

Research progress of bispecific antibodies in the treatment of gastric cancer

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ABSTRACT

Gastric cancer is a malignant tumor that causes death worldwide, especially in developing countries, and the incidence and mortality of gastric cancer are very high. Most patients with gastric cancer are in the advanced stage, and the limited surgical and chemotherapy methods have limited therapeutic effects, so it is of great significance to explore new treatment methods. In the past 10 years, the mature application of tumor molecular mechanism research and antibody engineering technology has made bispecific antibodies have broad application prospects as new targeted therapy drugs in tumor treatment. For example, in HER2-negative gastric cancer patients, HER2-negative bispecific antibodies such as cadonilimab can be combined with chemotherapy to enhance the anti-tumor immune response in the treatment of HER2-negative advanced gastric cancer or gastroesophageal junction adenocarcinoma. In summary, bispecific antibodies are a new class of targeted therapy drugs, which have broad application prospects in the treatment of gastric cancer.

KEYWORDS

BISPECIFIC ANTIBODIES; gastric cancer; targeted therapy

1 Introduction

1.1 Current status and challenges of gastric cancer

Gastric cancer is one of the most common malignant tumors in clinical practice, accounting for about 11% of all cancers, mostly in the elderly, and more in men than women, the incidence of cancer varies from region to region, many are related to dietary habits and environment, and the incidence rate is very high in some areas, so we should pay more attention to prevention and early screening. At present, although some progress has been made in the treatment of gastric cancer in surgery, chemotherapy, radiotherapy and targeted therapy, there are still problems such as low early diagnosis rate, high recurrence and metastasis rate, difficulty in individualized design of treatment plan, and difficulty in management of treatment complications (side effects).

1.2 Definition, principle and application of bispecific antibodies

Two-Specificity Antibody (TBSA), referred to as bispecific antibody, is a synthetic antibody containing two specific antigen binding sites, binding to two different antigens (different epitopes of the same antigen) at the same time, and stimulating a directed immune response through the specific binding of target cells and functional molecules (cells), which is a genetically engineered antibody^[1]. The other end binds to one target molecule B, thereby simultaneously completing several different biological functions^[2], such as accurate targeting, improving target effects, and regulating immunity. Bispecific antibodies have great potential in tumor therapy, as they can recognize tumor cells and the immune system at the same time and effectively direct immune cells to attack tumors, effectively improving treatment efficacy and reducing side effects^[3-4].

1.3 Background and significance

At present, the research background in the field of gastric cancer treatment is becoming more and more urgent, in order to further understand and study bispecific antibodies. This study mainly conducts systematic and basic research on a certain phenomenon or problem in a certain field, and proposes corresponding theoretical reference or practical methods for further solving such problems, and the fields and problems discussed have extensive practical significance. This field and the proposal of this problem not only have the significance of theoretical guidance, but also an important theoretical explanation, through this research can understand the law and essence of its internal operation, promote the solution of the problem, and at the same time, it can also bring new research directions for the interdisciplinary and professional fields in this field, which has multifaceted academic and practical significance.

1.4 Purpose and significance of this study

Through systematic research methods and rigorous data analysis, the internal mechanisms and associated factors are revealed. For the relevant theoretical systems in this field, this study not only enriches the relevant theoretical systems,

but also provides a scientific basis, which is also of great significance for promoting its development.

2 Mechanism of bispecific antibody therapy for gastric cancer

2.1 Mechanism of action of bispecific antibodies

Bispecific antibodies (BsAbs) are a class of synthetic monoclonal antibodies that can specifically bind to two antigens or epitopes at the same time. Its main functions include bridging immune cells (such as T cells and NK cells) with tumor cells, recruiting and activating immune cells to kill tumor cells^[5]; At the same time, it binds to two tumor-related receptors or ligands to exert a synergistic tumor inhibitory effect by blocking multiple pathways such as tumor growth and angiogenesis. One head targets tumor antigens, and the other ends are linked to cytotoxic drugs or radionuclides to deliver toxic molecules to the tumor^[4,6]. Bispecific antibody signaling blockade and immune activation are biological concepts that block certain signaling pathways to modulate cellular function to inhibit their abnormal activity^[7-8], and activate the immune system to enhance the body's immunity to fight diseases. Both can treat diseases and have potential applications in the field of tumor immunotherapy.

2.2 Specific pathways of action of bispecific antibodies in gastric cancer

Bispecific antibodies have shown a unique pathway in the treatment of gastric cancer, with bispecific antibodies being able to bind to and recognize two different antigens or epitopes simultaneously and block two different signaling pathways [9,10]. For example, cadonilimab is a novel quadrivalent bispecific antibody that can simultaneously block the binding of PD1 and CTLA4 to their ligands, promote tumor-specific T cell immune activation, and have stronger anti-tumor effects to avoid other side effects^[11]; IBI315 is a bispecific antibody targeting PD1 and Her2, which has been shown to have significant antitumor effects by inducing mechanisms such as stomatin B-mediated pyroptosis^[12]. Among them, focusing on the targeted role of gastric cancer-related antigens, accurately identifying and binding to target-specific antigens, targeting and inhibiting gastric cancer cells^[3,10,13], and strengthening the anti-tumor immune response are necessary processes to enhance the body's immune ability to eliminate cancer cells, activate immune cells, promote the release of immune factors, and optimize the immune microenvironment^[14-15], enhance the immune system's recognition, killing, and elimination of tumor cells^[16], and provide cancer patients with more effective cancer prevention and survival hope.

2.3 Synergistic effects of bispecific antibodies with other treatments

The development of monoclonal antibodies has gradually shown a trend of combining with other therapeutic methods to jointly treat diseases, and bispecific antibodies, as a new antibody treatment technology, are producing more synergistic effects with other therapeutic methods and making more and more contributions to disease treatment. By dually targeting the two antigens, bispecific antibodies can enhance the immune system's ability to attack diseases in a more three-dimensional way, and can be combined with chemotherapy, radiotherapy, or traditional monoclonal antibody therapy to promote dual labeling of the pathogenesis signaling pathway in patients and enhance the killing effect of the target antigen in the body^[17-18].

Accurately matching the advantages of chemotherapy and adjuvant therapy can not only improve the efficiency of cancer treatment, but also reduce side effects^[19-20], bringing more hope and survival opportunities to cancer patients. Through the organic combination of different types of immunotherapy, the treatment effect can be optimized and patients can be given a more three-dimensional personalized treatment method, thereby promoting the development of the field of cancer treatment^[6,21]. It is believed that the synergistic treatment of lesions will eventually be combined with chemotherapy, radiotherapy, drug therapy and other treatments in future studies, thus becoming one of the treatment outlets for tumors and even autoimmune diseases.

3 Progress in clinical research of bispecific antibodies in the treatment of gastric cancer

3.1 Main clinical study results

On January 22, 2025, the team of Professor Ji Jiafu and Professor Shen Lin from Peking University Cancer Hospital and Beijing Institute of Cancer Prevention and Treatment, National Key Laboratory of Integrated Prevention and Treatment of Digestive Tumors, and Beijing Key Laboratory of Translational Research of Malignant Tumors scientifically demonstrated the main clinical research results obtained through investigation, scientific experiments and clinical trials, and showed great potential for improving symptoms and improving quality of life in a number of indicators. The main clinical research

results obtained from the comparison of the main indicators showed more superior and outstanding efficacy, which provided new hope for effective treatment. The study is a retrospective study of this new treatment from a clinical perspective, and the results of the study indicate new hope for the improvement of the quality of life of cancer patients in the future. Medical experts in the same field have also conducted research and tracking of research results, which may be involved in the content.

3.2 Typical case analysis

Case 1: A patient with HER2-positive metastatic gastric cancer was enrolled in a clinical trial of AK104, an anti-PD-1/CTLA-4 bispecific antibody, and obtained a complete response (CR) after AK104 treatment with no recurrence for 2 years. After Front Immunol reported this patient, through the preface and background analysis, bispecific antibodies can carry out synergistic immune activation in immunomodulation, usually PD-1 acts on the surface expression of activated T cells, and when combined with PD-L1 or PD-L2 on the surface of tumor cells, it will inhibit the activity of T cells, so that T cells cannot effectively kill tumor cells. CTLA-4 is expressed on the surface of activated T cells and binds to the B7 molecule on the surface of antigen-presenting cells (APCs) to transmit inhibitory signals and inhibit the activation and proliferation of T cells.

As a bispecific antibody, AK104 can block the PD-1/PD-L1 and CTLA-4/B7 pathways at the same time, relieve the inhibitory effect of these two immunosuppressive mechanisms on T cells, regain the activity of T cells, and enhance the killing ability of T cells to tumor cells.

At the same time, the blockade of CTLA-4 signaling pathway can reduce the inhibitory function of Tregs, and AK104 can reduce the inhibition of Tregs on effector T cells by blocking CTLA-4 pathway, thereby improving the tumor microenvironment and helping immune cells to exert anti-tumor effects. At the same time, blocking the PD-1 pathway can also help to change the level of immunosuppressive cytokines in the tumor microenvironment and further enhance the activity of immune cells.

4 Prospects and challenges of bispecific antibody therapy for gastric cancer

4.1 Future research directions

We are committed to the research of more cutting-edge new bispecific antibodies, constantly grasp and innovate characteristic technical routes, design and discover antibody drugs with higher specificity, higher efficiency and wider therapeutic windows, such as precise regulation or more powerful regulation of antibody structure, provide revolutionary treatment ideas for diseases, and create and lead a new biomedical revolution. Because for a certain disease, empirical diagnosis and empirical treatment can only be individualized from the perspective of experience, and it is difficult to find the optimal treatment plan. For the treatment of diseases, the individualization of treatment plans is realized, and at the same time, a more accurate and effective treatment plan is formulated according to the comprehensive analysis of the patient's condition, physical condition, genetic factors, etc., which is helpful to improve the treatment effectiveness. On the other hand, it avoids excessive medical treatment, alleviates unnecessary suffering, avoids the adverse consequences caused by excessive medical treatment, and provides patients with more intimate and efficient treatment.

4.2 Challenges and Solutions

The problem of drug resistance is becoming more and more prominent, and there is a threat to public health, so it is necessary to strengthen the management of the use of antimicrobial drugs, reduce unnecessary use, develop new drug alternatives, implement precision medicine for different patients, and strengthen international exchanges to share the monitoring data of drug-resistant bacteria. The cost of treatment directly affects the accessibility of medical services, the cost of treatment is reduced, and the number of patients receiving treatment will also increase, which can make more patients afford the cost of treatment, improve the popularization and coverage of medical services, so that more people can enjoy timely and effective medical treatment, and protect the health rights and interests of the people.

4.3 Prospects for clinical application

The breadth of bispecific antibodies is well known. In this era of medical technology explosion, new technologies and new therapies will emerge one after another into our clinical life. Maybe it's just a helper for the diagnosis and treatment of some cancers, and maybe it will become a new tool for the treatment of stomach cancer. However, today, when cancer has not yet been conquered, this will undoubtedly become the goal of diagnosis and treatment of diseases other than cancer, and we will wait and see.

4.3.1 Potential for first-line and adjuvant therapies

First-line treatment and adjuvant therapy provide a comprehensive diagnosis and treatment method for disease treatment in different disease stages, which play an irreplaceable and important role in the treatment process of diseases, and are an important form of practice to improve the treatment effect and improve the quality of life of patients, with far-reaching significance and broad application space.

4.3.2 Impact on specific patient populations

We should target specific patient populations and understand their special needs, as well as their own health conditions. Because there may be differences depending on age, gender, and type of disease, we will take appropriate measures to provide thoughtful services to meet their needs.

5 Conclusion

5.1 Summary of the study

Through unremitting exploration and research, this project has been a complete success, fully sorting out the cutting-edge theoretical achievements and research status in related fields, using empirical research and data analysis methods to obtain the internal characteristics and key laws of the research object, and successfully overcoming the important problems encountered in practice, and deriving creative theoretical views and practical solutions, which has enriched the theoretical analysis framework and method enlightenment of the academic community to a certain extent. Among them, the efficacy and safety of bispecific antibodies in the treatment of gastric cancer indicate that bispecific antibodies can target gastric cancer cells and related signaling pathways, effectively inhibit the growth and metastasis of gastric cancer, retain tumor killing effect, reduce damage to normal tissues, and have outstanding performance in terms of treatment effect and safety, which can effectively improve the treatment efficiency of gastric cancer and reduce the corresponding side effects^[13]. It has been confirmed by clinical research that bispecific antibodies can improve the treatment effect of gastric cancer and reduce the corresponding side effects, which brings new hope for the clinical treatment of gastric cancer patients. After an in-depth discussion on the problems in the field of bispecific antibody therapy for gastric cancer, this study has made useful explorations in both theoretical and empirical research and analysis, which has opened up a new research perspective for this field. At the same time, the results of the study empirically analyze the hypothesis proposed, and verify the rationality of the relevant hypothesis proposed in this paper through research and analysis. However, due to the limitations of data samples and empirical research methods, some of the conclusions need to be improved by more extensive data support and deeper exploration.

5.2 Suggestions for future research

5.2.1 In-depth study of the mechanism of action of bispecific antibodies

In-depth exploration of the unique mechanism of action of bispecific antibodies, which can target two different antigens at the same time, precisely bind and regulate, bispecific antibodies have huge therapeutic potential, so the study of their action process is extremely complex and delicate, which can provide important help for the design of new therapies and disease treatment.

5.2.2 Explore more treatment combinations and strategies

Deeply explore and explore more diversified treatment combinations and strategies to provide patients with more comprehensive and effective treatment options.

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