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Role of rebiopsy in metastatic breast cancer at progression

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ABSTRACT

Alteration of biomarkers is well-documented in breast cancer at locoregional recurrence or metastasis attributed to tumor heterogeneity and change in biology. There is a lack of literature on alteration of biomarkers in metastatic breast cancer (MBC) at progression. We included 32 patients of upfront MBC. Estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2/neu documented at baseline and at progression. Median age was 46 (range 26-72) years. Estrogen receptor altered in 6 (18.75%) patients [4 (12.5%) positive to negative and 2 (6.25%) from negative to positive], progesterone receptor altered in 8 (25.3%) patients (6 [18.75%] positive to negative and 2 [6.25%] negative to positive) and human epidermal growth factor receptor 2/neu altered in 5 (15.6%) patients (all were positive to negative). Therapy was changed as per new receptor status. Documentation of change in receptor status may be justified to determine further therapy and prognosis in MBC at progression.

ARTICLE INFO

Keywords: Metastatic breast cancer progression; Rebiopsy; Receptor change

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Introduction

Breast cancer is a heterogeneous disease. Around 5%-10% patients present with upfront metastasis and 20%-30% patients develop metastasis during as reported in the western literature.[1,2] Incidence of metastatic breast cancer (MBC) has been reported around 5%-25% from various centers in India.[3,4] MBC carries a poor prognosis, 5-year and 10-year overall survival have been reported 22% and 5% from the Indian subcontinent.[3]

Various previous studies have documented changes in biomarkers at the time of metastasis in early and locally advanced breast cancer. But in this study, we have documented changes in receptor status in MBC patient at the time of progression. Data from developing countries is lacking and it may help to decide further therapy and channelize government resources in a better way where the burden of disease is mainly catered by tertiary care centers.

Materials and methods

We retrospectively reviewed the records MBC patients who registered in our breast cancer clinic between December 2013 and July 2018. A total of 380 patients of upfront metastasis got registered during this period. Though it is not a part of a routine protocol to do a biopsy of MBC at progression, we have repeated biopsy in a small group of 28 patients at progression. Two patients underwent palliative mastectomy at progression. One patient required oophorectomy for ovarian ablation at disease progression and found to have ovarian metastasis. One patient required surgical reduction of the pathologic fracture, biopsy was taken from the bone. So a total of 32 patients considered for analysis.

Biomarker (ER [estrogen receptor], PR [progesterone receptor], and human epidermal growth factor receptor [HER2]/neu) status was documented at baseline and at progression. Baseline biopsy was taken from the breast. Several sites from where the rebiopsy was taken in this cohort were breast 5 (17.2%), liver 6 (20.7%), lymph node 10 (34.5%), skin 5 (17.2%), ovary 1 (3.4%), bone 1 (3.4) and unknown site 1 (3.4%). Tissue samples for histopathologic analysis were obtained by true cut biopsy or surgical resection.

Pathology: Immunohistochemistry and fluorescent in situ hybridization

Hormone and HER/2neu were tested by the standard immunohistochemistry method and the results were interpreted by 2 pathologists. Allred scoring was used for reporting ER/PR receptor status. A score of 3 and more was considered positive.[5] HER2/neu status was tested as per the American Society of Clinical Oncology/College of American Pathologists guidelines.[6] A score of 3+ was considered positive and 2+ was considered equivocal. All 2+ results of Her2 neu were confirmed by the fluorescent in situ hybridization method as per standard guideline. Histologic type was assessed according to world health organization standard and histologic grade was assessed according to Nottingham modification of the Bloom-Richardson system.[7]

Statistical analysis

Clinical, pathologic and radiological details were documented from the hospital records include age, gender, menopausal status, side, histology, biomarker status (ER, PR, and HER2/neu), stage, site of metastasis and primary therapy. Data was analyzed using SPSS version 23. Nominal data presented as number and percentage, continuous data presented as medians and range (Table 1).

Table 1
Baseline characteristics (N = 32).

Age (median, range), years	46 (26-72)
Sex	1 (3.1%) Male, 31 (96.9%) Female
Premenopausal female	17 (53.1%)
Postmenopausal female	14 (43.8%)
Duration of symptoms (median, IQR), months	7 (3-14)
Side	Right: 11 (34.4%) Left: 18 (56.2%) Bilateral: 3(9.4%)
Histology	Invasive ducal carcinoma: 31 (96.9%) Invasive lobular carcinoma: 1 (3.1%)
TNM at baseline stage	All were metastatic
HR positive	12 (37.5%)
HR and HER2/neu receptor positive	10 (31.3%)
HER2/neu receptor positive	5 (15.6%)
TNBC	5 (15.6%)
Bone metastasis	18 (56.3%)
Lung/Pleural metastasis	10 (31.3%)
Liver metastasis	9 (28.1%)
Non regional lymph node metastasis	8 (25%)
Other metastasis (bone marrow and ovary)	1 (3.1%)
Combination chemotherapy	20 (62.5%)
Single-agent chemotherapy	7 (21.9%)
Hormonal therapy (N = 22)	21 (95.4%)
Targeted therapy (N = 15)	Trastuzumab: 8 (53.3%) Trastuzumab + Pertuzumab: 2 (13.3%)

ER, estrogen receptor; HR, hormone receptor (ER or PR or Both); IQR, interquartile range; PR, progesterone receptor; TNBC, triple negative breast cancer.

Table 2
Alteration in biomarkers between primary tumor and at metastasis (N = 32).

Receptor status	Positive to negative	Negative to positive	Positive to positive	Negative to negative
ER	4 (12.5%)	2 (6.25%)	18 (56.25%)	8 (25%)
PR	6 (18.75%)	2 (6.25%)	12 (37.5%)	12 (37.5%)
HR	3 (9.35%)	2 (6.25%)	19 (59.4%)	8 (25%)
HER2/neu	5 (15.6%)	**None**	10 (31.3%)	17 (53.1%)

ER, estrogen receptor; HR, hormone receptor (ER or PR or both); PR, progesterone receptor.

Results

Patient characteristics

Baseline characteristics at are given in Table 1. Median age of presentation was 46 (range 26-72) years, most common histology was infiltrating ductal carcinoma. All patients included in the study were of upfront MBC. Median duration of symptoms before patient diagnosed MBC was 7 (IQR 3-14) months.

Baseline hormone receptor positive were 12 (37.5%), hormone and HER2/neu positive were 10 (31.3%), only HER2/neu positive were 5 (15.6%) and 5 (15.6%) were triple negative breast cancer. The most common sites of metastasis were bone followed by lung, liver, nonregional lymph. One patient had metastasis in ovary and bone marrow.

As per institute protocol, most of our patients received combination or single-agent chemotherapy after diagnosis of metastasis. Out of 22 patients, 21 received hormonal therapy (tamoxifen, anastrozole, or letrozole) as per the physician's choice. One patient who was hormone positive was also HER2/neu positive, so he received the targeted agent in first-line therapy with chemotherapy. Out of 15 patients who were positive for HER2/neu, only 10 (66.6%) patient could manage to receive targeted agents (trastuzumab/pertuzumab) as given in Table 1.

Alteration in biomarkers at the time of progression

Alteration in biomarker status documented from baseline to progression as given in Table 2. ER altered in 6 (18.75%) patients, 4 (12.5%) switched from positive to negative and 2 (6.25%) from negative to positive. PR altered in 8 (25.3%) patients, 6 (18.75%) switched from positive to negative and 2 (6.25%) from negative to positive. Overall hormone receptor changed in 5 (15.6%) patients, 3 (9.35%) switched from positive to negative and 2 (6.25%) from negative to positive. HER2/neu altered in 5 (15.6%) patients, all converted from positive to negative and none from negative to positive. Patients whose receptor status was the same are given in Table 2.

Therapeutic impact of the alteration in receptor status

Patients who had gain (negative to positive) of hormone receptors were started on hormonal agents. Patients having triple negative breast cancer received chemotherapy in our cohort. Those patients who had loss of HER2/neu status were positive for hormone receptor. They were started on hormonal agents.

Discussion

Management of MBC is a challenge in developing countries like India, where a tertiary health care center manages maximum such cases. There is an unmet need for personalized treatment strategies to decrease health care expenditure. Documentation of change in receptor status at progression may help to improve disease management and patient care.

Several previous studies documented receptor status change in early and advanced stage breast cancer at locoregional progression or metastasis. In our previous study, we observed changes in receptor status in 23.7% patients for ER, 28.9% patients for PR, and 14.7% patients for the HER2/neu receptor.[8] There are only limited studies which documented change in MBC at progression. One such study by Lower et al, reported change between the first and second metastases; 18.8% for ER, 19.8% for PR, and 10.7% for HER2/neu.[9] Where as, it was 18.75% for ER, 25.3% for PR, and 15.6% for HER-2/neu in present study. PR is the most common receptor which shows the change at progression.

National comprehensive clinical network and American Society of Clinical Oncology/College of American Pathologists guideline recommend repeating receptor status in primary and MBC.[6,10] However, there are no guidelines for repetition of receptor status in MBC patients at progression. Receptor alteration signifies that disease progression is associated with a change in tumor biology or tumor heterogeneity.[11,12]

To the best of our knowledge, this is a first study from developing country to document change in MBC at progression. Our study has a small sample size, but it can generate a hypothesis for further prospective studies. If we consider a change in tumor biology after progression, when and how many times rebiopsy should be done is still an unanswered question. We strongly consider that patient with the oligometastatic disease at progression, late relapse and patient who behave clinically worse as per receptor status should be subjected for rebiopsy. If there is an opportunity where the patient is undergoing any surgical procedure, tissue should be obtained for hormone status documentation. We have documented the alteration in receptor status in 4 such patients, 2 underwent palliative mastectomy, 1 oophorectomy, and 1 repair of the pathologic fracture. Prospective studies are required to document prognostic implication of change in hormone status at multiple progressions.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2018.12.001.

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