Commentary

HER2/neu as target in gastric adenocarcinoma

Bulent Cetin[1], Ahmet Ozet[2]

[1]Department of Internal Medicine, Division of Medical Oncology, Recep Tayyip Erdogan University Faculty of Medicine, Rize 53100, Turkey; [2]Department of Internal Medicine, Division of Medical Oncology, Gazi University Faculty of Medicine, Ankara, Turkey

Correspondence to: Bulent Cetin. Department of Internal Medicine, Division of Medical Oncology, Recep Tayyip Erdogan University Faculty of Medicine Rize 53100, Turkey. Email: caretta06@hotmail.com.

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Gastric adenocarcinoma (GAC), a heterogeneous disease characterized by epidemiologic and histopathologic differences across countries, is a leading cause of cancer-related death. The modest activity and substantial toxicity of cytotoxic chemotherapy has raised the question, does palliative systemic therapy with available agents have clinical utility? In the setting of metastatic disease, many active chemotherapy agents can produce meaningful response alone or in combination with other agents, but the duration of response is often limited. Recent additions to the armamentarium include trastuzumab and ramucirumab, which have shown some survival advantage when added to cytotoxic(s). The *HER2* proto-oncogene is the gene encoding the human EGF receptor 2. *HER2* amplification or protein overexpression [found in 20% of gastric cancer (GC)] is clearly associated with accelerated cell growth and proliferation and the response to the monoclonal anti-*HER2* antibody, trastuzumab. *HER2* was more likely to be positive in patients with esophagogastric junction (EGJ) tumors than in more distal tumors (33% versus 20%); patients with diffuse GC were much less likely to have an *HER2*-positive (6%) tumor (1).

Table 1 summarizes representative important clinical trial results in *HER2/neu*-positive GAC. The preliminary results of the ToGA trial have been recently reported (2). Among 3,807 patients, 594 patients had *HER2*-positive GC. They were randomized to receive either 5-FU/cisplatin or capecitabine/cisplatin given every 3 weeks for six cycles or the same chemotherapy plus trastuzumab. The median OS was 13.8 months in the patients treated with trastuzumab plus chemotherapy and 11.1 months in the patients treated with chemotherapy. The most effective overall survival (OS) was seen in the immunohistochemical (IHC)-3+ group, with an HR of 0.66. In the IHC-2+ group, there was a trend toward benefit but it was not statistically significant, and treatment with trastuzumab was ineffective in the last group of patients, the 22% with IHC-0 or 1+. Trastuzumab has subsequently has been incorporated as a standard therapeutic options for patients with this disease. However, the benefit from trastuzumab diminished considerably when the results were reanalyzed after a longer follow-up by the U.S. Food and Drug Administration (the hazard ratio increased from 0.73 to 0.80, and the OS difference narrowed to a meager 1.4 months).

Lapatinib is the first dual inhibitor of *HER1* (EGFR1) and *HER2* (EGFR2). In contrast to the ToGA trial of the therapeutic antibody trastuzumab, results have been disappointing for *HER2* directed kinase inhibitors. Two trials studied the reversible *EGFR/ERBB2* inhibitor lapatinib in the second-line setting (4) and in the first-line setting (3), both yielding negative results. Lapatinib was evaluated in the phase III TYTAN study in the 2nd line setting for advanced GC. In Asian patients, 261 patients were randomly assigned to receive either weekly paclitaxel or paclitaxel + lapatinib and addition of lapatinib was not associated with an improvement in survival (P=0.104) (4). Benefit from the addition of lapatinib to first-line chemotherapy was also not shown in the TRIO013/LOGIC trial of capecitabine /oxaliplatin with or without lapatinib for first-line treatment in 545 patients with advanced gastroesophageal cancer (3). The primary end point of OS was 12.2 months compared with 10.5 months, with an HR of 0.9, but was not statistically significant (P=0.35). In prespecified subgroup analysis, Asian patients (median survival 16.5 versus 10.9 months, HR 0.68) and those under age 60 (median survival 12.9 versus 9 months, HR 0.69) seemed to benefit from lapatinib. Additionally,

Table 1 Major clinical trials in gastric adenocarcinoma (GAC) with *HER2/neu* targeted agents

Target	Trial	Type of study/line	Patients selection method	Regimen	Results (primary endpoint)	Reference
HER2	ToGa	Phase III/first	HER2 IHC	5-FU/capecitabine cisplatin ± trastuzumab	Positive (OS)	Bang *et al*. 2010 (2)
HER2	LOGIC	Phase III/first	HER2 amplification	Lapatinib *vs*. XELOX	Negative (OS)	Hecht *et al*. 2016 (3)
HER2	TYTAN	Phase III/second	HER2 amplification	Paclitaxel + lapatinib *vs*. paclitaxel	Negative (OS)	Satoh *et al*. 2014 (4)
HER2	GATSBY	Phase II/III/second	HER2 IHC	TDM1 *vs*. paclitaxel or docetaxel	Negative (OS)	Knag *et al*. 2016 (5)

IHC, immunohistochemical; OS, overall survival.

a phase III study of apatinib versus placebo was reported. This study randomized 267 patients who had progressed on at least two lines of therapy to apatinib (n=181 patients) or placebo (n=92). Patients assigned to apatinib experienced a longer median overall survival (6.5 versus 4.7 months, HR 0.709, P=0.0149) (6). Until further information becomes available, we suggest not using lapatinib as the initial therapy for the treatment of advanced esophagogastric cancer.

The current use of molecular diagnostics, specifically gene expression arrays, is leading to an explosion of subcategories, so that by the second decade of the new millennium, several hundred distinct neoplastic disease entities are likely to be recognized, each following its own, reasonably predictable clinical course and exhibiting its own responsiveness to specific forms therapy. With the passage of time, cancer diagnoses will increasingly be made using bioinformatics rather than the trained eyes of a pathologist. Based upon observations from the molecular data, the The Cancer Genome Atlas (TCGA) team proposed a classification system where GAC is divided into four subtypes: EBV-positive, microsatellite-unstable, genomically stable and chromosomal instability (CIN) (7). Mesenchymal-like GCs had the worst prognosis, followed by *TP53*-inactive, *TP53*-active and finally microsatellite-instability tumors. Cell cycle-related genes such as *CCND1*, *CCNE1* and *CDK6* are commonly amplified in GC. For instance, *CCNE1* is frequently co-amplified with *HER2* (8) and GC patients with *CCNE1/HER2* co-amplification typically developed resistance to lapatinib, a small molecular HER2 inhibitor (9).

The level of *HER2* gene amplification significantly predicts sensitivity to therapy and overall survival in advanced GC treated with trastuzumab-based chemotherapy. A mean *HER2/CEP17* ratio of 4.7 was identified as the optimal cutoff value discriminating sensitive and refractory patients (P=0.005). Similarly, the optimal cutoff for predicting survival longer than 12 months was 4.45 (P=0.005), and for survival longer than 16 months was 5.15 (P=0.004) (10). High levels of *HER2* amplification should be considered as a predictive biomarker in LOGIC patients. These data not yet available but it should be dealt with in a separate article in the future.

In terms of guidelines, patients with *HER2*-positive metastatic disease would be considered eligible if they were IHC 3+ or 2+ fluorescence *in situ* hybridization (FISH) positive or 2+ IHC with *in situ* hybridization positivity. The criteria for *HER2* positivity on surgical and biopsy specimens are of some measure of complication and differ slightly based on GC as opposed to breast cancer, particularly because the expression in GC is somewhat spottier and less diffuse as opposed to breast cancer. The potential adequacy of a single small biopsy to accurately assess *HER2* status is questionable as opposed to a surgical specimen (11-13). How many unique specimens should be tested also remains unresolved (14-16). Similarly, the relationship between the level of *HER2* amplification and the outcome of *HER2*-positive GC treated with anti *HER2/neu* agents remains unclear (17). In addition, whether there is concordance in *HER2/neu* results if metastatic cancer or primary cancer is tested, remains generally unresolved (18-20). Today, the association between *HER2* expression/amplification and prognosis in esophagogastric cancer remains unknown.

So despite the failure of lapatinib, other approaches for *HER2*-positive disease are under way, again based on the benefits of various approaches in breast cancer. Trastuzumab emtansine (T-DM1) is a novel antibody-drug conjugate. T-DM1 consists of the cytotoxic agent DM1 (derivative of maytansine) linked to trastuzumab. The EMILIA trial for patients with *HER2/neu*-positive breast cancer was positive, resulting in a survival benefit of 5.8 months; however, a T-DM1 trial for *HER2/neu*-positive GAC in the second-line setting was a disappointment (5). Pertuzumab is that monoclonal antibody that blocks the dimerization of *HER2* to other *ERBB* family components and therefore

has been shown to be effective when added to trastuzumab in HER2-positive breast cancer. One question is: is there a benefit of adding pertuzumab to trastuzumab in *HER2*-positive GC? The JACOB study included patients with previously untreated *HER2*-positive gastric and GE-junction adenocarcinoma who were randomized to standard fluoropyrimidine, cisplatin, trastuzumab treatment, plus or minus pertuzumab. It is being evaluated in an ongoing clinical trial that is expected to conclude by the end of 2016. Ultimately, the biggest challenge of drug development now and in the future is to demonstrate long-term efficacy: does a drug being tested have significant effects on extending the life expectancy of cancer patients, doing so with acceptable levels of side-effect toxicities? And do we dare to hope that it can achieve durable responses, including cures?

Summary and recommendations

GC remains an important problem worldwide. The majority of patients with esophageal or GC will require palliative treatment at some point in the course of their disease. In recent years, a better understanding of the biological properties of tumors and the development and application of molecular targeted drugs have created hope for the individualized treatment of advanced GC. At the present time, trastuzumab remains the only drug of this type that has demonstrated efficacy, in combination with cytotoxic chemotherapy, in GC. The National Comprehensive Cancer Network (NCCN) suggests the addition of trastuzumab to chemotherapy in patients with *HER2*-positive tumors (as defined by 3+ IHC staining or FISH positivity), as long as they do not have a contraindication to trastuzumab. The future prospects are excellent for defining biomarker based subsets of patients and the application of specific therapeutics.

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Footnote

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