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Original Research Article

Expression of Her2Neu in gastric adenocarcinoma: An institutional study

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ABSTRACT

Introduction: Trastuzumab has been recently proposed as a treatment for patients with HER2-positive advanced/metastatic gastric cancer. Since most patients have inoperable disease at diagnosis, accurate assessment of HER2 status on biopsy specimens is essential to select the patients who may benefit from therapy.

Objective: Evaluate the immunohisto chemical expression of HER2 in gastric cancer from biopsies, surgical resection specimens, and evaluate their correlation with currently known clinical and histopathological prognostic factors.

Materials and Methods: Samples from 52 patients of both sexes and all age groups diagnosed with gastric cancer were analyzed. Immunohisto chemistry was performed using the HER2 antibody, and its evaluation was made, taking into account incomplete basolateral staining or only lateral staining.

Results: HER2 over expression was confirmed in 14(27.6 %) cases of which 13(93.8 %) cases were of intestinal type whereas only 1(6.2 %) case of diffuse type adenocarcinoma. There was no difference in HER2 over expression in relation to the age, gender, tumor site, tumor differentiation and stage.

Conclusion: As anti-HER2 therapies are becoming the standard of care in gastric cancer, currently available data indicate that IHC should be used as the screening test, and the pathologist has an important role to ensure an accurate testing of HER2 status in these tumors. HER2 over expression is more prevalent in the intestinal sub type. The relatively high percentage of HER2 positive tumors may provide a useful target for immunotherapy of these cancers.

1. Introduction

Gastric cancer is one of the oldest documented malignancies which has been described as early as 3000 BC in hieroglyphic inscriptions and papyri manuscripts from ancient Egypt. Gastric cancer has a global but variable geographic distribution, being most common in Asian countries such as Japan and China.[1] According to GLOBOCAN 2018 data, Stomach cancer is still the third leading cause of cancer death in both sexes worldwide. Gastric cancer is a biologically heterogeneous disease with many genetic and epigenetic variations. Surgical resection is the mainstay of treatment which is almost curative in very early stage of the disease. The survival rate of patients with advanced resectable gastric or gastro-oesophageal junction (GEJ) cancers, however, remains poor despite of the new treatment strategies.

Understanding of the mechanisms of oncogenesis helped in developing targeted chemotherapy where cancer cells are specifically targeted with minimal damage to normal cells. The oncogene Her2/neu, is located on the chromosome 17q21. It is a member of EGFR family, act through

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transmembrane protein kinase pathway. In carcinoma, HER2 acts as an oncogene, mainly because high level amplification of gene introduces protein over expression in the cellular membrane and subsequent acquisition of malignant cell. Its gain of function is associated with increased cell motility, invasiveness, angiogenesis, resistance to apoptosis, and metastatic potential.

In recent years targeted therapy is being used in the treatment of many cancers. Her2neu is mainly targeted for breast cancers, recently it has been introduced in gastric cancer treatment. As per ToGA trial 2010 Trastuzumab in combination with 5-FU & Cisplatin is recommended by EU & US-FDA in cases of HER2-positive metastatic adenocarcinoma of the stomach or gastro-esophageal junction.[2]

Her 2/ neu over expression and amplification can investigated by different modalities, from which IHC is routinely used in many institution and is also cost effective.

2. Materials and Methods

A prospective study of 2 years was conducted in the Department of Pathology, M.K.C.G. Medical College, Brahmapur. From the total 121 cases [107 biopsies & 14 gastrectomies] received during the study period 41 were benign cases, 2 cases of GIST and 3 cases of dysplasia were excluded and hence 65 cases of gastric adenocarcinoma constituted the study group. Detailed clinical details along with all investigation findings were collected in each case. All gastrectomy / gastric biopsy specimens were fixed in 10% neutral buffered formalin. Routine processing was done and H&E sections were prepared. H&E slides in each case was evaluated independently. IHC for Her2neu using DAKO antibody was done in the selected cases. The Immunohistochemistry slides were scored by two pathologists independently following the scoring system of Hoffman et al. Statistical analysis was done using SPSS.

3. Results

Her2neu positivity i.e.+3 positivity was observed in 40% cases. (Table 1). When Her2neu positive status was compared to the age of the patients, a slight prevalence was observed in the younger age group i.e. 70% in 51-60 years age group followed by 41-50 years. (Table 2). But this observation was not statistically significant. Similarly a slight male preponderance i.e. 41% Her2neu positivity was noted which was also statistically insignificant (41%). (Table 3). Body of the stomach was the most common location associated with Her2neu positivity [42%], but again it was statistically not significant. However a statistical significant observation was noted when Her2neu status was compared with respect to the histologic type and the histologic differentiation. Her2neu positivity status is seen highest in intestinal type i.e. 45% followed by diffuse type (9.1%) (Table 4). Her2 status is seen highest i.e. 53% in moderately differentiated carcinoma followed by well differentiated carcinomas. (Table 5).

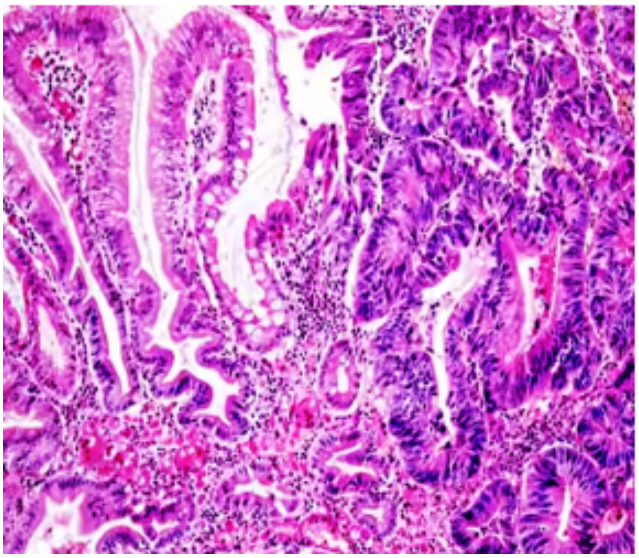

Fig. 1: Well differentiated adenocarcinoma (HP)

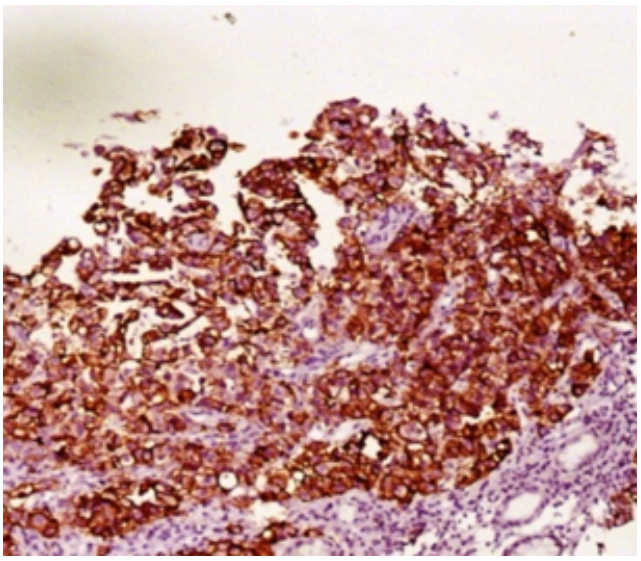

Fig. 2: Well differentiated adenoca, Her2 score 3+

Table 1:

Her2	Number of cases	%
Positive	30	40
Negative	45	60
Total	75	100

The observations noted in the present study are in accordance to the observations made by several other studies as depicted in a tabular form below.Table 7

Table 2:

Age in years	Her2+ve	Her2-ve	Chi square $(x)^2$ p value
31-40	2(40%)	3(60%)	
41-50	3(60%)	2(40%)	
51-60	7(70%)	3(30%)	6.293 >0.05
61-70	13(36%)	23(64%)	
71-80	5(26%)	14(74%)	
Total	30(40%)	45(60%)	

Table 3:

Table 3 Gender	Her2+ve	Her2-ve	Chi-square $(x)^2$ p value
Male	24(41%)	35(59%)	
Female	6(38%)	10(62%)	0.053 >0.05
Total	30(40%)	45(60%)	

Table 4:

Tabele 4Histological type	Her2+ve	Her2-ve	Chi-square(x^2) p value
Intestinal type	29(45%)	35(55%)	
Diffuse type	1(9.1%)	10(91%)	
Total	30(40	45(91%)	

Table 5:

Histological grade	Her2 +ve	Her2-ve	Chi-square $(x)^2$ p value
Well differentiated	2(18%)	9(82%)	
Moderately differentiated	27(53%)	24(47%)	11.394 0.03
Severe differentiated	1(8%)	12(92%)	
Total	30(40%)	45(60%)	

Table 6: Scoringsystem by Hoffman et al

Score	Surgical specimen staining pattern	Biopsy specimen staining pattern	Her2neu overexpression assessment
0	No reactivity or membranous reactivity in <10% of tumor cells	No reactivity or No membranous reactivity in any tumor cells	Negative
1+	Faint/barely perceptible membranous reactivity in ≥10% of tumor cells: cells are reactive only in part of their membrane	Tumor cell cluster with a faint/barely perceptible membranous reactivity irrespective of percentage of tumor cells stained	Negative
2+	Weak to moderate complete, basolateral, or lateral membranous reactivity in ≥10% of tumor cells	Tumor cell cluster with a weak to moderate complete. basolateral, or lateral membranous reactivity irrespective of percentage of tumor cells stained	Equivocal
3+	Strong complete, basolateral, or lateral membranous reactivity in ≥10% of tumor cells	Tumor cell cluster with a strong complete, basolateral, or lateral membranous reactivity irrespective of percentage of tumor cells stained	Positive

4. Discussion

Gastric cancer, one of the oldest known human malignancy, is considered surgically curative in 90% of cases when diagnosed early in the stage i.e. Stage 0 [TisN0M0] / Stage 1A [T1N0M0].[3] But early diagnosis is a rare occurrence due to the delayed symptoms and most are usually diagnosed in later stages with locally advanced disease. In such cases the local recurrence rate was found to be high even with a tumor free surgical margin. This may be due to the presence of occult micro-metastases that cannot be dealt by surgery alone. This led to the development of universal consensus on multimodal treatment approach comprising of surgery with neoadjuvant / adjuvant chemotherapy or chemoradiation. The last decade has seen significant developments in our under-standing of molecular biology of gastric cancer

Table 7: Depicting the comparison of the present study findings with other authors.

Authors	%age of Her2neu positivity	Age	Sex	Location	Histological Type	Histological grade
Carlos Go´mez-Martin et al	10.1%	No	No	_	Intestinal	_
Sangram Keshari Panda et al	18.7%	No	No	No	Intestinal	Moderate
Varalaxmi et al.	35.86%	_	_	_	Intestinal	Well
NadwaSubhi Al-Azow et al.	30%	_	_	_	Intestinal	_
Ling Shan et al	9.8%	No	No	GEJ	Intestinal	Well & moderate
Juliana Elizabeth Jung; Sérgio Ossamu Ioshii	8.4%	No	No	No	No	_
Kourosh Movagharnejad et al	10%	No	No	No	No	No
H. Amrani Hassani Joutei et al	26.53%	No	No	No	Intestinal	Well & moderate
Paola Figueroa-Barojas et al	35%	Yes, > 60 yrs	Male	_	Intestinal	_
Sukru Yildirim et al	11.5%	No	No	_	Intestinal	Moderate
H.R. Raziee et al	26%	No	No	_	Intestinal	Well
Present study	**40%**	**No**	**No**	**No**	**Intestinal**	**Moderate**

where specific cellular targets may be selectively modulated to inhibit tumor progression. Also molecular targeted therapies have significantly emerged as an effective treatment and improved clinical outcomes of many common malignancies, including breast, colorectal, and lung cancers. Targeted molecular-based therapy capitalizing on genes and gene products harbored in gastric and gastroesophageal adenocarcinomas may provide an additional therapeutic method of intervention in advanced tumors.

The study was performed in 65 proven cases of adenocarcinoma of stomach of which 54 were biopsy and 11 gastrectomy specimens. The incidence was highest in the old age i.e. 61 – 70 years, 65.6 years was the mean age observed in the study. A distinct male preponderance was noted with a M:F ratio of 3.76:1. Location wise pylorus was the most prevalent site [53%] in the study followed by GEJ and cardiac end. The prevalent endoscopic appearance of the lesions was ulcerative type accounting for 53% of cases according to the Borman's classification. As per According to Lauren classification the commonest histological type was Intestinal type [85%] and rest 15% are diffuse type. Moderately differentiated tumours were the predominant (68%) type followed by poorly differentiated (17%) and well differentiated type (15%).

Her2neu is one of the four members of the human epidermal growth factor receptor (EGFR) family of transmembrane receptor tyrosine. The binding of different ligands, including epidermal growth factor (EGF) and TGF-alpha to the extracellular domain, initiates a signal transduction cascade that elicits cell cycle progression, cell proliferation, anti-apoptotic signals and survival, adhesion, migration, and differentiation.[4] HER2neu (HER2) is a proto-oncogene located on chromosome 17q21. It encodes a 185 kD transmembrane tyrosine kinase receptor protein.[5] HER2 oncoprotein was cloned and characterized by Akiyama et al in 1986. No molecule in the field of oncology has been more extensively or more successfully targeted for therapeutic intent than the product of the c-erbB2 gene known as HER2/neu. The HER2/neu molecule is expressed in a wide range of normal tissues, over-expressed in a variety of tumor types, with or without gene amplification, and is an established target for anti-tumor therapeutics. HER2 amplification and/or overexpression have also been observed in colon,[6] bladder.[7] ovarian,[8] Fallopian tube,[9] endometrial,[10] lung,[11] uterine cervix,[12] head and neck,[13] prostate,[14] pancreatic,[15] salivary gland,[16] esophageal[17] and gastric[18] carcinomas.

In the present study among all cases the Her2neu positivity (+3 positivity) was observed to be 40%. (Table 1) Though increased Her2neu expression was noticed in 51 – 60 years age group (71% positivity) compared to other age groups, male sex (41% positivity) & tumor located in the body of the stomach (42% positivity), these observations were not statistically significant. (Table 2 – 4) However the observation of increased Her2neu expression in relation to the histologic subtype and the degree of differentiation of the tumor were statistically significant.

With the publication of the results of the Trastuzumab for Gastric Cancer trial (TOGA), it has been approved by the US FDA and the European Medicines Agency (EMA) as a 1^{st} line treatment for advanced HER2-positive gastric and gastro-esophageal cancers and hence routine HER2neu testing will be included in the diagnostic work-up of patients with advanced gastric cancer. The most commonly used techniques currently applied in routine testing are FISH and IHC. FISH is the gold standard, but the advantage of IHC is that the method is inexpensive in terms of reagents and equipment. The ToGA trial further demonstrated the high concordance rate of 87.2% between HER2/neu amplification conducted by FISH analysis and

overexpression evaluated by IHC study.[19] So it was advised to perform IHC initially on every gastric cancer specimens and FISH to be performed in cases with 2+ IHC scoring. Interpretation and scoring guidelines of Her2neu is different from that of the breast cancer as gastric tumors exhibit more intratumoral heterogeneity of HER2neu overexpression.[20]

All the studies except that of Juliana Elizabeth Jung, Sérgio Ossamu Ioshii & Kourosh Movagharnejad et al found statistically significant relationship of Her2neu overexpression with intestinal type of adenocarcinoma of stomach. However, the reasons for the selective overexpression in intestinal histological type remain complex and unclear. The association of this oncogene with a specific histologic tumor type may indicate that together there may be preferential expression of certain characteristics but all cases of the histologic subtype do not overexpress Her2neu hence this cannot be the only factor involved.[21]

5. Conclusion

1. The present study in accordance to the TOGA trial findings advocates routine Her2neu testing in the diagnostic workup of patient with advanced gastric cancer.
2. Her2neu IHC is subject to assay & interob server variability, so standardization and internal and external proficiency testing is an absolute prerequisite, especially because IHC Scoring system of gastric cancer is different from breast.
3. FISH Her2neu is required in cases where IHC is equivocal.

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7. Conflicts of Interest

No conflicts of interest.

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