The Egyptian Journal of Hospital Medicine (October 2021) Vol. 85 (1), Page 3431-3435

Frequency and Clinical Features of Over-Expressed HER2 in Egyptian Breast Cancer Women Patients

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ABSTRACT

Background: Overexpression of human epidermal receptor protein-2 (HER2) is correlated to a poor prognosis in breast cancer (BC) patients who respond well to anti-HER2 therapy.

Objective: Therapeutic procedures for treating HER2-positive breast cancer (BC) patient address HER2 protein. According to reports, the expression of HER2 oncogene and its relationship to clinicopathological factors in BC patients is yet unknown.

Patients and methods: The present study involved 50 patients who were diagnosed histologically with invasive primary breast carcinoma. The PR, ER, and HER2 immunohistochemistry testing was conducted on the formalin fixed paraffin-embedded blocks of patient's breast tissue. The relationship between HER2 status and clinicopathologic diagnostic characteristics was investigated using analysis of variance and the Chi-Square Test.

Results: Invasive lobular carcinoma (ILC) was the most common histological type, accounting for 86% of cases. The highest percentage of patients was grade II (66.7 %), tumour size (2-5) cm accounted for 73.3 % of cases, and lymph node metastases were present in 84 %. The majority of the individuals were diagnosed at stage II (66.7 %). The majority of patients had moderate Nottingham prognosis index (66.7 %). 60 % and 33.3 % of women tested positive for the estrogen and progesterone receptors, respectively. 53.3 % of the women tested positive for HER2. Histological type ($p = 0.049$*) and histopathology grade ($p = 0.002$**) were both significantly associated with HER2 overexpression.

Conclusion: HER2 positive expression could produce further evidence about the inadequate diagnosis of BC and could be utilized for pre-choice of BC patients with HER2-overexpressing who demonstrated resistance to hormonal treatment.

Keywords: Clinical features, Over-expressed HER2, Breast cancer.

INTRODUCTION

Breast cancer (BC) is the most often diagnosed cancer in Egyptian women and the second leading cause of death. BC incidence rates are increasing in virtually every area. In Egypt, BC ranks first among female malignancies, accounting for 22,038 (16.4 percent) of all cancers and 9,148 (10.3%) of all cancer-related fatalities [(1)]. BC incidence had grown by more than 23% in the last six years (from 1.7 million new patients in 2012 to 2.1 million in 2018) [(2)]. Despite high survival rates in many wealthy countries, Egypt's 5-years survival rate has remained low, ranging from 28 % to 68%, according to many studies [(3)].

Despite the fact that the illness is prevalent all over the world, it has a wide range of incidence, mortality, and survival rates, which might be due to a number of variables such as population structure, lifestyle, genetic factors, and environment [(4)].

Only 2% of surveyed Egyptian women had any form of clinical screening (mammogram, ultrasound, or clinical breast examination [CBE]) and only 6% conducted breast self-examination, according to a study by the Egyptian Ministry of Health [(5)].

BC is a heterogeneous disease that is caused by a variety of variables [(6)]. We urgently need to strengthen BC control procedures by raising knowledge about the need of early cancer detection, screening, and proper treatment. BC has a wide range of clinical, pathological, and molecular characteristics, all of which have various prognostic and therapeutic implications. The status of progesterone receptors (PR), estrogen receptors (ER), and human epidermal receptor protein-2 (HER2) is now routinely assessed to guide BC management and prognosis, as these hormone receptors have been demonstrated to have a significant impact on the clinical outcomes [(7)].

HER2 is a transmembrane tyrosine kinase receptor protein that is encoded by the HER2/neu proto-oncogene on chromosome 17q. It regulates cell proliferation, differentiation, and survival, as well as death. Overexpression can result in a 40-100-fold increase in protein expression [(8)]. Abnormalities of HER-2 have been found in roughly 15-20% of BC [(9)]. The discovery of new anti-HER2 targeted treatments for management of BC has resulted from a better knowledge of the underlying mechanisms of HER2 overexpression in the occurrence of the BC [(10)]. Anti-HER2 targeted therapy have a significant response rate in HER2 positive patients. Thus, the overexpression or amplification of HER2 has prognostic and therapeutic significance estimating around 50-75% of response rate to hormonal therapy. The immunohistochemical evaluation of HER2 in combination with ER and PR is a common clinical

Received: 15 /6 /2021
Accepted: 11 /8 /2021

procedure that has recently been integrated into the therapy of BC patients in Egypt, where data on HER2 is lacking [11, 12].

The goal of this study was to determine the HER2 status and its relationship to clinicopathologic variables in women's breast carcinomas to optimize therapy decision in patients with newly diagnosed BC.

PATIENTS AND METHODS

This study was conducted on 50 women their tumours were biopsied and diagnosed as BC. They were recorded at the National Cancer Institute (NCI) in Egypt from January 2017 to December 2017. Only cases with clear and detailed documentation were considered. The UICC TNM Classification System of BC [13] and the American Joint Committee on Cancer Staging were used to define the composite stage of BC [14].

Patients' demographic and clinicopathological data, such as age, family history, tumour size, lymph nodal status, histological grade, clinical stage, and type of tumour, were obtained from medical records using a checklist.

Immunohistochemistry (IHC) examination:

The immunohistochemistry analysis was carried out on 5um breast tissue sections that were normally stained with hematoxylin and eosin. The Novocastra Epitope Retrieval Solution (Leica Biosystems Newcastle Ltd.) was used to perform immunohistochemistry (IHC) on a Leica® BONDTM staining platform according to the kit instructions. An expert pathologist analysed and graded (Estrogen and Progesterone) receptor (ER, PR) and HER2 expression. The pathologist used the HER2 scoring criteria for BC, which were as follows: 0: no or partial membranous staining in fewer than 10% of tumour cells, 1+: partial membranous staining in more than 10% of tumour cells, 2+: complete but weak to moderate membranous staining in more than 10% of tumour cells, 3+: complete and strongly positive membranous staining in more than 10% of tumour cells. Cells with HER2 negative expression were given ratings of 0, while cases with HER2 overexpression were given values of 1.

Ethical Approval:

All procedures performed in the study involving human participants were in accordance with the Ethical Standards of the Ethics Committee of National Cancer Institute, Cairo University, Egypt (No. 201716064.4). This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The collected data were coded, processed and analyzed using SPSS software packages for Windows, versions 25.0 [SPSS, Inc., Chicago, USA]. The continuous variables were performed using descriptive statistics (e.g., median, interquartile range (IQR), percentage, and frequency). For analysis of distribution, Mann Whitney U test was used to assess the association between the HER2 status and the patients 'age. Comparison of numerical variables was done by using Chi-square test with likelihood ratio [LR], or Fischer's exact test to evaluate the significance of association between the variables. P-values equal or below 0.05 were considered significant.

RESULTS

50 women with invasive primary BC were diagnosed in this study, with a median (IQR) age of 48.50 years (extremes: 26–64 years). Premenopausal women were the most likely to develop BC (60 %). 86 % of the patients had invasive lobular carcinoma (ILC). 66.7 % of carcinomas were grade II, 26.7 % were grade III, and 6.7 % were grade I. Overexpression of HER2 was found in 53.3 % of patients. The frequency of HER2 and clinicopathologic characteristics in the study population were shown in table (1).

Association between status of HER2 and clinicopathologic variables:

HER2 status was not significantly associated with age of patients ($p = 0.448$), clinical stage ($p = 0.561$), menopausal status ($p = 0.654$), family history ($p = 0.526$), tumor size ($p = 0.745$), lymph node metastases ($p = 0.743$), metastases (0.526), ER ($p = 0.765$), and PR ($p = 0.604$). However, the HER2 positivity was significantly related to histological type ($p = 0.049$) and strongly related to histopathological grade ($p = 0.002$). The relationship of HER2 expression with clinicopathologic characteristics was shown in table (2).

Table (1): Clinicopathologic features of BC patients (N = 50).

Parameter	Number of patients N (%)
Age (years)	
Median (IQR)	48.50 (16)
Extremes	26 - 64
Histologic type	
IDC	5 (10)
ILC	43 (86)
Other Type	2 (4)
Histopathology grade	
I	3 (6.7)
II	33 (66.7)
III	13 (26.7)
Clinical Stage	
Stage 1	5 (10)
Stage 2	33 (66.7)
Stage 3	12 (23.3)
Menopausal status	30 (60)
Premenopause	20 (40)
Postmenopause	
Lactation History	23 (46.7)
Yes	27 (53.3)
No	
Family History	
Positive	38 (76.7)
Negative	12 (23.3)
Tumor size	
T1	8 (16.7)
T2	37 (73.3)
T3	5 (10)
Lymph-Node Status	42 (84)
Positive	8 (17)
Negative	
Metastases	
M0	38 (76.7)
M1	12 (23.3)
ER	
Positive	20 (60)
Negative	30 (40)
PR	
Positive	17 (33.3)
Negative	33 (66.7)
HER-2	
Positive	23 (53.3)
Negative	27 (46.7)
Molecular subtype	7 (13.3)
ER+PR+Her2+	3 (6)
ER+PR-Her2+	17 (33.3)
ER-PR-Her2-	10 (20)
ER+PR+Her2-	13 (26.7)
ER-PR-Her2+	

Table (2): Association of HER2 status with clinicopathologic variables in BC patients (N = 50).

Variables	HER2+ N = 23 (%)	HER2- N = 27 (%)	p
Median age (IQR)	45.50 (19)	51 (10)	0.448
Histologic type			
IDC	—	5 (18.6)	
ILC	23 (100)	20 (74)	
Other Type	—	2 (7.4)	0.049*
Histopathology grade			
I	—	2 (7.4)	
II	3 (14.3)	18 (66.6)	
III	20(85.7)	7 (26)	0.002**
Clinical Stage			
Stage 1	3 (13)	2 (7.4)	
Stage 2	13 (57)	20 (74)	
Stage 3	7 (30)	5 (18.6)	0.561
Menopausal status	15 (65)	15 (55.6)	
Premenopause	8 (35)	12 (44.4)	0.654
Postmenopause			
Lactation History	13 (57)	10 (37)	
Yes	10 (43)	17 (63)	0.281
No			
Family History			
Yes	7 (30.4)	5 (18.5)	0.526
No	16 (69.6)	22 (81.5)	
Tumor size			
T1	4 (17.4)	5 (18.5)	0.745
T2	16 (69.6)	20 (74.5)	
T3	3(13)	2 (7.4)	
Lymph-Node Metastases	20 (87)	22 (81.5)	
Positive	3 (13)	5 (18.5)	0.743
Negative			
Metastases			
M0	16 (69.6)	22 (81.5)	0.526
M1	7 (30.4)	5 (18.5)	
ER			
Positive	10 (43.5)	10 (37)	0.765
Negative	13 (56.5)	17 (63)	
PR			
Positive	7 (30.4)	10 (37)	0.604
Negative	16 (69.6)	17 (63)	

DISCUSSION

The IHC assessment of HER2, PR, and ER is already a significant marker and important for the proper clinical management of BC patients in low-resource countries, such as Egypt. BC patients with HER2 overexpression have a higher chance of recurrence, have a shorter overall survival time, and have a higher fatality rate [15]. The frequency and outcome of HER2-overexpressed BC should be studied in order to improve therapeutic approaches and individualise targeted medicines in distinct tumour subgroups with newly diagnosed BCs. Anti-HER2 targeted therapy has significantly improved the prognosis of HER2 positive patients [16].

The goal of this study was to verify the HER2 status of Egyptian women with BC and to see if there was a relationship between HER2 expression and clinicopathological characteristics. HER2 is overexpressed in 53.3 % of newly diagnosed BCs in Egyptian women, according to our findings. This finding is similar to those discovered in a more recent Saudi Arabian study, which found a higher estimate of HER2 overexpression, with 29.9% positive among Saudi women with newly diagnosed BC between 2007 and 2013 [17]. BC is detected in younger age groups (45.50 years), in more advanced stages, and with aggressive behavior, according to the findings of our study.

On the other hand, there was a study found that the diversity of HER2 overexpression was due to the loss of HER2 antigen during the under or extended fixation of breast specimens, as well as the different antibodies utilized [18]. They found that fixation had no effect on the DNA of HER2, which was examined by FISH regardless of the storage period of paraffin-embedded blocks of breast tissue, implying that FISH is more accurate in identifying HER2 overexpression than IHC [19]. The predictive and prognostic value of HER2 with other prognostic factors, including age, clinical stage, menopausal status, histologic type, histological grade, family history, tumor size, lymph node metastases, lactation history, PR, and ER are important for efficient patient treatment. The median age and the menopausal status of our study population were independent from HER2 status, although premenopausal women overexpressed more HER2 than postmenopausal women. Similar results were observed by several authors [20, 21]. The presence of HER2 was not associated with the presence of ER or PR. Our findings are consistent with those of other studies [22, 23]. However, they differ from those of other studies [15, 24, 25], that demonstrated an inverse relationship between HER2 overexpression and PR and ER expression levels. It's believed that the lack of a correlation between HER2 status and hormonal receptor is due to high-rate ER/PR negativity caused by pre-analytical variables such as fixation insufficiency [26].

This research found that HER2 overexpression was significantly correlated to the Nottingham grade ($p = 0.002$). The presence of HER2, the high tumour grade, and the young age of our study cohort are all unfavourable clinicopathologic characteristics, as evidenced by the literature [13, 27, 28]. These patients, on the other hand, should get anti-HER2 targeted therapy plus chemotherapy, which will almost certainly improve their chances of survival that is indicating that HER2+ patients with BC have a more severe pattern. This correlation has been shown in several research [20, 21, 25, 28].

In reality, the HER2 oncogenic activity is observed in a variety of processes that regulate breast epithelial development. Overexpression of HER2 causes uncontrolled cell proliferation, which leads to BCs. HER2 positive is related to a greater mitotic index, which is one of the components of the Nottingham grade that indicates the severity of BC [29, 30]. The overexpression of HER2, the high tumor grade, and the young age of our study population were unfavourable clinicopathologic factors, which are in accordance with the literature data of some studies [31, 32]. In contrast, these patients should receive anti-HER2 targeted therapy and chemotherapy, which likely improve their survival.

Although there was no statistically significant relationship between HER2 status and tumour size ($p = 0.745$), our result is consistent with past research, which found that over-expression of HER2 was slightly more common in patients with smaller tumours (less than 5 cm) [33, 34]. Moreover, the present study found a significant correlation between histologic type and HER2 status ($p = 0.049$), which is in accordance with other result [35].

CONCLUSION

The presence of HER2 in BC specimens is a key factor in diagnosis, prognosis, and clinical management. The association of HER2 positivity with relatively high-grade BC may indicate the subtype's aggressiveness in young women. The current study assists in the selection of patients who may benefit from chemotherapy or targeted therapy for better survival rate. These findings support the use of HER2 expression as a predictive and prognostic marker in cancer patients.

Authors Contribution: All the authors contributed equally to this work.
Conflicts of interest/Competing interests: The authors declare no conflict of interest.
Financial support and sponsorship: Nil.

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