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Triple Negative Breast Cancer: Alarming Burden and Future Challenges in Indian Perspective

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Abstract: **Breast cancer accounts for the highest number of cases of cancer in females worldwide including India. Triple negative breast cancer is a very aggressive and heterogeneous variant of breast cancer. They present early in young females with large sized lumps, high histological grade, and advanced stage at the time of diagnosis. They have increased tendency to metastasize with frequent relapses. It forms a large proportion of breast cancer patients in India and its tumor biology and behavior is poorly understood. There is lack of a hormonal or targeted therapy due to absence of hormone receptors with early recurrences despite of timely medical and surgical intervention. This review provides a general overview and understanding of the triple negative breast cancer and the future challenges it poses in Indian scenario.**

Index Terms: **Breast Cancer, Hormonal therapy, Recurrence, Triple negative breast cancer, Tumor biology**

I. Introduction

Cancer remains a scourge for the mankind**.** After lung cancer, breast cancer is the second most common form of cancer. It is the most common cancer among females worldwide. It accounts for 11.6 % of total cancer with 2,088,849 newly diagnosed cases and 626,679 annual deaths despite improvement and refinements in diagnostic and treatment modalities (Ferlay et al, 2018). They are a complex and diverse group of cancer and have various molecular subtypes. Tumors that don't express estrogen receptors (ER), progesterone receptors (PR) and human epidermal growth factor receptor 2 (HER2) are labelled as triple negative breast cancer (TNBC) (He, Jiang, Chen & Wang, 2018) (Fig. 1). The outcome in terms of long term survival and disease free interval is poor (Haffty et al, 2006; Rakha et al, 2007). They have unique pathological, molecular, and clinical behaviour. TNBC comprises of about 15-20 % of total breast cancers. They have characteristic aggressive clinical behavior and insensitivity for endocrine and anti-HER2 targeted treatment strategies (Bauer et al, 2007; Rhee et al, 2008). Thus, surgery and chemotherapy, in combination or individually are the only treatment options available. Despite TNBC being sensitive to chemotherapy, metastasis and early relapses are common and the prognosis is poor (Carey et al, 2006).This report focuses on the challenges and consequences of striking increment in the incidence of TNBC in Indian women.

II. Methods

We made a search of relevant published literature using PubMed, Medline, EMBASE and Google Scholar on the ever-increasing TNBC numbers in the world. The frightening increase in the incidence, especially in Indian women and the associated factors were given special prominence in course of the literature review.

III. Indian Scenario: an alarming Burden

A. Epidemiology

Breast cancer is the most common cancer in Indian women accounting for 27.7% with 162,468 newly detected cases and 87,090 deaths in 2018 (Kishor & Kiran, 2019). An increasing trend in rates of breast cancer incidence has been noted in the urban population of the country. The age adjusted rate (AAR) in the urban areas is 21 to 28.3 per 100,000 compared to 8.6 per 100,000 in rural India (Sambasivaiah et al, 2004). Despite of the ever-increasing cases of breast cancer in India, the epidemiological data and study is scant.

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The mean age of presentation of the breast cancer in India is less than 50 years, which is lower than that in the developed countries (Raina et al, 2005). Eighty percent of patients are below 65 years. They are often diagnosed late with about 70% belonging to advanced clinical stage at presentation (Raina et al, 2005).

TNBC prevalence in India varies in between 27% to 35% in literature and is estimated to be around 31 % (Sandhu, Erqou, Patterson & Mathew, 2016) (Table I). This estimation is similar to that of African American race while being almost double than the prevalence in white women (Trivers et al, 2009). As TNBC is considered highly aggressive among the various subtypes of breast cancer, its high prevalence may be a contributing factor to the high mortality among Indian breast cancer patients.

B. Risk Factors

The risk factors for TNBC include age at presentation < 50 years, African American race, high body mass index (BMI), multiparity, young age at menarche, early age at first pregnancy, absence of breast feeding (Carey et al, 2006; Morris et al, 2007; Bauer et al, 2007; Millikan et al, 2008). Numerous factors may be accounted for such large proportions of TNBC as reported in studies performed for Indian breast cancer patients. The probable causes could be early age of onset of cancer; lifestyle changes like dietary factors and high BMI; reproductive factors, such as high parity; socio-economic status; and screening procedure and practices (Brewster, Chavez-MacGregor & Brown, 2014). The possible genetic susceptibility of Indian women to TNBC may be an additional determinant. Directed and focussed research of these determinants will help to establish a plausible causation and temporality.

IV. Clinical and Pathological characteristics

TNBCs have multitude of distinctive hostile clinicopathological characters, including young age of onset and large size of tumor (Gluz et al, 2009; Chen et al, 2007). The histological features include high proliferative activity and grade, absent infiltrative margin, focal necrosis, lack of gland formation, central scar/fibrotic foci and presence of predominant lymphoplasmacytic infiltrates (Gluz et al, 2009; Cleator et al, 2007; Thike,et al 2010; Marginean et al, 2010). Having said that, most of these features are not specific, and are found in other high grade hormone receptor positive breast cancers. Whilst TNBC make up 25-30% of grade 3 tumors, about 77-90% of TNBCs are grade 3 (Rakha et al, 2007; Carey et al, 2006; Thike et al, 2010). They are mostly (80-93%) poorly differentiated ductal carcinoma of no special type. The second most common type is invasive lobular carcinoma constituting 1-2% of total TNBCs (Thike et al, 2010). Nearly all the cases of typical medullary carcinomas have a triple-negative phenotype, comprising ~2% of TNBCs (Thike et al, 2010). Atypical medullary breast cancer and cancers arising in younger age group carrying the BRCA1 mutation almost exclusively exhibit TNBC phenotype.

Table I. Various Cross-sectional analysis with prevalence of TNBC in these studies in breast cancer patients in India.

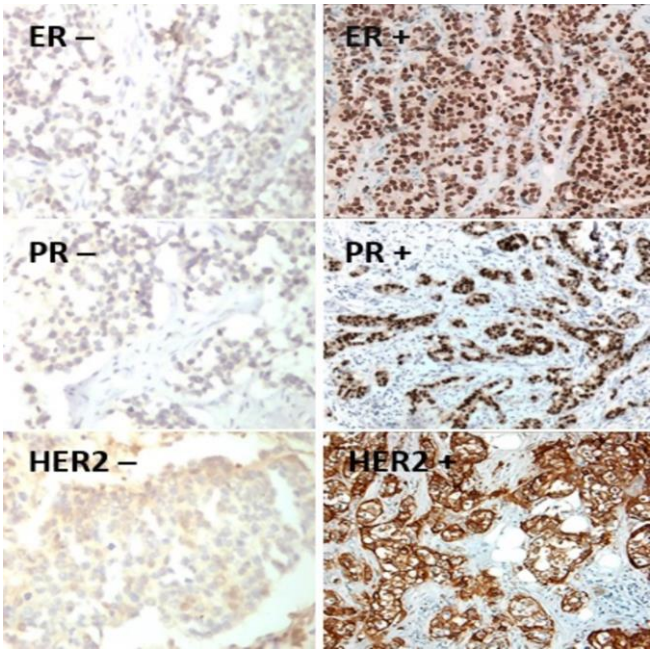
	Time Span	Total Cases	Mean Age (yrs)	Tumor Sze>5cm %*	Grade 3 Disease %*	Positive Nodes %*	TNBC %†
North							
Verma et al, 2012	2008-9	100	53.3	3	19	49	17
Nigam et al, 2014	2004-11	142	49	NR	NR	66.4	39.4
Nabi et al, 2015	2009-13	180	50.5	16.6	43.3	62.7	34.4
Doval et al, 2015	2008-11	1284	52.1	NR	44.4	52.9	23.8
East							
Sen et al,2012	2008	72	43	29.1	58.3	58.3	27.8
Nandi et al, 2014	2011-12	135	52	37.8	58.5	38.5	13.3
Jana et al, 2014	2007-8	242	54.6	52.1	69.8	89.7	46.7
Sharma et al,2012	2010-13	972	46.1	24.8	63	54.6	31.9
West							
Singh et al, 2014	2009-10	82	50	NR	NR	47.6	34.1
Akhtar et al, 2015	2012-14	85	50	64.7	43.5	66	43.5
Mane et al, 2015	2007-12	521	47	26.7	NR	NR	25.3
Ghosh et al, 2011	2008	1922	49	NR	75.4	NR	31
South							
Zubeda et al, 2013	2001-07	300	50	NR	NR	NR	46
Patnayak et al, 2015	2001-10	352	50.7	10.9	35.2	65.4	22.7
Rao et al, 2013	2009-11	126	NR	19.8	15.9	47.6	50
Ambroise et al, 2011	2009-10	321	53.8	7.8	33.3	58.2	25.2
Lakshmaiah et al, 2014	2012-13	322	NR	NR	NR	NR	26.1

(Sandhu et al, 2016)
TNBC, triple negative breast cancer; NR, not reported

*Percentage of subjects having the disease
†Disease prevalence in the study group

TNBCs usually lack affiliation with an obvious component of in situ cancer (Rakha, 2008; Yanget al, 2008; Hugh et al, 2009). Nevertheless, when they are associated with ductal carcinoma in situ (DCIS), the nuclear grade is generally high (Thike et al, 2010). The low incidence of their association may be due to quick progression of TNBCs into invasive cancers and/or annihilation of the precursor of DCIS by the rapidly spreading invasive constituent (Dabbs et al, 2006). The incidence of association of TNBC and the lymph node stage varies among different studies; with some reporting no association at all (Rakha, 2008; Kusinska et al, 2005) whereas others associate

Fig. 1. Immunohistochemistry (IHC) for ER, PR and HER2 receptors. The IHC on left hand side is typical of TNBC.



them with node negativity (Tischkowitz et al, 2007; Tan et al, 2008) or positivity (Den et al, 2007). The majority of studies reported a clear association of TNBC with large primary tumors (Chen et al, 2007), which may indicate rapid growth rates of these tumors (Dabbs et al, 2006; Seewaldt et al, 2007).

TNBCs mostly express proteins that are hallmark of basal epithelial cells of breast or the ones associated with rapid multiplication and bad prognosis. The various studies report 50-80% expression of basal cytokeratins (CK5/6, CK14 & CK17), P-cadherin, vimentin and EGFR (Rakha, 2008; Rakha et al, 2009). The others include nestin, osteonectin, c-KIT, caveolins 1 and 2, laminin and aB crystallin (Rakha, 2008). Mutation of TP53 gene is seen in a high proportion of TNBCs (Jumppanen et al, 2007; Langerod et al, 2007) and so are the alterations in pRB and cell cycle checkpoint at p16 G1/S (Subhawong et al, 2009; Gauthier et al, 2007). A minority of TNBC harbors aneusomy (Gilbert et al, 2008).

However, TNBCs do respond better to chemotherapy than the other subgroups. A study examining the response of patients with TNBC to neoadjuvant chemotherapy demonstrated that pathologic complete response (pCR) rate is higher in individuals with TNBC compared to the non-TNBC patients (Liedtke et al 2008). On the other hand, TNBC patients having a residual disease post neoadjuvant chemotherapy had remarkably shorter post-recurrence survival than the non-TNBC residual cancer patients (Liedtke et al 2008). Studies also showed that the risk of recurrence is time-dependent. The risk of relapse, metastasis and mortality is higher for TNBC patients during the first three years after therapy, when compared to non TNBC subjects; the risk for relapse after three years for TNBC patients is actually lower than non-TNBC suggesting that the highest risk for relapse in this group is 4 to 6 years after treatment (Liedtke et al 2008). Relapse in TNBC patients has a worse prognosis in comparison to non-TNBC subtypes. Additionally, there is a high rate of brain and lung metastasis in patients with TNBC, with a noticeable increase in brain metastasis from tumors that express EGFR and basal cytokeratin (Peppercorn et al, 2008).

V. Current Diagnostics and Therapeutics

A. Evaluation

The diagnosis of breast cancer in a clinical setup requires a methodical clinical, radiological and pathological examinations. Mammography has the widest application but absence of unusual features in TNBCs, results to an imprecise diagnosis (Schmadeka, Harmon & Singh, 2014). In order to overcome the limitations of mammography, ultrasonography having higher sensitivity (>90%) should be contemplated (Herranz & Ruibal, 2012), however, its limited reliability for detection of benign tumors restricts it use in TNBC. MRI has high positive predictive values and is sensitive for diagnosing TNBC, but high false positives eventually lead to painful biopsies that could have been avoided (Dogan & Turnbull, 2012). TNBC detection by these radiological investigations requires experience and expertise. Hence, immunohistochemistry (IHC) and onco-pathologist play a crucial role in identifying TNBCs relying on the characteristic property of absence of hormonal receptors (ER, PR) and HER-2 in tumor tissue specimen (Kreike et al, 2007).

B. Treatment Options

Once the correct diagnosis of TNBC is made taking into consideration the metastatic propensity, chemotherapeutic sensitivity, relapse and grim prognosis, a therapeutic strategy is adopted. Treatment interventions are mostly restricted to cytotoxic chemotherapy with anthracyclines and taxanes, surgery and radiotherapy. These constraints warrants improvement in the presently accessible diagnostic tools and therapeutics along with consideration of revolutionary techniques and methods.

The first option in TNBC is Breast conservation treatment (BCT). It is an effort to circumvent mastectomy. However, high tumor recurrences despite radiation therapy demands for mastectomy supplemented with radiotherapy (Kyndi et al, 2008). TNBCs lack hormonal receptors rendering Hormonal therapy useless. Thus, chemotherapy is currently the cornerstone of systemic therapy (Bayraktar & Glück, 2013). Taxanes and anthracyclins are commonly used chemotherapeutic agents showing encouraging response in TNBC (Shi, Jin, Ji & Guan, 2018), but this non-targeted cytotoxic approach of drug delivery demands a resolution with innovative research and technologies. TNBC is a rapidly proliferating and aggressive tumor, but has a surprisingly better response to chemotherapy; sometimes termed

as TNBC paradox. However, early relapses and metastasis are common and the prognosis is grim (Carey et al, 2007).

VI. Future Challenges

With the alarming rate of increment in the incidence of TNBC in India, it demands great scientific attention and allocation for advancement in the field. For selecting the optimal treatment strategies at present, it is imperative to classify breast cancers on the basis of shared molecular characteristics.

TNBC shows overwhelming expression of EGFR in not less than 50 % of the cases which is much higher compared to other breast cancer variants (Dent et al, 2007). This explains why EGFR inhibitors are being developed as targeted therapy for aiding in management of TNBC. Such novel strategies demand further research and development. Of particular interest are the other targets like angiogenesis that can serve as therapeutic targets in a subset of breast cancer patients (Cleator et al, 2007; Pal et al, 2009).

The daunting burden of aggressive TNBCs pose an uphill task for healthcare specialists and scientists in India and the world. The first stride in this course would be to establish a prospectively governed, community based database of breast cancer patients besides dependable histopathology assessment.

Conclusion

TNBCs are a group of heterogeneous breast tumors with distinctive histopathology, molecular biology and a varied clinical response to various forms of treatment. They have a rapid clinical course and early recurrences in spite of timely medical intervention, which reflects the aggressive tumor biology. There is a dearth of adequacy in available therapeutics which requires enforcement and appurtenances with superior targeted therapies to address these tenacious tumors. It mandates further research on the escalation of available chemotherapeutic regimens and discovery of target therapies aimed at decreasing recurrences and improving survival in this patient population. The designing and formulation of a novel, tailored treatment requires a greater comprehension of the tumor progression and evolution. Various novel molecular targets and drugs for treatment are under research and evaluation, but before these can be instituted in the clinical practice, the discovery of authentic and predictive biomarkers is indispensable.

Conflict of interest

The authors declare that they have no conflicts of interest.

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