DOI: 10.53469/jcmp.2025.07(03).10

Application of Immune Checkpoint Inhibitors in Common Gynecological Malignancies

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Abstract: ***Gynecological malignant tumors threaten women's lives and property, among which cervical cancer, endometrial cancer, ovarian cancer and other malignancies have a high incidence rate and mortality trend with the change of women's lifestyle and the aggravation of their psychological load in recent years. Therefore, standardized and efficient treatment of gynecological malignancies is crucial for maintaining long-term survival and a happy life for female patients. At present, immunotherapy has turn into the fourth cancer therapeutic tool after traditional operation, chemotherapy, and radiation therapy. In recent years, with the increasing attention to immunotherapy for gynecological tumors, immune checkpoint inhibitors is widely used in clinical practice of gynecological tumors in China, and their clinical efficacy is outstanding. This article summarizes clinical use and occurrence of adverse events of immune checkpoint inhibitors in gynecological tumors in recent years, and explores the therapeutic prospects of immune inhibitors in gynecological tumor diseases, in order to promote the development and innovation of tumor immunotherapy in the future.***

Keywords: Immunotherapy, Immune checkpoint inhibitors, Gynecological malignant tumors, Adverse events.

1. Introduction

Gynecological malignant solid tumors pose a serious threat to women's life and health. Adjuvant treatments such as radiotherapy and chemotherapy for advanced, recurrent, and metastatic gynecological tumors have poor efficacy and prognosis. Cervical cancer is the fourth disease in the world in terms of incidence rate and mortality. Human papillomavirus (HR-HPV) infection is the main cause of its onset, among which HPV16 and 18 go hand in hand with the incidence of cervical cancer. Sun Na et al. conducted HPV gene subtype testing on 500 cervical cancer patients admitted to Tangdu Hospital of the Second Affiliated Hospital of the Air Force Medical University from 2018 to 2023. The research results showed that the HR HPV positivity rate was 76.80%, with HPV16 accounting for as high as 48.96%; HPV18 accounts for 12.50%. Endometrial cancer is a female reproductive malignant tumor second only to the morbidity of cervical cancer. At present, the incidence rate is on the rise [3], closely related to obesity, hyperglycemia, etc. [4], about 90% of which are endometrioid adenocarcinoma [5]. Ovarian cancer has the highest death rate among gynecological malignancies, with epithelial ovarian cancer being the most common. Due to insidious early symptoms, 70% of patients are diagnosed in the late stage, and the 5-year survival rate is only about 40%. Immunotherapy is a treatment method that targets the body's own immune abnormalities by providing exogenous enhancement or inhibition of abnormal states, in order to achieve anti-tumor effects. In the 19th century, immune cells were discovered and gradually perfected; In the 20th century, the concept of tumor antigens was proposed [7]; Until today, immunotherapy, as an innovative breakthrough in the field of tumor treatment, has become an important treatment method for various types of tumors. At present, immunotherapy commonly used in clinical practice includes Immune checkpoint inhibitors, molecular targeted therapy, multi-target combination therapy, adoptive cell therapy, cytokine therapy, etc.

In recent years, immunotherapy mainly using immune checkpoint inhibitors has demonstrated good efficacy in the healing of malignant solid tumors, offering a new curative ideas for sick person with gynecological malignant solid tumors. In 2021, *Clinical Application Guidelines for Immune Checkpoint Inhibitors in Gynecological Tumors (hereinafter referred to as the "Guidelines"*) were compiled and published by the Gynecological Oncology Branch of the Chinese Medical Association. The guidelines indicate that immune checkpoint inhibitors can benefit patients with advanced, recurrent, and metastatic gynecological malignant solid tumors, with endometrial cancer showing the best therapeutic effect [8].

2. Immune checkpoint

Immune checkpoint (IC) refers to the molecular mechanism that affects the function of immune cells during the immune response process. They are composed of two different types of cellular active molecules, one called immunosuppressive molecules and the other called activators. The function of immune checkpoints is to suppress or promote the immune system's response to potential external threats, and the normal functioning of these checkpoints can prevent the occurrence of various immune diseases.

2.1 The Mechanism of Action of IC

IC involve programmed death receptors and their ligands that can be eradicate by the immune system. The specific mechanism of action is to inhibit the binding of programmed death receptors and their ligands, improve the immune function of the patient's body, and thus have the ability to recognize and attack tumor cells [6]. Classic immune checkpoint molecules such as programmed death receptor-1 (PD) and cytotoxic T lymphocyte associated protein (CTLA) -4 can all play an important part in maintaining the balance of the immune system by delivering inhibitory signals to T cells, avoiding their overactivation. Treating cancer not only requires killing cancer cells through radiation therapy and chemotherapy, but also emphasizes enhancing the patient's

immune function. Starting from restoring the function of immune checkpoint molecules such as “sentinels”, restoring the combat effectiveness of T cells, enhancing the body’s own immune ability, and ultimately defeating cancer.

2.2 Immune Checkpoint Inhibitors (ICI)

ICI are a new series of anti-cancer drug designed to suppress immune checkpoints in the immune system. They are used to sensitize or enhance the immune system to strike tumor cells to tumors, achieving higher efficacy than traditional cancer treatment methods. Its mechanism of action is to enhance the anti-tumor immune response of T cells by restraining the function of negative immune regulatory molecules on the surface of T cells, thereby producing anti-neoplasm immune effects [6]. Targeted immune checkpoint molecules provide inhibitory signals to T cells, and immune checkpoint inhibitors can prevent this immunosuppressive effect, allowing T cells to recognize and attack cancer cells, enhance immune responses, and produce persistent anti-tumor immune responses in some patients [10]. Immunoassay inhibitors such as CTLA-4 and PD-1 have been widely used in clinical therapy of multiple types of tumors to regulate immune stability and avoid attacks on normal tissues and cells of the body.

3. Application of ICI in Gynecological Malignancy

In clinical practice, ICI (such as CTLA-4), programmed death receptor-1 (PD-1) and its ligand (PD-L1) have been widely used in the treatment of various tumors. The clinical practice guidelines for cervical cancer, uterine and ovarian cancer published by NCCN in 2018 suggest that pembrolizumab can be applied to recurrent cervical cancer, endometrial cancer and ovarian cancer with high microsatellite instability (MSI-H) or error repair (dMMR), marking the opening of immunotherapy in the clinical treatment of gynecological tumors.

3.1 Application of ICI in Cervical Cancer

The proportion of MSI-H in cervical cancer patients is relatively low (2.62%), but TMB-H accounts for 14.9%. The expression rate of PD-L1 is relatively high, reaching 34.4% to 96.0%, indicating that PD-1 inhibitors may be used for the treatment of metastatic/recurrent cervical cancer [12]. The US FDA has obtained the efficacy of Pembrolizumab for cervical cancer in the KEYNOYE_158 (NCT02628067) clinical trial. This study included 98 patients with cervical cancer, including 77 (79%) who had a PD-L1 score of 1 or above and received at least one course of chemotherapy. The treatment method is to administer 200mg within 3 weeks until intolerable toxic side effects or disease progression occur. So far, there have been nearly 20 clinical trials of immune checkpoint inhibitors for the treatment of cervical cancer, but most of them are in the first or second stage. The GOG3016 randomized phase clinical study (NCT03257267) compared and evaluated the therapeutic effects of PD-1 inhibitors and chemotherapy on recurrent or metastatic cervical cancer. The data showed that simipilimumab achieved good efficacy, becoming the first PD-1 inhibitor to demonstrate OS benefits in second-line treatment of recurrent or metastatic cervical cancer. Although pembrolizumab has been approved as a second-line therapy for cervical cancer, according to publicly available data, its therapeutic efficacy ranges from 10% to 30%.

3.2 Application of Immune Checkpoint Inhibitors in Endometrial Cancer

Up to now, 25 clinical trials have involved endometrial cancer. Because most studies are conducted in phase 2 clinical trials, there is currently limited research data available. Some are still in the second phase of research, and there is currently very little published clinical data. In patients with endometrial cancer, PD-1/PD-L1 is highly expressed, with an expression rate of 40% to 80% in endometrioid adenocarcinoma, 10% to 68% in serous carcinoma, and 23% to 69% in clear cell carcinoma. Meanwhile, endometrial cancer is also a tumor with a high incidence of MSI-H and/or dMMR, reaching 31.37%, while TMB-H accounts for 11.2% [13]. In the clinical trial of Keynote-158 [14], 79 evaluable efficacy endometrial cancer patients showed an objective response rate of 48% after treatment with Pembrolizumab; The disease control rate is 66%; 1. The overall survival rates at 2, 3, and 4 years were 69%, 64%, 60%, and 60%, respectively. The incidence of ≥ 1 treatment-related adverse event is 12%, and the incidence of immune-mediated adverse events or infusion reactions is 7%. Advanced/recurrent endometrial cancer is a gynecological malignancy that benefits greatly from ICI treatment.

3.3 Application of Immune Checkpoint Inhibitors in Ovarian Cancer

The highest mortality rate among gynecological tumors is undoubtedly ovarian cancer, with epithelial ovarian cancer being the most common, with 60% of patients diagnosed at advanced stages. Most ovarian cancers are serous epithelial ovarian cancers, with very few MSI-H cases reported [15-16], accounting for only 1.37%, TMB-H accounts for 1.47%, and PD-L1 expression accounts for 10-30%. It is generally believed that ovarian cancer has the worst therapeutic effect in gynecological tumor immunotherapy. Although there are some targeted therapies for tumors, such as the anti angiogenic drug Bevacumab and PARP inhibitors, the 5-year survival rate is less than 50%, and there has been no significant improvement in their disease survival rate in recent decades. So, we need to search for new ways to treat ovarian cancer. According to relevant information, nearly 60 related clinical trials have been conducted so far. It is gratifying that 8 projects are currently undergoing phase III trials. The treatment methods include immune checkpoint inhibitors combined with chemotherapy and targeted therapy. For example, a phase III clinical trial began in November 2017 (NCT03353831), which evaluated the clinical efficacy of a combination therapy of bevacizumab and chemotherapy with bevacizumab. However, the third phase of clinical research has just begun and there is no clinical data available.

4. Immune Related Adverse Events

4.1 Immune Related Adverse Events (irAEs)

Immune checkpoint inhibitors activate autoimmune T

lymphocytes to resist tumors, but also have immune attack effects on multiple systems and organs of the body, leading to irAEs in patients [17]. IrAEs can occur at any time during treatment or several months after the end of treatment. If ICI is combined with treatment, the risk of irAEs increases and the onset time is often advanced. Su Xiaoni et al. believe that the risk factors for irAEs may include individual factors, immune cell factors, autoantibody factors, inflammatory cytokines or chemokines, HLA factors, gut microbiota factors, previous treatment and medication factors, comorbidities factors, ICI types, combination therapy and blood drug concentration factors, and others [18].

4.2 The Mechanism of Action of irAEs

irAEs is a complex immunological process, in which tumors, immune cells, and the patient's own immune status jointly participate in the occurrence of irAEs. Firstly, similar to the mechanism of traditional autoimmune diseases, killing tumors releases a large amount of tumor associated antigens and neoantigens, which have homology with self antigens. Self reactive T lymphocytes may mistakenly recognize self cells that have been engulfed, processed, and presented by antigen-presenting cells. These self reactive T lymphocytes become the "culprits" that mediate the onset of irAEs, becoming an important characteristic that distinguishes irAEs from traditional autoimmune diseases [19].

4.3 Common Adverse Reactions

In clinical research on gynecological tumors, the safety of using ICI is generally consistent with the safety of monotherapy and combination therapy in other known tumor types.A investigate [20] evidence that the probability of toxic events occurring with PD-L1 inhibitors is 74.3%, while CTLA-4 inhibitors are 85%. In the CheckMate 277 study, the incidence of irAEs at any level of Nivo + pilimumab was 77%, and the incidence of grades 3-4 was 33%, both lower than those in the chemotherapy group. But there are still a few patients who die due to toxicity, and a meta-analysis [21] found that the mortality rate caused by ipilimumab is 1.08%; The mortality rate of PD-1 inhibitors is 0.36%; The mortality rate caused by PD-L1 inhibitors is 0.38%. The common irAEs in ICI treatment for gynecological tumors are often manifested as thyroid dysfunction, diarrhea, etc. The incidence of severe irAEs is low and can manifest as liver dysfunction, colitis, etc.

4.4 Management of irAEs

The ASCO guidelines for the management of irAEs propose five key points: prevention, assessment, examination, treatment, and monitoring, and advocate for early detection, early treatment, and multidisciplinary consultation. The principles for handling irAEs include baseline assessment, careful screening, regular monitoring, and follow-up, with identification and timely intervention being key.

5. Outlook and Summary

Immunotherapy, as a new breakthrough in tumor treatment, has shown certain efficacy and advantages in clinical treatment. Immune checkpoint inhibitors inhibit autoimmune cells, enhance immune response, maintain autoimmune homeostasis, and block tumor progression. The current ICI demonstrate diversity and persistence in the treatment of gynecological malignancies, bringing more hope and opportunities to patients. However, the drugs used in clinical ICI are relatively single, the combinations between drugs are monotonous, and adverse events have not been fully controlled, so further research is still needed to bring more benefits to clinical practice.

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