ORIGINAL ARTICLE

Discordance of biomarker status in recurrent breast cancer

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Abstract

Objective: To study the pattern of percentage change of biomarker status in recurrent breast cancer and to compare it with its primary biomarker.

Methods: Patients with recurrent breast disease presenting to the Breast Unit of Liaquat National Hospital and Medical College, Karachi, between January 2004 and January 2011 were included in this study. Outcome of interest was any change in the biomarker status of oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 (HER2/neu) with respect to their respective primary status. SPSS 18 was used for statistical analysis.

Results: The study had a total of 58 female patients with biopsy-proven recurrent breast carcinoma with a mean age of 46±11.3 years. Time to recurrence varied between 2 to 3 years with a mean of 2.3±1.9 years. Invasive ductal carcinoma was the most prevalent recurrent tumour (50/58 patients: 86%). There was a change of 25.9% in oestrogen receptor status (p<0.01); change of 36.2% in progesterone receptor status (p=0.036); and 22.4% change in Her2/neu status (p=<0.01). Of the 42 (72.27%) patients who were triple negative at presentation, 30 (71.4%) remained triple negative (p=0 .02). Six of the 16 (37.5%) patients became triple negative upon recurrence (p<0.01).

Conclusions: The study demonstrated that there was indeed a change in biomarker status in patients presenting with recurrent breast carcinoma. There is need for clinicians to check biomarker status in recurrent breast cancer patients as it may assist a shift in the management plan

Keywords: Changes in receptors, Recurrent breast cancer, ER, PR, Her2/neu. (JPMA 64: 163; 2014)

Introduction

Breast cancer is a heterogeneous disease and its management is based on the diseases' status and its tumour biology. In each patient, treatment is tailored according to the factors to drug response mainly Hormonal and human epidermal growth factor receptor 2 (Her2/neu) status.

Conventionally, the trend has been to continue with hormonal therapy for years if patient's primary tumour is hormone-positive, and when a tumour recurs, it is assumed that no change in biological features would occur in the recurrent disease compared to the primary one and the behaviour of the recurrent tumour is the same as that of the primary, so treatment could be directed as per the primary pathology. This has been questioned recently.[1]

Recent studies comparing samples from primary tumour and recurrent disease have demonstrated change in Oestrogen receptor (ER), progesterone receptor (PR) and Her2/neu status.[2] Recurrent disease is not only a challenge to treat after the exhaustion of first-line management but it is also important to be sure that patient responds to the treatment given after the recurrence.[3]

The dearth of local studies from Pakistan on the topic was the impetus behind the planning of the current study since not only we would be able to give better treatment to the patients, but also help increase survival. Hence, the aim of this study was to quantify the percentage of tumour that changes receptor status for ER, PR and Her2/neu between original and recurrent disease.

Patients and Methods

The retrospective cohort study was conducted From January 2002 to January 2011 at the Department of General and Breast Surgery, Liaquat National Hospital and Medical College, Karachi.

For the purpose of the study recurrence included both loco-regional and systemic recurrences. All female patients having biopsy-proven recurrent breast carcinoma were included, while patients in whom biopsy of the recurrent carcinoma was not possible were excluded.

All patients who underwent surgery for breast carcinoma during the study period and developed recurrence were studied for change in biomarker status. Data was retrieved and reviewed from patient's records and biomarker status of patients having recurrent disease were studied and compared with initial status. All data

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was entered into a specified performa on Excel Spread Sheet and the same was used for statistical analysis.

Formal approval from ethical review committee was also taken . Since this was a retrospective study and involved review of data alone from the archives, so obtaining formal consent for the same was not valid. However, all patients had signed the standard consent as per the hospital's requirements, which clearly states permission to the use the data for any research as long as patient's confidentiality was maintained.

Immunohistochemistry (IHC) method was used to assess the ER, PR and Her2/neu status. Initial testing was done on Dako Envision System. Criteria for ER/PR positivity was ascertained using H-scoring: 1.< 50 receptor count was taken as negative; 2. >50 receptor count was considered as positive.

Her2/neu testing was also done using Dako Envision system for analysing monoclonal antibodies to c-erb B2. Criteria for positivity was ascertained by: 2. Score of 0 and +1 was taken as negative; 2+ were further tested for Fluorescence In Situ Hybridization (FISH); and 3. 3+ were taken as positive for Her2/neu receptor.

All slides were reviewed by consultant pathologist(s) with the same academic/credentials, hence eliminating interpretation bias. The pathologists were not aware of the status of receptor in the primary carcinoma. The hospital's histopathology department is ISO 9001 certified for quality management and accredited by the College of American Pathologists (CAP)

All data was entered and analysed SPSS version 18.0. Descriptive statistics were used to summarise categorical variables and reported as frequencies and percentages, and proportion difference of pre- and post-recurrence was observed by McNemar test. P<0.05 was considered significant.

Results

During the study period, 540 patients underwent surgery for breast carcinoma. Of them 58 (10.7%) female patients with biopsy-proven recurrent breast carcinoma were included in the study. The mean age was 46±11.3 years (range: 28-64 years). Mean time to recurrence was 2.3±1.9 years. Invasive Ductal carcinoma was the most prevalent recurrent tumour among (50/58 patients: 86%). There was initially 26 (44.8%) ER+ve patients, 27 (46.6%) PR+ve and 28(48.3%) HER2/neu+ve patients. Analysis of the recurrent breast cancer demonstrated that the ER staining was positive in 30 (51.7%), PR in 19 (32.7%), and HER2 in 45 subjects. Change in ER occurred in 15 (25.9%) patients, 21 (36.2%) in PR and 13 (22.4%) in HER2/neu (Table-1).

Table-1: Change in Hormonal Receptor Status.

Parametres	EREr	PRPr	HER2/neu
Initial Status	26	27	28
Percentage	44.8%	46.6%	48.3%
Recurrence	30	17	37
Percentage	51.7%	29.3%	63.8%
Change in Status	15*	21**	13***
Percentage	25.9%	36.2%	22.4%

*Changes from ER positive to negative : 4 & from negative to positive: 6.
**Changes in PR Positive to negative : 16 & from Negative to Positive: 5.
***Changes in Her 2 neu Negative to Positive: 6 & Negative to Positive: 5.
ER: Oestrogen receptor. PR: Progesterone receptor. HER2/new: Human epidermal growth factor receptor 2.

Table-2: Comparison with different studies.

Study	ER Status	PR Status	HER2/neu
Our Study	25%	36%	22.4%
BRITS[1]	10%	24.2%	2.9%
Kuukasjarvi et-al[2]	36%		
Price K et-al[3]	33%		
Sari et-al[7]	36%	54.2%	14.7%
Amir et-al[1]	56%	44%	
Simmons et-al[1]	64%	36%	8%

ER: Oestrogen receptor. PR: Progesterone receptor. HER2/new: Human epidermal growth factor receptor 2.

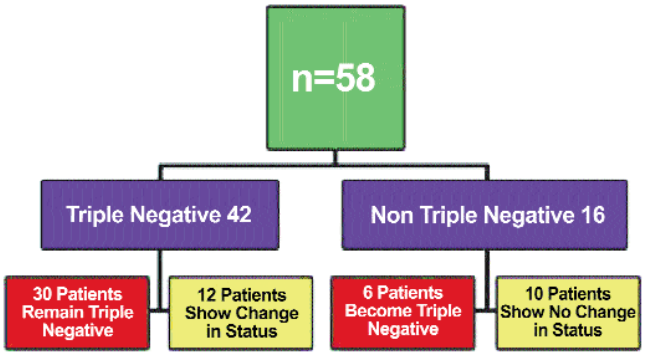

Figure: Change in Triple Negative Status in Recurrence Breast Cancer.

The change in ER (p<0.01), PR (p=0.04) and Her2/neu (p<0.01) status was statistically significant. Of the 42 (72.2%) patients who were triple negative at presentation, 30 (71.4%) remained triple negative (p=0.02), while 6 of the 16 (37.5%) patients became triple negative upon recurrence (p<0.01) (Figure).

The mean time to first recurrence of breast cancer following completion of primary therapy was nearly 2.3±1.9 years. All of the 58 patients had a modified radical

mastectomy done at the time of diagnosis.

Discussion

Change in receptor status in recurrent breast carcinoma has emerged as a relatively new and recent discovery, which has prompted a paradigm shift in the management of the disease. This concept has led to reconsideration of the old school thought that there is no change in hormonal receptors and that recurrence should be treated with the same therapy. It has been observed that changes in hormonal receptor, especially downgrading, leads to poor response to hormonal therapy.[2]

It is important to observe the status of biomarkers due to increased use of targeted therapies. Molecular alterations may be associated with receptor changes as endocrine and growth signalling pathways are involved in invasion and metastasis, accounting for discordance in the receptor status from primary to recurrence or metastasis.

This change in status can either be a result of tumour biology, error or inconsistency in measurement of the hormonal receptors.[4] There is a debate whether these changes are as a result of genetic drift, colonel expression, intra-tumoural heterogeneity, systemic effects of chemotherapy or hormonal therapy[5,6] is still not known. However, providing targeted therapy is beneficial.

In our study population, we saw a relatively young age of recurrence (46 years), while it is much higher in the Western world (63 years).[7] On the topic of interest, there has been so far not many studies and among them the largest studies conducted to date (BRITS) had 205 patients. BRITS demonstrated that change in biomarker status occurs in case of recurrent breast carcinoma and depicted the change in ER and PR to be statistically significant, which are comparable to the results in our study population (Table-2).

Pusztai L et al[8] also recommended establishing tissue diagnosis for the type of tumour pathology as it can influence the outcome and prevent harm to the patient.

The limitation of the current study is that any switch in treatment plan based upon the findings of change of receptor status which would affect the overall survival was not studied. Besides, it was a retrospective study and had all the limitations that studies of suchy a nature carry. Also, it is well established that shorter the time of relapse, younger the patient, initial negative status, and recurrence while on treatment or shortly after treatment are important denominators of change of receptor status, which was not evaluated by the current study.

Conclusions

The study demonstrated that there was indeed a change in biomarker status of patients presenting with recurrent breast carcinoma. There is a need for clinicians to check biomarker status of recurrent breast cancer patients as this may assist shift in the management plan.

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