TOPIC HIGHLIGHT

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Targeting receptor tyrosine kinases in gastric cancer

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Abstract

Molecularly targeted therapeutic agents are constantly being developed and have been shown to be effective in various clinical trials. One group of representative targeted oncogenic kinases, the receptor tyrosine kinases (RTKs), has been associated with gastric cancer development. Trastuzumab, an inhibitor of ERBB2, has been approved for the treatment of gastric cancer, although other receptor tyrosine kinases, such as epidermal growth factor receptor, vascular endothelial growth factor, platelet-derived growth factor receptor, c-Met, IGF-1R and fibroblast growth factor receptor 2, are also activated in gastric cancer. The promising results of the trastuzumab clinical trial for gastric cancer resulted in the approval of trastuzumab-based therapy as a first-line treatment for human epidermal growth factor receptor 2-positive patients. On the other hand, the trial examining bevacizumab in combination with conventional chemotherapy did not meet its primary goal of increasing the overall survival time of gastric cancer patients; however, a significantly higher response rate and a longer progression-free survival were observed in the bevacizumab arm of the trial. Other clinical trials, especially phase Ⅲ trials that have tested drugs targeting RTKs, such as cetuximab, panitumumab, gefitinib, erlotinib, figitumumab, sorafenib, sunitinib and lapatinib, have shown that these drugs have modest effects against gastric cancer. This review summarizes the recent results from the clinical trials of molecularly targeted drugs and suggests that further improvements in the treatment of advanced gastric cancer can be achieved through the combination of conventional drugs with the new molecularly targeted therapies.

Core tip: Since the finding of receptor tyrosine kinases (RTKs) about thirty years ago, its functions have been examined over the years as key regulators of proliferation, differentiation, and metastasis. Several RTKs are activated in advanced gastric cancer (AGC) and various RTK inhibitors have been developed as tailored therapy. The results of recent clinical trials evaluate the effectiveness of targeting RTKs. Unfortunately, recent progress in the development of RTK-targeted therapy for AGC patients has been modest. To provide maximal therapeutic benefits, well-designed clinical trials and combinations with appropriate drugs are required. In addition, new predictive biomarkers are immediately obliged to guide the selection of a drug-sensitive patients' population.

INTRODUCTION

Gastric cancer is the second leading cause of cancer-related death worldwide[1,2]. The high mortality rate is due to the lack of effective therapy for advanced stages of the disease. Conventional therapy options for gastric cancer include surgery, chemotherapy, radiation therapy and combination treatments. In the early stages, the disease can often be cured through complete surgical removal of the tumor[3]. However, because gastric cancer results in few symptoms during the early stages, most patients are usually diagnosed after the cancer has progressed to an advanced stage. Moreover, even after surgical resection, tumors will recur in many patients, resulting in short survival times. The 5-year survival rate of gastric cancer has remained at 20%-25% in the western world[4]. Therefore, the high mortality rate underscores the need for effective medical treatments for patients with advanced stages of gastric cancer[3].

Receptor tyrosine kinases (RTKs) consist of ligand-binding extracellular domains which identify the subfamilies of RTKs, a transmembrane domain and a tyrosine kinase motif, and the activation of these kinases has been shown to play an important role in the control of many fundamental process, such as growth, differentiation, adhesion, migration and apoptosis[5-8]. The activation and overexpression of RTKs were initially reported in various cancers[9,10]. Currently, RTK inhibitors have been validated through clinical trials, and some agents have received regulatory approval, such as trastuzumab for the treatment of advanced breast cancer[10], gefitinib for non-small cell lung carcinoma[11] and cetuximab for metastatic colon cancer[12]. Unlike other solid tumors, which are predominantly associated with specific signaling pathways, such as the HER-2 pathway in breast cancer, the genetic and molecular pathogenesis of gastric cancer may be more complex[13,14]. In gastric cancer, although the amplification of RTKs, such as ErbB2, c-Met and fibroblast growth factor receptor (FGFR) 2, is associated with cancer progression, the only approved inhibitor is trastuzumab, an ErbB2-targeting antibody[15]. Trastuzumab came into use after the release of promising efficacy results from the Trastuzumab for Gastric Cancer (ToGA) trial[16]. Additionally, other RTKs have also emerged as potential targets for the future treatment of gastric cancer.

In this review, we delineate the underlying molecular basis of the RTK pathways and summarize the current results of the clinical phase Ⅲ trials (Table 1) and ongoing clinical trials that are targeting RTKs in patients with gastric cancer. Additionally, we also present future possibilities for the improvement of RTK inhibitor efficacy and for the identification of new strategic targets for gastric cancer treatment.

RTKS IN CELLULAR SIGNALING

RTKs are transmembrane glycoproteins that are activated by binding to their cognate ligands, resulting in the phosphorylation of tyrosine residues on the receptor and downstream signaling proteins. Fifty-eight of the 90 known protein tyrosine kinases are also receptors[5]. Various RTKs have been normally associated with intracellular signal transduction including growth, differentiation, adhesion, migration, and apoptosis (Hubbard and Till). In various types of cancer, many signaling pathways including cell proliferation, differentiation, and metabolism pathways, are activated by RTK dimerization[6,17]. In general, RTK activation occurs through ligand-induced dimerization, in which a bivalent ligand and two receptor molecules form a dimeric complex[18]. Two main processes are required for RTK activation: the enhancement of the intrinsic catalytic activity and the creation of binding sites to recruit downstream signaling proteins. Importantly, tyrosine autophosphorylation is critical for both of these processes. Autophosphorylation of tyrosine residues located in the activation loop of the kinase domain stimulates kinase activity, whereas autophosphorylation in the juxtamembrane, kinase insert and carboxy-terminal regions generates docking sites for modular domains that recognize the phosphotyrosine residues in specific sequences[19].

RTKS IN GASTRIC CANCER

The RTK family consists of 58 kinases, and each is characterized by ligand-binding extracellular domains which identify the subfamilies of RTKs, a tansmembrane domain and a tyrosine kinase motif[5]. Of those kinases, the known RTKs are separated into 21 families, such as the epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR) and FGFR families, which are characterized by similar structures and the potential of dimerization in gastric cancer[20]. Additionally, it has been reported that the expression of platelet-derived growth factor (PDGF) and platelet-derived growth factor receptor (PDGFR) are involved in gastric cancer growth[21]. Each RTK inhibitor is dia-

Table 1 Phase Ⅲ trials of targeted Receptor tyrosine kinases in advanced gastric cancer				
Clinical trial	Line of treatment	RTK inhibitor	Chemotherapy	Status
ToGA	First	Trastuzumab	FP or XP	Completed
AVAGAST	First	Bevacizumab	XP	Completed
EXPAND	First	Cetuximab	XP	Completed
REAL-3	First	Panitumumab	EOX	Completed
LoGIG	First	Lapatinib	OX	Ongoing
TYTAN	Second	Lapatinib	T	Ongoing

ToGA: Trastuzumab for gastric cancer; AVAGAST: Avastin in gastric cancer; EXPAND: Erbitux in combination with xeloda and cisplatin in advanced esophago-gastric cancer; REAL-3: Randomized ECF for advanced and locally advanced esophagogastric cancer 3; LoGIG: Lapatinib optimization study in ErbB2 (HER-2) positive gastric cancer; TYTAN: Lapatinib (Tykerb) with paclitaxel (Taxol) in Asian ErbB2+ (HER+) gastric cancer study; F: 5-fluorouracil; P: Cisplatin; X: Capecitabine; E: Epirubicin; T: Paclitaxel.
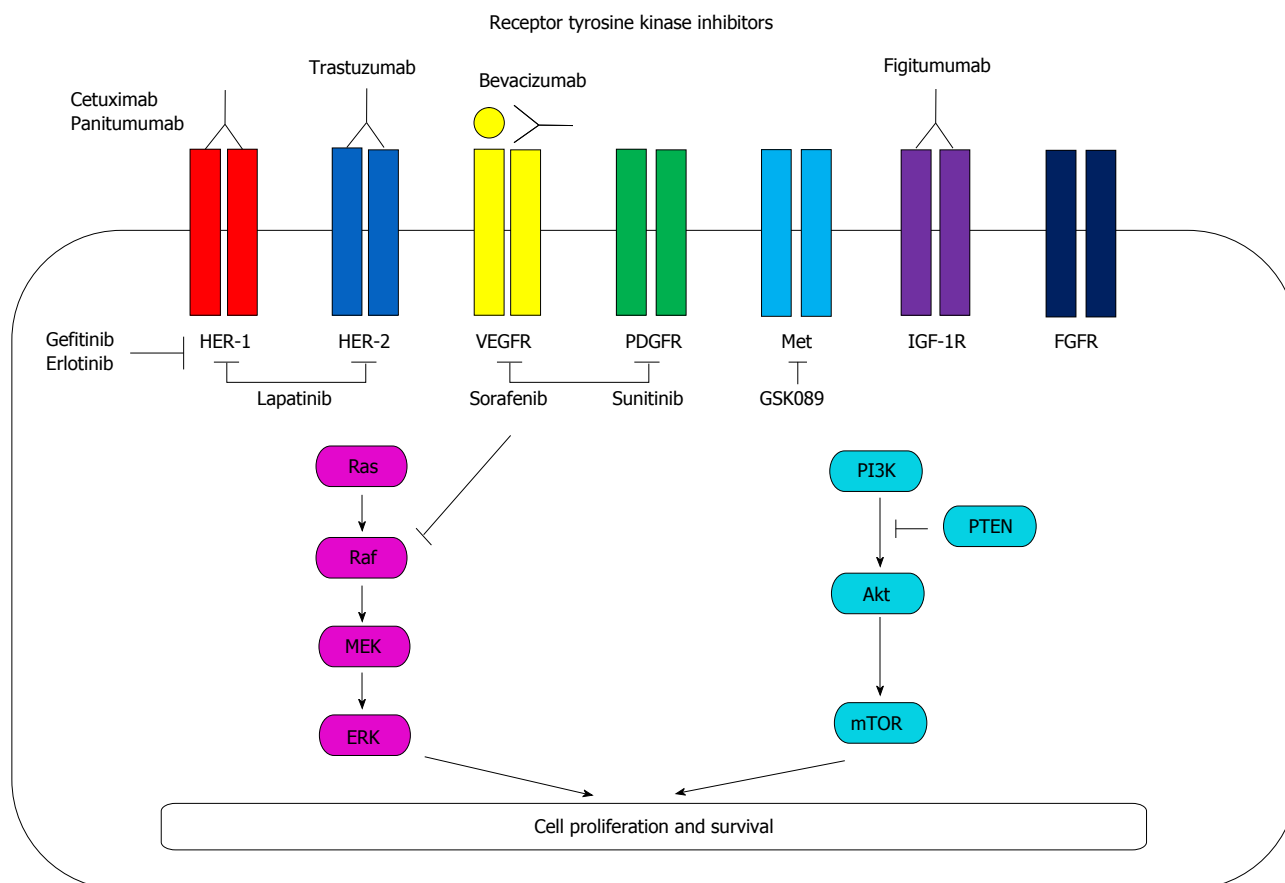
Figure 1 Receptor tyrosine kinase inhibitors. VEGFR: Vascular endothelial growth factor receptor; PDGFR: Platelet-derived growth factor receptor; IGF-1R: Insulin-like growth factor 1 receptor; FGFR: Fibroblast growth factor receptor; HER: Human epidermal growth factor receptor; PTEN: Phosphatase and tensin homolog.

gramed in Figure 1 and inactivates various RTKs. Among these RTK inhibitors, monoclonal antibodies, such as cetuximab and panitumumab, trastuzumab and fugitumumab directly bind to each RTK and inhibit its signaling. Bevacizumab also binds vascular endothelial growth factor (VEGF) and inhibit VEGFR signaling. Gefitinib and erlotinib competes with the binding of ATP to the tyrosine kinase domain of EGFR and lapatinib blocks phosphorylation of HER-1 and HER-2. Sorafenib inhibits the enzyme RAF kinase and VEGFR-2/PDGFR-beta signaling cascade. Sunitinib also blocks VEGFR-2/PDGFR-beta and c-kit. In addition, GSK089 inhibits c-Met and blocks its signaling (Figure 1).

Common alterations and mutations of RTKs have been identified in gastric cancer. Interestingly, Deng *et al*[22] showed that druggable alterations in RTKs occurred in 37% of gastric cancer patients; the most frequently amplified RTK was FGFR2 (9.3%), followed by KRAS (8.8%), EGFR (7.7%) and ERBB2 (7.2%)[22]. Furthermore, the RTK amplification status was shown to be an independent marker of poor prognosis in gastric cancer patients according to Cox multivariate analysis, and this result was independent of chromosomal instability.

Recently, together with Tyro3, Axl and Mer receptor tyrosine kinases are aberrantly expressed in numerous human cancers. It has been reported that Axl and Mer inhibition constitutes a novel therapeutic strategy that may

enhance the efficacy of standard chemotherapy in glioblastoma multiforme[23], non-small cell lung cancer[24,25] and breast cancer[26]. In gastric cancer, combination of Axl and Mer expressions correlated inversely with patient prognosis[27]. Inhibition of these RTKs may provide potential targets for AGC.

In our recent study, the levels of EGFR, ErbB2, FGFR1, FGFR2, insulin R and EphA4 were increased in human gastric cancer tissues compared with normal mucosa according to a protein array[28]. Additionally, ErbB2 was most activated in the human gastric cancer cell lines MKN45, MKN74, MKN1 and MKN7[28]. Therefore, these findings suggest that these molecules may be potential targets for selective therapy in gastric cancer. We will summarize the clinical trials for the newly established modalities related to RTK expression in gastric cancer.

RTK TARGETED THERAPY

The insufficient effect of chemotherapy on advanced gastric cancer has resulted in the development of new biological therapies that modulate various targets of signal transduction pathways that are overexpressed in gastric cancer. A large number of molecularly targeted drugs have been clinically developed to inhibit angiogenesis as well as to specifically inhibit the human epidermal growth factor receptor, platelet-derived growth factor receptor

and c-MET receptor.

TARGETING HER-2

HER-2 (ErbB2) is a member of the ErbB2/HER family, which is comprised of four receptors including HER-1 (EGFR), HER-2, HER-3 and HER-4. Of these receptors, the targeting of HER-2 has been the most successful for the treatment of advanced gastric cancer. HER-2 overexpression is observed in 10%-38% of gastric cancer patients[29-31]; however, the effect of HER-2 expression on the prognosis of AGC remains controversial[32-35]. Recently, Bang *et al*[16] reported that HER-2-positive patients using Immunohistochemistry (IHC) scoring system had a superior outcome when treated with conventional chemotherapy with trastuzumab, which selectively binds to HER-2 and inhibits its downstream signaling pathway, in the ToGA trial. Although this result suggests HER-2 is not a negative prognostic factor, it might be confounded by various factors, such as the second line therapy or intestinal subtype. Additionally, IHC scoring system in gastric cancer is different from that of breast cancer[36].

First-line trastuzumab-based trials in AGC patients were reported in 2006[37]. Prior to the ToGA trial[16], three phase II trials evaluating the effectiveness of trastuzumab in AGC patients were presented. The results from the first phase II trial of trastuzumab combined with cisplatin and docetaxel showed that a radiological response was observed in 4/5 HER-2-positive patients (defined as IHC3+ or FISH+) with metastatic gastric cancer or gastroesophageal junction carcinoma patients[37]. In the second phase II trial, HER-2-positive (defined as IHC2+ and FISH+ or IHC3+) AGC or gastroesophageal junction adenocarcinoma patients were treated with 75 mg/m^2 cisplatin and trastuzumab (8 mg/kg loading dose followed by 6 mg/kg for future cycles) every 21 d until disease regression, and there was a 35% response rate in the 17 evaluable patients who received a median of two cycles of treatment[38]. Taken together, the overall response rate (ORR) was 35%-44% in the trial arm consisting of trastuzumab combined with conventional chemotherapy.

The ToGA trial was an open-label, international, phase III, randomized controlled trial that was undertaken in 24 countries[16]. In total, 594 patients with gastric or gastroesophageal junction cancer that overexpressed HER-2 protein (as determined by immunohistochemistry or gene amplification by fluorescence *in situ* hybridization) were randomly assigned to the study treatments (trastuzumab plus chemotherapy, *n* = 298; chemotherapy alone, *n* = 296); of these patients, 584 were included in the primary analysis (*n* = 294 and *n* = 290, respectively). The median overall survival in the trastuzumab plus chemotherapy arm was 13.8 mo (95%CI: 12-16) compared with 11.1 mo (95%CI: 10-13) in the chemotherapy alone arm (HR = 0.74, 95%CI: 0.60-0.91, *P* = 0.0046). The study met not only the primary endpoint of improved overall survival but also the secondary endpoint of improved response rates and progression-free survival. Ad-

ditionally, a 2.7 mo gain in median survival was observed in the intent-to-treat population. In the ToGA study, no significant overlapping toxicity was evaluated, except for cardiac dysfunction[16]. Trastuzumab is correlated with an increased risk of cardiotoxicity[39], similar to anthracyclines, which are frequently used in the treatment of breast and gastric cancers. Trastuzumab-related cardiac dysfunction is largely reversible by removal of the antibody[40] and has been classified as type II chemotherapy-related cardiac dysfunction[41]. In the ToGA study, the left ventricular ejection fraction was monitored every 12 wk during treatment. The regimen was well tolerated, and the hematological toxicity for the chemotherapy doublet was within the expected levels. Interestingly, no additional toxicity was observed, except for an asymptomatic reduction in the left ventricular ejection fraction to below the normal range, which was reported in 5.9% of the patients. Notably, although this patient group has a relatively short life expectancy, the addition of trastuzumab did not compromise the patients' quality of life[42].

TARGETING EGFR

The EGFR is intrinsically expressed in various organs, including the skin, gut and renal tissues. EGFR overexpression is observed in 27%-64% of gastric cancers, especially in the more proximal tumors[43,44], and is correlated with older age, more aggressive histology and higher disease stage; additionally, EGFR expression is a poor prognostic factor[43].

Cetuximab (Erbitux, Imclone Systems) is a recombinant humanized murine monoclonal antibody against EGFR and is the most investigated anti-EGFR therapy in gastric cancer. In the first line phase II trials, six non-randomized trials investigated the addition of cetuximab to doublet chemotherapy[45-49]. The response rate of the above studies ranged from 41% to 63%, and the median overall survival ranged from 9 to 16.6 mo. A randomized phase II study comparing the addition of cetuximab to three discrete chemotherapies was reported at ASCO 2010. None of the treatment arms that included cetuximab exhibited a better survival outcome compared with the conventional control arms. In 2011, preliminary data from another phase II study demonstrated that there was no clinically significant benefit associated with the addition of cetuximab to docetaxel and oxaliplatin[50]. Additionally, the results of the large, randomized, phase III EXPAND study (NCT00678535), which investigated the addition of cetuximab to cisplatin and capecitabine chemotherapy, were presented in 2013[51]. The median progression-free survival (PFS) for the 455 patients administered the capecitabine-cisplatin plus cetuximab treatment was 4.4 mo (95%CI: 4.2-5.5) compared to 5.6 mo (95%CI: 5.1-5.7) for the 449 patients treated with capecitabine-cisplatin alone (HR = 1.09, 95%CI: 0.92-1.29; *P* = 0.32). Additionally, 83% of the patients in the chemotherapy plus cetuximab group and 77% of the patients in the chemotherapy group experienced grade 3-4

diarrhea, hypokalemia, hypomagnesemia, rash and hand-foot syndrome.

Panitumumab is a humanized monoclonal antibody that targets EGFR. Van Cutsem *et al*[52] reported a phase Ⅲ trial of panitumumab plus best supportive care compared to best supportive care alone in patients with advanced colorectal cancer that failed to respond to 5-FU, irinotecan and oxaliplatin. However, there are very few reports of this agent being used to treat AGC patients. Recently, the results of a randomized, open-label, phase Ⅲ trial for patients with previously untreated advanced esophagogastric cancer (REAL3) were revealed; this study examined two groups of esophagogastric cancer patients treated with epirubicin, oxaliplatin and capecitabine with or without panitumumab[53]. The median overall survival of the 275 patients with advanced esophagogastric adenocarcinoma in the epirubicin, oxaliplatin and capecitabine (EOC) treatment group was 11.3 mo (95%CI: 9.6-13.0) compared to 8.8 mo (95%CI: 7.7-9.8) in the 278 patients treated with modified-dose EOC plus panitumumab (mEOC+P) (HR = 1.37, 95%CI: 1.07-1.76; P = 0.013). The main adverse events that were observed during this trial were grade 3-4 diarrhea (48/276 mEOC+P patients 17% *vs* 29/266 EOC patients 11%), rash (29/276 mEOC+P patients 11% *vs* 2/226 EOC patients 1%), mucositis (14/276 mEOC+P patients 5% *vs* 0/226 EOC patients) and neutropenia (35/276 mEOC+P patients 13% *vs* 74/226 EOC patients 28%)[53]. On the other hand, other EGFR monoclonal antibodies, such as matuzumab and nimotuzumab, resulted in even shorter PFS times when combined with chemotherapy (compared with chemotherapy alone) in randomized phase Ⅱ trials[54,55].

Gefitinib and erlotinib, which are EGFR tyrosine kinase inhibitors (TKIs), were assessed in phase Ⅱ trials; however, these drugs produced unsatisfactory results when used as monotherapies for gastric cancer patients. These inhibitors were effective first-line treatments against gastroesophageal cancer (GEJ), but were not effective for gastric cancer patients, when examined in a phase Ⅱ study[56]. On the other hand, combination therapy with 5-FU, oxaliplatin and erlotinib demonstrated that the ORR was greater than 50% in patients with esophageal or GEJ cancer[57].

COMBINED TARGETING OF HER-2 AND EGFR

Lapatinib is a receptor tyrosine kinase inhibitor that inhibits both HER-2 and EGFR. A phase Ⅱ trial demonstrated that lapatinib could achieve an ORR of 7% and a 20% rate of disease stabilization[58]. Regarding adverse events, one patient each experienced grade 4 cardiac toxicity and vomiting in 47 patients with metastatic gastric cancer. Additionally, two patients experienced grade 4 fatigue. In another study, lapatinib had restricted single-agent activity. Only two of 21 previously treated patients had durable, stable disease[59]. Remarkably, these disappointing results were expected, as lapatinib was adminis-

tered to both HER-2+ and HER-2- patients.

Two phase Ⅲ trials are ongoing to determine the utility of lapatinib as a first- and second-line treatment for AGC patients. The first trial, the Lapatinib Optimization Study in ErbB2 (HER-2)-Positive Gastric Cancer (LoG-IC) trial, is investigating lapatinib as a first-line treatment in combination with capecitabine and oxaliplatin[60]. The second trial, the Lapatinib (Tykerb) with paclitaxel (taxol) in Asian ErbB2+ (HER-2+) Gastric Cancer (TYTAN) trial, is investigating second-line paclitaxel treatment with or without lapatinib in Asian patients[61]. Importantly, HER-2-patients were excluded from the target AGC patients in these trials. The results of these interesting trials will determine whether lapatinib will be used to treat patients with AGC.

TARGETING VEGFR

Bevacizumab is a monoclonal antibody that inhibits vascular endothelial growth factor-A (VEGF-A), and the broad clinical activity of bevacizumab in antiangiogenic therapies has been reported[62-66]. Various phase Ⅱ trials of bevacizumab plus chemotherapy have been reported for AGC patients[67-70]. An ORR of 42%-67% was achieved, and the median TTP was 6.6-12 mo, whereas the OS time was 8.9-16.2 mo. Grade 3-4 thromboembolic diseases were reported in approximately 25% of the patients, and gastric perforation was observed in up to 8% of the patients in the phase Ⅱ trials.

The phase Ⅲ Avastin in Gastric Cancer (AVAGAST) trial was designed to evaluate the efficacy of adding bevacizumab to first-line capecitabine-cisplatin treatment for advanced gastric cancer. In total, 774 patients were randomly separated and administered capecitabine and cisplatin with or without bevacizumab[71]. In this trial, cisplatin was administered for the six cycles; capecitabine and bevacizumab were administered until the disease progressed or unacceptable toxicity developed. The primary end point was overall survival (OS). The ORR significantly improved with the addition of bevacizumab (46% *vs* 37%; P = 0.0315), and the median PFS was also significantly longer (6.7 *vs* 5.3 mo; HR = 0.80; 95%CI: 0.68-0.93; P = 0.0037)[71]. Additionally, the clinical outcomes were different depending on the geographical region. Survival was extended in Pan-American patients who were treated with bevacizumab; however, this was not the case for Asians or Europeans, despite the better prognosis of the latter. Differences in population genetics, patient selection and second-line chemotherapy may explain these results. Furthermore, biomarker studies will elucidate the reasons underlying the differences in efficacy. Interestingly, Ohtsu *et al* reported that angiogenic markers, such as plasma VEGF-A and tumor neuropilin-1, can have predictive value for the clinical outcomes of patients with gastric cancer treated with bevacizumab in the AVAGAST randomized phase Ⅲ trials[72]. These results may lead to a better understanding of the study outcome. The most common grade 3-5 adverse events in both arms of

the trial were neutropenia, anemia and appetite loss, and these events occurred at similar rates with or without bevacizumab[71].

COMBINED TARGETING OF VEGFR AND PDGFR

Sorafenib and sunitinib are multitargeted TKIs that inhibit angiogenesis by targeting VEGFR, PDGFR and other signaling pathways. Sorafenib is a multitarget inhibitor of BRAF, VEGF, PDGFR and the Ras/Raf/MERK/ERK pathway. A phase II study was performed to assess the combination of oxaliplatin and sorafenib as a second-line therapy for AGC after treatment with cisplatin and fluoropyrimidine first-line therapy. Among 40 AGC patients, the CR was 2.5%, and the SD was 47.2%. The median PFS was 3 mo (95%CI: 2.3-4.1), and the median OS was 6.5 mo (95%CI: 5.2-9.6). The median OS was 9.7 mo when the time-to-progression during the first-line chemotherapy was > 6 mo and was decreased to 5.6 mo when the time-to-progression was < 6 mo ($P = 0.04$)[73]. Grade 3-4 neutropenia (9.8%), thrombocytopenia (7.3%) and neurotoxicity (4.9%) were reported. The combination of oxaliplatin and sorafenib in AGC patients previously treated with cisplatin and fluoropyrimidine appeared safe; however, these results did not support the implementation of a phase III trial[73].

Sunitinib suppresses PDGFR, Kit, rearranged during transfection (RET), Flt-3 and VEGFR. A phase II study of single-agent sunitinib as a second-line treatment for AGC patients treated with one prior chemotherapy regimen was performed, and 2.6% of the enrolled patients had a partial response, whereas 25 patients (32.1%) had stable disease. The median PFS was 2.3 mo, and the median OS was 6.8 mo. Grade 3-4 thrombocytopenia and neutropenia were reported in 34.6% and 29.4% of the patients, respectively[74]. In another phase II trial, disease stabilization was reported in five out of 14 patients[75]. These results suggested that single-agent sunitinib did not have sufficient clinical value as a second-line treatment for AGC. Sunitinib is unlikely to be further developed into a first-line treatment or to be used in combination with chemotherapy due to the complete failure of sunitinib to change the survival outcome of other solid tumors when combined with chemotherapy[76].

TARGETING OTHER RTKS AND NEW COMBINED TARGETING OF HER2 AND VEGF

The overexpression and activation of c-Met, an RTK for hepatocyte growth factor, induces proliferation and anti-apoptotic signals[77]. c-Met was found to be overexpressed in human gastric cancer cells both *in vitro*[78] and *in vivo*[79]. Amplification of the *MET* gene can be used to determine the response to Met inhibition *in vitro*[55]. A phase II study of GSK1363089 (GSK089, formerly XL880), a c-Met TKI, demonstrated that this compound had minimal activity in metastatic gastric cancer patients, and liver dysfunction, fatigue and venous thromboembolism were reported as adverse events[80].

Insulin-like growth factor 1 receptor (IGF-1R) expression is correlated with poor outcome in AGC patients[81], and treatment with the IGF-1R antibody figitumumab in conjunction with docetaxel was well tolerated and in a phase I trial of advanced solid tumor patients[82]. FGFR may be a targetable RTK, as the secretion of the FGF family by fibroblasts stimulates the proliferation of scirrhous gastric cancer cells[83]. Additionally, mutations in FGFR are associated with the development of gastric cancer[84], and selective inhibitors of FGFR may be used in clinical trials for AGC patients[85].

In addition, AXL receptor tyrosine-kinase family, such as axl/ufo and nyk/mer protein kinases, co-operatively correlates with the cancer progression, metastasis and patients' prognosis in gastric cancer[27]. The specific ligand growth arrest-specific gene 6 (Gas6) binds to Axl and Gas6-Axl signaling pathway enhanced cellular survival and invasion and suppressed apoptosis via Akt family during gastric carcinogenesis[86]. Gas6-Axl signaling could be a potential therapeutic target in gastric cancer.

Recently, Singh *et al*[87] reported combined blockade of HER-2 and VEGF brings about greater growth inhibition in HER-2 overexpressing gastric cancer xenografts. This result suggests that new combination therapy using inhibitors of HER-2 and VEGF may represent a new approach for the treatment of HER-2 positive AGC patients.

CONCLUSION

Effective RTK inhibitors have been developed over the years, and their potential usefulness will increase further as preclinical data using gastric cancer models continue to demonstrate their effectiveness. Several RTKs are activated in advanced gastric cancer; therefore, targeting these RTKs may lead to tailored therapy. Unfortunately, recent progress in the development of RTK-targeted therapy for AGC patients has been modest. Well-designed clinical trials and combinations with appropriate drugs are required to provide maximal therapeutic benefits. Furthermore, new predictive biomarkers are immediately needed to guide the selection of a potentially drug-sensitive cohort of patients.

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