

Triple Negative Breast Cancer: A Unique Type of Breast Cancer

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Keywords: Breast cancer; Triple negative breast cancer; Estrogen; Hormone receptor

Introduction

Breast cancer is just not a single localized disease but it can show metastasis to the lymph nodes and other distant organ. There are different types of breast cancer. It can even be called a family of diseases which may transfer from one generation to another, altering the disease pattern as a genetic one. All breast cancers initially harbour in different tissues of the breast. Therefore, all the breast cancers apparently seem to be similar, but actually differ in causes and region of causes. The type of breast cancer affects prognosis (outcome) and treatment options [1].

Types of breast cancer

Breast cancer is divided into two broad categories: non-invasive and invasive.

Non-invasive (*in situ*) breast cancer: This type of cancer is defined by the cancerous cells localized in one particular portion of breast and do not follow any metastasis.

Invasive (infiltrating) breast cancer: In this particular case, cancerous cells show metastasis and spread to other parts of the body through the bloodstream and lymph nodes. Breast cancer can also be classified based on where in the breast the disease started (e.g., milk ducts, lobules), how the disease grows, and other factors [2].

Triple Negative Breast Cancer (TNBCs)

The definition of breast cancer has evolved, with triple-negative breast cancer (TNBC) defined as ER negative, PR negative and lacking over expression of HER2; luminal-A cancers are defined as ER positive and histologically low grade; luminal-B cancers are also mostly ER positive but may express levels of hormone receptor and are often high grade; HER2-positive cancers show amplification and high expression of the *HER2* gene [3]. Approximately 75% of TNBCs express basal markers and, consequently, the triple-negative sub-type is frequently, and erroneously, taken as a surrogate marker for the basal-like sub-type [4,5]. Triple-negative tumours account for 10–20% of invasive breast cancers and this sub-type carries a poorer prognosis than the luminal tumours [6-8].

Epidemiology of TNBC

Perou et al. [9] were the first to describe the various molecular sub-types or molecular profiles of breast cancers. They described four sub-types based on cDNA micro-arrays, including a basal-like sub-type of breast cancer, and noted that most triple-negative tumours clustered in the basal-like sub-type [9]. Since then, multiple studies of gene expression profiling have advanced the understanding of the molecular diagnosis of breast cancer, providing the background for oncologists to use the triple-negative phenotype to describe the basal-like molecular sub-type [10-13]. Of the global breast cancer burden, it has been estimated that ~170000 are TNBC and are often, but not always, basal-like breast cancer [14-16]; another study has estimated that ~75% are basal-like.

Using the population-based California Cancer Registry data, Bauer et al. [17] identified women diagnosed with TNBC between 1999 and 2003 to investigate potential differences between TNBC compared with other breast cancers in relation to age, race/ethnicity, and socio economic status, stage at diagnosis, tumour grade and relative survival. A total of 6370 women were identified as having TNBC and were compared with the 44 704 women with other breast cancers.

Stead et al. [18] identified women with invasive breast cancer diagnosed between 1998 and 2006, with data available on tumour grade, stage, ER, PR and HER2 status, and patient age, body mass index (BMI) and self-identified racial/ethnic group. They recruited 415 patients who were racially and ethnically diverse; 47% were obese and 72% of tumours were ER positive and/or PR positive, 20% were triple negative and 13% were HER2 positive.

Epidemiology of TNBC in India

Breast cancer is the most common cancer in India. For example, in 2012, it is estimated that approximately 145,000 new patients were diagnosed with breast cancer in India, and nearly 70,000 women died of the disease [7]. Age-standardized 5-year breast cancer survival for Indian women diagnosed with breast cancer is 60% compared with >80% in Western countries. Whereas breast cancer incidence seems to be increasing in the country, epidemiology of the disease is inadequately studied. Prevalence of TNBC in India is reported to be higher than that observed in Western populations; however, there is considerable variation in prevalence rates reported by studies from the region. It is important to obtain a reliable summary estimate of the prevalence of TNBC in India to address the growing burden of breast cancer in the country [19].

Symptoms of TNBC

In general, TNBC do not differ from other breast cancers but it has some unique features:

Receptor status

Tests that detect receptors level for estrogens, progesterone and HER2 will be negative. Hormonal therapy only worked when only progesterone or estrogens receptor level are comparatively lesser.

Cell type

Triple-negative breast cancer resembles the basal cells lining the

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Received: December 12, 2016; Accepted: January 23, 2017; Published: January 30, 2017

Citation: Sood A (2017) Triple Negative Breast Cancer: A Unique Type of Breast Cancer. Reconstructive Surgery and Anaplastology 6: 164. doi: 10.4172/2161-1173.1000164

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breast ducts. The cells may also be of higher grade, which means they may have tendency to become cancerous cell.

Triple negative cancer is unique

TNBC is not likely to be found on a mammogram than some other types of breast cancer. Compared to other types, it tends to grow faster. It can be treated, but it may recur early and spread to other parts of the body. The reason behind this is lack of target specific treatment [20].

TNBC Risk Factors

General risk factors

Age: Women under age 40-50 are more likely to get triple-negative breast cancer than women over age 60. In current scenario, younger women age between 23 and 30 also have triple negative breast cancer.

Race: It is more common among African, American and Hispanic women than Asian and non-Hispanic white women.

Genetics

BRCA1 mutation: *BRCA1* and *BRCA2* are genes that help in repair damaged DNA. Mutations in *BRCA1* and *BRCA2* can cause cancer and can be inherited from one generation to another generation within family members. Women with the *BRCA1* gene mutation have a higher risk of developing TNBC [21].

Currently Approved Therapies and Treatment Strategies

There is currently no preferred standard chemotherapy for previously treated patients with TNBC, as previous randomised studies in the metastatic setting have not addressed the predictive values of the molecular subtypes of breast cancers. Treatment is therefore selected (as for other subtypes) from a number of current recommended agents that are approved in the general breast cancer population. Conventional treatments for relapsed patients are limited, particularly, because standard chemotherapeutic regimens containing anthracyclines and taxanes have usually already been given in the adjuvant and neoadjuvant settings.

Anthracyclines and taxanes have been suggested as rechallenge regimens in patients with 6–12 months of disease-free survival following completion of adjuvant chemotherapy and recurrence. There are few data on the use of anthracycline- and taxane-containing rechallenge regimens as first- or second-line therapy for metastatic breast cancer, and there is therefore a lack of reliable evidence documenting their efficacy [22].

The major cause of metastatic treatment failure is multidrug resistance to standard therapies, which can be either primary (preceding drug exposure) or acquired resistance (induced by treatment) [23,24]. Patients with progression or resistance may be given non-cross-resistant agents such as capecitabine, gemcitabine, vinorelbine or albumin-bound paclitaxel, and combination regimens with these agents have demonstrated efficacy in studies in patients with anthracycline-pretreated advanced breast cancer [24,25]. Superior survival has been demonstrated with capecitabine plus docetaxel combination therapy compared with docetaxel alone in anthracycline-pretreated patients with advanced breast cancer [26], and until the recent approval of ixabepilone, capecitabine was the only additional agent that was US Food and Drug Administration (FDA)-approved following failure of anthracycline/taxane therapy [27]. The use of multidrug regimens in the treatment of patients with metastatic breast cancer is controversial, particularly when first-line trials of combination regimens have not always addressed the questions directly relevant to daily clinical practice.

The 2009 European School of Oncology Metastatic Breast Cancer Task Force (6th European Breast Cancer Conference) recommended sequential monotherapy for advanced breast cancer, and patient- and disease-related factors to be used in determining which patients would benefit from combination regimens, who remain poorly defined [28]. Other consensus groups have arrived at a recommendation to administer polychemotherapy for aggressive disease with associated risks to inner organ function [29]. Therefore, given the aggressive nature of TNBC and the need for tumour shrinkage in most cases, the authors would recommend a multidrug regimen rather than a single-drug regimen for this subtype.

Platinum-based regimens have attracted some attention as potential TNBC therapies, and their use has been supported by the strong association of TNBC tumours with germline mutations in the *BRCA1* gene, with 10% of TNBC tumours having *BRCA1* mutation (90% of *BRCA1*-mutated tumours are TNBC, and 80-90% of *BRCA1*-associated breast cancers display a basal-like phenotype) [30,31].

Efficacy of Recently Approved Therapies

Eribulin has recently been European Medicines Agency (EMA) approved for advanced or metastatic breast cancer in patients who have progressed after at least two chemotherapeutic regimens for advanced disease and who received prior anthracycline and taxane regimens where suitable.

Eribulin was most effective in hormone receptor-negative patients who had a 34% decreased risk of death compared with TPC chemotherapy, and in TNBC patients, who had a 29% risk reduction, whereas it was least effective in patients who received eribulin without a treatment history that included capecitabine [32].

Ixabepilone is an epothilone antimicrotubule agent, which was FDA approved in 2007 for locally advanced or metastatic breast cancer in combination with capecitabine after failure of anthracycline/taxane therapy.

Patients treated with ixabepilone plus capecitabine demonstrated a 25% reduction in the estimated risk of disease progression (HR=0.75, 95% CI 0.64–0.88) compared with patients who received capecitabine only. The ORR of patients was also greater for the ixabepilone-treated group (35% vs. 14% for capecitabine). However, grade 3/4 treatment-related adverse events were more frequent in the ixabepilone treatment group than in those receiving capecitabine only, with a greater rate of neuropathy (21% vs. 0%), fatigue (9% vs. 3%) and neutropenia (68% vs. 11%) [33].

The use of anti-angiogenic therapies for TNBC is supported by the highly proliferative nature of TNBC and the importance of vascular endothelial growth factor (VEGF) in the microvascular proliferation of this disease. The anti-VEGF monoclonal antibody bevacizumab has shown benefit in some TNBC subgroups if combined with taxanes and other agents [34-36].

The anti-VEGFR tyrosine kinase inhibitors sunitinib and sorafenib have shown some activity in breast cancer trials with significant TNBC populations, with a 15% response rate reported for sunitinib in a phase II trial [37]; however, neither agent is currently approved for the treatment of breast cancer. The EGFR-directed monoclonal antibody cetuximab is FDA and EMA approved for the treatment of colorectal and head and neck cancer.

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