

The Current Approach to the Prognosis and Treatment of HER2 (erbb2) in Gastric/Gastroesophageal Cancers: Review Article

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Abstract

HER2 protein has become a prominent target in the light of studies investigating prognostic and predictive factors in gastric and gastroesophageal carcinoma. HER2 overexpression occurs in a significant proportion of this carcinomas and HER2 overexpression plays a role in tumor progression and angiogenesis in early stage gastric carcinomas.

Regardless of age, sex, tumor type, and stage, HER2 positivity should be verified in all cases of gastric and gastroesophageal junction carcinomas using IHC analysis-if necessary, using ISH analysis as well-and trastuzumab treatment should be administered based on these positivity results.

Keywords: *Stomach; HER2; Gastric Carcinomas; Gastroesophageal Junction Carcinomas*

Despite the significant advances in oncology and surgery in recent years, gastric carcinomas remain one of the most lethal malignancies worldwide. The tumorigenesis mechanisms of gastric and gastroesophageal carcinomas remain unclear [1]. The most important prognostic factor in gastric carcinomas is the TNM stage. However, different prognoses can be observed in patients with the same TMN stage. More importantly, determining whether a complete response could be achieved using a standard oncological treatment remains challenging [2].

HER2 protein has become a prominent target in the light of studies investigating prognostic and predictive factors. The HER2 protein overexpression is considered to increase proliferation activity and suppress tumor cell apoptosis [3].

HER2, a proto-oncogene located on chromosome 17 and a member of the epidermal growth factor receptor (EGFR) family, initiates signaling pathways that lead to cell division, proliferation, differentiation and apoptosis. It is alternatively known as CD340, HER-2, erbb2, and NEU. HER2 is expressed in normal epithelial cells; amplification and/or overexpression of this gene have been reported in approximately one-third of the cases with breast cancer and in 10% - 40% of those with gastric cancers [4,5]. In patients with gastric adenocarcinoma, HER2 overexpression may vary depending on the histological type and tumor differentiation. It has been reported that the intestinal type exhibits more overexpression than diffuse type and that medium differentiated carcinomas demonstrate more overexpression than poorly differentiated carcinomas [6].

Currently, the National Comprehensive Cancer Network (NCCN) recommends trastuzumab (Herceptin) treatment in patients with inoperable or locally advanced gastric and gastroesophageal carcinomas [6]. Prior to applying this treatment protocol to patients, HER2 overexpression should be determined using immunohistochemical (IHC) or *in situ* hybridization (ISH) analysis performed on the paraffin slides used for histopathological examination, and treatment should be accordingly initiated [1]. A phase III randomized controlled study performed in 2010 has reported that trastuzumab was effective in prolonging surveillance in patients with HER2-positive gastric and gastroesophageal junction adenocarcinomas [7] (Figure). Although HER2 appears as an important prognostic factor in gastric cancer, the literature is contradictory on the subject. Several studies have failed to demonstrate a relationship between HER2 overexpression and poor prognosis [3,8].



Figure: Carcinoma infiltrating the esophagus in the cardioesophageal junction.

There are ongoing clinical studies on HER2 in patients with gastric carcinoma. A study conducted in 2018 has demonstrated a relationship between HER2 overexpression and tumor angiogenesis intensity and reported that HER2 overexpression may affect antiangiogenic treatment during patient selection [1]. Another study conducted in 2018 has shown that HER2 gene amplification occurs during the early stages of gastric cancer and that it shows heterogeneity in certain cases; further, the authors have reported that it may play a role in tumor progression in early stage gastric cancer [9].

In a study conducted in 2018, Nadaf, *et al.* have reported that HER2 positivity was not significantly correlated with age, sex, tumor type, grade, and stage, and therefore, HER2 should be tested in all cases of gastric carcinoma regardless of the clinicopathological findings to provide a personalized treatment [10].

An HER2 IHC analysis includes 4 different scores ranging between 0 and 3. A score of 0 or 1 is considered negative, a score of 2 is considered equivocal, and a score of 3 is considered positive. NCCN panel recommends ISH analysis only for cases with an IHC score of 2. However, certain centers routinely use ISH analysis to verify cases that have IHC scores of 2 and 3. Verifying cases with scores of 0 and 1 using ISH analysis is not required, and trastuzumab is not recommended in such cases [6].

In conclusion, it is important to note that HER2 overexpression occurs in a significant proportion of gastric and gastroesophageal carcinomas, with certain recent studies reporting that HER2 overexpression plays a role in tumor progression and angiogenesis in early stage gastric carcinomas. Therefore, regardless of age, sex, tumor type, and stage, HER2 positivity should be verified in all cases of gastric and gastroesophageal junction carcinomas using IHC analysis-if necessary, using ISH analysis as well-and trastuzumab treatment should be administered based on these positivity results.

Disclosure of Conflict of Interest, Grant Support and Financial Disclosures

None to declare.

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