immune system to combat tumors. For patients who do not respond to PD-1 inhibitors or develop resistance, switching to other inhibitors may improve efficacy. To predict treatment outcomes, the academic community has developed several predictive markers. TMB testing, also known as tumor mutation burden, can determine the probability of gene mutations in tumor tissues. The more mutated genes there are, the higher the likelihood of producing abnormal proteins, thus increasing the probability of immune system recognition. This finding, through the detection of PD-L1 protein expression levels, can more effectively activate the bodys anti-tumor immune response, thereby enhancing the effectiveness of immunotherapy. Currently, this is mainly achieved using immunohistochemical methods at the cellular protein level. Tumor tissues obtained after surgery or biopsy are stained with specific antibodies, and pathologists judge the expression based on the depth of staining under a microscope.

2.1.4. Side effects and safety assessment

The overall side effects of PD-1 and PD-L1 inhibitors are much less severe than those of traditional cancer treatments such as radiation therapy and chemotherapy. Common side effects include fever, fatigue, dizziness, generalized muscle pain, and somnolence, with a clinical incidence of about 30%. Additionally, patients may experience infusion reactions, including chills or shivering, itching or rash, difficulty breathing, and dizziness. It is important to note that patients at the end stage of their disease, bedridden, or with uncontrolled acute bacterial infections should not use PD-1 inhibitors. For patients who respond well to PD-1 inhibitor therapy, the effects are usually more durable, but studies show that nearly 30% of patients may develop drug tolerance. In such cases, switching to PD-L1 monoclonal antibody inhibitors can be considered. Research on PD-1 and PD-L1 inhibitors is ongoing globally. A significant advancement is their potential for broader cancer treatments, including CC and liver cancer, which have been approved for clinical use.

2.1.5. The latest advances in CC

The new drug injection Socazolimab has been approved for the treatment of recurrent or metastatic CC, an anti-PD-L1 monoclonal antibody drug with good overallla safety evaluation, low probability and severity of side effects, and a total survival of 14.7 months.

2.2. CTLA-4

2.2.1. Function, structure and clinical significance

CTLA-4, also known as CD512, is a cytotoxic T-lymphocyte-associated protein 4, a type of protein receptor, leukocyte differentiation antigen, and transmembrane receptor on T cells. It is an immune checkpoint that can downregulate the immune response. CTLA-4 works in concert with CD28, binding to B7 molecule ligands and B7 molecules to induce T cell deactivation, participating in the negative regulation of the immune response [6]. CTLA-4 is also a member of the immunoglobulin superfamily, expressed by activated T cells. It continuously stimulates CD28 homologs to bind with CD80 and CD86 on antigen-presenting cells, transmitting inhibitory signals to T cells. This allows it to compete with the ligands of CD28. CTLA-4 transmits inhibitory signals to T cells, while CD28 transmits stimulatory signals. Therefore, T cell receptor and CD28-mediated T cell activation leads to increased expression of CTLA-4. Clinically, CTLA-4 can protect the body from autoimmune diseases and serves as a target for cancer therapy. Variations in the CTLA-4 gene are associated with type 1 diabetes, primary biliary cholangitis, and other autoimmune diseases. Patients typically exhibit symptoms of immune system disorders. Dysregulation syndrome includes extensive T-cell infiltration across multiple organs.

2.2.2. Drug effect and applications

The relatively high binding affinity of CTLA-4 makes it a potential therapy for autoimmune diseases. On one hand, it exerts its immunosuppressive effect by regulating T cells; on the other hand, it is expressed after resting T cells are activated. As a feedback mechanism, it balances the intensity of adaptive immune responses through cytokine production such as T cell differentiation, proliferation, cell contact, and migration. Due to the high affinity binding between CTLA-4 antibodies and the CTLA-4 molecule, they can mediate depletion or functional blockade, thereby enhancing T cell activation and immune responses against cancer. Currently, there are five CTLA-4 inhibitors available globally: ipilimumab, tislelizumab, sintilimab, etc [6]. These drugs are used to treat malignant melanoma, renal cell carcinoma, CC, liver cancer and other diseases.

2.2.3. Side effects and safety assessment

CTLA-4 inhibitors can disrupt peripheral tolerance and immune homeostasis, leading to indiscriminate attacks by the immune system on normal tissues and organs, thus triggering adverse immune events known as irAEs. To effectively prevent such events, early explorations of T-cell repertoire changes during treatment have found that alterations in T-cell clonality are more predictive of irAEs than the occurrence of these events. This suggests that detecting new T-cell clonalities in

the early stages of treatment may effectively predict the onset of irAEs. CTLA-4 has raised expectations for combination immunotherapy among clinicians, but several issues remain. For example, compared to other immunosuppressants, there are fewer drug options, a narrower range of indications, and a lack of optimal dosing and treatment strategies.

2.2.4. The latest advances in CC

Candunil is a PD-1/CTLA-4 bispecific antibody drug, which has been used in first-line clinical treatment and achieved good efficacy. It is mainly used in phase III clinical studies for the treatment of recurrent or metastatic CC.

3. Combined Treatment

3.1. Chemotherapy

3.1.1. Introduction

Combination chemotherapy usually refers to the simultaneous or sequential use of multiple chemotherapeutic drugs in a single chemotherapy course. Compared with monotherapy, combination therapy has obvious advantages, so monotherapy has become a history, and almost all cancer treatment is combination therapy [7].

3.1.2. Application status

Some current studies indicate that the combination of chemotherapy and immunotherapy has an additive effect. Chemotherapy can disrupt the activity of immune-suppressing cells such as regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages. Additionally, chemotherapy can promote immune responses by inducing apoptosis in tumor cells and upregulating dendritic cell maturation. For individuals whose physical condition is sufficient to receive immunotherapy alone, the key question is whether combining chemotherapy can effectively improve clinical cure rates错误!未找到引用源。 [7].

3.1.3. Side effects, evaluation + future

Before combining chemotherapy with radiation therapy, the patient's response to treatment is evaluated to determine the effectiveness of drug therapy. The main side effects come from chemotherapy and immunotherapy. The side effects of chemotherapy are mostly similar to those commonly seen in traditional cancer treatments, typically manifesting as decreased white blood cells, neutropenia, anemia, and thrombocytopenia. There may also be multiple bleeding points, such as nosebleeds, gum bleeding, and even cerebral hemorrhage. Immunotherapy can lead to immune-related pneumonia, immune-related myocarditis, and immunemediated skin damage. However, in most cases, the immunosuppressants associated with the combination of chemotherapy and immunotherapy can complementarily alleviate the side effects related to traditional cancer treatments.

3.1.4. The latest advances in CC

The main combination is bevacizumab in conjunction with paclitaxel and platinum-based drugs. Bevacizumab is the first targeted drug approved for anti-tumor angiogenesis, exerting its anti-tumor effects by specifically targeting vascular endothelial growth factor. It has been used to treat various malignant tumors and has proven effective. Paclitaxel and platinum-based drugs primarily inhibit normal cell division by stabilizing microtubules within cells and preventing their disassembly. The combination of these two drugs can produce a synergistic effect, enhancing the cure rate.

3.2. Cytotherapy

3.2.1. Introduction

Cytokine therapy, also known as adoptive cell therapy, is a treatment that typically uses cells from the patient's own immune system to eliminate cancer. Cytotoxic T lymphocytes can bind to antigenic

markers on the surface of cancer cells, specifically recognizing and eliminating them, preventing their invasion and growth within the body [8].

3.2.2. Applications

Cancer cell infiltration therapy and engineered T-cell receptor therapy have shown significant effects in treating cancers such as kidney cancer, breast cancer, non-small cell lung cancer (NSCLC), and CC. Additionally, chimeric antigen receptor T-cell therapy (CAR-T) has broken through the limitation that cancer cells must present mutated antigens on their surface for T cells to recognize and eliminate them, further advancing these two cell therapies. Improved CARs can directly activate T cells by recognizing naturally expressed antigens on the surface of cancer cells, thereby killing them [9]. This therapy has been successfully applied to malignant tumors of the blood system, especially B-cell leukemia. This highlights the important advantages of combined cell therapy.

3.2.3. Side effects and safety assessment

When CAR-T cells are infused into a patient's body, they exert an anti-tumor effect but can also trigger cytokine release syndrome, which poses a severe threat to life. Cytokine release syndrome (CRS) is a severe systemic inflammatory response syndrome caused by immune effector mechanisms, particularly in CAR-T cell therapy, triggered by immune activation and the massive release of cytokines. Specifically, it is an overreaction resulting from the excessive activation of immune cells, primarily occurring after immune cells bind to relevant antigens on target cells, activating T cells and leading to the destruction or apoptosis of target cells, followed by the release of cytokines into the bloodstream. Symptoms typically include, but are not limited to, fever, hypotension, hypoxemia, capillary leakage, and multi-organ dysfunction. Mild CRS can be managed with supportive treatments such as antipyretics and fluid replacement. Severe CRS requires more aggressive treatment, including the use of anti-inflammatory drugs or immunosuppressants, a combination therapy. Therefore, enhancing the safety of CAR-T cell therapy and reducing its associated toxicity is a key focus of subsequent research. rh is especially important. Currently, small molecule switches for CAR-T cells are being developed to minimize treatment-related toxicity.

3.2.4. The latest advances in CC

Cell therapy is also widely used in cancer treatment, including genetic engineering to transform a patients T cell into immune cells that can recognize and attack tumors. Its more direct use in treating tumors has also made significant progress in the field of CC.

3.3. Dual Drug Immunotherapy

3.3.1. Introduction

Dual-drug immunotherapy for cancer. Currently, the most commonly used combination is the use of PD-1 antibodies in conjunction with CTLA-4 antibodies. The PD-1 antibody activates effector T cells to kill tumors, while the CTLA-4 antibody reactivates them during the differentiation stage, converting them into effector T cells to exert antitumor immune effects [10]. This suggests that the mechanisms of action of PD-1 and CTLA-4 antibodies complement each other, enhance each others effects, and do not significantly overlap in drug tolerance mechanisms. Their combination therapy can significantly enhance tumor immune response.

3.3.2. Applications

Two antibody combination immunotherapy regimens have been tested in various solid tumor trials and partially completed clinical studies, including melanoma, NSCLC, hepatocellular carcinoma, etc, all of which have received market approval. The core advantage of bispecific therapies lies in their synergistic effect, not only activating the immune systems cytotoxic capabilities but also blocking alternative pathways for tumor escape, thus overcoming the inherent limitations of monoclonal antibodies [11].

3.3.3. Side effects and safety assessment

Although dual-drug immunotherapy improves the bodys immune function to kill tumors through interaction, its complex mechanism inevitably damages normal cells. Different side effects typically appear several weeks or even months after treatment, but most are mild and reversible. Rash appears earliest, usually within 2-4 weeks of treatment. Diarrhea generally occurs 4-6 weeks after treatment. Additionally, hepatotoxicity and other adverse immune responses become more common 6-8 weeks after treatment. When these adverse reactions occur, stronger or timely intervention may be necessary [12]. The development of cancer bispecific antibodies has a broad prospect with diverse structures and rich mechanisms of action. Many drugs are still in the clinical research stage, and more drugs are expected to come soon.

3.3.4. The latest advances in CC

In recent years, bimodal immunotherapy has made remarkable progress in the treatment of CC, especially providing a new research direction for the treatment of advanced CC. However, there are still limited drugs that can be fully applied in the treatment of CC, which need further research.

4. Emerging Immunotherapies

Biological markers primarily refer to indicators that can be objectively assessed and measured, reflecting the pathological processes under physiological or disease conditions, as well as the biological effects of medical interventions. Based on their application value, they can be categorized into diagnostic, monitoring, pharmacological effects, predictive, prognostic, and risk biomarkers. The completion of human genome sequencing has ushered in an era of continuous research and development to discover genetic biomarkers. Currently, biological markers are widely used in the biopharmaceutical industry and are one of the key research directions. In oncology, biological markers are also extensively applied in diagnosis, prognosis, and targeted therapy. They provide robust and specific monitoring and detection strategies, characterized by reliability, high cost-effectiveness, repeatability, and high functionality [13]. In recent years, based on the discovery of tumor markers, various immunoassay methods have been developed, providing great convenience for cancer treatment. Drug targets refer to the positions where drugs bind to large molecules in the body. These targets include receptors, enzymes, ion channels, transporters, immune systems, genes, and more. Therefore, drugs can effectively bind in the body to achieve therapeutic effects. Tumor cells usually colonize in normal tissues and can form a tumor microenvironment together with stromal cells, immune cells and their secreted factors, vascular endothelial cells and extracellular matrix components.

5. Conclusion

This article reviews different immunotherapies for CC and compares and analyzes various immunosuppressants and their efficacy to some extent. By analyzing the treatment principles of different therapies, it can more intuitively summarize the characteristics and applicability of various immunotherapies. The article does not yet provide a clear explanation for more specific or diverse drugs in immunosuppressant therapy. Based on this article, further in-depth research on immunosuppressant therapy for CC will continue. Multiple immunotherapy approaches have shown certain therapeutic effects and curative conditions in cancer immunotherapy and CC treatment. The aforementioned studies indicate that under certain basic treatment standards, there is still room for improvement in the application of immunosuppressants in CC treatment.

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