Clinical Challenge and New Strategy of Monoclonal Antibody Therapy for Gastric Cancer

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Abstract: Gastric cancer is one of the highly lethal diseases in the world, which is complex and hard to treat. The main risk factors of gastric cancer are an unbalanced diet and hereditary substances, which are common in modern society. Thus, more and more researchers focus on gastric cancer to find out better methods to survive patients including extending their lifespan and enhancing life quality. Currently, immunotherapy is becoming a vital treatment method due to its safety and high efficiency. Human epidermal growth factor receptor 2 (HER2) is one of the most important targets of advanced gastric and gastroesophageal junction cancer and is involved in the pathogenesis and poor prognosis. Several monoclonal antibody drugs for treating HER2-positive breast cancer, such as Trastuzumab and Pertuzumab, may also be beneficial to patients with HER2-positive gastric cancer. This paper discussed the mechanism, problems, and the evolution of these potential monoclonal antibody drugs for gastric cancer and hope to provide a new sight in immunotherapy of gastric cancer.

1. Introduction

Gastric cancer is the third most lethal disease in the world with over 70% of non-cardia gastric cancer cases and 90% of chronic gastric cancer cases. In terms of survival, the results have been unsatisfactory, due to surgery combined with adjuvant and neoadjuvant chemotherapy remains the preferred treatment. Molecular targeted therapy has gradually been the preferred medication in many adjuvant regimens. And molecularly targeted medications have some targets. PD-1, VEGFR2, HER2, and other targets can be used to treat gastric cancer. The HER2 is the most commonly utilized molecular targeting medication among so many targets points. HER2(Human epidermal growth factor receptor 2)-positive subtype. HER2-targeted drugs were originally developed to treat breast cancer. However, ten years ago, it was found that some gastric cancer cases also present HER2 overexpression. HER2 molecular-targeted medicines have been used to treat patients and HER2 inhibitors are also widely utilized today thus molecular-targeted drugs have been used to treat HER2-positive gastric cancer for a while and many clinical trials were carried on in the past decade. Here, we introduced the mechanism of current drug targets for gastric cancer including HER2, EGFR, PD-1, and VEGFR2, as well summarized their monoclonal antibody drugs and the recent clinical trials to discuss their clinical potential for gastric cancer [1-4].

2. Current therapy of gastric cancer

As a result, a combination of neoadjuvant chemoradiotherapy, and immunotherapy is the primary treatment for advanced gastric cancer [5].

2.1 Surgery

Due to gastric cancer being one of the most common malignant tumors in the digestive system, surgery is the first line of gastric cancer therapy, but can highly influence the quality of life. Resection of the stomach based on tumor location, and the classic operation for gastric cancer are total

gastrectomy and subtotal gastrectomy. To guarantee the oncologic resection and avoid metastasis, lymphadenectomy is performed together, and endoscopic resection and minimally invasive access are two main ways [5].

2.2 Radiotherapy

For advanced gastric cancer and distal recurrence, radiotherapy is essential. It helps patients control cancer cell transfer and improve their survival of patients. However, radiotherapy has many side effects on the human body, for example, it affects the tumor microenvironment including tumor blood vessels and cells of the immune system and damages endothelial cells and the immune system [6].

2.3 Chemotherapy

Chemotherapy has been defined as a very useful therapeutic. It can be used alone or in combination with surgery and radiotherapy. Although a history of chemotherapy is relatively short, its value and the treatment result are significant for treating cancer. However, the side effects of chemotherapy cannot be ignored, for its agents affect multiple organ systems

2.4 Immunotherapy

Nowadays, immunotherapy is becoming a powerful clinical strategy for treating cancer and have gotten remarkable advance and multiple immunotherapy drugs have been approved by FDA, such as a monoclonal antibody, a molecularly targeted drug, which is used wide-ranging in treating cancer. And, it has been achieved for some cancer. It also has huge potential therapy values and brings survival for patients.

Table 1. Clinical trials classified molecular targets for gastric cancer [2].

Signaling pathway	Molecular target	Therapeutic agents	Type of trial	Line of treatment	Phase	Patient's stage
EGFR	HER2	Trastuzumab ± 5-FU/cisplatin/capecitabine	Multicenter, randomized, open-label	First	III	Advanced gastric cancer, HER2-positive
		Pertuzumab ± trastuzumab/5-FU/cisplatin/capecitabine	Multicenter, randomized, double	First	III	Metastatic gastric cancer, HER2-positive
VEGF/VEGFR	VEGFR2	Ramucirumab + BSC *vs* placebo + BSC	Randomized, quadruple	First	III	Metastatic/locally recurrent gastric cancer
		Ramucirumab ± paclitaxel	Multicenter, randomized, double	Second	III	Metastatic, refractory gastric cancer
Immune Checkpoint	PD-1	Pembrolizumab *vs* pembrolizumab ± 5FU/cisplatin or capecitabine	Multicenter, non-randomize	Second/third	II	Metastatic/recurrent gastric cancer

			d, open-label			
		Pembrolizumab *vs* paclitaxel	Randomized, open-label	Second	III	Advanced gastric cancer

3. Mechanisms of molecular targeted drugs

As table 1 shown, HER-2, PD-1, EGFR, and VEGFR-2 are the different drug targets of gastric cancer. Antitumor cell monoclonal antibodies are wide of mechanism against with tumor, achieving tumor cells elimination by blocking the ligands combine with its growth factor receptor. However, for treating most cancer cells, it is antibody-dependent cellular cytotoxicity (ADCC) to activate immune effectors by Fc receptor-bearing effector cells and kill the targeted tumor cell [12]. ADCC mechanism included main 4 steps: 1. Targeted cell recognition with Fc receptor, combine on the surface of the Fc receptor. 2. Kinase's sign effector in vivo. 3. Triggering of three main downstream signaling pathways, which led cytotoxic to release. 4. Killing the target cancer cells [13][14].

3.1 HER-2

Human epidermal growth factor receptor 2 (encoded by ERBB2 and commonly known as HER2) is the first biomarker available in clinical practice for patients with GC. HER2 is a member of the EGFR family and has tyrosine kinase activity, whose overexpressed causes breast cancer, gastric cancer, lung cancer, etc. [3]. It doesn't have an accurate ligand, which is significantly different from other family members. Its activity is after homodimerization or heterodimerization with other family members when HER-2 is overexpressed in cancer cells of the membrane, it is more than normal in adult tissue, therefore it less sensitive to the toxicity of HER2 targeted drugs [10].

3.2 EGFR

EGFR is a transmembrane protein that is a receptor for the EGF family of extracellular protein-ligand. EGFR and other receptor tyrosine kinase in humans are associated with diseases, such as Alzheimer's. When EGFR is overexpressed, associated with a variety of tumors forming. Thus, interruption of EGFR signaling or inhibition of intracellular tyrosine kinase activity is effective to prevent the growth of EGFR-overexpressing tumors and improve the patient's condition [10].

3.3 PD-1

PD-1, called CD279, is a protein on the surface of T-cell and B cells. By regulating the immune system, it can promote self-tolerance by suppressing T-cell inflammatory activity. It not only prevents autoimmune disease but also can prevent the immune system to kill cancer cells. PD-1 can promote apoptosis of antigen-specific T-cells in lymph nodes. PD-1 regulates the immune system's response to cells in the human body by reducing T cell inflammatory activity and down-regulating the immune system [10]-[12].

3.4 VEGFR2

VEGF receptors are receptors for a vascular endothelial growth factor (VEGF). There are three main subtypes of VEGFR, numbered 1, 2, and 3. Inhibitors of VEGFR are used in the treatment of cancer. Vascular endothelial growth factor (VEGF) is an important signaling protein involved in both vasculogenesis and angiogenesis [10].

4. Molecular targeted drugs

Trastuzumab, a molecular-targeted drug that extends overall survival and progression-free survival in HER2-positive breast cancer, may also be beneficial in HER2-positive gastric cancer patients [2].

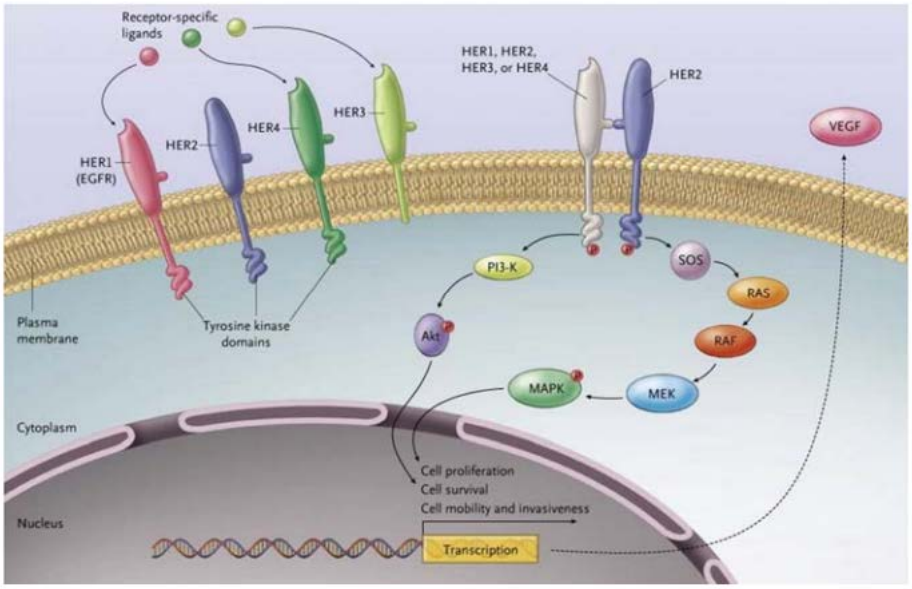

Figure 1. Mechanism of Trastuzumab [13].

4.1 Trastuzumab

Trastuzumab is a recombinant IgG1 kappa, humanized monoclonal antibody produced in CHO cell cultures that bind to the extracellular domain of the human epidermal growth factor receptor protein with high affinity in a cell-based assay (Kd = 5 nM) (HER2). It is used to treat human epidermal growth factor receptor (HER)-2+ metastatic cancers in which the HER-2 oncogene has been amplified or the HER-2 protein has been overexpressed in tumors. It is thought that HER2 overexpression or gene amplification can be seen in 20–30% of malignancies, and that enhanced HER2 activation activates many downstream pathways, leading to aberrant cell proliferation [14-17].

In initial trials, trastuzumab is very efficacy and safe, however, with an increase of trials, researchers have realized that trastuzumab is pernicious to cardiac dysfunction. In the phase III trial, the patients have targeted by anthracycline early, looking back at the cases in clinal trials that have been treated in trastuzumab. In 1219 patients analyzed in the CREC report, 174 met at least one of the above criteria (14%) [16-18].

It is a humanized mAb against extracellular tyrosine kinase receptor HER2. Trastuzumab is the first of the molecularly targeted drug for use in HER overexpression breast cancer patients. As a humanized IgG1, trastuzumab binds to FccRIII on immune effector cells and is a potent mediator of antibody-dependent, cell-mediated cytotoxicity. Trastuzumab is given by slow injection into a vein and injection just under the skin. Common side effects include fever, infection, cough, headache, trouble sleeping, and rash [17][18].

Table 2. Phase I, open-label clinical trials of trastuzumab [19].

The first patient recruited	1 June 1992	9 November 1992	6 October 1992
The last patient recruited	27 July 1992	4 March 1993	26 October 1992
Number of patients recruited	16	17	15
Age range (years)	29-67	30-71	40-71
Treatment	Trastuzumab along	Trastuzumab along	Trastuzumab +cisplatin
Herecepti does	Single dose 10-500mg	Weekly 10-500mg	Weekly 10-500mg

To assess the safety, maximum tolerated dose, and pharmacokinetics of trastuzumab, three open-label Phase I clinical studies (Table 1) were conducted in patients with refractory (grade 4) HER2-positive metastatic breast cancer. Weekly intravenous infusion schedules were maintained until disease progression, depending on trastuzumab clearance rates determined from preclinical trials. Cisplatin was given in doses of 50 or 100 mg/m2. Only a small number of patients (N-15-17) were included in these Phase I trials, which is typical of such studies, and enrollment was completed in a short period. Trastuzumab is well tolerated by most people [20-24].

Based on animals and mechanism of action, trastuzumab may cause harm to pregnant women and the fetus. During pregnancy, it causes oligohyramnios sequnce mainfesting. For neonatus, the symptoms are pulmonary phpoplasia, skeletal abnormalities, and neonatal death.

Thus, pertuzumab (2012), adotrastuzumab (2013), and ado-trastuzumab emtansine (2013) were approved by FDA [20-24].

4.2 Pertuzumab

Pertuzumab is an antineoplastic agent that is used in combination with other antineoplastic agents to treat HER2 metastatic breast cancer. Recently, it has also been used to treat HER-2 gastric cancer [1].

Pertuzumab is a recombinant humanized monoclonal antibody that targets the human epidermal growth factor receptor 2 protein's extracellular dimerization domain (subdomain II) (HER2). It is made up of two heavy chains and two light chains, each with 448 and 214 residues. It was approved by the FDA in 2012 for use in the treatment of metastatic HER2 cancer in combination with docetaxel and another HER2-targeted monoclonal antibody, trastuzumab. Its indications have since been expanded to include use as both a neoadjuvant and adjuvant therapy in the treatment of HER2 cancers with a high risk of recurrence [21][24][27].

Pertuzumab works as an antineoplastic agent by binding to and inhibiting the activity of HER2, an oncogene implicated in the development of numerous cancers.Pertuzumab, like other therapeutic monoclonal antibodies, has a relatively long duration of action, necessitating dosing every three weeks. Drugs that inhibit HER2 activity, such as pertuzumab, have been linked to the development of cardiotoxicity (specifically, left ventricular dysfunction) - a baseline assessment of left ventricular ejection fraction (LVEF) should be performed prior to starting pertuzumab therapy, and at regular intervals throughout therapy, to ensure LVEF remains within normal limits [21-24].

4.3.1 Left Ventricular Dysfunction

In many cases, the molecularly targeted drug Pertuzumab is used alongside chemotherapy drugs anthracyclines to treat related cancers. And chemotherapeutic drugs play an important role in the treatment of cancer, and anthracyclines have been used before molecular targeted drugs. The combination of Pertuzumab and anthracyclines, or anthracyclines followed by Pertuzumab, can cause left ventricular systolic dysfunction (LVFE)Withhold PERJETA dosage for at least 3 weeks following symptoms: a reduction in LVEF to less than 40%, or a reduction in LVEF from 40% to 45 percent with a 10% or larger absolute decrease from pretreatment values. If the LVEF has recovered to greater than 45 percent or 40 percent to 45 percent, PERJETA may be continued. 35 was linked to a drop in absolute values of less than 10% below pre-treatment levels. If the LVEF has not improved or has deteriorated further following a repeat evaluation in roughly 3 weeks, cessation of PERJETA should be carefully considered [26][27].

4.3.2 Hematologic: Neutropenia febrile

Pertuzumab treatment might also cause blood issues. During the first three therapy cycles, patients who received had a higher risk of febrile neutropenia than those who did not [27].

4.3.3 Immune Hypersensitivity reactions/anaphylaxis

Pertuzumab can also wreak havoc on the immune system. Pertuzumab-treated patients have experienced serious hypersensitivity responses and have died. As a result, when using pertuzumab,

patients' vital signs should be regularly checked. Grade 4 Nci-ctcae Bronchospasm or acute respiratory distress syndrome are hypersensitivity reactions (anaphylaxis) (ARDS). The molecularly targeted medicine should be discontinued immediately, and therapy should be prohibited for the rest of one's life [24][25].

4.3.4 Embryo-Fetal Toxicity

The molecular-targeted medicine, on the other hand, should not be administered to pregnant women. Even though the medicine has not been evaluated in humans, toxicity experiments on animals have been carried out, according to the findings.

Pertuzumab's effects may extend throughout the third trimester of pregnancy. When fed to cynomolgus monkeys during organ development, pertuzumab induces oligohynios, delayed kidney development, and fetal death [24][25].

4.3.5 Overall Survival

The rate of survival is a key criterion for assessing the efficacy of molecularly targeted medications. At 2 years, 80.5 percent (95 percent CI, 76.5 to 84.4) and 69.7 percent (95 percent CI, 65.0 to 74.3), respectively; at 3 years, 68.2 percent (95 percent CI, 63.4 to 72.9) and 54.3 percent (95 percent CI, 49.2 to 59.4), respectively; and at 4 years, 57.6 percent (95 percent CI, 52.4 to 62.7) and 45.4 percent (95 percent CI Pertuzumab showed a consistent benefit in exploratory analyses in predefined subgroups. The hazard ratio for death from any cause was 0.80 in patients who had previously received trastuzumab (47 patients in the pertuzumab group and 41 patients in the control group) (95 percent CI, 0.44 to 1.47). At 2 years, 80.5 percent (95 percent CI, 76.5 to 84.4) and 69.7 percent (95 percent CI, 65.0 to 74.3), respectively; at 3 years, 68.2 percent (95 percent CI, 63.4 to 72.9) and 54.3 percent (95 percent CI, 49.2 to 59.4), respectively; and at 4 years, 57.6 percent (95 percent CI, 52.4 to 62.7) and 45.4 percent (95 percent CI Pertuzumab showed a consistent benefit in exploratory analyses in predefined subgroups. The hazard ratio for death from any cause was 0.80 in patients who had previously received trastuzumab (47 patients in the pertuzumab group and 41 patients in the control group) (95 percent CI, 0.44 to 1.47) [26][27].

In addition, these two HER2-targeted drugs have been used to treat HER2-related cancers for many years and have achieved great success in treating gastric cancer caused by HER2 overexpression. However, the adverse effects of drugs cannot be ignored and reducing the side effects of drugs is still a field of focus in the future [26][27].

5. Conclusion

In conclusion, gastric cancer caused by HER2 overexpression can be greatly improved through using different molecular targeted drugs and the combination of targeted drugs and chemotherapy drugs. Improving the therapeutic effect of drugs is still a very important key point. Moreover, the development of targeted drugs in the future will bring hope to the survival of more patients with gastric cancer caused by HER2 overexpression. At the same time, it is also important to reduce the targeted drugs in adverse effects.

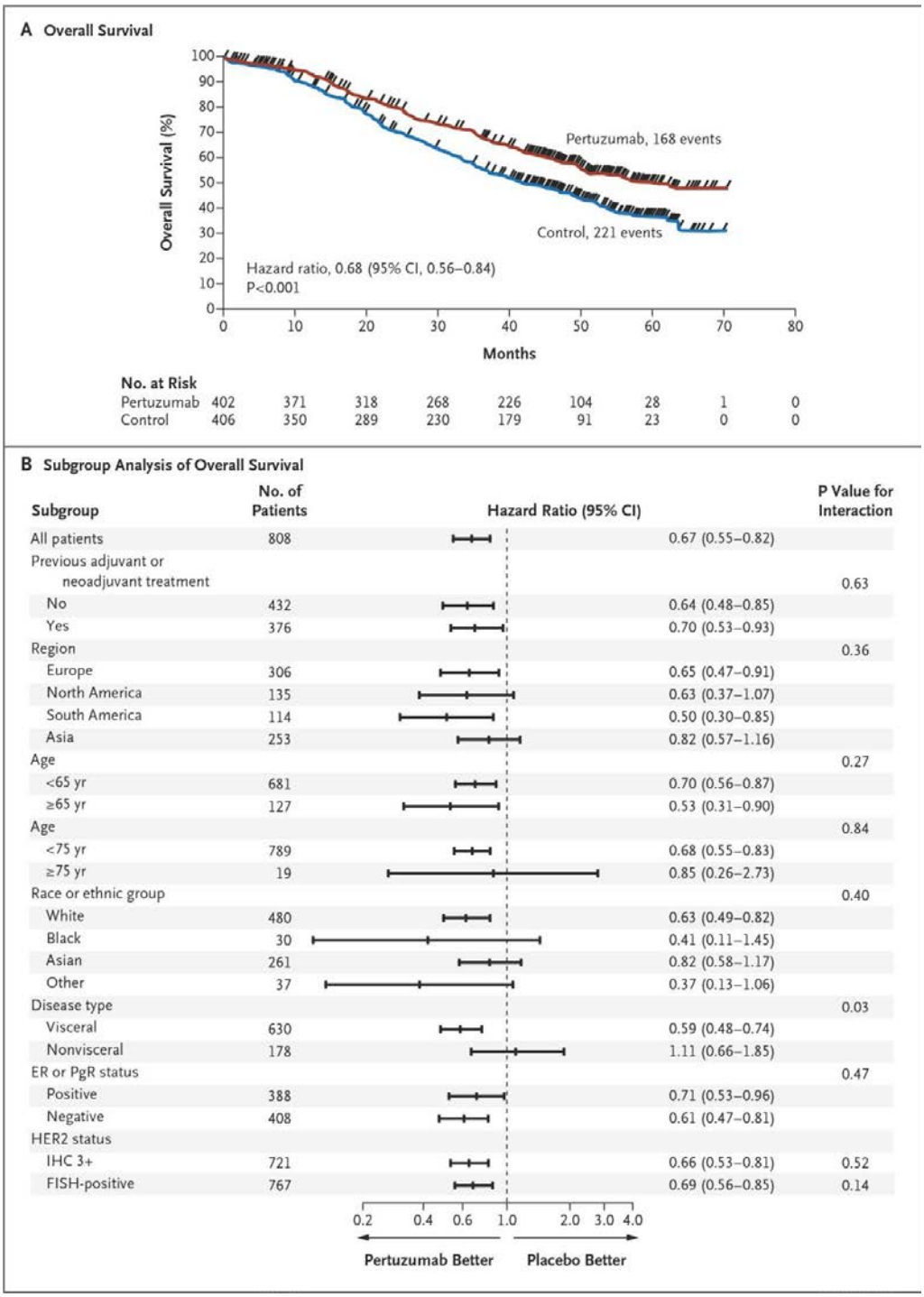

Figure 2 HER-2 Pertuzumab overall survival [27]

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