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RESEARCH ARTICLE

TRIPLE-NEGATIVE BREAST CANCER: THERAPEUTIC STRATEGIES

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ABSTRACT

Triple-negative breast cancer (sometimes abbreviated TNBC) refers to any breast cancer that does not express the genes for estrogen receptor (ER), progesterone receptor (PR) or Her2/neu, detected in 8-20% of cases, the most aggressive with a poor prognosis.. Breast cancer (BC) is the most frequent tumor worldwide. In 2016, 1,380,000 new cases and 458,000 deaths for BC were reported worldwide, of which there were 332,000 new cases and 79,000 deaths in Asia. Although the improvement in early diagnosis and adjuvant therapy has reduced mortality, BC is still the main cause of death for cancer in women both in industrialized and in developing countries. In Uzbekistan, BC is the most frequent tumor in women (47%), with about 17,000 new cases diagnosed in 2016. BC is a heterogeneous disease, and therefore, a "golden standard" treatment, suitable for all the molecular types of cancer, is not available. The most important biological markers, not only for classification of BC but also for, the therapeutic strategy are the hormonal receptors (estrogen (ER] and progesterone (PgR] receptor) and the HER2 receptor status. This article provides a literature review in terms of perceptions of prevalence, etiology, risk factors, diagnosis, therapeutic strategies and prognoses of triple negative breast cancer.

INTRODUCTION

Over the past decade, our understanding and treatment of breast cancer has undergone a metamorphosis, shifting from a generally homogeneous approach to a more sophisticated view as guided by gene expression analysis (Swain, 2013; Perou *et al*., 2009). Multiple studies have reproducibly identified the intrinsic breast cancer subtypes, which include several luminal subtypes characterized by expression of hormone receptor–related genes, and two hormone receptor–negative subtypes—the HER2-positive/ER-negative subtype and the "basal-like" subtype. Contrary to the luminal subtypes, the basal-like subtype is characterized by low expression of ER- and HER2-related genes and clinically is usually, but not always, ER/PR–negative and lack HER2 over expression, thereby constituting the "triple-negative" phenotype. Multiple studies have demonstrated that the intrinsic subtypes vary by prognosis, with inferior outcomes illustrated among the two hormone receptor–negative subgroups as compared to the luminal subtypes (Sorlie, 2012; Sorlie *et al*., 2009). They may also differ in other important ways. Recent studies suggest that patients with triple-negative breast cancer have a high incidence of visceral metastasis, including brain metastasis (Heitz *et al*., 2012; Liedtke, 2013). Unlike the other subtypes, targeted agents specifically aimed at triple-negative breast tumors are not yet available, intensifying the need and interest in advancing novel therapeutic strategies beyond chemotherapy for this subset of high-risk patients.

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This review will focus on the molecular and clinicopathologic features, epidemiology and risk factors, prognosis, and current and future therapeutic strategies for patients diagnosed with triple-negative breast cancer, including a brief discussion of intracranial disease.

Definitions and Molecular Features

It is important to clarify the relationship between triple-negative breast cancer and the basal-like phenotype. Triple-negative is a term based on clinical assays for ER, PR, and HER2, whereas basal-like is a molecular phenotype initially defined using cDNA microarrays (Perou *et al*., 2009; Sorlie *et al*., 2012). Although most triple-negative breast tumors do cluster within the basal-like subgroup, these terms are not synonymous; there is up to 30% discordance between the two groups (Bertucci, 2013; Cleator, 2009; Kreike *et al*., 2009; Nielsen, 2010). In this review we will use the term "basal-like" when microarray or more comprehensive imunohistochemical profiling methodology was used, and "triple-negative" when the salient studies relied on clinical assays for definition. In order to fully understand the molecular and pathologic features classically associated with the triple-negative phenotype, a review of the normal mammary gland parenchymal cells, including their immunophenotype, is essential. The more central luminal cells classically express low-molecular-weight cytokeratins including CK7, CK8, CK18, and CK19, along with MUC1 alpha-6 integrin, BCL1, ER, PR, and GATA3. Classically, basal-like breast cancers have been characterized by low expression of ER, PR, and HER2 and high expression

of CK5, CK14, caveolin-1, CAIX, p63, and epidermal growth factor receptor (EGFR, HER1), which reflects the mammary gland basal/myoepithelial cell component (Liedtke *et al*., 2013; Bertucci *et al*., 2013). Among this list of markers characteristic of triple-negative breast tumors, several are potentially targetable, notably HER1/EGFR. A member of the "basal cluster" intrinsic gene list, HER1/EGFR is expressed in approximately 60% of basal-like breast tumors (Nielsen *et al*., 2014; Korsching *et al*., 2012). Finally, several molecules integrally involved in DNA repair are aberrantly expressed in triple-negative breast cancer, which may have implications for chemotherapy sensitivity. High p53 IHC expression or p53 gene mutations are common in basal-like breast cancer (Sorlie, 2012; Troester, 2016). Furthermore, one series illustrates that 82% of basal-like breast cancers expressed a p53 mutation compared with only 13% in the luminal A subtype ($P < .001$) (Sorlie *et al*., 2012). Several additional and targetable molecular pathways implicated in the pathogenesis of basal-like breast cancer include the mitogen-activated protein (MAP) kinase pathway, the Akt pathway, and the poly ADP-ribose polymerase 1 (PARP1) pathway, which will be addressed in more detail in the context of BRCA1 and therapeutics below (Cleator, 2009).

Association with BRCA1 Mutation Status

It has been observed that the majority of BRCA1-associated breast cancers are triple-negative and express a high proportion of basal-like cytokeratins (CK5, 14, 17), as well as P-cadherin and HER1/EGFR (5-6]. The BRCA1 tumor-suppressor gene, originally identified in 1994 by positional cloning on chromosome 17q21, is a multifocal protein in many normal cellular functions including DNA repair, transcriptional regulation, cell cycle checkpoint control (Perou, 2009; Heitz *et al*., 2012). Clinical Characteristics, Epidemiology, and Risk Factors Triple-negative breast tumors have been characterized by several aggressive clinicopathologic features including onset at a younger age, higher mean tumor size, higher-grade tumors, and, in some cases, a higher rate of node positivity (Bertucci, 2013; Cleatorm 2009). A histologic study of basal-like tumors, of which all were ER/HER2–negative, illustrated marked increases in mitotic count, geographic necrosis, pushing borders of invasion, and stromal lymphocytic response (Kreike *et al*., 2009). The majority of triple-negative breast carcinomas are ductal in origin; however, several other aggressive phenotypes appear to be overrepresented, including metaplastic, atypical or typical medullary, and adenoid cystic (Cleatorm 2009; Bertucci, 2013; Kreike *et al*., 2009).

In parallel with our understanding of the molecular basis of triple-negative breast cancer, our awareness of the epidemiology and risk factors associated with this disease process has matured, specifically related to age and race. Among approximately 500 women evaluated in the Carolina Breast Cancer Study, those with basal-like tumors (defined as ER-negative, PR-negative, HER2-negative, CK 5/6-positive, and/or HER1-positive) were more likely to be African-American (prevalence of 26% vs 16% in non–African-Americans) and premenopausal (24% vs 15% postmenopausal). These investigators observed a particularly high prevalence of basal-like tumors among premenopausal, African-American women compared to postmenopausal African-American women and non–African-American women of any age (39% vs 14% and 16%, respectively; $P < .001$) (Sorlie *et al*., 2009; Heitz *et al*., 2012; Liedtke *et al*., 2013; Bertucci *et al*., 2013] These findings are consistent with several large-scale, population-based studies indicating that triple-negative breast cancers are more likely to occur among premenopausal women of African-American descent (Böcker *et al*., 2009; Gottlieb *et al*., 2012]. Several epidemiologic studies have provided insight into risk factors associated with triple-negative breast cancers. Further examination of approximately 1,400 breast cancer cases in the Carolina Breast Cancer Study illustrated that compared to luminal A tumors (ER-positive and/or PR-positive and HER2-negative), basal-like breast tumors were more likely to arise among women with a younger age at menarche, higher parity, younger age at full-term pregnancy, shorter duration of breast-feeding, and higher body mass index (BMI) and waist-to-hip ratio (WHR), especially among premenopausal patients.

Similarly, the Polish Breast Cancer Study demonstrated a stronger reduction in risk associated with increasing age at menarche for basal-like tumors compared to luminal A–type breast cancer. Among premenopausal women, increasing BMI was associated with a reduced risk of luminal but not basal-like breast cancers (Nakano *et al*., 2012]. These findings illustrate that breast cancer risk factors vary by molecular subtype (luminal A, basal-like, etc), supporting subtype-specific approaches when examining risk factors and prevention. Triple-negative breast cancer is a subtype of breast cancer that is clinically negative for expression of estrogen and progesterone receptors (ER/PR) and HER2 protein. It is characterized by its unique molecular profile, aggressive behavior, distinct patterns of metastasis, and lack of targeted therapies.

Although not synonymous, the majority of triple-negative breast cancers carry the "basal-like" molecular profile on gene expression arrays. The majority of BRCA1-associated breast cancers are triple-negative and basal-like; the extent to which the BRCA1 pathway contributes to the behavior of sporadic basal-like breast cancers is an area of active research. Epidemiologic studies illustrate a high prevalence of triple-negative breast cancers among younger women and those of African descent. Increasing evidence suggests that the risk factor profile differs between this subtype and the more common luminal subtypes. Although sensitive to chemotherapy, early relapse is common and a predilection for visceral metastasis, including brain metastasis, is seen. Targeted agents, including epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), and poly (ADP-ribose) polymerase (PARP) inhibitors, are currently in clinical trials and hold promise in the treatment of this aggressive disease (Rudland, 2017).

Prognosis

The inferior prognosis associated with triple-negative breast cancer was originally recognized in the initial studies examining outcome by intrinsic subtype. These studies uniformly demonstrated a poorer prognosis among patients with breast cancer classified as "basal-like," particularly compared to those in good-prognosis subclasses (ie, luminal A) via gene expression profiling (Nielsen *et al*., 2014; Nayar *et al*., 2015]. Women with triple-negative breast cancer were much more likely to develop a recurrence during the first 3 years following therapy with rapid declines thereafter.

Patients with non–triple-negative disease demonstrated more consistent rates of recurrence over the follow-up period (Sorlie *et al*., 2009; Heitz *et al*., 2012; Liedtke *et al*., 2013; Bertucci *et al*., 2013; Cleator *et al*., 2009.

Patterns of Recurrence

In addition to a distinct pattern of timing of recurrence, we are increasingly recognizing unique patterns of relapse site among triple-negative breast cancer patients. Studies have consistently shown that more aggressive visceral and soft-tissue relapse are more common and bone relapse less common among those diagnosed with triple-negative vs ER-positive disease (Rudland *et al*., 2017; Rakha *et al*., 2014].

Brain Metastasis

An estimated 15% of all patients diagnosed with breast cancer will develop brain metastasis. This figure, however, is likely an underestimate, as autopsy studies report a 30% rate of subclinical disease. Despite currently available therapies including corticosteroids, whole-brain radiotherapy, surgical resection, stereotactic radiosurgery, and supportive care, survival following a diagnosis of brain metastasis remains quite poor, with a median survival of only 6 months and 1-year survival approximating 20% (Bertucci, 2013; Cleator *et al*., 2009). Another series of 38 patients with brain metastasis treated between 2013 and 2016 also found inferior median survival for patients with triple-negative (3.7 months) vs HER2-positive (9 months) and ER/PR/HER2–positive (15 months) disease ($P = .015$) (Kreike *et al*., 2009; Nielsen *et al*., 2014; Böcker *et al*., 2009). Significant efforts are focusing on the prediction of patients at highest risk for subsequent breast cancer–related brain relapse, including both clinical nomograms and gene expression strategies (Gottlieb *et al*., 2012; Lazard *et al*., 2015; Nakano *et al*., 2012). The majority of these efforts, however, have been directed at patients with HER2-positive disease. The above studies provide ample evidence that predictive, preventive, and therapeutic strategies in the setting of triple-negative intracranial relapse remain a challenge.

Therapeutic Strategies

Although triple-negative breast cancer is associated with a generally poor breast cancer–specific outcome, it is not resistant to chemotherapy.

Anthracycline/Taxane–Based Chemotherapy

Two neoadjuvant studies shed light upon the relationship between chemosensitivity and outcome. Both revealed proportionally higher sensitivity to anthracycline- or anthracycline/taxane–based chemotherapy for basal-like/ER-negative breast cancers compared to luminal/ER-positive subtypes. One study compared clinical response among over 100 patients (32% basal-like (ER-negative, HER2-negative], 10% HER2-positive/ER-negative, 58% luminal (ER-positive]) treated with neoadjuvant AC (doxorubicin (Adriamycin]/ cyclophosphamide) chemotherapy and found the highest response rates among those classified as basal-like (85%) and HER2-positive (70%), compared with luminal (47%; $P < .0001$). Despite initial chemosensitivity, disease-free survival ($P = .04$) and overall survival ($P = .02$) remained poorest among those with basal-like and HER2-positive tumors compared to luminal tumors (Nakano *et al*., 2012]. In both series, patients with a pathologic complete response had excellent outcomes regardless of subtype. Patients with residual disease following neoadjuvant therapy were at highest risk for recurrence. Thus, the poorer outcome among triple-negative patients was attributed to a higher rate of recurrence among patients with residual disease. These studies of chemotherapy response and patterns of recurrence highlight the value of neoadjuvant studies. They also reveal that while there are patients with triple-negative disease who are well-treated with conventional cytotoxic therapies, this subtype in particular requires more effective upfront therapies capable of eradicating disease. Traditionally, chemotherapy has been the mainstay of systemic treatment for triple-negative breast cancer, since currently available targeted agents, including endocrine therapy and HER2-directed therapies, are ineffective. As previously mentioned, triple-negative breast cancer is highly responsive to primary anthracycline and anthracycline/taxane chemotherapy; however, a high risk of relapse remains if tumor is not eradicated (Rudland *et al*., 2017; Rakha *et al*., 2014; Laakso *et al*., 2005]. Preclinical and clinical studies indicate that tumors with BRCA1 dysfunction harboring deficient double-stranded DNA break repair mechanisms are sensitive to agents that cause DNA damage, such as platinum agents (cisplatin and carboplatin) (Korsching *et al*., 2012; Troester, 2016).The association between triple-negative breast cancer and BRCA1 mutation status has led to several (neo)adjuvant and metastatic studies illustrating activity of platinum-based regimens in the treatment of triple-negative breast cancer, although how this activity compares with that of other cytotoxics remains unclear (Arnes *et al*., 2005; Foulkes *et al*., 2003; James *et al*., 2007; Laakso *et al*., 2005; Lakhani *et al*., 2005).

Targeted Strategies

More recently, scientific efforts aimed at dissecting the biology of triple-negative breast cancer have revealed several promising targeted strategies including EGFR-targeted agents, antiangiogenic agents, and PARP inhibitors.

EGFR Inhibitors

As mentioned previously, EGFR expression is seen in approximately 60% of triple-negative breast tumors, thus providing a rational, targeted treatment approach (Nielsen, 2014). Cetuximab (Erbitux) a monoclonal antibody targeting EGFR, elicits little response to single-agent therapy in the setting of advanced triple-negative breast cancer (Böcker *et al*., 2009; Gottlieb *et al*., 2012; Lazard *et al*., 2015; Nakano *et al*., 2012). However, a phase II trial evaluating the combination of gemsitabin and carboplatin (area under the concentration-time curve (AUC]2, weekly for 3 of 4 weeks) reported a response rate of 18% and overall clinical benefit rate of 27% among 32 patients with advanced pretreated triple-negative breast cancer. Time to progression was 2 months, and overall survival was 12 months, which reflects the aggressive nature of this disease (Nayar, 2015; Troester *et al*., 2016). A second study evaluating the combination of and carboplatini or without gemsitabini reported response rates of 49% and 30%, respectively, among 42 patients with pretreated triple-negative breast cancer. The incidence of toxicity, including grade 3/4 fatigue, diarrhea, vomiting, neutropenia, and thrombocytopenia, was higher among patients who received carboplatini (James *et al*., 2007].

Antiangiogenic Agents

The antiangiogenic agent bevacizumab (Avastin), a monoclonal antibody targeting all forms of vascular endothelial growth factor (VEGF)-A, is active in a variety of solid tumors including breast cancer. The landmark study E2100 illustrated improvement in progression-free survival (11.8 vs 5.9 months, HR = 0.60, $P < .001$) when adding bevacizumab to paclitaxel chemotherapy compared with single-agent paclitaxel alone in first-line treatment of metastatic disease. Subset analyses indicated that the treatment effect persisted among ER/PR–negative patients (HR = 0.53, 95% confidence interval = 0.40–0.70) in this largely (> 90%) HER2-negative patient population (Nielsen *et al*., 2014; Nakano *et al*., 2012). Additionally, small-molecule inhibitors of the VEGF pathway appear to have activity in the subset of pretreated triple-negative breast cancer; definitive studies are underway (Böcker *et al*., 2009; Lazard, 2015). Several contemporary studies are examining antiangiogenic strategies alone or in tandem with other investigational approaches in triple-negative breast cancer, for example, is a neoadjuvant study examining the benefit of carboplatin added to paclitaxel and the benefit of added to primary chemotherapy (Nakano *et al*., 2012; Nayar *et al*., 2015]. Echoing the oft-noted need for better tissue correlates in targeted therapy trials, this is a clinical trial with correlative science studies embedded; pretherapy research biopsies are mandatory. This trial, which is expected to open to accrual in the fall of 2008, will not only help answer two specific clinical questions in triple-negative breast cancer the role of platinum agents and the role of antiangiogenics but in addition, it will provide crucial data regarding response and resistance patterns within this subtype.

Conclusion

In summary, triple-negative breast cancer largely represents a subtype of breast tumors with unique molecular and clinical characteristics, distinctive risk factors and patterns of recurrence, association with BRCA1 mutation status, inferior prognosis, and expanding therapeutic options. Multiple excellent approaches to improved care of triple-negative breast cancer, including DNA-damaging agents such as gemsitabine with platinums, targeted agents against EGFR and VEGF, and PARP inhibitors are under investigation. Current research strategies are aimed at better understanding both the risk factors and the biology underlying triple-negative breast cancer, with the goal of developing preventive measures and improving treatment strategies for this challenging subtype of breast cancer.

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