Targeting the Human Epidermal Growth Factor Receptor 2 in Esophageal Cancer

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The importance of human epidermal growth factor-2 (HER2) in terms of prognosis and aggressiveness of growth has long been known in breast cancer, and interruption of its growth cascade by agents such as trastuzumab and lapatinib has markedly improved outcomes for these patients with HER2 overexpression.

HER2 overexpression also occurs in many other tumor types, including esophageal cancer. In this disease, a different scoring system for determining overexpression is used. Limited data exist concerning the biological and therapeutic implications of HER2 overexpression in esophageal cancer. One trial, the so-called ToGA trial, included patients with advanced gastric and gastroesophageal junction (GEJ) tumors that overexpressed HER2. Patients who received trastuzumab plus cisplatin-based chemotherapy had more responses and longer progression-free and overall survival than those who received the chemotherapy alone. Enthusiasm concerning these results must be tempered by the facts that only 25% of the study group had GEJ tumors and, of these, only 33% had HER2 overexpression. Thus, the role of trastuzumab in the management of HER2-overexpressing esophageal cancers remains to be determined. In addition to presenting data on the HER2 cascade, the authors review clinical trials performed to date and also present the validated standard scoring system for HER2 overexpression in esophageal cancer.

Introduction

The incidence of squamous cell carcinoma of the esophagus is decreasing in the United States; however, the incidence of adenocarcinoma arising from Barrett's esophagus is increasing dramatically.1 In the United States, an estimated 17,460 cases of esophageal cancer were diagnosed in 2012, and 15,070 deaths were expected from the disease.2

Despite significant improvements in our understanding of disease biology, the 5-year survival rate for esophageal cancer remains low. Targeted agents have failed to add any meaningful survival benefit in this patient population, despite promising preclinical data. Outcomes in patients with locoregional resect-
able esophageal cancer have slightly improved since multimodality therapy was incorporated into the treatment of this patient population.

The majority of patients with metastatic esophageal cancer will require palliative treatment. Cytotoxic chemotherapy can improve quality of life and prolong survival in patients with advanced esophageal cancer. Despite a large number of clinical phase II and III trials, there is no consensus on the best regimen to treat metastatic esophageal cancer. Combination chemotherapy regimens yield higher response rates than do single agents, but they translate into only modestly longer durations of disease control and survival at the expense of increased toxicity. Targeted therapies, such as epidermal growth factor receptor (EGFR) inhibitors, vascular endothelial growth factor receptor (VEGFR) inhibitors, and other pathways, have shown promising results in phase II trials by improving outcomes in patients with metastatic esophageal cancer. However, in a phase III trial targeting VEGFR, they did not translate into better overall survival. Trials with EGFR inhibitors are ongoing (CALGB 80403/ECOG 1206).

### The Human Epidermal Growth Factor Receptor 2

The human epidermal growth factor receptor 2 (HER2) is a member of the EGFR family. The HER2 oncogene encodes for a 185-kD transmembrane glycoprotein receptor with intracellular tyrosine kinase activity. HER2 is a cell membrane surface-bound receptor tyrosine kinase and is involved in signal transduction, leading to cell growth and differentiation (Fig 1). It is encoded within the genome by HER2/neu. None of the EGF family of ligands is known to activate HER2; however, HER2 is the preferential dimerization partner of other members of the ErbB family. The HER2 gene is a proto-oncogene and is located at the long arm of human chromosome 17.

### Targeting HER2 in Esophageal Cancer

Amplification of HER2 has been described in tissue samples from different malignancies such as breast, gastric, and ovarian cancers. Further investigation correlated HER2 overexpression and poor prognosis in ovarian and breast cancers. A study of gastric cancer from Japan has shown HER2 amplification...
and HER2 protein expression by immunohistochemistry (IHC) in 11.9% of tumors, with a negative effect on overall survival. However, these results have not been reproduced, and several other studies with different expression rates have since been published.

Advanced cardiac, gastric, and esophageal cancers arising at the gastroesophageal junction (GEJ) have a similar anatomic distribution, similar histologic features, and currently similar treatment. The majority of studies discussed in this article enrolled 80% of patients with gastric adenocarcinoma. To date, no studies evaluating anti-HER2 treatment in strictly esophageal cancer have been reported.

Multiple institutions have published their data about the rate of HER2 overexpression in esophageal adenocarcinoma (Table 1). A high concordance of HER2 amplification, both by IHC and by fluorescence in situ hybridization (FISH), has been reported in tissues obtained from gastric/GEJ primary tumors compared with regional lymph node or distant metastases. This observation suggests the therapeutic utility of trastuzumab in HER2-amplified metastatic disease.

**Standard Definition of HER2 Overexpression in Gastric and GEJ Tumors**

The evaluation of HER2 immunostained samples must be performed using the modified gastric cancer testing protocol, as outlined by Hofmann et al. The major difference in scoring HER2 IHC staining in gastric cancer, compared with the methodology used for breast tumors, is that an incomplete basolateral or lateral stain alone is taken into account when scoring a gastric tumor. The three guidelines in the scoring of HER2 in gastric cancer are: (1) a minimum of 5 cohesive, unequivocally positive tumor cells should be present when reporting a biopsy sample as positive for HER2, (2) a minimum of 10% of positive tumor cells is required for reporting a positive HER2 reaction in a resected specimen, and (3) the use of antibodies approved by the US Food and Drug Administration (FDA) is recommended for the selection of HER2-positive gastric tumors.

As for the intensity of the score, a strong (+3) HER2 reactivity of the tumor cells may be detected with the naked eye, and even at low magnification (×2.5), it will exhibit the membranous localization. For a moderately intense HER2 stain (+2), a ×10 magnification is necessary to be certain that the stain is localized to the cellular membrane. Finally, a weak HER2 stain (+1) will require high magnification (×40) to prove it is membranous (Fig 2).

It is also important for scoring pathologists to be aware of well-described pitfalls in HER2 IHC scoring: (1) HER2 false positivity may be seen in areas of intestinal metaplasia (Fig 3A) and reactive atypia near gastric ulcers, (2) the stain should be scored only if localized to the cellular membrane; cytoplasmic and/or nuclear stains represent false-positive results (Fig 3B), and (3) stain within nonneoplastic lesions as well as “edge” and crushing artifacts of tumor cells represents a nonspecific stain and should be ignored. For the validation of HER2 staining in gastric cancer, we follow the guidelines recently published.

**Trastuzumab in Esophageal Cancer: The Clinical Aspect**

Interest in combining trastuzumab with cytotoxic chemotherapy in patients with gastric or GEJ tumors goes back to early 2000: a small phase II study evaluated trastuzumab combined with a cisplatin/docetaxel doublet in HER2-positive metastatic gastric and/or GEJ adenocarcinomas and elucidated a radiologic response in 80% of patients. The results were preliminary, and the final findings have not been published. In another unpublished study, 21 patients with HER2-positive advanced gastric or GEJ adenocarcinoma were treated with cisplatin and trastuzumab. The total response rate was only 35%. No grade 4 toxicity related to trastuzumab was reported in any of these trials.

**Trastuzumab for Gastric Cancer (ToGA) Study**

An open-label, international, phase III randomized controlled trial undertaken in 24 countries. Patients with gastric or GEJ adenocarcinoma overexpressing the HER2 protein by IHC or gene amplification were included. These patients were randomized to receive capecitabine and cisplatin or fluorouracil (5-FU) with cisplatin (given every 3 weeks for 6 cycles) or chemotherapy in combination with intravenous trastuzumab. In the trastuzumab arm, 20% of patients had GEJ disease compared with 17% in the chemotherapy-only arm. A HER2 positivity rate of 22.1% was reported, with the highest proportion in GEJ tumors (33.2% compared with 20.9% in gastric tumors). Patients who

<table>
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<th>FISH</th>
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IHC = immunohistochemistry, FISH = fluorescence in situ hybridization, NA = not available.
completed 6 cycles of treatment in the trastuzumab arm were allowed to continue on trastuzumab until disease progression. The improvement in median survival was 2.7 months in the intent-to-treat analysis in patients who received trastuzumab (median overall survival, 13.8 months compared with 11.1 months, with a hazard ratio of 0.74; 95% confidence interval, 0.60–0.91; \( P = .0046 \)). Response rate, time to tumor progression, and duration of response were significantly higher in the trastuzumab-plus-chemotherapy group as well. The median survival in the chemotherapy-only arm was higher than expected for this patient population and could be related, at least in part, to the high proportion of Asian patients in the

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**Fig 2A-D.** — HER2 IHC scoring guidelines, as used in the ToGA trials. In brief, any membranous stain including incomplete basolateral or lateral stain alone is counted. (A) Score 1 is assigned if the membranous stain is detected only at 40×; (B) score 2 is assigned if the membranous stain is detected at 10×; and (C) score 3 is assigned to samples showing membranous staining at 2.5×. Panel D is an HER2-negative tumor. The negativity of the stain must be evaluated at 40×.

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**Fig 3A-B.** — Pitfalls in HER2 IHC scoring. Well-known pitfalls in scoring HER2 by IHC include areas of (A) intestinal metaplasia and (B) reactive atypia, which may show a cytoplasmic, granular stain and areas of tumor where the stain is localized to the nucleus or cytoplasm but not to the cellular membrane. These areas should not be considered when assigning the HER2 IHC score.
study (55%). A treatment benefit was found in all the predefined subgroups including GEJ tumors.

Cardiotoxicity is a known side effect of trastuzumab, and monitoring of cardiac function is recommended when using this agent, especially when trastuzumab is combined with anthracyclines. In patients with gastric or GEJ cancers, the use of trastuzumab in combination with epirubicin has not been prospectively evaluated. Until further data are available, replacing epirubicin with a noncardiotoxic agent is an acceptable alternative. Patients should undergo monitoring of left ventricular ejection fraction every 3 to 4 doses during treatment.

**Lapatinib in Gastric and GEJ Adenocarcinomas**
A small-molecule dual tyrosine kinase inhibitor of EGFR and HER2, lapatinib is an effective oral agent in trastuzumab-resistant advanced breast cancer.\(^{12,26}\) Lapatinib monotherapy in gastric tumors (but not GEJ tumors) was evaluated in a phase II study, which showed limited single-agent activity, with a 12% response rate.\(^{27}\) This was an unselected population and did not include patients with GEJ tumors. A second phase II study of lapatinib monotherapy in 25 patients with EGFR- and/or HER2-positive adenocarcinoma of the esophagus that progressed with previous therapy reported no objective responses. Two patients had stable disease.\(^{28}\)

**Conclusions**
Multiple clinical trials are currently evaluating the role of trastuzumab or lapatinib in human epidermal growth factor receptor 2 (HER2)-overexpressing gastroesophageal junction (GEJ) and gastric tumors in patients with advanced or locally advanced resectable disease. The majority of studies enrolled 80% of patients with gastric adenocarcinoma. Studies specific to GEJ metastatic disease are lacking. A randomized, open-label phase III trial is evaluating concurrent radiation therapy with paclitaxel and carboplatin with or without trastuzumab in treating patients with HER2-overexpressing, locally advanced esophageal adenocarcinoma (ClinicalTrials.gov identifier: NCT01196390). Other studies are planned or currently recruiting patients to assess trastuzumab or lapatinib in metastatic disease in combination with standard chemotherapy as well as with targeted therapy.

Primary and secondary resistance to chemotherapy or targeted therapy is a major obstacle of treatment of all malignancies including esophageal cancer. Mechanisms of resistance to trastuzumab in breast cancer are summarized in Table 2. Overcoming resistance has been extensively studied in breast cancer but not in esophageal or gastric cancer. One option will be to add or switch to lapatinib. Another option may include coinhibiting other pathways such as epidermal growth factor receptor (EGFR), insulin-like growth factor 1 receptor (IGF-1R), and c-Met to overcome resistance.

Preclinical testing and well-designed randomized studies are needed in this patient population. Extrapolating data from the breast cancer literature and applying the same concepts in treating esophageal or gastric cancer is not recommended. The use of anti-HER2 antibodies as single-agent, maintenance, and adjuvant or neoadjuvant therapies is not advised at this point outside of a clinical trial.

The chemotherapy used in the ToGA trial consisted of cisplatin and fluorouracil.\(^{25}\) Combining trastuzumab with different cytotoxic agents might be an acceptable option with close monitoring, especially when using other cardiotoxic drugs. It is important to note that patient selection should be based on the assessment of HER2 immunohistochemical reactivity of the tumors. Such evaluation should be performed by diligently following the stringent criteria outlined in the literature and summarized previously. It is also wise to implement a quality assurance/quality control process within the pathology department to continuously ensure that criteria are diligently applied by all pathologists.

Trastuzumab can be safely added to cytotoxic agents in the treatment of metastatic and unresectable esophageal adenocarcinomas. The use of trastuzumab beyond disease progression, in the adjuvant or perioperative setting, is not recommended at this time, until further safety and efficacy data are available from well-designed clinical trials.

**Table 2. — Proposed Mechanisms of Trastuzumab Resistance**

<table>
<thead>
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<td>Activation of Akt</td>
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<td>PI3K activation</td>
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<td>Activation of epidermal growth factor pathway (EGFP)</td>
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<tr>
<td>Activation of insulin-like growth factor 1 receptor (IGF-1R)</td>
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<td>PTEN = phosphatase and tensin homolog, PI3K = phosphatidylinositol 3-kinase</td>
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References


