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Updates in HER2 Testing in Gastric Cancer

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Introduction

Gastric adenocarcinoma is a major cause of morbidity and mortality in the world with median overall survival being less than a year [1-4]. Advanced gastric adenocarcinoma is associated with a dismal prognosis, and increasing survival time, even by a few months, can be significant in this patient population [3,5,6]. Recently there was a major breakthrough in the treatment of gastric cancer, which arose by studying a therapy currently used for treatment of another solid tumor, HER2 positive breast carcinoma. Trastuzumab, a monoclonal antibody that targets the extracellular domain of the HER2 receptor, has become standard first-line treatment in this classification of breast carcinomas [7-10]. A recent clinical trial (ToGA) using trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-esophageal junction cancer showed an increase in overall survival in advanced (inoperable locally advanced, recurrent, or metastatic) gastric cancer treated with chemotherapy plus trastuzumab versus chemotherapy alone [1]. This was the first time a biological therapeutic was proven to increase survival in gastric cancer. Critical to the ToGA trial was determining which patients would be eligible for randomization - i.e. which patients had tumors that over-expressed HER2. Therefore, not only was trastuzumab shown to prolong survival in patients with advanced gastric cancer, but a protocol was proposed for HER2 testing in gastric cancer in a corollary study [11]. HER2 interpretation in gastric cancer is similar to, but slightly different than interpretation in breast cancer. Hofmann put forth an initial proposal, which was subsequently validated with minor clarifications added by Ruschoff [11,12]. The modifications in gastric cancer HER2 interpretation are related to heterogeneity (percentage of cells positive and different criteria in biopsies versus resections) and physiology (pattern of staining - basolateral/lateral versus complete circumferential staining). The ToGA study established trastuzumab as a viable treatment option in advanced gastric cancer and led to approval by the Food and Drug Administration (FDA) and the European Union for its use in combination with chemotherapy in that setting [13,14]. The most recent National Comprehensive Cancer Network (NCCN) Guidelines recommend trastuzumab with chemotherapy for patients with advanced or metastatic cancer, if the tumor is HER2 positive as confirmed by immunohistochemistry (IHC 3+) or fluorescence in situ hybridization (FISH score ≥ 2 for IHC 2+ tumors).

HER2 Testing

Correlating amplification and overexpression

There is a high degree of concordance between HER2 overexpression detected by immunohistochemistry and by fluorescence in situ hybridization (FISH) in breast cancer [15]. Multiple studies have demonstrated a similar high concordance in gastric cancer cases between immunohistochemical overexpression (IHC3+) and fluorescence in situ hybridization amplification [11,12,14,16,17]. As expected, concordance between HER2 IHC2+ and amplification is more variable. The subset of cases showing IHC/FISH discordant results may be due to heterogenous HER2 protein expression [16]. Concordance improves when the immunoscoring modifications recommended by Hofmann are applied (basolateral versus complete staining, lower percentage cells positive in resections, cluster of positive cells in a biopsy - see Table 1).

	Specimen	IHC Positive (3+)	FISH Positive
Breast*	Biopsy	Uniform, strong circumferential membrane staining in ≥ 30% of cells (chicken wire pattern)	20 cohesive tumor cells showing highest gene count (count additional 20 if ratio 1.8-2.2) HER2/CEP17 ratio ≥ 2.2
	Resection	Same	Same
Gastric**	Biopsy	≥ 5 Cells Moderate-strong complete basolateral or lateral only staining	20 cohesive tumor cells showing highest gene count (count additional 20 if ratio 1.8-2.2) HER2/CEP17 ratio ≥ 2.0 HER2 signals >6
	Resection	≥ 10% Cells Moderate-strong complete basolateral or lateral only staining	20 cohesive tumor cells showing highest gene count (additional 20 if ratio 1.8-2.2) HER2/CEP17 ratio ≥ 2.0 HER2 signals > 6

*ASCO/CAP
**Ruschoff/Dietel

Table 1: HER2 Testing Scoring Criterion: Breast versus Gastric cancer.

Given the degree of tumor heterogeneity in gastric cancer, modified methods for HER2 fluorescence in situ hybridization (FISH) and silver in situ hybridization (SISH) should be considered. ISH should be directed based on the corresponding IHC-stained slide [14,18]. The clinical relevance of intratumoral heterogeneity is yet to be determined. One recent study showed evidence to suggest prognostic differences between cases showing heterogeneous versus homogenous HER2 gene amplification [14,17].

Other practical issues in HER2 testing

Practical issues in HER2 testing are related to the biology of HER2 (i.e. tumor heterogeneity) as well as our current testing methods (preanalytic variables, differences in commercially available IHC assays). As in breast cancer HER2 testing protocols, strict guidelines for preanalytic tissue handling should be followed [18,19]. Standardized preanalytic tissue handling will also enable further studies to characterize the reason for discordant IHC/FISH results. Despite tumor heterogeneity, studies have shown good correlation between biopsy and surgical resections. The use of biopsy tissue, which is immediately put into a fixative after removal from the patient, allows for standardized fixation and reduces error [18]. Yet, the diagnostic material provided in a biopsy is markedly variable and exhaustion of biopsy material may lead to other problematic issues. Current immunohistochemical methods (HercepTest and 4B5) should also be reviewed, considering that differences in sensitivity

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for detecting HER2 amplification were noted in the Rüschoff et al. guideline validation paper [12].

HER2 Biology in Gastric Cancer

Predictive, not prognosticating

Despite the advance in gastric cancer treatment offered by the ToGA trial, it also left many questions unanswered. While treating patients with HER2 positive tumors lengthens survival, there is significant controversy in the literature about whether or not HER2 itself is an independent prognostic factor. Some studies have shown an association with poor prognosis [20-30] while other studies have shown no association between HER2 status and outcome in patients with gastric cancer [31,32]. Another recent study of patients with metastatic (Stage IV) gastric cancer who received chemotherapy without trastuzumab [13] showed HER2 status had no impact on overall survival or progression free survival. This suggests that HER2 overexpression may not be associated with more aggressive disease or resistance to chemotherapy in metastatic cancer. The study did show an association between HER2 positive status and Lauren's intestinal histology and liver metastases. Recently published data from the United Kingdom Medical Research Council's TransMagic study showed that HER2 status is not a prognostic indicator in early cancer; it also showed HER2 cannot be used to select patients for epirubicin, cisplatin and infused 5-fluorouracil (ECF) chemotherapy [16]. All of this is in contrast to breast cancer, where HER2 has been shown repeatedly to be a poor prognostic indicator [33]. Some of this discrepancy may be related to the absence of a standardized definition of "HER2 positive" in gastric cancer prior to Hofmann [11]. Pre-analytic variables may also play a role. And of course, it is possible that breast and gastric cancers have different biology. Nonetheless, even though HER2 may not be an effective prognosticator, determination of HER2 status is critical if use of trastuzumab is being considered.

Clinicopathologic factors

Isolating the clinicopathologic factors that are associated with HER2 overexpression may help identify patients that might benefit from treatment with trastuzumab. Reported rates of HER2 overexpression and/or amplification range from 7% up to 34% in advanced disease, depending on the study group, with most cases in the range of 15-25% [1,11-13,24,27,29,34,35]. The rate of HER2 positivity seems to be lower in early gastric cancer, ranging from 10.4% to 13.6% [16,32]. Despite the variability in overexpression rates, most studies support a strong association between HER2 positive status and Lauren's intestinal-type adenocarcinomas [1,11-13,29]. Interestingly, this correlates with the significant differences noted in the epidemiological and molecular characteristics between these two histologic subtypes (intestinal and diffuse type gastric adenocarcinomas). As stated previously, HER2 overexpression is associated with liver metastases [13]. Further examination of these associations may provide insight into targeted testing and treatment.

Current clinical studies on trastuzumab

Multiple Phase II and III clinical trials are underway to further examine trastuzumab in combination with different chemotherapy regimens, including Capecitabine and Oxaliplatin, in advanced gastric cancer; one of these studies includes chemoradiotherapy (TOXAG study). Given the results of the ToGA trial, other targets related to HER2 are under investigation, including trastuzumab in combination with poziotinib (a pan-HER inhibitor), pertuzumab (HER dimerization inhibitor), lapatinib (which inhibits HER2 and EGFR), bevacizumab (VEGF-A inhibitor) (http://www.clinicaltrials.gov/ct2/results?term=trastuzumab+gastric+cancer&pg=1 accessed 6/21/2013).

Conclusion

Advanced gastric cancer is a major cause of morbidity and mortality worldwide. The ToGA trial was the first to show improved survival in patients whose tumors overexpress HER2 when they were treated with transtuzumab + chemotherapy versus chemotherapy alone. Treatment with trastuzumab requires assessment of tissue samples for HER2 overexpression and requires pathologists to keep abreast of current testing and interpretation guidelines. The role of HER2 in gastric carcinogenesis is under investigation, as is its role in other human cancers. Also under investigation is the optimal manner to use trastuzumab in HER2 positive solid tumors.

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