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Research Article

Her2/neu Expression by Antigen-antibody in Patients with Gastric Carcinomas

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Abstract

Background : Globally, stomach cancer is linked to significant morbidity and fatality rates. The literature shows considerable variations in the prevalence of Her2/neu overexpression in gastric cancer. Moreover, research has shown conflicting results about its predictive significance. There haven't been many research done in Egypt on Her2/neu expression in stomach cancer. Thus, the purpose of this study is to assess the expression of HER-2/neu in gastric carcinomas and explore the relationship between it and the clinicopathological features of respectable stomach cancer in Egyptian patients.

Methods : From 2007 to 2013, 76 patients with stomach cancer had radical gastrectomy at the Gastroentrology Centre in Mansoura, Egypt, for the purpose of this study. Every clinicopathological finding was updated. By using a Beecher manual microarrayer, four TMA blocks were created from formalin-fixed, paraffin-embedded tumour tissues. Her2/neu was immunohistochemically stained on 4 µm thick sections sectioned from TMA blocks.

Results : 35 cases (46.1%) were negative, while 41 cases (53.9%) were positive. Positive Her2/neu expression was determined to be the only statistically significant relationship with Lauren intestinal type. Although this association does not approach statistical significance, Her2/neu positive expression was linked to poorly differentiated grade, late clinical stage, deeper tumour invasion, and an increase in the number of LN metastases. The other clinical pathologic markers and HER2/neu positive did not correlate.

Conclusion : Approximately 54% of resectable gastric cancinomas had HER2/neu positive. The Lauren intestinal type and positive Her2/neu expression were revealed to be the only statistically significant relationships.

Keywords : *Gastric cancer; Her2/neu; Carcinoma; Tumor*

Introduction

Globally, stomach cancer is linked to significant morbidity and fatality rates. Gastric cancer ranks ninth in Egypt among all cancers, accounting for 1.7% of all cancer cases in males [1]. stomach carcinoma accounts for 90 to 95% of instances of stomach cancer, making it the most prevalent malignant tumour. Numerous classification methods, such as the WHO classification [3] and the Lauren classification [2], can be used to categorise stomach cancer histopathologically. Lauren divides gastric carcinoma histologically into two main categories: intestinal-type (which accounts for 53% to 60% of cases) and diffuse-type (30%), with the remaining 10% being mixed or indeterminate forms. Four main kinds of stomach carcinoma are recognised by the WHO classification (2010): papillary, tubular, mucinous, and signet ring cell carcinomas.

The proto-oncogene human epidermal growth factor receptor-2 (Her2/neu) is found on chromosome region 17q21.It is responsible for encoding the transmembrane tyrosine kinase receptor protein, which controls signal transmission in cell survival, proliferation, and differentiation [4]. The initial reports of gastric cancer in 1986 mentioned HER2 gene amplification and protein overexpression [5]. The clinical need for Her2/neu assessment is growing quickly in order to select patients who qualify for trastuzumab treatment, which was recently introduced for patients with advanced gastric cancer [6]. Due to inherent variations in tumour biology, such as inadequate membrane staining and intratumoral heterogeneity of Her2/neu expression, which are frequently detected in gastric tumours, Her2/neu testing for gastric cancer differs from testing for breast cancer [7]. The prevalence of Her2/neu overexpression in gastric cancer ranges greatly in the literature from 4.4% to 53.4% [8]. Moreover, research has produced conflicting results about the prognosis significance of Her2/neu; most studies have suggested that Her2/

neu exhibits more aggressive biological behaviour and greater recurrence frequencies, whereas a small number of studies have not supported the prognostic relevance of Her2/neu [9]. There haven't been many research done in Egypt on Her2/neu expression in stomach cancer. Therefore, the purpose of this study is to assess the expression of HER-2/neu in gastric carcinomas and explore the relationship between it and the clinicopathological features of Egyptian patients' resectable stomach cancers.

Methods

This retrospective analysis was carried out on 76 patients with stomach cancer who, between 2007 and 2013, underwent radical gastrectomy at the Gastroentrology Centre in Mansoura, Egypt. Age, gender, location, size, shape, histological type as classified by the WHO and Lauren, WHO tumour grade, depth of invasion (T), lymphovascular invasion, perineural invasion, number of lymph node (LN) metastases, distant metastasis, and TNM staging were all revised clinicopathological data.

Using formalin-fixed, paraffin-embedded tumour samples, Beecher manual microarrayer was used to create four tissue microarray (TMA) blocks. Cut sections (4 μm thick) from TMA blocks were immunohistochemically stained and then mounted on coated slides. The DAKO kit was utilised, which is the Peroxidase/DAB+, Rabbit/Mouse, Produktionsvej 42, DK-2600, Glostrup, Denmark, Detection System. The enzyme and chromogen used are horseradish peroxidase and diaminobenzedene hydrochloride (DAB). Membranous stain that was clearly brown was regarded as positive. Each core's proportion of Her2/neu immunopositive tumour cells was calculated in the area with the highest density of these cells. When less than 10% of tumour cells exhibited faint, incomplete membranous or basolateral staining, it was deemed negative (Score 1). When 10% or more of immunopositive cells exhibited weak to moderate membranous or basolateral staining, it was deemed positive (Score 2). Positive (+3) is defined as basolateral or strong complete membranous staining of at least 10% immunopositive cells [10]. Scores of (0) and (1) were regarded as negative cases, whilst scores of (2) and (3) were regarded as positive situations.

Results

Her2/neu immunohistochemical results

35 cases (46.1%) were negative, and 41 cases (53.9%) were positive (Figure 1). According to Lauren categorization, the only statistically significant relationship between Her2/neu expression and histological type was discovered to be more expressed in intestine type (P=0.03) (Table 2). Although not statistically significant (p=.827), we found a higher percentage of HER-2/neu positivity among poorly differentiated grade tumours (61.5% were HER-2/neu positive versus 38.5% were HER-2/neu negative). Similarly, higher depth of tumour invasion (53.6% of pT3 were HER-2/neu positive versus 46.4% were HER-2/neu negative), increasing number of LN metastases (60% of cases that have >9 LN metastasis were HER-2/neu positive versus 40% were HER-2/neu negative), and late pathological stage (85.7% of stage VI were HER-2/neu positive versus 14.3% were HER-2/neu negative) were all associated with Her2/neu positive expression (Table 2). This correlation, while, is not statistically significant.

Discussion

Over the past ten years, there has been increased interest in the overexpression of the Her2/neu molecule in gastric cancer and its relationship to the disease's prognosis. In this investigation, we looked at Her2 expression in 76 gastric cancer specimens that had a radical gastrectomy. Our study's estimated rate of Her2/neu positivity is 54%, more than twice as many positive tumours as those reported by Giuffrè et al. [11], who found a Her2 overexpression rate of 21.10% in a small cohort of gastric adenocarcinomas. Furthermore, in two recent Egyptian studies, the overall HER2/neu positive rate was 28.8% and 11.1% [12,13]. This could be explained by the following: 1-Due to budgetary constraints, we did not undertake Fluorescence in Situ Hybridization in this investigation; hence, we regarded all cases with scores of 2+ and 3+ as positive. 2. Because we used TMA sections and they used whole tissue sections, there are methodological differences between our data and theirs that make comparisons challenging. 3. While in our investigation we considered entire membranous or basolateral staining of ≥ 10% immunopositive cells as positive, Ishaky et al. [13] determined HER-2 positivity as continuous membranous staining in at least 10% of tumour cells.

Reports on the overexpression of Her2/neu in gastric cancers range from 8.2% to 62.5% [14]. There may be a difference in the populations behind this disparity in the frequency of Her2/neu positivity. Also, the adoption of varied scoring standards for immunostained slides of stomach cancer may reveal to be an important cause in this different range [15]. Additionally,

methodological variations could be the cause of the disparity in these results, particularly when considering TMAs and tumoral protein expression heterogeneity. Furthermore, it is improbable that all intestinal-type tumours arise from the same outside sources, which could account for the variations in HER-2/neu overexpression predominance. documented in a number of investigations [16].

Numerous studies, including the ToGA trial, have demonstrated that the pathological characteristic most consistently linked to HER-2/neu positive is the Laurén's intestinal subtype [17]. Comparably, our research demonstrated a substantial distinction between the overexpression of Her2/neu in diffuse gastric carcinomas, which were more expressed in the intestinal type, and Laurén's intestinal carcinomas. Given the significant correlation between intestinal type and Her2/neu positivity as well as the high prevalence of Laurén's intestinal subtype in our patients (about 62% of cases), this could account for the high percentage of Her2/neu positive tumours in this study cohort (approximately 54%). Hashem et al.'s recent Egyptian study [18] discovered that Her-2 was overexpressed in roughly 10% of cases. Their group revealed a complete domination of the diffuse-type Laurén's Her2/neu is a novel therapeutic target for gastric cancer, however its significance as a prognostic indicator for this tumour remains debatable. In fact, HER-2/neu overexpression has been shown in several trials to be a poor prognostic marker in gastric cancer [19]. Although this association does not approach statistical significance, the study found that the presence of Her2/neu positive status was linked to clinicopathological characteristics of tumour development, including greater grade, late stage, deeper invasion, and an increasing frequency of LN metastases. HER2 overexpression is substantially more common in advanced gastric cancer tumours with tubular histotype, high histological grade, advanced stage, and high Ki-67 labelling index, indicating that it may be a poor prognostic factor [19].

Similar to Fassan et al. [20], our investigation revealed no correlation between the age or gender of the patients and HER2/neu positive. Additionally, in line with Chua et al. [21], we were unable to find any evidence of a significant relationship between Her2 expression and the location, size, or form of the tumour.

In line with Chua et al. [21], HER2/neu positive in our series did not substantially correlate with lymphovascular tumour emboli and perineural invasion. El-Gendi et al. [12] have revealed a noteworthy correlation between the pathologic T stage and the HER2/neu positive status and lymphovascular emboli.

Conclusion

Approximately 54% of resectable gastric cancinomas had HER2/neu positive. The Lauren intestinal type and positive Her2/neu expression were revealed to be the only statistically significant relationships. HER2/neu positive did not correlate with any other clinical pathologic criterion.

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