

HER2 Expression in Gastric Adenocarcinoma: A Study in a Tertiary Care Centre in Bahrain

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Abstract

Aim: Stomach cancer is the fourth most common cancer worldwide. It is a significant cause for morbidity and mortality globally. HER2 (Human Epidermal Growth Factor 2) status in gastric carcinoma has been studied worldwide, however there is sparse published data from Bahrain. Hence, this study was taken up to evaluate HER2 overexpression in gastric adenocarcinoma patients and to assess the relationship between its expression and clinicopathological tumor parameters.

Study design and settings: Retrospective study was conducted in Salmaniya Medical Complex-The main tertiary care center in Bahrain, over a 5 years period.

Study material: All the partial and complete gastric resection specimens and biopsies received in that period. HER-2 Immunohistochemistry (IHC) was done on most of the cases and the reports were reviewed for its expression in formalin-fixed paraffin-embedded tissue samples. Fluorescence *In Situ* Hybridization (FISH) was done for equivocal cases on IHC.

Data analysis: The data was analyzed using Microsoft Excel 2013.

Results: HER2 overexpression was confirmed in 4 (7.4%) cases of which 3 (75%) cases were of intestinal type whereas only 1 (25%) case of diffuse type adenocarcinoma.

Conclusion: HER2 positivity was more common in the intestinal type of gastric cancer compared to the diffuse type. Positivity of HER2 was found more in small biopsies as compared to the resection specimens in this study. HER2 overexpression was more in females, age more than 55 years old and in moderately and poorly differentiated adenocarcinoma. HER2 overexpression was not analyzed with the cancer stage because of data limitations.

Keywords: Stomach cancer; Immunohistochemistry; Trastuzumab; Adenocarcinoma

Introduction

Human epidermal growth factor receptor 2 (HER2), also known as CerbB-2 and ERBB2, is a proto-oncogene located on chromosome 17q21 that encodes a transmembrane protein with tyrosine kinase activity that was first discovered in Breast cancer cells and its amplification is associated with adverse outcome [1,2]. After that, many studies discovered the presence of HER2 amplification in other cancers such as colon cancer, ovarian cancers and gastric and gastro-esophageal cancers [3]. Because of the recent introduction of trastuzumab for the treatment of patients with advanced stage gastric cancer, the clinical need for HER2 assessment is increasing [2].

In gastric and gastroesophageal cancers, HER2 overexpression differs widely according to the literature. It also differs from the HER2 overexpression in Breast cancer. That is because of the biological behavior and tumor heterogeneity and the pattern of the HER2 IHC staining found in gastric cancers. Interobserver variations between pathologists in the interpretation of the HER2 IHC stain can (Table 1) affect the result of HER2 IHC testing also [2]. This study aims to estimate the number of gastric and gastroesophageal cancer diagnosed at Salmaniya Medical Complex-The main tertiary care center in Bahrain in the last five years. Moreover, we assess the HER2 overexpression in these cancers and compare it to results from the studies in the region and world. And also to study the correlation between HER2 positivity and the various clinicopathological factors.

Subjects and Methods

All the partial and complete gastric resection specimens and biopsies received in Salmaniya Medical Complex in the period between January 2016 to January 2021 were included in the study. Some of the patients did received chemotherapy. Histopathological examination was done for the

tumor on H&E stained slides.

The tumors were classified into intestinal type adenocarcinoma and diffuse type adenocarcinoma according to Lauren's classification. The differentiation of the tumors (mainly the intestinal type) were classified as well differentiated adenocarcinoma with >95% of glands formation (Grade I), moderately differentiated with 50% to 95% glands formation (Grade II) and poorly differentiated with <50% glands (Grade III) [4]. Diffuse type adenocarcinoma was considered as a poorly differentiated adenocarcinoma. Immunohistochemistry (IHC) for HER2 which were done on formalin-fixed paraffin-embedded sections of specimens results were collected from the histopathology reports of the cases. Few cases which are included in the study were not examined for HER2 IHC. Equivocal IHC results of some cases were sent for Fluorescence In Situ Hybridization (FISH) assay overseas and there results are included in the study.

HER2 expression scores were interpreted according to ASCO/CAP (Table 1).

Statistical analysis

Statistics were done by Office Excel 2013.

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| Score | Surgical specimen | Biopsy | HER2 overexpression assessment |
|-------|---|--|--------------------------------|
| 0 | No membranous staining or staining of <10% of the tumor cells | No membranous staining or staining only in rare cells (less than 5 cohesive cells) | Negative |
| 1+ | Staining is weak or detected in only one part of the membrane in ≥ 10% of the cells | Staining is weak or detected in only one part of the membrane of at least 5 cohesive cells | Negative |
| 2+ | Moderate/weak complete or basolateral membranous staining in ≥ 10% of the cells | Moderate/weak complete or basolateral membranous staining of at least 5 cohesive cells | Equivocal |
| 3+ | Strong complete or basolateral membranous staining in ≥ 10% of the neoplastic cells | Strong complete or basolateral membranous staining of at least 5 cohesive cells | Positive |

Table 1: Immunohistochemistry scoring for human epidermal growth factor receptor 2 expression in gastric and gastroesophageal junction cancer [10].

Results

A total of 69 specimens were studied with the age range between 32 to 90 years. The mean age was 62.1 years. The gender distribution was as follows: 24 are females (34.8%) and 45 are males (65.2%). Out of the 69 cases, 47 cases (68.1%) were small biopsies, 14 cases (20.3%) were partial gastrectomy specimens and 8 cases (11.5%) were slides from other hospitals for review.

In our study we found that most of the gastric adenocarcinoma diagnosed in our hospital were from the intestinal type (66.7%) and diffuse type accounts for (33.3%) only. We found also that majority of these tumors were moderately differentiated (52.2%) followed by poorly differentiated adenocarcinoma (44.9%) while the well differentiated tumors accounts for only 3% of total cases.

HER2 IHC testing was performed on 54 cases out of 69 cases. There were no reports for HER2 IHC tests in I-SEHA system for 15 cases out of 69 cases. Out of these 54 cases, HER2 amplification were found in 4 cases only (7.4%). Three of these cases were sent for HER2 gene FISH assay overseas after having an equivocal IHC result (score 2+). One case only was found positive on the HER2 IHC test (Score 3+) done in our hospital lab.

Moreover, it was sent for a Confirmatory FISH assay and the HER2 gene amplification was detected.

In our study, the HER2 gene amplification was more in the intestinal type adenocarcinoma (75%) while it was less in diffuse type adenocarcinoma (25%) (Table 2). Two of these cases were moderately differentiated adenocarcinoma and the other 2 were poorly differentiated adenocarcinoma. These results correlate with the studies in the literature, where most of the studies found that HER2 gene amplification in gastric cancer is more in the intestinal type adenocarcinoma, grades 2 and 3 (moderately and poorly differentiated adenocarcinomas, respectively) [4]. When HER2 positivity was analyzed according to type of specimen, we found that all the HER2 positivity were in the small biopsies. The rate was higher as compared to the resection specimens. Out of 47 small biopsies 4 (8.5%) showed HER2 overexpression, whereas no cases out of 14 (0%) resected specimens showed HER2 positivity.

In our study, we could not correlate the stage of the patient disease with the over expression of HER2 gene, because all the cases were diagnosed on biopsy specimens and after that, the patient will be referred to the oncology center in other hospital in Bahrain. So no follow up could be done to their disease stage.

| Histological subtype | No. HER2 IHC test done (%) | No. HER2 Positive (%)* | HER2 IHC Score | | | | Inconclusive |
|----------------------|----------------------------|------------------------|----------------|--------|--------|-------|--------------|
| | | | 3+ IHC | 2+ IHC | 1+ IHC | 0 IHC | |
| All tumors (n=69) | 54 (78.26%) | 4 (7.4%) | 1 | 5 | 10 | 37 | 1 |
| Diffuse (n=23) | 19 (35.2%) | 1 (25%) | 0 | 3 | 3 | 12 | 0 |
| Intestinal (n=46) | 35 (64.8%) | 3 (75%) | 1 | 2 | 8 | 25 | 1 |

Note:* Defined as cases demonstrating HER2 FISH amplification and/or 3+ HER2 IHC staining. *FISH indicates fluorescence in situ hybridization; IHC, immunohistochemistry.

Table 2: HER2 FISH and IHC by gastric carcinoma histologic subtypes.

Discussion

Gastric and Gastroesophageal cancers are of the most common cancers worldwide. Surgical treatments are the most frequent modalities used to treat it [3]. However, the late stage that most patients present with, made the neoadjuvant chemotherapy the first line treatment before the surgical resection option. The chemotherapy drugs effectiveness seem to have a stabilized plateau. Hence, using new targeting drugs treatments for this type of cancer is now evolving [2].

In general, most of patients with advanced gastric cancer have poor survival rate even with perioperative chemotherapy [2]. Moreover, the survival rate in gastric cancer is link to many factors like the patient age, tumor location and histological type along with tumor stage. The latter, is considered the most important prognostic factor. However, studied show that patients in the same tumor stage with the same histological tumor type also

have different survival rate [2]. That is why, looking for the overall prognostic parameters is essential to assess the survival rate in patients with such disease.

Carcinogenesis in stomach cancer is multifactorial like in other types of cancers. That include environmental, genetic and immunological factors. H.pylori infection being the most common environmental factor contributing to development of stomach ulcers and malignancies [5]. Genetic factors include multistep process with multiple accumulative actions of activation of oncogenes and inactivation of other tumor suppressor genes. Several genes alterations which are linked to stomach carcinomas are associated with HER2 gene amplification. They have special clinicopathological characteristics [2].

HER2/neu gene is one the Epidermal Growth Factor Receptor (EGFR) family which include includes EGFR/HER1, HER2/neu, HER3 and HER4

[5]. This family of genes contributes to most malignancies development. Each receptor of these consists of an extracellular ligand-binding domain, an intracellular domain with kinase activity and a short, lipophilic, trans-membrane domain [5,6]. Activation of any EGFR triggers a network of signaling cascade that promote tumor cell proliferation, migration, adhesion and angiogenesis and decrease in apoptosis [2]. HER2 does not bind to any known ligand, instead, it is the preferred heterodimerization partner for other members of the HER family [7]. HER2 is encoded by a gene located in chromosome 17q21 [7]. In carcinomas, HER2 acts like an oncogene, with its amplification it promotes more transmembrane protein synthesis and eventually accentuating the potential of a malignant cell [7]. Recent studies shows that HER2 gene is linked to so many cancers in different organs such as Breast cancer, gastric and gastroesophageal cancer, colon cancer and ovarian cancer [7].

Trastuzumab (Herceptin) is a monoclonal antibody which directly binds to HER2 protein extracellular domain of the receptor and it blocks its downstream signaling pathway promoting an antibody dependent cell-mediated cytotoxicity by activating apoptotic signals in tumor cells [8]. Using this targeted drug in gastric cancer patients with HER2 gene amplification shows promising results in improving survival rate in those patients [9].

Detecting HER2 gene amplification in gastric cancer is done either by Immunohistochemistry (IHC) for HER2 which were done on formalin-fixed paraffin-embedded sections of specimens or by Fluorescence *In Situ* Hybridization (FISH) assay.

Gastric cancer show a unique IHC staining pattern different than breast cancer staining pattern including high incidence of tumor heterogeneity (defined as 30% of tumor cells staining positive or only focal staining of tumor cells in up to 30% of HER2 positive cases) [10]. Another difference from the breast cancer staining is that in gastric cancer the staining pattern found more in intestinal type – gland forming tumors with incomplete, basolateral, or lateral staining in addition to complete membrane staining and all these are considered as positive with immunohistochemistry [11] (Table 1).

HER2 FISH assay is done like the standard protocols of Fluorescence *In Situ* Hybridization (FISH) assay and then it is scored based on ToGA FISH scoring scheme for HER2 testing in gastric and gastroesophageal junction cancer as follows: Negative, HER2/CEP17 ratio <2.0; and positive, HER2/CEP17 ratio ≥ 2.0 [12].

The role of HER2 gene overexpression in gastric cancer prognosis remains controversial as some studies failed to find a correlation between the two factors in patient survival rate and other studies found that patients with gastric cancer with HER2 gene overexpression have actually a poorer prognosis even with the treatment with the targeted therapy Trastuzumab [9].

Nevertheless, many studies found that there is a significance of HER2 overexpression in the prognosis and therapy of gastric carcinoma. That necessitates the routine HER2 testing in all gastric carcinomas workup because Trastuzumab is now approved for the treatment of metastatic HER2 positive gastric adenocarcinomas.

In our study, HER2 IHC testing was performed on 54 cases out of 69 cases. Out of these cases, only 4 cases had HER2 gene amplification. One case only had a positive HER2 IHC staining test (Score 3+). The rest 3 cases had equivocal IHC staining (Score 2+) and were sent for FISH assay overseas which came as positive for the HER2 gene amplifications (HER2/CEP17 ratio ≥ 2.0).

We found that HER2 gene amplification was more in female patients (8.3%), with age more than 55 years old (7%). All the HER2 positive cases were diagnosed on small biopsies (100%) and the intestinal type adenocarcinoma is accounting for 75% of the cases most of them are moderately to poorly differentiated adenocarcinoma (Table 3). Our results did not find a correlation between the stage of the patient disease with the over expression of HER2 gene, because all the cases were diagnosed on biopsy specimens and after that, the patient will be referred to the oncology center in other hospital in Bahrain. So no follow up could be done to their disease stage.

| | Number | Positive | Percentage |
|---------------------------|--------|----------|------------|
| Sex | | | |
| Male | 45 | 2 | 4.44% |
| Female | 24 | 2 | 8.3% |
| Age | | | |
| 55 or less | 26 | 1 | 3.9% |
| >55 | 43 | 3 | 7% |
| Type of specimen | | | |
| small biopsy | 47 | 4 | 8.5% |
| resection | 14 | 0 | 0% |
| slide review | 8 | 0 | 0% |
| Histological type | | | |
| intestinal | 46 | 3 | 75% |
| diffuse | 23 | 1 | 25% |
| Differentiation well-diff | 2 | 0 | 0% |
| Moderately-diff | 36 | 2 | 5.6% |
| Poorly-diff | 31 | 2 | 6.4% |

Table 3: Relationship between HER2 expression and clinicopathologic features in patients with gastric cancer.

Conclusion

In concordance with the studies conducted worldwide, our study concluded that HER2 positivity was more common in the intestinal type of gastric cancer compared to the diffuse type. Positivity of HER2 was found more in small biopsies as compared to the resection specimens in this study. HER2 overexpression was more in females, age more than 55 years old and in moderately and poorly differentiated adenocarcinoma. Cancer stage was not correlated with HER2 overexpression because of data limita-

tions. We also concluded that with the known significance of HER2 overexpression in the prognosis and therapy of gastric carcinoma, routine HER2 testing in all gastric carcinomas workup is necessary because Trastuzumab is now approved for the treatment of metastatic HER2 positive gastric adenocarcinomas.

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