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Survival analysis of triple negative breast cancer patients treated with Anthracycline based chemotherapy: A Retrospective Study from Central part of India

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ABSTRACT

Introduction: Triple negative breast cancer (TNBC) is diagnosed more frequently in younger and premenopausal women. TNBC are biologically aggressive tumours, not benefited from hormonal or targeted therapy although some reports suggest that they respond well to chemotherapy. The aim of our study is was to assess the response of anthracyclines based adjuvant chemotherapy in triple negative breast cancer.

Materials and Methods: This is was a retrospective study conducted on 100 post-operative patients, histopathologically proven ductal Carcinoma Breast, from January 2016 to March 2017 presenting to tertiary care centre. All patients were triple negative as assessed by immunohistochemistry and fluorescence in situ hybridization technique. Patients were planned for six cycles of Anthracycine based combination adjuvant chemotherapy. Data were analyzed by SPSS 20 and survival analysis was done.

Results: A total of 100 patients were included in this study. Out of these,18patients (18%) were defaulted after chemotherapy, 29 patients (29%) were lost during subsequent follow ups and 49 patients (49%) had disease free survival (DFS) and 4 patients (4%) survived with bone metastasis. The median survival was 18 months, disease free survival was 7.8 months and 3 year overall survival (OS) was 18.6 months.

Conclusions: TNBC represent a challenge for the patients and the clinician due to its poor prognosis and fewer treatment options. The adjuvant Anthracycline -based combination chemotherapy predict improved long term outcomes for TNBC.

1. Introduction

Breast cancer is a heterogeneous disease with different characteristics such as age, tumor stage, lymph node involvement and pathologic grade which are associated with disease prognosis.[1–3] With rising incidence and awareness, breast cancer has become the commonest cancer in urban Indian females and the second commonest in the rural Indian women.[4] Over 100,000 new breast cancer patients are estimated to be diagnosed annually in India.[5] With a rising trend in incidence reported from various registries of National Cancer Registry Program, presently India has become the country with the largest estimated number of breast cancer deaths worldwide.[6]

Triple negative breast cancers (TNBCs) are defined as the lack of expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2).[7] These cancers occur in approximately 10% to 25% of all patients with breast cancer with significant heterogeneity existing within the group of patients diagnosed with TNBC. The primary goal of this

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study was to assess the response of anthracyclines based adjuvant chemotherapy in triple negative breast cancer.

2. Materials and Methods

The retrospective study was done on 100 post-operative patients, who were proven ductal carcinoma on histopathology. Patient identifier data were anonymized to preserve patient confidentiality. The study period of the study was from January 2016 to March 2017. All 100 patients were triple negative as assessed by immunohistochemistry and fluorescence in situ hybridization technique.

ER and PR positive were defined as positive immunohistochemical staining in more than 10% of tumor cells. HER-2 status was determined according to the guideline recommended by College of American Pathologists.[8] Immunohistochemistry assay with anti-HER2 antibodies was used to identify HER negative (0 and 1+) or positive (2+ and 3+). HER2 gene amplification was determined by fluorescent in situ hybridization (FISH). Tumors with a positive FISH result were considered as HER2 positive. Parameters assessed included age at the time of diagnosis, tumor histology, nuclear grade, lymphovascular invasion, perineural invasion, tumor size, pathologic tumor (T) and nodal (N) score, OS and type of surgery.The immunostaining procedures were performed using formalin-fixed, paraffin-embedded tissue sections. The sections were immunohistochemically stained for ER, PR, HER2, HMWCKs, c-Kit and EGFR according to the protocols. Tumors negative for ER, PR and HER2 were considered as triple-negative.

Patients were planned for six cycles of Anthracycline based combination adjuvant chemotherapy. Data was analyzed using SPSS v 20. Disease free survival and overall survival durations were analyzed with the Kaplan-Meier method. Comparisons among clinical variables were performed with Person Chi-square test. All tests were 2-tailed and the statistical significance was set as $P<0.05$.

3. Results

A total of 100 patients were included in this study. Demographic profile of the study subjects are shown in Table 1. Most of the women belongs to rural area (53%). As far as age group is concerned, majority i.e. 48% are in age group of 40-50 years followed by 30-40 years age group.

Out of these, 18 patients (18%) were defaulted after chemotherapy, 29 patients (29%) were lost during subsequent follow ups. 49 patients (49%) had disease free survival (DFS)and 4patients (4%) survive with bone metastasis. The median survival was 18 months, disease free survival was 7.8 months and 3 year overall survival (OS) was 18.6 months.

Table 1: Demographic characteristics of patients.

Profile		
	Rural	53
	Urban	47
Age group		
	20-30 years	6
	30-40 years	38
	40-50 years	48
	>50 years	8

Table 2: Clinicopathological Features of Triple-negative Breast Cancer.

Characteristics		
Age (mean)	44.6 years	
Menstrual history	Pre menopausal	48
	Peri menopausal	38
	Post menopausal	14
Laterality	Right	32
	Left	65
	Bilateral	3
Tumour size	<2cm	1
	2-5cm	6
	>5cm	93
LN Status	Negative	1
	Positive	99
Stage	I	1
	II	1
	III	94
	IV	4
Surgery	MRM	98
	BCS	2
Axilla clearance	Yes	5
	NA	95
Histological grade	I	13
	II	23
	III	64
LN status	Positive	98
	Negative	2
Extracapsular extension	Present	56
	Negative	33
	NA	11
Lymph-vascular invasion	Present	76
	Absent	24

Table 3: Showing the end result of events in survival analysis.

Event	**No. of Patients**
Defaulted after chemotherapy	18
Lost during subsequent follow ups	29
Disease free survival	49
Bone metastasis	4

4. Discussion

Breast cancer is a heterogeneous disease comprising of distinct biological subtypes with diverse natural history, presenting with varied spectrum of clinical, pathological and molecular features with different prognostic and therapeutic implications. Increasing burden of breast cancer has led to enormous change in the treatment strategies due to discovery of specific prognostic and predictive biomarkers that enable the application of more individualized targeted therapies following hormone receptor testing.[9,10]

Basal like cancer accounts for 15% of all breast carcinoma, 75% being triple negative. Studies have shown that this phenotype is more common in young African women facing worse prognosis compared to other ethnic group as observed by other researchers.[11,12] In 2009, a case control study showed 2.5 fold increased risk for Oral Contraceptive Pill (OCP) users using for more than one year than women using for less than a year or never.[13] Other associations with the triple negative subtype include higher parity and lack of or shorter duration of breast feeding.[14] As per the results of some studies, association of obesity is consistent with TNBC.[15-20][15–20] Patients with triple negative breast cancers tend to present at younger age and with more advanced cancer.[21–23]

Earlier studies had reported that TNBC phenotype show significantly higher FDG uptake compared to ER, PR positive and HER2/NEU negative, probable explanation may be related to aggressive biology of the tumor.[24] At the current time, TNBC lack any specific targeted therapy. Combined chemotherapy is the standard treatment like anthracycline, taxanes, ixabepitine and platinum agents. BRCA1 related TNBC appears to be particularly susceptible to chemotherapy involving Platinum based agents and Taxanes.[25,26]

In the present study, TNBC is common in younger groups. This observation was concordant with many other studies conducted by many other people in the previous decade.[27–30] However few studies have shown higher incidence of TNBC in postmenopausal women[29,31,32] In one published study in Turkey, no significant difference in age was found in both two groups.[33]

According to the literature, patients with TNBC present with relatively larger size compared to non TNBC group which is consistent with our results.[30,31,34] Aggressive tumour biology and rapid growth and proliferation are possible explanations for these findings.

In our study a high rate of node positivity was found in TNBC. Comparing the histological subtypes, IDC NOS comprised maximum number of cases. Similar results were observed in other studies conducted over the other countries.[34–38] The patients in our study were mostly diagnosed with grade III tumor, which is similar to the findings of other studies.[30,31,34,36] This finding is consistent with the explanation of aggressive tumour biology and high potential for visceral and bone metastasis.

Results from our study showed that 4% of the cases presented with bone metastasis during follow up. Approximately half of the cases had a disease free survival(DFS) of 7.8 months which is similar to the results obtained from other studies.[31,34]

Some patients (29%) were lost during subsequent follow ups and 18% had defaulted after chemotherapy. This along with less number of cases in the study population are the main limitation of our study. Also, we did not directly assess tumors for molecular subtype. We did not have information on percent staining of ER or PR by IHC, nor did we have information on cytokeratin or epidermal growth factor receptor staining; these variables may influence the proportion of patients with true basal subtype, and separate triple-negative tumors into different prognostic groups. Another drawback is the short duration of follow-up as the longer follow-up may make clearer differences in OS and DFS between two subgroups.

5. Conclusion

The disease stage at presentation is an important prognostic factor influencing the treatment failure and survival among TNBC. The increasing tumor size is related to lymph node positivity. The adjuvant Anthracycline-based combination chemotherapy predict improved long term outcomes for TNBC. Future analyses will be needed on the prognostic significance of tumor size and nodal status in the triple-negative subset, and on variations in patterns of care.

6. Source of funding

None.

7. Conflict of Interest

None.

References

1. Brenton JD, Carey LA, Ahmed AA. Molecular classification and molecular forecasting of breast cancer: ready for clinical application. *J Clin Oncol*. 2005;23:7350–7360.
2. Elston CW, Ellis IO, Pinder SE. Pathological prognostic factors in breast cancer. *Crit Reu Oncol Hematol*. 1999;31(3):209–223.
3. Soerjomataram I, Louwman MW, Ribot JG, Roukema JA, Coebergh JW. An overview of prognostic factors for long term survivors of breast cancer. *Breast Cancer Res Treat*. 2008;107(3):309–330.
4. Takiar R, Vijay CR. An alternative approach to study the changes in the cancer pattern of women in India. *Asian Pac J Cancer Prev*. 1988;11:1253–1256.
5. Nandakumar A, Anantha N, Venugopal TC. Survival in breast cancer: a population-based study in Bangalore, India. *Int J Cancer*. 1995;60:593–596.
6. Nandakumar A, Gupta PC, Gangadharan P, Visweswara RN, Parkin DM. Geographic pathology revisited: development of an atlas of cancer in India. *Int J Cancer*. 2005;116:740–754.
7. Liedtke C, Mazouni C, K RH. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. *J Clin Oncol*. 2008;28:1275–1281.

8. Wolff AC, Hammond ME, Schwartz JN. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol*. 2007;25:118–145.
9. Quiet CA, Ferguson DJ, Weichselbaum RR, Hellman S. Natural history of node negative breast cancer, a study of 826 patients with long term follow up. *J Clin Oncol*. 1995;13:1144–1151.
10. Sharma M, Sharma JD, Sarma A, Ahmed S, Kataki AC, et al. Triple Negative Breast Cancer in People of North East India: Critical Insights Gained at a Regional Cancer Centre. *Asian Pac J Cancer Prev*. 2014;15(11):4507–4511.
11. Reynolds S. Spotlight: triple -negative breast carcinoma disproportionately affects African American and hispanic women. *NCI Cancer Bull*. 2007;4.
12. Chutstecka Z. Survival Disadvantage Seen for TNBC. *Medscape Med News*. 2008;.
13. Dolle JM, Dating JR, White E. Risk factors for TNBC in women Under age 45. *Cancer Epidemiol Biomarkers Prev*. 2009;18:1157–1166.
14. Moore MA, Ariyaratne Y, Badar F. Cancer epidemiology in South Asia- past, present and future. *Asian Pac J Cancer Prev*. 2010;11:49–66.
15. Phipps AI, Malone KE, Porter PL, Daling JR, Li CI. Body size and risk of luminal, HER2−over-expressing, and triple-negative breast cancer in postmenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2008;17:8–86.
16. Millikan RC, Newman B, Tse CK, Moorman PG, Conway K, et al. Epidemiology of basal-like breast cancer. *Breast Cancer Res Treat*. 2008;109(1):123–139.
17. Stead LA, Lash TL, Sobieraj JE, Chi DD, Westrup JL, et al. Triple-negative breast cancers are increased in black women regardless of age or body mass index. *Breast Cancer Res*. 2009;11(2).
18. Troester MA, Swift-Scanlan T. Challenges in studying the etiology of breast cancer subtypes. *Breast Cancer Res*. 2009;11(3).
19. Kwan ML, Kushi LH, Weltzien E, Maring B, Kutner SE, et al. Epidemiology of breast cancer subtypes in two prospective cohort studies of breast cancer survivors. *Breast Cancer Res*. 2009;11(3).
20. Lara-Medina F, Perez-Sanchez V, Saavedra-Perez D, Blake-Cerda M, Arce C, et al. Triple-negative breast cancer in Hispanic patients: high prevalence, poor prognosis, and association with menopausal status, body mass index, and parity. *Cancer*. 2011;117(16):3658–3669.
21. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, et al. breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *Jama*. 2006;295(21):2492–2502.
22. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. *Clin Cancer Res*. 2007;13(15):4429–4434.
23. Yang XR, Sherman ME, Rimm DL, Lissowska J, Brinton LA, et al. Differences in risk factors for breast cancer molecular subtypes in a population-based study. *Cancer Epidemiol Biomarkers Prev*. 2007;16(3):439–443.
24. Basu S, Chen W, Tchou J. Comparison of triple negative and estrogen receptor positive/progesterone receptor positive/HER 2 negative breast carcinoma using quantitative fluorine-18 flurodeoxyglucose/positron emission tomography imaging parameters: a potentially use full method for disease characterization. *Cancer*. 2008;112:995–1000.
25. Hudis CA, Gianni L. Triple negative breast cancer. An unmet medical need. *Oncologist*. 2011;16:1–11.
26. Thike AA, Cheok PY, Jara-Lazaro AR. Triple- negative breast cancer: clinicopathological characteristics and relationship with basal-like breast cancer. *Mod Pathol*. 2010;23:123–133.
27. Anderson WF, Luo S, Chatterjee N, Rosenberg PS, Matsuno RK, et al. Human epidermal growth factor receptor-2 and estrogen receptor expression, a demonstration project using the residual tissue repository of the Surveillance, Epidemiology, and End Results (SEER) program. *Breast Cancer Res Treat*. 2009;113(1):189–196.
28. Cheang M, Voduc D, Bajdik C. Basal- like breast cancer women. *NCI Cancer Bull*. 2008;4.
29. Iwase H, Kurebayashi J, Tsuda H. Clinicopathological registration committee of the Japanese breast cancer society. *Breast Cancer*. 2010;17.
30. Li CY, Zhang S, Zhang XB. Clinicopathological and prognostic characteristics of triple-negative breast cancer (TNBC) in Chinese patients: a retrospective study. *Asian Pac J Cancer Prev*. 2013;14:3779–3784.
31. 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. *Cancer*;109:1721–1728.
32. Ambroise M, Ghosh M, Mallikarjuna VS, Kurian M. Immunohisto-chemical profile of breast cancer patients at a tertiary care hospital in South India. *Asian Pac J Cancer Prev*. 2011;12:625–629.
33. Ma KK, Chau WW, Wong CH. Triple negative status is a poor prognostic indicator in Chinese women with breast cancer: a ten year review. *Asian Pac J Cancer Prev*. 2013;13:2109–2114.
34. Somali I, Ustaoglu BY, Tarhan MO. Clinicopathologic and demographic evaluation of triple- negative breast cancer patients among a Turkish patient population: a single center pack up our microscopes? *Pathol*. 2013;43:1–8.
35. Ferlay J, Soerjomataram I, Ervik M. GLOBOCAN 2012 v 1.0, Cancer incidence and Mortality Worldwide: IARC Cancer Base No. Lyon, France ; 2013,. Available from: http://globocan,iarc.fr.
36. Carey LA, Perou CM, Livsay CA. Race, breast cancer subtypes, and survival in the Carolina breast cancer study. *JAMA*. 2006;295:2492–2502.
37. Yuan ZY, Wang SS, Gao Y. Clinical characteristics and prognosis of triple-negative breast cancer: a report of 305 cases. *Ai Zheng*. 2008;27:561–565.
38. Yuli C, Shao N, Rao R. BRCA1a has anti-tumor activity in TN breast, ovarian and prostate cancers. *Oncogene*. 2007;26:6031–6037.

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