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ANALYSIS OF F HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 (HER2/NEU) EXPRESSION IN GASTRIC ADENOCARCINOMA

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Abstract:

Introduction: *Gastric carcinoma is a substantial health-care problem worldwide, with over 6.8% of total new cancer diagnoses and 8.8% of total cancer-related deaths annually.*

Aims and objectives: *The main objective of the study is to analyse the human epidermal growth factor receptor 2 (Her2/Neu) expression in gastric adenocarcinoma.*

Material and methods: *This descriptive study was conducted in Ayub Medical College, Abottabad during October 2018 to March 2019. The data was collected from 100 gastric adenocarcinoma patients. Formalin-fixed, paraffin-embedded samples of tumors and corresponding normal stomach tissues from gastric cancer patients were evaluated for HER2 protein and gene amplification using immunohistochemistry (IHC) and fluorescence* in-situ *hybridization (FISH) analysis.*

Results: *The data was collected from 100 patients of adenocarcinoma. The median age was 62 years. Of all the tumors examined, 31 (15.74%) were located in the cardiac region, 42 (21.32%) in the body, and 122 (61.93%) in the pylorus. The majority (98.98%) of the samples were primary tumors with only 2 recurrent tumors identified. According to Lauren classification, 63 (31.98%) tumors were intestinal-type and 134 (68.02%) were diffuse-type or mixed-type carcinomas.*

Conclusion: *It is concluded that HER-2/NEU is significantly overexpressed in low-grade gastric carcinoma, and overexpression is not dependent on various other clinicopathological parameters.*

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INTRODUCTION:

Gastric carcinoma is a substantial health-care problem worldwide, with over 6.8% of total new cancer diagnoses and 8.8% of total cancer-related deaths annually. It is the third leading cause of cancer mortality in the world. Incidence is highest in Japan, Eastern Asia, South America, and Eastern Europe; whereas Canada, Northern Europe, Africa, and the United States of America have the lowest incidences. Gastric cancer is the second most common cause of cancer deaths in Indian population [1].

Among the causative and risk factors for carcinogenesis, *Helicobacter pylori* infection and dietary factors have been proven to play an important role. Less common causes include chronic atrophic gastritis, hypertrophic gastropathy, gastric polyps, low socioeconomic status, and obesity [2]. Dominant hereditary predisposition for gastric cancer is reported in familial adenomatous polyposis, Lynch syndrome, Li–Fraumeni syndrome, and germline mutation of E-cadherin gene. Surgery is the mainstay of treatment but the majority of patients present with advanced, inoperable disease, where treatment is palliative and median survival is just 3 months with supportive care alone [3].

Chemotherapy improves survival in patients with advanced gastric cancer, and combination regimens are superior in this respect to monotherapy. Human epidermal growth factor receptor 2 (HER2) is a 185-kDa transmembrane tyrosine kinase receptor and its gene amplification and protein overexpression play an important role in the proliferation, apoptosis [4], adhesion, angiogenesis and aggressiveness of many solid tumors, including; breast, colon, bladder, ovarian, uterine cervix, esophageal and gastric cancer [5].

Herceptin (trastuzumab) has been approved in the European Union and the United States for use in combination with 5-fluorouracil (5-FU) or capecitabine plus cisplatin for the first-line treatment of patients with HER2-positive metastatic adenocarcinoma of the stomach or gastroesophageal junction according to the results of the 2010 trastuzumab for gastric cancer (ToGA) trial [6].

Aims and objectives:

The main objective of the study is to analyse the human epidermal growth factor receptor 2 (Her2/Neu) expression in gastric adenocarcinoma.

MATERIAL AND METHODS:

This descriptive study was conducted in Ayub Medical College, Abottabad during October 2018 to March 2019. The data was collected from 100 gastric adenocarcinoma patients. Formalin-fixed, paraffin-embedded samples of tumors and corresponding normal stomach tissues from gastric cancer patients were evaluated for HER2 protein and gene amplification using immunohistochemistry (IHC) and fluorescence *in-situ* hybridization (FISH) analysis. None of the patients had undergone prior preoperative radiation, chemotherapy or targeted therapy. The probability of survival for different subgroups was calculated using the Kaplan-Meier method and the survival curves plotted using log rank inspection.

RESULTS:

The data was collected from 100 patients of adenocarcinoma. The median age was 62 years. Of all the tumors examined, 31 (15.74%) were located in the cardiac region, 42 (21.32%) in the body, and 122 (61.93%) in the pylorus. The majority (98.98%) of the samples were primary tumors with only 2 recurrent tumors identified. According to Lauren classification, 63 (31.98%) tumors were intestinal-type and 134 (68.02%) were diffuse-type or mixed-type carcinomas. Poorly differentiated tumors (grades I and II) comprised 25.89%, whilst 74.11% of tumors were moderately differentiated (grades III and IV).

Table 01: Correlation of human epidermal growth factor receptor 2 expression with clinico-pathological characteristics

Clinico-pathological characteristics	***n***	**HER2**		χ^2	***P* value**
		Positive	**Negative**		
Sex				1.2736	0.2591
Male	132	27 (20.45)	105 (79.55)		
Female	65	9 (13.85)	56 (86.15)		
Age (yr)				1.3056	0.2532
< 60	88	13 (14.77)	75 (85.23)		
≥ 60	109	23 (21.10)	86 (78.90)		
Tumor site[1]				0.0409	0.9798
Cardiac	31	6 (19.35)	25 (80.65)		

Body	42	8 (19.05)	34 (80.96)		
Pylorus	122	22 (18.03)	100 (81.97)		
Lauren classification				6.5759	0.0103
Intestinal	63	18 (28.57)	45 (71.43)		
Diffuse/mixed	134	18 (13.43)	116 (86.57)		
Tumor differentiation				16.6003	< 0.0001
Well-differentiated	51	19 (37.25)	32 (62.75)		
Poorly-differentiated	146	17 (11.64)	129 (88.36)		
TNM classification				0.6754	0.879
I	13	2 (15.38)	11 (84.62)		
II	46	7 (15.22)	39 (84.78)		
III	98	20 (20.41)	78 (79.59)		
IV	40	7 (17.50)	33 (82.50)		

DISCUSSION:

The cribriform histological pattern has been attributed to tumors showing an architecture made of straight packed glands with not uniform distributed lumina, without interposed stromal tissue [1, 2]. This peculiar pattern has been identified in invasive carcinomas rising in many different organs, such as prostate, breast, lung, colon, thyroid, skin, and stomach [7]. In this latter localization, a specific cribriform gastric carcinoma (CGC) has not been described in the last WHO classification of gastrointestinal tract tumors [8], even if the identification of cribriform pattern may have interesting practical prognostic implications for oncologists. In fact, it has been reported that CGC was associated with higher stage, lymphovascular and perineural invasion as well as with lower disease-free survival rate in comparison to conventional histotypes of gastric carcinomas (GC) [9]. In detail, the cribriform pattern has been reported in 9% of unselected consecutively collected casuistry of gastric carcinomas (GC) with unfavourable prognostic outcome. By immunohistochemistry, neoplastic elements present in CGC were diffusely stained with CK7 and CK19, but focally for CK20. Moreover, MUC5AC has been also reported as positive, while hormone receptors, CDX2, MUC1, MUC2, and GCDFP-15, were always unexpressed [10].

Human epidermal growth factor receptor 2 (HER2) is a 185 kDa transmembrane tyrosine kinase receptor, member of the EGFR family, which plays a central role in growth factor signal transduction [9]. HER2 overexpression/amplification is involved in the development of various solid tumors, playing a pivotal role in oncogenic tumorogenesis and representing one of the most important therapeutic target in oncology.

CONCLUSION:

It is concluded that HER-2/NEU is significantly overexpressed in low-grade gastric carcinoma, and overexpression is not dependent on various other clinicopathological parameters. Furthermore, to avoid the inconsistency in results and for better reporting of HER-2/NEU overexpression in gastric carcinoma, we suggest to follow a standardized protocol.

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