Original Article

A Study of Triple Negative Breast Cancer at a Tertiary Cancer Care Center in Southern India

Lakshmaiah KC, Das U, Suresh TM, Lokanatha D, Babu GK, Jacob LA, Babu S

Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India

Address for correspondence:
Dr. Umesh Das,
Department of Medical Oncology,
Room no-5, OPD Block, Kidwai Memorial Institute of Oncology,
Bengaluru - 560 029,
Karnataka, India.
E-mail: drumesh.das07@gmail.com

Abstract

Background: Triple negative breast cancers (TNBCs) are a diverse and heterogeneous group of tumors that by definition lack estrogen and progesterone receptors and amplification of the HER-2 gene. The majority of the tumors classified as TNBCs are highly malignant, patients are usually young and only a subgroup of patients responds to conventional chemotherapy with a favorable prognosis. Various studies have been reported in western literature on TNBCs, all highlighting the poor prognosis of this subtype. However, extensive data from India is lacking. **Aim:** The aim of this study was to analyze the epidemiological and clinical profile of TNBCs at our institute. **Materials and Methods:** This was the retrospective study carried out in Tertiary Cancer Care Center in South India. Case files of all breast cancer patients were reviewed from the hospital database registered in 1 year and TNBC patients were selected for the study. Patient's characteristic, treatment, and histological features were analyzed. **Results:** A total of 322 patients were registered during the period of 1 year and 26% (84/322) of total patients were TNBC. Median age of presentation was 44.5 years. About 94% (79/84) of patients had first full-term delivery before the age of 30 years. The most common presenting symptom was left sided breast lump. Locally advanced and early breast cancer (EBC) was 51% (43/84) and 42% (36/84), respectively. Metastatic breast cancer was seen in five patients. The highest numbers of patients were node negative disease (36.9%) [31/84], followed by N1 30.95% (26/84). Most of the patients had high-grade tumor. 94% (34/36) of cases of EBC had undergone upfront modified radical mastectomy. Invasive ductal carcinoma was the predominant histology except one who had medullary carcinoma. Twenty-four patients received neoadjuvant chemotherapy (NACT). There was no pathological complete remission, but all patients responded to NACT. Metastatic disease was seen in five patients. All patients had bone metastasis. **Conclusions:** TNBCs are highly aggressive subtype, with high grade with limited treatment options and very poor prognosis. Incidence is more in our country than the western literature. Even in our country also the incidence is varies in different region. TNBCs are significantly associated with young aged patients. There was a lack of association between tumor size and lymph node positivity.

Keywords: Breast cancer, Triple negative, Invasive ductal carcinoma

Introduction

Breast cancer is the most common female cancer and the leading cause of cancer deaths worldwide. It is the most common cancer among females in urban India.[1] With development of various modern technologies, with collaboration of pathology and genetic study, breast cancer now no more considered as homogenous disease, it is a very heterogeneous disease despite their common tissue of origin. Research in molecular pathology and molecular genetics have shown a number of distinct subtypes of breast cancer. Currently, only a limited number of clinical, pathologic, and molecular factors help clinicians make decisions on therapy selection and evaluate prognosis at the time of diagnosis. Depending on gene expression data, breast cancer divided into five subtypes, consist of luminal A and luminal B, HER-2 expressing, basal-like, and normal breast-like.

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Triple negative breast cancers (TNBCs) are a group of primary breast cancers, which lack the expressions of the estrogen receptor (ER), the progesterone receptor (PR) and HER-2, in addition to being positive for basal cytokeratin (CK) 5/6 or epidermal growth factor receptor (EGFR). Although the triple-negative phenotype has been considered as sufficient to identify the "basal-like" tumors, increasing evidence has shown the terms "basal-like" and "TNBCs" are not synonymous.[2] The definition of basal-like breast cancers has been evolving and though there are no universally agreed upon criteria to define it, the panel developed by Nielsen *et al*.[3] are generally accepted in practice - basal-like cancers are negative for hormone receptors (HRs) and HER-2, in addition to being positive for CK5/6 or EGFRs. Various studies have been reported in western literature on TNBCs, all highlighting the poor prognosis of this subtype of breast cancer. However, extensive data from India is lacking. The aim of this study was to analyze the epidemiological and clinicopathological profile of TNBCs at our institute.

Materials and Methods

This was the retrospective study carried out in Tertiary Cancer Care Center in South India. Case files of all breast cancer patients were reviewed from the hospital database registered in 1 year (August 2012 and July 2013) and TNBC patients were selected for study. Patient's characteristic (age, pre/postmenopausal status, family history of breast/ovarian/other cancer), treatment and histological features were analyzed. Diagnosis of breast cancer was primarily based on clinical presentation, imaging (mammogram, ultrasound of breast) and histopathological studies. Staging was done with X-ray chest, ultrasound abdomen for localized disease with the addition of bone scan and computed tomography for locally advanced disease and metastatic disease. Patients were staged in accordance with American Joint Committee on Cancer (AJCC)-7 (tumor node metastasis) staging system. TNBC was defined as ER negative, PR negative, and HER2 neu negative cancers. These tests were carried out with standard Food and Drug Administration approved kits by IHC. For each patient in the database, antibody staining of a set of paraffin embedded slides for ER and PR was carried out. A HER-2 report of 3 + by IHC was considered to be positive. Those IHC score for HER-2 neu were 2+, confirmation was done by fluorescence *in situ* hybridization. HER-2 score of 0 or 1 was considered negative. Baseline epidemiological and tumor characteristics of triple negative cancers were analyzed for all 84 patients. Patients were broadly divided into three categories, early breast cancer (EBC), locally advanced breast cancer (LABC), and metastatic breast cancer. EBC has been defined as tumors of not more than 5 cm diameter, with either impalpable or palpable but not fixed lymph nodes and with no evidence of distant metastases. This corresponds to tumors that are T1-2, N0-1, M0 according to AJCC-7. LABC was defined as T-stage ≥T3 and/or N-stage ≥N2 without any evidence of distant metastasis. MBC was defined as any breast cancer with evidence of distant metastasis.

Results

A total of 322 patients were registered during the period of 1 year and 26% (84/322) of total patients were TNBC on immunohistochemistry analysis of receptor status. Median age of presentation was 44.5 years with range of 22-67 years. 72.6% (61/84) of patients were <50 years of age [Table 1]. 22% (19/84) patients were age ≤35 years. The median age of menarche was 14 years. More number of patients (62%) [52/84] was rural background than urban (38%) [32/84]. All patients were married in our present study and the median age of first full-term pregnancy was 22 years with minimum age of 15 years and maximum age was 32 years except four who were nullipera. About 94% (79/84) of patients had first full term delivery before the age of 30 years. The most common presenting symptom was breast lump. Left sided (58.3%) [49/84] was more common than the right side. Bilateral breast cancer was found in eight patients, five patients had synchronous bilateral breast cancer and three patients had metachronous breast cancer. The median duration of symptom was 3 months. The average number of children was 2.4. History of breastfeeding was present in 94% (79/84) patients. Family history of breast cancer was elicited only in two patients. In one patient mother died of breast cancer at 40 years of age and other patient's elder sister had breast cancer.

In our study, of 84 TNBCs 51% (43/84) were locally advanced and EBC was seen in 42% (36/84) of cases. Metastatic breast cancer was seen in five patients [Table 2]. T2 diseases were the most common (35.7%) [30/84] and T1 disease was the least common (1.1%) [1/84] presentation. T3 and T4 diseases were seen in 33% (28/84) and 25% (21/84) of cases, respectively. The highest numbers of patients

Table 1: Risk factors

Factors	Number of patients (%)
Age (years)	
<50	61 (72.61)
>50	23 (27.38)
Median age at menarche	14 years
Age at full-term pregnancy (years)	
<30	79 (94.0)
>30	5 (5.95)
Number of children	
Average	2.35
Maximum	6
Breastfeeding	79(94)
No breastfeeding	5(5.95)
Menopausal status	
Premenopausal	50 (59.52)
Postmenopausal	34 (40.47)
Family history of breast cancer/ ovarian cancer	2 (1 mother at 40 years died, 1 sister)

were node negative disease (36.9%) [31/84], followed by N1 (30.95%) [26/84], N2 (28.58%) [24/84] and least common was N3 (3.57%) [3/84] [Table 3]. High-grade tumor was seen in 74 patients (88%) and 10 (11.9%) patients were Grade 2 disease. No Grade 1 tumor was seen.

About 94% (34/36) of cases of EBC had undergone upfront modified radical mastectomy. Breast conservation surgery was done in one patient. Invasive ductal carcinoma was the predominant histology except one who had medullary carcinoma. Tumor size 2.1-5 cm was seen in 66% (24/36) patients. 80% (29/36) were high-grade tumors. Pathological node negative disease was seen in 69% (25/36) of EBC cases, which was followed by N1 nodal status (16.7%) [6/36] [Table 4]. Perinodal spread was seen in three case of lymph node positive disease. Lymphovascular emboli in histopathology, which indicate poor prognosis, were seen in five patients.

Of 43 LABC patients, 24 patients received neoadjuvant chemotherapy (NACT). Anthracycline-based chemotherapy was the most commonly used chemotherapeutic agents. Only one patient received taxane-based chemotherapy. There was no pathological complete remission, but all patients had clinical and pathological responded to NACT [Table 5].

Metastatic disease was seen in five patients. All patients had bone metastasis. Bone and visceral metastasis was seen in three cases. One patient had brain metastasis at presentation.

Discussion

Molecular classification of breast cancer has revealed that breast cancer is a heterogeneous disease. This heterogeneity of the disease signifies the prognosis and response to therapy. Among the subgroups of breast cancer, TNBC is particularly feared because it is associated with a poor clinical outcome highly aggressive disease and it has no specific systemic treatment.[4] However, clinical data on TNBC in Indian populations are limited. Thus, we investigated the clinicopathological features of lymph node-negative TNBC in Indian women.

In our study, TNBC was 26%. In their study Carey *et al*.[5] they found that the prevalence of the TNBC subtype among patients with breast cancer in the US was 26.4%; among non-African American patients with breast cancer this prevalence was 23%. Bauer *et al*.[6] have reported that in the US the prevalence of TNBC breast cancer among patients with all forms of breast cancer was 12.4% and that this prevalence was highest among nonHispanic black patients with breast cancer, at 24.6%. In India, the incidence of TNBC was varies from 12.5% to 29.8%[7-9]

The median age of our patients was 44.5 years, quite younger than the Western data. Dent *et al*.[4] have reported that the median age of TNBC patients were 53 years. Younger median age in Indian population was supported by another two Indian studies.[7,8] This finding of younger median age most likely reflects the general trend of breast cancers occurring a decade earlier in Indian population than western data. In our study, premenopausal patient was more than the postmenopausal. 26% of patients in our study were ≤35 years, which indicate TNBC patients were younger than other types. Our result was supported by two Indian studies.

In our study, clinical Stage III diseases were common (51%) followed by Stage II (41%). This result was favored by Ram Prabu *et al*.[7] and Dent *et al*.[4] studies [Table 6]. It is well-known that in HR positive breast cancers, there is a definite increase in the incidence of lymph node positivity with increasing size of the tumor. This has been nicely highlighted in the study by Dent *et al*.[4] where they have shown that in TNBCs even small tumors have a high chance of lymph node positivity. In our study, the most of the patients were node negative disease (36.9%), followed by N1 (30.95%) and N2 (28.58%). N3 (3.57%) diseases were less number.

Table 2: Stage

Factors	Number of patients (%)
Clinical stage	
I	1 (1.1)
II	35 (41.66)
III	43 (51.19)
IV	5 (5.95)
Early breast cancer	36 (42.85)
Locally advanced breast cancer	43 (51.19)
Metastatic breast cancer	5 (5.95)

Table 3: T and N stage

T stage	Number (%)	N stage	Number (%)
T1	1 (1.1)	N0	31 (36.90)
T2	30 (35.71)	N1	26 (30.95)
T3	28 (33.33)	N2	24 (28.57)
T4	21 (25)	N3	3 (3.57)

Table 4: Tumor size and lymph node status

T status	Positive node	Negative node
0-2	0	2
2.1-5	9	20
>5	1	4

Table 5: Respond to NACT

NACT	Number of patients	pCR	PR	PD
Anthracycline-based	23	0	23	0
Taxen+anthracycline	1	0	1	0
Total	24	0	24	0

NACT: Neoadjuvant chemotherapy, pCR: Pathologic complete response, PR: Partial remission, PD: Progressive disease

Table 6: Comparison of various Indian and Western studies of triple negative breast cancer

	Ram Prabu *et al.*[7]	Suresh *et al.*[8]	Dent *et al.*[4]	Present study
Incidence (%)	24.4	12.5	11.2	26
Median age of presentation (years)	46.6	49	53	44.5
Stage (%)				
I	2.8	13	9.8	1.1
II	31.8	62	24.2	41.7
III	47.7	15	66	51.2
IV	17.7	10	-	5.9
Grade (%)				
Low	-	-	-	-
High	43	61	66	88

Preoperative or NACT is an option in patients with early-stage and LABC. Neoadjuvant treatment had been compared with standard, postoperative adjuvant chemotherapy in terms of improving survival and facilitating local therapies. Unfortunately, NACT does not improve overall survival as shown in (NSABP) B18 trial.[10,11] NACT may convert a unresectable, LABC to an operable tumor,[12-14] and in primarily operable tumors, down staging results in increase chance of breast conservation rates.[10,15,16] The preoperative setting could provide an opportunity to study the impact of systemic therapies on breast cancer biology.[17] TNBCs are known to be highly chemosensitive with higher pCR rates than HRs positive tumors. In our study, of 43 locally advanced patients 24 patients received NACT. Anthracycline-based chemotherapy was the most commonly used chemotherapeutic agents. Only one patient received taxane-based chemotherapy. There was no pathological complete remission, but all patients responded to NACT.

In our study, metastatic disease was seen in five patients. All patients had bone metastasis. Bone and visceral metastasis was seen in three cases. One patient had brain metastasis at presentation. The main limitation of our study was the lack of testing for basal CK5/CK6. Further, large scale prospective trials incorporating basal CK markers and gene expression profiling are required for complete characterization of these tumors and to identify a positive marker that can facilitate targeted therapy.

Conclusion

Triple negative breast cancers are highly aggressive subtype, with high-grade with limited treatment options and very poor prognosis following progression after standard anthracycline or taxane regimens. TNBCs are more common in our country than the western literature. Even in our country also the incidence is varies in different region. TNBCs are significantly associated with young aged patients. There was a lack of association between tumor size and lymph node positivity.

Acknowledgments

Department of surgical oncology ,department of pathology and radiation oncology , kidwai memorial institute of oncology.

References

1. ICMR Cancer Registry 2004: Consolidated Reports of the PBCR and HBCR's. ICMR; 2001-2003. p. 13.
2. Badve S, Dabbs DJ, Schnitt SJ, Baehner FL, Decker T, Eusebi V, *et al*. Basal-like and triple-negative breast cancers: A critical review with an emphasis on the implications for pathologists and oncologists. Mod Pathol 2011;24:157-67.
3. Nielsen TO, Hsu FD, Jensen K, Cheang M, Karaca G, Hu Z, *et al*. Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma. Clin Cancer Res 2004;10:5367-74.
4. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, *et al*. Triple-negative breast cancer: Clinical features and patterns of recurrence. Clin Cancer Res 2007;13:4429-34.
5. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, *et al*. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA 2006;295:2492-502.
6. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: A population-based study from the California cancer Registry. Cancer 2007;109:1721-8.
7. Prabu MP, Raina V, Shukla NK, Mohanti BK, Deo SV. A study of triple-negative breast cancer at a Cancer Institute in India. J Clin Oncol 2011;29:15. [Suppl; abstr e11548].
8. Suresh P, Batra U, Doval DC. Epidemiological and clinical profile of triple negative breast cancer at a cancer hospital in North India. Indian J Med Paediatr Oncol 2013;34:89-95.
9. Ghosh J, Gupta S, Desai S, Shet T, Radhakrishnan S, Suryavanshi P, *et al*. Estrogen, progesterone and HER2 receptor expression in breast tumors of patients, and their usage of HER2-targeted therapy, in a tertiary care centre in India. Indian J Cancer 2011;48:391-6.
10. Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, *et al*. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998;16:2672-85.
11. van der Hage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L. Preoperative chemotherapy in primary operable breast cancer: Results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol 2001;19:4224-37.
12. Hortobagyi GN, Ames FC, Buzdar AU, Kau SW, McNeese MD, Paulus D, *et al*. Management of stage III primary breast cancer with primary chemotherapy, surgery, and radiation therapy. Cancer 1988;62:2507-16.
13. Danforth DN Jr, Lippman ME, McDonald H, Bader J, Egan E, Lampert M, *et al*. Effect of preoperative chemotherapy on mastectomy for locally advanced breast cancer. Am Surg 1990;56:6-11.
14. Schwartz GF, Birchansky CA, Komarnicky LT, Mansfield CM,

Cantor RI, Biermann WA, *et al*. Induction chemotherapy followed by breast conservation for locally advanced carcinoma of the breast. Cancer 1994;73:362-9.

15. Semiglazov V, Eiermann W, Zambetti M, Manikhas A, Bozhok A, Lluch A, *et al*. Surgery following neoadjuvant therapy in patients with HER2-positive locally advanced or inflammatory breast cancer participating in the NeOAdjuvant Herceptin (NOAH) study. Eur J Surg Oncol 2011;37:856-63.
16. Fisher B, Brown A, Mamounas E, Wieand S, Robidoux A, Margolese RG, *et al*. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol 1997;15:2483-93.
17. Gralow JR, Burstein HJ, Wood W, Hortobagyi GN, Gianni L, von Minckwitz G, *et a*l. Preoperative therapy in invasive breast cancer: Pathologic assessment and systemic therapy issues in operable disease. J Clin Oncol 2008;26:814-9.

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