Her 2/Neu Overexpression in Gastric Cancer

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ABSTRACT:

BACKGROUND :

Overexpression of Human epidermal growth factor receptor 2(Her2/neu) Protein has been observed in many human cancers including gastric cancer . Gastric cancer remains the most common cause of cancer –related death worldwide. Her2/neu overexpression in gastric cancer associated with poor prognosis and shorter survival rate , the assessment of this protein for selection of eligible patients for treatment with trastzumab in addition to conventional chemo therapy.

OBJECTIVE:

To evaluate the Her2/neu over expression in gastric cancer by immunohistochemical Technique and to find the correlation between the protein exopression and clinicopathological Parameters as age ,sex, histological types and grade of the tumor.

MATERIALS AND METHODS :

This is a pro-& retrospective study conducted at the pathology department of Al-Jamhuri Teaching hospital and some private laboratories . A total of 30 cases of gastric cancer were collected and diagnosed in the period spanning from April 2010 to April 2012, .An immunohistochemical technique was used for the assessment of Her2 against age,sex, histological types and grade of tumor

RESULTS :

The mean age of the patients was 54.5 years ranging from 30 to 87 years, Her2/neu overexpression was shown in 30% of the cases , in this study there is no relation between Her2 positivity and age or sex, , it was associated with histological types p-value = 0.04,where as 42.6 % of the intestinal type show immunoreactivity and 11.1% of diffuse type,while two cases of mixed types were shown no reactivity(0.0%). Her2 positivity was associated with moderate differentiated tumor (50%) more than poorly differentiated (20%) but not reaching the statistical significance.

CONCLUSION:

Her2/neu positivity was found in 30% of gastric cancer , there is no relation between the age or sex of the patient & Her2 positivity while intestinal type and moderately differentiated tumor were associated with high percentage of Her2 positivity.

KEY WORDS : gastric cancer, her2/neu over expression.

INTRODUCTION:

Overexpression of the human epidermal growth factor receptor 2 (HER2/neu) protein has been observed in many human cancers , including breast, colon, endometrial , cervical , urothelial, lung adenocarcinoma, ovarian, salivary glands and more recently gastric and gastroesophageal junction adenocarcinoma [(1).]

The HER2 protein (HER 2/neu ,ErbB-2) is encoded by proto-oncogene located on chromosome region 17q21, it is 185-kDa transmembrane tyrosine kinase receptor and a member of epidermal growth factor receptors(EGFRs) ,can influence many aspects of tumor cell biology ,including cell proliferation , apoptosis, adhesion , migration and differentiation [(2)].

Gastric cancer is one of the most common tumors and remains the second most common cause of cancer-related death worldwide [(3)]. Over the past half century the histological classification of gastric carcinoma has been largely based on Lauren's criteria, in which intestinal type and diffuse type adenocarcinoma are the two major histological subtypes, plus mixed type [(4).]

The positivity rate of Her2 in gastric cancer vary from about 7-43% this positivity of Her2 appears to be associated with poor prognosis ,more aggressive disease and shorter survival [(5)]

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Recently, Her2/neu was introduced as a predictive biomarker for the treatment of gastric cancer(GC) with trastuzumab which is an antibody targeting Her2/neu and is applied in combination with conventional chemotherapy for the treatment of Her2/ neu-positive advanced GC [6]

Since the costs for trastuzumab therapy are high and side effects are significant, accurate selection of eligible patients for this therapy is crucial. HER2 protein expression assessment is conducted by immunohistochemical technique(IHC) which considered as routine test for patient with gastric carcinoma either primary or metastatic tumor in pathology laboratories [7]. While Her2 gene amplification detected by advanced technique fluorescence in situ hybridization(FISH) in cases where the Her2 positivity by IHC is equivocal [5,7]

The aim of this study is to evaluate the Her2/neu expression in gastric adenocarcinoma by immunohistochemical technique and to find the correlation between this protein expression and clinicopathological parameters as age, sex, histological types and grade of the tumor.

MATERIALS AND METHODS :

A pro- and retrospective study was conducted after permission approval granted by Nineveh ministry office. Thirty samples of primary gastric adenocarcinoma (endoscopic biopsy or surgical specimen) were collected at two years period (from April 2010 to April 2012) diagnosed at Al-Jamhuri Teaching Hospital and private Laboratories in Mosul city.

The information about the patient including age & sex was taken from the patients' reports . All histologic parameters including growth pattern (according to Lauren classification – intestinal ,diffuse ,mixed) [8] and tumor grade (well, moderately ,or poorly differentiated) were identified and recorded after review of all available hematoxylin –eosin slides.

Immunohistochemical staining was performed according to the manufacturer's guidelines on 4-µm thick formalin-fixed unstained, paraffin-embedded tissue sections ,using the commercially available rabbit anti-human her2/neu protein and reagent kit (DAKO Hercep Test™) .

The immunohistochemical assessment of Her2/neu according to scoring guidelines proposed by Hoffman et al [9] .

This scoring system differ from that used for Her2/neu assessment in breast cancer, the differences including the pattern of Her2/neu immunohistochemical staining, the intensity & the percentage of tumor cells expressing Her2/neu either in biopsy or resection specimens.

Scoring of Her2/neu:

score 0: no reactivity or membranous reactivity in <10% of cells at x40 magnification

score +1: faint or partial membranous immunoreactivity in >10% of tumor cells at x40 magnification

score +2 : weak/ moderate complete or basolateral /lateral membranous reactivity in >10% of tumor cells x10-x20

score +3: moderate /complete or basolateral /lateral membranous immunoreactivity at low magnification. For biopsy specimens single cluster or ≥ 5 cohesive tumor cells enough for scoring Her2/neu immunostaining .

score 0/+1 is regarded as Her2/neu Negative while Score +2/+3 is regarded as Her2/neu Positive.

Statistical analysis was done by using Fisher-Exact test where the P-value 0.05 or less is considered statistically significant.

RESULTS:

The study enrolled thirty cases of primary gastric adenocarcinoma,(twenty six endoscopic biopsies and four surgical resection specimens).

The range of patients' age between 30-87 years old ,the mean age was 54.5 years . Half of the patients were male while the other fifteen were female. The intestinal type of gastric adenocarcinoma was 19(63.3%) ,while diffuse and mixed types represented 9(30%) and 2 cases (6.7%) respectively.

Grading for the nineteen cases of intestinal type was shown10 cases of moderately differentiated, the rest 9 cases were poorly differentiated, however the well differentiated type wasn't found in this work.

Her2 positivity in this study was 30% (nine cases) including both score +2 & score +3 (4&5 cases respectively) , 21 (70%) of cases were Her2 negative (score 0/+1).

Table 1 illustrated the relation of Her2 immunoreactivity with the age groups .

Out of 15 males 5(33.3%) and 4 (26.7%) females out of 15 were showed Her2 positivity, however the p-value did not reach the statistical significant(Table 2).

According to the histological types there were eight cases (42.2%) was positive for Her2 out of 19 cases of intestinal type , while only 1(11.2%) out of 9 diffuse type cases were Her2 positive ,while no reactivity for Her2 in mixed type (2cases) .There was statistical significant

between the Her2 positivity & the histological type p-value was 0.04 (Table 3)
Five cases (50%) out of the ten cases with Moderate differentiated grade were shown Her2 positivity , while only 4cases(20%) were shown immunoreactivity for Her2 out of 20 cases with poorly differentiated ,this positivity had statically not significant with the grading in this work (Table 4).

Table 1 : Her2 status correlated to the age group.

Age	Her2 (-ve) No. (%)	Her2 (+ve) No. (%)	P-value
31-40	2 (40.0)	3 (60.0)	0.1
41-50	5 (62.5)	3 (37.5)	0.4
51-60	5 (71.4)	2 (28.6)	0.6
61-70	6 (85.7)	1 (14.3)	0.2
71-80	3 (100.0)	-	-

Table 2: Her2 status versus the sex.

Gender	Her2 negative 0/+1 No.	%	Her2 positive +2/+3 No.	%	Total
Male	10	66.7	5	33.3	15
Female	11	73.3	4	26.7	15

Table 3: Her2 in relation to the histological types.

Histological type	Her2 (-ve) No. (%)	Her2 (+ve) No. (%)
Intestinal	11 (57.4)	8 (42.6)
Diffuse	8 (88.9)	1 (11.1)
Mixed	2 (100.0)	-

Table 4: Her2 in relation to the grade.

Grade	Her2 (-ve) No. (%)	Her2 (+ve) No. (%)
Moderate differentiate	5 (50)	5 (50)
Poorly differentiate	16(80)	4 (20)

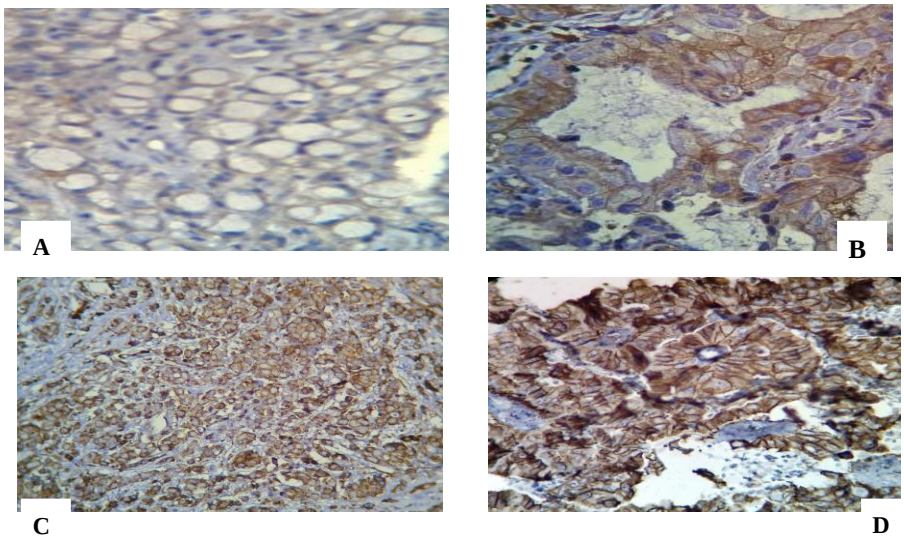

Figure 1: A &B Her2 negativity (score 0 , score +1 respectively).
C&D Her2 positivity (score +2 & score +3 respectively).

DISCUSSION :

The analysis of Her2/neu status in gastric cancer has evolved to be very important task for subsequent response to anti-molecular therapy(Trustzumab) in addition to conventional therapy[10].

The Her2/neu protein overexpression in gastric adenocarcinoma of this work was 30%,fit with the range shown by other studies[11,12,13,14,15], the discrepancy of Her2 positivity could be related to the different populatin studied but the application of different scoring criteria for immunostained slides of gastric adenocarcinoma may emerge to be an impotartant cause in this different range [2].

detection of Her2/neu is considered mandotary in some centers in the world being the immunohistochemical test as primary test followed by FISH if needed especially for cases show score +2(equivocal) because may become Her2 negative [5].

There was no relation between the age or sex of the patient and Her2 positivity as shown by many studies[11,12,16] and the current one although Guan Zhen et al found a significant correlation between Her2 positivity and age of the patients [17].

As in breast cancer ,Her2 positivity related to histological type (more in invasive ductal carcinoma than lobular carcinoma) gastric carcinoma show Her2 overexpression more evident in intestinal histological subtype (42.3%) versus diffuse subtype (11.3%) & nul for mixed type with statistical significance p-value (0.014) this is in agreement of other studies [1,3,11,12,18].

Her2 overexpression was identified in 50% of moderate differentiated gastric cancer (5 out 10) while 25% of poorly differentiated (4 cases out of 20) , although this results didn't reach statistical significant this may be due to small size and the well differentiated grade didn't emerge in this study [15,16,17,18].

CONCLUSION:

In this study Her2/neu overexpression was 30%of gastric cancer in Mosul City, with correlation to intestinal type of adenocarcinoma more than diffuse or mixed subtypes, and there is association with moderate differentiated grade than poorly differentiated tumor. There was no correlation between age or sex with Her2/neu overexpression.

REFERENCES:

1. Hechtman J. F. and polydorides A.D. HER2/neu gene amplification in gastric and gastroesophageal junction adenocarcinoma . Arch Pathol Lab Med .2012; 136:691-97.
2. Wang S., Zheng G, Chen L., *etal*. Effect of HER-2/ neu Over-expression on Prognosis in Gastric Cancer : A Met-analysis . Asian Pac J Cancer Prev.2011;12:1417-23.
3. Chu T. C.and Merret N. D. Clinicopathologic factors associated with HER2-positive gastric cancer and its impact on survival outcomes-A systematic review . Int.J.Cancer 2012;130:2845-56.
4. Hu B, El Hajj N., Sittler S., *etal*.. Gastric cancer: Classification, histology and application of molecular pathology. J Gastrointest Oncol 2012;3:51-261.
5. Ruschoff J., Dietel M. , Baretton G., *et al*.HER2 diagnostic in gastric cancer – guideline validation and development of standardized immunohistochemicl testing. Virchows Arch.2010;457:299-307
6. V. S. Warneke , H.-M. Behrens , C. Böger, *etal*. Her2/neu testing in gastric cancer: evaluating the risk of sampling errors. Ann Oncol 2012; 00: 1-9.
7. Moelans C. B., van Diest J.P, A.Milne N.A,*etal* . HER-2/neu Testing and Therapy in Gastroesophageal Adenocarcinoma. Pathology Research International , 2011; 674182:10 .
8. Dicken J B., Bigam L. D., , Cass C., *etal*.Gastric Adenocarcinom Review and Considerations for Future Directions. Ann Surg .2005;241:27–39.
9. Hofmann M, Stoss O, Shi D, *etal*. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. Histopathology . 2008;52 :797–805.
10. Jeung J., Patel R. , Vila L., *etal*.Quantitation of HER2/neu Expression in Primary Gastroesophageal Adenocarcinomas Using Conventional Light Microscopy and Quantitative Image Analysis. Arch Pathol Lab Med .2012;136:610-17.
11. Gravalos C.and Jimeno A.. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. Ann Oncol . 2008;19: 1523–1529
12. Yan S., Hu Y, Fan J., *etal*. Clinicopathologic significance of HER-2/neu protein expression and gene amplification in gastric carcinoma. World J Gastroenterol 2011;17:1501-6.
13. Mrklic I, Bendic A, Kunac N, *etal*. Her-2/neu assessment for gastric carcinoma: validation of scoring system. Hepatogastroenterology. 2012;59:300-3.

14. León-Chong J., Lordick F., Kang Y. K., *etal*. HER2 positivity in advanced gastric cancer is comparable to breast cancer. J Clin Oncol, ASCO Annual Meeting Proceedings Part I. 2007;25.

15. Raziee H.R., Kermani A. T., Ghaffarzadegan K., *eta*l. HER-2/neu Expression in Resectable Gastric Cancer and its Relationship with Histopathologic Subtype, Grade, and StageIranian. IJ B MScien. 2007;10:139-45.

16. Fassan M., Ludwig K., Pizzi M. ,*etal*. Human epithelial growth factor receptor 2 (HER2) status in primary and metastatic esophagogastric junction adenocarcinomas. Hum Pathol .2012;43:1206–12.

17. Zhen Yu G. · Chen Y and Wang J J. Overexpression of Grb2/HER2 signaling in Chinese gastric cancer: their relationship with clinicopathological parameters and prognostic signifigance. J Cancer Res Clin Oncol .2009;135:1331–39.

18. Tafe L. J., ; Janjigian Y.Y., Zaidinski M., *etal*. Human Epidermal Growth Factor Receptor 2 Testing in Gastroesophageal Cancer Correlation Between Immunohistochemistry and Fluorescence InSitu Hybridization. Arch Pathol Lab Med. 2011;135:1460–65.