IMMUNOHISTOCHEMICAL EXPRESSION OF HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR-2 IN GASTRIC ADENOCARCINOMA IN PAKISTAN

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ABSTRACT

Objective: To determine the frequency of immunohistochemical expression of Human Epidermal Growth Factor Receptor 2 (HER2) in gastric and gastro esophageal junctional adenocarcinoma.
Study Design: Cross-sectional study.
Place and Duration of Study: Department of Histopathology, Pakistan Naval Ship (PNS) Shifa Hospital Karachi, from Oct 2014 to Oct 2015.
Material and Methods: All specimens of gastric and gastroesophageal adenocarcinoma, irrespective of age of patient, histological type and grade of the tumor were included. Poorly fixed specimens and specimens with scanty tumor tissue were not included.
Results: Majority of the patients belonged to 51 to 65 years of age group with mean age of 58.58 (SD ± 5.56) years. Gender distribution showed that 46 (69.6%) were males and 20 (29.33%) were females. Overall frequency of HER2 expression was 38% (n=25) in cases of gastric adenocarcinoma.
Conclusion: Expression of HER-2 receptor in gastric adenocarcinoma in this study was 38% and it was associated with histological grade and type of adenocarcinoma. HER-2 more frequently expressed in well differentiated than undifferentiated carcinomas with non-significant *p*-value i.e. (0.139) and in intestinal type phenotype with significant *p*-value less than (0.05).

Keywords: Gastric adenocarcinoma, Human epidermal growth factor receptor, Trastuzumab.

INTRODUCTION

Gastric and gastro-oesophageal junction cancers account for the second most common causes of cancer related mortality globally[1]. Gastric adenocarcinoma is one of the most frequent tumors by which one million people per year are effected and is the second leading cause of cancer related mortality all over the world[2]. The incidence and cancer related mortality of gastric cancer have been slowly reducing for the past several decades, however it still remain high in Asian countries[2,3]. In Pakistan the incidence of gastrointestinal tract cancer is 6.9% in males and 4.9% in females[3].

Human Epidermal Growth Factor Receptor-2 (HER-2) protein is a 185-KD transmembrane tyrosine kinase receptor located on the long arm of chromosome 17 (17q21) and is a family member of human epidermal growth factor receptor (EGFR). HER2 positive cells directly contribute to pathogenesis and aggressiveness of the diseases. Expression of HER2 is associated with poor prognosis. Herceptin (Trastuzumab) a monoclonal antibody that acts against human epidermal growth factor (HER2) is an effective and well tolerated treatment for HER-2 positive gastric adenocarcinom. HER-2 positive tumors are associated with worse survival as compared to tumors that do not overexpress HER-2[1-3]. Therapy with trastuzumab (HER2- directed monoclonal antibody) alters the natural history of HER2-positive adenocarcinoma from a histologically aggressive disease to one with improved prognostic outcome[4].

Trastuzumab has been approved by the food and drug administration (FDA) and the European Union for patients with HER2-positive gastric and gastroesophageal (GE) junction adenocarcinoma[5].

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In one of the studies, trastuzumab in combination with other chemotherapeutic agents as compared to chemotherapy alone showed a significant improvement in overall survival (OS; 13.8 versus 11.1 months), progression-free survival (PFS; 6.7 versus 5.5 months), and response rate (Complete + Partial Response; 47 versus 35%). Notably, patients with strongly HER2-positive tumors (immunohistochemistry, IHC 2 +/FISH+ or IHC 3+) derived the greatest overall survival benefit with the addition of trastuzumab to chemotherapy (16.0 versus 11.8 months)[5].

Score	Staining Patteren	HER2 Over Expression
0	No reactivity or membranous reactivity in <10% of tumor cells.	Negative
1+	Faint or barely perceptible membranous reactivity in >10% of tumor cells, cells are reactive only in part of their membrane.	Negative
2+	Weak to moderate complete lateral /basolateral reactivity in >10% of tumor cells.	Equivocal
3+	Strong complete lateral/basolateral membrane reactivity in >10% of tumor cells.	Positive

Table: Comparison with international studies.

Study	No of cases (n)	% age of HER2 positive
A. Sekaran et al (India)	52	23 (44.2%)
Sannat et al (Iran)	70	36 (51)
Present study (Pakistan)	66	25(38%)

Treatment of choice for gastric adenocarcinoma is surgical resection, which is more efficient only in early stages of gastric cancer.

MATERIAL AND METHODS

It was a cross-sectional study done at department of Histopathology, Pakistan Naval Ship (PNS) Shifa Hospital Karachi, Pakistan over a period of twelve months from October 2014 to October 2015. Total 66 cases were included in this study. Sample size was calculated by using WHO

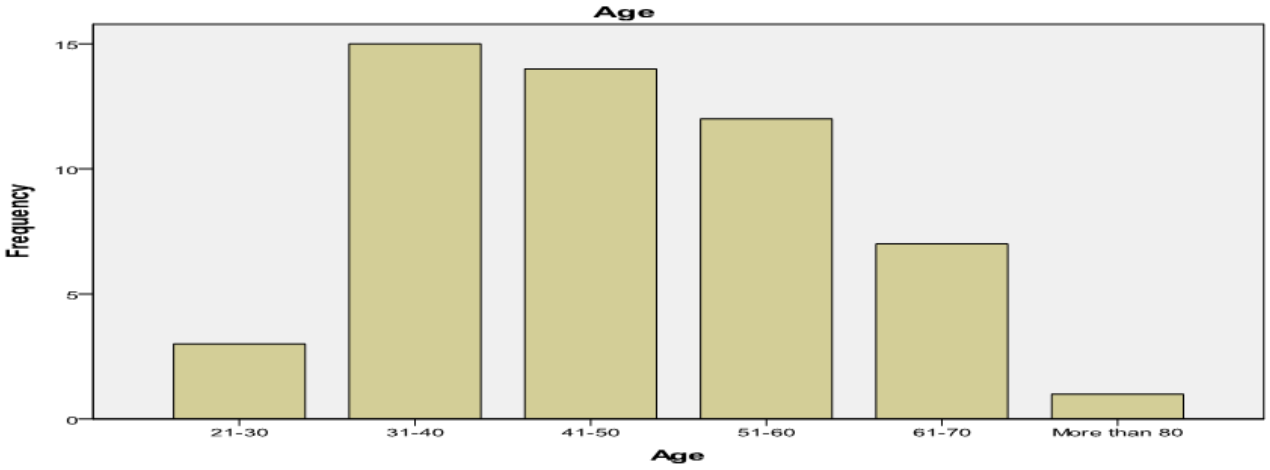

Figure-1: HER2 expression with age distribution in decades (n=66).

Recently most commonly used method for assessment of HER2 status is immunohisto-chemistry. HER2 scoring system for gastric adenocarcinoma is based on degree of intensity of reactivity complete or incomplete and percentage of reactive cells[6].

sample size calculator according to the following prameters, confidence level 95%, anticipated population proportion 44.2% and absolute precision 12%. Sampling technique was non-probability consecutive sampling. All specimens of gastric and gastroesophageal adenocarcinoma, irrespective of age of patient, histological type and grade of the tumor were included. Poorly fixed specimens and specimens with scanty tumor tissue were not included.

Formalin fixed paraffin embedded tissue sections of gastric and gastroesophageal junctional adenocarcinoma were selected as per inclusion criteria. Immunohistochemistry assay for HER2 was performed. Immunohistochemistry results were interpreted. Strong complete lateral/basolateral membrane reactivity in more than 10% of tumor cells (3+) were taken as positive.

Data Analysis

By using Statistical Package for Social Sciences (SPSS Version 17) statistical analysis was done. Descriptive statistics were calculated for quantitative and qualitative variables. Mean and standard deviation (SD) were calculated for quantitative data like patient's age. Frequencies and percentages were calculated for qualitative variables like HER-2 overexpression and patient's gender.

RESULTS

During the study a total of 66 cases of gastric and gastroesophageal adenocarcinoma were included. The patients' ages ranged from 30 to 85 years with mean age ± SD was 58.58 ± 5.56 as (fig-1) Out of 66 patients 46 (69.6%) were males and 20 (30.30%) were females (fig-2). Out of 66 patients, intestinal type morphologyy was found in 40 (61%) and diffuse type was found in 26 (39%) patients as shown in (fig-3). Well differentiated histopathological grade was found in 38 (58%) and poorly differentiated was found in 28 (42%) patients. Out of total, 25 (38%) cases of gastric adenocarcinoma showed positive immunohistochemical expression of HER2, while 41 (62%) cases were negative (fig-4). According to histologicl grade 13 (52%) of 25 cases of well differentiated and 12 (48%) cases of undifferentiated gastric adenocarcinoma were HER-2 positive with non significant *p*-value i.e. (0.139). Similarly HER-2 expression was more common in intestinal type phenotype 17 (68%) than diffuse type 8 (32%) with significant *p*-value i.e. (0.03).

DISCUSSION

This study was designed to assess the frequency of immunohistochemical expression of

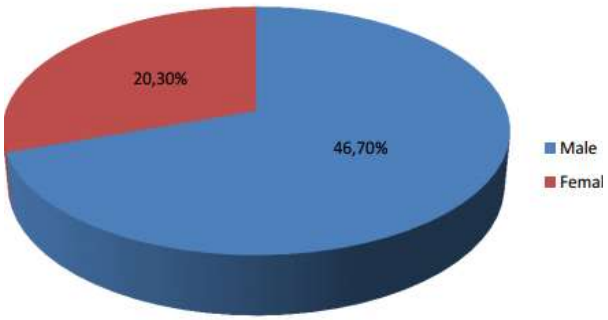

Figure-2: Gender distribution(n=66).

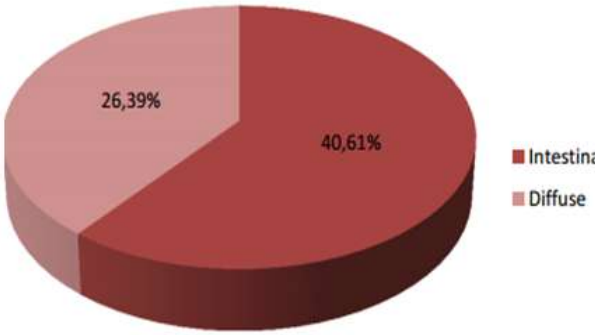

Figure-3: Distribution of histopathological type (n=66).

HER-2 in gastric and gastrooesophageal junction adenocarcimnoma. HER2 evaluation is a new emerging prognostic factor for the gastric and gastrooesophageal junction adenocarcimnoma. Its expression can be assessed by immunohistochemistry, fresh in situ hybridization techniques and polymerase chain reaction. Among these techniques, immunohistochemistry is reasonably good, reliable & cost effective. On the basis of HER2 positivity, an additional treatment modality can

be introduced in the form of targeted therapy against HER2 receptor. HER2 positivity is scored on immunohistochemistry according to the percentage of the tumour cells, showing immunoreactivity for HER2 antibody. More than 10% complete membranous staining of tumour cells is taken as positive (fig-5). The literature shows great variability in the results regarding expression of HER 2 in gastric adenocarcimnoma.Various studies show great variation in immunohistochemical expression of HER2 in gastric and gastro esophageal junction adenocarcimnoma, ranging from 5% to 91%[6].

Overexpression and amplification of HER-2, was described decades ago[7,8], It occurs more in well differentiated adenocarinoma than undifferentiated and occur in 5%-30% of intestinal and <10% of diffuse type of gastric adenocarcinoma[5,9]. In gastric adenocarcinoma with intestinal type phenotype,the HER2 positivity ranges from 8-34% whereas,in distal diffuse gastric carcinoma it is 1-7%[10].

HER2 is a transmembrane tyrosine kinase receptor protein with 185-KD. Overexpression of HER2 is associated with poor prognosis. Hoffman scoring criteria is used for HER2 sccoring as shown in table[11].

HER2 overexpression in primary gastric adenocarcinoma varies in different populations. In addition to chemotherapy, anti HER2 therapy is recommended in advanced, recurrent or metastatic disease. Therefore early assessment of status of HER2 receptor is necessary at the time of diagnosis of gastric adenocarcinoma[12]. Survival benefits have been demonstrated in randomized trial[5].

The current study shows HER2 positivity rate of 38% (25 out of 66). Sannat et al (2013) in north west of Iran found overexpression of HER2 receptor to be 51% in gastric adenocarcinoma[13].

Overexpression of HER2 was observed more in well differentiated gastric adenocarcinoma 13 out 25 cases (52%) than in undifferentiated group i.e. 12 out of 25 (48%) cases. Similarly overexpression was more frequently observed in intestinal type phenotype than diffuse type.

CONCLUSION

HER2 overexpression (positivity) in gastric adenocarcinoma in this study was 38% and it was significantly associated with phenotype of the tumor more with intestinal type tumors than diffuse type. Moreover, molecular targeted therapy in the form of Transtuzumab (Anti HER-2) can be instituted as an additional treatment modality tool in the patients with HER-2 positive gastric adenocarcimnoma.

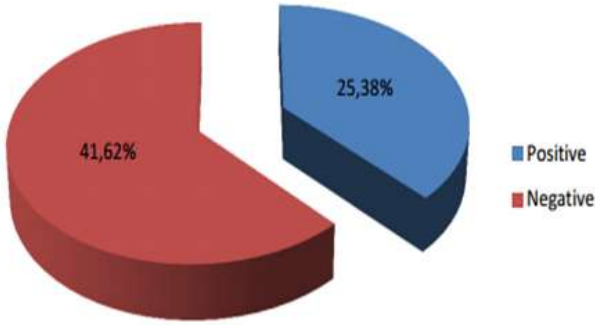

Figure-4: Frequency of immunohisto chemical expression of HER2 (n=66).

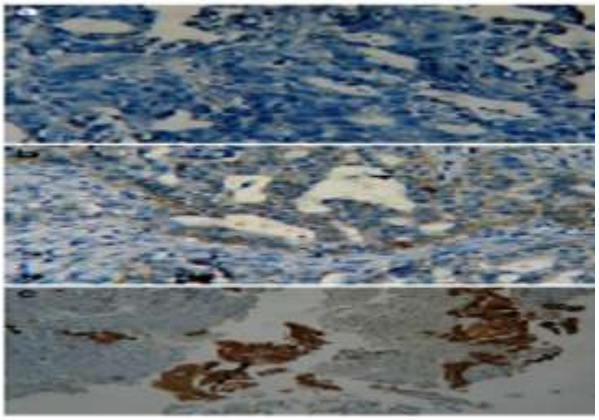

Figure-5: a-No cell membrane staining noted in tumor cells(score-0), b-Weak membranous staining of tumor cells (score-2+), C-Strong complete membranous staining in >10% tumor cells (score3+).

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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