INTRODUCTION

Breast cancer is the most common malignancy in women. An estimated 1 million cases of breast cancer are diagnosed annually worldwide and 400.000 patients die from the disease every year.\(^1\) Multiple oncogenes, tumor suppressor genes, and sex steroid hormones and their receptors are involved in the genesis and development of breast cancer. Breast cancer is a heterogeneous malignancy that has many subtypes with different biological behaviors, clinicopathological features, and molecular characteristics. The treatment responses and prognosis of different subtypes of breast cancer also differ markedly. Implementation of mammography screening, improved adjuvant systemic treatment, and decreased hormone replacement therapy use have decreased both the incidence and mortality of breast cancer in developed countries over the past five years; worldwide, however, the incidence of breast cancer is increasing.\(^2,3\)

ABSTRACT

Triple-negative breast cancer is a subtype with poor outcome, no targeted therapy and high recurrence rates after adjuvant therapy. This review discusses the frequency, clinical expression, molecular subtypes, and therapeutic options of triple-negative breast cancer.

Key words: Breast cancer, Triple-negative

Received: November 16, 2011 • Accepted: November 21, 2011

ÖZET

Triple-Negative Meme Kanseri: Sıklık Moleküler Alt Tipler ve Tedavi Seçenekleri

Triple-negative meme kanseri, kötü sonuçları olan, hedefe yönelik tedavisi olmayan ve adjuvant tedavi sonrası nüks oranı yüksek bir alt tipdir. Bu derlemede triple-negative meme kanserinin sıklığı, klinik ekspresyonu, moleküler alt tipleri ve tedavi seçenekleri tartışılmaktadır.

Anahtar kelimeler: Meme kanseri, Triple-negative

Geliş Tarihi: 16 Kasım 2011 • Kabul Ediliş Tarihi: 21 Kasım 2011
Triple-negative breast cancer (TNBC) is defined by the lack of protein expression of the estrogen receptor (ER) and progesterone receptor (PR) and the absence of HER2 protein overexpression. TNBC accounts for approximately 15% of breast cancers\[^{[4]}\]. Although recently in the limelight and discussed frequently, TNBC is not a new type of breast cancer. TNBC is important for both researchers and clinicians because it has a poor disease-free and overall survival, no effective specific targeted therapy is readily available for TNBC, and TNBC cases cluster in premenopausal women.

**CLINICAL EXPRESSION and MOLECULAR SUBTYPES of TNBC**

Breast carcinomas can be divided into 18 different subtypes based on their histomorphological characteristics\[^{[5]}\]. A large majority of breast tumors are designated as invasive ductal carcinoma no special type (NST)\[^{[6]}\]. NST is defined as a tumor that does not exhibit sufficient morphological features to be categorized as one of the other subtypes\[^{[5-7]}\]. The histological categorization of breast tumors fails to divide tumors into different disease entities with type-specific prognosis and treatment possibilities. The largest NST subtype has an inhomogeneous prognosis\[^{[6]}\].

Gene expression profiling has been introduced into the clinical literature during the past decade as research suggests that assessing the expression of multiple genes in a tumor sample may reflect programs turned on by DNA alterations and predict tumor behavior. A new approach to characterizing breast tumors uses their molecular characteristics. The seminal work by Perou et al. and Sorlie et al. suggests a classification of breast cancer subtypes based on gene expression patterns they called "molecular portraits" of breast cancer\[^{[8,9]}\]. Among the categories they defined were the luminal A and B tumor types (typically ER or PR positive), HER2 gene-amplified tumors, and a newly recognized class called "basal-like" due to the expression of basal keratins. Basal tumors typically lack ER, PR, and HER2, and are often referred to as triple negative, although not all basal-like tumors are triple negative. Overall, TNBCs share striking similarities with basal-like breast cancers (BBCs), and so a number of studies have considered them as the same. Approximately 20-25% of TNBCs are not basal-like on gene expression arrays\[^{[10,11]}\]. Similarly, there are BBCs that are not triple-negative, and these also constitute approximately 20-25% of cases. Therefore, in clinical trials examining basal-like biology and using the triple-negative phenotype to identify patients, the potential for misclassification exists.

Triple-negative disease encompasses more than one molecular subtype that shows a different prognosis and implies distinct therapeutic options. For example, non-basal-like TNBC does not behave like basal-like TNBC, as it has a better prognosis despite a reduced response to adjuvant chemotherapy\[^{[12-14]}\]. Basal-like TNBC has a specific expression profile that distinguishes it from other breast tumors, including enhanced expression of Ki-67, vimentin, laminin, and p53, but reduced Bcl-2 expression, compared with other subtypes\[^{[15,16]}\]. Several studies found that expression of the tumor suppressor PTEN was lost more frequently in basal-like TNBC than in non-basal-like TNBC\[^{[17-19]}\]. Other genes that tend to be mutated more frequently in basal-like TNBC, as compared to other breast tumors, are the tumor suppressor retinoblastoma gene (RB1) and the KRAS oncogene, both well known to enhance tumor growth\[^{[19]}\].

Besides mutations, other genetic changes differ among distinct subtypes, such as copy number alterations (CNAs). In more than 30% of the basal-like TNBC cases, two specific CNAs are found: gene amplification and chromosomal deletion\[^{[16,19]}\]. In searching for the pathways that lead to the development of basal-like TNBC, several studies have found that BRCA1-related breast cancers are associated with the basal-like TNBC subtype, and the basal-like TNBC expression profiles resemble those of BRCA1-related breast cancers\[^{[20-22]}\]. This resemblance gave rise to the idea that BRCA1 mutations play a role in the development of basal-like TNBC. Some studies have investigated epigenetic changes, such as DNA methylation, influencing the expression of BRCA1 in basal-like TNBC. However, DNA methylation does not seem to play a supportive role, given that BRCA1 methylation is similarly frequent in basal-like and non-basal-like TNBC\[^{[23,24]}\]. Studies have linked basal-like TNBC to epidermal growth factor receptor (EGFR) expression\[^{[25]}\]. This receptor, like HER2, is a potent stimulator of cell-growth-activating pathways and stimulates tumor growth when activated\[^{[26]}\]. EGFR expression could be one of the causes of the poor disease outcome of basal-like TNBC. Since newly developed therapies target EGFR, an assessment of EGFR expression, as performed commonly for HER2, could have therapeutic relevance\[^{[27,28]}\].
The claudin-low tumor subtype constitutes only approximately 5% of tumors, falls in the triple-negative spectrum, and has a significantly poorer outcome. This subtype is characterized by low expression of luminal markers and high expression of mesenchymal markers and is associated with a bad prognosis; it is also thought to be derived from stem cells[29].

**THERAPEUTIC OPTIONS: FUTURE DIRECTIONS for TNBC**

Adjuvant therapeutic options for TNBC can be divided into two groups, cytotoxic agents and targeted therapies. Chemotherapy and antiangiogenic drugs known to be effective in triple-negative disease, as well as advances in chemotherapy, have benefited this patient group in particular. Currently, there is no effective strategy for selecting which patients would benefit the most from these agents. Potential approaches in triple-negative disease include more targeted chemotherapy, growth factor pathway approaches, and *BRCA1*-driven approaches.

Cytotoxic therapies, e.g. combined treatment with anthracyclines or taxanes, achieved good tumour regression rates in the neoadjuvant setting, but also showed considerable recurrence during the first five years after therapy. Patients with triple-negative, basal-like breast cancer (TNBBC) have increased pathologic complete response (pCR) rates compared to non-TNBC patients, especially to taxanes and anthracycline agents[30]. In spite of the better response to chemotherapy, the prognosis of TNBC is still worse than that of other breast cancer subtypes, due to a higher likelihood of relapse in patients with residual disease[11,12,30]. Another group of cytotoxic agents showing good results in TNBBC are the platinum-containing agents, such as cisplatin and carboplatin[31]. Study of Sirohi et al. reported a clinical response rate of 88% in TNBBC after neo-adjuvant treatment with platinum containing cytotoxic agents, compared to 55% clinical complete response rate in other breast tumours[32]. However, the overall five-year survival was still worse for TNBBC compared to tumours of other subtypes.

Many antiangiogenic treatments have been introduced or are currently under development, and may hold promise for patients with TNBC. There are much data on bevacizumab in breast cancer. Although specific clinical subsets that benefited were not well characterized in further analyses, it was determined that patients with triple-negative disease benefited as much as, if not more than, the average[33]. This was also demonstrated in some subset analyses of tyrosine kinase inhibitor approaches, including vascular endothelial growth factor receptor inhibition.

The basal cluster includes EGFR, which has been of interest in preclinical studies for several years. EGFR is present and expressed on tissue microarrays from basal-like tumors, and TNBC cell lines show EGFR-dependent growth and proliferation. EGFR is considered a sensible target in TNBC. Cetuximab, which is an anti-EGFR monoclonal antibody, has been added to chemotherapy for TNBC[34].

Poly (ADP-ribose) polymerase (PARP) inhibition is another therapeutically valuable mechanism in patients with triple negative disease. PARP inhibition involves synthetic lethality, meaning cell death by targeting more than one pathway, when impairment of one pathway alone is not lethal[35]. In a normal cell subject to certain types of DNA damage there are several mechanisms available to repair the damage, including homologous recombination, which is *BRCA1*-dependent, and base excision repair, highlighted because it is a PARP-dependent function.

**CONCLUSION**

In developed countries, there has been a remarkable reduction in mortality from breast cancer, but almost all of that benefit has occurred in the ER- and HER-2-subsets. TNBC is a unique subgroup, with a specific molecular profile, aggressive behavior, a relative lack of effective therapies, and a poor prognosis. Targeted therapies, like PARP inhibitors and EGFR-targeting agents, are additional promising therapeutic options.

**REFERENCES**

presented at: 29th Annual San Antonio Breast Cancer Symposium; December 14-17, 2006; San Antonio, TX.


Address for Correspondence
Bahri ÇAKABAY, MD
Department of Surgical Oncology
Faculty of Medicine
University of Ankara
Ibn-i Sina Hospital
Ankara-Turkey
E-mail: surgeonbahri@gmail.com