Biomedical Data Science
2025, VOL. 5, NO. 2, 94-98
DOI: 10.47297/wspbdsWSP2752-630517.20250502

Focus on Gastric Cancer and Explore Immunotherapy

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ABSTRACT
Gastric cancer, as a malignant disease that poses a significant threat to human health, has become an important global public health issue. China is a country with a high incidence of gastric cancer. Its prevalence and mortality rates have generally remained high. The effectiveness of traditional treatment methods is limited, especially for advanced gastric cancer. In recent years, with the breakthroughs in immunotherapy research, it has been applied as a new treatment method in the field of gastric cancer treatment and occupies an important position. However, the currently widely used immune checkpoint inhibitors still have limitations in terms of the beneficiary population and efficacy, and are accompanied by drug resistance and toxic reactions. Adoptive cell therapy, immune vaccines, etc. are still in the clinical research stage. This article reviews the epidemiology, risk factors, immune mechanisms of gastric cancer, its application research in gastric cancer, the problems faced, and the future development directions.

KEYWORDS
Gastric cancer; immunotherapy

1 Background

Gastric cancer, originating from the gastric mucosal epithelium, is a malignant disease with a relatively high mortality rate. Its incidence ranks among the top in various types of cancers. China has a large population base and a medium level of the Human Development Index. Coupled with the increasing trend of population growth and aging year by year, the prevention and control situation of gastric cancer has become more severe, and the medical economic burden is also continuously rising[1]. This disease is asymptomatic or has non-specific manifestations in the early stage. The lesions are difficult to detect, and there is a lack of efficient and convenient detection methods. Therefore, there are often phenomena of low screening rates and high misdiagnosis rates. In addition, the public has insufficient awareness of the disease and lacks the awareness of seeking medical treatment, often delaying the treatment opportunity and causing the condition to deteriorate rapidly. As a result, most patients are often in the middle and advanced stages when diagnosed. At this stage, even if interventions such as surgery, radiotherapy, chemotherapy, or targeted therapy are used, the curative effect is difficult to meet expectations. The proportion of patients with a survival period of more than 5 years remains low, and the prognosis is not optimistic[2].

With the rapid development of modern science and technology and medical technology, the treatment policy of gastric cancer has undergone significant changes. Currently, the model of surgery combined with comprehensive perioperative adjuvant treatment is mainly adopted, and the treatment plan is becoming more and more mature. Although the current clinical needs have been met to a certain extent, there are still several deficiencies. For example, the curative effects vary due to individual differences, the applicable scope of treatment is limited, the trauma and complications caused by surgery, as well as potential risks such as drug resistance, recurrence, toxicity and radiation. Therefore, it is particularly necessary to break through the existing bottlenecks and further improve or explore new treatment strategies. The treatment method of using the human immune system to fight cancer has injected new vitality into the treatment field of gastric cancer. At present, this emerging treatment method has shown great development potential. However, it also faces numerous challenges and problems. This article mainly reviews gastric cancer and immunotherapy, aiming to popularize the risk knowledge of gastric cancer, look forward to the development prospects of immunotherapy, and hope to provide new research perspectives for medical researchers and promote the progress of gastric cancer treatment.

2 Epidemiology

The epidemiological characteristics of gastric cancer are closely related to geographical distribution, population, and lifestyle. Based on the data released by the Global Cancer Observatory in 2022, a comprehensive analysis shows that the number of new cases of gastric cancer is 978,000 (4.9%), and the number of deaths is 662,000 (6.8%). It ranks fifth among all malignant tumors. East Asian countries are high-incidence areas, among which China has a relatively high proportion, with the incidence and mortality rates being 37% and 39% respectively[3]. Gastric cancer is more common in middle-aged and elderly people. The incidence increases with age. There are obvious gender differences. The male population faces a

higher risk of illness and death. However, in some areas, female patients are more common among young people aged 40 and below, and the incidence in this age group has shown an upward trend in recent years. Due to the uneven distribution of medical and economic resources, as well as differences in hygiene conditions and eating habits, there are also significant differences in the cancer spectrum between urban and rural areas. In the case of gastric cancer, the incidence proportion in rural areas (8.87%) is higher than that in cities (6.48%), and the death proportion (11.27%) is also higher than that in cities (9.15%)[4-5].

The pathogenesis of gastric cancer is complex and involves multiple factors. Besides the influences of economy, geographical distribution, age, gender, etc, it also includes Helicobacter pylori infection, Epstein-Barr virus infection, genetic history (family history, gene mutations), bad living habits (long-term smoking, excessive alcohol consumption, irregular diet, consumption of high-salt pickled and processed foods, insufficient intake of fruits and vegetables, obesity), gastric precancerous lesions (atrophy, intestinal metaplasia, dysplasia), etc[6].

3 Gastric cancer and immunotherapy

3.1 Immune mechanisms and classification

A complex ecosystem composed of various components such as the extracellular matrix, cancer cells, immune cells, and blood vessels is called the tumor microenvironment. It keeps the body in an immunosuppressive state, helps tumors evade immunity, and thus leads to malignant cell growth and treatment resistance[7]. Traditional treatments have a double-edged effect on immune regulation: exacerbating immune system suppression or partially activating it. In contrast, the new therapy, immunotherapy, achieves anti-cancer effects by reversing immunosuppression, activating and enhancing the immune response, and remodeling the immune microenvironment[8-9].

Immunotherapy mainly includes the following types: (1) Immune checkpoint inhibitors (PD-1/PD-L1/CTLA-4 inhibitors): T cells in tumors usually highly express inhibitory receptors (such as PD-1 and CTLA-4). After these receptors bind to their ligands, they will inhibit the function of T cells, thereby weakening the body's immune response. Such drugs can restore the immune activity of T cells by specifically blocking these inhibitory signaling pathways, enabling the effective elimination of malignant cells[10]; (2) Adoptive cell immunotherapy (chimeric antigen receptor T/NK cell therapy): By extracting and isolating host immune cells, and using genetic engineering techniques to transform them into chimeric antigen receptor cells, which are then expanded and reinfused to recognize tumor antigens and enhance the immune defense and killing ability[11]; (3) Tumor vaccines (cellular vaccines, peptide vaccines, and nucleic acid vaccines): Using specific antigens generated by somatic mutations to initiate and enhance the immune response, break the immune escape mechanism, and promote the apoptosis of mutated cells[12].

3.2 Research on the classification of gastric cancer and the application of immunotherapy in gastric cancer

3.2.1 Classification and Significance of Gastric Cancer

Histological classification of gastric cancer: intestinal type, diffuse type, mixed type. Molecular classification: EBV-positive type, accounting for <10%, caused by human herpesvirus, with high-frequency PIK3CA mutations and overexpression of PD-L1[13]; microsatellite highly unstable type (MSI-H type), with an incidence of <35.3%, caused by DNA mismatch repair deficiency (dMMR), high mutation load, and high expression of PD-L1[14]; genomic stable type (GS type), accounting for approximately 20%, associated with diffuse gastric cancer, low mutation load[15]; chromosomal instability type (CIN type), accounting for nearly 50%, mainly seen in intestinal gastric cancer, with chromosomal abnormalities and receptor tyrosine kinase amplification[16]. Molecular classification reveals the biological characteristics of gastric cancer, provides a basis for individualized and precise treatment strategies, evaluates prognosis[17], and targets PD-1, PD-L1/HER2/vascular endothelial growth factor/CLDN18.2, etc. for treatment.

3.2.2 Clinical application and research status

In current clinical practice, immune checkpoint inhibitors are most widely used, especially in the treatment of advanced gastric cancer. Single immunotherapy or combination treatment strategies are adopted. The CPS (Combined Positive Score) is used to reflect the expression level of PD-L1 protein, and this is used as an indicator for predicting the therapeutic effect. When the score is≥1, the indicator is positively expressed. The higher the value, the better the treatment effect[18].

The following are some applications and clinical studies of immunotherapy for gastric cancer: For patients with positive HER-2 expression and CPS≥1, the first-line treatment regimen: Pembrolizumab (a PD-1 inhibitor) + Trastuzumab (an anti-HER2 targeted drug) + chemotherapy; For patients with negative HER-2 expression and CPS≥5, the preferred

regimen: Immune checkpoint inhibitor + chemotherapy[19-20]; For MSI-H/dMMR gastric cancer: Monotherapy with immunotherapy can lead to significant benefits. Dual immunotherapy or a combination of immunotherapy and chemotherapy can also be chosen[21]; For EBV-positive gastric cancer (EBVaGC): It is highly sensitive to immunotherapy. Early studies have shown that treatment with PD-1 inhibitors is effective in some patients, and dual immunotherapy regimens are also under exploration[22]; For CLDN18.2-positive gastric cancer: The targeted CAR-T cell therapy (CT041) has controllable safety and anti-cancer activity. The combination of targeted drugs and immunotherapy can enhance the therapeutic effect, but further clinical trials are still needed for verification[23-24]; Perioperative period: Immune checkpoint inhibitors can significantly improve the pathological remission rate in neoadjuvant therapy and can also be beneficial in postoperative adjuvant therapy, but the survival period is still unclear[25-26]. In addition to the above, there are many other related studies on immunotherapy, such as anti-angiogenic drugs/radiation therapy can enhance efficacy of immunosuppressants[27-28]. Therapeutic vaccines and NK cell therapies also have significant anti-cancer effects, and relevant research is being actively promoted[29-30].

4 Some problems faced

4.1 Drug resistance and recurrence

Tumor heterogeneity refers to the differences in genetics, phenotype, and function among tumor cells due to different degrees of differentiation. The interaction between heterogeneity and the microenvironment increases the difficulty of treatment, leading to drug resistance and recurrence. During immunotherapy, it can induce a persistent immune response in some patients. However, due to factors such as tumor cell mutations, abnormal antigens and signaling pathways, immune suppression in the microenvironment, and tumor heterogeneity, the immune-tumor dynamic response occurs, resulting in treatment resistance, manifested as initial non-response, adaptation after response, and recurrence after treatment[31].

4.2 Toxic reaction

Immune checkpoint inhibitors can disrupt immune homeostasis and expose organ-specific antigens by affecting T cells during treatment, leading to tissue-specific toxicity and widespread autoimmune responses. The toxicity of the two is additive. Common adverse reactions include: gastrointestinal, hepatic, endocrine, cutaneous, pulmonary toxicity, etc., as well as rare but fatal reactions: neurological and cardiovascular toxicity[32-33].

4.3 Biomarkers and beneficiary populations

At present, the main immune-related biomarkers include PD-L1, MSI-H/dMMR, Epstein-Barr virus, and tumor mutational burden (TMB). The beneficiary populations are screened based on high expression or positive results. Novel biomarkers include peripheral blood circulating tumor DNA, host biomarkers, and gut microbiome, etc., which also show good clinical application potential in the evaluation of immune efficacy. However, at present, the number of biomarkers that have been clinically validated to be effective is limited, which is insufficient to cover all potential beneficiary populations. Moreover, there are problems such as inconsistent detection methods and threshold criteria, limited evaluation by a single indicator, results being easily affected by tumor heterogeneity, and high costs[34-35].

4.4 The impact of Helicobacter pylori on the efficacy of immunotherapy

H.pylori, as an important carcinogenic factor for gastric cancer, not only promotes the occurrence of gastric cancer but may also synergize with the gut microbiota to enhance or inhibit the efficacy of immunotherapy. It is expected to become a biomarker for predicting the response to immunotherapy[36].

5 Future development direction

Immunotherapy has broad prospects. At present, there are still many blank areas that urgently need to be further explored and expanded by researchers. In the future, it will steadily move forward in the directions of precision, combination, and innovation technology-driven. To accelerate the application process of immunotherapy, in-depth collaboration among multiple disciplines such as medicine, biology, and computer science is required. Combining cutting-edge technologies such as nanotechnology and artificial intelligence, the existing diagnosis and treatment strategies need to be improved and standardized, including optimizing the combination of treatment methods, precisely grasping

the application timing, reasonably controlling the treatment course and dosage, effectively managing drug resistance, recurrence, and toxicity problems, as well as strengthening the control of risk factors, improving screening and diagnostic technologies, and clarifying prognostic indicators. In addition, the genotyping of gastric cancer still needs to be continuously studied, the relevant mechanisms between gastric cancer and immunotherapy need to be further analyzed, the key factors affecting the curative effect need to be identified, and new drugs need to be developed. It is expected that in the future, the early diagnosis rate can be increased, benefiting more patients, enhancing the treatment effect, reducing the incidence of drug resistance, recurrence, and adverse reactions. By formulating the best individualized medical plans for patients, the survival period can be maximally extended, the quality of life can be improved, and more hope and possibilities can be brought to patients.

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