Original Article

HER-2 Positivity and Correlations with other Histopathologic Features in Breast Cancer Patients - Hospital Based Study

Mahmoud S Al-Ahwal
Department of Medicine, King Abdul Aziz University Hospital, Jeddah, Saudi Arabia.

Abstract

Objective: To review HER-2 status and its correlation with all other prognostic histopathological features of all Breast Cancer (BC) patients diagnosed between January 2000 and December 2004 at King Abdul Aziz University Hospital (KAUH) in the western region of Saudi Arabia.

Methods: Histopathology specimens were examined by Immunohistochemistry (IHC) and labeled as HER-2/neu positive when Hercep Test score was three plus (3+).

Results: HER-2/neu was reported only in 145 patients out of 260. Out of 145 patients, it was positive in 41 patients (28.3%), negative in 104 patients (71.7%). Correlations between HER-2/neu status and age, race and other prognostic histopathologic features revealed: No correlation with age (or ≤40 Y vs >40 Y with a p-value of 0.552), race (Saudis vs Non-Saudis with a p-value of 0.133), histopathology subtype (p=0.980), tumor size (p=0.455), number of positive lymph nodes (p=0.660), tumor grade (p=0.062), lymphovascular invasion (p=0.055) and progesterone receptor (PR) status (p=0.069) but positive correlation only with estrogen receptor status (ER) (p=0.003).

Conclusion: HER-2/neu over expression was positive in 28.3% of the tested specimens of BC which is consistent with what was reported in literature. It was found to correlate inversely with ER status. Routine testing is mandatory because of its prognostic value and impact on further management (JPMA 56:65;2006).

Introduction

Breast cancer is the leading malignancy in females and it accounted for 20.6% of all newly diagnosed female cancers (5,617) in Saudi Arabia.[1] The mean age at diagnosis is 49 years. Breast cancer is a multifactorial disease. Several hereditary and acquired genetic alterations are known to introduce genomic instability, resulting in a disbalance between cell proliferation and cell death, and ultimately in tumor growth development and progression. In the process of tumor growth and progression, a large number of hormones, growth factors, receptors, signal transduction pathways and proteases are involved, forming valuable targets for new (molecular) biological therapies.[2] Several histological features have prognostic significance, such as histopathological subtypes, tumor grade, lymphovascular invasion, ER and PR status, Proliferation markers and DNA content, peptide hormones, growth factors and their receptors, oncogenes and tumor suppressor genes.[3] HER2/neu is the human homologue of the neu gene, called HER2 or C-erbB2, shares extensive homology with EGF-R (C-erbB1). HER2/neu or its protein p185 is overexpressed in 10-35% of BC.[4] It is considered one of the poor prognostic factors in breast cancer. The overall survival was significantly better for patients without HER2/neu receptor markers compared to patients with HER2/neu overexpression (p=0.007).[5] This study presents the results of HER-2 status and its correlation with all other prognostic histopathological features of Breast Cancer (BC) patients at KAUH, Saudi Arabia.

Table 1. Characteristics of 260 breast cancer patients.

Character	Frequency	%
Sex:		
Female	257	98.9
Male	3	1.1
Age:		
≤ or 40 Y	81	31.2
> 40 Y	179	68.8
Race:		
Saudi	100	38.5
Non Saudi	160	61.5
Tumour site:		
Right	135	51.9
Left	115	44.2
Bilateral	2	0.8
Unknown	8	3.1
Histopathology:		
Infiltrating Ductal Carcinoma	229	88.1
Lobular Carcinoma	12	4.6
Medullary Carcinoma	4	1.5
Papillary Carcinoma	4	1.5
Others	11	4.3
HER2/neu status:		
Positive (IHC 3+)	41	15.8
Negative	104	40.0
Unknown	115	44.2

IHC: Immunohistochemistry.

Materials and Methods

Histopathology reports of all patients diagnosed to have BC between January 2000 and December 2004 at KAUH were reviewed. All available data regarding demographic and prognostic histopathologic features were collected and analyzed. Histopathologic features were; histopathology subtype, tumor size, number of lymph nodes, tumor grade, lymphovascular invasion, ER and PR status and HER2/neu oncogene overexpression. Histopathology specimens were examined by Immunohistochemistry (IHC) and labeled as HER-2/neu positive when Hercep Test score was three plus (3+) only and all other results were considered negative. All unknown cases were excluded from the study. Results of HER2/neu status were analyzed by using simple descriptive statistical analysis (frequency distribution, cross tabulation, chi-square and Fishers exact test) by SPSS statistical program and then correlated with age, race and all available prognostic features.

Table 2. HER2/neu Oncogene (HER-2) overexpression analysis (excluding unknown cases) and its correlation with all other Histopathological features in breast cancer patients.

Histopathological features	HER2/neu Oncogene		
	3 + ve	-ve	
	No.(%)	No.(%)	p-value
Histopathology:			
Infiltrating Ductal Caricinoma	36 (87.8)	93 (89.4)	
Lobular Carcinoma	1 (2.4)	3 (2.9)	
Medullary Carcinoma	1 (2.4)	3 (2.9)	0.980
Papillary Carcinoma	1 (2.4)	2 (2.9)	
Others	2 (4.9)	3 (2.9)	
Tumor size:			
T1 (< 2 cm)	11 (26.8)	29 (27.9)	
T2 (2-5 cm)	21 (51.2)	39 (37.5)	
T3 (5-10 cm)	4 (9.8)	11 (10.6)	0.455
T4 (> 10 cm)	0 (0)	2 (1.9)	
Unknown	5 (12.2)	23 (22.1)	
Number of Lymph nodes:			
Negative	21 (51.2)	53 (51)	
1 - 3	8 (19.5)	21 (20.2)	
4 - 9	4 (9.8)	10 (9.6)	0.660
10 or >	2 (4.9)	1 (1)	
Unknown	6 (14.6)	19 (18.3)	
Tumor grade:			
G.I	6 (14.6)	13 (12.5)	
G.II	15 (36.6)	60 (57.7)	
G.III	19 (46.3)	26 (25)	0.062
G.IV	0 (0)	0 (0)	
Unknown	1 (2.4)	5 (4.8)	
Lympho-vascular Invasion:			
Yes	12 (29.3)	13 (12.5)	
No	18 (43.9)	56 (53.8)	0.055
Unknown	11 (26.8)	35 (33.7)	
Estrogen Receptor status:			
Positive	8 (19.5)	47 (45.2)	
Negative	33 (80.5)	57 (54.8)	0.003
Unknown	0 (0)	0 (0)	
Progesterone Receptor status:			
Positive	15 (36.6)	54 (51.9)	
Negative	26 (63.4)	50 (48.1)	0.069
Unknown	0 (0)	0 (0)	

Results

Two hundred and sixty histopathology reports of BC patients were reviewed. All characteristic features (sex, age, race, tumor site, histopathology subtype and HER2/neu status) are summarized in Table 1. Almost all were females and 3 (1.1%) were males. Age distribution ranged from 20 to 87 years with a mean age of 47 years. Two thirds (61.5%) were >40 years of age while 31.2% were equal or <40 years. Correlation of HER2/neu status with age showed that HER2 was positive in 14 patients (34.1%) of the young age group (≤40 years) versus 27 patients (65.9%) of >40 years (p=0.552). HER2/neu status was found positive in 41 patients (15.8%) of the total cases reviewed and 28.3% of the tested specimens, negative in 104 patients (40%) of the total cases and 71.7% of the tested specimens. One hundred and fifteen (44.2%) were excluded from the study because they were unknown. Correlation of HER2/neu status with all other prognostic features, are summarized in Table 2. There were no significant correlation between HER2/neu status and the following features; Histopathology subtype (p=0.980), tumor size (p=0.455), number of positive lymph nodes (p=0.660), tumor grade (p=0.062), lymphovascular invasion (p=0.055) and PR status (p=0.069). The only positive significant correlation was found with ER status which is inversely correlated with HER2/neu oncogene over expression (p=0.003).

Discussion

Multiple different oncogenes have been described previously to be amplified in BC including HER2, EGFR, MYC, CCND1, and MDM2. Gene amplification results in oncogene overexpression but may also serve as an indicator of genomic instability. As such, presence of one or several gene amplifications may have prognostic significance.[6] In our study, only 41 out of 145 patients (28.3%) were positive for HER2/neu (3+) and 104 were negative (71.7%). This is similar to what was reported in literature. Regarding age, almost one third of our patients (31.2%) were equal or less than 40 years of age. Primary BC arising before age 40 are far more aggressive and likelier to metastasize and reduce patients survival than those arising in older patients, regardless of hormone receptor status.[7] Only 40% of breast tumors arising before age 45 overexpress ER, but these ER positive younger age tumors appear more proliferative and genetically unstable (higher nuclear grade, more frequent p53 abnormalities) than the more prevalent ER positive tumors arising later in life.[8] In literature, HER2 and EGFR overexpression tend to decline with age and the opposite with ER overexpression which tends to increase with age.[7] In this study, correlation of HER2 overexpression with age showed that 14 patients (34.1%) were positive in the young age group and 27 patients (65.9%) were above 40 years. Regarding race, HER2 overexpression revealed no significant difference.

Correlation of HER-2/neu with all other prognostic features revealed that it is inversely correlated with ER status (HER-2 was positive in only 19.5% of BC patients with positive ER status vs 80.5% positive in BC patients with negative ER status). Regarding HER-2/neu and PR status, HER-2 was positive in only 36.6% of BC patients with positive PR and 63.4% of patients with negative PR status which did not reach statistical significance. Eppenberger-Castori et al. reported that erbB2/HER2 overexpressing BC express much lower levels of both ER and PR protein as compared to breast tumors lacking erbB2/HER-2 overexpression.[9] The reported studies suggest that the magnitude of reductions in both ER and PR levels may in part explain the apparent clinical resistance of these tumors to selective estrogen receptor modulators like tamoxifen.[10] HER-2 gene amplification was also found to be significantly associated with high tumor grade. HER-2 amplification was found to be an independent poor prognostic factor of tumor grade, tumor size and lymph node status.[6] In our study, tumor grade III was higher in HER-2 positive patients (46.3%) than HER-2 negative ones (25%) but it did not reach statistical significance.

Assessment of HER2/neu overexpression in BC patients has an impact on prognosis and treatment modality. Trastuzumab is a recombinant humanized monoclonal antibody that targets the extracellular domain of the HER2 growth factor receptor. Addition of trastuzumab to chemotherapy for patients with metastatic BC who are HER-2 (3+) improves survival. In conclusion, HER-2/neu overexpression is positive in 28.3% of the tested specimens of BC patients at KAUH which is consistent with what was reported in literature. It was found to correlate inversely with ER status. Routine testing is mandatory either by IHC or by FISH method because of its prognostic value and impact on further management.

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