Carcinoma of the stomach is the fourth most common cancer and second most frequent cause of cancer-related mortality in the world.\textsuperscript{1-8} Surgical intervention, including gastrectomy with lymphadenectomy, is currently the only potential curative therapy in localized disease.\textsuperscript{3,5,6,8,9} However, gastric adenocarcinoma is often diagnosed in its late stage, and chemotherapeutic treatment modalities have unfortunately proven relatively ineffective, generally resulting in low survival rates, high recurrence rates, and overall poor prognoses.\textsuperscript{1,2,5-8,10-13}

Targeted molecular-based therapy capitalizing on genes and gene products harbored in gastric and gastroesophageal adenocarcinomas may provide an additional therapeutic method of intervention in advanced tumors.\textsuperscript{5,6,11,14} The oncogene HER2/neu, located on chromosome 17q21, is a member of the Human Epidermal Growth Factor Receptor family, which regulates cellular functions, such as proliferation, differentiation, motility, migration, adhesion, and apoptosis, through a transmembrane protein kinase.\textsuperscript{2-7,9,11,12,14} Oncogene amplification and subsequent increased protein expression is thought to mediate cell transformation in the initiation and progression of carcinogenesis and metastasis.\textsuperscript{8} HER2/neu amplification occurs in approximately 10\% to 30\% of breast adenocarcinomas and correlates with a poor prognosis, including shorter survival rates and resistance to adjuvant chemotherapy and endocrine therapy.\textsuperscript{4,6-9,11,13,15} HER2/neu testing has become the standard of care for invasive adenocarcinoma of the breast, because Herceptin\textsuperscript{\textregistered} (Trastuzumab), a recombinant humanized IgG1 monoclonal anti-HER2 antibody, offers an effective treatment modality for HER2/neu positive tumors.\textsuperscript{7,12,15,16}

HER2/neu is also amplified in many other solid tumors, including those of the lung, head and neck, salivary gland, endometrium, uterine cervix, ovary, fallopian tube, prostate, urinary bladder, colon, and pancreas.\textsuperscript{5,7,9,11,15} In upper gastrointestinal tract adenocarcinomas, the percentages of tumors with HER2/neu amplification vary widely, ranging from approximately 2\% to 45\% of gastroesophageal, 8.2\% to 53.4\% of gastric, and 11\% to 73\% of esophageal adenocarcinomas.\textsuperscript{1,3,5-11,13-18} The 2009 ToGA (Trastuzumab for Gastric Cancer) trial reported that of locally advanced, recurrent, or metastatic tumors, approximately 33\% of gastroesophageal junction and 22.1\% of gastric adenocarcinomas were HER2 positive by either immunohistochemical (IHC) study or fluorescence in-situ hybridization (FISH) analysis.\textsuperscript{1,4,8,9,12,16} The
ToGA trial further demonstrated high concordance rate of 87.2% between HER2/neu amplification conducted by FISH analysis and overexpression evaluated by IHC study.\textsuperscript{1,6,8,11,16} The prognostic relevance of HER2/neu amplification and overexpression in gastric cancer is controversial, but some studies have shown an association with poor outcome, aggressive disease, and shorter survival.\textsuperscript{3,5,6,8-12,15,16,18}

Compared with standard chemotherapy treatment alone in the ToGA trial, the increased median overall survival with the addition of Trastuzumab in patients who were either IHC(3+) or FISH(+) was only a modest 2.7 months (11.1 months with chemotherapy alone compared to 13.8 months with the addition of Trastuzumab).\textsuperscript{2,4,7-9,12,16,17} However, in patients who were IHC(3+) or [IHC(2+) and FISH(+)] (high protein expression) and received chemotherapy plus Trastuzumab, the median overall survival improved by 4.2 months (11.8 months with chemotherapy alone compared to 16 months with the addition of Trastuzumab).\textsuperscript{1,2,7-9,11,16,17} Therefore, IHC should be utilized as the initial screening modality in HER2/neu testing, and cases equivocal/2+ for HER2 overexpression can be referred for FISH analysis.\textsuperscript{1,4,8,9,16,17} The HER2/neu status assessment algorithm in gastroesophageal and gastric adenocarcinoma, which follows the inclusion criteria of the ToGA trial and was proposed by the European Medicines Agency, is depicted in Figure 1.

\textbf{Figure 1: Proposed algorithm for chemotherapy treatment with the addition of Trastuzumab eligibility in inoperable locally advanced or metastatic gastroesophageal and gastric adenocarcinoma}\textsuperscript{1,4,9}
Studies have demonstrated intratumoral heterogeneity for both HER2 overexpression and HER2/neu amplification in gastroesophageal and gastric adenocarcinomas; and it is not clear how diverging heterogeneity occurs in tumor cells or how this phenomenon is relevant to targeted HER2 monoclonal antibody response. Nonetheless, because intratumoral heterogeneity may result in false-negative results in endoscopic biopsies, multiple biopsies are desirable for HER2/neu status assessment, if feasible.

The ToGA trial showed that treatment of HER2/neu-positive advanced gastroesophageal and gastric adenocarcinoma with Trastuzumab, in addition to standard chemotherapy (capecitabine or fluorouracil plus cisplatin), improved the response rate, median progression-free survival, and overall survival, providing evidence that these tumors are potential responders to monoclonal antibody-based therapy targeting the HER2 protein. Trastuzumab was well tolerated when administered concomitantly with chemotherapeutic agents, and it is the first biological agent to show a survival benefit in advanced gastroesophageal and gastric adenocarcinoma. The Food and Drug Administration (FDA) has approved Trastuzumab in combination with chemotherapy for metastatic gastric and gastroesophageal adenocarcinoma in patients without prior anticancer treatment. Although, the ToGA trial included tumors that were inoperable, the role of Trastuzumab in the adjuvant setting may be promising. Many researchers advocate assessment of HER2/neu status as a standard component of routine diagnostic work-up in advanced gastroesophageal and gastric adenocarcinoma to identify patients who would benefit from targeted monoclonal antibody therapy.

References


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