FREQUENCY OF HER-2/NEU RECEPTOR POSITIVITY AND ITS ASSOCIATION WITH OTHER FEATURES OF BREAST CANCER

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Background: Carcinoma breast is the commonest malignancy of females all over the world and second leading cause of death due to cancer among females. In Pakistan it is more common at a young age contrary to the West where it is more common in old age (after 60 years). The objectives of this cross sectional study were to determine the frequency of HER-2/neu receptor over-expression and its association with some of the features of breast cancer like patient age, ER/PR status, tumour size, histological grade and axillary lymph node involvement. **Methods:** This study was conducted at Surgical C Unit, Postgraduate Medical Institute of Lady Reading Hospital, Peshawar, from January 2007 to December 2007. Study included all patients with breast cancer admitted in Surgical 'C' unit LRH, Peshawar for Modified Radical Mastectomy (MRM). The resected specimens were sent to histopathologist for immunohistochemical (IHC) studies (HER-2/neu receptor and ER/PR) and detailed histopathological analysis including tumour subtype, size, histological grade and involvement of axillary lymph nodes. Patients refusing HER-2/neu receptor immunohistochemistry were excluded from the study. Name, age, sex, other relevant data, detailed history and clinical examination findings and results of investigation were recorded. Data was analyzed with SPSS version 10. **Results:** This study included 24 female patients of breast cancer having modified radical mastectomy (MRM). Age distribution ranged from 32-75 years with a Mean±SD of age 48.3±18.2 years. Fifteen out of 24 patients (62.5%) were >40 years, while nine patients out of 24 (37.5%) were ≤40 years of age. The HER-2/neu receptor status was found positive in 11 patients (45.9%) and negative in 13 patients (54%) of the total cases.HER-2/neu receptor positivity was not significantly associated with histopathological sub-type ($p>0.05$), number of axillary lymph nodes involved ($p>0.05$) and histological grade ($p>0.05$). While, it was significantly associated with tumour size ($p<0.05$) and negative ER/PR status ($p<0.05$). Conclusion: Due to high prognostic significance and frequency in Pakistani females with breast cancer, HER-2/neu receptor should be checked in all patients with breast cancer so that the positive cases should have herceptin therapy and benefit from anthracycline based chemotherapeutic agents which can improve survival in these patients.

Keywords: Breast carcinoma, HER-2/neu, ER/PR

INTRODUCTION

Carcinoma of the breast is the commonest malignancy of females all over the world and second leading cause of death due to cancer among females. In Pakistan it is more common at a young age contrary to the West where it is more common in old age (after 60 years).[1] All women regardless of their racial or ethnic origin or heritage are at risk of developing breast cancer. Variations in breast cancer incidence rates among multicultural populations suggest that etiologic factors differ in their biologic expression and impact on disease outcome. Key among those factors that affect breast carcinoma development are the roles of genetics and environment, the reproductive experience, the effect of endogenous and exogenous hormones in women, the change in immune status and host vulnerability, and the biologic determinants of breast carcinoma.[2]

Approximately one in every nine Pakistani women is likely to suffer from breast cancer. This is one of the highest incidence rates in Asia. Amazingly Pakistani women show an incidence rate of 50/100,000 and in the neighbouring country India with similar socio-cultural background the incidence rate is 19/100,000. Differences in diet, racial or genetic factors may provide a partial explanation but it needs to be sorted out.[3]

Several histopathological features have prognostic significance in breast cancer like cancer subtypes, tumour grade, lymphovascular invasion, oestrogen and progesterone receptor status, proliferation markers and DNA content, peptide hormones, growth factors and their receptors, oncogenes, and tumour suppressor genes.[4,5]

HER-2/neu is the human homologue of the neu gene, called HER-2 or c-erbB-2, which shares extensive homology with epidermal growth factor receptor (EGF-R). HER-2/neu or its protein P185 is overexpressed in 10-35% of breast cancer patients.[6] It is considered one of the poor prognostic factors in breast cancer. The overall survival rate is significantly better for patients without HER-2/neu receptor markers vs those with HER-2/neu receptor overexpression.[7] Trastuzumab is a monoclonal antibody that targets HER-2/neu extracellular domain and

helps in improving survival in patients with over expressed HER-2/neu receptor.

The present study aims at determining the frequency of HER-2/neu receptor and its association with some of the other features of breast cancer like age, race, tumour size, histological grade, number of axillary lymph nodes involved and ER/PR status.

PATIENTS AND METHODS

The study included 24 female patients with breast cancer. They were admitted through surgical outpatient department. Detailed history, clinical examination and relevant investigations were carried out. Patients were assessed in terms of fitness for surgery and general anaesthesia. Informed written consents were taken. They were operated on elective list by senior consultants. MRM was performed in all the patients. They were closely followed up for any postoperative complications. The specimens were sent to histopathologist for detailed analysis including IHC for ER, PR and HER-2/neu receptor.

This study was conducted in Surgical 'C' Unit Lady Reading Hospital Peshawar from January, 2007 to December, 2007 over a period of one year. All patients with breast carcinoma of either sex undergoing MRM followed by detailed histopathological analysis of the specimen, including immunohistochemical (IHC) staining for ER, PR and HER-2/neu receptors were included. A Hercep test score of 3+ was considered as positive and score less than this (0+, 1+, 2+) was taken as negative for HER-2/neu receptor. Patients refusing Hercep test were excluded from the study.

Detailed results of available data were collected. Results of HER-2/neu status were analyzed using SPSS version 10 and then associations were tested with age, race, tumour size, tumour grade, axillary lymph node involvement and ER/PR status, using Chi-square test.

RESULTS

This study included 24 patients of breast cancer having modified radical mastectomy (MRM). All patients were female. Age distribution ranged from 32-75 years with a Mean±SD of age 48.3±18.2 years. Fifteen out of 24 patients (62.5%) were >40 years, while nine patients out of 24 (37.5%) were ≤40 years of age. The HER-2/neu receptor status was found positive in 11 patients (45.9%) and negative in 13 patients (54%) of the total cases. HER-2/neu receptor positivity was not significantly associated with histopathological sub-type (p>0.05), number of axillary lymph nodes involved (p>0.05) and histological grade (p>0.05). It was significantly associated with tumour size (p<0.05) and negative ER/ PR status (p<0.05).

All the characteristic features including age, race, laterality, tumour subtype and HER-2/neu status are given in Table-1. Association of HER-2/neu status with other prognostic features is summarized in Table 2.

Table-1: characteristic features of breast cancer patients

	Frequency	%
Age		
≤40 years	9	37.5
>40 years	15	62.5
Race		
Pakistani	16	66.6
Afghani	8	33.3
Tumour laterality		
Right	10	41.6
Left	14	58.3
Histopathology		
Invasive ductal carcinoma	22	91.7
Lobular carcinoma	0	0
Papillary carcinoma	1	4.1
Mixed invasive ductal and	1	4.1
HER-2/neu status		
Positive (IHC 3+)	11	45.8
Negative (IHC 0+, 1+, 2+)	13	54.1

Table-2: HER-2/neu receptor status and its association with histolopathological features

Histopathological features	HER-2/neu +ve	HER-2/neu -ve	p-value
Histopathological subtype			
Infiltrating ductal carcinoma	10 (90.9%)	12 (92.3%)	>0.05
Lobular carcinoma	0	0	
Papillary carcinoma	1 (9.0%)	0	
Mixed invasive ductal and lobular carcinoma	0	1 (7.7%)	
Tumour size			
T2 (<5cm)	1 (9.0%)	6 (46.1%)	<0.05
T3 (5-10cm)	6 (54.5%)	7 (53.8%)	
T4 (>10cm)	4 (36.4%)	0	
Number of lymph nodes			
Negative	1 (9.0%)	2 (15.4%)	>0.05
1–3	0	2 (15.4%)	
4–9	3 (27.3%)	6 (46.1%)	
≥10	7 (63.6%)	3 (23.0%)	
Tumour Grade			
I	0	1 (7.7%)	>0.05
II	2 (18.2%)	5 (38.5%)	
II	9 (81.8%)	7 (53.8%)	
ER status			
Positive	1 (9.0%)	10 (76.9%)	<0.001
Negative	10 (90.9%)	3 (23.0%)	
PR status			
Positive	2 (18.1%)	10 (76.9%)	<0.001
Negative	9 (81.8%)	3 (23.0%)	

DISCUSSION

The HER-2/neu gene is a proto-oncogene that is amplified in 10–30% of breast cancers. New drugs for targeted therapy, such as Herceptin, are effective for patients with HER-2/neu-positive tumours, making it necessary to have a non-costly and accurate method to assess HER-2/neu status.[8] Her-2/neu over

expression can be detected by immunohistochemical analysis and fluorescence in situ hybridization techniques in biopsy specimen. Using the IHC technique and DAKO scoring system, scores of 0, 1+, 2+ are defined as negative and 3+ as positive.[9]

Trastuzumab, also called Herceptin is used for targeted therapy in patients with HER-2/neu positive tumours, improving survival and thus making it necessary to assess HER-2/neu status in patients with breast cancer.[8]

In our study HER-2/neu status was checked in 24 patients of breast cancer having MRM. HER-2/neu was found positive in 11 patients (45.8%) and negative in 13 patients (54%). Al-ahwal MS in his study conducted in February 2006 in Saudi Arabia has reported 28.3% of his patients positive for HER-2/neu receptor.[4] Ariga R, in 2005, has reported 15% of breast cancer patients positive for HER-2/neu receptor.[10] Naqvi *et al*, in 2002 has reported 33% positive over-expression for HER-2/neu receptor.[11] Naqvi *et al*, in another study in December 2007 in Karachi, Pakistan has observed 31% positive over-expression for HER-2/neu receptor.[12]

Regarding age, almost 1/3 of our patients (37.5%) were ≤40 years of age. Primary breast carcinoma rising before 40 years age are far more aggressive and likelier to metastasize and reduce patients' survival than those arising in older patients, regardless of hormone receptor status.[13] In this study, association of HER-2/neu with age showed that seven patients were positive in the young age group and four patients were positive in the age group above 40 years. This is similar to what is reported in literature, that HER-2/neu over expression tends to decline with age.[13] Al-ahwal has reported 34.1% of his young patients (≤40 years) positive for HER-2/neu receptor and 65.9% of those above 40 years of age.[4] Regarding race, HER-2/neu receptor over expression revealed no significant difference. This is similar to what has been reported by Alahwal.[4]

In our study HER-2/neu receptor revealed a significant association with ER/PR status (HER-2/neu was positive in only 9.0% of cases with positive ER status vs 91% of cases with negative ER status. HER-2/neu was positive in 18% of PR positive cases vs 81.8% of PR negative cases). Al-ahwal in his study has also mentioned this inverse association between HER-2/neu and ER status. In his study HER-2/neu was positive in only 19.5% of cases with positive ER status vs 80.5% of cases with negative ER status.[4] Regarding HER-2/neu and PR status, it was observed by Al-ahwal that HER-2/neu was positive in 36.6% of cases with PR positivity and 63.4% of cases with a negative PR status.[4] Huang HJ in his study carried out in Taiwan in the year 2005 has also reported that ER and PR negative breast cancers were more often HER-2/neu positive than hormone receptor positive cancers, both for ER (28.7% vs 6.8%) and PR (19.9% vs 5.9%).[9] Ariga R in his study in Chicago in the year 2005, has also pointed out this inverse correlation between HER-2/neu and ER/PR status of patients with breast cancer. He has mentioned that HER-2/neu was overexpressed in 10% of ER positive cases vs 28% of ER negative cases and 7% of PR positive cases vs 25% of PR negative cases.[10] Ivkovic-kapicl T in the year 2007 in Serbia has reported that out of 23 HER-2/neu positive cases ER and PR status was negative in 61% and 69%, respectively.[14] Unfortunately there is no local study available to describe this inverse association between HER-2/neu and ER/PR status.

In literature, HER-2/neu receptor amplification is found to be an independent poor prognostic factor of tumour grade, tumour size and lymph node status.[15] In our study, increasing tumour size was significantly associated with HER-2/neu positivity ($p<0.05$). Naqvi SQH in the year 2002 in Karachi has mentioned a statistically significant correlation ($p<0.05$) between HER-2/neu over expression and tumour size.[11] In another study in December 2007 he has again mentioned a statistically significant correlation ($p<0.05$) between HER-2/neu overexpression, tumour size and lymph node status.[12] Ivkovic Kapicl has also mentioned statistically significant correlation between HER-2/neu protein over expression and large tumour size and ER/PR negativity.[14] No significant association was observed between HER-2/neu positivity and tumour grade, histopathological subtype and number of axillary lymph nodes involved ($p>0.05$). Huang has mentioned that tumour grade is positively correlated with HER-2/neu overexpression.[9] Ariga has also found a positive association between HER-2/neu and high histological tumour grade.[10] Taucher has mentioned that HER-2/neu over expression was correlated significantly with ER/PR negativity, high tumour grade (grade III) and young age.[16] Tokatli F in the year 2005 in Turkey has reported 20% of his patients positive for HER-2/neu and a significant association was observed between HER-2/neu and increasing number of involved axillary lymph nodes ($p= 0.014$).[17] Almasri NM has observed that HER-2/neu was over expressed in 24% of cases and receptor over expression was inversely related to ER/PR status and it was associated with young age at presentation, larger tumour size and high number of involved axillary lymph nodes.[18] Looi LM, in Malaysia, in the year 1998, has found a negative correlation between ER and HER-2/neu over expression. He has mentioned that c-erbB-2 overexpression was significantly more prevalent in grade III tumours ($p<0.005$).[19]

It is obvious from above national and international studies that HER-2/neu over expression is significantly associated with ER/PR negativity, young age, high tumour grade, large tumour size and increased number of axillary lymph node involvement. Assessment of HER-2/neu over expression in breast cancer patients has an impact on prognosis and treatment modality.

CONCLUSION

Routine testing for HER-2/neu receptor over expression is recommended in all patients of breast cancer, especially those presenting at a younger age, with a large size tumour and a negative ER/PR status because of its prognostic significance and impact on further management with herceptin and anthracyclines based chemotherapeutic agents.

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