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The HER Family: a Vital Target for Advanced Gastric Cancer Therapy

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ABSTRACT

Gastric cancer is one of the leading causes of cancer-related death. Unfortunately, the majority of gastric cancer patients are diagnosed at advanced stages. For these patients systemic chemotherapy is the standard treatment. However, prognosis remains dismal. Therefore, molecular targeting therapy is developed. Among all these targets, the human epidermal growth factor receptor (HER) family seems to provide the most promising perspective. Recently, several large phase III trials on anti-HER agents in gastric cancer have come to conclusions. In this review, we will discuss available investigations and clinical evidence of anti-HER agents for the treatment of advanced gastric cancer and provide insight into future treatment.

Key words: Humans, stomach neoplasms, human epidermal growth factor receptor, epidermal growth factor receptor, antibody, treatment outcome.

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Abbreviations: AGC: Advanced gastric cancer; **OS:** Overall survival; **HER:** The human epidermal growth factor receptor; **EGFR:** Epidermal growth factor receptor; **TGF:** Transforming growth factor; **PI3K:** Phosphatidylinositol-3-kinase; **MAPK:** Mitogen activated protein kinase; **mTOR:** Mammalian target of rapamycin; **ERK:** Signal–related kinase; **JAK:** Janus kinase; **STAT:** signal transducer and activator of transcription; **GEJC:** Gastroesophageal junction cancer; **ORR:** Overall response rate; **TTP:** Median time to progression; **PFS:** Progression free survival; **ATP:** Adenosine triphosphate; **FDA:** Food and Drug Administration; **IHC:** immunohistochemistry; **FISH:** Fluorescent in situ hybridization; **IL:** Interleukin.

INTRODUCTION

Despite a substantial downtrend in most parts of the world, gastric cancer is still one of the leading causes of cancer-related death (Jemal et al., 2011; Bertuccio et al., 2009). Because of the non-typical early symptoms, the majority of gastric cancer patients are diagnosed at advanced stages.

Surgical resection is the cardinal curative treatment, but it can only be performed in a tiny minority of advanced gastric cancer (AGC) patients with a certain risk to recur locally or distantly. Effectiveness of other combining treatments, such as peri-operative chemotherapy or chemoradiotherapy remains limited. Absolute benefits from chemotherapy plus surgery compared with surgery alone were only 5.8% at 5-year survival rates (from 49.6 to 55.3% respectively) (Group et al., 2010). The median overall survival (OS) in the surgery alone group was twenty-seven (27) months as compared with thirty-six (36) months in the chemoradiotherapy after surgery group; the hazard ratio for death was 1.35 (95% confidence interval, 1.09 to 1.66; P=0.005) (Macdonald et al.,., 2001). However, most patients are either unresectable with metastatic settings or develop relapse after curative surgery. Under these circumstances, systemic chemotherapy is the gold standard of palliative treatment, achieving a median survival time ranging between six (6) and eleven (11) months (Wagner et al., 2005). This dismal prognosis was not improved by a third chemotherapy agent adding to two-drug regimens which has a remarkable additional toxicity (Cunningham et al., 2008; Van Cutsem et al., 2006). AGC patients usually have

poor general conditions and may not be able to tolerate the toxicity of traditional cytotoxic drugs. To a certain extent, the development of conventional cytotoxic agents has hit a plateau.

As understanding of molecular mechanism underlying carcinogenesis goes deeper, the rationally designed drugs that target over-expressed or aberrant components of signaling transduction pathways specific to gastric cancer develop. These targets include circulating growth and angiogenic factors, cell surface receptors and other molecules modulating intracellular signaling pathways. Among all these targets, the human epidermal growth factor receptor (HER) family seems to provide the most promising perspective (Fornaro et al., 2011; Gomez-Martin et al., 2014). Contemporary anti-HER targeted therapies of many common malignancies have progressed rapidly over the past decade, such as breast and colorectal cancers. Unfortunately, the development of anti-HER agents for gastric cancer is relatively slow.

Recently, several large phase III trials on anti-HER agents in gastric cancer have come to conclusion. In this review, we available investigations and clinical evidence of anti-HER agents for the treatment of AGC was summarized and insight into future treatment provided.

THE HER FAMILY

The human epidermal growth factor receptor (HER) family, also known as the ErbB protein family consists of four members: HER-1 (epidermal growth factor receptor [EGFR]), HER-2, HER-3, and HER-4 (Boonstra et al., 2007).

EGFR is a trans-membrane glycoprotein containing an extracellular binding domain, a trans-membrane domain and an intracellular protein tyrosine kinase domain. Specific ligands, epidermal growth factor (EGF) and transforming growth factor (TGF) alpha bind to the extracellular domain leading to the intracellular tyrosine kinases activation and subsequently receptor auto-phosphorylation which initiate intracellular downstream signal transduction pathways. These downstream pathways include the phosphatidylinositol-3-kinase (PI3K) pathway, central Ras/Raf/mitogen activated protein kinase (MAPK) pathway, Akt/mammalian target of rapamycin (mTOR) pathway, signal–related kinase (ERK) kinase (MEK)–ERK pathways, and the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway.

HER-2 is also a tyrosine kinase receptor existing on the cell surface. Unlike EGFR, HER-2 alone can be activated without any ligands binding, which is involved in the signal transduction pathways. All these signaling pathways in turn regulate DNA synthesis, cell survival, proliferation, apoptosis, migration, adhesion, cell cycle progression, and angiogenesis, and treatment resistance (Boonstra et al., 2007; Dhanasekaran and Johnson, 2007; Schlessinger, 2004; Pai and Tarnawski, 1998; Pai and Tarnawski, 1998; Arteaga, 2003).

EGFR is expressed in different normal human tissues and has been observed to be over-expressed in multiple tumors. In gastric cancer, EGFR over-expression has been reported in 8 to 63% of tumors (Takehana et al., 2003; Terashima et al., 2012; Tokunaga et al., 1995; Kim et al., 2008; Matsubara et al., 2008) and is correlated with degree of invasion, metastasis and a poor prognosis (Tokunaga et al., 1995; Gamboa-Dominguez et al., 2004). Similar to EGFR, some researchers reported that HER-2 positive were associated with metastases, high relapse rate and short survival time (Tokunaga et al., 1995; Matsubara et al., 2008; Im et al., 2005; Allgayer et al., 2000; Kim et al., 2011).

EGFR TARGETING AGENT

Anti-EGFR monoclonal antibodies

Cetuximab

Cetuximab is a recombinant mouse/human chimeric IgG1 monoclonal antibody targeting EGFR. It binds to the extracellular portion of EGFR with high affinity on both normal and tumor cells which competitively inhibits binding of natural ligands, prevents activation of tyrosine kinase resulting in down regulation. In both locally advanced and metastatic settings of gastric or gastroesophageal junction cancer (GEJC), cetuximab was extensively evaluated as monotherapy (Chan et al., 2011) or in combination with radiation and chemotherapy.

Several phase II trials (Table 1) have investigated the activity and safety of cetuximab combined with various chemotherapeutic agents in the first-line treatment, such as 5-fluorouracil, leucovorin, Irinotecan (FOLFIRI) --- FOLCETUX study (Pinto et al., 2007) and Moehler's study (Moehler et al., 2011), docetaxel / cisplatin --- DOCETUX study (Pinto et al., 2009); weekly cisplatin and 24-hour infusion of high-dose 5-fluorouracil and leucovorin (Yeh et al., 2009); 5-fluorouracil / folinic acid / Irinotecan (FUFIRI) (Kanzler et al., 2009); 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX) (Han et al., 2009) / (FUFOX) (Lordick et al., 2010); capecitabine, oxaliplatin (XELOX) (Kim et al., 2011); irinotecan, cetuximab (Woll et al., 2011); docetaxel, oxaliplatin (Richards et al., 2013); 5-fluorouracil, oxaliplatin (Zhang et al., 2014) and capecitabine+cisplatin (Zhang et al., 2014). To sum up, these trials have reported encouraging overall response rates (ORRs) of 38 to 68.6% median time to progression (TTP) or progression free survival (PFS) ranged between 5.0 and 12.8 months and median overall survival (OS) of 9.0 to 16.6 months, suggesting an additional clinical benefit over chemotherapy alone.

Cetuximab combined with FUFOX (oxaliplatin 50 mg/m^2, 5-FU 2000 mg/m^2, and DL-folinic acid 200 mg mg/m^2 d1, 8, 15 and 22 qd36) achieved a relatively high response rate of 65% and TTP of 7.6 months in comparison with FOLFOX

Table 1. Phase II and III Trials of Cetuximab in Advanced Gastric Cancer.

Author	Phase	No.of assessable patients	Agents combined with cetuximab	Line of treatment	ORR (%)	TTP/PFS (months)	OS (months)
(Zhang et al., 2014)	II	47	Capecitabine+Cisplatin	First	53.2	5.2	10.8
(Zhang et al., 2014)	II	30	5-fluorouracil +Oxaliplatin	First	54.8	12.8	14.0
(Lordick et al., 2013)	III	455	Capecitabine+Cisplatin	First+ Second	30	4.4	9.4
(Richards et al., 2013)	II	75	Docetaxel+Oxaliplatin	First	38	5.1	9.4
(Tebbutt et al., 2013)	II	38	Docetaxel	Second	6	2.1	5.4
(Schonnemann et al., 2012)	II	63	Irinotecan	Second	11	2.8	6.1
(Moehler et al., 2011)	II	48	5-fluorouracil+folinic acid +Irinotecan (FUFIRI)	First	46	9	16.5
(Woll et al., 2011)	II	35	Irinotecan+Oxaliplatin	First	63	6.2	9.5
(Kim et al., 2011)	II	44	Capecitabine+Oxaliplatin (XELOX)	First	52.3	6.5	11.8
(Lordick et al., 2010)	II	46	5-fluorouracil+Leucovorin+Oxaliplatin (FUFOX)	First	65	7.6	9.5
(Han et al., 2009)	II	38	5-fluorouracil+Leucovorin+Oxaliplatin (FOLFOX)	First	50	5.5	9.9
(Kanzler et al., 2009)	II	49	5-fluorouracil+folinic acid +Irinotecan(FUFIRI)	First	42	8.5	16.6
(Yeh et al., 2009)	II	35	5-fluorouracil+Leucovorin+Cisplatin	First	68.6	11	14.5
(Pinto et al., 2009)	II	72	Docetaxel/Cisplatin	First	41.2	5.0	9.0
(Pinto et al., 2007)	II	38	5-fluorouracil+Leucovorin+Irinotecan (FOLFIRI)	First	44.1	8.0	16.0

ORR: Overall response rate; **TTP:** Time to progression; **PFS:** Progression free survival; **OS:** Overall survival.

(oxaliplatin 100 mg/m^2 and leucovorin 100 mg/m^2 administered as a 2-h infusion followed by a 46-h continuous infusion of 5-fluorouracil 2400 mg/m^2 every 2 weeks for a maximum of 12 cycles) in advanced gastric cancer patients (Han et al., 2009; Lordick et al., 2010). Worthy of mention, cetuximab was also evaluated as second-line treatment with a modest efficacy in patients with gastro-esophageal and metastatic gastric cancer who are refractory to first-line chemotherapy (Tebbutt et al., 2013; Schonnemann et al., 2012; Park et al., 2010).

The correlation between EGFR expression and response to cetuximab is controversial. Zhang et al. (2014) found that patients with EGFR strong expression showed great tumor shrinkage, longer PFS and OS. Some other trials also reported EGFR over-expression might predict cetuximab efficacy (Moehler et al., 2011; Han et al., 2009). On the other hand, there are also some trials failing to find the presence of EGFR or a K-ras mutation be associated with treatment outcomes (Lordick et al., 2010; Park et al., 2010).

The most frequent grade 3/4 toxic effects observed were neutropenia, diarrhea, nausea and skin toxicity (Moehler et al., 2011; Pinto et al., 2009; Lordick et al., 2010; Kim et al., 2011; Woll et al., 2011; Richards et al., 2013).

Phase II trials have proved the effectiveness of cetuximab combined with chemotherapy for advanced gastric cancer with acceptable side effects and low rates of treatment-related death rates (Pinto et al., 2007). Actually, one of these toxic effects, skin rash, merits a special attention. Several studies have revealed that severity of skin rash was significantly associated with prolonged survival, making

cutaneous toxic reaction a potential predictor for treatment response (Lordick et al., 2010; Lordick et al., 2010; Zhang et al., 2014; Schonnemann et al., 2012; Park et al., 2010).

Unfortunately, the open-label, randomized phase III trial expands. Lordick et al. (2013) found that addition of cetuximab to capecitabine and cisplatin in the first-line treatment of unselected patients with advanced gastric or gastroesophageal junction cancer provided no benefit compared with chemotherapy alone with increased rates of drug-related adverse events. In addition, EGFR tumour expression was generally low, and the EGFR immuno-histochemistry score was not associated with PFS or overall survival in either treatment group. To a certain extent, the powerful evidence of efficacy of cetuximab in gastric cancer is scarce. Further molecular classification and candidate biomarkers are still needed.

Matuzumab

Matuzumab is a humanized monoclonal antibody IgG1 against EGFR. A phase I study showed promising anti-tumour activity and feasible tolerability in matuzumab combined with ECX regimen (epirubicin, cisplatin, capecitabine) as first-line therapy for patients with EGFR-positive advanced oesophagogastric cancer (Rao et al., 2008). On this basis, a multicentre, randomized open-label phase II study which enrolled seventy-two (72) patients with metastatic oesophagogastric cancer was conducted. In this trial, patients were randomly assigned to matuzumab plus ECX regimen arm or the same ECX regimen arm alone.

Disappointingly, the addition of matuzumab to ECX did not improve objective response: 31% for ECX/matuzumab as compared with 58% for the ECX arm (P = 0.994). There was no significant difference in median PFS or in median OS (Rao et al., 2010). Although, matuzumab combined with high-dose 5-fluorouracil, leucovorin and cisplatin in the first-line treatment of patients with EGFR-positive advanced gastric and esophagogastric adenocarcinomas demonstrated an acceptable safety profile with modest anti-tumor activity (Trarbach et al., 2013). Whether matuzumab should be examined in further trials is controversial.

Panitumumab

Another fully humanized monoclonal antibody targeting EGFR is IgG2. Although, it has been approved for the treatment of EGFR-positive chemotherapy-refractory metastatic colorectal cancer (Van et al., 2007), available data of panitumumab in gastric cancer is scarce. There were only several trials of panitumumab for esophagogastric and distal esophagus cancer. A randomized Phase II /III study conducted by Okines et al. (2010) recommended the dose of epirubicin, oxaliplatin, and capecitabine (EOC) with or without panitumumab for advanced esophagogastric cancer was epirubicin 50 mg/m^2, oxaliplatin 100 mg/m^2, capecitabine 1,000 mg/m^2/d, and P 9 mg/kg in every 3 weeks. Sadly, the REAL3 trial found that addition of panitumumab to EOC chemotherapy did not increase overall survival and the researchers alleged that panitumumab cannot be recommended to an unselected population with advanced oesophagogastric adenocarcinoma (Waddell et al., 2013). Similarly, another phase II study showed panitumumab combined docetaxel and cisplatin as a part of neoadjuvant chemoradiotherapy in patients with locally advanced distal esophagus. Adenocarcinoma had a little effectiveness with considerable toxicity (Lockhart et al., 2014). Further evaluation of this regimen in an unselected population is not recommended.

Anti-EGFR tyrosine kinase inhibitors (TKIs)

The anti-EGFR TKIs are oral small molecules that competitively bind adenosine triphosphate (ATP), leading to inhibition of EGFR autophosphorylation and activation of the signal downstream transduction (Herbst et al., 2004).

Gefitinib

Gefitinib is an anti-EGFR TKI approved by the FDA for the treatment of patients with advanced non-small-cell lung cancer in many countries (Fukuoka et al., 2003). However, in currently undergoing clinical trials for GEJC, gefitinib came out with disappointing results. For advanced gastric carcinoma patients, gefitinib reached the concentration sufficient to inhibit EGFR activation, but this did not translate into clinical benefit (Rojo et al., 2006). Another two phase II studies showed the failure of gefitinib in esophagus and gastro-esophageal junction cancer patients, as a monotherapy (Adelstein et al., 2012) or as addition to concurrent chemoradiotherapy (Rodriguez et al., 2010). Furthermore, Wang et al. (2012) proved that adenocarcinoma of esophagogastric junction rarely presents EGFR mutation, especially gefitinib-associated mutations. This means that the gefitinib-based gene target therapy may not merit further investigation for treating esophagus, gastric or gastroesophageal junction cancer.

Erlotinib

Anther common oral small molecules anti-EGFR TKI, erlotinib has been approved for the first-line or second-line treatment of advanced cancers, such as non-small-cell lung cancer and pancreatic cancer (Shepherd et al., 2005; Moore et al., 2007). Although, erlotinib has shown activity in GEJC, as for gastric cancer patients, it does not go any further. A phase II trial in patients with metastatic or advanced adenocarcinoma of the oesophagus and gastro-oesophageal

junction proved that modified FOLFOX6 and erlotinib had a modest efficacy (objective RR of 51.5%, median PFS of 5.5 months and median OS of 11.0 months) with an acceptable toxicity profile (Wainberg et al., 2011). Iyer et al. (2013) combined erlotinib with radiation therapy for elderly patients (>65 years) with esophageal cancer and found it to be tolerable. However, the only phase II trial of erlotinib involving gastric cancer turned out that the distal gastric adenocarcinomas stratum had no objective response and a median OS of 3.5 months as compared with the gastro-esophageal junction stratum, with an ORR of 9% and median OS of 6.7 months (Dragovich et al., 2007).

In general, based on the current evidence, although, anti-EGFR agents were well tolerated with toxicities; there was not enough clinical data to support the significant activity in the treatment of gastric cancer. It may thus be postulated that EGFR is not an appropriately potential target for therapy of advanced gastric cancer.

HER-2 targeting agent

Anti-HER-2 monoclonal antibodies

Trastuzumab

Trastuzumab is a recombinant humanized IgG1 monoclonal antibody against the HER-2 receptor. Binding of trastuzumab to the HER2 protein impedes heterodimerization to other EGF receptors and suppresses the autophosphorylation of HER2 resulting in deactivation of downstream signalling pathways. It can also increase endocytosis and destroy the cell surface receptors, inhibiting shedding of the extracellular domain and inducing antibody-dependent cytotoxicity.

Trastuzumab is the first monoclonal antibody that has been shown to prolong life in patients with a human epithelial malignant condition (Hudis, 2007). As a classic target agent for HER2- positive and node positive breast cancer, trastuzumab has been used in combination with chemotherapy as adjuvant therapy (Piccart-Gebhart et al., 2005; Romond et al., 2005; Smith et al., 2007) or as first-, second- or third-line monotherapy in a metastatic setting (Inoue et al., 2010). In 2009, trastuzumab was approved by the European Commission for the treatment of HER-2 positive gastric cancer. Later, in combination with chemotherapy trastuzumab was recognized by U.S. Food and Drug Administration (2011) and European Medicines Agency (2011) as first-line therapy in HER2 positive GC and GEJC.

In recent years, clinical investigation in trastuzumab has been actively pursued. Table 2 summarizes the results of trastuzumab-based first-line treatment trails for AGC. In combination with conventional chemotherapy agents such as cisplatin, fluorouracil, capecitabine and oxaliplatin, trastuzumab achieved an ORR of 32 to 68%, a TTP/PFS of 5.1 to 10.4 months and an OS of 13.8 to 21.0 months. These results demonstrated its potent anti-tumor activity in gastric cancer.

The ToGA (Trastuzumab for Gastric Cancer) trial (Bang et al., 2010) is an open-label, randomized multicenter phase III study conducted in 122 centres across twenty-four (24) countries in HER2-positive patients who had advanced gastroesophageal and gastric adenocarcinoma. The patients were randomized to receive chemotherapy (5-FU or capecitabine and cisplatin) alone or chemotherapy in combination with trastuzumab. The primary endpoint of OS was significantly improved in the trastuzumab combined arm (median OS 13.8 vs 11.1 months; p= 0.0046). Other parameters also statistically increased with the addition of trastuzumab, including PFS (6.7 vs 5.5 months; p= 0.0002) and RR (47 vs 35%; p= 0.002). More importantly, toxicity brought by the addition of trastuzumab to chemotherapy was very mild. There were neither increasing overall rates of adverse events nor differences in cardiac adverse events between the two treatment arms. The most common toxicities, such as nausea, neutropenia, vomiting and anorexia were totally acceptable.

Since the approval of trastuzumab as a new option for HER2-positive advanced gastro-esophageal and gastric cancer patients, Her-2/neu expression is now examined routinely by immunohistochemistry (IHC) and fluorescent *in situ* hybridization (FISH). HER2 positivity is defined as a score of 3+ on IHC. Samples with an equivocal IHC 2+ score should be retested by FISH. Patients with IHC2+/FISH+ are still eligible for trastuzumab. In the ToGA trial, the enrolment of patients was even allowed with a FISH+/IHC1+ or 0. Because of the biological heterogeneity of gastric cancer cells, the scoring system for HER-2 positivity in gastric cancers is specific and differs from the standard system for breast cancer. Using this system, there have been studies showing that HER-2 positivity rates were higher in GEJC than GC and in intestinal than diffused or mixed histology type (Bang et al., 2010, 2009) and HER-2 expression is positive in 10 to 22% GC patients (Bang et al., 2010, 2009; Gravalos et al., 2011).

As the ToGA trial shown, benefits increased in patients with higher levels of expression of HER2 (IHC 2+/FISH+ or IHC 3+) than in those with lower levels (FISH+/IHC 0 or 1+). Gravalos et al. (2011) have drawn the same conclusion: higher baseline HER extracellular domain levels were associated with better outcome in terms of response and survival. A recent study led by Satoh et al. (2014) also delivered a very promising result. Compared with chemotherapy alone, trastuzumab plus chemotherapy prolongs time to deterioration of health-related quality of life and increases quality-adjusted survival in patients with HER2-positive gastric or gastroesophageal junction cancer.

On the whole, trastuzumab is an efficient targeted agent for advanced gastric cancer with well toleration and improving quality-adjusted survival. Further research should be done to explore the range and details of its

Table 2. Phase II and III trials of Trastuzumab in first-line treatment of advanced gastric cancer.

Author	Phase	No. of assessable patients	Agents combined with Cetuximab	ORR (%)	TTP/PFS (months)	OS (months)	Toxicities (>10%)
(Bang, 2010)	III	584	Cisplatin + fluorouracil/capecitabine	47	6.7	13.8	Vomiting (50%) and Neutropenia (53%) (Grade 3)
(Gravalos et al., 2011)	II	228	Cisplatin	32	5.1	-	Asthenia (27%) neutropenia (18%) and Anorexia (14%)
(Kurokawa et al., 2014)	II	53	S-1+Cisplatin	68	7.8	16	(grade 3 or 4) Neutropaenia (36%) Anorexia (23%) and Anaemia (15%)
(Choo et al., 2014)	II	30	S-1+cisplatin	63	7.4	14.6	Anorexia (50%). Fatigue (47%). Diarrhea (47%). Nausea (37%). Neutropenia (33%). Anemia (27%) and Mucositis (27%)
Ryu et al., 2014)	II	55	Capecitabine+ Oxaliplatin	67.3	9.8	21.0	(grade 3 or 4) Neutropenia (18.2%), Anemia (10.9%) and Neuropathy (10.9%)
(Gong et al., 2014)	II	51	Capecitabine+ Oxaliplatin	66.7	10.4	-	(grade 3 or 4) thrombocytopenia (21.6%) and Neutropenia (13.7%)

ORR: Overall response rate; **TTP:** Time to progression; **PFS:** Progression free survival; **OS:** Overall survival.

applications, such as clinical trials evaluating trastuzumab in the peri-operative and adjuvant setting and subgroup analyses of the effect of trastuzumab according to various baseline pathophysiological characteristics. In addition, in order to guarantee the long-term benefits, preventive research of primary or acquired resistance to trastuzumab must be carried out on schedule.

Anti-HER-2 and anti-EGFR tyrosine kinase inhibitors (TKIs)

Lapatinib

Lapatinib is an oral, dual tyrosine kinase inhibitor of EGFR and HER-2. A recent study shows that lapatinib plus capecitabine is superior to capecitabine alone in women with HER2-positive advanced breast cancer which has progressed after treatment with regimens included anthracycline, taxane and trastuzumab (Geyer et al., 2006).

Compared with the promising results in HER-2 positive breast cancer, the effectiveness of apatinib in therapy of AGC is not that clear. A phase II trial of lapatinib as first-line monotherapy in forty-seven (47) patients with advanced or metastatic gastric cancer reported excellent tolerability but modest single-agent activity (9% PR, median time to treatment failure 1.9 months, median OS 4.8 months). Notably, in this trial lapatinib was given to an unselected population. An exploratory analysis of potential molecular markers revealed gene expression of HER2, interleukin (IL)-8, genomic polymorphisms IL-8, and vascular endothelial growth factor correlated with OS (Iqbal et al., 2011).

Another important study is TyTAN, a randomized, phase III study, which evaluated lapatinib plus paclitaxel versus

paclitaxel alone as the second-line treatment of HER2-amplified AGC in Asian populations. In TyTAN, lapatinib plus paclitaxel demonstrated activity in the second-line treatment of patients with HER2 FISH-positive IHC3+ AGC but did not significantly improve OS in the intent to treat the population (Satoh et al., 2014).

Conclusion

The heterogeneity of gastric cancer makes the development of biologic drugs very slow. The failure of cetuximab in EXPAND trial gave us a reason to suspect EGFR as a potential therapeutic target for gastric cancer. This may be the explanation why lapatinib, a dual inhibitor of both EGFR and HER2 cannot achieve a better curative effect than trastuzumab even with selected patient populationin TyTAN trial. However, there is still a lot of hope for the future targeted therapy in gastric cancer. The positive result of the ToGA trial proved the effectiveness of the addition of trastuzumab to combination chemotherapy. Now, trastuzumab is not only the first approved inhibitor which can improve the overall survival significantly, but also considered as first-line treatment for HER2 positive AGC.

To some extent, the success of the ToGA trial was associated with refined patient selection. Using the optimal therapeutic regimens on the right patient population is a crucial part of individualized treatment. Identifying patients through specific molecular profiling and prognostic markers will allow us to enroll patients who will benefit most from the designed targeted therapy. Moreover, except for conventional cytotoxic drugs, an effective therapy strategy may involve trastuzumab in combination with other targeted agents, such as vascular endothelial growth factor, mammalian target of rapamycin, hepatocyte growth factor receptor and cyclooxygenase-2inhibitors. Finally, many other anti-HER family agents are currently under investigation and development of new agents is still urgently needed.

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