

Original Research Article

Human epidermal growth factor receptor 2/neu and the clinico-pathological profile in breast cancer: an observational study at a tertiary care hospital in Central India

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ABSTRACT

Background: Breast cancer is the most commonly occurring cancer in women and the second most common cancer overall. Owing to a unique pattern of presentation in terms of clinical and biological features, finding their mutual association may be important and may help predict prognosis. HER2 (human epidermal growth factor receptor 2)/neu is one such important immunohistochemical factor that is considered to be more prevalent amongst Indians and therefore makes up for an emerging area for studies. The study aimed to assess the patients of breast carcinoma in terms of their HER2/neu statuses and find out their association with clinical parameters.

Methods: This was a prospective comparative study conducted in department of surgery, Hamidia hospital, Bhopal, India, with a total duration of 1 year between November 2018 to September 2019 including a total of 98 consecutive in house breast carcinoma patients.

Results: A total of 98 breast cancer patients were tested for HER-2/neu gene presence. Of these 25 (25.5%) samples tested positive and 73 (7.48%) tested negative. A comparison of the two groups revealed that none of the clinic-pathological factors tested were found to have a statistically significant association with the HER2/neu status.

Conclusions: It appeared that there is no defining factor in terms of clinic-pathological presentation that helps to separate significantly HER-2/neu positive with HER-2/neu negative cases with breast cancer. Still, immunohistochemical marker analysis should be an integral part of the overall work up of the breast cancer patients because of its both prognostic and therapeutic application and significance.

Keywords: Indian women, Ca breast, HER2/neu, Immunohistochemical markers

INTRODUCTION

With an estimated 2.3 million new cases, female breast cancer has now become the most commonly diagnosed cancer and the most common cancer in the women in both developed and the less developed world as per the GLOBOCAN 2020.¹ The burden of breast cancer on Indian healthcare is not disregardable. With having taken over cancer cervix in terms of being the most common cancer, breast cancer now appears as an emerging challenge to the growing Indian population.

The ever old concept of breast cancer being a single disease is disregarded as it is now evident to be a multitude of maladies. There exists some racial basis for such varied presentation and outcome for breast cancer but the cause is not entirely explained. It has, however been shown in many studies that the difference in molecular markers may explain the reason behind it, besides predicting the prognosis.

Essentially, breast cancer is categorized into 3 major subtypes based on the presence or absence of molecular

markers for estrogen or progesterone receptors and human epidermal growth factor 2 (ERBB2; formerly HER2): hormone receptor positive/ERBB2 negative (most common pattern), ERBB2 positive and triple-negative (tumors lacking all 3 standard molecular markers).

HER-2/neu (ERBB2) is a proto-oncogene from the superfamily of epidermal growth factor receptor. Its over expression is linked to malignant transformation of normal breast epithelium. Study of HER2/neu is important since it helps plan the management better, besides being a prognostic marker. Trastuzumab, a humanized monoclonal antibody against the extracellular domain of HER2, has been found to be effective in treatment of the patients with gene amplification of HER-2/neu.² Alterations in the proto-oncogene HER-2/neu have been extensively studied in the western population, however, there remains a paucity of data on prognostic significance of HER-2/neu in Indian breast cancer.

Such rapid and alarming rates and a varied presentation in terms of clinical, pathological and molecular make up and the possible treatment outcomes, besides limited publications being in the area, necessitate a thorough understanding and research into the subject. This study, HER-2/neu and the clinico-pathological profile in breast cancer: an observational study at a tertiary care hospital in Central India was therefore, taken up at Gandhi medical college, Hamidia hospital, aiming to understand the biological aspects of the disease, in order to treat the patients suffering from breast carcinoma better. The objectives of the study were to know the incidence of HER-2/neu expression in the patients of Central India and to further correlate its expression with various clinico-pathological characteristics at presentation like tumor size, lymph node status, clinical stage and the histological grade.

METHODS

The present study was a prospective study, being conducted in the department of surgery, Gandhi medical college and Hamidia hospital, Bhopal, Madhya Pradesh, a tertiary referral centre in Central India. After getting approval from the ethical committee, the study was conducted for a period of 1 year from November 2018 to October 2019. The study included all the consecutive 98 patients of breast carcinoma taking admission in our unit within the aforementioned timeframe. Study tools were the case records. After obtaining proper consent from the patients, the data was being recorded and analysed on parameters like tumor size, lymph node status, clinical stage, pathological grade of the tumor and HER2/neu profile. HER-2/neu expression was examined by immunohistochemical method and the patients were categorized into groups for an ease of comparison based on their biomarker profile, that was, HER2/neu positive

and HER2/neu negative. The statistical analysis of the data was performed using SPSS version 25.0. The demographic characteristics had been summarized using simple descriptive statistics. The categorical data was analysed using Chi square or Fisher's exact test. For quantitative data comparison between two groups, Mann Whitney U test was used. The results on quantitative parameters were computed and their mean and standard deviation obtained. As the level of significance was fixed at 0.05, a p=0.05 was deemed statistically significant.

Inclusion criteria

All in house female patients of carcinoma breast taking admission within the specified time frame were included in the study.

Exclusion criteria

All male patients diagnosed with carcinoma breast, recurrent carcinoma breast, patients lost to follow up were excluded.

RESULTS

Out of all the 98 patients that matched the inclusion criteria and were included in the study, 25 (25.5%) were found to be HER2/neu positive and 73 (74.8%) were HER2/neu negative (Figure 1).

Stratification of tumor size at the time of presentation was performed in 3 groups, group 1 (tumor size ≤ 2 cm), group 2 (2-5 cm) and group 3 (≥ 5 cm) in diameter. Most common size among both HER2/neu+ and HER2/neu- group was found to be ≥ 5 cm (group 3: 17 patients, 68% in HER2/neu+ group and 8 patients, 65.75% in HER2/neu- group). There was no presentation with size < 2 cm (group 2) from HER2/neu group.

For lymph node status, most common presentation was N1 for both the groups (10 patients, 40% in HER2/neu+ group and 23 patients, 31.5% in HER2/neu- group).

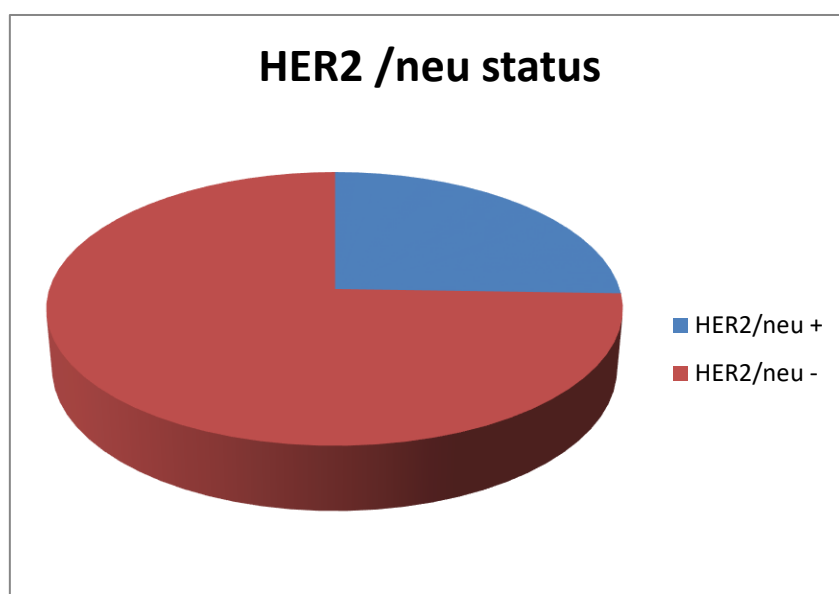
In terms of clinical staging, both stage II and III were found to be most frequent (18 patients, 32% in HER2/neu+ group and 33 patients, 45% in HER2/neu- group for stage II versus 9 patients, 36% in HER2/neu+ group and 27 patients, 36.98% in HER2/neu- group for stage III).

In terms of histological grading, majority of the patients in both the groups had grade II or grade III presentation at the time of diagnosis, while there was not a single case of grade I presentation from HER2/neu positive group.

The end results of all these clinical and pathological parameters and their association with HER2/neu was found to be statistically insignificant (Table 1).

Table 1: Association between the expression of HER2/neu with clinico-pathological parameters.

Parameters	HER2 neu -ve (n=73)		HER2 neu +ve (n=25)		P value
	No.	%	No.	%	
Tumor size (in mm)					
Upto 2	1	100.0	0	0.0	0.83
2-4.9	24	75.0	8	25.0	
≥5	48	73.8	17	26.2	
Lymph node					
N0	14	70.0	6	30.0	0.64
N1	23	69.7	10	30.3	
N2	14	66.7	7	33.3	
N3	12	85.7	2	14.3	
Clinical stage					
I	4	66.7	2	33.3	0.45
II	33	80.5	8	19.5	
III	27	75.0	9	25.0	
IV	9	60.0	6	40.0	
Pathological grade					
I	8	100.0	0	0.0	0.21
II	42	71.2	17	28.8	
III	23	74.2	8	25.8	

**Figure 1: HER2/neu status.**

DISCUSSION

Breast cancer in young women is perilous and a serious healthcare burden. HER2 status determination was important as several studies indicated that HER2/neu over expression was an important indicator for low response to chemotherapy with CMF and tamoxifen and overall decreased survival.^{2,3} Over expression of the HER-2/neu oncogene has been reported in 17% to 27% of all cases of breast cancer in the western population.^{4,6} Comparing the literature from across Asia, a study from

Malaysia showed that 31.5% of breast cancers were HER2-neu positive, while in another study from Pakistan, 39% samples tested HER2 positive.^{7,8} A study from Indore, Central India found 40.2% of tumors to be HER2/neu positive.⁹ However, in our study, HER2/neu positivity was present in 27.10% of the cases. The observation was close to a study conducted in New York which reported a HER2/neu over expression of 26.89%.⁵

In terms of tumor size at the time of presentation, in our study, from group 1 tumors, none of the cases were

HER2 positive, of the group 2 tumors 25% and of the group 3 tumors, 26.2% were HER2 positive. Contrastingly, in a study conducted by Azizun-Nisa et al in group 1 tumors, 44.44% were HER2 positive, of the group 2 tumors 34.18% were HER2 positive and of the group 3 tumors, 39.62% were HER2 positive.¹⁰ This could arise from the fact that in a resource poor area of India, particularly our institute where majority of the patients were from lower socioeconomic strata and uneducated background, presentation at much advanced state was commonly observed.

In another Asian study conducted by Naqvi et al in Karachi on 72 cases of invasive IDC, HER-2/neu over expression was seen in 31% of the cases with a significant relationship ($p < 0.05$) between HER2/neu over expression, lymph node status and tumour size.¹¹

However, in our study no significant association between HER2/neu over expression and tumor size, lymph node status and clinical stage could be derived.

In our study, no cases of grade I carcinoma were found to have HER2 positivity, while 17 (28.8%) cases of grade II carcinoma and 8 (25.8%) of grade III carcinoma were found to be HER2 positive. However, in a study conducted by Azizun-Nisha et al HER-2 was positive in 1 (10%) case of grade I carcinoma, 31 (37.35%) cases of the grade II carcinoma and 24 (42.11%) cases of grade III carcinoma.¹⁰

Our study, however, had some limitations, most important of which remained a small sample size which could not represent the entire population and advanced stage of presentation due to lack medical infrastructure and basic awareness amongst women in peripheral areas of India, which probably can account for no significant association of clinical presentation with the receptor status.

CONCLUSION

Breast cancer is a complex disease, with the patients facing challenges throughout the course of disease. In our study, it was concluded that there is no absolute feature in terms of clinico-pathological presentation which could help delineate HER2/neu positive from HER2/neu negative cases with breast cancer. In a resource limited area of the country such as Central India, most women tend to present with advanced stage at the time of presentation. Since early presentation is the cornerstone to effective management and better outcome of the disease, efforts must be taken to educate women about the issue by providing better deliver of the healthcare to the remote areas. Only then, such a study could be effectively conducted and the various aspects of this disease could be effectually unfolded. Ergo, assessment of immunohistochemical markers for the management of breast cancer patients is still strongly advocated and

should not be missed in order to guide the treatment and to provide best therapeutic options.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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