CLINICAL INVESTIGATION

Results and implications of the Trastuzumab for Gastric Cancer (ToGA) trial

Amplification of the *HER2* gene and/or overexpression of its encoded protein have been observed in a proportion of patients with advanced gastric cancer (AGC). Activity of trastuzumab, a humanized monoclonal antibody against HER2, has been investigated in preclinical AGC models, anecdotal case reports and a few pilot trials. More recently, the Phase III Trastuzumab for Gastric Cancer (ToGA) trial found that trastuzumab treatment improved overall survival in AGC patients with amplification or overexpression of HER2. This article will describe the results of the ToGA trial, its impact on treatment of patients with AGC and the implications of these findings.

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Despite a worldwide decrease in incidence, gastric cancer remains the fourth most common cancer and the second most common cause of cancer-related mortality worldwide [1,2]. Most patients present with advanced metastatic or surgically unresectable disease with poor prognosis, although a higher proportion of patients in Asian countries, including Korea and Japan, where individuals are screened for gastric cancer, are candidates for potentially curative resection. Although chemotherapy is the standard of care in patients with advanced or recurrent gastric cancer, median overall survival is less than 1 year, with response rates of approximately 20–40% [3]. There is therefore an unmet need for more efficacious and less toxic treatment options in patients with advanced gastric cancer (AGC).

The recent development of molecularly targeted agents has added to the armamentarium of systemic therapeutic agents used to treat breast, colon and lung cancers. Angiogenesis and the epidermal growth factor (EGF) receptor (EGFR) pathway have been the major molecular targets actively investigated in the treatment of AGC. Data from several preclinical *in vitro* and *in vivo* studies, case reports and interim results of small Phase II trials have suggested that trastuzumab, a monoclonal humanized IgG1 murine antibody that targets the extracellular portion of the EGFR 2 (or HER2), may be effective in patients with HER2-positive AGC [4–11].

A recent Phase III study, the Trastuzumab for Gastric Cancer (ToGA) trial, compared fluoropyrimidine plus cisplatin with or without trastuzumab in patients with HER2-positive AGC; the results were presented at the 2009 American Society of Clinical Oncology (ASCO) annual meeting and have recently been published [12]. The addition of trastuzumab prolonged overall survival, the primary end point of the trial [12]. Thus, trastuzumab has become the first biologic agent to show a survival benefit for patients with advanced gastric or esophagogastric junction cancer. We will briefly describe the background, rationale, design, results and impact of the ToGA trial.

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Background & rationale of the ToGA trial

Targeted therapy has changed the paradigm in the treatment of advanced cancers. Imatinib, a small-molecule tyrosine kinase inhibitor that inhibits bcr-abl, c-kit and platelet-derived growth factor receptor-α, has revolutionized the treatment of chronic myeloid leukemia and gastrointestinal stromal tumors. Trastuzumab has also significantly improved treatment outcomes in patients with early and advanced breast cancer [13]. Results of a pivotal Phase III trial showed that the addition of trastuzumab to either an anthracycline plus cyclophosphamide or a taxane regimen for the treatment of patients with HER2-positive metastatic breast cancer reduced the risk of death by 20% [14]. Furthermore, addition of trastuzumab to adjuvant chemotherapy reduced the risk of recurrence by 39–58% and the risk of death by 24–59% [15–18]. Trastuzumab is a good example of 'targeted therapy' in that it satisfies all three of its prerequisites: a target with known functional relevance, validated assay to measure the target and therapeutic agents specific for the target.

HER2, initially discovered in 1985, is a 185-kDa transmembrane receptor in the HER family of receptor tyrosine kinases, which also includes HER1, HER3 and HER4 [19,20]. Unlike the extracellular domains of the other three HER family receptors, HER2 can dimerize in the absence of a ligand and, once activated, can induce signaling that promotes cell proliferation and survival. *HER2* gene amplification or protein overexpression occurs in 15–25% of breast cancers, as well as in lung, colorectal, bladder and ovarian cancers [21]. The different levels of HER2 expression in normal breast and HER2-overexpressing breast carcinomas, together with the key role of HER2 in tumor progression, have made HER2 an ideal target for specific therapeutic approaches. Amplification or overexpression of HER2 has also been demonstrated in 7–34% of patients with AGC [4,22,23].

The activity of HER2 blockade in gastric cancer was first investigated in preclinical models. A combination of two anti-HER2-specific antibodies inhibited the growth of the human gastric tumor cell line, NCI-N87, *in vitro* and in a xenograft model before trastuzumab had become available [24]. Trastuzumab was found to enhance the cytotoxicity of doxorubicin in its first report on gastric cancer cells [6]. Trastuzumab inhibited the growth of NCI-N87 cells *in vitro* and in *in vivo* xenograft tumors [4] and enhanced the survival rate of mice with peritoneally disseminated MKN-45P cells, a variant line of MKN-45 expressing a higher level of HER2 [5]. Moreover, treatment with cisplatin and trastuzumab resulted in a synergistic inhibitory effect on SNU-216 cells [7], and the combination of capecitabine, cisplatin and trastuzumab, the combination used in the ToGA trial, markedly inhibited the growth of NCI-N87 and 4-1ST gastric cancer cells [8].

Preliminary clinical data, including case reports and Phase II trials, have suggested that trastuzumab has potential clinical benefits in patients with HER2-positive AGC. For example, the combination of trastuzumab plus oxaliplatin induced a complete response (CR) in a woman with metastatic gastric cancer overexpressing HER2 (immunohistochemistry [IHC] 3+) [9]. Moreover, trastuzumab monotherapy induced a partial response (PR) in an 88-year-old man with a liver metastasis who progressed after treatment with capecitabine; this PR was maintained for more than 3 years after additional treatment with 5-fluorouracil (5-FU) and proton beam therapy [10]. In a pilot trial, one of three patients with IHC 3+ AGC who had progressed during previous platinum- or 5-FU-based chemotherapy achieved PR after trastuzumab monotherapy for more than 24 weeks [11]. In a Phase II trial with five patients, trastuzumab in combination with docetaxel and cisplatin induced an 80% response rate (1 CR/3 PR/1 stable disease) [25], whereas a second Phase II trial with 21 patients showed that trastuzumab and cisplatin achieved a 35% overall response rate and a 52% disease-control rate in 17 evaluable patients [26]. These encouraging results led to a large randomized Phase III trial that selected patients based on HER2-positive status.

Design

The ToGA trial was an open-label, multicenter, international, comparative Phase III study. Patients were recruited from 24 countries in Asia (including Australia), Europe, South and Central America and South Africa. Asians comprised approximately 50% of enrolled patients because the highest recruitment was in Korea, Japan, China and Russia. Patients were randomized to receive trastuzumab plus chemotherapy with fluoropyrimidine (5-FU or capecitabine) plus cisplatin or chemotherapy alone. Patients were stratified by Eastern Cooperative Oncology Group performance status, chemotherapy regimen, extent of disease, primary cancer site (gastric vs gastroesophageal junction) and measurability of disease. As the primary end point was overall survival, crossover to trastuzumab at the time of disease progression was not allowed. Secondary end points included progression-free survival, time-to-progression, overall response rate, duration of response and safety.

Although the choice of fluoropyrimidine (5-FU or capecitabine) was made by each investigator, 88% of patients received capecitabine, resulting in a good efficacy and favorable toxicity profile. Capecitabine was shown to be noninferior to infusional 5-FU in two Phase III

randomized trials, ML17032 and REAL-2 [27,28], while a meta-analysis of these two trials showed that capecitabine was superior in overall survival to infusional 5-FU (hazard ratio [HR]: 0.87; 95% CI: 0.77–0.98; p = 0.02) [29]. In addition, capecitabine has a definite advantage, namely convenience in administration as an oral agent.

After randomization, chemotherapy was administered every 3 weeks for six cycles. In the trastuzumab group, however, trastuzumab was administered by intravenous infusion at 8 mg/kg on day 1 of the first cycle and at 6 mg/kg on day 1 of subsequent cycles, until disease progression or unacceptable toxicity. The median numbers of cycles of chemotherapy and trastuzumab were six and eight, indicating that patients received two additional cycles of trastuzumab.

Data analysis

Based on the assumption that the addition of trastuzumab would extend overall survival from 10 to 13 months, the planned sample size was 584 patients, allowing for a 10% drop-out rate. Two interim efficacy analyses were planned, the first after 230 events (50%) and the second after 345 events (75%), with the latter considered the final analysis by the independent data-monitoring committee.

From September 2005 to December 2008, 3803 patients were screened for eligibility and 810 of them were HER2 positive. Excluding 216 patients for failing at least one entry criterion, 594 were actually randomized, 298 to the experimental arm and 296 to the control arm, at 122 centers in 24 countries. Ten patients, four in the experimental and six in the control arm, were further excluded because they did not receive any study drug, due to withdrawal of consent, violation of study entry criteria, administrative error, treatment refusal and other violations.

HER2 in AGC

The ToGA trial enrolled only HER2-positive patients following central assessment of HER2. Two FDA-approved methods are currently used to assess HER2 status in breast cancers; IHC, which measures HER2 protein expression, and FISH, which assesses gene amplification. The ToGA trial utilized a modification of the HER2 scoring systems currently used in breast cancers. A score of IHC 3+ by standardized breast cancer criteria (HercepTest™, Dako, Denmark A/S) or a HER2:CEP17 (centromeric probe 17) ratio of at least 2 by PharmDX (Dako) have been defined as positive for HER2 overexpression or amplification [30]. However, two important modifications were made to the IHC scoring system used for breast cancer to accommodate the difference between gastric and breast cancers (Table 1) [23,101]. Samples were scored as IHC 2+/3+ even if membranes were incompletely stained, depending on the intensity of membranous reactivity. Incompletely immunoreactive membranes (typically 'U' shaped) may be due to the higher frequency of glandular formations in gastric tissue, where basolateral (but not luminal) membranes were stained. The second scoring modification was due to the level of tumor heterogeneity. Heterogeneity was seen in approximately 4.8% of samples with moderate or strong HER2 IHC reactivity, and was higher than in breast cancer (1.4%). Furthermore, cohesive, immunopositive (IHC 3+) and FISH+ areas of cells representing less than 10% of tumor cells were observed in several samples, suggesting that multiple biopsies may be necessary. According to HercepTest breast cancer scoring criteria, this type of reactivity should receive a negative score because the total area of reactive cells was less than 10%. Thus, the scoring system for AGC used membranous reactivity, regardless of the percentage of positively stained tumor

Table 1. Recommended scoring system to evaluate immunohistochemistry staining patterns in patients with advanced gastric cancer.

Intensity score	Surgical specimen – staining pattern	Biopsy specimen – staining pattern	HER2-overexpression assessment
0	No reactivity or membranous reactivity in <10% of tumor cells	No reactivity or membranous reactivity in any tumor cell	Negative
1+	Faint/barely perceptible membranous reactivity in ≥10% of tumor cells; cells are reactive only in part of their membrane	Tumor cell clusters with faint/barely perceptible membranous reactivity, regardless of percentage of tumor cells stained	Negative
2+	Weak-to-moderate complete, basolateral or lateral membranous reactivity in ≥10% of tumor cells	Tumor cell clusters with weak-to-moderate complete, basolateral or lateral membranous reactivity, regardless of percentage of tumor cells stained	Equivocal
3+	Strong complete, basolateral or lateral membranous reactivity in ≥10% of tumor cells	Tumor cell clusters with strong complete, basolateral or lateral membranous reactivity, regardless of percentage of tumor cells stained	Positive

cells in biopsy specimens, although a 10% cutoff for the number of reactive cells was retained for surgical specimens. These modifications, however, were made in a consensus meeting and were based on only 11 (of 168) tumors showing inconsistency between IHC and FISH analyses, without clinical correlation [23]. Ambiguity persists in the definition of tumor areas and numbers of tumor cells. As the results of the ToGA trial have become available, validation of the scoring system might further optimize the identification of patients with gastric cancer who may benefit from trastuzumab.

Additionally, the ToGA trial used a cutoff of HER2:CEP17 ratio of 2.0, unlike the current FISH criteria for classification in breast cancer, which use a cutoff of HER2:CEP17 ratio over 2.2 as HER2 FISH positive, less than 1.8 negative and 1.8–2.2 as equivocal [31,32], because the guidelines were introduced in 2007 after the ToGA trial had started in 2005. Equivocal FISH samples are required to be confirmed through additional cell counts or by repeating the FISH test in the guidelines. However, the recommendation to have three diagnostic ranges (not amplified, equivocal and amplified) may create challenges in the context of a binary treatment decision (to treat or not to treat) [33]. Furthermore, the necessity of equivocal range was questioned even in breast cancer as no data exist demonstrating that US FDA-approved criteria by the manufacturer are insufficient [33]. We do not believe that creating an equivocal range in AGC is currently justified, as the ToGA trial has provided a clear definition of HER2 positivity by FISH.

Using the above definitions, 22.1% of the tumors in the ToGA trial were HER2 positive. This rate, however, may not represent the epidemiologic spectrum of HER2 positivity in AGC, although the rate was consistent with the 7–34% rates reported previously [23,30]. Since HER2 assays have been used for over 10 years in breast cancer patients, prescreening at each site before referral to the central laboratory might have enriched the HER2-positive population in the ToGA trial. Furthermore, only 16% of patients would be potential candidates for trastuzumab treatment by the criteria of the European Medicines Agency, as approximately three-quarters of patients enrolled in the ToGA trial had IHC2+/FISH+ or IHC 3+ tumors. HER2-positivity rates were significantly higher in esophagogastric junction cancer than in AGC (33.2 vs 20.9%; p < 0.001) and in intestinal than in diffuse/mixed cancer (32.2 vs 6.1/20.4%; p < 0.001). Indeed HER2-positivity rates were higher in countries with the highest gastroesophageal junction:stomach cancer ratios, including France, Germany and the UK, and the highest intestinal:diffuse cancer ratios, including Australia, the UK and Japan [30]. Approximately 74% of the patients enrolled in the ToGA trial were

of the intestinal type, which may have been due to the higher HER2-positivity rate in the intestinal type, especially considering the worldwide decline in the incidence of the intestinal type [34,35].

HER2 gene amplification or protein overexpression is associated with poor prognosis in breast cancer patients, with a mean relative risk for overall survival of 2.74 [13]; however, the prognostic role of HER2 in gastric cancer is less clear, as several early studies failed to show an association between HER2 and prognosis [36,37]. Most studies, meanwhile, indicate that HER2 is a prognostic factor associated with worse clinical outcome [4,38–43]. These differences in the prognostic importance of HER2 may be due to methodological differences as well as different patient populations. The ToGA trial screened 3803 patients; of these, 810 were assessed as HER2 positive but only 294 were actually treated with trastuzumab. Since the ToGA trial is the only large clinical study in AGC patients that included central assessment of HER2 status by HercepTest (Dako) and HER2 FISH pharmDX (Dako), the standard laboratory methods, comparing overall survival in HER2-positive patients who were not treated with trastuzumab (n = 516) and HER2-negative patients screened for the ToGA trial would provide additional evidence on the prognostic significance of HER2 in advanced gastric or esophagogastric junction tumors, although heterogeneous treatment would be a confounding variable.

Efficacy results

Patient baseline characteristics were well balanced in the two treatment arms. Efficacy data are summarized in Table 2. The median follow-up period was 18.6 months for patients receiving trastuzumab plus chemotherapy and 17.1 months for those receiving chemotherapy alone. Trastuzumab plus chemotherapy, compared with chemotherapy alone, significantly improved overall survival, the primary end point, from 11.1 to 13.8 months (HR: 0.74; 95% CI: 0.60–0.91; p < 0.005) corresponding to a 26% reduction in death rate, and significantly enhanced progression-free survival from 5.5 to 6.7 months (HR: 0.71; 95% CI: 0.59–0.85; p < 0.001). Overall response rate was significantly increased by 12% in the trastuzumab arm (p = 0.0017). Results from intention-to-treat analysis including all the randomized patients were consistent with results from patients who were actually treated.

Post hoc, exploratory subgroup analysis indicated that the benefits of trastuzumab are related to the extent of HER2 protein expression. While the HR of overall survival in patients with IHC 0 or 1+ and FISH+ tumors (low HER2 subgroup, n = 148) was 1.07 (95% CI: 0.70–1.62), the median overall survival in patients with IHC

Table 2. Efficacy parameters in the Trastuzumab for Gastric Cancer (ToGA) trial.

End point	XP/FP (n = 290)	Trastuzumab + XP/FP (n = 294)	Hazard ratio (95% CI)	p-value
OS (median months)	11.1	13.8	0.74 (0.60–0.91)	0.0046
PFS (median months)	5.5	6.7	0.71 (0.59–0.85)	0.0002
TTP (median months)	5.6	7.1	0.70 (0.58–0.85)	0.0003
ORR (%)	35	47	1.70[†] (1.22–2.38)	0.0017
Patients with measurable disease (%)	37.4	50.9	1.74[†] (1.23–2.46)	0.0017
DoR (median months)	4.8	6.9	0.54 (0.40–0.73)	<0.0001
Clinical benefit rate (%)	69	79	1.66[†] (1.14–2.41)	0.0081

[†]Odds ratio.

DoR: Duration of response; FP: 5-fluorouracil plus cisplatin; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; TTP: Time-to-progression; XP: Capecitabine plus cisplatin.

2+/FISH+ or IHC 3+ tumors (high HER2 subgroup, n = 446) was markedly enhanced, from 11.8 months for chemotherapy alone to 16.0 months for trastuzumab plus chemotherapy with a HR of 0.65 (95% CI: 0.51–0.83). Based on these results, trastuzumab was approved for patients with IHC 3+ or IHC 2+/FISH+ advanced gastric or esophagogastric junction tumors [101]. The suggested algorithm for HER2 tests is depicted in Figure 1. Briefly, IHC should be the first test conducted, with IHC of 0 or 1+ considered negative and IHC of 3+ considered positive. If the IHC result is 2+, then FISH should be performed. The FISH test, in turn, can be positive or negative. Assessment of HER2 by FISH only without performing IHC can underestimate the true HER2-positive rate, since there is a FISH-/IHC 3+ rate due to HER2 upregulation for reasons other than gene amplification, such as increased transcription, increased mRNA and increased protein stability, which renders tumors sensitive to HER2 inhibition.

In assessing the predictive value of HER2, questions have arisen regarding whether it is necessary to rebiopsy patients with recurrent gastric or esophagogastric junction tumors if the primary site was HER2-negative. Even HER2 negative patients may have clones having amplified HER2, in case they are admixed with a higher proportion of HER2-negative clones making their FISH ratio less than 2. If the HER2-positive clones are more aggressive biologically, they may preferentially metastasize to other sites, as in breast cancer, suggesting that the metastatic or recurrent tumors may acquire HER2 gene amplification as these cancers progress [44]. Trastuzumab may therefore

have a therapeutic role in these patients, but additional studies in patients with gastric or esophagogastric cancer are required to clarify this issue.

Safety results

The overall safety profile was similar in the two arms, with no difference in the incidence of grade 3/4 (68% in both arms) and cardiac adverse events. Among the numerous chemotherapy regimens used to treat patients with AGC, the most popular worldwide is fluoropyrimidine plus cisplatin, with or without anthracycline, primarily epirubicin. The ToGA trial utilized the combination of a fluoropyrimidine and cisplatin, but without epirubicin, as the platform for combination with trastuzumab. Several other Phase III clinical trials of targeted agents in AGC have utilized similar platforms, including the AVAGAST trial (capecitabine plus cisplatin [XP] ± bevacizumab), the EXPAND (XP ± cetuximab) trial and the LoGIC (capecitabine plus oxaliplatin ± lapatinib) trial.
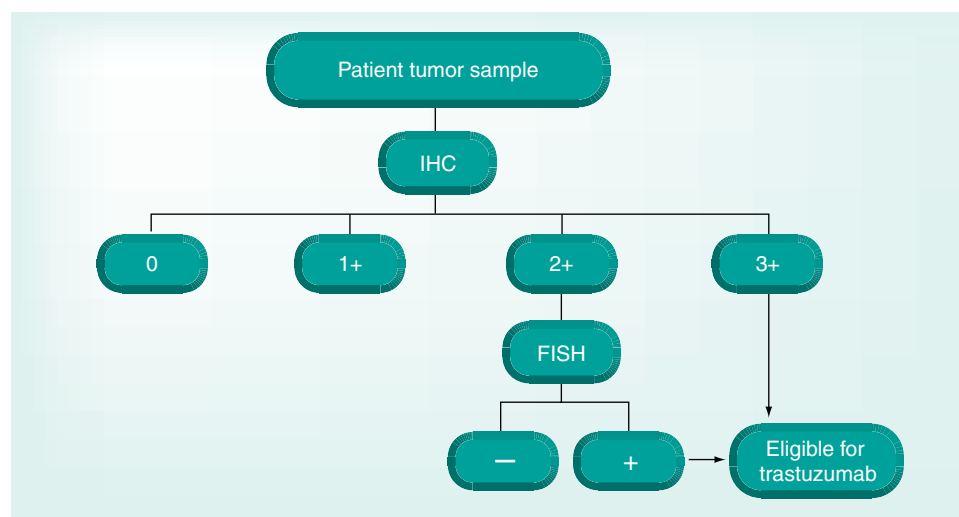
Figure 1. HER2 testing algorithm in metastatic gastric and esophagogastric junction cancers. FISH: Fluorescence *in situ* hybridization; IHC: Immunohistochemistry.

Although the number of patients experiencing cardiac dysfunction, defined as at least a 10% drop and to an absolute value under 50% in left ventricle ejection fraction, was low in both the experimental (5%) and control (1%) arms of the ToGA trial [12], the cardiac toxicity of trastuzumab is a major concern, especially in patients previously or concurrently exposed to anthracyclines [45,46]. In a pivotal Phase III trial of breast cancer patients, cardiac dysfunction was observed in 27% of patients treated with an anthracycline, cyclophosphamide plus trastuzumab, but in only 8% of patients treated with an anthracycline and cyclophosphamide alone [14]. Outside of research protocols, patients are not recommended to receive concurrent treatment with trastuzumab and anthracyclines [47]. Although administration of trastuzumab in combination with less cardiotoxic anthracyclines, such as epirubicin, may possibly be relatively safe, the combination of trastuzumab and anthracyclines cannot be recommended for routine practice until prospective evaluations exclude this safety concern. Furthermore, the role of anthracycline is rather controversial in trastuzumab-treated breast cancer patients with coamplification of *HER2* and *TOP2A* encoding topoisomerase II α, which is closely related to the *HER2* gene on chromosome 17 [46]. Although anthracycline is not popularly used in AGC, this issue may be extended to HER2-positive AGC and the role of anthracycline has yet to be investigated in trastuzumab-treated patients with HER2-positive AGC. Thus, the use in the ToGA trial of fluoropyrimidine plus cisplatin as the platform for trastuzumab was appropriate, although the results of this trial do not exempt physicians from the need for vigilant cardiac monitoring before and during trastuzumab therapy.

Future perspective

Trastuzumab has become the first targeted biological agent to show a survival benefit in patients with AGC or esophagogastric cancer. Trastuzumab lengthened overall survival by 2.7 months in the total HER2-positive population and 4.2 months in the high HER2-positive subpopulation. These increases are clinically meaningful in the treatment of AGC, especially when considering the superb safety profile of trastuzumab. The combination of trastuzumab and chemotherapy has become a new treatment option for patients with advanced HER2-positive gastric and esophagogastric junction tumors. Thus, HER2 status should be routinely included in the diagnostic work-up of patients with these cancers.

Positive results of the ToGA trial will expedite further investigations on the clinical utilization of anti-EGFR therapy in AGC. First, adjuvant clinical trials involving trastuzumab are anticipated, as trastuzumab reduced the risk of recurrence by approximately 50% and the risk of death by approximately 33% in breast cancer patients [15–18,48]. At present, a single-arm Phase II study of perioperative capecitabine and oxaliplatin plus trastuzumab is registered [102] and plans for additional trials are underway in Japan [48]. Since adjuvant therapy regimens vary among geographic regions, however, the inclusion of trastuzumab in each regimen should be explored. These include the incorporation of trastuzumab into postoperative chemoradiation or perioperative chemotherapy in the USA and Europe, and adjuvant chemotherapy alone in Asian countries.

It is also not known if trastuzumab therapy beyond progression will be beneficial, as it is in breast cancer. In a European trial, patients with HER2-positive locally advanced or metastatic breast cancer that progressed on one line of trastuzumab were randomized to capecitabine with or without continuation of trastuzumab. Time to progression was longer in the group on extended trastuzumab continuation (8.2 vs 5.6 months; p = 0.0338), although the trial was closed early as lapatinib, a tyrosine kinase inhibitor targeting HER1 and HER2, was shown to improve time to progression in patients who failed first-line chemotherapy with trastuzumab in the EGF100151 trial [49,50]. No significant incremental grade 3–4 toxicities were noted in the trastuzumab-containing arm.

Lapatinib, in combination with capecitabine plus oxaliplatin, is also being tested currently in a Phase III trial as first-line chemotherapy for HER2-positive AGC (LoGIC), and lapatinib in combination with weekly paclitaxel is being tested in patients who fail prior fluoropyrimidine and/or cisplatin (Tytan). The latter trial, however, does not address the same issue that was the focus of the lapatinib trial in breast cancer (EGF100151), which studied the role of lapatinib in patients who had progressed after treatment with trastuzumab plus chemotherapy. The current National Comprehensive Cancer Network guidelines for the treatment of breast cancer (v2.2010) [103] recommend that capecitabine plus lapatinib be the preferred treatment in patients who progress after treatment with an anthracycline, a taxane and trastuzumab. These guidelines, however, also allow continuation of trastuzumab after progression of first-line trastuzumab plus chemotherapy in patients with metastatic breast cancer. Treatment paradigms in breast cancer have become rather complicated, as both trastuzumab and lapatinib are available as treatment options following progression after first-line trastuzumab. In addition, results from a Phase III trial, in which patients with heavily pretreated metastatic breast cancer and disease progression on trastuzumab therapy were randomized to

lapatinib monotherapy or trastuzumab plus lapatinib, showed that the combination increased progression free survival, from 8.1 to 12 weeks (p = 0.008) [51]. Thus, despite the complexity, continued HER2 blockade is important in HER2-positive breast cancer patients. Prospective clinical trials using the same strategies in patients with HER2-positive gastric cancer will focus on whether trastuzumab or lapatinib can benefit patients who failed first-line chemotherapy containing trastuzumab. In addition, future trials of trastuzumab monotherapy may provide additional advantages, compared with best supportive care, in HER2-positive AGC patients with poor performance or elderly patients, similar to findings that trastuzumab monotherapy is active in patients with advanced breast cancer [52].

In the ToGA trial, the median time to progression in the trastuzumab plus chemotherapy arm was 7.1 months. In other words, at least half of patients develop resistance to trastuzumab after approximately 7 months. Given that the majority of patients with AGC develop progressive disease, we need not only to develop a better understanding of the mechanisms of resistance, but also to find ways to individualize therapy. Lessons can be learned from the breast cancer setting, where some patients develop resistance over time despite an initial response to trastuzumab. Several potential mechanisms of resistance explored in metastatic breast cancer include alterations in the phosphoinositide 3-kinase pathway, phosphatase and tensin homolog, IGF-1 receptor and truncated HER2 receptor [53]. Furthermore, new therapeutic strategies directed against HER2 in patients with advanced breast cancer will no doubt also be explored in patients with AGC. These include pertuzumab, a monoclonal antibody that inhibits HER2–HER3 dimerization by binding to a distinct site on the HER2 extracellular domain; tanespimycin, an inhibitor of heatshock protein 90, which plays an important role in maintaining HER2 function; trastuzumab–DM1, an antibody–drug conjugate consisting of trastuzumab linked to the microtubule poison maytansine; ertumaxomab, a trifunctional antibody that targets HER2, CD3 and activating FCγ receptors and simultaneously recruits and activates FCγRI and FCγRIII-positive accessory cells, leading to phagocytosis of tumor cells; and neratinib, a potent irreversible pan-HER tyrosine kinase inhibitor [53].

In addition to trastuzumab and lapatinib, several targeted agents have been under investigation in clinical trials. The results of the AVAGAST trial, comparing capecitabine plus cisplatin with or without bevacizumab, an anti-VEGF monoclonal antibody, in patients with AGC, were presented at the 2010 ASCO annual meeting [54]. The trial failed to meet the primary end point of overall survival superiority, although the addition of bevacizumab showed a significant improvement in progression free survival and overall response rate with an acceptable safety profile. The anti-EGFR1 monoclonal antibodies, cetuximab and panitumumab, are also being evaluated in Phase III trials (the EXPAND and the REAL-3, respectively) in patients with AGC.

In conclusion, the ToGA trial successfully utilized a molecular characterization to enrich a cohort of patients who might potentially benefit from treatment with trastuzumab and trastuzumab has become the first efficacious molecularly targeted agent to treat patients with advanced gastric and esophagogastric cancers. These results should expedite further clinical research to parallel the development in HER2 blockade strategies in breast cancer.

Executive summary

- Trastuzumab is the first biological agent to show a survival benefit in patients with advanced gastric/esophagogastric junction cancer, reducing the risk of death by 26% compared with chemotherapy alone and increasing median overall survival to 13.8 months in patients with amplification and/or overexpression of HER2.
- The survival benefit provided by trastuzumab plus chemotherapy was most evident in patients with high levels of HER2 protein expression (immunohistochemistry 2+/FISH+ or IHC 3+), with median overall survival of 16.0 vs 11.8 months for patients with lower levels of HER2 expression.
- Trastuzumab in combination with chemotherapy can now be considered a new standard of care for patients with HER2-positive advanced gastric or esophagogastric junction adenocarcinoma.
- HER2 testing should be routinely performed in patients newly diagnosed with advanced gastric or esophagogastric junction cancer.
- Future clinical trials exploring trastuzumab in the adjuvant setting or continuing beyond progression may expand its role in the treatment of HER2-positive gastric/esophagogastric junction cancer.

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