

Relationship of Expression of HER2/neu with other Prognostic Factors in Invasive Breast Cancers

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ABSTRACT

Background: Breast Carcinoma (CA Breast) is the commonest malignancy in females other than skin and is second to lung cancer as a cause of cancer deaths worldwide. The treatment of CA Breast has dramatically changed after the advent of molecular classification of CA Breast. The hormone receptors status and HER2/neu expression in CA Breast are weak prognostic but powerful predictive factors for CA Breast. HER2/neu expression in CA Breast patients generally imparts a poor prognosis and decreased survival to the disease. The objective of this study was to correlate the expression of HER2/neu with other prognostic factors in invasive carcinoma of breast.

Patients and Methods: We carried out a comparative cross sectional study in the Pathology department of Fatima Jinnah Medical University, Lahore from January 2015 to August 2017. A total of 163 cases of biopsy proven CA Breast, which had been reported as HER2/neu 3+ on immunohistochemistry (IHC), were reviewed. Data including age of the patient, size of the tumor, histological type of tumor, grade of tumor, and status of the regional lymph nodes were retrieved from the Pathology department. SPSS version 17 was used for analysis of the data.

Results: Out of the 163 cases, 83 cases were modified radical mastectomy specimens (MRM), while 80 cases were Tru-Cut specimens, incisional biopsies and wedge biopsies. Only 1 patient in this study was male, rests were females. Age ranged from 23 to 80 years, 87.7 % patients were ≥ 35 years. Invasive carcinoma of no special type (NST) was seen in 158, 2 cases were invasive lobular carcinoma, and 3 cases were mucinous carcinoma. The tumors were graded using the Bloom Richardson grading system. None was grade I, 138 cases (84.7%) showed histological grade II, rest 25 cases (18.3%) had grade III morphology. Amongst the MRM cases, only 9 cases (11%) showed tumor size ≤ 2 cm, 74 cases (89%) showed tumor size > 2 cm. Out of the 83 MRM cases, 64 cases (77%) showed regional lymph node metastasis.

Conclusion: Our results showed that HER2/neu expression in CA Breast patients is related with increasing age, more often with invasive carcinoma (NST) as compared to other histological types, bigger tumor size, higher histological grade and presence of lymph nodes metastasis.

Keywords: HER2/neu, cancer breast, prognostic factors

INTRODUCTION

Breast cancer (CA Breast) is the commonest occurring malignancy in women around the world and the second commonest cause of mortality in females.¹ Estimated global incidence rate of breast cancer is 1.6 million per year.² It is the most frequently reported cancer in women in Pakistan, making one third of all the malignancies in females presenting to the Nuclear Medicine, Oncology and Radiotherapy Institute (NORI) in Islamabad.³

There are many factors which influence the prognosis of the disease and predict its response to a given treatment. Major prognostic factors in patients with invasive breast carcinoma include

status of lymph nodes, size of tumor, histological type, histological grade and age of the patient.⁴ Estrogen and progesterone receptors are important and useful predictive markers in CA Breast. The presence of progesterone and estrogen receptors in the tumor correlates with good response to hormonal therapy and chemotherapeutic agents and an overall better prognosis.⁴ The human epidermal growth factor receptor 2 (HER2/neu) is a receptor having intrinsic tyrosine kinase activity and is a part of the epidermal growth factor receptor (EGFR) family. ERBB2 gene present on chromosome 17q21

encodes for this protein.⁵ Amplification of HER2/neu is seen in 18–20% of breast cancers. HER2/neu expression correlates with high grade tumors, involvement of the lymph nodes, mortality and dismal prognosis. HER2/neu expression predicts response to trastuzumab [Herceptin] therapies and anthracycline based chemotherapy. HER2/neu positive cases show resistance to hormonal therapy.^{6,7}

Since HER2/neu expression in CA Breast imparts poor prognosis and decreased survival, this study was conducted to correlate HER2/neu overexpression in CA Breast with other prognostic factors including tumor size, histological grade, histological type, and status of the regional lymph nodes and age of the patient.

PATIENTS AND METHODS

This was a cross sectional comparative study carried out at the Pathology department of Fatima Jinnah Medical University, Lahore from January 2015 till August 2017. A total of 163 cases of biopsy proven CA Breast were included. The IHC was performed on formalin-fixed paraffin-embedded (FFPE) sections using primary monoclonal antibodies (DAKO). HER2/neu expression was scored using the scoring system in CAP (College of American Pathologists) protocols.⁸ Cases exhibiting intense, complete membranous (circumferential) staining in greater than 10% of invasive tumor cells were scored 3+ (strong positive). Specimens with HER2/neu 3+ on IHC were further reviewed. Data including age of the patient, the histological type and grade of the tumor, size of tumor and status of the regional lymph nodes were retrieved from the pathology department. Analysis of the data was performed using the SPSS version 17.

RESULTS

The study consisted of a total of 163 cases of biopsy proven CA Breast, which were reported as HER2/neu 3+ on IHC. Out of the 163 cases, 83 cases were modified radical mastectomy specimens (MRM), while rest 80 cases were smaller tissue biopsies including Tru-Cut, incisional and wedge biopsies.

Only 1 patient (0.6%) in this study was male, rest were females (99.4%). Age of patients ranged from 23 to 80 years, mean 38±10 years. Three age groups were made, first group (<35 years), second group (35-50 years), and third group (>50 years). Twenty patients (12.3%) fell in group 1, 99 patients

(60.7%) in group 2 and 44 patients (27%) in group 3. Invasive carcinoma of no special type was observed in 158 (97%) cases, 3 cases (1.8%) were mucinous carcinoma and 2 cases (1.2%) were invasive lobular carcinoma (ILC). The tumors were graded using the Bloom Richardson grading system.⁴ None was grade I, 138 (84.7%) cases had grade II morphology, and 25 (15.4%) cases showed grade III morphology. Amongst the MRM cases, only 9 (10.8%) specimens revealed tumor size ≤ 2cm whereas 89.2% (74 specimens) had tumor size > 2cm. Out of the 83 MRM cases, 64 cases (77.1%) showed regional lymph node metastasis, whereas 19 cases (22.9%) showed negative regional lymph nodes.

DISCUSSION

The patient population in this study had age range from 23 to 80 years with a mean of 38±10 years. More than 87% of patients with HER2/neu overexpression were ≥ 35 years. These results are similar to a study carried out at Combined Military Hospital, Rawalpindi.⁹ Ninety-seven percent HER2/neu positive cases were invasive carcinomas of no special type (NST). Aziz-un-Nisa and colleagues carried out a study at Agha Khan University Hospital, Karachi in 2006. They studied 150 cases. In their study, HER2/neu positivity was limited to majority of invasive ductal carcinoma (IDC) and a few invasive lobular carcinomas, whereas mucinous CA, metaplastic CA and adenoid cystic CA did not show HER2/neu positivity.¹⁰

This study showed that none of the HER2/neu positive case was grade I, 84.6% were grade II, and 15.3% were grade III. Increased number of Grade II tumors (84.6%) in this study is different from that of Aziz-un-Nisa.¹⁰ and colleagues and Kapiçlı.¹¹ and associates who found more patients in Grade III. Prati and group also found out that HER2/neu positivity is proportionally associated to increasing grade in IDC.¹² The size of tumor in this study varied from 0.5 to 8 cm. Eighty nine percent of the tumors were more than 2cm in size, only 11% were less than 2 cm. Kapiçlı and group observed that percentage of HER2/neu positive cases increased from 8 % to 40%, as the size increased from T1 to T4 lesion.¹¹ Aziz-un-Nisa and Friends also reported that HER2/neu positivity is more common in T2 lesions as compared to T1.¹⁰

This study showed that 64 out of 83 cases of MRM (77 %) had regional lymph node metastasis. These results are very close to the study of Aziz-

un-Nisa and associates who reported 71.3% of their HER2/neu positive cases to have lymph node metastasis.¹⁰ The results of this study were further strengthened by various other studies. An observational cross sectional study done at Armed Forces Institute of Pathology, Rawalpindi from 2004 to 2007 showed HER2/neu positivity was associated with increasing age, and large tumor size. Out of the 722 cases, showing HER2/neu positivity, invasive ductal carcinoma was the predominant subtype, and 70.8% cases showed lymph node metastasis.¹³ In another cross sectional study from Holy Family Hospital Rawalpindi cancers with HER2/neu positivity were greater in size, average size 7.9±3 cm, as compared to HER2/neu negative cancers (mean size 5±2 cm). Twenty five out of 36 (69.4%) HER2/neu positive cases showed lymph node metastasis in that study.¹⁴

Faheem and friends carried out a study at the Nuclear Medicine, Oncology and Radiotherapy Institute (NORI) in Islamabad. Out of their 478 HER2/neu positive cases, only 16 cases had tumor size ≤ 2cm. 462 cases had tumor size > 2cm. 66 cases were lymph nodes negative. 412 cases were lymph nodes positive.³ Siadati and group conducted a study on 300 cases in Iran in 2015. They observed that increased expression of HER2/neu correlated with high histologic grade and metastasis to lymph node. However, they found no correlation with age and tumor size.¹⁵ Tong and friends found out that HER2/neu expression in CA Breast patients did not correlate with the age and tumor size, but was associated with the histological type and grade, TNM stage, lymphovascular invasion and involvement of the lymph nodes.² Tiwari and colleagues observed that all 6 cases (100%) which were HER2/neu positive had invasive carcinoma (NST), 1 case was grade I (16.6%), 4 patients had grade II disease (66.8%) and 1 case was grade III (16.6%), and 5 out of 6 cases had lymph node metastasis.⁵

CONCLUSION

The results of this study showed that HER2/neu expression in carcinoma breast patients is associated with increasing age, more often with IDC as compared to other histological types, larger size of tumor, higher histological grade and presence of lymph nodes metastasis. Association of HER2/neu overexpression with higher grade and higher stage tumors explains well its poorer prognosis and decreased overall survival.

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