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RESEARCH ARTICLE

CLINICAL SCENARIO OF TRIPLE NEGATIVE BREAST CANCER AT A TERTIARY CARE CENTRE IN SOUTHERN RAJASTHAN

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ABSTRACT

Back ground: Triple negative breast cancer TNBC) patients are subset of breast cancer patients who test negative for estrogen receptor(ER), the progesterone receptor(PR), and the human epidermal growth factor receptor 2(HER-2) and show different biological behavior. As racial disparity is seen in presentation and prognosis of breast cancer, we studied the clinicopathological features and patterns of recurrence in this group of patients in our local population

Aims and Objectives: To know biological behavior of TNBC in local population by comparing clinical features, prognostic factors, and outcome of this group with non triple negative breast cancer patients (non-TNBC)

Material and Methods: A cohort study of 352 patients of breast cancer tested for hormone receptor was included in the study. Depending on hormone status patients were grouped into TNBC and non-TNBC. Clinical variables, patterns of relapse and outcome of patients in two groups were evaluated with median follow up of eight ten years.

Results: Among 352 patients included 76 were TNBC and 276 were non-TNBC cases. TNBC had significant correlation in terms of tumor size ($p<0.001$), decreased tumor mobility ($p=0.001$), fixation of lymph node ($p=0.001$), number of lymph node involved ($p=0.046$) and higher grade of tumor ($p<0.001$). TNBC was associated with poor relapse free survival (RFS) ($p=0.010$) overall survival ($p<0.001$).

Conclusion: TNBC are aggressive tumors with poor relapse free and overall survival. Large population based prospective studies are needed to characterize these tumors.

INTRODUCTION

Breast cancer being the most common cancer among women is a heterogeneous disease with varied responses to treatment and outcomes. Spectrum of breast cancer survival varies from slow growing indolent tumors to aggressive tumors with poor survival despite treatment. Discovery of hormone receptor and oncoprotein genes in last decade has become the landmark in management of breast cancer as the treatment went beyond local and systemic treatment and focused on receptor modulation. Even though technological advances in past fifty years have helped in making diagnosis of breast cancer at an early stage, there are certain subset of breast cancer associated with poor outcome despite adequate treatment. Recent data has suggested that Triple Negative Breast Cancer (TNBC) have different clinical outcome and poor response to multimodality of treatment (Liedtke *et al*., 2008 and Yin *et al*., 2009) there by putting clinical oncologists in dilemma about most appropriate management of these patients. This subset of breast cancer presents as aggressive tumor with early relapse, poor chemotherapeutic responses and poor survival (Bauer *et al*., 2007; Rebecca Dent *et al*., 2009 and Lund *et al*., 2009). Racial disparity and international variation in incidence and outcome of breast cancer is an unexplained but most striking feature of breast cancer. African American individuals do poorly in terms of presentation of disease (Deshpande *et al*., 2009) and survival rates but Chinese and Malaysians do not show poor survival (Tan *et al*., 2008). In Indian subcontinent there is huge disease burden. Incidence of breast cancer in India being 20.01 per 100000 population, mortality being 4.32 per 100000 population and Disability Adjusted Life Years (DALYs) is 8,89,224 (Assessment of burden of non- communicable diseases: Parks textbook of Preventive and Social medicine, 2011). According to Indian Council of Medical Research (ICMR) data with population based cancer registries, breast cancer has emerged as leading cause of cancer and is rapidly replacing cancer cervix as the most common cancer among women in India (Nandakumar *et al*., 2010). However there is

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scarcity of data available about behavior of these tumors in our population. So the main objective of our study was to know the behavior and prognosis of TNBC as compared to non-TNBC tumors with respect to clinicopathological features, relapse free survival (RFS) and overall survival (OS) in our homogeneously treated population at a single institution.

MATERIALS AND METHODS

We conducted observational study of patients of breast cancer treated at The Breast Clinic, in Department of Surgery, Rabindranath Tagore Medical College, Udaipur, Rajasthan, the only tertiary care hospital in Southern Rajasthan. Data collection of breast cancer was started in 2002 and continued with follow up till 2012. Patients whose receptor testing was performed were included in the study. Base line data collected included demographic characteristics (residence, age at diagnosis, education, socioeconomic status, age of menarche, age at first child, menopausal status), tumor characteristics (tumor size, location, mobility, associated skin changes, histology), lymph node positivity, metastasis, receptor status, grade of tumor. Data as per records were meticulously entered initially in breast cancer registers and later track of records was kept using Microsoft access software. Patients were staged according to standard tumor lymph node and metastasis (TNM) staging.

Socioeconomic status, rural and urban distributions were noted. Tumor size was based on pathological reports and Bloom Richardson scoring (BRS) was used for grading of tumor. Receptor assay was performed by using Immunohistochemistry (IHC) analysis on formalin fixed, paraffin embedded breast cancer tissue. Based on IHC assay ER, PR status in which a report of 10% or greater of cells that had nuclear staining for ER and PR was considered positive. Detection system used was HRP Polymer using anti ER antibody and anti PR antibody (clone for ER antibody was ER-SP1 and PR antibody was SP2). The HER2/neu oncoprotein amplification was demonstrated by IHC method and proportion of membrane staining scored from 0 to 3+. For our study purpose only 3+ staining was considered over expression and weak staining (2+) and incomplete staining was considered negative result. Patients with Estrogen receptor (ER) negative, Progesterone Receptor (PR) negative and HER-2 negative were grouped as TNBC. Non TNBC group was identified either Hormone receptor positive or HER-2 positive
Relapse free survival (RFS) was measured from date of first definitive treatment to date of first relapse or death from any cause. Overall Survival (OS) was measured from date of diagnosis to the date of death from any cause. Post operative adjuvant chemotherapy was instituted according to National Cancer Center Network (NCCN) guidelines with anthracycline and taxanes based chemotherapy. Duration of follow up was from december 2001 to december 2011 and Survival data were collected through telephonic contact, postal enquiry or during follow up visit.

Statistical analysis

Base line demographic variables and tumor characteristics were compared between TNBC and non- TNBC group using *t* test for means and Chi Square test for frequency variables. Results were considered significant with $p < 0.05$ and highly significant when $p < 0.01$. Kaplan- Meir survival analysis done to know overall survival, relapse free survival and The Log Rank test was done know the statistical significance of differences observed between the groups. In order to determine significance of prognostic factors with RFS and OS, Cox regression model with multivariate analysis was used. Data were analyzed using SPSS soft ware for windows version 17(SPSS, Inc, Chicago, IL, USA).

RESULTS

Out of 1382 patients of breast cancer treated at our institution, 352 patients with receptor assay were included in the study. Among 352 patients included in study 76 (21.6%) were TNBC and 276 (78.4%) were Non TNBC patients. The median age for breast cancer presentation was 50 years with average age 49.73 years (49.5± 10.7) in non TNBC group and 50.63 years (50.4 ± 10.9) in TNBC group (p=0.91). The clinicopathological features of patients are summarized in Table 1. Nearly half of patients, 175 (49.7%) belonged to rural background and 177 (50.3%) were from urban area and the distribution among the two groups was significant (<p=0.001). Most of the patients, 230 (65.3%) were in stage II and 121 (34.4%) in stage III, and only 1 patient in stage I. Stage IV patients with poor survival were excluded from the survival analysis. 304 patients underwent Modified Radical Mastectomy (MRM), 48 patients Breast Conservation surgery (BCT). Among 328 patients who underwent adjuvant systemic chemotherapy 38 patients were managed with CMF regimen (mainly in 90s), 235 with anthracycline based regimen (CAF or CEF), 47 patients with combination of anthracycline and taxanes and 8 patients with only taxanes. Median duration of follow up was 80 months (range 1 to 120 months) and 65 (18.5%) patients had relapse of disease during follow up period.

ER positivity was seen in 136 patients and PR positivity in 147 patients and HER-2 positivity in 203 patients. When clinicopathological features were compared we found that TNBC correlated with large size (mean size 6.55 cm), which was statistically significant (p=0.001), decreased lump mobility (p =0.001), clinically palpable lymph nodes (p=0.010), fixation of tumor ($p < 0.001$), histologically positive lymph node (p=0.046), higher grade of tumor (p<0.01). Survival analysis using Kaplan – Meier plot showed poor survival in TNBC group for RFS and OS (p=0.010 and p=0.001 respectively). The plots are shown in Fig 1 and Fig 2.
On multivariate Cox regression analysis for Relapse Free Survival, menopausal status (p=0.007), tumor size (0.018), progesterone receptor (p=0.006) were correlated with shorter RFS. On multivariate Cox regression analysis for Overall Survival, Age (p=0.032), menopausal status (p=0.010), size of tumor (p=0.005) and grading of tumor (p=0.021) correlated with poor overall survival. Results of both analyses are depicted in Table 2 and Table 3.

DISCUSSION

Genetic and molecular studies based on DNA microarray technology have proved beyond doubt that breast cancer is heterogeneous.

Table 1. Clinicopathological characteristics of study patients

		TNBC (n= 76)	NON TNBC (n= 276)	p
1	Age(mean in years)	50.63	49.73	0.91
2	Residence			
	rural	63	112	0
	urban	13	164	
3	Menopausal status			
	Pre-Menopausal	29	107	0.517
	Post- Menopausal	47	169	
4	Age of menarche (mean,in years)	14.9	15.23	0.591
5	Age at first child(mean, in years	19.4	20.4	0.034
6	Parity			
	< 3	54	193	0.485
	> 3	22	83	
7	Tumor size (mean, in cm)	6.55	4.19	0
8	Fixation of Lymph node			
	fixed	59	14	0.001
	not fixed	17	262	
9	Metastasis			
	lung	08	08	
	liver	13	02	
	bone	8	05	
	multiple	17	04	
	spine	00	01	
	brain	01	00	
	others	03	00	
	No metastasis	226	56	
10	Clinical Stage			
	1	0	1	0
	2	13	217	
	3	63	58	
11	Tumor mobility			
	yes	16	273	0.001
	no	60	3	
12	Chemotherapy			
	CMF	15	23	
	CAF / CEF	49	186	
	PACLITAXEL	3	5	
	PACLITAXEL+EPIRUBICIN	6	41	
	NONE	3	21	
13	HPA Grade			
	I	0	93	0.001
	II	12	148	
	III	64	34	
	none	0	1	
14	Estrogen receptor (ER)			
	positive	0	136	0.001
	negative	76	140	
15	Progesterone receptor (PR)			
	positive	0	147	0.001
	negative	76	129	
16	Her-2/neu receptor (HER-2)			
	positive	0	203	0.001
	negative	76	73	
17	Radiotherapy			
	yes	72	262	0.57
	no	4	14	
18	Hormonal therapy			
	yes	49	120	0.001
	no	27	156	
19	Outcome			
	Expired	26	30	0.001
	Lost	12	14	
	Well	38	232	
20	relapse free survival			
	no relapse	55	232	0.029
	relapse	21	44	
21	overall survival			
	expired	26	30	0.001
	survived	50	246	

Table 2. Independent variables related to relapse free survival (Cox multivariate analysis)

	S E	Hazard Ratio	p value
TNBC	1.26	3.82	0.287
age	0.046	1.043	0.363
menopausal	0.901	11.43	0.007
size	1.351	0.041	0.018
ER	1.175	0.722	0.781
PR	1.069	18.66	0.006
Her2/nue	1.125	2.426	0.431
lymph node	0.756	3.913	0.071
grading	0.707	1.097	0.896

Table 3. Independent variables related to overall survival (Cox multivariate analysis)

	S E	Hazard Ratio	p value
TNBC	2.52	3.093	0.654
age	0.049	1.111	0.032
menopausal status	0.954	11.865	0.01
size	0.98	0.064	0.005
ER	1.815	4.702	0.394
PR	1.577	0.673	0.801
Her2/neu	2.24	2.565	0.674
lymph node	0.795	0.395	0.243
grading	0.998	0.1	0.021

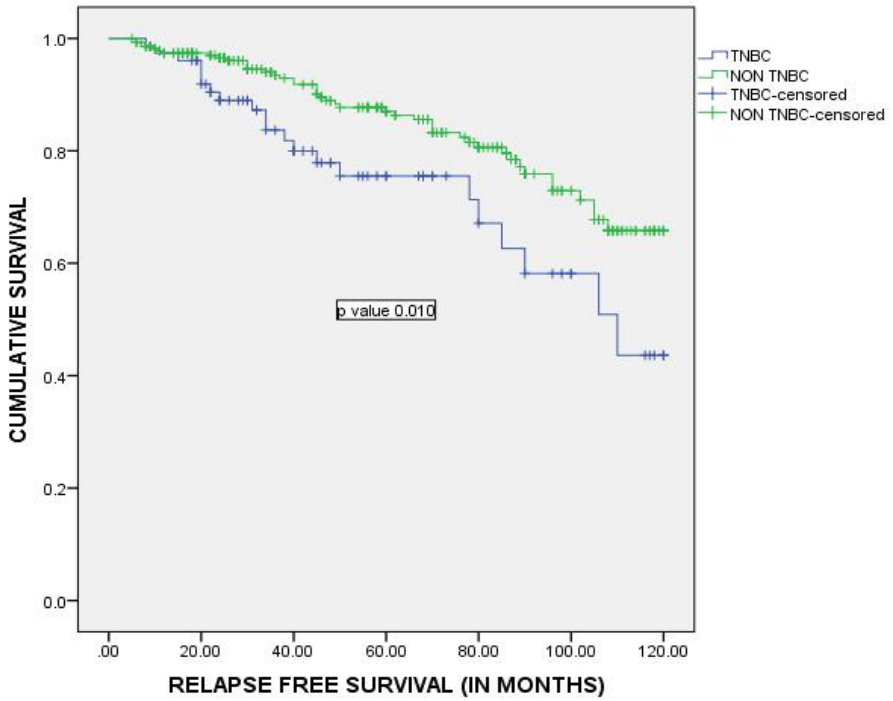

Fig. 1. Kaplan Meier survival curve for prediction of relapse free survival (RFS)

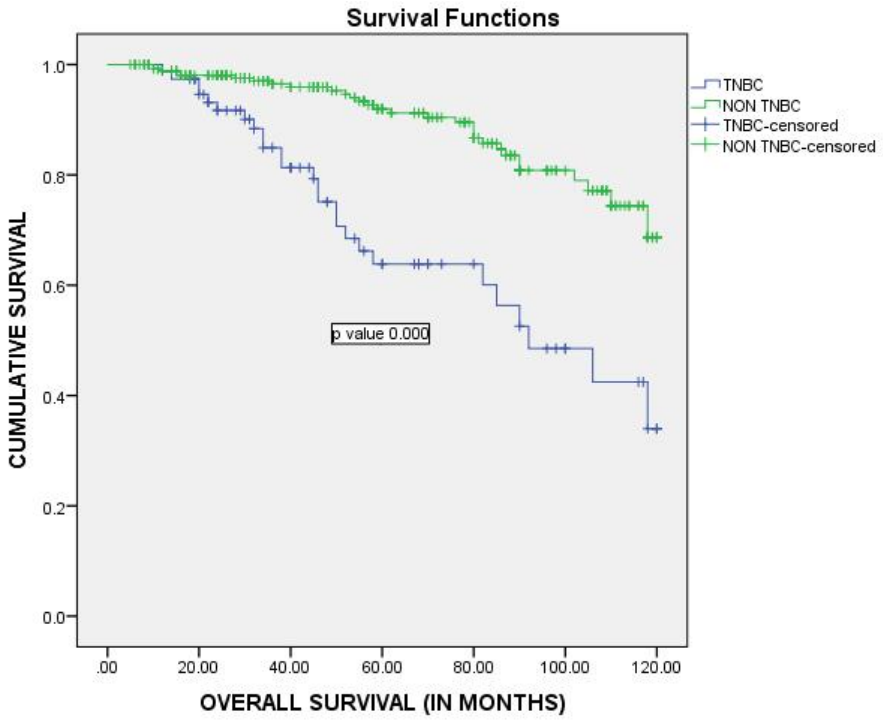

Fig. 2. Kaplan Meier survival curve for prediction of overall survival (OS)

Receptor classification of breast cancer has raised several questions regarding patient treatment and prognosis as tumor biology differs in each group. It is complicated by racial disparity in presentation and outcome. This clinically challenging entity is an area of active research. We undertook this study to see risk profile and outcome in our patients as compared to western population. Age, parity, race, age at menarche, age at time of first child, menopausal status and socioeconomic status are significantly associated with development of TNBC (Amend *et al*., 2006; Carey *et al*., 2006; Carrizosa and Carey, 2005 and Whitworth, 2006). Among race African American women have high prevalence, low socioeconomic status, young age at presentation and worst survival (Bauer *et al*., 2007 and Morris *et al*., 2007). Recently high parity, nulliparity, early age of first child has been shown to be important risk factor for TNBC (http://www. medscape.com/viewarticle/738415). Our study however showed predominance of breast cancer in middle age in both the groups (p=0.91) and no significance with regard to parity, age at menarche, socioeconomic status.

Age at first child happened to be significantly associated between the two groups (p=0.034) with TNBC patients having younger age (mean=19.4 years) of bearing first child compared to non TNBC (mean=20.4 years). Perou *et al*. (2000) were the first group of researchers to describe various molecular subtypes of breast cancer. In this study we included only TNBC group which is different from "basal like" phenotype group. Although most triple negative are clustered with basal like group, these terms cannot be used synonymously as there is up to 30 % discordance between the two groups (Bertucci *et al*., 2008; Cleator *et al*., 2007; Kreike *et al*., 2007 and Nielsen *et al*., 2004). TNBC is only clinical assay based definition where as "basal-like" is defined on basis of microarray or comprehensive gene expression profiling. Classically basal like breast cancers have been characterized by low expression of ER, PR and HER2 and high expression of CK5, CK14, caveolin-1, CAIX, p63 and epidermal growth factor receptor (EGFR) (Swain, 2008 and Rakha *et al*., 2008).

TNBC are characterized by aggressive histology, large tumor size and node positivity and higher grade (Carey *et al*., 2006 and Dent *et al*., 2007). In our study also TNBC group had large tumor at presentation (mean size= 6.5cms), decreased tumor mobility, fixation of lymph node in axilla at presentation, higher pathological grades. Triple negative tumors have demonstrated poor prognosis with high recurrence rates and low survival. Although most of the relapses in our study occurred in first 3 years (mean 17.6 months), TNBC was not prognostic factor for RFS which is similar to views expressed by other Asian authors (Tan *et al*., 2008 and Miller *et al*., 2007). Statistically significant poor Overall survival (p= 0.001) was noted in TNBC group compared to non TNBC which is in accordance with western studies (Liedtke *et al*., 2008; Mersin *et al*., 2008 and Fulford *et al*., 2007). However our results differ from other Asian studies (Yin *et al*., 2009 and Tan *et al*., 2008). Even though much has been debated regarding TNBC subgroup it is essential that we understand the molecular characteristics of this group and determine accurate markers which may be used in identification and treatment of this group as there is significant overlap between this group and "basal like" tumors. Also there is need to invent and develop novel molecular targeted therapy against this group as these tumors are resistant to most chemotherapy regimens with poor survival (Tan *et al*., 2008). Promising targeted strategies include EGFR inhibitors like Cetuximab (O'Shaughnessy *et al*., 2007), PARP inhibitors (Kopetz *et al*., 2008), antiangiogenic agents like bevacizumab (Miller *et al*., 2007), used alone or in combination with platinum group of molecules (carboplatinum) is an area of fertile research. We acknowledge the limitations of our study which has small sample size. We did not evaluate role of obesity and body mass index (BMI) in present study and few patients were lost to follow up (10.9%). In conclusion our study indicates that triple negative patients have aggressive clinicopathological characters compared to non triple negative group and show poor relapse free survival and overall survival. Fertile research needs to be done in India to invent novel molecular targeted therapy and new chemotherapy strategy against this group. Conflict of interest: The authors do not have any disclosable interest

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