Triple-Negative Breast Cancer

Who Should Receive Neoadjuvant Chemotherapy?

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KEYWORDS

• Triple-negative breast cancer • Neoadjuvant chemotherapy
• Breast-conserving surgery

KEY POINTS

- Progress in the treatment of triple-negative breast cancer (TNBC) remains an important challenge.
- Given the aggressive biology and high risk of distant recurrence, systemic chemotherapy is warranted in most patients.
- Neoadjuvant chemotherapy benefits patients with locally advanced disease by downsizing the tumor and increasing the probability of breast-conserving surgery.
- Clinical and pathologic responses provide important prognostic information, which makes neoadjuvant therapy an attractive approach for all patients with TNBC.
- Clinical research in the neoadjuvant setting is focused on improvement in pathologic complete response rates and outcomes of patients with residual disease.

INTRODUCTION

With advances in genetic studies, breast cancer has been identified as a heterogeneous disease with distinct subtypes that respond variably to different therapies. The concept of classifying breast tumors into subtypes was first described by Perou and colleagues,[1] who used gene expression profiling and identified 4 subtypes, including estrogen receptor (ER)–positive luminal-like, basal-like (BL), human epidermal growth factor receptor 2 (HER2)-positive, and normal breast. Triple-negative breast cancer (TNBC) is commonly defined as the absence of estrogen, progesterone, and HER2 receptors (ER-negative, progesterone receptor [PR]-negative, and HER2-negative), with estrogen and progesterone negativity defined as less than 1% of tumor cells staining using the current American Society of Clinical Oncology (ASCO) and College of American Pathologists guidelines.[2] When TNBCs are evaluated

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histopathologically, they are often, but not always, BL (approximately 85%).[3] Therefore, TNBCs are often erroneously thought of as interchangeable with the BL subtype although they are not the same entity. TNBC is a heterogeneous disease in itself and Lehmann and colleagues[4] identified 6 specific subtypes of TNBC using gene expression profiles from 21 breast cancer data sets, including 2 BLs (BL1 and BL2), an immunomodulatory, a mesenchymal, a mesenchymal stem–like, and a luminal androgen receptor (LAR). The investigators concluded that these subtypes of TNBC demonstrate distinct phenotypes with diverse gene expression patterns with variable sensitivity to different targeted therapies.

INCIDENCE AND CLINICAL PRESENTATION

Approximately 10% to 17% of breast cancers are classified as TNBCs based on standard immunohistochemical staining for ER, PR, and HER2.[5,6] In contrast to hormone receptor (HR)-positive tumors, they are more often high-grade invasive ductal carcinomas of no special type that have higher mitotic indices with central necrotic zones and lymphocytic infiltration.[7] They are more likely to present as a palpable mass[5,7,8] and tend to develop as interval breast cancers, which are invasive tumors that become clinically apparent between annual screening mammograms.[9,10] They are more responsive to chemotherapy compared with luminal tumors.

Despite their overall aggressive behavior, several studies have found that TNBCs are less likely to metastasize to the axillary lymph nodes.[5,11,12] In terms of metastatic disease, TNBCs more often spread to the brain and lungs.[5,13,14] Distant recurrences also tend to appear earlier than other subtypes. Dent and colleagues[15] studied a cohort of 1601 women with breast cancer of whom 180 had TNBC. They found that these women had an increased likelihood of death (hazard ratio 3.2; 95% CI, 2.3–4.5; $P<.001$) within 5 years of diagnosis compared with all other subtypes. They also demonstrated that the risk of distant recurrence peaked at approximately 3 years with a rapid decline thereafter compared with the other subtypes, where the risk of recurrence was constant. In a follow-up study, the same group also found that women with TNBC were 4 times more likely to experience a visceral metastasis within 5 years of diagnosis compared with all other subtypes.[14] Using the National Comprehensive Cancer Network (NCCN) Breast Cancer Outcomes Database, Lin and colleagues[5] found that TNBC was associated with worse breast cancer–specific survival (BCSS) and overall survival (OS) (hazard ratio for BCSS 2.99; 95% CI, 2.59–3.45; $P<.0001$; and hazard ratio for OS 2.72; 95% CI, 2.39–3.10; $P<.0001$) compared with HR-positive, HER2-negative tumors. TNBC was also associated with a dramatic increase in the risk of death within 2 years of diagnosis in this study, which likely reflects the tendency for these tumors to develop distant recurrence within this time period.

EPIDEMIOLOGY

TNBC disproportionately affects younger, premenopausal women.[5–8,16] In particular, those with a high body mass index are at higher risk.[5,17] The data regarding standard risk factors for the development of breast cancer, such as parity, oral contraceptive use, age at menarche, and their relationship to TNBC, are still not clear.[18]

TNBC is more frequently diagnosed in African American women as well as women of African descent compared with other breast cancer subtypes.[5,6,8,16,19] The Carolina Breast Cancer Study found that the BL breast cancer subtype was more prevalent among premenopausal African American women compared with postmenopausal African American women as well as women of other ethnicities of any age with a shorter survival compared with other subtypes.[16] Using California Cancer Registry data,