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ORIGINAL ARTICLE

Frequency of HER-2 NEU Receptor Positivity and its Relationship with Estrogen Progesterone Receptors in Patients of Breast CA

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ABSTRACT

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 Surgery ward unit 2, Fatima Memorial Hospital, Lahore, from June 2015 December 2015. Study included all patients with breast cancer admitted in Surgery unit 2 of FMH, Lahore 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 50 patients of breast cancer having modified radical mastectomy (MRM). Age distribution ranged from 45-61 years with a Mean±SD of age 52.2±4.3 years. 30 out of 50 patients (62.5%) were >52 years, while 20 patients out of 50 (40%) were ≤40 years of age. The HER-2/neu receptor status was found positive in 30 patients (60%) and negative in 20 patients (40%) of the total cases 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 breast is the one of most common causes of cancer related deaths, morbidity, hospital visits and anxiety among the females in Pakistan ranging from aged 3rd decade to sixth decade of life such that it constitutes a major health care problem. Situation in our city is no different. According to an estimate, MRM (modified radical mastectomy) is the leading elective surgical procedure done in tertiary care hospitals of our country. According to Bailey and Love, the incidence of CA breast is increasing worldwide especially countries like Pakistan and India where cousin marriages are favoured1. Breast CA is a familial disease2. Important causes behind are cousin marriages. Late detection and denial of screening programs by the women of low socio economic status are blamed to be the main causative factors of such a high incidence of the disease.

Tumour antiges, by definition, are the protein receptors of the cells of the epithelium of a malignant tumour. They may arise from the stroma of the tissue or the parenchyma. In case of Breast, hormones like estrogen and progesterone are said to act on the stromal and glandular (ductal) parts of breast respectively. From the last decade, epidermal type growth factors like HER2 u, is also mapped out in the mastectomy specimen and the patients are being treated accordingly. Numerous Pharmocologic agents that selectively block the ER (estrogen receptors) and PR (progesterone receptor) are made available in the markets at very economical rates. Likewise, the monoclonal antibody named Transtuzumab is also available that block the proliferation of tumor cells mediated by Her2 u receptors. Since then, the management of patients having undergone mastecomies has changed drastically such that 5 year median survival after successful mastectomies has risen to 95% with such agents. It has become mandatory for breast surgeons to order the detection of these receptors in the mastectomy specimen.

It has been observed that patients undergoing mastectomies in younger age group harbor Her2 nu receptors in their tumours where as those are menopausal have estrogen and progesterone receptors. However if there are no receptors found in the tumour specimen, called triple negative, such patients carry very poor prognosis. On the contrary, the presence of Her2 u receptors alone means a significant risk factor for tumour recurrence with poor prognosis. This poses challenge to our physicians, breast surgeons and even histopathologists With Mastectomies and good adjuvant chemotherapy and hormone therapy, patients of CA breast have a new horizon of treatment.

The present study is to determine the frequency of HER-2/nu receptor and its association in breast cancer, we will also consider factors like age, race, tumour size, histological grade, number of axillary lymph nodes involved and ER/PR status.

MATERIAL AND METHODS

Total number of 50 patients with breast cancer are included. They were admitted through surgical OPD. Detailed history, clinical examination and relevant investigations were carried out. Patients were assessed in terms of fitness for 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 Surgery unit 2 of Fatima Memorial Hospital Lahore from June 2015 to December 2015 over a period of six months. All patients with breast carcinoma 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 50 patients of breast cancer having modified radical mastectomy (MRM). All patients were female. Age distribution ranged from 45-61 years with a Mean±SD of age 52.7±4.3 years. 30 out of 50 patients (60%) were >50 years, while twenty patients out of 50 (40%) were ≤50 years of age. The HER-2/neu receptor status was found positive in 30 patients (60%) and negative in 20 patients (40%) 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: Age distribution

Mean	Median	Standard deviation	Range
52.7 yr	53.0 yr	4.3 yr	45-61 year

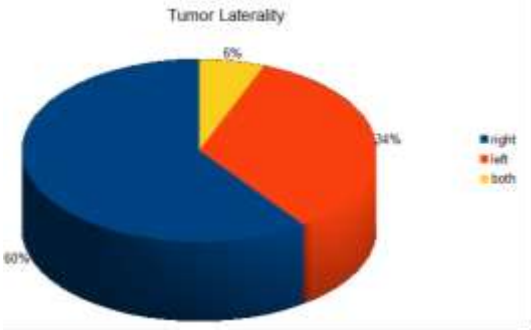

Figure 1: Tumor Laterality

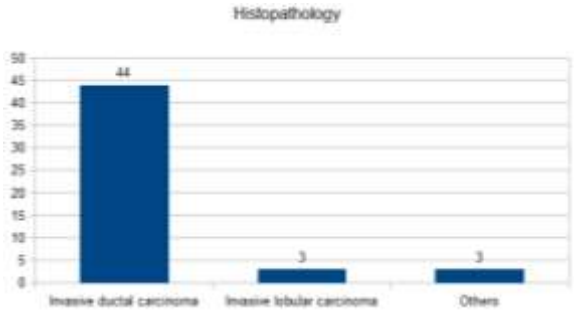

Figure 2: Histopathology

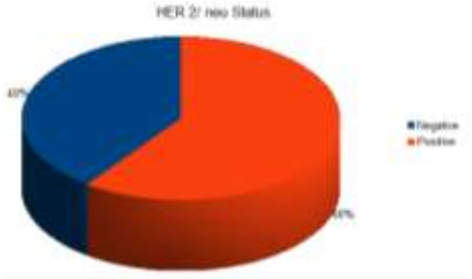

Figure 3: HER 2/ neu Status

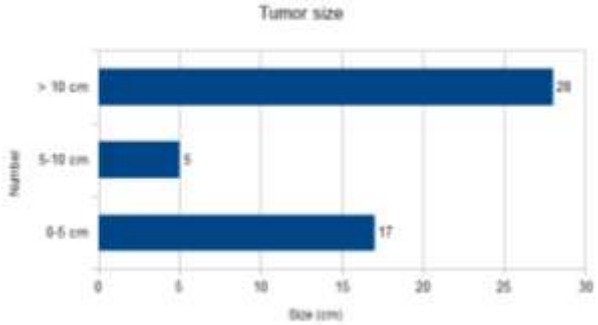

Figure 4: Tumor size

Table 2: Lymph nodes, Tumor grade, ER, PR status

Variable	Categories	Frequency	Percentage
Lymph node	1-3	3	6
	4-9	12	24
	>10	35	70
Tumor grade	I	32	63
	II	12	24
	III	6	12
ER status	Positive	45	90
	Negative	5	10
PR status	Positive	45	90
	Negative	5	10

DISCUSSION

The HER-2/neu gene is a proto-oncogene that is amplified in up to 30 % of breast cancers. New drugs for targeted therapy, such as Herceptin, are effective for patients with HER-2/neu. This makes it necessary to have an accurate method to assess HER-2/neu status.8 Her-2/neu over expression can be detected by immunohistochemical analysis and techniques like FISH (fluorescence in situ hybridization) 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 all 50 patients of breast cancer having MRM. HER-2/neu was found positive in 30 patients (60%) and negative in 20 patients (40%). 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 2/3 of our patients (60%) were ≤55 years of age. Breast carcinoma arising before 40 years age is said to be far more aggressive and likelier to metastasize. This reduces patients' survival 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 is declining 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 90% of cases with positive ER status vs 10% of cases with negative ER status. HER-2/neu was positive in 90% 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 relation 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 nodes. However in our study, the results were surprising. There were some cases in our study that were post menopausal and were found to have a positive Her2/neu receptor status. Assessment of HER-2/neu over expression in all breast cancer patients has an impact on prognosis and treatment options.

CONCLUSION

Routine testing for HER-2/neu receptor over expression is recommended in all patients of breast cancer, regardless of age of patient at the time of presentation, 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 drugs of chemotherapy.

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