FREQUENCY OF HER-2/NEU POSITIVITY IN CARCINOMA BREAST PATIENTS IN TERTIARY CARE HOSPITALS OF BALOCHISTAN

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ABSTRACT

Objective: To examine the frequency of human epidermal growth factor receptor 2 (HER-2)/neu positivity in carcinoma breast patients in tertiary care hospitals of Balochistan.

Methodology: This multi-center study was conducted in the Department of Surgery, Bolan Medical Complex Hospital and Sandeman Provincial Hospital, Quetta-Balochistan, from January 01, 2015 to June 30, 2015. All female patients undergoing surgery for carcinoma (Ca) breast with age 25 to 65 years, duration more than 6 months, size of tumor 2 cm and above and Ca breast grade 1-3 were included. Breast tissue was sent for histopathology and HER-2/ neu immunostain (neu) by immunohistochemistry.

Results: Mean age of the patients was 57.06 ±8.91 years and mean BMI 25.04 ±5.51 Kg/m². Most of the patients (n=76, 92.7%) were married, smoking status was found in 4 (4.9%), pre-menopausal status in 13 (15.9%), oral contraceptive use in 11 (13.4%), family history of breast carcinoma in 22 (26.8%), lactation in 18 (22%) and multi-parity in 55 (67.1%). HER-2/neu was found to be positive in 19 (23.2%) patients.

Conclusion: Higher frequency of HER-2/neu positivity was found in carcinoma breast patients in tertiary care hospitals of Balochistan.

Key Words: Carcinoma breast, HER-2/neu positivity, Balochistan

INTRODUCTION

Breast cancer is the most common malignancy all over the world[1]. In Pakistan, 1 in every 9 women are likely to suffer from carcinoma of breast. Compared to western women, Asians women show the highest incidence of breast cancer rate. Pakistani and Indian community have breats cancer with the rate of 50/100,000 and 19/100,000, respectively. Pakistani women suffering from breast cancer are usually multiparous and belong to younger age group[1]. In a study, mean age of patients at the time of diagnosis was 43.5 years[3]. This geographic variation in presentation and incidence of breast cancer can be attributed to racial and genetic differences and environmental exposure that vary throughout the world[4].

Estrogen, progesterone and HER-2/neu receptors affect the overall prognosis of breast cancer[5]. The HER-2/neu (c-erb-b2) gene, encoding a member of the ERBB or HER transmembrane tyrosine kinase receptor protein is located on chromosome17q[6]. It is the human analogue of the neu gene, called HER-2/neu or c-erb B2. It is considered one of the poor prognostic factors and is found higher in our population though limited data exists. 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 receptors[7]. The activation of the receptor begins as the ligand attached to a receptor and a cascade of interaction of receptors to the nearby similar receptor occurs, a process commonly known as dimerization. Further process leads to phosphorylation and signaling cascades[8]. HER-2/neu is an important prognostic factor and strong predictor of response to trastuzumab[9]. However, it is a common practice in Pakistan, especially in Balochistan, that tests for receptor positivity in histopathology specimens are not requested[10].

In Pakistan, multiparity and breastfeeding have significant associations with breast cancer[11]. This means the biological behaviour of breast cancer in Pakistani population is different. HER-2/neu positivity could be a factor responsible for this aggressive behaviour of breast cancer in Pakistani women. There is limited data published on HER-2/neu frequency all over Pakistan, while data seen in studies done on different receptors shows geographical variation in frequency even within

Asia, 22% in a study in Karachi[12], 28.4% in a Bangladeshi study[13] and 45.9% in a study in Abbotabad[14]. The rationale of the study is that the data is variable within geographical areas as stated above[12-14]. Therefore the present study was designed to assess the magnitude of HER-2/neu positivity in Ca breast patients in Balochistan. Thereby policies could be devised for routine screening and treatment.

METHODOLOGY

This was a descriptive cross sectional study with duration of six months from January 2015 to June 2015. It was conducted at Department of Surgery in Bolan Medical Complex Hospital and Sandeman Provincial Hospital, Quetta-Pakistan. After informed consent from patient or from next to kin, the Ethical committee review was taken. Patients included were females with age 25-65 years, undergoing surgery for Ca breast having duration >6 months, size of tumor 2cm and above, carcinoma breast grade 1-3. The exclusion criteria consisted of male patients with Ca breast, patients refusing to test for her-2/neu receptors and previously operated cases. The sampling technique was non probability, consecutive method. The sample size of study was taken keeping prevalence of HER-2/neu positivity in Ca breast patients as 22%[12], absolute precision at 9% and confidence level at 95%. The sample size was 82 patients with breast cancers undergoing surgery. Patients meeting the inclusion criteria were admitted in Department of Surgery at Bolan Medical Complex Hospital and Sandeman Provincial Hospital, Quetta. History regarding the duration of condition, ethnicity, marital status, parity, lactation, intake of oral contraceptives and family history of the disease was taken. The consultants having post fellowship experience of greater than two years performed the surgery. Breast tissue was sent for histopathology and HER2/neu staining by immunohistochemistry. Breast Cancer with presence of lump in breast /fungating mass proven to have malignant cells on biopsy and HER-2/neu positivity by immunohistochemistry staining of the tissue with score of 3+ i.e, uniform intense membranous staining was considered as positive HER-2/neu receptors.

SPSS version 17 for windows was used for entry of data and analysis. Age and duration of condition, extent of lump, height, weight and BMI were calculated and presented as mean ±SD. Frequencies and percentages were calculated for HER-2/neu positivity, menopausal status, smoking status, oral contraceptives use, family history of Ca breast, marital status, lactation and parity. Effect modifiers like age, duration of condition, size of the lump, family history of Ca breast, smoking status, lactation, BMI and oral contraceptive use, marital status, parity, menopausal status were controlled through stratification. Chi square test was used and significance level was set at less than or equal to 0.05.

RESULTS

Mean age of the patients was 57.06 ±8.91 years. Majority of the patients (n=69, 84.10%) had age >50 years. Mean weight of the patients was 57.71 ±6.45 kg, height 1.59 ±0.05 meters and BMI 25.04 ±5.51 Kg/m^2. Majority of the patients (n=53, 64.6%) had BMI of ≥30 Kg/m^2.

Size of the tumor was found to be >4cm in 40 (48.8%) patients. Mean duration of condition was 8.41 ±1.21 months. Majority of the patients (n=48, 58.5%) had ≥8 months of duration of condition. A vast number of patients (n=76 ,92.7%) were married, smoking status was found in 4 (4.9%), pre-menopausal status in 13 (15.9%), oral contraceptive use in 11 (13.40%), family history of breast carcinoma in 22 (26.80%), lactation in 18 (22%) and para >3 in 55 (67.10%), as shown in table 1.

Frequency of HER-2/neu positivity was found in 19 (23.2%) patients (Figure 1).

DISCUSSION

Breast cancer is causing the most mortality in recent years. Apart from histopathological studies, breast cancers are diagnosed with various techniques, such as immunohistochemistry (IHC) and human epidermal growth factor receptor 2 (HER 2) expression and amplification by FISH and IHC in selecting the best choice for suitable therapy[15]. We studied the frequency of HER-2/neu positivity in carcinoma breast patients in tertiary care hospitals of Balochistan. The diagnosis of breast cancer through HER2/neu status is of increased significance. Compared to other usual diagnostic tools such as immunohistochemical assays (which are qualitative), the HER-2/neu analysis is semi-quantitative. The overall staining mechanism depends on the number of receptors a cell contains. The cells with less than 20,000 receptors showed no (0) staining, whereas with 100,000 receptors showed partial membrane staining (less than 10% among these showed full membrane staining or 1+). Light and moderate membrane staining was observed in 10% cells with nearly 500,000 receptor (2+). However, cells with 2.3 million receptors showed strong staining in more than 10% of the cells.

Studies have shown that protein expression level is basically associated with the number of gene copies, nevertheless the modification occurs due to the technical issues significantly affecting the tissue sampling[6,9,16]. However, alterations can be impacted significantly by technical issues, especially in archival, fixed, paraffin-embedded tissue samples. There are many drawbacks of immunohistochemical analysis such as proper management and storage; duration and fixation; concentration of antigen recovery; kinds of antibody (polyclonal vs monoclonal); proper sample control system; and the problems in applying a subjective slide scoring

Table 1: Comparison of HER-2/neu positivity (n=82)

Demographics		HER-2/neu Positivity		P value
		Yes (n=19)	No (n=63)	
Age (in years)	≥50 (n=13)	4 (30.8)	9 (69.2)	0.479
	>50 (n=69)	15 (21.7)	54 (78.3)	
Duration of condition (in months)	<8 (n=48)	12 (25)	36 (75)	0.641
	>8 (n=34)	7 (20.6)	27 (79.4)	
BMI (in Kg/m^2)	≥30 (n=59)	12 (22.6)	41 (77.4)	0.878
	>30 (n=43)	7 (24.1)	22 (75.9)	
Lump Size (in cm)	≥4 (n=42)	10 (23.8)	32 (76.2)	0.888
	>4 (n=40)	9 (22.5)	31 (77.5)	
Family History of Breast Carcinoma	Yes (n=22)	13 (59.1)	9 (40.9)	0.001
	No (n=60)	6 (10)	54 (90)	
Smoking Status	Yes (n=04)	3 (75)	1 (25)	0.037
	No (n=78)	16 (20.5)	62 (79.5)	
Lactation	Yes (n=18)	2 (11.1)	16 (88.9)	0.218
	No (n=64)	17 (26.6)	47 (73.4)	
Married	Yes (n=06)	2 (33.3)	4 (66.7)	0.619
	No (n=76)	17 (22.4)	59 (77.6)	
Parity	Para ≥3 (n=27)	4 (14.8)	23 (85.2)	0.209
	Para >3 (n=55)	15 (27.3)	40 (72.7)	
Menstrual Status	Pre-menopausal (n=13)	4 (30.8)	9 (69.2)	0.479
	Post-menopausal (n=69)	15 (21.7)	54 (78.3)	
History of Oral Contraceptive Use	Yes (n=11)	7 (63.6)	4 (36.4)	0.002
	No (n=71)	12 (16.9)	59 (83.1)	

Figure 1: Frequency of HER-2/neu positivity in carcinoma braest patients (n=82)
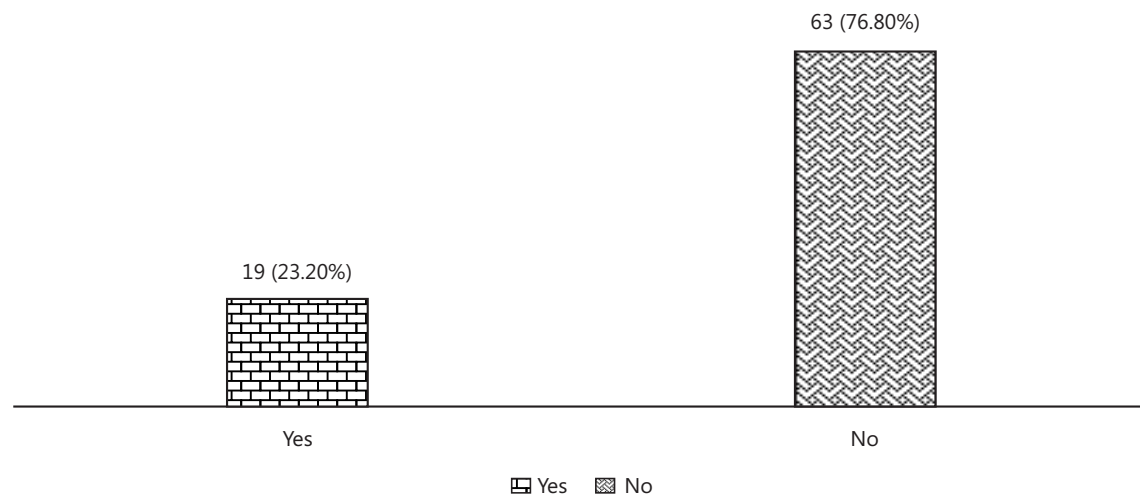
system. HER-2/neu protein detection has widely been reported as the suitable replacement of immunohisto-chemical analysis especially in a large multitumor tissue block and a large panel of available antibodies. The standardization of HER-2/neu immunohistochemical slide scoring has remained a critical issue in the application of HER-2/neu testing designed to predict response to the anti–HER-2/neu antibody drug, trastuzumab (Herceptin, Genentech, South San Francisco, CA).

Our study found frequency of HER-2/neu positivity in 19 (23.2%) patients. In Pakistan, Atif et al[15] investigated the role of the immunohistochemical markers i.e. ER and PR in breast cancer and they found that HER-2/neu marker was positive in more than 45% of the patients. Among these, four patients had age 50 years or less; while 15 of them were above 50 years. Age, duration, BMI, lump size, lactation, marital status, parity and menstrual status were found as non-significant factors among the HER-2/neu positive patients with breast cancer (p value >0.05). Similar results were observed in India by Patnayak et al[16] and Goud et al[17], who found that age, duration of condition, BMI, lump size, lactation, marital status, parity and menstrual status were non-significant parameters in breast cancer patients diagnosed on the basis of HER-2/neu. However, in India, another study by Zubeda et al[18] found that the age factor was highly significant in breast cancer in HER-2/neu positive patients.

On the other hand, family history and smoking habits were quite significant in HER-2/neu positive cancer patients in our study (p value 0.001 and 0.037 respectively). Similar results were observed in studies of Goldvaser et al[19] who studied the correlation of smoking with that of the breast cancer in Israel and their results showed that only 28.2% had the smoking history whereas Laidi et al[20] (in Morocco) observed 0% relativity between HER-2/neu and breast cancer. There are precise residues of tyrosine, which activate HER-2/neu. Some non-ligands receptors for HER-2/neu have also been discovered which proceed with the dimerization of ERBB family memebers. Due to its diversity in ligands and cellular cross links, HER-2/neu offers diversity in signaling. Heterodimers of HER-2/neu show more stability and potency in signaling the combination of the receptors without HER-2/neu[21]. It is the human analogue of the neu gene, called HER-2/neu or c-erb B2 and is considered one of the poor prognostic factors.

The family history of the breast cancer was found the most significant in this study. Similar results have been observed in Israel by Goldvaser et al[19] their findings showed that almost 40% of the patients with HER-2/nue positive had family history of breast cancer. The breast cancer frequency in women at the age of 15-49 years is double in developing countries than in the developed countries. From 1980 to late 1990, the breast cancer frequency enhanced about 30% in Western countries. Such an increase was possibly was due to variations in reproductive patterns and increased screening of the disease[22].This trend was likely due to changes in reproductive patterns and increased screening. In the previous era, its incidence rates rose in many Asian and African countries[22]. In countries where mammography is available, its adherence to recommendations for regular screening is associated with reduced mortality from breast cancer. Over the past two decades, breast cancer mortality has been stable or decreasing in many countries in Europe and North America[22]. A variety of risk factors for breast cancer have been well-established by epidemiologic studies carried out to date, in addition to increasing age and female sex. These risk factors include non-modifiable factors such as race, ethnicity, and genetics, as well as modifiable exposures related to diet, physical inactivity, exogenous hormones, and certain female reproductive factors[23].

CONCLUSION

Higher frequency of HER-2/neu positivity was found in carcinoma breast patients in tertiary care hospitals of Balochistan.

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