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Mechanism for treatment of gastric cancer: indirect comparison of trastuzumab and apatinib

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Abstract:

Gastric cancer is the fifth most prevalent type of cancer globally. It is the third leading cause of cancer-related mortality worldwide. Gastroscopy serves as a dependable foundation for the medical professional's diagnostic process. And a biopsy is more accurate. A medical professional utilizes CT, endoscopic ultrasound, PET, and laparoscopy to ascertain the stage of gastric carcinoma. As a disease with macromolecular and phenotypic heterogeneity, the main treatment for gastric cancer in its early stage is endoscopic resection. Advanced gastric cancer is commonly managed through sequential regimens of chemotherapy, initiated with a first-line treatment cocktail comprising platinum and fluorouracil. Targeted therapies approved for the treatment of gastric cancer include trastuzumab (first-line human epidermal growth factor receptor type 2 (HER2) positive patients), Apatinib (oral small molecule vascular endothelial growth factor receptor 2 (VEGFR2) inhibitor), Lamuzumab (anti-angiogenesis second-line), and nivolumab or pembrolizumab (anti-PD-1 third-line). Therapeutic modalities approved for the management of gastric cancer encompass trastuzumab (as a first-line agent for patients with human epidermal growth factor receptor type 2 (HER2)-positive status), Apatinib (an oral small-molecule inhibitor of vascular endothelial growth factor receptor 2 (VEGFR2), Lamuzumab (an anti-angiogenic agent for second-line therapy), and nivolumab or pembrolizumab (as third-line treatments targeting programmed cell death protein 1 (PD-1)). This article reviews the mechanism of action, clinical application and safety of apatinib and trastuzumab. Complexity, diversity of cancer and effect, safety of using drugs make the combination of drugs in trend.

Keywords: Trastuzumab, apatinib, targeted therapies, drug combination, gastric cancer

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1. Introduction

Presently, there is a notable increase in the incidence of gastric cancer, with over one million new cases being diagnosed annually. It ranks as the world's fifth most prevalent malignant tumor [1]. Advanced stages of gastric cancer bear a high mortality rate, ranking among the top three leading causes of cancer-related mortality [2]. Most patients are diagnosed when the cancer has been metastatic. The situation makes the treatment of cancer more difficult. In the early stages of cancer (stage 1), operation is the most useful way for treatment, but only limited to treatment in a small area. Radiation therapy can cure cancer and reduce recurrence, but other healthy cells, tissues and organs can be destroyed [3]. For chemotherapy, they truly reduce the morbidity and mortality of patients. As well as radiation therapy, almost every drug of therapy does harm to the original cells, especially fast-growing cells like hair and fingernails. Side effects cannot be ignored [4, 5]. Occasionally, following chemotherapy, cancer cells that were initially subdued by the medication develop resistance to it. Subsequent recurrence precludes curative re-treatment. These are all the limitations of traditional therapy for cancer.

Targeted therapies work as a new way for treatment of cancer which was used around the 1990s. They can act on the specific cancer cell (target) to prevent the growth, separate of cancer cells. The target may be a protein molecule inside the tumor cells or a gene segment. Therapeutic agents within the realm of targeted therapy encompass monoclonal antibodies and small molecule inhibitors. This kind of therapy shows many benefits. The most important thing is that it can deliver drugs in a very efficient way and have less toxicity [6]. And they can be done more times and used in a larger area (in later stage), since the cancer cells have already spread to other organs. Thus, targeted-treatment can efficiently increase living time of patients. Currently in China, two approved targeted therapies, trastuzumab and Apatinib, are available. Globally, other targeted drugs such as ramucirumab and pembrolizumab are also utilized. Trastuzumab, a recombinant humanized IgG1 monoclonal antibody, targets the extracellular domain of human epidermal growth factor receptor type 2 (HER2). In one trial of patients with advanced gastric cancer treated with trastuzumab, overall survival (OS) improved by 2.7 months compared to chemotherapy alone [7]. In other patients with metastatic gastric cancer, apatinib is also a better option. Apatinib is a small molecule tyrosine kinase inhibitor. It selectively inhibits vascular endothelial growth factor receptor-2 (VEGFR2)and inhibits tumor angiogenesis by blocking its downstream signaling [8]. Studies have shown that apatinib has better safety, tolerability and treatment efficacy.

The current review comprehensively summarizes the pertinent literature and scholarly conference proceedings pertaining to the therapeutics of trastuzumab and apatinib within the context of gastric cancer, encompassing both preclinical and clinical research domains. It delineates the criteria for selecting superior targeted therapeutics and explores the potential of drug combinations under varied clinical scenarios, aiming to optimize therapeutic outcomes. Consequently, these findings are anticipated to extend the therapeutic utility for patients with advanced gastric cancer, while ensuring acceptable levels of toxicity with manageable side effects.

2. Research progress of trastuzumab and apatinib

Since 1975, with the advent of hybridoma technology and the production of monoclonal antibodies, a multitude of researchers have dedicated extensive focus to the implementation of antibody-targeted therapies for the treatment of cancer patients. Trastuzumab and apatinib are now a wider application and used as targeted therapy for advanced gastric cancer.

2.1 Mechanism of trastuzumab

Trastuzumab monoclonal antibody is a kind of humanization monoclonal antibody, it can choose to act on cytoplasm of HER2-positive cells, and reduce its activity, then inhibit the growth of tumors. Trastuzumab monoclonal antibody was originally developed to treat breast cancer. It found that 25-30% of primary breast cancer patients show HER2 positive. HER2 overexpression is found not only in breast cancer, but also in some ovarian cancer, gastric cancer, metrocarcinoma and biliary tract cancer. Highly expressed tumors show strong transfer ability and infiltration ability. They show poor sensitivity to chemotherapy, prone to recurrence. Combination chemotherapy is also effective for metastatic breast cancer [9]. Use antibodies to treat cancer needs to act to specific receptors on the cancer cell. This receptor is HER2 in breast cancer. Use of trastuzumab as a targeted drug was one of the earliest methods to treat metastatic breast cancer which HER2 tested positive [10].

However, gene amplification and product overexpression of HER2 also exist in gastric cancer. Advanced gastric adenocarcinoma and gastroesophageal junctional cancer demonstrate a higher prevalence of positivity in the latter. Trastuzumab has been validated as a primary therapeutic modality for the treatment of gastric adenocarcinoma [11].

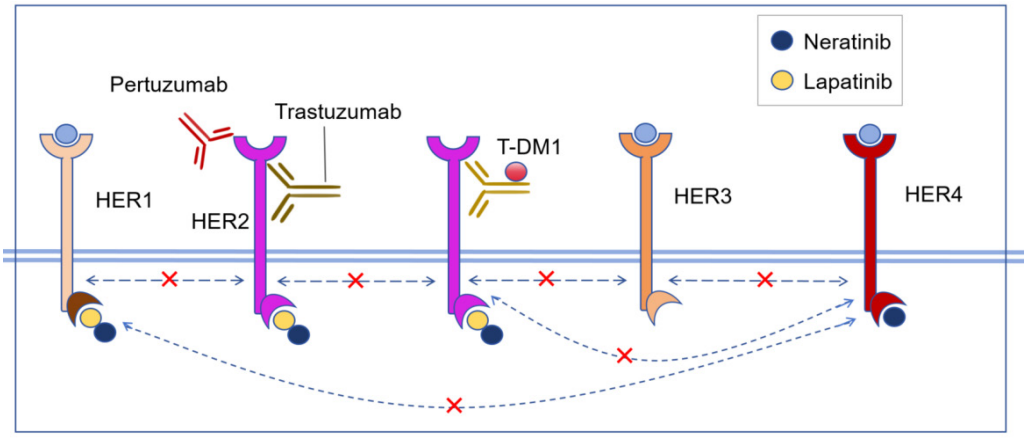

Fig 1. The mechanism of targeted drugs which point to HER2. *Reproduced from Pharnexcloud. Copyright Yao Rong Yun Digital Technology (Chengdu) Co., Ltd.* Different kinds of receptor of HER need to be inhibited with different inhibitors though they have similar structure. Cells with overexpression of HER2 can also be killed by antibodies, like pertuzumab and trastuzumab, but the binding site shows different. Antibodies can act at the same time [12].

HER2 belongs to the HER family, which includes HER1, HER2, HER3 and HER4, they can combine with other receptors and form a group. This group of receptor form heterodimers, they interact with different kinds of ligands to stimulate the transfer of signal through the cell. And the mechanism of trastuzumab drug is to downregulation HER2 protein, preventing the formation of heterodimer which contain HER2, preventing incision of HER2, inhibit production of blood vessel and induction of immunity mechanism [13]. This drug can be treated alone or combined with chemotherapy as auxiliary.

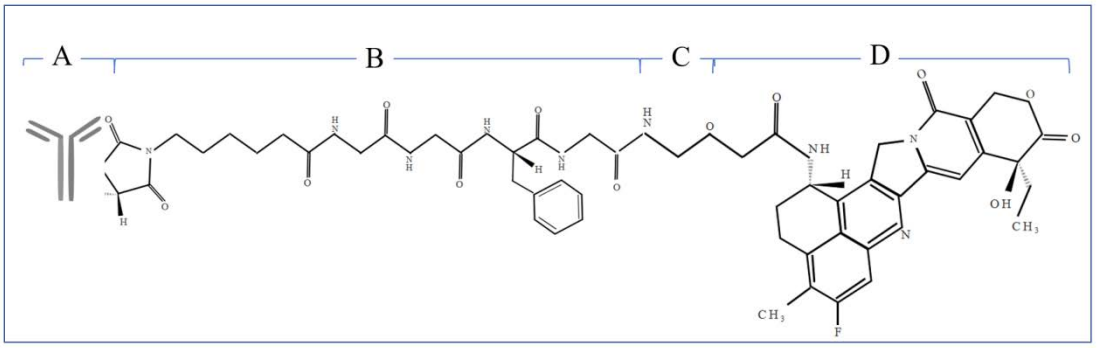

Fig 2. The mechanism of trastuzumab deruxtecan (T-DXd). T-DXd serves as an antibody-conjugated therapeutic agent, including antibody as the main part (A), linker (B), self-immolativeregion (C), and payload DX-8951f derivative DXd (D). All of these four parts decide the effects of the drug. *Reproduced from [14]. Copyright 2024, Elsevier B.V.*

In order to treat cancer better, people combine chemotherapy drugs with targeted therapy drugs. This kind of drug is called antibody-drug conjugate (ADC). An ADC consists of a monoclonal antibody conjugated with a small-molecule cytotoxin through a chemical linker. This combination harnesses the targeting ability of monoclonal antibody therapeutics and the high potency of small molecule toxins, enhancing the efficacy and specificity of anti-cancer treatments. Trastuzumab deruxtecan is this kind of drug. T-DXd plays its effects relying on trastuzumab recognizing HER2-expressing tumor cells, and then enters the cells through endocytosis and pinocytosis. The linker is degraded by lysosome enzymes, releasing the payload topoisomerase I inhibitor exatecan derivative, thus imparts cytotoxic effect towards tumor cells [14]. The antibody part of T-DXd is trastuzumab monoclonal antibody, which can recognize tumor antigens and guide effector molecules to target cells. The main body of linker is built up by glycyl-glycyl-phenylalanyl glycyl, which offer stability to plasma of ADC and avoid the toxic act on other cells, make sure of the high efficiency.

Moreover, there is self-immolative region between anti-

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bodies and effector molecules, it can hydrolysis rapidly in acid condition inside the tumor, and release effector molecules, kill the cells around. In conclusion, trastuzumab and antibody conjugate drugs are used in treating breast cancer. They show anti-HER2 receptors, so the structure of drugs may be similar to the drug which treats gastric cancer. They are the same mechanism. In the drug antibody part can identify the protein (antigen) of tumor, then let payload reach target cell.

Trastuzumab monoclonal antibody is chiefly used in treating HER2-positive metastatic gastric adenocarcinoma or adenocarcinoma of gastroesophageal junction. Experiments show that most drugs which can target against HER2 in breast cancer do not show effect in gastric cancer, except trastuzumab. But the experiment also shows that there are side effects for the treatment, like Myelosuppression and interstitial lung disease [15]. And using trastuzumab for treatment still needs a lot of tests and research.

2.2 Mechanism of apatinib

Apatinib is a kind of highly VEGFR2 inhibitors of styrosine kinase, which can prevent tumor vessel from producing and transferation. The main mechanism of this inhibitor is to competitive binding with tyrosine ATP binding site, act as a competitive inhibitor. It can highly selective inhibit the activatity of VEGFR2. The affinity of apatinib to VEGFR2 is higher than most of other drugs. Through decreasing cellular glutathione levels and increasing lipid peroxidation levels, it can cause induced ferroptosis in gastric cancer cells. Apatinib can induce glutathione peroxidase-mediated lipid peroxidation, then lead to the multi-drug resistant cancer cell ferroptosis. Moreover, apatinib can also inhibit translation of glutathione peroxidase [16].

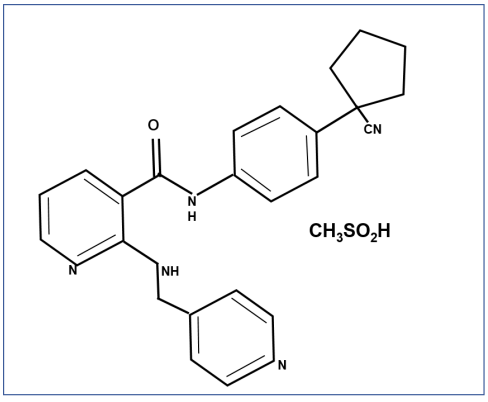

Fig 3. The chemical molecular structure of Apatinib Mesylate.

Apatinib Mesylate molecule formula is C24H23N5O·CH4SO3. The drug is used to treat the patients which at lease accept 2 kinds of systemic chemotherapy then recurrent advanced gastric adenocarcinoma or adenocarcinoma of the gastroesophageal junction.

In past research, VEGF and VEGFR are involved in tumor progression and metastasis, and they could be therapeutic targets [17-19]. In Fig 4, the mechanism of drug is shown clearly. Apatinib is a new type of antiangiogenic drugs. It is the first drug that has been proved effective and safe after failing in standard chemotherapy of advanced gastric cancer from all over the world. The downstream consequences of VEGFR2 activation within the vascular endothelium encompass cell proliferation, migration, permeability, and survival. Apatinib acts through bind to the receptor (antigen), VEGFR to inhibit VEGF, which is a competitive inhibitor to lower the rate of substrate. Then inhibit phosphorylation of VEGFR to make tumor cells lose its function. Apatinib can be used to treat gallbladder carcinoma, advanced breast cancer, advanced liver cancer, advanced non-small cell lung cancer, advanced ovarian carcinoma, especially used to treat advanced gastric cancer. From a control experiment in the hospital of the university, the rate of controlling of disease of patients who accept treatment by apatinib mesylate is 51.06%, objective remission rate is 6.38%, effect of treatment is significant.

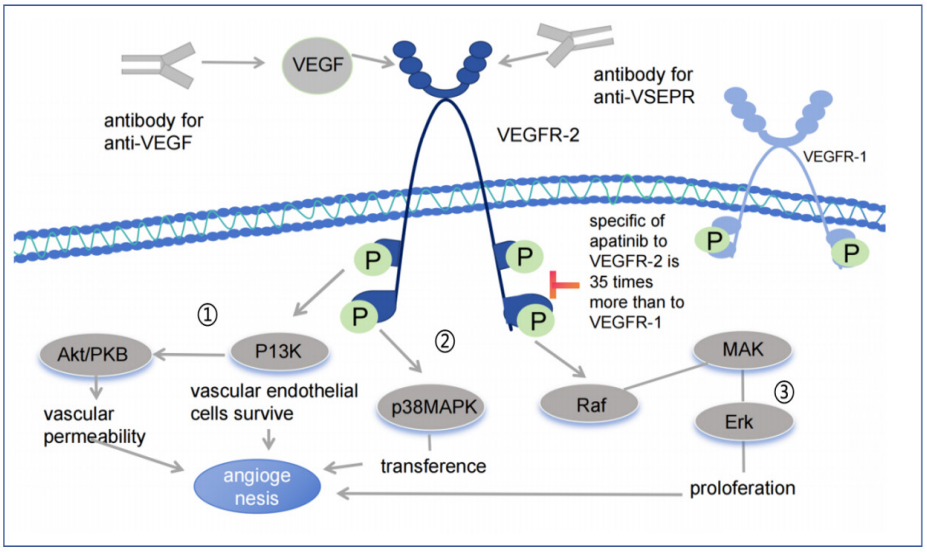

Fig 4. The mechanism of apatinib which points to VEGFR2. Reproduced from [20]. Copyright 2005, Springer Nature. ① P13K-Akt/PKB signal pathway. PI3K produces phosphorylated tyrosine residue when be stimulated, then provide anchor point by PI3K, then complete downstream signaling. ② VEGF-p38/ MAPK signal pathway. Apatinib can inhibit the formation of neovascularization and to enhance the apoptosis of rat non-small cell lung cancer (NSCLC) by modulating the VEGF/MAPK/NF-kB signaling pathway [19]. ③ RAF-MEK-ERK signal pathway. The molecule transmits extracellular signals across the cell membrane receptors, thereby mediating the expression of cellular all oproteins and participating in the regulation of cellular processes such as proliferation, differentiation, apoptosis, autophagy, and other malfunctions [21].

2.2 Side effects of trastuzumab and apatinib

Both trastuzumab and apatinib are employed in the clinical management of cancerous conditions. As research into the etiology of cancer progresses, targeted therapies for gastric cancer are demonstrating enhanced efficacy. To HER2-positive gastric cancer, the group trastuzumab monoclonal antibody combined with chemotherapy has more survival benefit than pure chemotherapy group, total time of survival can extent to 13.8 months. In the topic of difference between trastuzumab and apatinib used in treating cancer. However, they still have many side effects, trastuzumab cause heart problems, do harm to the digestive system, respiratory system, and adverse reactions of the lymphatic system and skin problem.

To prove the side effects of trastuzumab, it found the drug will decrease the function of contraction of left ventricle. Cardiac failure sometimes shows in the patients who accept the treatment of the drug. In one experiment, researchers compared rats given trastuzumab with rats given the same amount of saline. They observed the apoptosis of myocardial cells in rats. The data indicate that the ratio of the number of apoptosis-positive nuclei and total myocardial nuclei is higher in observation group (48.15 ± 7.37) %, lower in control group (31.29 ± 5.38) %, which proves that the drug can lead to apoptosis of myocardium cell [22].

Apatinib may lead to high blood pressure, proteinuria gastrointestinal reaction, and hind-foot syndrome, canker sore. Because cancer cells have different kinds of receptors, using more than one drug to act on different receptors can increase the efficiency of the treatment of cancer (including the inhibit of growth and killing of cancer cells). The combination of different drugs shows important effects. Before making sure of the combination of different drugs, the research of whether the side effects can be increased is important, because the safety of drugs is the first.

3. Combination of trastuzumab and apatinib

The treatment duration for gastric cancer extends over an extended period, so basic chemotherapy regimens can show drug resistance occurs easily, and antineoplastic drugs can produce immunity inhibit when killing the cancer cells, reduce body resistance, which leads to series ad-

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verse reaction, make worse effect. As the technology has developed, more tumor markers have been discovered, including HER2, MET, TP53, PD-1, CTCs, cfDNAs, miRNAs, exo-some and VEGFR2, etc. This provides a new way to diagnose and treat gastric cancer. Some patients have two or more tumor markers detected at the same time. To find effective ways of combination of using drugs is meaningful.

By searching literature, we know that the research about the combination of trastuzumab and pertuzumab is relatively much more. Pertuzumab has a similar mechanism with trastuzumab, and it can bring to the different position of the receptor of HER2. Both of them belong to the monoclonal antibody part. They show good success in treating cancer. Trastuzumab combined with chemotherapy and radiotherapy is also common for cancer treatment. Some researchers also research the combined utilization of trastuzumab with docetaxel, pyrotinib, cis-platinum, lapatinib, piper sillie and so on [23, 24]. There are also examples of other different kinds of combination of medicine, including “bevacizumab and atezolizumab”, “lenvatinib and pembrolizumab”, “apatinib and camrelizumab”, which use two monoclonal antibodies together, and both of them combine inhibitor and monoclonal antibodies. In China, some researchers combine trastuzumab with Chinese medicine. Like some active parts of radix sophorae flavescentis, astragalus can help treat cancer. Some articles also show that taxol, which is derived from taxus, can be used to treat cancer combined with trastuzumab monoclonal antibody. These attempts proved effective in treatment. At present, the introduction of combining trastuzumab and apatinib is not enough. We have two results of research in Jiujiang and Heze (two cities of China).

3.1 Experiments of drug combination

Trastuzumab monoclonal antibody is antibody to anti-HER2, can inhibit the growth of tumor by preventing human epidermal growth factor combine with HER2. Apatinib is novel tyrosine kinase inhibitors which found in recent years, specific act on VEGFR2, inhibit the production of new blood vessel of cancer cell, can also reverse P-glycoprotein-mediated tumor resistance.

One experiment in a medical specialty university of He ze (a city of China) showed that apatinib combined with trastuzumab can have better effect than using a single one in inhibition of cell proliferation and promotion of apoptosis. The reason may use trastuzumab alone to inhibit HER2 may not work enough to control vascular growth factor mediates blood vessels, and it leads to the activation of angiogenic alternative pathways. When combining the two drugs together, can increase the inhibit effect efficiently, accelerate the death of gastric cancer cells [25]. According to a hospital in Jiu jiang (a city of China), a research called the effects when trastuzumab monoclonal antibodies combine with apatinib to serum tumor marker levels and quality of life. Which aims at 84 patients with gastric cancer. The researchers divided 84 gastric cancer patients into two groups, A and B, with 42 people in each group. Group A was administered trastuzumab, whereas Group B received a combination therapy involving trastuzumab in conjunction with apatinib. The experiment was concluded by comparing the serum tumor marker level, quality of life score and the occurrence of adverse reactions between the two groups. The researchers found that after treatment, serum tumor marker levels in group B were lower than those in group A, and quality of life scores were higher than those in group A. The incidence of adverse reactions in group B was 4.76%, lower than 21.43% in group A [26]. This proves that trastuzumab combined with apatinib is effective in the treatment of gastric cancer.

Because of the lack of research of combining trastuzumab monoclonal antibody and apatinib. It still has more space for research. Researchers may give discussion of the complementary of the mechanism of the two drugs. The perfect treatment plan of treatment and nurse after treatment is worth more research.

4. Expectation of therapy of targeted medicine

Although the utilization of selective pharmacological interventions for cancer treatment harbors numerous benefits, it currently resides in an exploratory phase within the clinical spectrum. Target-specific multi-target problem remains the bottleneck of treatment. Therefore, the next stage for targeted drugs may carry out in-depth research in the following aspects.

4.1 Research on combination drugs

Explore a variety of combinations to see which one is better. Or explore whether there are different combinations of drugs for patients with different stages of cancer. Researchers can make more practices on why to choose trastuzumab monoclonal antibody and apatinib for combination, method of administration. Then show the results of research through experiment reports, analyse the personal example.

4.2 Research on reducing side effects

Systemic treatments have a lot of side effects, and people may experiment with how to reduce them and how to care for them. In real treatment, many patients use more

support measures to improve self-immunity after using targeted medicine. For example, they may use some Chinese medicine, like trepang, Ganoderma lucidum spore, nut, and so on. They want to recover faster after treatment. And nursing after an operation has been more and more paid attention to.

5. Conclusion

The essay develops a review through reports from articles and websites which are published in. In the writing process, we also interview relevant physicians in city hospitals to give some guidance. Doctors with experience point out that standardized and accurate detection of HER-2 expression in laparoscopic biopsy specimens is vitally important for molecular typing of gastric cancer and selection of anti-HER-2 targeted drug therapy. More patients will benefit only if treatment is more regulated and risks are adequately assessed.

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