Introduction

Breast cancer is the most common cancer among women in the United States, the second most common cause of cancer death, and the main cause of death in women ages 45 to 55 years. In 2009, approximately 192,370 American women were diagnosed with breast cancer, and an estimated 40,170 women died of the disease.\(^1\) Triple-negative breast cancer (TNBC) accounts for approximately 15% of breast cancers.\(^2\) Although recently in the limelight and frequently discussed, TNBC is not a new type of breast cancer. In fact, the term has recently been coined to describe a subtype of breast cancer that lacks expression of the estrogen receptor (ER) and progesterone receptor (PR) and does not overexpress human epidermal growth factor 2 receptor (HER2) protein. TNBC is a subtype of breast cancer that overlaps with the “basal-like” breast cancer. TNBC has significant clinical implications.

Methods: The epidemiology, diagnosis, clinical course, prognosis, and pathology of this subtype of breast cancer are reviewed. The authors compare the “triple-negative” and “basal-like” definitions of breast cancer. A discussion of both standard and experimental treatments for TNBC is included.

Results: The poor prognosis of high-grade TNBC relates to poor disease-free interval in the adjuvant setting, shortened progression-free survival in the metastatic setting, and the lack of targeted therapy. However, not all TNBCs are associated with a poor prognosis.

Conclusions: Although chemotherapy is the main current treatment of this subtype of breast cancer, new agents such as PARP inhibitors, which show promise in the treatment of TNBC, are currently in clinical trials.

Epidemiology

An estimated 1 million cases of breast cancer are diagnosed annually worldwide.\(^3\) Of these, approximately 170,000 are of the triple-negative (ER−/PR−/HER2−) phenotype.\(^3\) Of these TNBC cases, about 75% are “basal-like.”\(^4\) The prevalence of TNBC is highest in premenopausal African American women; a recent report notes that 39% of all African American premenopausal women diagnosed with breast cancer are diagnosed with...
TNBC. The prevalence of TNBC in this same age group in non-African American women is much less, at approximately 15%. These ethnic or menopausal differences are not seen in either the ER+/HER2+ breast cancer subgroup or the ER+/HER2- subgroup.

Multiple other studies and abstracts have confirmed that TNBC occurs in a higher percentage of African American women. Of these TNBC cases, about 75% are also of the basal-type molecular classification. As presented initially in 2006 at the San Antonio Breast Cancer Symposium in a study of racial differences in the prevalence of triple-negative invasive breast tumors, researchers found that the incidence of triple-negative disease among African American women was more than twice that among white women. They also reported that 47% of tumors in African American women were “triple-negative” compared with 22% in white women. After adjusting for age and stage at diagnosis, African American women were almost 3-fold more likely than white women to have triple-negative tumors.

These disparities in incidence among different racial groups leads us to question whether genes or mutations predispose women, particularly premenopausal African American women, to TNBC. Studies have shown that breast cancers in women with germ-line BRCA1 mutations are more likely to be triple-negative and high-grade. Gene expression studies have confirmed this phenomenon and also that BRCA1-associated breast cancer appears to cluster in the basal-like subtype.

Pathologic and Molecular Features

Although the terms basal-like breast cancer and TNBC are often used interchangeably, they are not synonymous. TNBC refers to the immunophenotype of the breast cancer that is immunologically negative to ER, PR, and HER2. These immunological studies are done on formalin-fixed and paraffin-embedded tumor sections. Basal-like breast cancer refers to the molecular phenotype of the tumor that has been defined by cDNA microarrays. Of these TNBCs, about 75% of them are of the basal-like type.

Perou et al were the first to describe the various molecular subtypes or molecular profiles of breast cancers. They described four subtypes based on cDNA microarrays, including a basal-like subtype of breast cancer, and noted that most TNBCs clustered in the basal-like subtype. Since then, multiple studies of gene expression profiling have advanced the understanding of the molecular diagnosis of breast cancer, thus providing the background for oncologists to use the triple-negative phenotype to describe the basal-like molecular subtype.

The luminal subtypes of breast cancers express high amounts of luminal cytokeratins and express genetic markers of luminal epithelial cells and normal breast cells. In contrast, basal-like breast cancers tend to express cytokeratins associated with basal types of cancers, as they arise from the outer basal layer.

Basal-like breast cancers are typically high-grade and poorly differentiated when examined morphologically. While the TNBC phenotype is defined by immunohistochemistry, no established diagnostic criteria have been identified for basal-like breast cancer on a morphological basis. In general, basal-like breast carcinomas are morphologically consistent with a high nuclear grade, high mitotic count, and necrosis (Fig 1), such as a grade 3 invasive ductal carcinoma, not otherwise specified (Fig 1). Some have the histomorphology of medullary carcinoma or metaplastic carcinoma. It has also been reported that almost 82% of basal-like breast cancers express p53 compared with 13% in the luminal A subgroup.

A subset of TNBC and basal-like breast cancer that is of low histological grade includes secretory, adenoid cystic, acinic cell, and apocrine breast carcinoma. Useful immunohistochemical markers for characterizing basal-like carcinomas are CK5 (Fig 2), CK6, CK14, CK8/CK18, p63, P-cadherin, vimentin, epidermal growth factor receptor 1 (EGFR1 [or HER1]), c-kit, and other growth factors such as insulin-like growth factor receptor (IGFR).

Not all basal-like carcinomas are HER2-. A study found that 23% of basal-like tumors, which are defined by gene expression study, were HER2+. Therefore,
HER2 immunoreactivity should not be used to rule out a basal-like carcinoma.

It is important to realize that TNBC and basal-like breast cancer are not all of high histological grade. For the above-mentioned low-grade tumors, the clinical management strategies outlined in this article are not applicable. Therefore, oncologists need to be aware of this when using triple-negative to define a potentially aggressive group of breast cancers. Although the majority of TNBCs are basal-like and the majority of basal-like breast cancers are triple-negative, there is approximately a 25% discordance between the two descriptive subgroups. However, for the remainder of this article, the TNBC phenotype is used to represent this molecular subtype.

**Clinical Course and Prognosis**

TNBCs are biologically aggressive; although some reports suggest that they respond to chemotherapy better than other types of breast cancer, prognosis remains poor. This is due to two factors: shortened disease-free interval in the adjuvant and neoadjuvant setting and a more aggressive clinical course in the metastatic setting.

Triple-negative tumors have a good initial response to chemotherapy, particularly anthracycline and taxane-based therapy. Although these tumors are initially sensitive to standard neoadjuvant chemotherapy, they continue to exhibit a short disease-free survival. Recently published neoadjuvant studies have clarified the fact that patients who have a good pathologic outcome from surgery also have a good clinical response. However, within the group of patients who have residual disease after completing neoadjuvant chemotherapy, a worse prognosis is seen in the triple-negative subgroup.

Carey et al. examined the relationship of neoadjuvant chemotherapy response to clinical outcome among three breast cancer subtypes. They used immunohistochemical profiles to represent molecular subtypes of breast cancer. The three groups compared were the HER2+/hormone receptor-negative (HER2 overexpressed) subtype, the hormone receptor-negative and HER2- (basal-like) subtype, and the hormone receptor-positive (luminal) subtype. They followed a prospectively maintained data set of patients with breast cancer treated with neoadjuvant anthracycline-based chemotherapy — doxorubicin plus cyclophosphamide (AC). They then analyzed each subtype for clinical and pathologic response to neoadjuvant chemotherapy and examined the relationship of this response to distant disease-free and overall survival. After neoadjuvant AC, 75% received subsequent chemotherapy, and all patients who were hormone receptor-positive received endocrine therapy.

The chemotherapy regimen and the pretreatment stage did not differ by subtype. The clinical response to AC neoadjuvant therapy was higher in the HER2+/ER- (70%) and basal-like (85%) subtypes than in the luminal subtype (47%; \( P < .0001 \)). Pathologic complete response occurred in 36% in the HER2+/ER- group, 27% in the basal-like group, and 7% in the luminal subtype \( (P = .01) \). Of interest, despite displaying initial chemosensitivity, patients with the basal-like and HER2+/ER- subtypes had worse distant disease-free survival \( (P = .04) \) and overall survival \( (P = .02) \) than those with the luminal subtype. This worse outcome among the basal-like and HER+/ER- subtypes was due to higher relapse among those patients with residual disease after completing neoadjuvant chemotherapy \( (P = .003) \).

In another study, TNBC was associated with increased risk for visceral metastases \( (P = .0005) \), lower risk for bone recurrence \( (P = .027) \), and shorter postrecurrence survival \( (P < .0001) \). If pathologic complete response (pCR) was achieved, patients with TNBC and non-TNBC had similar survival \( (P = .24) \). In contrast, patients with residual disease had worse overall survival if they had TNBC compared with non-TNBC \( (P < .0001) \). This study concluded that patients with TNBC have increased pCR rates compared with those without TNBC and that those with a pCR have excellent survival. However, patients with residual disease after neoadjuvant chemotherapy have significantly worse survival if they have TNBC compared with those without TNBC, particularly in the first 3 years.

Even in early-stage TNBC, early relapse is common. There is a predilection for visceral metastasis, including lung, liver, and, notably, brain metastasis. Current estimates are that approximately 15% of TNBC patients develop brain metastasis. The risk for developing brain metastasis is higher for patients with TNBC than with other types of breast cancer. Studies show have shown that even in patients with cerebral metastasis, TNBC patients have a poor prognosis, as metastasis to the brain occurred earlier.

According to NCCN guidelines, treatment of T1N0 breast cancer is based on both tumor size and cellular characteristics. Oncologists tend to treat patients with T1N0 TNBC with more aggressive chemotherapy, in both the neoadjuvant and adjuvant setting. When examining the number of patients treated and also the type of adjuvant chemotherapy administered, triple-negative T1N0 patients have greater recurrence risk despite this more aggressive therapy. In 2007, researchers from the Swedish Cancer Institute from Seattle, Washington, reported that patients with T1N0 TNBC have twice the risk of recurrence, despite receiving more aggressive treatment.

In addition to having a short disease-free survival, triple-negative breast tumors are aggressive in the metastatic setting, significantly contributing to the shortened overall survival. Progression-free survival is estimated to be 4 months at best in TNBC for first-line therapy, even with bevacizumab-based therapy.

**Future Directions in Research**

Although TNBC is sensitive to chemotherapy, early relapse is more likely in patients with TNBC than with other subtypes, and visceral metastasis, including brain metastasis, is commonly seen. Targeted agents that are currently being investigated include EGFR, vascular...
endothelial growth factor (VEGF), poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors.

The antiangiogenic agent bevacizumab (Avastin), a monoclonal antibody targeting VEGF is active in many solid tumors including breast cancer. Miller et al. demonstrated a significant improvement in progression-free survival (11.8 vs 5.9 months, hazard ratio [HR] = .60; P < .001) when adding bevacizumab to paclitaxel chemotherapy compared with single-agent paclitaxel alone in first-line treatment of metastatic disease. Examining the TNBC subset of patients in this study confirmed the same improvement (HR = .53; 95% confidence interval, 0.40–0.70). Most oncologists would strongly consider an Avastin combination for first-line therapy when treating patients with metastatic TNBC.

The fact that the majority of BRCA1-associated breast cancers are also triple-negative and basal-like has led researchers to question the extent to which the BRCA1 pathway contributes to the behavior of sporadic basal-like breast cancers. It has been shown that basal-like breast carcinomas frequently harbor defects in DNA double-strand break repair through homologous recombinations such as BRCA1 dysfunction. The DNA-repair defects characteristic of BRCA1-deficient cells confer sensitivity to poly(ADP-ribose) polymerase 1 (PARP1) inhibition.

The PARP1 gene encodes a chromatin-associated enzyme that modifies various nuclear proteins. This gene is involved in the molecular events leading to cell recovery from DNA damage. When PARP1 is inhibited, breaks in double-strand DNA accumulate that, under normal conditions, would be repaired via homologous recombination. Both BRCA1 and BRCA2 are required for the homologous recombination pathway to function properly. Therefore, cell lines deficient in either BRCA1 or BRCA2 are sensitive to PARP1 inhibition, resulting in cell death and apoptosis. Intuitively, inhibition of the PARP pathway should benefit patients with BRCA-associated malignancies. However, as stated above, not all TNBC cases are associated with BRCA mutations.

Several PARP1 inhibitors are currently in clinical development and hold promise in TNBC and basal-like breast cancers. As presented in a plenary session in 2009, the results of a randomized phase II study with BSI-201 (a PARP inhibitor) showed benefit in patients with TNBC who had two or fewer previous lines of chemotherapy. When BSI-201 was combined with gemcitabine and carboplatin, the clinical benefit rate improved to 62% compared with 21% in the gemcitabine and carboplatin alone arm (P = .0002). Clinical benefit rate is defined as complete response plus partial response plus stable disease for at least 6 months. In addition, the overall response rate was notably improved in the BSI-201 arm at 48% compared with the control arm at 16%. Progression-free survival was improved to 6.9 months in the BSI-201 arm vs 3.3 months in the gemcitabine and carboplatin alone arm. Currently, many initial trials on targeted therapy with PARP inhibitors are underway to study their use in the treatment of TNBC. In addition, several new agents are being investigated that may be beneficial for patients with this subgroup of breast cancer.

References
2. Kaplan HG, Malmgren JA, Atwood MK. Impact of triple negative phenotype on breast cancer prognosis. Poster presented at: 29th Annual San Antonio Breast Cancer Symposium; December 14-17, 2006; San Antonio, TX.