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Research Article

Prognostic Factors and Survival Analysis of Patients with Triple Negative Breast Cancer - A Retrospective Study

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ABSTRACT
Introduction: Breast cancer accounts for the highest number of cases of all the cancers in females worldwide including India where it has an increasing trend of 27. 7 % with 162,468 newly detected cases and 87,090 deaths (11.1 % of the total cancer-related deaths) in India as per Global cancer statistics (GLOBOCAN) 2018, The triple-negative breast cancers (TNBC) are considered as the most malignant subtypes with a multitude of distinctive hostile clinicopathological characteristics, like the age of onset and large size of the tumour, higher tumour grade, the early peak of recurrence, and a worse 5-year overall survival rate.
Materials and Methods: This single-institution retrospective study included a TNBC patient cohort determined as per histopathological guideline according to WHO classification and histological grade of tumours based on Nottingham histological score which was treated in the Department of Radiation Oncology, Kurnool Medical College, Kurnool between January 2023 and December 2023.
Results: 33 patients were eligible for this study as non-metastatic TNBC. Of the total 325 cases of breast cancer cases reported in the study period, non-metastatic TBNC came around 20 % (67 cases). The median age at diagnosis was 51.36 ± 11.393 (range, 30.0-80.0 years). Patient characteristics are shown in Table 1. Only 6 % had a family history of breast cancer. The majority of the patients were premenopausal (53.75 %). Most of the patients had ductal carcinoma (92. 5%) followed by metaplastic (4.5 %) and medullary carcinoma (3.0 %). Clinically, majority of the patients were of T2 stage (41.9 %) and N1 stage (59.6 %). Composite clinical stage 2 dominated (49.5 %) followed by stage 3 (46.3 %) and stage 1 (4.2 %). 62.8 % were of p T2 stage and 36 % idiopathic neutropenia (inp) N0 stage which constitutes major portion. Pathological nodal positivity was seen in 46.3 %. Clinically and pathologically tumour stage and the nodal stage was proportionate on cross tab analysis. Nodal density ≤ 0.05 was present in 65.7 % of the patients, whereas 34.3 % of patients had nodal density ≥ 0.05. Lymphovascular invasion was positive in 22.4 % (N = 7) and was absent in 77.6 % of the patients. Margin positivity was present in 4 patients (11.9 %).
Conclusion: Triple-negative breast cancer is a heterogeneous disease and poses a major challenge and uphill task during treatment as these tenacious tumours have aggressive tumour biology. In the absence of biomarker-based therapeutic methods, targeted treatments neglect one significant desired outcome aimed at minimizing recurrences and improving survival in this patient population. There are many developments in treatments for metastatic triple- negative breast cancer, such as poly-ADP ribose polymerase (PARP) inhibitors, EGFR targeted therapies and tailor-made therapies but in non-metastatic breast cancer there is a dearth of adequacy in available therapeutics as treatment is still heavily dependent on available chemotherapeutic regimens.

Keywords: Breast Cancer, Overall Survival Rate, Idiopathic Neutropenia, EGFR Targeted Therapies.

INTRODUCTION

Breast cancer accounts for the highest number of cases of all the cancers in females worldwide including India where it has an increasing trend of 27. 7 % with 162,468 newly detected cases and 87,090 deaths (11.1 % of the total cancer-related deaths) in India[1] as per Global cancer statistics (GLOBOCAN) 2018, The triple-negative breast cancers (TNBC) are considered as the most malignant subtypes with a multitude of distinctive hostile clinicopathological characteristics, like the age of onset and large size of the tumour, higher tumour grade, the early peak of recurrence, and a worse 5-year overall survival rate.[2]

Seventy to 80% of all breast cancers are positive for estrogene (ER) or progesterone receptors (PgR). In contrast, the human epidermal growth factor receptor (HER2) protein over expression and/or HER2 gene are

over expressed and/or amplified, respectively, in approximately 15–20% of the patients only, with around half of these coexpressing hormone receptors. The remaining 10–15% of breast cancers is negative for ER, PgR and HER2. These are defined as triple negative breast cancer (TNBC).[3]

TNBC comprises of about 15 - 20 % of total breast cancers in Indian females, The mean age of presentation is less than 50 years[3], which is lower than invasive breast cancers in Western populations often diagnosed in late-stage with a majority (about 70 %) at an advanced clinical stage at the time of diagnosis.[4,5]

This study describes the clinicopathological characteristics and intends to analyse prevalence, recurrence rate and survival of TNBC patient cohort treated in Department of Radiation Oncology, Kurnool Medical College, Kurnool, and Andhra Pradesh.

OBJECTIVES

The study's purpose was to look into the clinical behaviour and poor prognosis of triple negative breast cancer patients in AP, as well as how different prognostic factors can aid in focused treatment planning. The analysis of the effect of prognostic factors on triple negative breast cancer was secondary objective. There have been many such studies published in the Western world, but very few have been recorded from India, and this will be the first from AP.

MATERIALS AND METHODS

Study Design: A single-institution retrospective study.

Study Location: Department of Radiation Oncology, Kurnool Medical College, Kurnool.

This single-institution retrospective study included a TNBC patient cohort determined as per histopathological guideline according to WHO classification and histological grade of tumours based on Nottingham histological score which was treated in the Department of Radiation Oncology, Kurnool Medical College, Kurnool between January 2023 and December 2023.

All the patients were classified according to the American Joint Committee on Cancer (AJCC TNM) 7th edition. A total of 162 breast cancer cases were reported during that period, of which 33 patients were TNBC. The data retrieved included: patient's characteristics (age at diagnosis, menopausal status, and family history), tumour characteristics (grade, size, nodal involvement and metastases at presentation), composite and pathological stage, number of involved lymph nodes, node density, and treatment received (surgery, chemotherapy, and radiotherapy) and recurrence data (type, size, and date). Disease-free survival was defined from the start of primary therapy to the date of disease recurrence, or last follow-up. Overall survival was defined as the time from the date of the start of primary therapy to the date of death or the last follow-up.

Statistical Analysis:

Statistical evaluation was done using IBM SPSS version 20. Data were described in terms of mean ± standard deviation (SD) or frequencies and percentage when appropriate. The 5-year disease-free survival and overall survival were estimated using the Kaplan-Meier method. P-value < 0.05 was considered statistically significant. Univariate analysis of prognostic factors was done by log-rank test and multivariate analysis by Cox regression model.

RESULTS

33 patients were eligible for this study as non-metastatic TNBC. Of the total 325 cases of breast cancer cases reported in the study period, non-metastatic TBNC came around 20 % (67 cases). The median age at diagnosis was 51.36 ± 11.393 (range, 30.0-80.0 years). Patient characteristics are shown in Table 1. Only 6 % had a family history of breast cancer. The majority of the patients were premenopausal (53.75 %). Most of the patients had ductal carcinoma (92. 5%) followed by metaplastic (4.5 %) and medullary carcinoma (3.0 %). Clinically, majority of the patients were of T2 stage (41.9 %) and N1 stage (59.6 %). Composite clinical stage 2 dominated (49.5 %) followed by stage 3 (46.3 %) and stage 1 (4.2 %). 62.8 % were of p T2 stage and 36 % idiopathic neutropenia (inp) N0 stage which constitutes major portion. Pathological nodal positivity was seen in 46.3 %. Clinically and pathologically tumour stage and the nodal stage was proportionate on cross tab analysis. Nodal density ≤ 0.05 was present in 65.7 % of the patients, whereas 34.3 % of patients had nodal density ≥ 0.05. Lymphovascular invasion was positive in 22.4 % (N = 7) and was absent in 77.6 % of the patients. Margin positivity was present in 4 patients (11.9 %).

	Variable	N (%)
Age (years)	≤50	18 (55.2 %)
	>50	15 (44.8 %)
Family History	Yes	2 (6%)
	No	63 (94 %)
Menopausal status	Premenopausal	18 (53.7 %)
	Postmenopausal	15 (46.3 %

Table 1. Patients' Characteristics (N = 67)

		Frequency	%
Clinical tumour stage	T1	1	3%
	T2	18	53.7%
	T3	11	31.3%
	T4	4	11.9%
Clinical nodal stage	N0	12	34.3%
	N1	17	50.7%
	N2	4	13.4%
	N3	1	1.5%
Composite stage	1	1	3.0%
	2	20	61.2%
	3	12	35.8%
Pathological tumour stage	PT1	1	3%
	PT2	22	45%
	PT3	9	17%
	PT4	2	3%
Pathological nodal stage	PN0	18	53.7%
	PN1	8	23.9%
	PN2	6	17.9%
	PN3	2	4.5%
Grade	1	2	6%
	2	16	49.3%
	3	16	44.8%
Lymphovascular invasion	Present	7	22.4%
	Absent	26	77.6%
Margin	Negative	30	88.1%
	Positive	4	11.9%
Histology	Ductal	31	92.5%
	Medullary	1	3%
	Metaplastic	1	3%
Pathological complete response	Present	3	25%
	Absent	9	75%
Nodal density	≤ 0.05	22	65.7%
	> 0.05	12	34.3%
Postoperative radiation	Yes	20	61.2%
	No	13	38.8%
Surgery	MRM	30	91%
	BCS	3	9%
Chemotherapy	Neoadjuvant	12	35.8%
	Adjuvant	21	64.2%
Chemo protocol	Anthracycline	2	9%
	Anthracycline taxane sequential	25	76.1%

	Anthracycline and taxane concurrent	5	14.9%
Local recurrence	Yes	2	6%
	No	31	94%
Metastasis	No metastasis	20	61.2%
	Bone	1	3%
	Lung	6	16.4%
	Liver	1	3%
	Brain	3	9%
	Multiple sites	3	7.5%

Table 2. Tumour Characteristics, Treatment Lines and Patterns of Failure

Variable		Disease Free Survival		Overall Survival	
		%	P-Value	%	P-Value
Age	≤ 50 years	54.1%	0.395	56.8%	0.11
	> 50 years	66.7%		76.7%	
Menopausal status	Premenopausal	55.6%	0.592	58.3%	0.211
	Postmenopausal	64.5%		74.2%	
Grade	1	100%	0.02	100%	0.112
	2	69.7%		72.7%	
	3	43.3%		53.3%	
Clinical tumour stage	T1	100%	0.0001	100%	0.0001
	T2	77.8%		83.3%	
	T3	42.9%		47.6%	
	T4	12.5%		25%	
Clinical nodal stage	N0	78.3%	0.0001	82.6%	0.0001
	N1	58.6%		67.6%	
	N2	22.2%		22.2%	
	N3	0%		0%	
Pathological tumour stage	PT1	100%		100%	
	PT2	64.4%		71.1%	
	PT3	47.1%		47.1%	
	PT4	33.3%		66.7%	
Pathological nodal stage	PN0	83.3%	0.0001*	83.3%	<0.0001
	PN1	56.3%		81.3%	
	PN3	8.3%		8.3%	
	PN4	0		0	
Lymphovascular invasion	Yes	33.3%	0.012	46.7%	0.052
	No	67.3%		71.2%	
Nodal density	≤ 0.05	72.7%	0.1	75%	0.01
	> 0.05	34.8%		47.8%	
Pathological complete response (neoadjuvant cases only)	Yes	66.7%	0.1	83.3%	0.088
	No	27.8%		38.9 %	

Table 3. Univariate Survival Analysis

Variable	Disease Free Survival HR (CI)	P Value	Overall Survival HR (CI)	P value
Age	1.04 (0.96 - 1.12)	0.340	1.02 (0.94 - 1.12)	0.673
Menopausal status	0.64 (0.12 - 3.43)	0.603	0.3 (0.05 - 1.94)	0.205

Grade	1.38 (0.55 - 3.44)	0.495	0.97 (0.34 - 2.80)	0.960
Clinical tumour stage	3.79 (1.89 - 7.60)	0.001	3.03 (1.40 - 6.56)	0.005
Clinical Nodal Stage	0.67 (0.27 - 1.68)	0.396	1.74 (0.73 - 4.17)	0.211
Pathological tumour stage	0.66 (0.30 - 1.44)	0.292	0.57 (0.23 - 1.38)	0.21
Pathological nodal stage	5.30 (2.22 - 12.63)	0.0001	4.45 (1.85 - 10.67)	0.0001
Lymphovascular invasion	1.21 (0.42 - 3.5)	0.727	1.17 (0.41 - 3.38)	0.767
Nodal density	0.537 (0.186 - 1.55)	0.25	0.44 (0.13 - 1.41)	0.166

Table 5. Multivariate Survival Analysis

DISCUSSION

TNBC, particularly in Indian women, has a frightening increase in incidence, and remains a challenge and scourge for clinicians to obtain treatment. TNBC has not only characteristic of aggressive clinical behaviour and insensitivity for endocrine and HER-2 targeted therapeutic strategies but also has the tendency for rapid metastasis and early relapses.

More in-depth studies have now separated TNBC into various subtypes based on their molecular characteristics in the modern period. Lehman et al discovered six distinct subtypes of androgen receptors in TNBC by studying their gene expression profiles: basal-like 1 and 2, immunomodulatory, mesenchymal, mesenchymal stem-like, and luminal androgen receptors.12 Burstein et al. proposed a new classification for TNBC, dividing it into four subtypes: luminal androgen receptor, mesenchymal, basal-like immune-suppressed, and basal-like immune-activated. The basal-like immune-activated subtype was found to be associated with a positive prognosis in the same study.

TNBC with its heterogeneous nature and theses several subtypes which have different natural histories and may react to different treatment Approach based on chemotherapy, targeted therapy and immunotherapy. Based the approach to TNBC care remains challenging primarily because of its other high proliferative activity and grade, absence of infiltrative margin, focal necrosis, absence of gland formation, central scar / fibrotic foci, and existence of predominant lymphoplasmacytic infiltrates, rendering surgery and chemotherapy the only available treatment choices in combination or individually. Various studies from India and the western world have estimated TNBC in between 27 % to 35 % in literature and is estimated to be around 31 % as reported by Sandhu, et al. Lakshmaiah et al. Suresh et al. The mean age of TNBC in our study was 51.6 years which was almost similar to our studies to that described in various studies in Western literature from the Indian perspective Chintalapani et al.

CONCLUSION

Triple-negative breast cancer is a heterogeneous disease and poses a major challenge and uphill task during treatment as these tenacious tumours have aggressive tumour biology. In the absence of biomarker-based therapeutic methods, targeted treatments neglect one significant desired outcome aimed at minimizing recurrences and improving survival in this patient population. There are many developments in treatments for metastatic triple- negative breast cancer, such as poly-ADP ribose polymerase (PARP) inhibitors, EGFR targeted therapies and tailor-made therapies but in non-metastatic breast cancer there is a dearth of adequacy in available therapeutics as treatment is still heavily dependent on available chemotherapeutic regimens. For improved survival and positive clinical outcomes, we can look for the use of predictive biomarkers which are indispensable and can help in designing a targeted treatment approach currently being used in metastatic triple-negative breast cancer treatment. In current era of immunotherapy, novel biomarkers that can predict immunotherapeutic response must be identified and implemented as soon as possible for better outcomes. In Indian clinical setup and especially centres like Kurnool will be heavily benefitted with this enforcement and appurtenances with superior targeted therapies to address a challenging disease like TNBC. The

identification of predictive biomarkers, as well as a comprehensive understanding of their clinical and molecular diversity, are critical for future therapeutic changes. It will aid in the advancement of TNBC care by implementing a new receptor based targeted approach in the adjuvant and neo adjuvant stages rather than the metastatic stage for more selective and effective disease therapy and better outcome.

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