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An overview of triple negative breast cancer for surgical oncologists

Shiva Sharma [a], Mitchel Barry [a, *], David J. Gallagher [a], Malcolm Kell [a], Virgilio Sacchini [b]

[a] Mater Misericordiae University Hospital, Dublin, Ireland
[b] Breast Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

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ABSTRACT

Triple negative breast cancers (TNBCs) represent a distinct subgroup of breast cancers with an immunohistochemical phenotype that is negative for oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2). The aim of this article is to provide a broad overview of recent developments in the diagnosis and management of TNBC for surgical oncologists. This overview discusses the subtypes of TNBC and the relationship between this type of breast cancer and the BRCA1 gene. In addition, the article explores recent advances in the treatment of TNBC from a surgical, radiation, and medical oncology point of view. Lastly, evolving therapeutic strategies that have potential to enhance outcomes for patients with TNBC are also discussed.

Search strategy and selection criteria:

PubMed, Medline, EMBASE, and the Cochrane database were searched between 2005 and 2014 for papers published regarding triple negative breast cancer. The following search terms were used: "breast cancer"; "triple negative breast cancer"; "receptor negative breast cancer"; "ER negative breast cancer"; "PR negative breast cancer"; "HER-2 negative breast cancer"; "carcinogenesis of triple negative breast cancer"; "molecular biology"; "epidemiology"; "genetics"; "diagnosis"; "staging"; "surgery"; "radiation therapy"; "adjuvant chemotherapy"; "neo-adjuvant chemotherapy"; and "metastatic triple negative breast cancer". References were cross checked appropriately. Previously published papers from 2005 to 2014 were selected on the basis that they provided a major contribution to the management of triple negative breast cancer. Studies and abstracts, presented at oncology meetings over the last 12 months that demonstrated novel or evolving concepts in the treatment of triple negative breast cancer were also included where appropriate.

1. Introduction

Triple negative breast cancers (TNBCs) account for 15%–20% of all breast cancers and are defined by an immunohistochemical absence of expression of the oestrogen receptor (ER), the progesterone receptor (PR) (less than 1% oestrogen and progesterone staining by immunohistochemistry) and the human epidermal growth factor receptor 2 (HER-2) (not overexpressed by fluorescence in situ hybridization) [1]. Therefore, targeted therapies such as trastuzumab and hormonal therapies are ineffective and thus TNBCs are associated with an inferior prognosis [2]. In this review, the molecular biology, epidemiology, and genetic associations, and the clinical complexities involved in the diagnosis and treatment of TNBC, are discussed. In addition, a summary of the significant developments and advances in our understanding, and in the treatment of TNBC over the last 5 years are provided, and potential future therapies are explored.

2. Pathology and molecular biology of triple negative breast cancer

TNBCs represent a heterogenous pathologic entity with variable morphology and can be ductal, medullary, metaplastic, and adenoid cystic carcinoma of the breast [3]. Unlike other TNBCs, adenoid cystic carcinoma of the breast portends an excellent prognosis, with one small series reporting 87.5% (14/16 patients) survival with 6.5 years of follow-up [4]. In this overview, to avoid confusion, any reference to TNBC implies that adenoid cystic

* Corresponding author. Breast Service, Mater Misericordiae University Hospital, Dublin, Ireland.
E-mail address: mbarry@mater.ie (M. Barry).

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carcinoma has been excluded.

Historically, breast cancers were classified based on cellular morphology and the presence or absence of certain nuclear or surface receptors such as ER, PR and HER-2. Perou and colleagues used gene expression analysis to demonstrate the molecular heterogeneity of breast cancer and identified five distinct molecular subtypes of breast cancer [5]. Luminal A and B subgroups represent breast cancers with ER positivity, a third subgroup associated with HER-2 positivity, and a so-called normal subtype, which is positive for all receptors [5]. The fifth group is the basal-like subgroup which is associated with TNBC. In addition, RNA expression arrays of breast cancers suggest that different subtypes originate from different precursor cells with distinct progression pathways. TNBC or basal-like breast cancer resemble normal breast basal epithelial cells, and are thought to originate from the outer (basal) layer of the breast ducts (i.e., myoepithelial cells). These tumours stain positively for basal-cell (myoepithelial) cytokeratins 5, 6, 17, and epidermal growth factor receptor, and are negative for ER, PR, and HER-2 receptors [3]. TNBCs also possess a characteristic morphology with a high grade, a high mitotic count, and central necrosis with a pushing border of invasion [3]. Molecular profiling of TNBCs demonstrates p53 nuclear expression which is associated with a higher prevalence of underlying TP53 gene mutations [6]. TNBCs commonly express known markers of high proliferation such as MIB-1 and TOP2A (topoisomerase 2 alpha), and are associated with low levels of cyclin D1 and CCND1 expression [6]. This expression pattern is also observed in tumours arising in BRCA1 mutation carriers [6–9].

It is critical to point out early in this review that TNBC and basal-like breast cancers are not completely synonymous, and it is an error to use these terms interchangeably. Not all basal-like cancers are triple negative, and not all TNBCs have classic basal-like features. Based on the largest analysis to-date on all available gene expression data on TNBC, Rody and colleagues at the Goethe University in Germany reported that 73% of TNBC were basal-like tumours [10]. The remaining TNBCs were classified into phenotypes according to gene functions such as angiogenesis, inflammation, immune activity, proliferation, and apocrine activity. They identified a subset (high B-cell [immune system] and low IL-8 [inflammation]) that is associated with a more favourable prognosis. A similar study by Tan et al. analyzed 245 TNBCs and demonstrated that 19.4% of TNBCs were negative for basal markers and 7.3% of non-TNBCs expressed basal markers [6].

Further transcriptome analysis has subdivided TNBCs into six distinct biologic subtypes [11]. Each of these six clusters demonstrates unique gene expression patterns. Two basal-like subtypes (BL1 and BL2) are associated with DNA damage and cell cycle response genes, and appear to respond favourably to cisplatin in representative cell lines [11]. The two mesenchymal-like subtypes associated with cell differentiation, growth factor pathways, and epithelial–mesenchymal transition preferentially responded to a PI3K/mTOR inhibitor and dasatinib (an abl/src inhibitor) [11]. The other two remaining subtypes were a luminal subgroup associated with androgen-receptor signalling and an immunomodulatory subgroup characterized by immune cell surface antigens, receptors, and signal transduction genes. This luminal androgen receptor subtype demonstrated an increased sensitivity to the AR antagonist bicalutamide [11]. It is anticipated that ongoing molecular characterization of the heterogeneity of TNBC will advance our understanding of the biology of this disease, reveal novel therapeutic targets, and facilitate a more precise treatment approach for patients with TNBC.

3. Epidemiology, genetic, and risk factors for triple negative breast cancer

TNBC appears more common in premenopausal women of African and Hispanic descent, and represents 75% of tumours arising in patients who are *BRCA1* mutation carriers [12–15]. In a population-based study, Bauer and colleagues evaluated 6370 women with TNBCs and observed that women with TNBC were more likely to be under 40 years of age, of African ethnicity, and from areas of lower socioeconomic status [12]. Patients with TNBC also presented with larger tumours at a more advanced stage, associated with an inferior prognosis than non-TNBCs.

Historically, increased oestrogen exposure through the number of menstrual cycles was associated with an increased risk of breast cancer. Early menarche, and increasing age at first full-term birth or nulliparity, elevated an individual's risk of developing breast cancer. However, there are emerging data that this does not apply to TNBC. In a pooled analysis of 34 studies from the Breast Cancer Association Consortium, it was observed that these reproductive factors, and increased body mass index (BMI), were associated with ER/PR positive tumours but not with TNBCs [16]. These findings are supported in part by a meta-analysis that failed to demonstrate any relationship between the number of births and risk of ER/PR negative tumours [17].

The finding that increased BMI is not associated with TNBC is contradicted by other studies that have reported an association between obesity and insulin resistance and TNBC [18]. This may explain the higher prevalence of TNBC in African-American women who have a higher rate of central obesity [19]. According to the Carolina Breast Cancer Study, TNBCs are reported to be more common in premenopausal African/African-American populations (39%) and less common in postmenopausal African populations (14%) [20]. This is in stark contrast to Japanese populations where only 7% of breast cancers are triple negative and are associated with a 5-year overall survival (OS) of 86.2% [21]. Korean and Chinese studies have reported higher triple negativity rates of 14.7% and 19%, respectively [22,23].

A number of studies have confirmed that *BRCA1*-associated breast cancers are typically (57%–88%) TNBCs [24,25]. This association appears to be age related as Foulkes and colleagues observed that 81% of *BRCA1*-associated breast cancers diagnosed under 45 years of age were ER negative whereas only 62% of breast cancers diagnosed in women after 65 years were ER negative [26]. In addition, 24% of Ashkenazi Jewish patients under 65 years of age diagnosed with a TNBC are BRCA mutation carriers [24]. Young and colleagues evaluated the impact of molecular screening for *BRCA1* and *BRCA2* in 54 patients with TNBC who were 40 years of age or less and had no family history of breast cancer [27]. Eleven percent of this selected population had a deleterious *BRCA1* mutation, while 1.8% had a *BRCA2* mutation [27].

This finding is supported by Hartman and colleagues who profiled 199 unselected patients with TNBC and identified a BRCA 1/2 mutation in 10.6% [28]. In further analysis of TNBC patients ($n = 153$) without any first/second degree relatives with breast/ovarian cancer under 50 years of age, they reported a mutation rate of 5.2% [28]. According to the American Society of Clinical Oncology guidelines, genetic testing should be offered to women if the probability of detecting a mutation is greater than 10% [29]. Therefore, premenopausal women presenting with TNBCs with or without a family history of breast cancer may be considered for genetic testing for *BRCA1*. In contrast, testing for *BRCA2* in this population has a low yield of mutation detection, as *BRCA2* does not appear to be preferentially associated with the TNBC phenotype [27]. While this strong relationship between *BRCA1* and TNBCs has both clinical and biological relevance, the precise nature of this