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Target Therapy in Gastric Cancer

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ABSTRACT

Gastric cancer is the fifth most frequently diagnosed cancer and the third leading cause of cancer mortality. In advanced gastric cancer patients, the treatment outcomes are dismal. With the development of the molecular targeted therapy, the prognosis in patients with advanced and unresectable gastric cancer are improved. This article reviewed the molecular targeted agents in clinical use, their limitations and potential strategies to overcome them, and the future direction of target therapy in advanced gastric cancer.

Keywords: Gastric Cancer; Molecular Target Therapy; Human Epidermal Growth Factor Receptor-2 **(HER-2)**; Epidermal Growth Factor Receptor **(EGFR)**; Vascular Endothelial Growth Factor **(VEGF)**

INTRODUCTION

Although the global incidence of gastric cancer has declined, which is still the fifth most common cancer and the third leading cause of cancer-related death. Because of the asymptomatic feature of gastric cancer, the patients are often in advanced and incurable stage when first diagnosed. Systemic chemotherapy is often used in advanced gastric cancer **(AGC)**, but the

treatment outcomes are dismal, only 6-11 months [1]. Recent development of molecular targeted therapies have shown positive effect on prognosis of AGC, and HER-2 receptor inhibitors are the first molecularly targeted drugs that could improve prognosis in patients with AGC [2]. But even so, there are many problems with this treatment, the most important of which is the problem of resistance to drugs. To solve this problem, a series of novel molecular targeted drugs have been developed and some promising experimental results have been obtained, but few have been shown to be effective, possibly because of the biological heterogeneity of gastric cancer [3]. Therefore, the application of alternative drugs is important for AGC patients. This article reviewed the molecular targeted agents in clinical use, their limitations and potential strategies to overcome them, and the future direction of target therapy in AGC.

ANTI-ERBB FAMILY RECEPTOR TARGETING AGENTS

Anti-EGFR Targeting Agents

Panitumumab

Panitumumab is a human immunoglobulin **(Ig)** G2 monoclonal antibody directed against the EGFR. a randomized, open-label phase-Ⅲ trial was performed. Patients with previously untreated advanced gastric adenocarcinoma were randomized to receive either epirubicin, oxaliplatin and capecitabine **(EOC)** or modified EOC plus panitumumab. The results shown the addition of panitumumab did not increase overall survival **(OS)** of AGC patients when compared with the chemotherapy only group [4].

Cetuximab

Cetuximab is a mouse or human monoclonal antibody that targets the EGFR. The results of a randomized, open-label phase-Ⅲ trial shown no benefit with the addition of cetuximab to combination chemotherapy in AGC patients. Patients diagnosed with advanced gastric or gastroesophageal junction cancer were randomized to receive capecitabine and cisplatin combination chemotherapy with or without cetuximab as a first-line chemotherapy. No significant difference in progression free survival **(PFS)** in two groups [5].

Anti-HER2 Targeting Agents

Trastuzumab

Trastuzumab is a humanized monoclonal antibody directed against the HER2 receptor, which blocks HER-2 activity by binding to the domain Ⅳ of the extracellular domain [6]. Trastuzumab was the first molecule-targeted agent approved for the treatment of AGC patients with over-expression of HER-2, which based on research results of a randomized, prospective, multicenter, phase-Ⅲ (ToGA) study [2]. But with the problem emerged that the resistance of Trastuzumab in clinical application, the mechanism of acquired resistance to trastuzumab in AGC patients needs further investigation.

Pertuzumab

Pertuzumab is a monoclonal antibody that blocks HER-2 dimerization by binding the domain Ⅱ of the HER2 ectodomain [7]. Based on a pre-clinical study, in which the anti-tumor activity of combination immunotherapy with pertuzumab and trastuzumab was proved to be superior to a monotherapy with either antibody in a HER2-positive human gastric cancer xenograft model [8]. The dose of pertuzuma used in a phase-Ⅲ study was 840mg every three weeks for six cycles in addition to trastuzumab, capecitabine and cisplatin, showed a 55% partial response rate in patients with HER2-positive AGC without previously chemotherapy [9]. The accurate effect of Pertuzumab on AGC patients is still unclear.

Lapatinib

Lapatinib is a small molecule tyrosine kinase inhibitor that simultaneously inhibits phosphorylation of both EGFR and HER and prevents activation of the downstream signaling cascade. A pre-clinical study demonstrated effectiveness of lapatinib against HER-2 expressing gastric cancer cells which were resistant to trastuzumab [10]. But the results of several phase-Ⅱ and phase-Ⅲ clinical trials shown that application of lapatinib combined with chemotherapy has no significant advantage in term of OS and PFS in AGC patients [11-12].

Pan-HER Targeting Inhibitor Agents

Afatinib is a multiple tyrosine kinase receptors inhibitor of ERRB family exception of HER3. HER3 is observed over expression in trastuzumab resistant HER2-positive breast carcinoma cell lines, demonstrated that HER3 is is one of the molecules responsible for resistance to HER2 targeted therapies [13]. PF00299804, a pan-HER inhibitor combined with trastuzumab or chemotherapeutic agents was applied on gastric cancer cell lines in a preclinical study, the accurate results is on the way [14].

c-Met and mTOR Targeting Inhibitor Agents

c-Met is a RTK binding of hepatocyte growth factor **(HGF)** to its receptor, MET, initiates activation of downstream signal transduction pathways including MAPK cascades and the PI3K-Akt axis [15]. MET gene amplification and MET protein over expression have been reported with a frequency of 10%-20% in gastric cancer [16]. AGC Patients received epirubicin, capecitabine and cisplain with rilotumumab, a fully humanized monoclonal IgG2 antibody against HGF, and followed-up, the PFS of these patients were significantly improved [17]. PI3K inhibitors or mTOR inhibitors such as everolimus could overcome trastuzumab resistance in gastric cancer, but based on research results of a phase-Ⅲ clinical trial, everolimus shown no significate benefit on improving AGC patients' OS [18].
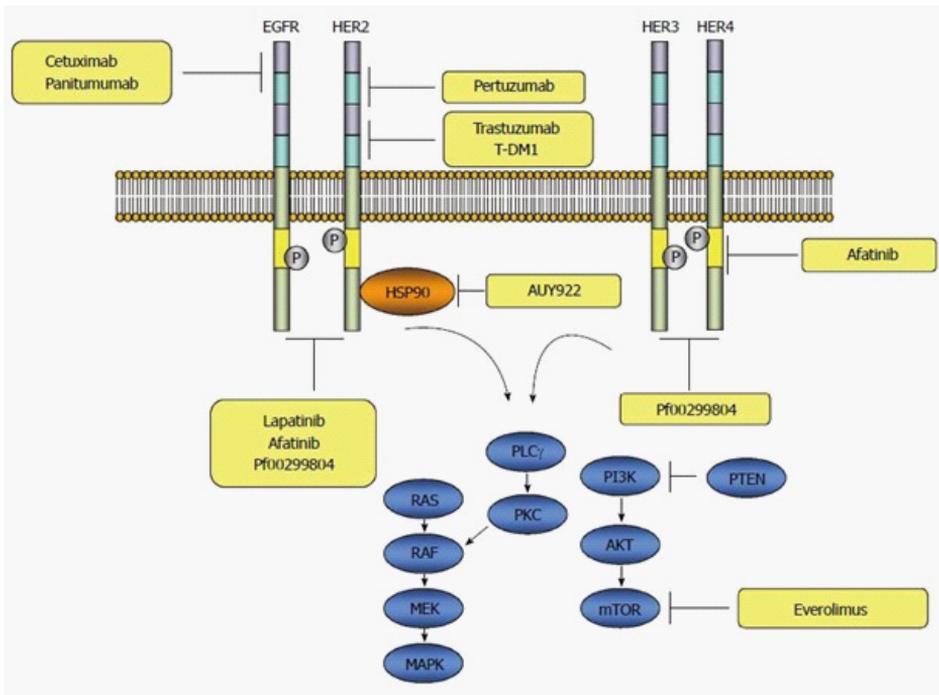
Figure 1. Signal transduction cascade through activation of ERBB receptors and schematic diagram of molecular targeting agents where they work. EGFR: Epidermal growth factor receptor; HER: Human EGFR; PLC-γ: Phospholipase C-γ; PKC: Protein kinase C; MEK: Protein kinase kinase; MAPK: Mitogen-activated protein kinase; mTOR: Mammalian target of rapamycin; PI3K: Phosphatidylinositol 3-kinase. (Cited from Lee S et al. Target therapy in gastric cancer. WJG. 2016, 22(3): 1179-1189).

ANTI-VEGF AND VEGFR FAMILY TARGETING AGENTS

Bevacizumab

Bevacizumab is a humanized monoclonal IgG1 directing against VEGF-A. A large randomized phase-Ⅲ trial evaluated the clinical benefit of the addition of bevacizumab to combination chemotherapy in AGC patients and found there has no significate difference in OS and PFS between the study group and control group [19].

Ramucirumab

Ramucirumab is a fully humanized IgG1 monoclonal antibody directed to the extracellular VEGF-binding domain of VEGFR-2 [20]. An international, randomized, double-blinded, placebo-controlled, phase-Ⅲ trial was conducted in patients with AGC, however, no significant improvement of PFS was observed by adding ramucirumab to mFOLFOX6 [21].

Apatinib

Apatinib is an small molecular inhibitor of VEGFR-2 tyrosine kinase. A multicenter, randomized, doubleblind, placebo-controlled phase-Ⅲ trial to evaluate the survival benefit of apatinib in AGC patients. Significantly improved OS was observed in patients treated with apatinib, meeting the primary objective [22].
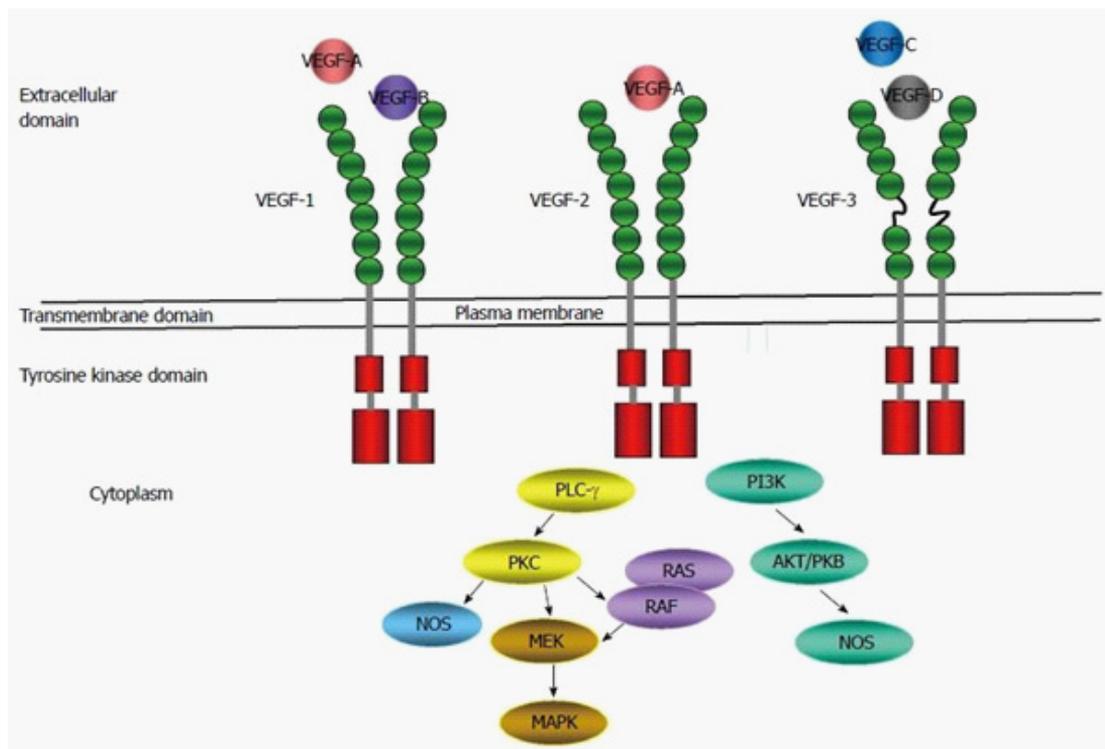

Figure 2. Vascular endothelial growth factor receptor and signal transduction. Binding of ligands to receptors leads to phosphorylation of the receptors by activation of receptor-kinase activity, which leads to subsequent signal transduction. VEGF: Vascular endothelial growth factor; PLC-γ: Phospholipase C-γ; PKC: Protein kinase C; MEK: Protein kinase kinase; MAPK: Mitogen-activated protein kinase; PI3K: Phosphatidylinositol 3-kinase. (Cited from Lee S et al. Target therapy in gastric cancer. WJG. 2016, 22(3): 1179-1189).

CONCLUSION

In gastric cancer, numerous targeting agents have been examined in clinical trials since the introduction of trastuzumab. However, few targeted agents have been successful in establishment as a standardized therapy. Resistance to trastuzumab is an emerging issue to be solved. By selecting targeted agents on the basis of known molecular mechanisms, a more potent activity of the molecular target agents would be expected.

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