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Molecular Targeting Therapy and Biomarker for Advanced Gastric Cancer

Kohei Shitara*, Toshihiko Doi and Atsushi Ohtsu

Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa, Chiba 277-8577, Japan

Summary

In recent years, various molecular target agents have been investigated for gastric cancer. Main targets are HER family pathway, angiogenesis system and PI3K-Akt-mTOR intracellular signaling system. The anti-HER2 antibody trastuzumab was shown to prolong the survival of patients with HER2-positive advanced gastric cancer, and is approved by the treatment in advanced gastric cancer. On the other hand, the anti-VEGF antibody bevacizumab could not show survival benefit despite certain effect in progression-free survival and response rate. mTOR inhibitor everolimus showed disease control rate of 54.7% in patients with previously treated gastric cancer in a Japanese phase II trial. However, subsequent global phase III trial, GRANITE-1, which compare everolimus with placebo, could not meet its primary endpoint of overall survival. Recent REAL-III trial also could not show survival benefit of EGFR antibody panitumumab. These three negative phase III trials strongly suggest the importance of developing biomarkers to predict the effectiveness of each agent.

Current Status of Chemotherapy for Advanced Gastric Cancer and Expectations for Molecular Targeting Therapy

Systemic chemotherapy is a standard treatment for unresectable advanced or recurrent gastric cancer. Commonly used first-line therapy is the combination of fluoropyrimidine and platinum-based chemotherapy with or without docetaxel or anthracycline [1]. Further second-line therapy with irinotecan or taxane is reported to improve the prognosis after disease progression with first-line treatment [2-4]. The prognosis of advanced gastric cancer treated with chemotherapy is, however, far from satisfactory, the median overall survival (OS) for patients who underwent chemotherapy was merely 1 year, thus there is an urgent need to develop of more effective treatment strategies. In the 1990's, the advancement of molecular biology allowed to elucidate cancer growth factors and their receptors, signal transmission molecules, cell cycle-related molecules, apoptosis-related molecules, and invasion- and metastasis-related molecules, which led to the development of several molecular target agents. The application of molecular target agents have led to marked improvement in overall survival of several types of cancers, and expansion in the use of molecular target agents, i.e. with gastric cancer, was also anticipated. At the annual meeting of American Society of Clinical Oncology (ASCO) Conference in 2009, it was reported that trastuzumab, a monoclonal antibody for HER2, significantly improve the survival of human epidermal growth factor receptor type-2 (HER2)-positive gastric cancer. This is the dawn of the era of molecular target agents for gastric cancer. Main targets are HER family pathway, angiogenesis system and PI3K-Akt-mTOR intracellular signaling system (Figure 1). In this paper, we present an overview of the current status of biomarkers and the development of molecular targeting therapy for gastric cancer, and describe future perspectives.

HER2-Targeted Therapy

HER2 protein (human epidermal growth factor receptor type-2), also known as HER2/neu or ErbB2, is a transmembrane receptor with a molecular weight of 185 kDa, and it belongs to the family of epidermal growth factor receptors (EGFR). HER family is composed of known four receptors: HER1 (epidermal growth factor receptor; EGFR), HER2, HER3 and HER4. And all receptors share a similar structure: an extracellular ligand-binding domain, a short hydrophobic transmembrane region, and an intracellular domain having tyrosine kinase activity (except for HER3). The HER2 receptor differs from other HER family receptors in that there are no known ligands that bind to HER2. The HER family, after the activation of its receptor, enables transmission of the growth factor activation signal through the MAPK, Akt and STAT downstream signaling pathways, inducing cellular responses including cell proliferation, differentiation and migration. It has been reported that HER2 gene amplification and protein over-expression in breast cancer is associated with treatment

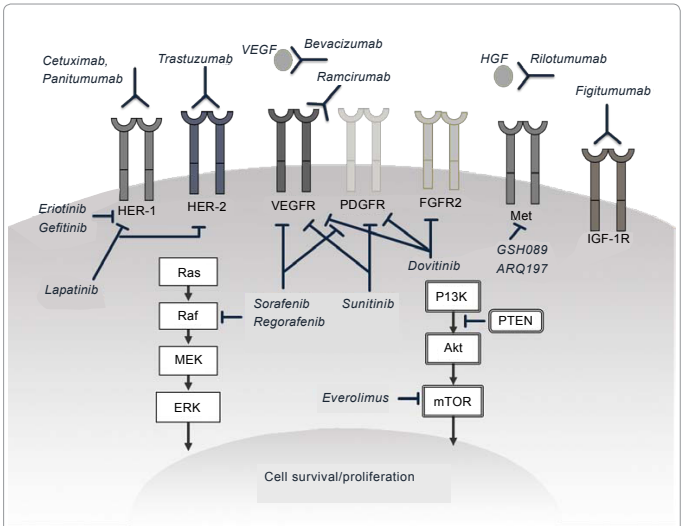

Figure 1: Molecular targeting therapy and its targets for Gastric Cancer.

***Corresponding author:** Kohei Shitara, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa, Chiba 277-8577, Japan, Tel: 81-47-133-1111; Fax: 81-47-134-6928; E-mail: kshitara@east.ncc.go.jp

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resistance, resulting in poor prognosis. The prognosis of patients with HER2 positive breast cancer is improved by introducing trastuzumab, which is an IgG1 monoclonal antibody against HER2 protein [5]. Trastuzumab can specifically recognize the extracellular domain of HER2 and inhibit signaling. An antitumor activity of trastuzumab has also been reported and is due to antibody-depended cellular cytotoxicity (ADCC).

HER2-positive cases have also been observed in gastric cancer. Hoffman et al. examined the HER2 status in 178 gastric cancer samples using immunohistochemistry (IHC) and FISH analysis [6]. They reported that IHC and FISH discrepancies occurred mainly due to the following reasons: (a) non-uniformity of staining between the basement membrane side (positive) and grandular lumen side (negative) of fundic gland cells, and (b) tumor formation of heterogeneous gastric cancer cells. Based on the above, a modified HercepTest™ has been devised, taking more into account the characteristics of gastric cancer. In general, IHC 3+ in breast cancer indicates a uniform staining of more than 30% of the tumor cells must show consistent strong staining [7]. In contrast, the modified HercepTest™ needs to only show intense staining in more than 10% of the tumor cells either in the circumference or basement membrane [6,8].

A ToGA multi-regional randomized trial was conducted to verify the clinical benefits of combination therapy with trastuzumab and standard chemotherapy regimens (i.e. cisplatin- and fluoropyrimidine (5-FU/capecitabine)-based chemotherapy; FC) for patients with HER2-positive gastric cancers [9]. Tumor samples from 24 countries have been assessed for HER2 status using a modified HercepTest™ where a HER2-positive result was defined as IHC 3+ or FISH positive. A total of 3807 tumor samples were screened for modified HercepTest™ of the 3807 samples screened, 3667 were assessable and 810 (22.1%) were HER2-positive [8,9]. The intestinal type exhibited a higher rate of HER2-positive than did the diffuse type (34% vs.6%); also, HER2 positivity was higher for adenocarcinoma of esophagogastric junction compared to gastric cancer (33.2% vs.20.9%). In the ToGA study, 584 samples were allocated to either the FC arm or the FC+trastuzumab arm. Median OS was significantly longer in the combination arm: 11.0 months for the FC arm versus 13.8 months for the FC+trastuzumab arm (HR 0.71, 95%CI; 0.59-0.85, p=0.0046, table 1) [9]. Both progression-free survival (PFS) and response rate were also significantly improved in the combination arm: 6.7 months vs. 5.5 months (p=0.0002, HR 0.71, 95%CI; 0.59-0.85) and 47.3% vs. 34.5% (p=0.0017), respectively. In the subset analysis of HER2 status, effect of trastuzumab was more prominent for IHC2+/FISH+ or IHC3+ patients (n=446): median OS was 11.8 months vs. 16 months (HR 0.65, 95%CI; 0.51-0.83). However, no clinical benefit with trastuzumab was observed for group that was IHC0/1+ and FISH+ (n=131): the median OS was 8.7 months vs. 10.0 months (HR 1.07, 0.7-1.62). Toxicity was within the expected range, and no decline in QOL was observed. From these results, for HER2-positive cases, trastuzumab showed a clear survival benefit, and the use of trastuzumab was approved in Japan in March 2011. Additionally, results of retrospective subset analysis suggest that it is applicable for group that is IHC2+/ IHC3+ and FISH-positive.

Study or author	Phase	Line	Target and eligibiity	N	Chemotherapy	OS	PFS	ORR	DCR
ToGA	III	1st	HER2 positive	584	FC	11	5.5	34.5	70
(ref. 9)			(IHC3 or FISH+)		FC+Trastuzumab	13.8	6.7	47.3	79
						HR 0.71, p=0.0046	*HR 0.71,p=0.0002*	*p=0.0017*	
			HER2 positive	446	FC	11.8			
			(IHC3+ or IHC2+/FISH+)		FC+Trastuzumab	16			
						HR 0.65			
REAL-3	III	1st	EGFR	553	EOC	11.3	7.4	42	63
(ref.27)					EOC+Panitumumab	8.8	6	46	64
			Not defined						
						HR 1.37, p=0.013	*HR 1.22, p=0.068*	*P=0.467*	
Kim et al	II	2nd	EGFR	77	Irinotecan+nimotuzumab	227 days	85 days	10.3	46.2
(ref. 28)					Irinotecan	293 days	73 days	18.4	47.3
			Not defined						
						HR 0.717, p=0.22	*HR 0.86 ,p=0.5668*		
AVAGAST	III	1st	VEGF	774	XP	10.1	5.3	37	66.7
(ref. 29)					XP+Bevacizumab	12.1	6.7	46	75.9
			Not defined						
						HR=0.87,p=0.1002	*HR=0.80,p=0.0037*	*p=0.0315*	
GRANITE-1	III	2nd/3rd	mTOR	656	Placebo	4.34	1.41	2.1	22
(ref.42)					Everolimus	5.39	1.68	4.5	43.3
			Not defined						
						HR 0.90,p=0.1244	*HR 0.66, p<.0001*		
Ivenson, et al.	II	1st	HGF	121	ECX	8.9	4.2	21	76
(ref.46)					ECX+rilotumumab	11.1	5.6	38	80
			Not defined						
						HR=0.73,p=0.215	*HR=0.64,p=0.045*	*p=0.089*	
			High c-Met	38*	ECX	5.7	4.6		
			(>50% of cell, exploratory analysis)		ECX+rilotumumab	11.1	6.9		
						HR=0.29	*HR=0.53*		

* Among 90 evaluable patients

Abbreviations; OS, overall survival; PFS, progression-free survival: ORR, overall response rate; DCR, disease control rate: HR, hazard ratio; FC, Capecitabine/5-FU+Cisplatin; XP, Capecitabine+Cisplatin; EOC, Epirubicin+Oxaliplatin+Capecitabine; ECX, Epirubicin+Cisplatin+Capecitabine

Table 1: Results of randomised studies of Molecular targeting therapy for Gastric Cancer.

Anti-HER2 Therapy and Biomarkers

Although trastuzumab prolongs survival of HER2-positive patients, it does not mean that trastuzumab is effective to all cases of HER2-positive. In breast cancer, it has been suggested from clinical trials that blocking HER2 and their pathways in a continuous manner contributes to tumor growth inhibition even after the disease progression. However, many cancer patients who initially responded to trastuzumab eventually experienced disease progression, suggesting that both natural resistance and acquired resistance to trastuzumab exist. With respect to resistance mechanisms, based on the studies on breast cancer, several mechanisms have been identified at: (1) the receptor level, (2) signal transduction level, and (3) crosstalk between receptors. As for (1), the following mechanism can be considered: HER2 protein molecules present on the cell surface are separated by proteolytic enzymes releasing the extracellular domain (ECD) which makes trastuzumab binding impossible. Upon release of the ECD, HER2 is now called p95 HER2. It has been reported that expression of p95 HER2 in patients with advanced breast cancer show resistance to trastuzumab [10]. Another study demonstrates that the membrane-associated mucin MUC4 (membrane associated glycoprotein mucin-4) covers the HER2 protein, preventing trastuzumab binding, therefore, developing resistance to trastuzumab [11]. As for (2), PTEN loss or activation of PI3K/AKT-mTOR pathway downstream of receptors [12-13] is reported to be one mechanism. In addition, antiapoptotic effect of survivin expression and expression of the cyclin-dependent kinase (Cdk) inhibitor p27 is reported to be as another mechanism. Finally, for (3), activation of the pathway through the IGF-1 (insulin like growth factor 1) or c-Met has been suggested [14], where c-Met is a receptor of HGF (hepatocyte growth factor). It is important to mention here that the results discussed here are based on HER2-positive breast cancer studies, and that, we need to evaluate whether or not similar trastuzumab resistance mechanisms apply to HER2-positive gastric cancer.

Lapatinib is an oral low-molecular-weight compound that reversibly binds to the cytoplasmic ATP binding site of HER1 (EGFR) and HER2 tyrosine kinase, blocks receptor phosphorylation and activation, thereby preventing subsequent downstream signaling activation. In vitro studies have shown an antitumor effect of lapatinib on p95 HER2-expressing tumors, hence, an antitumor effect of trastuzumab resistant tumors was expected. Randomised study which compare capecitabine+lapatinib with capecitabine alone for HER2-positive breast cancer patients after progression with therapies including trastuzumab showed that patients with capecitabine+lapatinib experienced significant prolongation of PFS leading capecitabine+lapatinib to become one of the standard treatments [15]. For gastric cancer, a phase II trial of lapatinib was conducted in 47 patients with advanced gastric cancer. However, the results obtained were by no means satisfactory: response rate 7% and PFS 2 months [16]. In also, out of 21 previously treated patients in another phase II study, only 2 cases of stable disease were observed with lapatinib [17], although these two trials did not limit patients to HER2-positive. Currently, the following two trials are ongoing for patients with HER2-positive gastric cancer in progress, and the results are awaited: (a) LoGIC trial which evaluates the combination of capecitabine/oxaliplatin ± lapatinib as first-line therapy, (b) TYTAN trial which evaluates the combination of paclitaxel ± lapatinib as second-line therapy for previously treated patients. Recently, randomized study for HER2-positive breast cancer, shown that pertuzumab, which inhibits formation of HER2-HER3 heterodimers and thereby inhibits crosstalk between receptors, was clearly effective in patients with HER2-positive breast cancer [18]. In also, TDM-1 (trastuzumab emtansine), which is a conjugate of the microtubules targeting agent, DM1, and the trastuzumab antibody, showed superior results compared with lapatinib plus capecitabine for patients with previously treated with trastuzumab [19]. Therefore, these agents are expected to show similar efficacy in HER2-psotive gastric cancer as well. Finally, for the mechanisms of resistance due to (3) crosstalk between receptors, the effectiveness of the combination of trastuzumab and the mTOR inhibitor for HER2-positive breast cancer has been suggested from phase II trial [20]. Other possible agents for these patients include: AKT inhibitor, PI3K inhibitor, c-MET inhibitor and SRC inhibitor.

EGFR-Targeted Therapy

EGFR (HER1) is expressed in not only normal tissue but in many malignant tumors, and is involved in tumor growth, invasion and metastasis. Although criteria to diagnose EGFR expression is not consistent and frequencies of EGFR expression are various, multiple reports have shown that EGFR was over-expressed in approximately 9-44% of gastric cancers and was linked to poor prognosis [21,22]. EGFR inhibitors which are currently used in clinical application can be divided into two categories: (a) small molecular weight compounds which inhibit tyrosine kinase, e.g. gefitinib, erlotinib, and (b) anti-EGFR antibody drugs, e.g. cetuximab, panitumumab. EGFR tyrosine kinase inhibitors are highly effective for non-small cell lung cancer and anti-EGFR antibodies contribute to prolonged OS of colorectal cancer and head-and-neck cancer. Efficacy of EGFR inhibitors have also been anticipated in gastric cancer, however, in a phase II trial with gefitinib, only 1 response was observed among 70 cases [23]. Another study with gefitinib showed response rate of 7% [24]. In a phase II trial with erlotinib for gastric adenocarcinoma, 4 patients experienced objective response (9%) and all of them were having esophagogastric junction cancer [25]. No patient had common EGFR somatic mutation. With respect to cetuximab, out of 35 cases with previously treated adenocarcinoma of esophagogastric junction, response rate was 3% and PFS was 1.6 months, which indicates that cetuximab was not sufficiently effective as monotherapy [26]. At the annual meeting of ASCO 2012, results of REAL-3 trial, which evaluated efficacy of combination chemotherapy with panitumumab, were reported [27]. Patients with previously untreated advanced oesophago-gastric cancer with unknown EGFR status were randomised to chemotherapy of epirubicin, oxaliplatin and capecitabine (EOC, E, 50 mg/m^2 on day 1; O, 130 mg/m^2 on day 1; and C, 1250 mg/m^2 per day on days 1-21) and treatment with modified EOC (E, 50 mg/m^2 on day 1; O, 100 mg/m^2 on day 1; and C, 1000 mg/m^2 per day on days 1-21) plus panitumumab (P; 9 mg/kg on day 1). Due to a significantly worse OS in the EOC+P arm, the trial was terminated prematurely after an annual independent data review in October 2011 revealed a 53% increased mortality in the EOC+P versus the EOC (p=0.006). Presented data in ASCO 2012 revealed that median OS was 8.8 months in the EOC+P arm compared with 11.3 months in the EOC arm (HR=1.37; p=0.013, table 1) [27]. Median PFS was also tend to be worse in the EOC+P arm than in the EOC arm (6.0 vs. 7.4 months, HR=1.22; p=0.068), although response rata was almost similar (46% vs. 42%). The EOC+P arm was associated with a significantly higher rate of grade 3/4 diarrhea (17.3% vs. 11.1%), skin rash (10.3% vs. 0.7%), and mucositis (5.1% vs. 0.0%). In contrast, the frequencies of hematological toxicities and peripheral neuropathy (1.1% vs. 6.7%) were lower in EOC+P, which were suggested to be due to lower dose of chemotherapy in EOC+P arm. Although detailed results of another phase III study, EXPAND, which assess efficacy of cetuximab in combination with capecitabine and cisplatin are

awaited, negative results of REAL-3 clearly indicated that biomarker is necessary to define patients who may benefit from treatment with EGFR antibodies for gastric cancer. In the randomized phase II trial to examine benefit of anti-EGFR antibody nimotuzumab as second-line therapy combined with irinotecan showed relatively better result for OS in combination arm (293 days vs. 227 days, HR 0.717; 95% CI, 0.420-1.224, table 1) [28]. According to the analysis of EGFR expression, better OS results were limited in patients with EGFR over-expression (EGFR2+/3+, N=14, OS 229.5 days vs. 385 days, HR 0.295), although number of patients with this subset is quite small. A further study limited to patients with high EGFR expression is currently being planned.

VEGF -targeted Therapy

Vascular endothelial growth factor (VEGF) is over-expressed in many tumor cells and has been shown to correlate with tumor growth, metastasis and prognosis. The anti-VEGF antibody bevacizumab has proven efficacy in several types of malignancies such as colon cancer, lung cancer, renal cancer, and ovarian cancer, and promising results have also been reported in phase II trials as a combination therapy for advanced gastric cancer. AVAGAST is a global phase III trial to evaluate additional benefit of bevacizumab to capecitabine (5-FU)+cisplatin for advanced gastric cancer. There was no significant difference in OS as the primary endpoint (12.1 months vs. 10.1 months, HR=0.87, 95%CI: 0.73-1.03, p=0.1002, table 1) [29]. In contrast, PFS was 6.7 months vs. 5.3 months (HR=0.80, 95%CI: 0.68-0.93, p=0.0037) and response rate was 46% vs. 37% (p=0.0315); significant better results were observed in the bevacizumab combination arm. The subgroup analysis by geographic region regarding median OS and PFS of the combination treatment group compared with the placebo arm were as follows; median OS was 13.9 months vs. 12.1 months (HR=0.97, 95%CI: 0.75-1.25) for Asian subgroup, 11.1 months vs. 8.6 months (HR=0.85, 95%CI: 0.63-1.14) for European subgroup, and 11.5 months vs. 6.8 months (HR=0.63, 95%CI: 0.43-0.94) for Pan-American subgroup. Median PFS was 6.7 months vs. 5.6 months (HR=0.92, 95%CI: 0.74-1.14) for Asian subgroup, 6.9 months vs. 4.4 months (HR=0.71, 95%CI: 0.54-0.93) for European subgroup, and 5.9 months vs. 4.4 months (HR=0.65, 95%CI: 0.46-0.93) for Pan-American subgroup. Thus differences between the two arms were more prominent in Europe and in the Pan-American region than in Asia. Second-line chemotherapy was more frequently used in Asian patients and may contribute to the better OS of Asian countries, although this may not explain fewer efficacies in PFS in Asian patients. A similar comparative study (AVATAR) was conducted in China, but the efficacy of bevacizumab was again not shown [30]. Several analyses according to organ metastasis and prognostic factor were carried out in AVAGAST study so far, but there was no indication that the benefits were confined to one particular subgroup. Recent retrospective study suggested ethnic difference in genetic polymorphisms of VEGF may contribute to different effect according to region, but this result need further validation [31].

Biomarkers to predict the clinical efficacy of bevacizumab had not been established, which was long thought to be an issue. A retrospective study based on randomised studies of bevacizumab for several types of cancers suggested that VEGF-A was correlated to therapeutic efficacy (i.e. effect for bevacizumab in patients with high VEGF-A levels exhibited greater benefits) [32]. In AVAGAST trial, patients with high baseline plasma VEGF-A levels showed a trend toward improved OS (HR 0.72; 95% CI, 0.57 to 0.93) vs. patients with low VEGF-A levels (HR, 1.01; 95% CI, 0.77 to 1.31; interaction P = 0.07). Patients with low baseline expression of neuropilin-1 also showed a trend toward improved OS (HR, 0.75; 95% CI, 0.59 to 0.97) versus patients with high neuropilin-1 expression (HR, 1.07; 95% CI, 0.81 to 1.40; interaction P = .06) [33]. Currently, prospective studies to evaluate VEGF-A level and bevacizumab efficacy for breast and lung cancer are ongoing. Furthermore, a global phase III trial (RAINBOW) to compare paclitaxel alone to paclitaxel given together with ramucirumab as second-line therapy is in progress: ramucirumab is an anti-VEGF receptor 2 antibody. Another type of agent which targets VEGF pathway is the low molecular weight compounds targeting mainly the tyrosine kinase of VEGF such as sorafenib and sunitinib. These tyrosine kinase inhibitors are one of the standard treatments for several malignancies such as renal cell cancer and hepatocellular cancer. Phase I trials testing sorafenib and sunitinib combined with standard chemotherapy for gastric cancer had been carried out but the toxicities have been an issue [34-35]. In a phase II trial with sunitinib in previously treated cases, response rate was 2.6% and stable disease rate was 34.7% and again, no sufficiently high efficacy was obtained [36].

PI3k-Akt-mTOR -targeted Therapy

PI3K/AKT pathway is a series of signaling pathways which transduce signals from cell membrane receptors (i.e. VEGF, HER2, IGF) to the cytoplasm. PI3K/AKT not only plays an important role in cell proliferation by acting on the anti-apoptosis and cell cycle, it also plays a role in protein translation and synthesis via mTOR (mammalian target of rapamycin) as well as angiogenesis. It has been reported that PI3K/AKT pathway is constitutively arandomisedctivated in many types of cancers, due to abnormalities of EGFR, HER2, PTEN, PIK3CA and TSC1. Furthermore, PIK3CA mutations and gene amplification, AKT gene amplification, loss of PTEN can activate PI3K/AKT/mTOR. It has been shown that in gastric cancer, PI3K/AKT/mTOR activation was observed in 30-60% of tumors [37]. The drug that has been most developed is the mTOR inhibitor including everolimus, temsirolimus, ridaforolimus, etc. which are approved as one of standard treatments for renal cell carcinoma and pancreatic neuroendocrine tumors. In hormone-receptor-positive breast cancer, the significant activity of mTOR inhibitor has been shown in a large randomised study [38].

Everolimus is an orally available mTOR inhibitor. In the phase I trial of everolimus, 1 partial response was observed in patients with adenocarcinoma of esophagogastric junction [39]. It has also been reported that partial response was observed in a Japanese phase I trial of everolimus in multi-drug resistance advanced gastric cancer [40]. Following these results, a Japanese phase II trial was conducted in patients who were previously treated with gastric cancer [41]. Although no partial response was observed, 29 of 53 patients achieved a stable disease, and the disease control rate was 54.7%. Moreover, 45.5% of the patients showed a tendency of tumor shrinkage. The median PFS was 2.73 months and the median OS was 10.1 months. Based on these results, a global phase III trial (GRANITE-1) was conducted to compare everolimus vs. placebo [42]. Patients with advanced gastric cancer who showed disease progression after prior treatment with first or second-line chemotherapy were assigned to daily administration of everolimus or placebo 10mg in a ratio of 2:1. 656 patients were registered in 23 countries: 439 were assigned to the everolimus group and 217 were assigned to the placebo group [42]. In also, 55.3% were registered in Asia and 47.7% were previously treated with one regimen. Disappointingly, OS as the primary endpoint could not show superior results of everolimus compared with placebo (5.39 months vs. 4.34 months; HR, 0.90; 95% CI, 0.75-1.08; P=0.1244, table 1). Although median value of PFS as the secondary endpoint was almost similar between two arms (everolimus 1.68 months vs. placebo 1.41 months),

the proportion of patients who were progression free and on treatment at 6 months was 3 times higher in everolimus than placebo (12% vs.4.3%) and overall PFS showed statistically favored results in the everolimus arm (HR, 0.66; 95% CI, 0.56-0.78; P<0.0001). Although there was no significant difference shown in the response rate (4.5% vs. 2.1%), the disease control rate (43.3% and 22.0%) was better in the everolimus arm. The common everolimus-related toxicities observed were: anemia (everolimus 16.0% vs. placebo 12.6%), anorexia (11.0% vs. 5.6%) and fatigue (7.8% vs. 5.1%), and were almost similar to those observed in other carcinomas. Although GRANITE-1 was one of the few large-scale randomised studies in this pretreated population with results anticipated, unfortunately, the primary endpoint was not achieved. The results of PFS and disease stabilization provided some evidence that they have anti-tumor effect for gastric cancer. It is worth mentioning here that an exploratory biomarker study in tissue and blood samples is being planned, however, at this moment, we do not know which biomarkers are appropriate for patients selection for treatment with mTOR inhibitor. So far several biomarkers such as S6K1 phosphorylation, Akt phosphorylation, down-regulation of CDK4 and cyclin D1 and BCL-2 expression, were evaluated in other types of cancer, none of them established as predictive biomarkers. In also, in the case where subjects are treated previously with chemotherapy, which is also the case of this GRANITE-1, tumor characteristics just before the start of chemotherapy might be different from that of archival tumor tissue, and this might affect analyses and results. Either way, we should wait for future reports.

HGF-c-Met Pathway and FGFR Pathway

c-Met, a receptor for hepatocyte growth factor, is known to have an effect on anti-apoptosis and cell proliferation, and in vitro and in vivo studies have shown its activation in gastric cancer. Although no clinical benefits of GSK1363089, a tyrosine kinase inhibitor of c-Met, was shown for previously treated gastric cancer [43], the efficacy of crizotinib, developed as c-Met inhibitor, has been shown the case of c-Met amplification [44], which suggests the possibility to limit its effectiveness depending on the expression and amplification of c-Met. At the annual meeting of ASCO 2012, results of phase II trial of tivanitinib (ARQ197), which is a selective, non-ATP competitive, small-molecule inhibitor of c-MET, for patients with pretreated gastric cancer were reported [45]. Thirty patients received tivantinib but no objective response was observed, and DCR was 36.7%. No obvious relationship of treatment outcome with biomarkers including c-MET gene amplification, c-MET, p-c-MET and HGF expression in tumor and serum HGF was identified in this patient's population [45]. Therefore more effective way to inhibit c-Met pathway or better patient's selection might be needed. The effectiveness of rilotumumab, an antibody to HGF, was reported in a randomised phase II trial [46]. Overall, favorable results was shown in rilotumumab plus chemotherapy compared with chemotherapy alone (table 1). Moreover, efficacy of rilotumumab was especially prominent for c-Met over-expression cases in the evaluation by IHC, and currently further randomised study targeting patients with high c-Met is being planned. For FGFR (Fibroblast growth factor receptor), activation in various malignant tumors has been suggested, and FGFR2 amplification in gastric cancer has been reported [47,48]. Furthermore, dovitinib, a FGFR inhibitor, has known clinical benefits in gastric cancer, and its efficacy is anticipated in clinical setting [48]. Early development trials have been carried out to study other kinds of inhibitors as therapeutic targets for gastric cancer, such as: heat shock protein 90 (HSP90), histone deacetylase (HDAC), etc [49].

Future Prospects

Additional benefits of trastuzumab in HER2 became evident from ToGA trials, and the first biomarker and molecular-target agent was introduced in gastric cancer. The outcome for the subsequent AVAGAST, GRANITE-1 and REAL-3 trials did not turn out like we hoped for; in fact, these results suggested the importance of narrowing down the target subject to yield as much benefit by using biomarkers in the early development of the molecular targeted agent. Besides HER2, which has already been established as therapeutic target, there are other possible therapeutic targets which are currently under investigation: EGFR, C-met and FGFR, and abnormalities in these pathways were found in 40% of gastric cancer patients [48]. With further accumulation of knowledge, individualized treatments for gastric cancer may be achieved in the future.

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