Current Progress in Human Epidermal Growth Factor Receptor 2 Targeted Therapies in Esophagogastric Cancer

Yelena Y. Janjigian, MD[a], Maria Ignez Braghiroli, MD[b,*]

KEYWORDS

• Esophagogastric cancer • HER2 • Targeted therapy • Trastuzumab • Pertuzumab • TDM-1 • Lapatinib

KEY POINTS

- Approximately 20% of EGC have ERBB2 (HER2) gene amplification or oncoprotein overexpression and HER2-directed therapy improves the outcome in metastatic disease.
- Immunohistochemistry analysis for EGC has different parameters than for breast cancer and requires a trained pathologist for evaluation.
- Trastuzumab is the standard treatment in combination with chemotherapy for HER2-positive advanced EGC.
- Studies investigating the use of HER2-directed therapy in early stages of disease are ongoing.
- HER2-directed imaging and patient-derived xenografts might be a useful tool to guide patient treatment and research.

INTRODUCTION

Gastric cancer is the third leading cause of cancer-related deaths worldwide.[1] Most patients are diagnosed with advanced disease and have a median overall survival (OS) of less than 1 year when treated with available cytotoxic chemotherapy.[2] HER2 is a validated therapeutic target in metastatic esophagogastric cancer (EGC). The HER2 proto-oncogene is located on chromosome 17q21 and encodes the 185-kDa transmembrane tyrosine kinase receptor HER2 (also known as HER2/neu, ERBB2, p185). Similarly to breast cancer, the prognosis of patients with HER2 amplified EGC improved when anti-HER2 therapy was added to conventional chemotherapy.[3] Overall, the HER2-positivity rate is around 20% for EGC, with variances according

[a] Gastrointestinal Oncology Service, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, 300 East 66th Street, Room 1033, New York, NY 10065, USA;
[b] Gastrointestinal Oncology Service, Memorial Sloan Kettering Cancer Center, 300 East 66th Street, Room 1033, New York, NY 10065, USA
* Corresponding author.
E-mail address: ignezbraghiroli@gmail.com

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to tumor histologic subtype and location.[4] The rates of HER2 positivity are the highest in esophagogastric junction and stomach cardia tumors, which is up to 30%.[3] In the mid and distal stomach, it is approximately 15% to 20%, and less than 5% of diffuse or signet ring cell type tumors are positive for HER2 amplification.[5,6]

DIAGNOSIS

Based on the benefit seen from HER2-directed therapy for advanced EGC, testing is currently recommended to all patients on diagnosis. Accurate assessment of HER2 status is essential to determine which patients will benefit from therapy. The test for HER2 in breast cancer is performed using immunohistochemistry (IHC), which shows the HER2 protein expression, and/or fluorescence in situ hybridization (FISH) or chromogenic in situ hybridization, which detects gene amplification.

For EGC, IHC evaluation uses parameters distinct from breast cancer. It is suggested that application of breast cancer scoring to gastric cancer may produce up to 50% false-negative rates on IHC.[7] In comparison with breast cancer, EGC has a higher incidence of tumor heterogeneity. Pathologists should be aware that more focal staining is common in EGC. Expression is mainly restricted to intestinal-type gland-forming cells, and there is incomplete, often basolateral or only lateral membranous IHC staining distribution, appearing as discontinuous HER2 membrane reactivity.[8] A positive IHC in the gastric cancer–specific scoring includes a strong but incomplete membrane staining in greater than or equal to 10% of the cells or greater than or equal to five clustered cells.[9] These criteria showed a high level of concordance between the IHC and FISH testing.

The current recommendation for HER2 evaluation in EGC is that IHC should be the first test performed, using validated assays. Results of IHC 3+, or a FISH ratio of the average HER2 gene copy number to chromosome 17 centromere (HER2/CEP17) greater than or equal to 2.0, are considered positive. Samples with equivocal IHC scores of 2+ should be retested by FISH or other in situ methods. IHC 0 to 1+ is considered HER2 negative.[10]

LOCALLY ADVANCED DISEASE

Currently, there are no definitive data supporting the use of anti-HER2 agents in the adjuvant or neoadjuvant treatment of patients with EGC (**Table 1**). Based on the encouraging results published with anti-HER2 therapies for localized breast cancer and together with the findings in advanced esophagogastric tumors, anti-HER2 therapies are now under investigation for earlier disease stages.

In 2013, a Spanish, multicenter, phase II study called NEOHX was initially presented and the final results were updated in 2015 (NCT01130337). This study evaluated the efficacy and toxicity profile for perioperative XELOX-T (capecitabine, oxaliplatin, and trastuzumab) followed by 12 cycles of adjuvant trastuzumab in monotherapy for patients with HER2-positive locally advanced but resectable stomach or esophagogastric-junction adenocarcinoma. The primary end point was disease-free survival (DFS) at 18 months and secondary end points included pathologic complete response rate (pCR), R0 resection rate, overall response rate, toxicity of preoperative treatment, and biomarker expression. A total of 63 patients were included. Before surgery, five patients stopped treatment because of toxicity. The overall response rate was 39%. Surgery was performed in 31 patients and 28 (78%) had an R0 procedure. Three patients had pCR (8.3%). After surgical resection, postoperative XELOX-T was administered to 24 patients, 22 of whom underwent trastuzumab monotherapy. With a median follow-up of 24.1 months, the 18-month DFS was 71% (95% confidence