HER2/neu: A Prognostic Marker for Ovarian Carcinoma

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Abstract

Background: Ovarian cancer is the second most prevalent gynecological malignancy. Its prognosis is poor with a five-year survival rate of <50% with the available therapies. There is a constant need for new biological markers. Therefore, we conducted the present study to evaluate the association between human epidermal growth factor receptor (HER2) neu and the clinicopathological features of epithelial ovarian cancer.

Method: A prospective, observational analytic study was conducted at Fauji Foundation Hospital, Rawalpindi between November 2018 and October 2019. It was a cross-sectional study with a quantitative correlational study design.

Results: We recruited 90 patients. The mean age of diagnosis was 53 ± 8.022 years; 81.1% (n = 73) had raised pretreatment CA-125 levels with stage III (56.7%, n = 51) and grade III (54.4%, n = 49) at presentation. It was seen that 24.4% (n = 22) of the tumors expressed HER2/neu, 65.6% (n = 59) were negative and 10% (n = 9) were equivocal. 72.2% had platinum sensitive disease. According to HER2/neu status, 20% HER2/neu positive patients had platinum sensitive disease and 3.3% had resistant disease; meanwhile, 47.8% HER2/neu negative patients had platinum sensitive disease and 10% were platinum resistant. HER2/neu expression was significantly associated with grade (*P* = 0.040) and pretreatment CA-125 levels (*P* = 0.032) whereas our study failed to show a significant association between stage (*P* = 0.383) and chemotherapy response (*P* = 0.055).

Conclusion: The current study demonstrated that HER2/neu was positive in 24.4% of the patients, which was significantly associated with grade and pretreatment CA-125 level. However, a longer follow-up is needed for survival analysis and establishment of HER2/neu as a prognostic marker for epithelial ovarian cancer.

Keywords: ErbB receptor, Carcinoma, Ovarian epithelial, Prognosis, Platinum sensitivity

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Introduction

Ovarian carcinoma is the second most prevalent gynecological malignancy worldwide as it accounts for 2.5% of all female cancer cases and 5% of cancer deaths worldwide.[1] It is the most common gynecological malignancy in Pakistan.[2] Its

Table 1. IHC criteria for scoring HER2/neu expression

HER2/neu IHC interpretation		
Staining pattern	Score	Assessment
No observable staining, or membrane staining that is incomplete and is faintly perceptible in <10% of invasive tumor cells.	0	Negative
Incomplete membrane staining that is faint/barely perceptible in >10% of invasive tumor cells.	+1	Negative
Circumferential membrane staining that is incomplete and/or weak in >10% of invasive tumor cells, or circumferential and complete intense membrane staining in <10% of invasive tumor cells.	+2	Weak positive/equivocal
Homogenous, dark, circumferential pattern in >10% of invasive tumor cells.	+3	Positive

HER2: Human epidermal growth factor receptor, IHC: Immunohistochemistry

prognosis is poor and the five-year survival rate is below 50% due to advanced stages at presentation.[3,4] Despite the advances in surgical techniques and chemotherapeutic agents, the majority of women still die after multiple lines of chemotherapy.[5] Thus, there is a constant need to explore newer targets in this malignancy in order to improve the outcome.

There are various prognostic factors in ovarian carcinoma, including both clinical and pathological factors (age of the patient, histopathological subtype, grade of the tumor, presence of ascites at diagnosis, disease stage, and pretreatment tumor markers).[6,7] Certain novel prognosticators are in clinical trials. These include epidermal growth factor receptor (EGFR) expression and human epidermal growth factor receptor (HER2/neu) overexpression.[8] In contrast to the high prevalence of breast cancer, relatively few studies have evaluated the importance of HER2/neu expression and its effect on tumor's response to chemotherapy in ovarian carcinomas.

HER2/neu overexpression has been widely studied in a number of solid tumors. It is expressed in 30% of breast cancers, 4%-20% of salivary gland tumors and non-small cell lung cancers, and 17%-52% of endometrial cancers among other cancer types.[9] It is also being investigated in various other tumors, such as ovary, colon, bladder, and head and neck cancers.[9,10] To date, the association between HER2/neu expression and ovarian cancer has been widely studied; however, the results remain controversial.[11]

HER2/neu receptor is a part of ErbB receptor family, which plays a central role in the pathogenesis of human cancers. They regulate cell growth, survival, and differentiation via multiple signal transduction pathways. Additionally, they participate in cell differentiation and proliferation, thereby leading to tumorigenesis.[12] HER2 gene is located on chromosome 17q21 and encodes a tyrosine kinase receptor of 185 kDa, the overexpression of which has been shown in 25 to 30% of ovarian cancers in various papers.[13] Although HER2/neu has been successfully targeted in breast cancer and gastric/gastroesophageal cancers, in ovarian cancer, it is still being investigated as a potential therapeutic target.[14,15] Therefore, this study aimed to evaluate the expression of HER2/neu protein in epithelial ovarian cancers and its association with other clinicopathological factors. We also sought to correlate its expression with platinum sensitivity.

The objectives of this study were to evaluate HER2/neu as a prognostic factor in epithelial ovarian cancer and to find out the association between HER2/neu overexpression and chemotherapy response in epithelial ovarian cancer.

Material and Methods

It was a prospective, observational analytic study with a quantitative correlational study design conducted at Medical Oncology Department, Fauji Foundation Hospital, Rawalpindi. The total study duration was 12 months from the time of approval (01-11-2018 until 31-10-2019). The Ethical Review Committee of Fauji Foundation

Table 2. Demographic and clinical features of the patients (n=90)

	Number of cases (n)	Percentage %
Age (years)		
≥ 40	05	5.6%
41-50	32	35.6%
51-60	37	41.1%
≥ 61	16	17.8%
Mean ± SD	53.02 ± 8.022	
Clinical stage at diagnosis		
I	19	21.1%
II	06	6.7%
III	51	56.7%
IV	14	15.6%
Ascites at presentation		
Ascites present	65	72.2%
No ascites	25	27.8%
Distant visceral metastases		
Metastasis present	14	15.6%
No metastasis	76	84.4%
Pretreatment CA-125 level		
Raised	73	81.1%
Normal	17	18.9%
Platinum response		
Platinum sensitivity	65	72.2%
Platinum resistance	13	14.4%
Platinum refractory	12	13.3%

SD: Standard deviation

Hospital approved the present work. We recruited 90 patients via consecutive non-probability sampling technique. The patients who met the following inclusion criteria were included:
1. All females aged 35-75 years with biopsy proven ≥ grade II epithelial ovarian carcinoma.
2. All treatment naïve patients.
3. All International Federation of Gynecology and Obstetrics (FIGO) stage Ic and above ovarian cancer patients.
4. All female patients who signed written consent.

The patients with the following features were excluded from the study:
1. All grade 1 and FIGO stage Ia and Ib epithelial ovarian cancer patients.
2. All female patients who took hormonal therapy.
3. Benign ovarian tumors and ovarian tumors of less common histologies.
4. All patients with any malignancy other than ovarian carcinoma.
5. Patients with heart disease, liver disease, or renal disease.
6. Pregnancy.

The following operational definitions were used in the study:

HER2/neu expression

Expression of HER2/neu protein detected via immunohistochemistry (IHC); described on a scale ranging from 0 to +3, according to ASCO/CAP guidelines (Table 1).[16]

Complete response

Defined according to the response evaluation criteria in solid tumors; (RECIST 1.1) defined by the European organization for research and treatment of cancer.[17]

Disappearance of all target and non-target lesions with normalization of tumor marker; any pathological lymph nodes (whether target or non-target) must be reduced in short axis to <10mm.

Target and non-target lesions

Once more than one measurable lesion is present at the baseline, all the lesions up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all

Table 3. Histological features of the patients (n=90)

	Number of cases	Percentage
Histological type		
Serous	59	65.5%
Cystadenocarcinoma	10	11.1%
Mucinous	6	6.7%
Clear cell	5	5.6%
Borderline	4	4.4%
Undifferentiated	4	4.4%
Endometroid	2	2.2%
Histological grade		
II	41	45.6%
III	49	54.4%
HER2/neu expression		
Positive	22	24.4%
Negative	59	65.6%
Equivocal	9	10%

HER2:Human epidermal growth factor receptor 2

involved organs, should be identified as the target lesions. All the other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions.

CA-125

A tumor marker of epithelial ovarian cancer with a reference range of 0-35U/ml according to Fauji Foundation Hospital, Rawalpindi laboratory.

CA125 >100U/ml was taken as 'increased' and any value ≤100U/ml was considered as 'normal';

A minimum of 50% reduction in CA-125 levels from a pretreatment baseline sample indicates response to chemotherapy.

Platinum-sensitive disease

According to National comprehensive cancer network (NCCN) guidelines, disease progressing with an interval of more than 6 months of completion of platinum-based therapy.[17]

Platinum-resistant disease

According to NCCN guidelines, the disease progressing within 6 months of completion of platinum-based therapy.

Platinum-refractory disease

According to NCCN guidelines, the disease progressing during therapy or within 4 weeks after the last dose of platinum-based chemotherapy.[17]

The subjects were recruited from both outpatient and inpatient departments after taking an informed consent. All the selected patients were staged clinically according to the FIGO staging system for ovarian cancer. Pretreatment CA-125 levels were obtained and IHC was applied for HER2/neu expression on histopathology samples of the patients. All the recruited patients underwent standard platinum-based chemotherapy with combination regimens given every 3 weeks for six cycles. Following the completion of the course of chemotherapy, the patients were assessed for disease response according to the RECIST 1.1 criteria. After the post-treatment response assessment, they were called for regular surveillance based on the recent NCCN guidelines for ovarian cancer treatment version 1.2020. The total follow-up period was 6 months from the last dose of chemotherapy and the subjects were categorized in various groups based on their platinum sensitivity.

We utilized SPSS version 23 for data analysis. Descriptive analysis included the means and standard deviations for continuous variables, like age and pre-treatment CA-125 levels. In analytical statistical evaluation, the frequencies and percentages were initially calculated for categorical variables, like histological subtypes, grade, ascites at the time of diagnosis, visceral metastases, and HER2/neu overexpression. In the second step, chi-square test was applied to find out the association between HER2/neu overexpression and established clinicopathological

Table 4. Association between HER2/neu expression and clinicopathological factors (n=90)

| | Her2/neu expression | | | |
	Positive n=22	Negative n=59	Equivocal n=9	*P* value
Clinical stage				
I	n= 2 (2.2%)	n= 15 (16.7%)	n= 2 (2.2%)	*P* = 0.383
II	n= 0 (0.0%)	n= 5 (5.6%)	n= 1 (1.1%)	
III	n= 15 (16.7%)	n= 32 (35.6%)	n= 4 (4.4%)	
IV	n= 5 (5.6%)	n= 7 (7.8%)	n= 2 (2.2%)	
Histological grade				
II	n= 5 (5.6%)	n= 32 (35.6%)	n= 4 (4.4%)	*P* = 0.040
III	n= 17 (18.9%)	n= 27 (30.0%)	n= 5 (5.6%)	
Pretreatment CA-125 level				
Raised	n= 21 (23.3%)	n= 47 (52.2%)	n=5 (5.6%)	*P* = 0.032
Normal	n= 1 (1.1%)	n= 12 (13.3%)	n=4 (4.4%)	

HER2: Human epidermal growth factor receptor 2

factors, such as stage of the disease, histological grade, and pretreatment CA-125 levels. In the last step, the association between HER2/neu expression and chemotherapy response was evaluated. A *P*-value of <0.05 was considered to be significant.

Results

In this study, 90 patients were enrolled. Overall, the mean age of the participants was 53 ± 7.437 years with a range of 38-72. The majority of them were in the age range of 40-60 years (81.9%). The mean pretreatment CA-125 level was 1262 ± 1683 and 81.1% (n = 73) had raised pretreatment CA-125 levels (Table 2).

When focused on the tumors' characteristics, the most common histological subtype was serous carcinoma, found in 65.5% (n = 59) of the subjects followed by cystadenocarcinoma (11.1%, n = 10). High grade (grade III) was found in 54.4% (n = 49) of the patients, making it the most frequently reported grade. For IHC, only 3+ patients were considered positive for HER2/neu expression and it was seen that 24.4% (n = 22) of the tumors expressed HER2/neu, 65.6% (n = 59)

were HER2/neu negative, and 10% (n = 9) were equivocal for HER2/neu expression (Table 3).

The majority of the patients presented with an advanced stage at the time of enrollment (stage III 56.7%, n = 51). Ascites was the presenting symptom in 72% (n = 65) of them and 15.6% (n=14) had distant visceral metastases at presentation (Table 2).

Among the total study population, 88.8% (n = 80) received neo-adjuvant chemotherapy whereas 11.2% (n = 10) received adjuvant treatment. All the patients completed their planned six cycles of chemotherapy. After 6 months of follow-up, the response to platinum treatment was assessed. At this point, 72.2% (n = 65) had platinum sensitive disease, 14.4% (n = 13) had platinum resistant disease, and 13.3% (n = 12) had platinum refractory disease.

As per study objective, chi-square test was applied to find out the association between HER2/neu and the others, establishing prognostic factors of ovarian cancer. Among them, the association between HER2/neu and FIGO stage was not statistically significant (*P* = 0.383). However, for the grade of the tumor (*P* = 0.040)

Table 5. Association between HER2/neu expression and chemotherapy response (n=90)

	Her2/neu expression			
	Positive **n=22**	**Negative** **n=59**	**Equivocal** **n=9**	*P* value
Chemotherapy response				
Platinum-sensitive	n= 18 (47.8%)	n= 43 (20.0%)	n= 4 (4.4%)	**P = 0.055**
Platinum-resistant	n= 3 (3.3%)	n= 9 (10.0%)	n= 1 (1.1%)	
Platinum refractory	n= 1 (1.1%)	n= 7 (7.8%)	n= 4 (4.4%)	

HER2: Human epidermal growth factor receptor 2

and the pretreatment CA-125 levels ($P = 0.032$), the association was statistically significant (Table 4).

Regarding platinum sensitivity and HER2/neu expression, it was seen that among HER2/neu positive patients, 20% (n = 18) were platinum-sensitive and 3.3% (n = 3) were platinum-resistant. In the HER2/neu negative group, 47.8% (n = 43) were platinum-sensitive, while 10.0% (n = 9) were platinum-resistant. ($P = 0.055$) This showed that HER2/neu expression was not associated with platinum sensitivity (Table 5).

Discussion

The present study aimed to investigate the role of HER2/neu expression in ovarian cancer as no such research has been conducted in Pakistan. Our study revealed that HER2/neu expression was significantly associated with grade ($P = 0.040$) and pretreatment CA-125 levels ($P = 0.032$). Nonetheless, there was no association between the stage ($P = 0.383$) and chemotherapy response ($P = 0.055$). Our literature search included Google Scholar, PubMed, and ProQuest.

HER2/neu is expressed in 30% of breast cancers and 35%-45% of pancreatic carcinomas.[18] Similarly, its expression in ovarian cancer is quite variable according to different studies. This variation is often due to the difference concerning staining, subjective analyses, and various methods used for scoring and interpretation, including both FISH and IHC methods. A study by Goel S et al. reported positive HER-2/neu expression (by IHC) in 24.2% of ovarian cancer patients.[19] Similarly, Shang et al., from China, reported HER-2/neu IHC positivity rate of 30.1% among their study

population.[13] However, one study by Demir et al., form Turkey, showed HER2/neu positivity in just 18.3% of ovarian cancer patients and both IHC +2 and IHC +3 pts were considered positive in their study.[11] Our study evaluated HER2/neu expression by IHC only and 3+ pts were considered positive for HER2/neu expression. The obtained results herein indicated HER2/neu positivity in 24.4% of the patients, which is comparable with most of the above-mentioned studies.

To establish the prognostic significance of HER2/neu, we evaluated its association with various prognostic markers of ovarian cancer. The correlation of HER2/neu with the stage of disease was insignificant. This result was in line with those reported by Demir et al. in Turkey, MA Ajani in South Africa, and Mutuiri et al. in Kenya.[11,20,21] Their study populations were similar to ours in terms of the mean age and advanced stage at presentation. HER2 analysis was performed by IHC in most of the studies and the data were collected over a longer period of time as compared to our work. However, most of the studies were retrospective studies. Thus, our prospective study reproducing the same results in a limited time span further confirms this finding.

In our study, HER2/neu expression had a positive association with a higher grade of tumor. This result was consistent with the studies conducted by Jamal Zidan in Israel and Sapna Goel et al. from India.[22,19] These studies had the same mean age as our subjects and a higher grade compared with ours. HER2/neu expression was also analyzed by IHC similar to our study. An

Table 6. Details of the studies included in discussion (supplementary table)

Studies	Number of cases (n)	Study design	*HER2 assessment method	*HER2 positivity (%)	Associations			
					Stage	Grade	CA-125 level	Platinum sensitivity
Goel S et al.[19]	74	Prospective	IHC with DAKO scoring	48%	-	+	Not studied	Not studied
Shang et al.[13]	136	Prospective	Western blot	24%	+	-	Not studied	Not studied
Demir et al.[11]	82	Retrospective	IHC with ASCO/CAP scoring	18.3%	-	Not studied	Not studied	-
Ajani et al.[20]	90	Retrospective	IHC with DAKO scoring	37%	-	-	Not studied	Not studied
Mutuiri et al.[21]	67	Prospective	IHC with ASCO/CAP scoring	13.4%	-	-	Not studied	Not studied
Zidan et al.[22]	43	Retrospective	IHC with ASCO/CAP scoring	30%	-	+	Not studied	Not studied
Wang et al.[3]	11	Retrospective	IHC with DAKO scoring	31.5%	+	-	+	Not studied
Chay et al.[24]	133	Prospective	IHC with DAKO scoring and FISH	27.4%	-	-	+	Not studied
Feng et al.[25]	875	Retrospective	IHC with ASCO/CAP scoring	4%	Not studied	Not studied	Not studied	-

HER2: Human epidermal growth factor receptor 2

investigation conducted on 63 Kenyan ovarian cancer patients studied the same association of HER2/neu with a higher grade, but failed to show significant results, as their study had only 13.4% HER2/neu positive cases (by IHC) and the sample size was small.[21] Ethnic differences were also shown to influence the level of HER2/neu expression in a study done on breast cancer patients; this can be the reason behind the low level of HER2/neu expression in the above-mentioned study.[23] This fact further needs to be explored since ethnic differences are becoming more and more significant in the era of targeted therapies.

HER2/neu expression also showed a positive association with pretreatment CA-125 levels. This association was investigated in two studies; one was conducted by Wang et al. in China. Their study had 111 ovarian cancer cases, collected retrospectively. HER2/neu analysis was done via IHC and it was positive in 31.5% of the patients. Their results were in line with ours.[3] The other study was published by Chay WY in Singapore.

It was a prospective study with 133 ovarian cancer patients, in which HER2 analysis was done via FISH showing 27.4% HER2 positive cases. This paper also indicated similar results concerning the association of HER2/neu with CA-125 levels.[24]

The last parameter evaluated in our study was platinum sensitivity and its association with HER2/neu expression. Our results revealed no significant association between the two parameters. In the literature review, two scientists worked on this association. Primarily, a retrospective work was conducted in 2013 by Demir et al., in which 82 patients were studied and HER2/neu was positive in 18.3% of the cases tested via IHC analysis. Among platinum-sensitive patients, 53% were HER2+ and 58% were HER2 negative. Meanwhile, among the platinum-resistant ones, 46% were HER2+ and 41.8% were HER2 negative. This result implied that HER2/neu expression was associated with platinum resistance, but did not reach the statistical significance.[11] Another study was conducted in China. It was a retrospective analysis of 875

patients, in which HER2/neu positivity (by IHC analysis) was limited to only 4% of the data. This paper also showed no association with platinum sensitivity, possibly due to smaller number of HER2/neu positive cases.[25] Both studies were conducted retrospectively and the data were collected over a longer time period. Our results, being obtained in a prospective study over a smaller time frame, further strengthens this association. The vast diversity of HER2/neu positivity in these two studies can be attributed to ethnic differences.[23]

All these findings suggest that HER2/neu expression can be considered as a prognostic marker in ovarian carcinoma; however, to establish this fact, further survival-related studies should be conducted. We aim to conduct a 5-year follow-up study to assess the survival patterns in our patients.

The constraints faced in the present work included time and that it was a single-institution study, which could be potentiated in the future in multi-center randomized studies with greater number of patients and including HER2/neu analysis with both IHC and FISH. Furthermore, our study population was small and the patients need to be followed up for a longer duration of time so that we could establish statistically significant results.

Conclusion

Survival of ovarian carcinoma is poor despite optimal surgical and chemotherapeutic management. Therefore, there is an urgent need for newer molecular markers, which is an active area of research in this regard with focus on biological targets and their significance. The current research indicated the statistically significant association between HER2/neu expression and certain clinical features, like the grade of the tumor and pretreatment CA-125 levels. Meanwhile, we could not detect any association with clinical stage or platinum responsiveness. Studies with a bigger sample size and longer duration are further required to establish HER2/neu as a prognostic marker for

ovarian cancer.

Conflict of Interest

None declared.

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