EUR. J. ONCOL., vol. 19, Suppl n. 1, pp. 5-7, 2014

HER-2 and Gastric Cancer

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In recent years, a number of drivers genetic changes have been found to be actionable in gastric carcinomas. In particular, the discovery of HER2 up-regulation in human malignancies has stimulated rapid growth in specific cancer drug development programs.

HER2 positivity in gastric carcinomas ranges from 7% to 42% of cases. Currently, tumors semi-quantitatively scored as 0 (no staining or <10% of positive cells) or 1+ (faint perceptible staining, >10%) by immunohistochemistry (IHC) are considered HER2 negative, while cases 3+ (moderate to strong; complete or basolateral membranous staining; >10%) are considered HER2 positive. In the case of 2+ score, in situ hybridization methods are used to further define the HER2 status. It is likely that the wide range of HER-2 positivity is linked to intratumoral heterogeneity in HER2 expression/amplification and the lack of uniformity and reproducibility in the criteria for defining HER2 positivity (2).

The prognostic role of HER2 in gastric cancers has been debated for years. Recent systematic revisions and meta-analyses suggested that HER2 up-regulation seems to be associated with adverse survival in gastric cancer patients (3, 4). But above all, HER2 positivity is a powerful predictive factor for the efficacy of anti-HER2 compounds. In fact, the results of ToGA trial marked the dawn of a new era of systemic therapy in patients with advanced gastric cancer (5). In the intention-to-treat population of this study, median OS was 13.8 months in those assigned to trastuzumab plus chemotherapy compared with 11.1 months in those assigned to chemotherapy alone (HR 0.74; 95%CI 0.60–0.91; p=0.0046). Median PFS also favored patients exposed to trastuzumab (6.7 months vs 5.5 months, HR 0.71; 95%CI 0.59–0.85; p=0.0002). Moreover, a statistically significant increase in response rate (47% vs 35%; p=0,0017) was reported for the trastuzumab-containing arm. In the population with the highest HER2 expression (IHC 3+ or IHC 2+/FISH positive) the survival advantage was even more pronounced (5). Novel HER2-inhibitors are under investigation. Among them, Lapatinib is an orally available, tyrosine kinases inhibitor (TKI) that targets the intracellular domain of both HER1 and HER2. Afatinib is an irreversible pan-HER TKIs, and Petuzumab is a humanized monoclonal antibody directed against the extracellular subdomain 2 of HER2 (5).

As far as the role of HER2 up-regulation in patients treated with chemotherapy alone is concerned, available studies do not allow any firm conclusion (6). For example, in the assessment of HER2 gene amplification in gastric and gastroesophageal junction adenocarcinomas in the INT-0116/SWOG9008 chemo-radiation trial (7), patients lacking HER2 amplification benefited from treatment. In the same study, among patients with HER2-amplified cancers, there was no significant difference in survival. On the opposite, in a Korean study (8), HER2-positivity in advanced gastric cancer patients treated with modified FOLFOX-6 showed association with poor prognosis. In the HER-2 analysis in patients enrolled in the perioperative epirubicin, cisplatin and fluorouracil chemotherapy MAGIC trial (9), there was no independent prognostic role of the biomarker. Finally, the supposed better prognosis of HER-2 positive patients in the chemotherapy-only

arm of the TOGA trial cannot be confirmed, given the lack of a HER-2 negative, chemotherapy-only arm (5).

Although the growing burden of translational and clinical data on the prognostic and predictive role of HER2 up-regulation in gastric cancer, there are a number of critical and poorly understood aspects that necessitate additional research in this field. First of all, intraglandular or intratumoral heterogeneity for HER2 overexpression/amplification may occur (10,11). Though the high level of agreement between HER2 status in primary gastric or gastroesophageal cancers and corresponding metastatic sites, HER2 analyses at both sites may improve predictive information. Also, it has been reported, that intratumoral HER2 expression/amplification heterogeneity may impact on the clinical outcomes (10, 11), and it could be among the mechanisms for anti-HER2 drugs resistance (10). The complexity of the mechanisms leading to primary or secondary resistance to Trastuzumab and other anti-HER2 compounds must be still elucidated. Several data about primary and secondary mechanisms of resistance to trastuzumab derive from studies in breast cancer (13). Amplification of the PI3K/Akt pathway is one of the most studied resistance mechanisms. Also, activation of other surface receptors may interfere with HER2 inhibition. For example, MET inhibitors as well as Insulin Growth Factor (IGF) receptor inhibitors could restore cell sensitivity to trastuzumab when c-MET or IGFR are abnormally activated (13). Interferences with the binding of trastuzumab to HER2 may also be a cause of resistance. For example, the appearance of truncated forms of HER2 , or the increased production of mucin 4 may cause the masking of the target (13). Loss of exon 16 causes the constitutive dimerization and activation of HER2 receptor. Finally, abnormal SRC activity and acquisition of the epithelial-mesenchimal transition (EMT) phenotype seem to be related to the development of resistance to HER2 inhibitors (13). We are currently addressing these issues in a novel transational study with combined MALDI-TOF (Matrix Assisted Laser Desorption Ionization - Time of Flight) proteomics, mutation sequencing and FISH analyses for multiple activated kinase/molecular pathways in 280 stage II-III gastric cancer cases. Preliminary data indicate that HER2 positivity frequently couples with SRC expression and dysregulation of epithelial-mesenchimal transition (EMT) proteins like Vimentin (overexpression) and E-Cadherin (reduced expression).

In conclusion, growing pre-clinical and clinical data indicate that additional efforts are needed for expanding the knowledge on the HER2 status and optimizing its prognostic/predictive role. In fact, the development of HER2 inhibitors may not require only a simple assessment of "HER2 positive" cases, but rather a deep knowledge on how and to what extent tumors are HER2 addicted.

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