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LETTER TO THE EDITOR

Therapeutic efficacy of immunotherapy for gastric cancer metastasis

Fei-Fei Xie, Su-Ting Qian, Hao-Yu Zhao, Qing-Sheng Liu

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Abstract

Gastric cancer (GC) metastasis is the main cause of poor prognosis for GC patients. In recent years, breakthroughs in immunotherapy have been made in the treatment of many kinds of cancers, providing new hope for patients with GC metastasis. This paper reviews the mechanism of immunotherapy in GC metastasis and its clinical application, and discusses and compares the research and efficacy of immunotherapy in patients with liver metastasis, lung metastasis, peritoneal metastasis and lymph node metastasis of GC. This study explores the challenges and future development directions of immunotherapy, and provides a theoretical basis and clinical guidance for the precise treatment of patients with GC metastasis.

Key Words: Gastric cancer; Metastasis; Immunotherapy; Liver metastasis; Lung metastasis; Peritoneal metastasis

Core Tip: Immunotherapy has gradually begun to be applied in the treatment of gastric cancer (GC) metastasis. Some studies have shown that liver metastases of advanced GC have a reduced immune response rate due to the presence of hepatic immune tolerance mechanisms. Therefore, the mechanism and efficacy of immunotherapy applied in other metastases are discussed. Previous studies have shown that immunotherapy has the best efficacy for lung metastasis and the worst efficacy for peritoneal metastasis, but it has a good safety profile and is promising for use in all GC metastases.

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TO THE EDITOR

Gastric cancer (GC) is a global health challenge, ranking as the fifth most common malignant tumor worldwide[1,2]. Over one million people are diagnosed with GC each year worldwide, and the five-year survival rate for GC patients is less than 40%[3]. Early GC (EGC) is similar to the common symptoms of gastritis, when it develops in the late stage that obvious symptoms are detected. However, EGC accounts for 50%-80% of all GC cases[4].Common complications of GC include gastrointestinal bleeding, perforation, pyloric obstruction, and metastasis[5]. Metastasis accounts for the majority of cancer-related deaths[6]. Common metastases from GC including those in the liver, lung, peritoneum, bone and pancreas are relatively rare[7,8]. Current treatment methods for metastasis include surgery, chemotherapy, immunotherapy, targeted therapy, conversion therapy, radiation therapy, and transhepatic arterial chemoembolization (TACE)[9]. Immunotherapy, an emerging anti-cancer strategy, recognizes and removes tumor cells by activating and enhancing the body's own immune system. In recent years, immunotherapy has shown significant efficacy in a variety of post-metastatic solid tumors, including malignant melanoma[10]. Research on immunotherapy for GC, non-small cell lung cancer, and breast cancer, including non-specific enhancer therapy, immune cell therapy, tumor vaccines, oncolytic viruses, and immune checkpoint inhibitors has been conducted[11-13]. These immunotherapies work by reactivating and maintaining the tumor immune cycle, restoring the body's normal anti-tumor immune response, and controlling and eliminating tumors[14]. In recent years, relevant studies have identified several potential predictive biomarkers for prognosis and immunotherapeutic efficacy across various tumors, such as SLC35A2, LMNB2, glycosylation-related genes, and EPHB2. The newly identified biomarkers offer valuable insights into the tumor dynamics and progression of various cancers, including GC. They also serve as predictive markers for tumor prognosis and immunotherapy for cancer metastasis[15-18]. The papers entitled "Analysis of the impact of immunotherapy efficacy and safety in patients with GC and liver metastasis"[19] and "Gastric cancer liver metastasis will reduce the efficacy of immunotherapy"[20], both in the *World Journal of Gastrointestinal Surgery*, aroused our interest. Due to their observations that liver metastasis from GC reduces the efficacy of immunotherapy, but few studies have examined whether secondary tumors after GC metastasis affect the efficacy of immunotherapy. Therefore, this paper aims to elucidate the immunological mechanisms underlying GC metastasis and to evaluate the therapeutic efficacy of immunotherapy for various metastatic manifestations of GC, thereby offering more precise and effective treatment options for patients with metastatic GC.

Characterization of the immune microenvironment in GC metastasis immunosuppressive cell infiltration

High infiltration of immunosuppressive cells, such as regulatory T cells, myeloid-derived suppressor cells and tumor-associated macrophages, is common in GC metastases. These cells inhibit the function of effector T cells by secreting inhibitory cytokines (*e.g.*, IL-10, TGF-β) and expressing immune checkpoint molecules (*e.g.*, PD-L1), thereby promoting tumor cell metastasis and survival[21]. GC liver metastases can siphon activated CD8+ T cells into the somatic circulation. This siphoning function leads to "immune deserts" causing a decrease in the effectiveness of immunotherapy[22].

Molecular expression of immune checkpoints

The PD-1/PD-L1 pathway is one of the most important immune checkpoints in GC metastasis. Studies have shown that the expression level of PD-L1 in metastatic GC tissues is significantly higher than that in primary foci, which may be one of the important mechanisms by which tumor cells evade immune surveillance. In addition, other immune checkpoint molecules, such as CTLA-4, TIM-3 and LAG-3, also play important roles in GC metastasis[23].

Tumor neoantigen load

Tumor neoantigens are tumor-specific antigens produced as a result of genetic mutations that can be recognized by the immune system. Tumor-associated antigens loaded DC vaccines in cancer treatment have been extensively investigated in clinical trials. Activation of neoantigen-specific CD4+ and CD8+ T cells increases the frequency of neoantigen-specific T cell clones. One patient with metastatic GC who received Neo-MoDC vaccination co-mediated with ICI and is now improving and has survived for > 25 months[24].

Cytokine network imbalance

During GC metastasis, the balance between cytokines and immune cells (*e.g.*, VEGF, IL-10, TGF-β) is disrupted, creating a microenvironment that favors tumor growth and metastasis. This imbalance in the cytokine network also affects the function and differentiation of immune cells[25].

IMMUNOTHERAPY IN METASTASES OF GC LIVER METASTASES

The liver is the most common site of GC metastasis, and the leading cause of death. The 1-year survival rate for patients with liver metastases is 15.1%[26]. Immunotherapies for GC liver metastases include the following: Systematic immunotherapy: For patients with unresectable GC with liver metastases, immune checkpoint inhibitors alone or in combination with chemotherapy may offer new treatment options. The KEYNOTE-061 study demonstrated that pembrolizumab shows good efficacy in patients with metastatic GC who had failed prior therapy, including those with liver metastases [27]. Local immunotherapy: Transhepatic arterial infusion of immunotherapeutic agents or combined embolization may improve local treatment outcomes. Combining PD-1 inhibitors with TACE may improve the prognosis of patients with liver metastases from GC[28].

Lung metastases

GC metastasizes to the lungs or chest cavity, manifesting as multiple lung metastases, carcinomatous lymphadenitis, or carcinomatous pleurisy[29]. Immunotherapy for lung metastases is similar to that for liver metastases. The use of immune checkpoint inhibitors such as PD-1 inhibitors (*e.g.*, pembrolizumab) and PD-L1 inhibitors (*e.g.*, nabulizumab) enhances the ability of T cells to kill cancer cells by blocking the interactions between PD-1 and PD-L1 and relieving the tumor's suppression of immune cells in tomors[30]. Cellular immunotherapy can be used as a kind of auxiliary treatment in patients with GC lung metastasis, collecting the patient's own immune cells, culturing and expanding them *in vitro* then infusing them back into the patient's body, to enhance the body's immune response to the tumor. It is used in combination with chemotherapy and radiotherapy to improve therapeutic effects[31].

Peritoneal metastasis

Peritoneal metastasis (PM) is a common site of advanced GC (AGC) metastasis, and is the most difficult type of metastasis to treat with a survival of 3-6 months[32]. Intraperitoneal immunotherapy: Direct injection of immunotherapeutic agents into the peritoneal cavity may increase local drug concentrations and reduce systemic adverse effects. Clinical trials have been conducted to evaluate the safety and efficacy of the intraperitoneal injection of CAR-T cells for the treatment of peritoneal metastatic GC[33]. Immunotherapy combined with hyperthermic intraperitoneal perfusion (HIPEC): Chemotherapy: Combining immune checkpoint inhibitors with HIPEC may have a synergistic effect. Pembrolizumab combined with HIPEC has shown promising results in the treatment of peritoneal metastases from GC[34].

Other metastases

The use of pembrolizumab as neoadjuvant therapy significantly improves the rate of complete pathological remission in patients with locally AGC metastases. In patients who have developed lymph node metastases, the use of postoperative immunotherapy may reduce the risk of recurrence. The results from the CheckMate 577 trial revealed that the use of nabulizumab as an adjuvant therapy significantly improved disease-free survival in patients with adenocarcinoma of the esophagus or gastroesophageal junction treated with neoadjuvant radiotherapy and surgery[35]. A case report of a reduction in previously metabolically active lymph nodes in the left clavicular region, abdominal cavity, retroperitoneum, and bilateral parietal iliac vessels following chemotherapy in combination with tirilizumab treatment was followed by maintenance of tirilizumab monotherapy for up to 2 years, with no evidence of recurrence during the concluding follow-up period[36].

Comparison of efficacy

The remission rate of AGC patients treated with PD-1 inhibitors in combination with chemotherapy ranges from 50% to 65%[37,38]. In the previous two articles, we reported that liver metastases reduce the effectiveness of immunotherapy. Patients with lung cancer presenting with bone metastases have lower PD-L1 expression, which tends to affect the tumor immune microenvironment and decrease the effectiveness of immunotherapy. Although this study addresses lung cancer bone metastases, a similar situation may also occur in GC lung metastases[39]. Compared with hepatic metastases, where the effect on T-cell apoptosis leads to systemic immunosuppression, pulmonary metastases are much smaller, and are therefore considered to have a lesser impact on immunotherapy. Another study showed that in the PD-L1 Low-expression cohort, there was a significant correlation between higher response rates to PD-1 inhibitor combination chemotherapy in patients with non-diffuse disease, GEJ cancers, distant lymph node metastases, hepatic metastases, non-peritoneal metastases, and HER2-positive patients[40]. According to the post hoc analysis of ATTRACTION-2, PM negatively impacted the therapeutic efficacy of navulizumab in GC salvage therapy. Similarly, in this study, PM was an independent risk factor for poor PFS and OS in the total population and in the PD-L1 Low-expression group receiving PD-1 inhibitors plus chemotherapy as first-line treatment.

DISCUSSION

Immunotherapy in patients with lung metastases has the best prognosis. Although liver metastasis reduces the effectiveness of immunotherapy in patients, combination with chemotherapy can still significantly improve the long-term prognosis with good safety. The efficacy of treatment for the PM of GC remains to be studied. The literature concerning lymph node metastasis mixed and needs a lot of experimental verification. However, immunotherapy for the treatment of GC metastasis has shown good application prospects and has brought new hope to patients with GC metastasis.

Identifying the optimal patient population for immunotherapy remains a challenge. Biomarkers such as PD-L1 expression, MSI-H status and tumor mutational burden are being evaluated to better select patients most likely to benefit. Further research is also needed to optimize combination strategies, including the timing and sequencing of immunotherapy with chemotherapy and other targeted therapies. Advances in new technologies, including ctDNA monitoring and artificial intelligence-based digital pathology, are expected to improve the precision of immunotherapy. By understanding the characteristics of the immune microenvironment of GC metastasis, optimizing the existing therapeutic strategies, and developing novel immunotherapeutic approaches, we believe that we will be able to provide more accurate and effective treatment options for patients with GC metastasis, ultimately improving their quality of life and prognosis.

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FOOTNOTES

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