Int.j.pathol.2023;21(1): 22– 26

Original Article

Human Epidermal Growth Factor Receptor-2 Overexpression in Epithelial Ovarian Cancers

Laila Zaib[1], Sumera Sharif[2], Maria Liaquat[3], Armaghana Qamar Khan[4], Sabeen Afshan [5] and Asma Khattak[6]

[1]Department of Pathology, Loralai Medical College, [2]Department of Pathology Christian Hospital Taxilla, [3,4,6]Department of Pathology, Pakistan Institute of Medical Sciences. [5]Department of Pathology, Sheikh Khalifa Bin Zayed Hospital, Quetta

ABSTRACT

Introduction: HER2 (human epidermal growth factor receptor-2) proto-oncogene encodes a protein belonging to the EGFR tyrosine kinase receptor family. Overexpression of HER2 initiates intracellular signaling pathways involved in cell proliferation, differentiation, migration, and apoptosis.

Objectives: To determine Her2 overexpression in epithelial ovarian cancers.

Materials & Methods; This Descriptive, cross-sectional study was carried out in the Department of Pathology, in Combined Military Hospital, Quetta from July 2017 to January 2018. A total of 95 biopsies and resected specimens of all patients with epithelial ovarian cancer of age 25-65 years were included. Patients with non-epithelial ovarian malignancies, malignancies in other organ systems, recurrent ovarian tumors, and radiotherapy given cases were excluded. After gross examination, the tissues were processed in an automatic tissue processor, and blocks were prepared, followed by cutting, slide preparation, and staining with hematoxylin and eosin (H&E) stain. Immunohistochemistry was used for overexpression (positive/negative) of Her2/neu.

Results: Mean age was 47.01 ± 10.74 years. The mean duration of the disease was 5.81 ± 2.01 months. The frequency of Her2 overexpression in epithelial ovarian cancer was seen in 23 (24.21%) cases.

Conclusion: It was concluded in this study that there was a high frequency of Her2 overexpression in epithelial ovarian cancers.

Keywords: Ovarian tumors, Her2, overexpression.

Introduction

One of the leading causes of death among gynecologic malignancies is ovarian cancer. Ovarian cancer is the fifth most common malignancy among females, and is ranked first among the various gynecological related cancer mortality.[1,2] Ahmad A et al in their study have shown the prevalence of malignant ovarian mass in 46% of women.[3] Patients usually present with recent onset of vague symptoms such as bloating, abdominal pain increased abdominal size, urinary urgency or frequency, and feeling of fullness.[4] In case of advanced disease due to ascites ,omental or bowel metastases patients experience distention, nausea, anorexia, or early satiety.[5]

Currently, few biomarkers are available for ovarian cancer.[6] Although various studies have shown the expression of estrogen receptor (ER) and progesterone receptor (PR) in ovarian malignancies, their clinical significance in relation to survival or prognosis still remains controversial.[7-9]

CORRESPONDENCE AUTHOR
Dr. Armaghana Qamar Khan
Pathology Department
Pakistan Institute of Medical Sciences
E-mail: armaghanakhan@gmail.com

HER2 (human epidermal growth factor receptor-2) is a proto-oncogene that encodes a protein belonging to the EGFR tyrosine kinase receptor family. Intracellular signaling pathways are initiated leading to cell proliferation, differentiation, migration, and apoptosis when HER2 is overexpressed.[10] HER2-positive expression in breast cancer is related to poor prognosis, but patients can benefit from anthracycline-based regimens.[11] Studies have shown that HER2/neu is overexpressed in approximately 20–30% of ovarian epithelial malignancies. Studies have suggested that increased HER2/neu expression in various malignancies is associated with poor patient survival. However, the results reported are based primarily on a small number of cases and remain controversial.[11-13]

Studies have shown that patients with Her2/neu-positive EOC have benefited from anti- Her2/neu monoclonal antibody treatment regimens, both at advanced, and early stages of the disease.[14] Yan et al[15], conducted a small cohort (n=85) on ovarian tumors and assessed them for HER2 amplification by immunohistochemistry (IHC), fluorescence in situ hybridization (FISH) and chromogenic in situ hybridization. His study showed Her2 overexpression

in 35.3% of the cases. Another study showed that 14% OCCCs (ovarian clear cell carcinomas) harbored Her2 gene overexpression.[16]

Her2 expression has been used as a prognostic marker and predictive marker in the treatment of breast carcinomas, but Her2 neu expression has not been studied in ovarian malignancies especially, in our population, therefore this study will not only provide the local status of the problem but will also be a useful addition to the existing literature.

Materials and Methods

This Descriptive, cross-sectional study was carried out in the Department of Pathology, in Combined Military Hospital, Quetta from July 2017 to January 2018. Sample size was 95, it was calculated using a WHO calculator with a 95% confidence level, 7% margin of error, and taking the expected frequency of Her2 overexpression in epithelial ovarian cancer as 14.0%[16] by using the following formula.

$sample\ size = n = (Z\_(1-\alpha/5\ P(1-P)\ \ )\text{^}2)/d\text{^}2$

Non-probability, consecutive sampling technique was used. Biopsies and resected specimen of all patients with epithelial ovarian cancers between ages 25-65 years were included. All non-epithelial ovarian malignancies, patients with malignancy in other organ systems, patients with recurrent ovarian tumors, Metastatic tumors to the ovary (assessed on history and medical record) and Patients taken radiotherapy were excluded.

Approval was taken from the ethical review board. Informed written consent for the study was taken from each patient. After gross examination, the tissues were processed in an automatic tissue processor and blocks were prepared, followed by cutting, slide preparation, and staining with hematoxylin and eosin (H&E) stain. Microscopy of all cases was carried out by a postgraduate resident along with a supervisor and diagnosis on slides was recorded. Immunohistochemistry was used for confirmation of primary diagnosis and results were interpreted by a consultant Pathologist (with at least 5 years of post-fellowship experience) for overexpression (positive/negative) of Her2/neu. All data along with registration number and diagnosis on immunohistochemistry were recorded on a predesigned proforma and were kept confidential.

Statistical analysis was performed using SPSS version 22.0. Mean and standard deviation was calculated for age and duration of disease. Type of ovarian carcinoma (serous/ mucinous/ endometroid/ clear cell), family monthly income, and overexpression of Her2 (Positive/ negative) were presented as frequency and percentage.

Effect modifiers like age, duration of disease, type of ovarian carcinoma (serous/mucinous/ endometroid/ clear cell), and family monthly income category were controlled through stratifications, and post-stratification Chi -square was applied to see their effect on outcome. P value ≤ 0.05 was considered as significant.

Results

Age range was 25 to 65 years with a mean age of 47.01 ± 10.74 years. Mean duration of disease was 5.81 ± 2.01 months. The distribution of patients according to family monthly income and type of tumor is shown in Table1 & Figure1 respectively.

Table-I: Age distribution of patients, duration of disease, family income (n=95).

Age (in years)	No. of Patients	%age
25-45	47	49.47
46-65	48	50.53
Duration (months)	No. of Patients	%age
>6 months	41	43.16
≤6 months	54	56.84
Monthly family income	No of Patients	%age
<10000	25	26.32
10000-20000	18	18.95
>20000	52	54.74

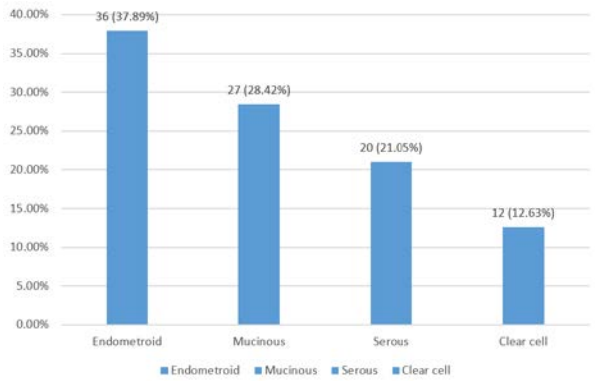

Figure 1 : Distribution of patients according to type of ovarian cancer (n=95)

Frequency of Her2 overexpression in epithelial ovarian cancer was seen in 23 (24.21%) of cases as shown in Figure 2.

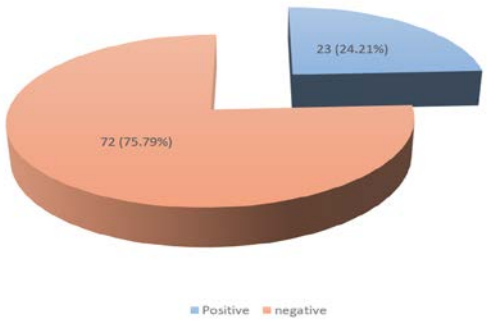

Figure 2: Frequency of Her2 overexpression in in epithelial ovarian cancer (n=95)

Stratification of Her2 overexpression with respect to age groups, duration of the disease, family monthly income and type of tumor in Table 2

Table 2: Stratification of Her2 overexpression with respect to age groups, duration of disease, Monthly family income and Type of tumor.

Age (years)	Her2 overexpression		P value
	Positive	Negative	
20-45	11	36	0.856
46-70	12	36	
Duration(months)			0.157
<6 months	16	38	
>6 months	07	34	
Monthly family income			
<10000	08	17	0.491
10000-20000	03	15	
>20000	12	40	
Type of Tumor			
Endometroid	09	27	0.848
Mucinous	06	21	
Serous	06	14	
Clear cell	02	10	

Discussion

Ovarian malignancies are usually diagnosed when distant metastasis has occurred.[17] A lot of patients show recurrences owing to lack of early efficacious screening programmes.[18] Previously cisplatin-based chemotherapy showed marked improvement in the overall survival of patients with ovarian malignancies. Till date such patients have less than 20% five-year survival .[19, 20]

Targeted oncological therapy against human epidermal growth factor receptor 2 (HER2/neu) is a way forward in the treatment of ovarian cancer, similar to Her/neu positive breast malignancies.[21] Studies suggest that around 20–30% of ovarian malignancies show Her 2 neu overexpression, associated with poor patient survival. However, this data is based on a comparatively minor number of cases and remain controversial.[22,] Since HER2/neu-positive ovarian malignancies can benefit from anti-HER2/neu monoclonal antibody, both at advance and early stages of the disease, it is therefore, important to determine the expression of HER2/neu at various clinical stages of ovarian malignancies before anti-HER2/neu treatment modalities may be considered.[23]

In this study 23 (24.21%) of cases showed Her2 overexpression in epithelial ovarian malignancies. Study by Yan et al[15], n=85 showed 35.3% of ovarian epithelial malignancies had her2 nue overexpression. The results of another study showed 14% OCCCs harbored Her2 gene overexpression.[16]

Study by Seidman et al. showed her 2 neu overexpression in 15% of early-stage and 37% of advanced-stage ovarian malignancies.[24] Similarly Kacinsky et al showed her 2 neu overexpression in 5% of early-stage and 17% of advanced-stage ovarian malignancies.[25] Overexpression was reported in 5 of 35 patients and classified as FIGO stage I/II, and 4 of the 69 patients were classified as FIGO stage III/IV.[26]

EOC which is positive for HER2/neu expression is associated with an unfavorable prognosis, similar to the breast.[27] In addition, a higher proportion of HER2/neu expression has also been reported in high-grade malignancies.[28] This study showed that the expression rate of HER2/neu in ovarian cancer was comparable with the reported rate of frequency of HER2/neu overexpression in 15–40% of breast cancer.[29] HER2/neu was expressed in all histological subtypes. Such similar findings were also noted by some other authors. Shang et al observed HER2 expression was much higher in serous (29%) and mucinous carcinoma (38%) than that in endometrioid (20%) and clear cell carcinoma (23.1%).[30]

HER2 expression is more commonly observed in the serous subtype and in older patients presenting with advanced stage of disease and high-grade of differentiation.[31]The rates of HER2 overexpression and/or amplification in ovarian cancer are variable, ranging from 2% to 66% Similar to EGFR.[32] Prognostic significance of HER2 has been studied but contradictory results. Although some studies have shown that HER2 expression is associated with poor survival, but others have not shown any relationship between HER2 expression and survival rate.[33,34]

A study conducted by Hellstorm et al showed that 25% of primary EOCs showed HER2/neu receptor overexpression. Pils et al. reported 27.6%, Marwah et

al. reported 38.0% and Sasaki et al. reported 12.8% of cases of ovarian cancers turned out to be positive for HER-2/neu overexpression.[35]

Conclusion

It was concluded that there was a high frequency of Her2 overexpression in epithelial ovarian cancers.

Conflict of Interest: Authors declare no conflict of interest.

Funding: No funding was received for this project

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HISTORY	
Date received:	26-11-2022
Date sent for review:	14-01-2023
Date received reviewers comments:	15-02-2023
Date received revised manuscript:	05-04-2023
Date accepted:	29-04-2023

KEY FOR CONTRIBUTION OF AUTHORS:

A. Conception/Study/Designing/Planning
B. Active Participation in Active Methodology
C. Interpretation/ Analysis and Discussion

CONTRIBUTION OF AUTHORS	
Author	**Contribution**
Laila Zaib	A,B,C
Sumera Sharif	B,C
Maria Liaquat	B,C
Armaghana Qamar Khan	A,B,C
Sabeen Afshan	A,B
Asma Khattak	B,C