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EDITORIAL OPEN ACCESS

Lights and shadows of HER2 testing in upper gastrointestinal carcinomas

Antonio Ieni, Valeria Barresi, Giovanni Tuccari

The HER2 overexpression and amplification were reported approximately in 15–20% of breast carcinomas and associated with shorter disease-free and overall survival [1, 2]. Trastuzumab is a humanized monoclonal antibody targeting HER2 that has been confirmed to significantly increase the disease-free and overall survival of women with tumors HER2 positive expression in breast cancer [2].

In recent years, it has been demonstrated that a considerable percentage of gastrointestinal adenocarcinomas show an HER2 gene amplification with a range from 6–23% [1, 3]. It has been described that Trastuzumab is able to inhibit tumor growth in gastric carcinoma cell lines, animal model and xenograft models [4]. The randomized ToGA study have demonstrated a 26% reduction in the risk of mortality when trastuzumab was added to the chemotherapy regime (hazard ratio, 0.74) for treating advanced gastric carcinomas, improving the response rate, median progression-free survival and overall survival [5].

HER2 amplification or overexpression has reported to be variable rates in gastric cancers; there is a general agreement that the HER2 overexpression is related to the primary tumoral site, which is more frequent in cancers located in gastroesophageal junction (24–35%) compared with those from others gastric localizations (9.5–21%) [6].

Antonio Ieni [1], Valeria Barresi [1], Giovanni Tuccari [1]

Affiliations: [1]Azienda Ospedaliera Universitaria "Gaetano Martino" and Department of Human Pathology "Gaetano Barresi", Section of Anatomic Pathology, University of Messina, Messina 98123, Italy.

Corresponding Author: Antonio Ieni, MD, PhD, Department of Human Pathology "Gaetano Barresi" A.O.U. Policlinic G.Martino Via Consolare Valeria 1, 98125 Messina - Italy; Ph: +39-90-2212536; Fax: +39-90-2928150; E-mail: aieni@unime.it

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The histological assessment and classification of neoplastic histotypes revealed that the intestinal is more likely to be HER2 positive (16–34%) compared with diffuse (2–7%) or mixed (5–20%) types [7]. Rarer histotypes of gastric carcinomas were also studied, including hepatoid carcinomas (HAS) that have been shown the highest HER2 immunoreactivity [7]. In particular, HER2 expression appeared to reflect the different biological behavior representing an independent prognostic factor, of two variants of gastric adenocarcinomas, as MRC considered a low-grade gastric malignancy associated with an excellent prognosis characterized by a low HER2 expression, compared to the HAS that exhibited an extremely poor prognosis and the top rate of HER2 positivity [8].

It is known, that esophageal adenocarcinomas mostly show histological intestinal tumor type characteristics related to the intestinal metaplasia caused by esophageal reflux [9]. Consequently, the higher HER2 positivity rates in esophageal adenocarcinoma in comparison with gastric adenocarcinoma could be related to the higher prevalence of intestinal tumor type. The explanation for the higher overexpression of HER2 in intestinal type adenocarcinoma has not been found an explanation yet [10], probably it may be attributable to the differences E-cadherin mutations in diffuse versus intestinal type of gastric cancer, similarly to that observed in the breast carcinoma [10].

Currently, there are two recommended methods in HER2 testing, such as immunohistochemistry (IHC) for protein expression and in situ hybridization (ISH) for gene amplification, although there is controversy regarding the validity of HER2 testing in upper gastrointestinal malignancies [11]. In contrast to breast cancer, the distribution of HER2-positive gastric cancer cells in tissue is heterogeneous, frequently multi-focal and incomplete membrane staining. Consequently, the ASCO/CAP guidelines for HER2 IHC testing used in breast cancer were not appropriate for upper gastrointestinal carcinomas (UGC) [12]. Therefore, a specific gastric cancer HER2 testing protocol has been developed, as follows: in surgical specimens, 0 in cases with negative staining; 1+ in tumors with a faint and discontinuous

membranous staining in <10% of neoplastic elements; 2+ (equivocal staining) when a light to moderate lateral, basolateral or complete membranous staining in > 10% of neoplastic elements; 3+ in cases with strong, intense lateral, basolateral or complete staining in >10% of neoplastic elements. In biopsy specimens, it has been recommended that a cluster of at least 5 positive tumor cells was the minimum required to qualify a result as positive, replacing the surgical specimens cut-off criteria of ≥10% [12]. In case of equivocal 2+ results, an ISH test is strongly recommended to clarify the HER2 status in represented by: fluorescence in situ hybridization (FISH), chromogenic in situ hybridization (CISH) and silver in situ hybridization (SISH). The convenience and the concordance between IHC and ISH methodologies in HER2 status of gastric cancer confirmed an high level of concordance [13].

As a rule, the HER2 testing is often done on neoplastic biopsy samples of primary lesions, which may not be representative of whole tumor, resulting thus false negatives that lead to under-treatment of patients [14]. In literature, the overall concordance range of HER2 status between biopsy and surgical specimens advanced gastric and gastroesophageal junction (GEJ) adenocarcinomas ranged from 74.1–96.1%, with a predictive positive value of 71.4% and a negative predictive value of 94.4% [14] indicating that the considerable heterogeneity of HER2 expression raises issues with respect to tumor sampling and block selection. At present no guidelines are available regarding the number of tumor blocks needed to be tested for HER2 expression. In gastrectomy specimens, it may be careful to analyze more than one representative tumor block, particularly when carcinomas showed a mixed histotype. It has been described, that the IHC HER2 analysis with a single block of the primary tumor could not be adequately confident to compensate for the heterogeneity of HER2 expression in a gastric cancer [15]; in fact, additional tissue blocks improved the rate to 20%, a value slightly higher than that obtained using 1 block (17%) [15]. Finally, the introduction of at least three tissue blocks might increase the positive rate to 50% approximately [16].

HER2 amplification seems to be associated with others clinicopathological features observed in patients affected by UGC (age, male gender, tumor size, serosal invasion and lymph node metastasis); even if its prognostic implication in gastric and esophageal cancer remains controversial [4]. Numerous retrospective studies have demonstrated that HER2 positivity is a prognostic factor associated with a worse survival [17]. Conversely, other reports failed to find any relationship between HER2 reactivity and prognosis, either in early gastric carcinoma either in advanced stage [18].

HER2 expression/amplification explored in esophageal adenocarcinomas revealing a positivity rate from 15–27%; but only in 4% of squamous cell carcinomas, representing an additional group of patients who might benefit from trastuzumab treatment [19]. However, HER2 positivity has been elsewhere reported in 17% patients affected by esophageal adenocarcinomas and it was significantly associated with lower tumor grade, less invasiveness, fewer metastatic nodes and presence of adjacent Barrett's esophagus [20]. Consequently, HER2 status has been suggested to represent an independent predictor of worse cancer-specific survival in these tumors as well as in squamous cell ones [20].

It is well known that a divergence HER2 molecular patterns between primary breast carcinoma and its corresponding either distant or locoregional metastases has been reported; this discordance has been also found in consecutive relapses of the same tumor, with cases turning from negative to positive and vice versa [21]. As a consequence, the need to assess HER2 status not only in the primary tumor, but also in its metastases, to establish if a particular therapy is considered actually appropriate [21].

In UGC, many papers showed that HER2 status varied in the metastatic lesions compared to the primary tumor and this discrepancy was more frequently encountered in distant metachronous metastases (87.5–94.9%) than in locoregional ones [22, 23]. In detail, in gastric cancer the discordance rate ranged from 2–24%, with a mean pooled estimated about 7%, with a pooled proportion of negative conversion of 17% and the positive conversion of 4% [23]. Moreover in primary esophageal carcinomas, the HER2 discordance was appreciable in 5% of cases of paired lymph node metastases and in 14% in distant metastases [19].

In order to explain this discordant phenomenon, a variety of reasons has been hypothesized including variability in technical assessment and/or pre-analytical factors, such as use of different fixation intervals and different staining procedures. To avoid the possibility that variability in HER2 status might depend on external factors, both neoplastic primary and metastatic gastric specimens should be collected during the same surgical procedure, without any influence of therapy and with a common tissue fixation methodology [21–23]. Finally, in our opinion HER2 status should be reassessed not only in metachronous metastases, but also in synchronous nodal metastases since it may have a relevant clinical impact for the therapeutic choice.

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Author Contributions

Antonio Ieni – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Valeria Barresi – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Giovanni Tuccari – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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