Current Status and Clinical Research Progress of Immunotherapy for Advanced Gastric Cancer

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Abstract: Advanced gastric cancer is a common digestive system tumor, and its treatment has always been a difficult problem. In recent years, with the rapid development of immunotherapy, the treatment effect of advanced gastric cancer has been significantly improved. This article introduces the current status and clinical research progress of immune checkpoint inhibitors in advanced gastric cancer. Commonly used immunotherapy methods include chemical drug therapy, biological therapy, and gene therapy, among which the immune checkpoint inhibitors are currently one of the most popular immunotherapy methods, including nivolumab, pembrolizumab, and atezolizumab, which target programmed death ligand 1 (PD-L1) low expression (1%–49%) and PD-L1 high expression (≥50%). The results of clinical studies have shown that immunotherapy can significantly prolong the survival of patients with advanced gastric cancer while having lower toxic side effects and better tolerance. However, immunotherapy also has some problems, such as drug resistance and repeated infection. Future research directions include exploring new immunotherapy methods, combination therapy, and individualized therapy.

Keywords: Gastric cancer immunotherapy; PD-1/PD-L1 monoclonal antibody; CTLA-4 monoclonal antibody

1. Introduction

Gastric cancer (GC) is one of the most common malignant tumors in the world, and China is a country with a high incidence of gastric cancer. More than 50% of gastric cancer patients in China are in the advanced stage when they are diagnosed, while early gastric cancer accounts for only 10%. However, the incidence and mortality rate of gastric cancer in China is significantly higher than those in Western countries, accounting for about 80% of men and 40% of women. It is estimated that there are about 260,000 new cases and about 300,000 deaths related to gastric cancer in China every year. Since the early symptoms of gastric cancer are not obvious, most patients in China are already in the advanced stage when they see a doctor, and the best timing for surgery has been lost. Chemotherapy is the first choice for the treatment of advanced gastric cancer. At present, the first-line treatment regimen recommended by domestic and foreign guidelines is combined chemotherapy based on irinotecan; after the failure of first-line treatment, second-line treatment options can be selected, including

fluorouracil, platinum-based chemotherapy, and immunotherapy. However, immunotherapy is a new tumor treatment method, and its effective rate is only about 5%–20% [1-6]. Therefore, finding more effective, safer, and tolerable immunotherapy is still an urgent problem to be solved. With the in-depth research and breakthroughs in the clinical practice of the new generation of programmed cell death protein 1 (PD-1) / programmed death ligand 1 (PD-L1) monoclonal antibodies and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) monoclonal antibodies, which all are immune checkpoint inhibitors, the usage of these monoclonal antibodies are gradually becoming more popular in the field of tumors and as a new tumor immunotherapy model.

2. Immune checkpoint inhibitors

The occurrence and development of tumors is a complex immune-mediated process, the essence of which is that the body's immune system recognizes the PD-L1 protein on the surface of tumor cells and activates it [7]. As an important immunosuppressive molecule, PD-L1 inhibits the body's anti-tumor immune response by interacting with PD-1 or CTLA-4, thereby promoting tumor progression. Therefore, inhibiting the expression of PD-L1 on the tumor surface can improve the efficacy of immunotherapy. At present, the immune checkpoint inhibitors (ICIs) marketed at home and abroad mainly include nivolumab, pembrolizumab, atezolizumab, and ipilimumab. Among them, nivolumab and pembrolizumab have been approved for the treatment of advanced gastric cancer, mainly for patients with positive PD-L1 expression. In addition, other immune checkpoint inhibitors are also under active development, including anti-CTLA-4 PD-1/PD-L1 inhibitors, anti-PD1/PDL1 inhibitors, and anti-PD-L1/PD-1 antibodies. Immune checkpoint inhibitors that have entered the clinical research stage mainly include nivolumab, pembrolizumab, and atezolizumab, which target PD-L1 low expression (1%–49%), PD-L1 high expression (≥50%), and other groups [8-13]. Among them, pembrolizumab and atezolizumab have been approved in the United States for the treatment of advanced or recurrent gastric cancer, and several other immune checkpoint inhibitors are also undergoing clinical trials. This article reviews the research progress of several immune checkpoint inhibitors.

2.1. PD-1/PD-L1 monoclonal antibody

Immunotherapy research for gastric cancer mainly includes preclinical research and clinical trials of PD-1/ PD-L1 inhibitors. Among them, the two most important clinical studies are BGB-A317-001 (NCT04839555) and BGB-A317-002 (NCT04536931), both of which have been approved by the U.S. Food and Drug Administration for the treatment of patients with relapsed or refractory gastric cancer, the primary endpoints are objective response rate (ORR) and disease control rate (DCR) [14,15]. A clinical trial comparing BGB-A317-002 with irinotecan combined chemotherapy and BGB-A317-002 single-agent chemotherapy in the treatment of advanced gastric cancer announced preliminary results at the annual meeting of the European Society for Medical Oncology (ESMO). A phase III clinical study aimed at evaluating the efficacy and safety of BGB-A317-002 combined with irinotecan chemotherapy in the treatment of advanced gastric cancer. A total of 612 patients with advanced gastric cancer were included in the trial, and the results showed that the ORR of the BGB-A317-002 group and the irinotecan combined with chemotherapy group were 19% and 8%, respectively, and the DCR of the two groups were 67% and 60%, respectively. Therefore, BGB-A317-002 combined with irinotecan chemotherapy has a good curative effect in the first-line treatment of advanced gastric cancer, and the adverse reactions are controllable.

2.2. CTLA-4 monoclonal antibody

CTLA-4 is a transmembrane glycoprotein composed of T cell receptor (TCR) and ligand (LgA) on the surface

of B cells. It is expressed on the surface of T cells and is an important immune regulator. Studies have found that CTLA-4 is expressed in gastric cancer, non-small cell lung cancer, and liver cancer, but not in normal tissues [16]. Five subtypes of CTLA-4 have been discovered, including LAG-4, LAG-2, and LgA. Among them, LAG-4 and LgA are the two main subtypes. LAG-4 mainly plays a role by inhibiting the activity of T cells, while LgA plays a role by binding to receptors on the surface of T cells. CTLA-4 blocks T cell activation and proliferation signaling by binding to receptors on T cells. Therefore, CTLA-4 plays an important role in regulating the immune activity of T cells, activating T cells, and regulating cytokine signaling. Current studies have proven that CTLA-4 inhibitors can effectively reduce T-cell infiltration in the tumor microenvironment and inhibit immune escape. In October 2018, the U.S. Food and Drug Administration approved the CTLA-4 monoclonal antibody MILA-C3 developed by Merck for the treatment of patients with metastatic gastric cancer. In clinical trials, MILA-C3 can prolong the overall survival (OS) of patients. In terms of overall survival, it was comparable to the platinum-based combination chemotherapy group [17]. However, MILA-C3 monotherapy may also cause serious adverse reactions, so further exploration and verification is needed in clinical practice.

3. Other immunotherapies

In addition to immune checkpoint inhibitors, other immunotherapies are also being explored, including adoptive cellular immunotherapy (ACT), cytokine-mediated cytotoxic therapy (CIK), and immune checkpoint blockades (ICBs) [18]. ACT is a method of releasing antigen-specific cytokines in patients, which activate the immune system's T cells to recognize and kill cancer cells. Current clinical studies have shown that ACT has limited therapeutic effects on advanced gastric cancer, and patients will experience severe adverse reactions after receiving ACT treatment, including pulmonary embolism, severe infection, liver failure, and neutropenia. Therefore, ACT has limited therapeutic effects on advanced gastric cancer. CIK is adoptive cellular immunotherapy mediated by $CD4^+$ and $CD8^+$ T cells, which can specifically activate $CD4^+$ and $CD8^+$ T cells. Current studies have shown that CIK is effective in the treatment of advanced gastric cancer, and no serious adverse reactions have been observed. ICB is a tumor-specific immune checkpoint inhibitor constructed using monoclonal antibodies, which can block PD-1/PD-L1 molecules on T cells, activate DC and T cells, and inhibit tumor growth. A study showed that ICB has limited effect in the treatment of patients with advanced gastric cancer and has certain side effects compared with immunotherapy.

4. Summary and outlook

Currently, clinical immunotherapy strategies for advanced gastric cancer mainly include combination chemotherapy, ICIs, and ICBs. However, these strategies have not met the clinical needs of advanced gastric cancer, nor have they achieved the expectation of improving the prognosis of patients. At present, in mainland China, clinical trials of ICIs for gastric cancer are in the recruitment stage, lacking unified standards and curative effect evaluation systems, and the entry threshold is high; ICB research is only in the clinical trial stage, and there is a lack of large-scale real-world data related to it. As more and more research data are published, we expect more ICIs and ICBs for gastric cancer to be approved in mainland China. It is believed that in the near future, gastric cancer immunotherapy will become a tumor treatment model that can be widely used clinically.

In summary, the exploration of new immunotherapies in the field of advanced gastric cancer is still in its infancy. Although there is no clinically approved immunotherapy for gastric cancer, it represents the direction of future development. It is believed that more immunotherapies for gastric cancer will be approved in the near future.

Disclosure statement

The author declares no conflicts of interest.

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