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Triple negative breast cancer: an Indian perspective

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Introduction: Breast cancer is the most common female cancer in the world. Triple negative breast cancer (TNBC) is a recently identified biological variant with aggressive tumor behavior and poor prognosis. Data of hormonal status from the Indian population is scarce due to financial constraints in performing immunohistochemistry evaluation. The present study aims to prospectively analyze receptor status of all breast cancer patients and identify TNBC and compare their clinical profile and short term survival with other non-TNBC group.

Materials and methods: All cytologically and histopathologically confirmed cases of carcinoma breast were prospectively enrolled. In a longitudinal study at tertiary care hospital in central India based on the hormonal status, they were further divided into TNBC and other groups. Comparison of risk factors, clinical profile and short-term survival was carried out.

Results: A total 85 patients were enrolled and of them 37 (43.7%) were TNBC. On comparing risk factors ie, age, age at menarche, total reproductive age, age at first child birth, and menopausal status – no statistical significance was observed between the TNBC and non-TNBC groups. But on comparison of clinical profile TNBC tumors were significantly large with majority of patients presenting as locally advanced breast cancer (83%). No statistical difference was observed in axillary lymph node status between two groups. TNBC tumors were histologically more aggressive (grade 3) compared to other groups. No statistically significant difference was observed in short term overall survival but all three deaths were observed in the TNBC group only and two local recurrences after surgery were observed in the TNBC group.

Conclusion: TNBC forms a large proportion of carcinoma breast patients in a central Indian scenario and needs more research to identify appropriate treatment planning considering aggressive histology and advanced presentation.

Keywords: triple negative breast cancer, TNBC, hormone receptor, breast cancer, ER, PR, HER2neu

Introduction

Breast cancer is the most common malignancy worldwide accounting for 21% of all cancers[1] and is the most common cancer among females in urban India.[2,3] It is a heterogeneous disease of different biological subtypes recognized by gene expression study using DNA microarray.[4] These biological subtypes are known to have varied clinicopathological and molecular features having prognostic and therapeutic implications. Hormone receptor analysis is now an established procedure in routine management of breast cancer but the cost of evaluation and non-affordability are key concerns in performing hormone receptor analysis in an Indian scenario. With increasing prevalence of locally advanced breast cancer (LABC) and aggressive tumors it is a good rationale to evaluate hormonal status of breast cancer in central India as there is paucity of hormone

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receptor data. Triple negative breast cancer (TNBC) is a recent concept and hot topic for research. It is also associated with aggressive tumors, seen in a younger age group, with shorter disease free survival. The present study aims to establish the hormone receptor status of patients presenting in a tertiary care hospital of central India and to determine the prevalence of TNBC and its clinical and biological behavior as well as its comparison with non-TNBC patients.

Materials and methods

All histopathologically and cytologically confirmed cases of breast cancer were prospectively enrolled in a longitudinal study at a tertiary care hospital in central India between 2012 and 2014. The present study had an ethical clearance from the Institutional Ethics Committee of the institute and patients were recruited after obtaining an informed consent in local dialect. Using a case sheet, demographic details, risk factors, clinical profile, and staging of disease was recorded. Confirmation of diagnosis was done by fine needle aspiration cytology and trucut biopsy in LABC cases. Metastatic work-up was done for all patients which included ultrasonography of abdomen and pelvis and chest X-ray and Tc_{99} bone scan in selected cases. Based on the clinical examinations and measurement of breast lump by Vernier caliper and systemic investigations, patients were categorized into three groups, 1) early breast cancer (EBC), 2) LABC, and 3) advanced breast cancer. The patients with EBC were treated with modified radical mastectomy followed by six cycles of adjuvant chemotherapy with cyclophosphamide, Adriamycin, and 5-Fluorouracil (CAF) followed by hormonal therapy depending on hormone receptor and menopausal status. All LABC patients underwent trucut biopsy for hormone receptor study before starting chemotherapy. Operable LABC patients were subjected to modified radical mastectomy and inoperable LABC patients received neoadjuvant chemotherapy, 2–3 cycles of CAF. Response to chemotherapy was assessed by measuring the lump with Vernier calipers before initiating the next chemotherapy cycle and was assessed using RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1. Those patients who showed clinical response by decrease in size of lump were given three cycles of neoadjuvant chemotherapy (CAF) followed by modified radical mastectomy, followed by three cycles of adjuvant chemotherapy (CAF). Those patients showing no clinical response after two cycles underwent modified radical mastectomy followed by six cycles of adjuvant chemotherapy (taxanes). Patients with positive surgical margins received local radiotherapy. Based on hormone receptor status and menopausal status patients were started on hormonal therapy.

Table 1 Showing comparison of menopausal status

Menopausal status	TNBC	Others	Total
Premenopausal	18 (48.64%)	32 (66.66%)	50
Postmenopausal	19 (51.36%)	16 (33.33%)	35
Total	37	48	85

Note: Chi-square 2.80, P=0.009.
Abbreviation: TNBC, triple negative breast cancer.

Hormone receptor status analysis was carried out on formalin fixed paraffin block embedded tissue sections. Estrogen receptor and progesterone receptor were considered positive if >1% tumor cell nuclei were immunoreactive and negative if it was otherwise. To establish HER2 status we used US Food and Drug Administration (FDA) approved Hercep test guidelines[5] (0 and 1 is negative, 2+ is borderline, 3+ is positive). Based on immunohistochemistry findings the cases were divided into two categories. TNBC and others. Comparison of both group parameters was done using SPSS version 16 (SPSS Inc., Chicago, IL, USA). Continuous variables, after checking normality of data, were compared using Student's *t*-test while categorical variables were evaluated using Pearson's chi-squared or Fisher's exact test as deemed appropriate. Multivariate analysis was carried out using Cox regression model. Due to short duration of follow-up survival analysis was not carried out.

Follow-up of patients was done every 3 months to look for locoregional recurrence, chest X-ray and ultrasonography of abdomen and pelvis were done to rule out metastasis.

Results

A total of 85 patients were recruited prospectively based on selection criteria from June 2012 to June 2014. The mean age of the patients was 50.01±11.592 years with a range of 25–75 years and of them 50 (58.8%) were postmenopausal while 35 (41.2%) were premenopausal.

Based on hormone receptor status evaluation, 37 patients were classified as TNBC and the remaining 48 patients were

Table 2 Comparison of risk factors in TNBC and others

Risk factors	Triple negative	N	Mean	*P*-value	95% CI
Age	TNBC	37	48.41	0.26	–7.88–02.19
	Others	48	51.25	(NS)	
Age at menarche	TNBC	37	15.08	0.447	–0.834–0.371
	Others	48	15.31	(NS)	
Total reproductive age	TNBC	37	27.43	0.845	–3.08–2.531
	Others	48	27.71	(NS)	
Age at first child birth	TNBC	37	21.41	0.220	–4.215–0.984
	Others	48	23.02	(NS)	

Note: Statistics by Student's *t*-test.
Abbreviations: TNBC, triple negative breast cancer; CI, confidence interval; NS, not significant.

Table 3 Showing comparison of tumor size

Size	TNBC	Others	Total
<5 cm	6	24	30
>5 cm	31	24	55
Total	37	48	85

Note: Chi-square 9.01, *P*=0.011.
Abbreviation: TNBC, triple negative breast cancer.

Table 5 Showing comparison of axillary lymph node status

Lymph node	TNBC	Others	Total
Present	27	29	56
Absent	10	19	29
Total	37	48	85

Note: Chi-square 0.960, *P*=0.3271.
Abbreviation: TNBC, triple negative breast cancer.

allocated to the other group having varied hormone receptor status. The mean age of TNBC group was 48.25 years as compared with the other group which was 51.25 years but it was statistically not significant (*P*=0.26). Menopausal status evaluation showed more premenopausal patients in the other group compared to TNBC group and the difference was statistically significant *P*<0.001 (Table 1).

On comparing the two groups for risk factors using univariate analysis, age of these patients, age at menarche, total reproductive age, age at first child birth, there were no statistically significant differences between the two groups (Table 2).

The duration of presentation was 7.5 months in TNBC group compared with 6.8 months in the other group and the difference was statistically insignificant (*P*>0.01), whereas the size of the tumor was larger in the TNBC group ie, >5 cm in 31 patients out of 37 patients, this was statistically significant on comparison with the other group (Table 3).

After excluding the advanced breast cancer group, two groups were compared as LABC and EBC, there was a significantly higher number of patients with LABC in the TNBC group suggestive of locally advanced and aggressive disease (*P*=0.001) (Table 4).

Positive axillary lymph nodes were observed in 72.97% in TNBC compared to 60.41% in the other group but this difference was not statistically significant (Table 5).

On comparing the two groups for Nottingham histological grading of the tumor it was observed that tumors in the TNBC group were higher than grade 3 as compared to others and this difference was statistically significant (Table 6).

On carrying out multiple logistic regression analysis, Nottingham grade and LABC was statistically associated with TNBC, suggesting aggressive behavior of TNBC. On further analysis, local recurrence was observed in two of the 37 TNBC patients compared to none in the other group. This difference was statistically not significant (Table 7) and overall short-term survival showed three deaths in TNBC compared to none in the other group but this difference was also statistically not significant (Table 8).

Discussion

There is an increasing burden of breast cancer worldwide and in India it is also a cause of concern to health providers and is an important area of research. Introduction of newer technological methods giving insights into tumor biology is also an important area of research solely because of paucity of Indian data and a high prevalence of LABC. The present research was aimed at identifying biologically aggressive tumors with the long-term aim of developing therapeutic strategies and predicting outcomes.[6] The present study is a prospective evaluation of the presence of triple negative cancer in a central Indian population and its comparison with risk factors, clinical presentation, and short-term outcome of other hormonal status malignancies.

The literature review shows TNBC accounts for 15% of all breast cancer.[7–9] More frequently observed and with worst prognosis in young black women.[10,11] In the present study this prevalence was 43.5% of all breast cancers and this is consistent with persistently higher prevalence quoted in Indian populations and ethnic groups (Table 9).[12–14]

Literature from India and the rest of the world showed TNBC was observed in a younger population[15] but the present study showed no significant age difference when compared with other groups and this is consistent with only one study from Turkey.[16]

Table 4 Showing comparison of disease stage

Type	TNBC	Others	Total
LABC	26	27	53
EBC	5	19	24
Total	31	46	77

Note: Chi-square 5.47, *P*=0.01.
Abbreviations: TNBC, triple negative breast cancer; LABC, locally advanced breast cancer; EBC, early breast cancer.

Table 6 Showing comparison of Nottingham histological grade

Nottingham grade	TNBC	Others	Total
1 and 2	13	35	48
3	24	13	37
Total	37	48	85

Note: Chi-square 12.13, *P*=0.0004.
Abbreviation: TNBC, triple negative breast cancer.

Table 7 Showing comparison of local recurrence

Recurrence	TNBC	Others	Total
No recurrence	29	46	75
Recurrence	2	0	2
Total	31	46	77

Notes: Fisher's exact test, P=0.1589. Advanced breast cancer cases excluded n=8.
Abbreviations: TNBC, triple negative breast cancer; ABC, advanced breast cancer.

On comparing the tumor size between the two groups, it was observed in the present study that tumors in the TNBC group were larger in size (more than 5 cm) as compared to the other group and this finding was quite consistent with the literature.[16,17] When this was further compared by staging it was evident that a large number of patients in the TNBC group had LABC, suggesting aggressiveness of the malignancy. Duration of presentation in both groups was similar. Considering that the duration of presentation in both groups were similar, increased occurrence of LABC in TNBC indirectly suggests aggressiveness of the disease. In TNBC there is controversy regarding axillary lymph node metastasis. Lymph node-negative breast cancer is widely reported in the literature but this is contrary to our study results with 73% TNBC patients showing involvement of axillary lymph nodes. These findings confirm results from a study from North East India.[12]

When evaluating the grade of tumors using the Nottingham grading score, there was a difference noted in tumors of the TNBC group compared to the other group, as the majority of TNBC tumors were of higher grades. These results are consistent with available literature.[18–21]

Though the present study also looked at the overall survival and local recurrence between the two groups with median survival period of 24 months, there was no significant difference noted between the two groups. However 8.1% patients in the TNBC group succumbed to breast cancer and there was 6.4% local recurrence which is quite significant clinically. This 2-year period is too short to comment on disease free and overall survival.

To conclude, this was a prospective study evaluating the hormone receptor status of breast cancer patients in central India. However, we tried to identify a subgroup of malignancy ie, triple negative phenotype which is a marker of basal type cell carcinoma. The prospective study also helped us to correlate the clinical status and risk factors which had no effect on tumor biology. Triple negative cancer is commonly a prevalent phenotype in patients of central India accounting for 43% of all breast cancer with high grade large tumors and early local recurrence and poor prognosis which needs a definitive review of treatment strategy as TNBCs do not respond to hormone therapy.

The only limitation of the study is its small sample size but it still gives insight into biological typing of breast cancer in central India which comprises of a non-White ethnic groups and clinical correlation with LABC with higher grades of histopathology.

Table 8 Showing comparison of short-term survival

Survival	TNBC	Others	Total
DFS	34	48	82
Death	3	0	3
Total	37	48	85

Note: Fisher's exact test, P=0.07.
Abbreviations: TNBC, triple negative breast cancer; DFS, disease free survival.

Table 9 Showing prevalence of TNBC worldwide

Author	Year	Country	Number of cases	Prevalence (%)
Dunnwald et al[7]	2007	USA	155,175	25
Bauer et al[17]	2007	USA	92,358	12.5
Rakha et al[8]	2007	UK	1,726	16.3
Onitilo et al[9]	2009	USA	1,134	13.4
Ambroise et al[13]	2011	India	2,001	29.8
Ma et al[19]	2012	Hong Kong	1,800	12
Li et al[20]	2013	People's Republic of China	21,749	12.18
Somali et al[16]	2013	Turkey	882	15
Zubeda et al[14]	2013	India	619	46
Sharma et al[12]	2014	India	972	31.9
Present study	2015	India	85	43.5

Abbreviation: TNBC, triple negative breast cancer.

Disclosure

The authors have no conflicts of interest in this work.

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