HER2 Testing for Gastroesophageal Cancer

HER-2/neu (HER2) is a proto-oncogene located on chromosome 17q21 and a member of the human epidermal growth factor receptor (EGFR) family. Patients with HER2-positive (i.e., amplification and/or over-expression of the gene) breast cancer have a relatively poor prognosis but increased survival rates when treated with trastuzumab (Herceptin) compared to conventional adjuvant chemotherapy alone; i.e., HER2 testing has both prognostic and predictive value. Based on the success of using HER2 gene status in treating metastatic breast cancers, the use of HER2 gene status in metastatic gastric and esophago-gastric junction (EGJ) tumor tissue is being explored as a potential predictive marker of response to trastuzumab in HER2 positive gastric and EGJ tumors.

HER2 testing – HER2 status is mainly assessed by immunohistochemistry (IHC) and/or chromo-genic (CISH) or fluorescence in situ hybridization (FISH). Other test technologies are also being explored, including multiplex ligation-dependent probe amplification (MLPA), quantitative PCR, and proteomic panels based on mass spectrometry.

The current standard for HER2 testing in breast cancer calls for initial testing by IHC: 0-1+ results are considered negative, 3+ as positive, and 2+ as equivocal and eligible for proceeding to FISH or CISH testing. If FISH/CISH is positive, the tumor specimen is considered as HER2 positive (for over-expression).

As validated in the ToGA trial, the HER2 testing criteria that must be used in evaluating both gastric carcinoma biopsies and surgical specimens significantly differ from those routinely applied in breast carcinoma. The number of stained cells necessary to consider a case as positive is different. There is much more frequent heterogeneity of HER2 positivity in gastric cancer compared with breast carcinoma. Less stringent correlation between HER2 amplification and protein overexpression is observed in gastric carcinoma, where more than 20% of cases may carry HER2 amplification, at low level, without HER2 expression. In these patients, in the ToGA trial, there was no apparent benefit from adding trastuzumab to chemotherapy.

Evidence Summary – Despite unanswered questions, the U.S. FDA (and the European Medical Agency) granted approval in 2010 for trastuzumab in combination with cisplatin and a fluoropyrimidine (either capecitabine or 5-fluorouracil), for the treatment of patients with HER2 overexpressing metastatic gastric or EGJ adenocarcinoma who have not received prior treatment for metastatic disease. No specialty society statements that address this issue were identified for this review.

Alert: HER2 testing is rapidly emerging as the standard of care for purposes of predicting (non-) response to trastuzumab in patients with gastric or EGJ cancer, thus its use is supported for all patients with advanced disease being considered for this drug.

Key Resources: