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,

Bauer and colleagues[6] identified that TNBCs were more likely to be found in women under age 40 and non-Hispanic black or Hispanic women. These women had poorer survival compared with women with other breast cancer subtypes regardless of stage, although these women also belonged to a lower socioeconomic status.

Several studies have also confirmed that patients with BRCA1 mutations more often develop TNBC.[20,21] Approximately 60% to 90% of BRCA1-associated tumors and 16% to 23% of BRCA2-associated tumors are TNBC.[20–22] Only approximately 15% of TNBCs, however, are associated with a BRCA1 or BRCA2 mutation.[23]

ADJUVANT VERSUS NEOADJUVANT CHEMOTHERAPY

Despite the poor prognosis of TNBC, studies have demonstrated that TNBC is more responsive to chemotherapy than other molecular subtypes.[24–26] Because common treatments used for patients with HR-positive and/or HER2-positive breast cancers are ineffective in TNBC, both NCCN and the European Society for Medical Oncology (ESMO) guidelines recommend the use of third-generation chemotherapy.[27,28]

A series of large randomized clinical trials have established that adjuvant (after surgery) and neoadjuvant (before surgery) administration of the same chemotherapy regimen yields similar results in disease-free survival (DFS) and OS.[29] In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial, there was no survival benefit for receiving doxorubicin and cyclophosphamide in the neoadjuvant setting compared with the adjuvant setting.[30] NSABP B-27 compared AC with preoperative or postoperative docetaxel and showed a significant increase in pathologic complete responses (pCRs) with the addition of preoperative docetaxel (26% vs 13%; $P<.0001$), but there was no significant difference in DFS or OS.[31,32] A meta-analysis of 9 randomized clinical trials also demonstrated no difference in OS, disease progression, or distant recurrence for women with breast cancer receiving adjuvant versus neoadjuvant chemotherapy.[33]

There is a lack of robust prospective data in TNBC restricted trial populations. Most clinical data have been derived from retrospective exploratory subgroup analyses, which suggested high sensitivity to chemotherapy in TNBC. These studies established the efficacy of anthracycline and taxane–based regimens and formed the basis of more recent clinical trials, particularly in the neoadjuvant setting for TNBC patients.

Although subgroup analyses of some individual trials have indicated mixed results for anthracycline-based therapy in TNBC subpopulations, most studies indicate a favorable effect in TNBC, including a meta-analysis of 5 randomized clinical trials.[34,35] Findings from multiple subgroup analyses of large phase III adjuvant trials support a role for taxanes in the adjuvant treatment of TNBC.[36–40] At this time, an anthracycline and taxane–based regimen remains standard of care for TNBC patients. Nonanthracycline regimens, such as taxane with cyclophosphamide, may be an appropriate choice for some patients, such as older patients and those with considerable comorbidities and cardiac risks.

Benefits of Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy, initially used only for locally advanced or inflammatory breast cancer, has become more common for patients with operable disease, especially in patients with TNBC.[30,31,41–45] This treatment approach allows more individuals to undergo breast-conserving surgery (BCS) and provides an assessment of response to treatment. In an era where individualization of therapy is highly valued, neoadjuvant chemotherapy allows the activity of novel agents or therapeutic combinations to be studied in vivo in a much shorter timeframe than with adjuvant trials.[46,47]

Surgical Outcomes

Neoadjuvant chemotherapy allows reduction of tumor volume in the primary tumor and the regional nodes, which can facilitate more options for surgical treatment. Several trials have demonstrated that tumors can be downsized with neoadjuvant chemotherapy, allowing for increased rates of BCS. In the NSABP B-18 trial, where patients were randomized to preoperative versus postoperative chemotherapy, lumpectomy was performed more frequently in the preoperative chemotherapy group compared with the postoperative group (67% vs 60%; $P = .002$).[48] In a retrospective study of 1242 patients treated at the Memorial Sloan Kettering Cancer Center with pathologic T1-2N0 TNBC, those who underwent BCS were compared with those who underwent total mastectomy without radiation. There was no significant difference in local recurrence, distant metastasis, overall recurrence, DFS, or OS between the 2 groups.[49] Although none of these patients received neoadjuvant chemotherapy, it can be extrapolated that similar results would be found in the neoadjuvant population because the NSABP trials established that there is no difference in survival based on the timing of chemotherapy delivery.

Pathologic Response to Chemotherapy

pCR is defined as the absence of residual invasive cancer on pathologic evaluation of the resected breast primary and regional lymph nodes after neoadjuvant therapy. Several neoadjuvant trials have shown that pCR predicts for long-term outcomes and is, therefore, a potential surrogate marker for DFS and OS. Achieving a pCR is more common in highly proliferating carcinomas like TNBC or HER2-positive tumors compared with luminal tumors.[50] A large pooled analysis comprised of 12 randomized clinical trials of neoadjuvant chemotherapy in breast cancer conducted by the Collaborative Trials in Neoadjuvant Breast Cancer international working group showed longer event-free survival (EFS) and OS in patients who achieved a pCR.[51] The association between pCR and long-term outcomes was strongest in patients with TNBC and in those with HER2-positive, HR-negative tumors who received trastuzumab.

Liedtke and colleagues[26] reported results from the MD Anderson Cancer Center for stages I to III breast cancer patients who received neoadjuvant chemotherapy. Patients with TNBC had significantly higher pCR rates compared with non-TNBC (22% vs 11%; $P = .034$), and those with a pCR had excellent survival, which was similar to non-TNBC patients. In contrast, patients with residual disease after chemotherapy had worse OS if they had TNBC compared with non-TNBC ($P<.0001$). A recently published cohort study with prospective follow-up of patients treated with an anthracycline and taxane–based neoadjuvant chemotherapy regimen demonstrated an estimated 10-year relapse-free survival of 86% for TNBC patients who achieved pCR versus only 23% for those with significant residual disease after chemotherapy.[52]

A summary of pCR rates from selected randomized clinical trials of neoadjuvant chemotherapy is shown in **Table 1**. In the GeparTrio trial, Huober and colleagues[53] reported a pCR rate of 38.9% in TNBC patients compared with 23.6% in HER2-positive disease and 11.2% in HR-positive patients. The attainment of a pCR predicted for improved DFS in TNBC patients (hazard ratio 6.67, $P<0.001$).[54] Similarly, in the Preoperative Epirubicin, Paclitaxel, Darbepoetin (PREPARE) trial, patients with a pCR had a significantly improved DFS rate (hazard ratio 2.27; $P = .001$).[55] The NeoAdjuvant Treatment (NATT) Trial study also showed significantly improved EFS and OS in patients with a pCR ($P = .03$ and $P = 0.04$, respectively).[56]

Overall, the available data suggest that pCR is associated with improved long-term outcomes and is an acceptable endpoint for neoadjuvant clinical trials. The pCR rates

Table 1
Selected randomized controlled trials of neoadjuvant chemotherapy in breast cancer

Study/Y	Tumor Size	Chemotherapy Regimen	Number of Patients Treated	Pathologic Complete Response (%)[b]	Pathologic Complete Response in Triple-Negative Breast Cancer (%)[b]
GeparDuo/2005[80]	T2–T3	AC-Doc vs ADoc	913	14.3% vs 7% (P<.001)	22.8% (P = .0001)
GeparTrio/2010[53]	T2–T4	TAC	2072	20.5%	38.9% (P = .0015)
GeparQuattro/2010[81]	T1–T4	EC-T	1421	22.3%	17.6%
Preoperative Epirubicin, Paclitaxel, Darbepoetin (PREPARE)/2011[82]	T2–T4	ddE-ddT-CMF vs EC-T	733	18.7% vs 13.2% (P = .04)	44.6% vs 30.4% (P = .12)
Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging and Molecular Analysis (I-SPY) 1/2012[83]	≥3 cm	AC-T[a]	221	27%	35%
European Organisation for Research and Treatment of Cancer (EORTC) 10994/2014[84]	T2–T4	FEC-T vs Doc-EDoc	1289	18%	31%
NeoAdjuvant Treatment Trial (NATT)/2016[56,85]	T2–T4	TAC vs TC	96	17.6 vs 6.8% (P = .11)	15.4% vs 4.3% (P = .35)

Abbreviations: AC, doxorubicin/cyclophosphamide; CMF, C-cyclophosphamide, M-Methotrexate, F-5-flourouracil; dd, dose-dense; Doc, docetaxel; E, epirubicin; TAC, docetaxel/doxorubicin/cyclophosphamide; TC, taxane with cyclophosphamide.

[a] 95% patients received a taxane after AC.

[b] pCR comparisons between the 2 chemotherapy regimens used in that trial.

in TNBC range from approximately 30% to 40% with anthracycline and taxane–based regimens. Efforts to further maximize pCR rates are under way by assessing the addition of different chemotherapeutic agents to standard regimens, including drugs, such as capecitabine, 5-Fluorouracil, vinorelbine, bevacizumab, everolimus, gemcitabine, and platinum agents.

Role of Platinum Agents in Triple-Negative Breast Cancer

Preclinical data suggest that TNBC tumors are more sensitive to DNA-damaging agents, such as platinum analogs, because of deficiencies in the BRCA-associated DNA repair mechanism.[57]

The Cancer and Leukemia Group B (CALGB) 40603 trial[58] showed that the addition of carboplatin to the standard neoadjuvant regimen of dose dense AC and T significantly increased pCR rates in the breast (60% vs 44%; P = .0018) as well as the axilla (54% v 41%; P = .0029). This study was not powered to assess EFS or OS and did not demonstrate any significant differences in these measures, although EFS did trend in the direction expected for the increase in the pCR rate seen with the addition of carboplatin.

The GeparSixto 66 study used a novel chemotherapy regimen consisting of weekly paclitaxel, nonpegylated liposomal doxorubicin and bevacizumab for 18 weeks and administered carboplatin weekly.[59] In addition to the improvement in pCR rates (37% to 53% with carboplatin; $P = .005$), similar to what was observed in the CALGB 40603 trial, GeparSixto also showed an improvement in DFS, specifically in TNBC patients randomized to the carboplatin arm (85.8% with carboplatin and 76.1% without; hazard ratio for consistency in the paper (HR) = 0.56; $P = .035$).

At this time, the role of carboplatin in the neoadjuvant setting for TNBC remains controversial and it is unclear whether its potential benefits outweigh the increase in hematologic toxicities. Given the improvement in responses, however, it is reasonable to consider its addition in high risk patients. Clinical trials are ongoing to further evaluate the role of platinum agents in patients with both BRCA and non-BRCA mutated TNBCs (NCT02413320 and NCT02547987).

Response-Guided Therapy

Neoadjuvant trials allow rapid assessment of drug efficacy and could theoretically expedite development and approval of treatments for breast cancer.[60] Neoadjuvant chemotherapy provides the opportunity to discontinue or change treatment in cases of nonresponsiveness. It also provides the opportunity for additional adjuvant therapy in patients with significant residual disease after neoadjuvant chemotherapy. There are few data, however, with these approaches. Response-guided therapy is a promising strategy to optimize and individualize treatment of breast cancer.

The CREATE-X study, a phase III trial, randomized patients with HER2-negative breast cancer and residual invasive disease after neoadjuvant chemotherapy with an anthracycline and/or taxane to adjuvant treatment with capecitabine at 1250 mg/m^2 twice daily, 2 weeks on/1 week off, for up to 8 cycles.[61] The estimated 5-year DFS was 74.1% with capecitabine compared with 67.7% in the control arm ($P = .005$). OS rates were 89.2% and 83.9%, respectively ($P < .01$). The TNBC subgroup experienced a 42% reduction in risk of death with capecitabine. Although there were more adverse events with capecitabine use, it is reasonable to consider this approach in high risk patients with significant residual disease especially in TNBC patients where there are no other standard adjuvant therapy options after completion of neoadjuvant chemotherapy.

An ongoing phase III trial is evaluating the role of adjuvant platinum-based chemotherapy, capecitabine, or observation in TNBC patients with residual disease after neoadjuvant chemotherapy (NCT02445391). Other approaches, such as genomically directed therapy (NCT02101385), immunomodulatory agents (NCT02954874), and vaccine strategies (NCT02427581), are being assessed in clinical trials in patients with residual TNBC after neoadjuvant chemotherapy.

SMALL TUMORS

Patients with breast cancer who have T1a,b ($\leq$1-cm) node-negative tumors generally have an excellent prognosis, with BCSS at 10 years exceeding 95%.[62,63] Outcomes for these patients vary, however, by biologic subtype.[64–69] The potential benefit of chemotherapy in small TNBCs remains unclear.

In a series of 194 TNBC patients from Memorial Sloan Kettering Cancer Center, both local-regional and distant recurrence-free survival were similar in T1mic/T1a and T1b tumors (94.5% vs 95.5%, respectively; $P = .81$). There were no differences in outcomes based on receipt of chemotherapy (95.9 vs 94.5%).[70] A recently published prospective cohort study within the NCCN reported on clinical outcomes of 4113 women

with T1a,b node-negative breast cancer of all subtypes with overall favorable prognosis.[71] For TNBCs, the 5-year distant relapse-free survival for T1a tumors was 93% without chemotherapy versus 100% with chemotherapy and for T1b tumors; it was 90% without chemotherapy compared with 96% with chemotherapy.

Patel et al.[72] recently reported survival outcomes in 13,065 patients with small TNBCs using the National Cancer Database. Tumor size was a strong predictor of survival. Compared with T1a tumors, hazard ratio for death was 1.43 (95% CI, 0.86–2.37) for T1b tumors and 3.00 (95% CI, 1.86–4.83) for T1c tumors. This study demonstrated a statistically significant 4-year OS benefit in patients with T1b and T1c tumors who received adjuvant chemotherapy compared with those who did not (97.1% vs 91.9% for T1b and 94.4% vs 80.6% for T1c, respectively; $P<.0001$ for both) whereas for T1a tumors, there was no significant difference seen (98.3% vs 93.7%; $P = .14$).

The NCCN guidelines do not recommend adjuvant chemotherapy for T1a TNBCs.[27] For T1b tumors, chemotherapy can be considered and there is a strong recommendation for chemotherapy in T1c tumors. In contrast, the St. Gallen 2015[73,74] and ESMO[28] guidelines recommend chemotherapy for all TNBCs regardless of the tumor size.

Patients with small TNBCs can undergo surgery first to fully assess the extent of disease and decide if chemotherapy is indicated. If a decision is to treat with chemotherapy before surgery based on other factors, such as young age, high grade, high Ki-67, and so forth, however, then the neoadjuvant approach can be considered for even small tumors given the prognostic information it provides with response assessment.

FUTURE DIRECTIONS

Currently, chemotherapy is used as systemic treatment in patients with TNBC; however, research is ongoing to identify actionable targets. TNBC is an aggressive subtype of breast cancer with a heterogeneous response to therapy. Lehmann and colleagues[75] reported that BL1 TNBC cell lines were the most sensitive to cisplatin and that the mesenchymal and mesenchymal stem–like lines were most sensitive to the Abl/Src inhibitor dasatinib. The clinical validity of the genomic subclassification of TNBC was confirmed by Masuda and colleagues[76] with a retrospective analysis of the response to neoadjuvant chemotherapy. The overall pCR in this study was 28%. In the BL1 subtype, the pCR was the highest (51%), in comparison with 0 in the BL2 subtype and 10% in the LAR subtype, clearly demonstrating the need to develop alternative treatments for some subgroups.

Potential targets and approaches, including DNA damage and repair, immunomodulation, HR modulation, and signaling pathway inhibition, are being evaluated to improve treatment and outcomes in TNBC. Although no biologic therapies are currently part of standard neoadjuvant therapy for TNBC, the poly ADP ribose polymerase (PARP) inhibitor veliparib is being studied in this setting. In a pilot study, the addition of carboplatin and veliparib doubled the pCR rate achieved with weekly paclitaxel and dose-dense AC in TNBC (51% vs 26% in control),[77] which led to an ongoing international randomized study comparing this combination to the control chemotherapy regimen with or without carboplatin (NCT02032277). The PD-1 inhibitor pembrolizumab is also being assessed in a phase III trial with neoadjuvant chemotherapy in TNBC patients to assess response rates (NCT03036488). The benefit of androgen blockage in the LAR subtype of TNBC has been shown in metastatic setting.[78,79] This approach is now being studied in the neoadjuvant setting with a phase II trial of enzalutamide, an antiandrogen drug, in combination with weekly paclitaxel for androgen receptor positive TNBC (NCT02689427).

SUMMARY

Progress in the treatment of 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 BCS. 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 pCR rates and outcomes of patients with residual disease. New targeted treatments and immunotherapeutic drugs are under development. The challenge is to conduct more focused studies due to the importance of heterogeneity in TNBC subtypes. Given the advantages neoadjuvant treatment offers, all patients with TNBC who are believed to be candidates for systemic chemotherapy should be considered for treatment in the neoadjuvant setting.

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