

# Progress in the Design of Molecular Targeted Drugs for Gastric Cancer

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**Abstract:** Gastric cancer is one of the most common cancers in China, and its pathogenesis is related to many molecular signaling pathways and related factors. The more critical molecular pathways include MET pathway, PI3K / AKT pathway, and MAPK pathway. In addition, the EGFR family and factors related to tumor angiogenesis are also important factors, which are closely related to tumor cell proliferation, apoptosis, and metastasis. The results of the study will provide new ideas and methods for the treatment of gastric cancer and lay the groundwork for the development of new gastric cancer drugs. On this basis, a variety of molecular targeted drugs have entered the clinical trial stage, among which, trastuzumab and apatinib have shown good efficacy. This paper summarizes the molecular pathogenesis of gastric cancer, and summarizes the mechanism of action, combination chemotherapy and research progress of trastuzumab and apatinib, so as to provide reference for future research on targeted therapy for gastric cancer.

**Keywords:** Molecular Targeted Drug; Trastuzumab Apatinib; Gastric Cancer Treatment.

## 1. Foreword

Gastric cancer ranks fifth in the world and is a major cause of cancer-related death.[1] In China, gastric cancer ranks the second place in men and the fourth place in the incidence of systemic malignant tumors in women. Moreover, the clinical manifestations of early gastric cancer are not very good, so many people find out that it is already intermediate and advanced. [2]Gastric cancer seriously threatens people's life and health. With the development of molecular biology, molecular-targeted drugs have become a major research hotspot in recent years. Trastuzumab is a targeted drug that can inhibit tumor cell proliferation by blocking the synthesis of HER 2 protein. [3]It is the best clinically effective and most widely used targeted drug for anti-Her-2 targeted therapy in gastric cancer. Apatinib is one of the targeted drugs for the treatment of advanced gastric cancer, and the clinical results show that the combination of apatinib can achieve better therapeutic results.

## 2. Molecular Mechanisms Involved in the Formation of Gastric Cancer

### 2.1. The Epidermal Growth Factor Receptor Family

#### 2.1.1. HER1/EGFR

The epidermal growth factor receptor (EGFR) is a signaling molecule widely present in cell membranes, such as epithelial cells, glial cells, and keratinocytes, which are expressed in many cell types, and their expression levels are regulated by a variety of signaling pathways. EGFR is a receptor widely present on a variety of tumor cells and plays an important role in tumor growth, proliferation, and differentiation. This is a receptor localized to the cell membrane and can be produced by binding to this receptor and converting from a single receptor to a dimer. EGFR dimerization is a ubiquitous phenomenon, and its primary mechanism is to activate signaling pathways such as MAPK

and AKT, and then regulate downstream signaling pathways. MAPK and AKT are key pathways that regulate cell growth, proliferation and survival.

#### 2.1.2. HER2/ErbB2

The HER2 gene is located on chromosome 17, its encoded protein is located in the cell membrane, its structure is similar to EGFR, and its intracellular segment also has tyrosine kinase protein activity. Among them, HER2 does not bind to EGFR, HER1/erbB1, HER3/erbB3/erbB4 and other proteins, thereby activating the MAPK/PIK3/AKT signaling pathway. HER2 is a very promising marker for prognosis in cancer patients and a very promising targeted therapy drug for cancer.

### 2.2. Tumor Neovascularization-related Factors

Vascular endothelial growth factor (VEGF), also known as vascular perception factor (VPF), is a prevascular growth factor with high specificity, which can improve blood vessel permeability, degenerate NDE, and cause ES to migrate, proliferate, and neovascularize. Vascular endothelial growth factor is a family that includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor (PGF).[4]

Among the known cytokines, VEGF has the strongest influence on tumor angiogenesis, mainly because VEGF can increase vascular permeability and promote cell proliferation and metastasis. In the study of early cancer and advanced gastric cancer patients, we found that VEGF-positive patients had larger tumor volume, deep invasion, high degree of metastasis, late clinical stage, short survival, and VEGF expression level is an independent risk factor for prognosis and liver metastasis in gastric cancer patients.

### 2.3. Other Pathways

#### 2.3.1. MET Thoroughfare

C-Met (cellin-mesenchymal transforming factors, referred to as cell interterminal transcription factor), is a receptor protein belonging to the tyrosine kinase. The c-Met signaling pathway is a key molecule that regulates embryonic development and tissue regeneration. Studies have shown that the C-Met pathway has abnormalities or mutations in various solid

tumors such as lung cancer, gastric cancer, liver cancer, breast cancer, skin cancer, colorectal cancer, etc.

Hepatocyte growth factor (HGF) can bind specifically to it, promote the phosphorylation of receptor protein tyrosine residues, and activate the cellular HGF / MET signaling pathway. The activation of HGF/MET signaling pathway can induce biological effects including cell proliferation, transformation, inhibition of apoptosis, metastasis, and angiogenesis.

### 2.3.2. The PI3K / AKT Pathway

PI3K-AKT signaling pathway is an important way to respond to external stimuli and promote cellular energy metabolism, cell proliferation, cell survival, growth and angiogenesis. This process is accomplished by phosphorylation of a series of substrates with serine or threonine as the main body. In this process, PI3K and AKT/pull-down are two important regulatory genes. From this, we took two genes of the PI3K-AKT signaling pathway as the source of its name. Phosphatidylinositol 3-kinase/protein kinases (PI3K) is an important intracellular protein involved in the regulation of angiogenesis. PI3K $\alpha$  binds to its receptor Tyrosine kinases (TK) to activate the protein, which mediates phosphorylation of members of the phosphatidylinositol 3-kinase (PI3K) family. They are also involved in multiple signal transduction pathways, including PDK 1 and AKT. Activated AKT can regulate cell functions through phosphorylation of various downstream factors, promote gastric cancer cell proliferation, inhibit its apoptosis, promote tumor angiogenesis, and promote gastric cancer resistance to chemoradiation chemotherapy.

### 2.3.3. MAPK Thoroughfare

Mitogen-activated protein kinase (MAPK) is an important signaling pathway, which includes MAPK, MKK and MAPK kinase three signaling processes. Three protein kinases are activated sequentially to synergistically regulate multiple physiological/pathological processes, such as cell growth, differentiation, stress, and inflammation. Although the MAPK pathway is one of the important pathways in gastric carcinogenesis, due to its own complexity, drugs targeting this pathway have not made great progress, and drugs truly entering clinical trials are relatively rare. Therefore, this article will not be described too much here.

## 3. Trastuzumab Treatment for Gastric Cancer

At present, targeted drugs are mostly used to treat HER 2 positive advanced gastric cancer. Trastuzumab (Trastuzumab) is a monoclonal antibody that binds to HER2 and inhibits its binding to the HER2 receptor (HER2). It acts as a kind of "firewall", preventing the binding of human EGF and tumor cells, which in turn prevents the growth of tumor cells. In addition, Trastuzumab can also activate autoimmune cells in the body, thereby destroying cancer cells, and trastuzumab prevents tumor cell proliferation by blocking the synthesis of the HER 2 protein.

### 3.1. Mechanism of Action

Trastuzumab is a monoclonal antibody against the outer membrane portion of the HER 2 receptor, which binds to block the downstream phosphatidylinositol (phosphatidylinositol3-kinase) PI3K / AKT and Ras / MEK tumor cell signaling, thus exerting an anti-tumor effect.[5] Herceptin (trastuzumab for injection) can be used either

intravenous or intramuscularly to treat certain types of cancer, including breast and gastric cancer. At present, Herceptin (Herceptin) is widely used in the treatment of HER 2-positive gastric cancer, and it has achieved a very good efficacy in this regard.

## 3.2. Recent Advances in the Diagnosis and Treatment of HER 2-positive Gastric Cancer: The Post-ToGA Era of Trastuzumab

In the ToGA trial, a preliminary comparative study of the monoclonal antibody trastuzumab (CTX042) and HER2+HER2 cisplatin 5-Fu+ (5-Fu+ cisplatin) was conducted for the first time. Our previous study found that after combining the two regimens, both regimens achieved good efficacy, reaching 57.6%, 7.7 weeks, and 10.8 weeks, respectively, and progression-free survival and overall survival of 8.9 months and 16.6 months, respectively. [6] This experiment was only performed in the chemotherapy group (group CTX042). In the treatment of HER2+ gastric cancer, the use of trastuzumab suggests that there may be more opportunities to use trastuzumab, because its greatest advantage is that its treatment of HER2+ gastric cancer is more mature, and physicians should consider its use from more dimensions. In addition, paclitaxel is often used as a second-line drug against HER2+ gastric cancer. Trastuzumab may also be used in combination with chemotherapy as a treatment regimen.

## 4. Apatinib for Gastric Cancer

### 4.1. Mechanism of Action

Apatinib is a novel small-molecule tyrosine kinase inhibitor with its highly selective competitive binding to the ATP binding site of VEGFR-2 in cells, is able to block downstream signaling and thereby inhibit tumor angiogenesis. The results showed that the expression rate of VEGFR was as high as 36% in all gastric cancer patients studied. [7] This result shows that VEGFR plays an important role in gastric cancer patients, and may affect the development of the disease and the treatment effect of gastric cancer patients through different mechanisms. Therefore, the development of antitumor drugs targeting VEGFR and VEGFR is currently a hot spot in the treatment of gastric cancer. As a new type of antitumor drug, Apatinib has shown good results in the clinical application of gastric cancer by inhibiting tumor neovascularization, and has been applied clinically gradually.

### 4.2. Apatinib Monotherapy and Combination Therapy

Many studies have shown that apatinib can be treated as a main drug or as a combined adjuvant drug in the clinical treatment of gastric cancer, with good efficacy. Apatinib is the first small molecule antiangiogenic targeted drug proved safe and effective after failing standard chemotherapy for advanced gastric cancer; the only oral formulation of gastric cancer targeting drug is easy to apply and has good patient compliance; apatinib provides new preferred drugs and treatment options for patients after failing standard chemotherapy for gastric cancer.

Phase III clinical trials have shown that apatinib is a third-line therapy with higher survival rates than chemotherapy. Therefore, as a new type of anti-tumor drug, Apatinib will

provide more clinical possibilities for its clinical application. Therefore, apatinib is expected to become the preferred chemotherapy drug for patients with intermediate and advanced gastric cancer. Zhang et al [8] conducted a study on the application of apatinib in second-line therapy, and the results showed that apatinib has significant efficacy in second-line combination chemotherapy, but the experimental sample was insufficient, so further research and discussion are still needed combined with the results of clinical trials. Apatinib can be combined with Targeol as the first-line treatment regimen for advanced gastric cancer, and similarly, the relevant clinical studies are still in the exploratory stage and are rarely reported.

Regarding the combination treatment of apatinib, Wang Lei et al. used the combination treatment regimen of apatinib and docetaxel to study and explore the effect of apatinib combination treatment in the second-line treatment of advanced gastric cancer. The results showed that it could effectively improve the disease control rate. In addition, the combination of apatinib and Tigo and trastuzumab has also achieved good results.

## 5. Conclusion and Outlook

The pathogenesis of gastric cancer is a complex pathological process, which involves many molecular signaling pathways and growth factors. With the in-depth research of molecular biology and other related fields, more and more molecules are found to have the potential as tumor markers of gastric cancer, which has laid a theoretical foundation for the design of molecular targeted drugs for gastric cancer. Despite the many factors associated with gastric cancer, the current study has not identified many factors that play a decisive role in the targeted therapy of gastric cancer due to the complexity of most signaling pathways. Among them, trastuzumab is the drug of choice for the treatment of patients with HER 2-overexpressing gastric cancer. Moreover, many studies have shown that apatinib can be used as a combination adjuvant or primary drug in the clinical treatment of gastric cancer with good results.

Trastuzumab combined with different chemotherapy options has achieved outstanding efficacy in both first-line and second-line treatments and cross-line treatments. Therefore, in the future research field, trastuzumab will promote advanced gastric cancer in future fields. A new idea to improve the therapeutic efficacy of HER 2, namely the synergistic effect of trastuzumab in combination with other targeted agents, was proposed.

At present, apatinib, as the main treatment drug, is widely used in the treatment of advanced gastric cancer patients, and it is also used as an adjuvant drug with chemotherapy drugs such as giiio or paclitaxel. However, a large number of clinical trials are still needed for the selection of combination chemotherapy drugs that can achieve the best efficacy, whether apatinib for second-line therapy can achieve better efficacy, and how to improve drug tolerance.

At the same time, the new antibody-drug conjugation system combines the high specificity of the monoclonal antibody with the high activity of small molecules, which is

expected to achieve more efficient anticancer effects, greater targeted therapeutic effects and fewer toxic side effects. Compared to conventional all-in-one or semi-humanized antibodies, ADCs are more specific and can enter the tumor efficiently. Compared with conventional fusion proteins, the detection of ADC drugs is simpler and more accurate, and due to its special structure and selectivity for tumor cells, it can greatly enhance the therapeutic effect and reduce toxic side effects. ADC drugs have attracted a lot of attention from researchers because of their advantages of significantly improving efficacy and reducing toxic side effects. Sichuan Tianheng Pharmaceutical and SystImmune (SystImmune) jointly announced that the U.S. FDA has approved a new drug (BL-B01D1) for the treatment of metastatic or inoperable NSCLC.

BL-B01D1 is the world's first EGFR x HER3 dual anti-ADC drug independently developed by the company, and the first drug approved by the NMPA on the ADC drug pipeline. It can be seen that ADC drugs have great potential, and the future deepening research on new antibody forms, delivery systems, non-internalized antigen targets, and new cytotoxic drugs can promote the development of ADC drugs.

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