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Targeted treatment of gastric cancer and its pathogenic mechanism

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Abstract. Gastric cancer (GC) is a malignant tumor with high morbidity and mortality in our country. The traditional treatment methods include operation, radiotherapy and chemotherapy. At present, it cannot be cured by traditional treatment. Targeted therapy is a treatment method for GC targeting specific targets. Currently, the main therapeutic targets developed include HER2, VEGF and EGFR. It has the advantages of less side effects and good efficacy, but it still has the defect of not fully covering the patient population. This paper mainly introduces targeted therapy of GC, an emerging treatment method, and obtains relevant information about the pathogenic mechanism and main drugs of its main targets HER2, VEGF and EGFR. By summarizing the above information, this paper hopes to provide reference for the future research of targeted therapy of GC and make contributions to the development of more new targets of GC in the future.

Keywords: Gastric cancer, targeted treatment, HER2, VEGF.

1. Introduction

GC is a malignant tumor originating from the gastric mucosal epithelium. The initial cancer cells are derived from the gastric mucosal epithelial cells. In the early stage, there are no obvious symptoms (a few patients may have mild discomfort such as distention and indigestion). In the advanced stage, abdominal pain and weight loss will occur. In the late stage, anorexia and anemia will occur, and in the end stage, severe wasting, dysthymia or cachexia will occur. GC is caused by a variety of factors, among which the most common causes include Helicobacter pylori infection, precancerous lesions, genetic factors (adverse environment) and dietary habits (unhealthy diet or irregular diet) [1].

The incidence of GC is unevenly distributed worldwide, with about 50% of new cases distributed in eastern Asia, mainly

GC is a common malignant tumor in China. The incidence of gastric cancer in men is second only to lung cancer, while in women, it ranks fourth, second only to breast cancer, lung cancer and colorectal cancer [2].

Traditional treatments for gastric cancer include surgery, chemotherapy and radiotherapy. Surgery is the main treatment method and is divided into radical gastrectomy, palliative surgery and palliative gastrectomy. Radical gastrectomy completely removes the tumor and its surrounding tissues and clears the surrounding lymph nodes in order to achieve a cure. Palliative surgery and palliative gastrectomy are mainly for patients with advanced gastric cancer, with the aim of relieving symptoms and improving

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quality of life, but they cannot completely cure the disease. Chemotherapy kills or inhibits cancer cells through drugs and can be used as an adjuvant treatment before or after surgery or as the main treatment. Radiotherapy uses high-energy rays to kill cancer cells and can be used as an adjuvant treatment before or after surgery or as the main treatment for advanced gastric cancer. Radiotherapy has fewer side effects, but its efficacy may be limited for some patients.

Although these traditional treatments can control the disease to a certain extent, their effectiveness is still limited. Data show that the median survival (MS) of gastric cancer patients receiving these treatments is still less than 1 year [3]. Therefore, further research and development of new treatments are urgently needed to improve the survival rate and quality of life of gastric cancer patients. Targeted therapy is a treatment method for specific targets of cancer cells. By using specific molecular target drugs, the mutated genes and related signaling pathways closely related to tumor survival can be regulated, so as to inhibit the growth and spread of cancer cells. In the treatment of advanced GC, targeted therapy has played a good effect and effectively filled the defects of traditional treatment methods.

Studies have shown that targeted therapy for GC has a significant effect on prolonging the survival of advanced patients, and can accurately identify and attack tumor cells containing abnormal proteins with high specificity and selectivity, so as to avoid unnecessary damage to normal cells [4].

This article will summarize the existing methods of targeted therapy for GC, in order to provide a theoretical basis for the clinical technology research of GC.

2. pathogenic mechanism

2.1. HER2

Anti-human epidermal growth factor receptor 2 (HER2) is the most clear clinical significance in current clinical studies, HER2 is a kind of HERs, which plays an important role in regulating cell proliferation, differentiation and survival [2]. It is a proto-oncogene encoded by ErbB2 on chromosome 17 [3]. HER2 protein binds to its ligands mainly by forming heterodimers with other members of the family, including EGFR (HER1 /erbB1), HER3 /erbB3, and HER4 / erbB4, and then mainly by causing receptor dimerization and autophosphorylation in the cytoplasmic tyrosine kinase region. Activation of tyrosine kinase activity [4]. Overexpression of HER2 in GC cells can form heterodimers with itself or other members of EGFR. Abnormal activation of signaling pathways in tumor cells is related to tumor occurrence, development, invasion and metastasis [5].

2.2. VEGF

Vascular endothelial growth factor (VEGF) is a homodimeric glycoprotein secreted by a variety of normal tissue cells and most tumor cells. VEGF is a specific mitogen of vascular endothelial cells, which plays a role in inducing angiogenesis. Tumor angiogenesis is a prerequisite for tumor growth. VEGF family and its receptor (VEGFR) play a key role in tumor angiogenesis, and some studies have shown that both are overexpressed in about 36%-40% of GC tissues [6]. VEGF expression is triggered by tissue hypoxia, which leads to tumor angiogenesis and promotes tumor growth and metastasis by inducing physiological and pathological angiogenesis in vivo [7].

2.3. EGFR

Epithelial growth factor receptor (EGFR), also known as ErbB receptor, belongs to the type Ⅰ tyrosine kinase receptor family and is a class of transmembrane glycoprotein receptor tyrosine kinases. It mainly includes four family members, including HER1, HER2, HER3 and HER4 [8].

EGFR signaling mainly occurs through polymerization after binding to the ligand under the stimulation of the ligand. The result of changing the protein in the form of dimer is that it leads to the activation of tyrosine kinase and the self-phosphorylation of the receptor, and then promotes cell differentiation, migration and angiogenesis through a variety of signal transduction pathways, and finally inhibits cell apoptosis [9]. EGFR is widely expressed in epidermal cells, stromal cells, some glial

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cells and smooth muscle cells. Overexpression of EGFR is often found when tumors occur. The high expression of EGFR, the promotion of tumor cell proliferation, the angiogenesis, the adhesion, the invasion and metastasis, the inhibition of tumor cell apoptosis.

The pathogenesis of GC involves multiple key molecules and signaling pathways. Among them, there are many related studies on HER2, VEGF and EGFR, and there have been clinical studies to develop targeted drugs. Targeted therapies targeting HER2, such as trastuzumab (Herceptin), have significantly improved the prognosis of patients with HER2-positive GC. The expression of VEGF is induced by tissue hypoxia and promotes tumor growth and metastasis by inducing physiological and pathological angiogenesis in vivo. Anti-VEGF treatments, such as bevacizumab (Avastin), have shown significant effects in inhibiting tumor growth, and new VEGF/VEGFR pathway blockers are also being developed. EGFR is widely expressed in epidermal cells, stromal cells, and some in glial cells and smooth muscle cells. During tumor occurrence, EGFR is often overexpressed. Highly expressed EGFR promotes tumor cell proliferation, angiogenesis, adhesion, invasion and metastasis, and inhibits tumor cell apoptosis. Drugs targeting EGFR, such as gefitinib (Iressa) and erlotinib (Tarceva), provide new options for GC treatment. In addition, the combined use of EGFR inhibitors with other anticancer drugs can improve treatment efficacy and overcome drug resistance. Therefore, the pathogenesis of GC is complex and diverse, in which HER2, VEGF and EGFR play key roles. Through in-depth understanding and research of these key molecules, new targeted drugs and treatment strategies can be continuously developed to improve the survival rate and quality of life of GC patients. This article will also discuss it further in the following sections.

3. HER2-targeted mAbs

The HER2 gene (also known as Neu or ErbB2) is located on human chromosome 17 (17q21) and encodes the membrane-penetrating glycoprotein p185. HER2 induces autophosphorylation of intracellular tyrosine residues by forming heterodimers with other ErbB family members, activating downstream signaling pathways and promoting tumor cell proliferation, invasion and migration. HER2 plays an important role in the biological behavior and pathogenesis of progression and is also an important target in the systemic treatment of progressed GC. There are two mechanisms of HER2-targeted therapy. The second type of survival, proliferation, and invasion is the induction of anti-tumor immunity through direct targeting of HER2 receptors by HER2 blockers, which triggers antibody-dependent cell-mediated cytotoxicity. HER2-targeted monoclonal antibody (mAb) therapeutic drugs and their mechanisms

MAb therapeutic drugs for HER2 target have strong anti-tumor specificity and are more effective than other targeted drugs. However, due to the large molecular weight of monoclonal antibodies, they are unable to cross the blood-brain barrier, so there are some limitations in the treatment of patients with brain metastases. The ToGA trial established trastuzumab in combination with cisplatin and fluorouracil (5-FU) as a standard treatment regimen for patients with HER2 overexpression-positive advanced gastroesophageal adenocarcinomas,It also benefitted the most from the asian group of patients with high expression of HER2 [10].

3.1. Trastuzumab

Trastuzumab is a recombinant humanized IgG1 mAb that targets the extracellular structural domain of HER2. It binds and blocks HER2-mediated cell signaling pathways with high affinity and induces antibody-dependent cytotoxicity. In the Phase III ToGA trial for patients with advanced GC, the addition of trastuzumab to a first- line chemotherapy regimen was found to prolong overall survival (OS) and progression-free survival (PFS) compared to chemotherapy alone. Trastuzumab in combination with XELOX or mFOLFOX6 has been shown to have an acceptable safety and efficacy profile in patients with HER2 overexpression-positive gastroesophageal cancer. The results of the phase III clinical randomized controlled trial (TOGA study) for patients with HER2-positive progressive gastric or gastroesophageal conjugate cancer at 3 years of follow-up showed that patients in the trastuzumab-combination-chemotherapy group had a median OS prolonged by 2.7 months compared with those in

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the chemotherapy group, with a risk ratio (HR) of 0.74, which is a slightly lower risk than that of the other agents. Although trastuzumab combined with chemotherapy has good efficacy in the treatment of HER2-positive advanced GC [11], it has not been fully popularized in China.

4. VEGR-targeted mAbs

VEGF is a specific mitogen for vascular endothelial cells, which induces angiogenesis in vivo. Tissue hypoxia triggers VEGF expression, which causes tumor neoangiogenesis, thereby promoting tumor growth and metastasis. VEGF is a homodimeric glycoprotein secreted by a variety of normal tissue cells and most tumor cells.The VEGF ligand family includes VEGF-A, VEGF-B, VEGF-C, VEGF-D and placental growth factor, and the most studied one is VEGF-A [12]. VEGF is triggered by tissue hypoxia, causing tumor neoangiogenesis, which promotes tumor growth and metastasis.

4.1. MAb therapeutic agents for VEGR targets and their mechanisms

Macrophages (TAM) are an important component of drug resistance associated with the tumor microenvironment. The receptor tyrosine kinase inhibitor sorafenib induces TAM recruitment, leading to drug resistance. As TAM is depleted, tumor cells that were initially resistant to VEGF therapy gradually regain sensitivity.

4.2. Bevacizumab

Bevacizumab is the first FDA-approved recombinant humanized IgG1 mAb targeting VEGF-A. It can block the activation of tyrosine kinase signaling pathway by inhibiting the binding of VEGF to VEGFR. Bevacizumab is the first recombinant humanized monoclonal IgGl antibody targeting VEGF, which can inhibit tumor angiogenesis and inhibit tumor metastasis. Research results show that bevacizumab can inhibit the proliferation of SGC-7901 cells in human GC and induce apoptosis. Bevacizumab combined with conventional chemotherapy in GC patients can significantly improve the therapeutic effect, prolong the survival period, and is well tolerated [13].

4.3. Ranibizumab

Ranibizumab is a recombinant humanized IgG1 mAb. body, can specifically bind to and block the activation of VEGFR 2, inhibiting tumor angiogenesis [14]. At present, ramorubicin has been approved by the U.S. Food and Drug Administration. Anti has been approved by the FDA for second-line treatment of GC, non-small cell lung cancer and colorectal cancers.

Table 1. Comparative Analysis

	HER2-Targeted Therapy	VEGF-Targeted Therapy
Primary Target	HER2 receptor on tumor cells	VEGF ligand promoting angiogenesis
Main Drugs	Trastuzumab	Bevacizumab, Ranibizumab
Mechanism	Blocks HER2 signaling and induces ADCC	Inhibits VEGF interaction with VEGFR, reducing angiogenesis
Clinical Outcomes	Improved OS and PFS; median OS extended by 2.7 months in ToGA trial	Enhances therapeutic effect and prolongs survival in combination with chemotherapy
Limitations	Ineffective for brain metastases due to large molecular weight	Potential resistance due to tumor-associated macrophages (TAM)

As shown in table 1, HER2 and VEGF-targeted mAbs have revolutionized the treatment of advanced gastric cancer by improving patient outcomes and offering more personalized therapy options. HER2-targeted therapies, such as trastuzumab, specifically inhibit tumor cell proliferation through HER2 blockade and ADCC induction. VEGF-targeted therapies, like bevacizumab and ranibizumab, inhibit angiogenesis and tumor growth by blocking the VEGF pathway. While both therapeutic approaches have shown significant clinical benefits, they also face limitations, including issues with drug resistance and limited efficacy in brain metastases. Small molecule TKIs present additional therapeutic options but require further clinical validation.

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5. Other drugs

Small molecule tyrosine kinase inhibitors, such as apatinib, are a novel targeted anti- VEGFR-2 drug. Apatinib significantly prolonged median OS and PFS in patients with advanced GC, according to a phase III clinical trial.In October 2014, apatinib was approved by the State Food and Drug Administration (SFDA) for the treatment of metastatic GC or adenocarcinoma of the gastroesophageal junction that has progressed after second-line chemotherapy. Sunitinib is an oral small molecule tyrosine kinase inhibitor that blocks the kinase structural domains of VEGF and PDGFR. In addition, targeted drugs against VEGF, such as sorafenib, exist, but their clinical efficacy needs to be verified in further randomized controlled trials.

6. Conclusion

This study reviewed the current major advances and clinical applications of targeted therapies for GC. By analyzing the roles of HER2 monoclonal antibodies (e.g., trastuzumab) and small-molecule tyrosine kinase inhibitors (e.g., apatinib, sunitinib) in the treatment of advanced GC, we found that targeted therapies significantly prolonged the OS and PFS of the patients, and provided a new therapeutic option for patients with advanced GC. However, targeted therapies also have certain limitations. For example, HER2-targeted drugs have limited therapeutic effects on brain metastases due to their large molecular weight and inability to cross the blood-brain barrier. In addition, targeted therapies may raise side effects and drug resistance issues, which affect the therapeutic efficacy. Existing clinical trials also have limitations in terms of sample size and trial design, which require further validation and consolidation of the results through randomized controlled trials with larger scale and long-term follow-up. Future research directions should focus on the development of novel targeted agents to overcome the limitations of existing drugs. In summary, although targeted therapy for GC still faces some challenges, it demonstrates great potential in improving patients' quality of life and prolonging survival. Through continuous research and clinical trials, we are expected to further optimize treatment options and promote the development of targeted therapy for GC, bringing more hope and well-being to patients.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order

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