Neoadjuvant and Adjuvant Chemotherapy Considerations for Triple-Negative Breast Cancer

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Abstract

Triple-negative breast cancers (TNBC) are an immunohistochemically defined subset of breast cancer that is negative for the estrogen receptor (ER), progesterone receptor (PR), and HER2, and represent a heterogeneous group of tumors based on expression profiling. Despite strides made in adjuvant chemotherapy regimens and in overall survival for patients with breast cancer, prognosis for patients with TNBC continues to lag behind those with ER+ or HER2+ tumors. Chemotherapy remains the standard of care for TNBC because no targeted therapies have been proven to be effective for this subtype. There is growing interest in the use of platinum agents in the neoadjuvant setting for TNBC but we await data from ongoing, randomized, adjuvant trials to understand if these agents have an impact on long-term outcomes. Patients with BRCA-mutant TNBC are a special subgroup who may benefit more from platinums and, potentially, from poly ADP ribose polymerase (PARP) inhibitors. Immune checkpoint inhibitors are promising in many cancer types and are investigational in combination with chemotherapy in the neoadjuvant setting. Growing attempts to develop biomarkers to guide therapy within TNBC may lead to more effective regimens or to novel therapeutic targets.

Key words: Triple-negative breast cancer, chemotherapy, platinum, *BRCA*

Introduction: Defining the Subtype

Triple-negative breast cancers (TNBC), defined by the absence of estrogen (ER), progesterone (PR), and HER2 receptors, account for approximately 15% of all breast cancers.[1] This subtype is more common in African-American women, younger women, and *BRCA1* mutation carriers.[1,2] They are disproportionately associated with early recurrences, particularly in the first 5 years after diagnosis, with recurrences that are more commonly visceral or CNS rather than bone.[3,4] Hormone receptor-positive breast cancer recurs at a rate of 3% to 5% per year over a patient's lifetime, while TNBC recurs at a rate of 10% to 15% per year for 3 years before declining.[2,5] In an analysis of nearly 45,000 women with a first primary breast cancer who were registered in the California Cancer Registry, TNBC had a 5-year survival rate of 77% compared to 93% for other subtypes.[6]

There is growing interest in molecular classification of breast cancers as we move towards precision medicine for this disease.[7] Genomic analyses of TNBC, including sequencing of several hundred primary TNBCs, revealed frequent mutation in *TP53* but few recurrent targetable mutations.[8,9] Mutations in DNA repair pathways are more common in TNBC relative to other breast cancer subtypes. There is particular interest in *BRCA1* mutation carriers, since about 70% of breast cancers that develop in this group are triple-negative.[10] However, *BRCA1* mutation carriers remain a minority among all TNBC, with 10% to 25% germline or somatic *BRCA1* mutation in most series[11,12] (**Figure 1**).

Gene expression is the most widely studied classification approach, stratifying breast cancers into 5 'intrinsic' subtypes: luminal A, luminal B, HER2-like, basal-like, and normal-like.[13,14] These intrinsic subtypes have been associated with long-term prognosis and predict response to neoadjuvant chemotherapy.[14] More than 70% of TNBC are basal-like, defined primarily by high proliferation-related markers as well as by increased expression of cytokeratins 5 and 17, EGFR, and the proto-oncogene c-kit. Each of the additional intrinsic subtypes is represented in lower frequency among TNBCs, while 15% to 40% of basal-like tumors are not triple-negative by immunohistochemistry[15] (Figure 1). More recent expression analysis of several hundred TNBC yielded a classification system for TNBC subpopulations based on 6 equally represented categories: basal-like 1, basal-like 2, mesenchymal-like, mesenchymal stem-like, luminal AR, and immunomodulatory.[16] This classification system correlates with pathologic response to neoadjuvant chemotherapy and may offer guidance on targeted therapies for subgroups within TNBC.[17]

Standard Chemotherapy Regimens in the Neoadjuvant and Adjuvant Settings

The goals of neoadjuvant chemotherapy include improving the

likelihood of breast-conserving surgery as well as assessing response to systemic therapy.[18] Given a lack of targeted therapy options in the adjuvant setting, most women with TNBC will be considered for chemotherapy at some point in their care. Neoadjuvant chemotherapy also provides important prognostic information: those women with no histologic evidence of residual invasive cancer in either breast or axillary lymph nodes (pathologic complete response [pCR]) have significantly improved long-term outcomes relative to women with residual disease (RD).[19] However, in a meta-analysis by Cortazar and colleagues, improvements in pCR were not associated with similar improvements in overall survival (OS) across breast cancers, suggesting that neoadjuvant chemotherapy outcomes are not an appropriate surrogate for long-term outcome for all breast cancer subtypes.[19]

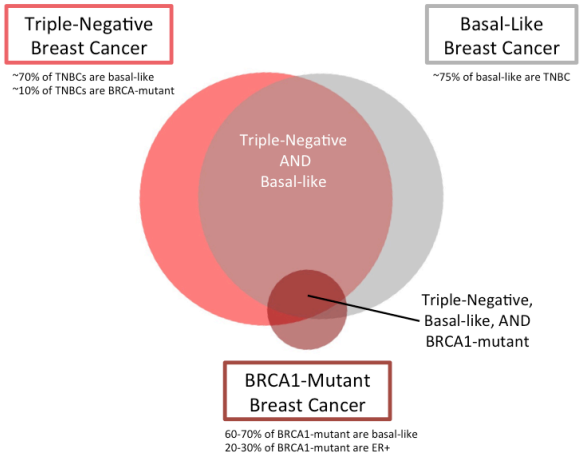
Among neoadjuvant regimens, sequential anthracycline-taxane chemotherapy represents a commonly used standard of care. The National Surgical Adjuvant Breast and Bowel Project (NSABP)-30 study suggested that, in the adjuvant setting, sequential therapy showed a small, but significantly improved disease-free survival (DFS) compared to concurrent regimens.[20] There is strong interest in whether adding agents to existing regimens or developing new regimens can both improve rates of pCR and improve long-term outcomes.

There are many potential regimens for standard chemotherapy for TNBC in the adjuvant setting, although the sequential, dose-dense anthracycline-taxane combination remains a common regimen for moderate-to-high risk TNBC.[20] The epirubicin-based regimen, including 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) followed by paclitaxel or docetaxel, are also acceptable regimens for patients with moderate-to-high-risk triple-negative disease.[21] Docetaxel plus cyclophosphamide (TC) is used in the United States and appears to be at least as effective as adriamycin plus cyclophosphamide (AC) for many patients; but this trial included a very small number of hormone receptor-negative patients.[22] The combination of cyclophosphamide, methotrexate, and fluorouracil (CMF) may be an alternative with less short-term and long-term toxicity but longer duration of therapy.[23,24]

The Role of Platinum Chemotherapy in TNBC

Interest in platinum agents emerged from data suggesting a high frequency of DNA repair defects in TNBC that may render TNBCs particularly susceptible to cross-linking agents[8], as well as evidence of high response rates in the metastatic setting.[25-27] The TNT trial prospectively randomized patients with metastatic or recurrent, locally advanced TNBC to either first-line carboplatin or docetaxel.[28] Overall response rates at 18 months were similar, with 31.4% for carboplatin and 35.6% for docetaxel, indicating that platinum is a viable first-line option but not superior to taxane therapy. A nonrandomized, phase II trial of single-agent platinum in metastatic TNBC demonstrated a slightly lower response rate of 25.6% across patients who had received 0-1 lines of chemotherapy for their metastatic disease.[26]

FIGURE 1. Overlap of Triple-Negative, Basal-like, and *BRCA1*-Mutant Breast Cancers.



Proportional representation of the overlap among triple-negative, basal-like, and *BRCA1*-mutant breast cancers. Most TNBC are basal-like (BLBC) and vice versa. While most *BRCA1*-mutant breast cancers are both TNBC and BLBC, only a small proportion of total TNBCs or BLBCs are *BRCA1*-mutant. Venn diagram created with BioVenn.[53]

The GeparSixto and CALGB/Alliance 40603 trials prospectively examined the addition of platinum to neoadjuvant chemotherapy regimens in TNBC. GeparSixto randomized patients with TNBC to receive paclitaxel, liposomal doxorubicin, and bevacizumab with or without carboplatin.[29] Along similar lines, in CALGB/Alliance 40603, patients with TNBC received paclitaxel weekly for 12 weeks followed by doxorubicin plus cyclophosphamide every two weeks for 4 cycles, and were randomized to receive concurrent carboplatin every 3 weeks for 4 cycles and/or bevacizumab every 2 weeks for 9 cycles.[30] The dose and schedule of platinum differed between trials: in GeparSixto, carboplatin area under the curve (AUC) of 1.5 was dosed weekly with liposomal doxorubicin and paclitaxel for 18 weeks, while in 40603, carboplatin AUC=6 was given every 3 weeks with weekly paclitaxel for a total of 12 weeks. Both trials demonstrated improved rates of pCR with the addition of carboplatin. In GeparSixto, the addition of carboplatin improved pCR rates (breast/axilla) from 36.9% to 53.2% and the *BRCA* carriers demonstrated an increase in pCR by 25% (P = .005).[29,31] CALGB/Alliance 40603 demonstrated an increase in pCR with the addition of carboplatin for breast/axilla (54% vs 41%; P = .0029).[30] Long-term outcomes data recently presented at San Antonio Breast Cancer Symposium, however, were divergent; there was improved DFS

with the addition of carboplatin in GeparSixto (HR, 0.56; 95% CI, 0.33-0.96; median follow-up 35 months) while CALGB/Alliance 40603 did not demonstrate improved event-free survival with addition of carboplatin (HR, 0.84; 95% CI, 0.58-1.22; median follow-up 39 months).[32,33]

The data for the addition of platinum to standard chemotherapy in the neoadjuvant setting are encouraging, but both studies were underpowered for long-term outcome end points, making it challenging to conclusively interpret benefit. One difference between the trials is that patients in the CALGB/Alliance study received an alkylating agent (cyclophosphamide) in addition to an anthracycline and taxane (with or without carboplatin), while in GeparSixto patients did not receive an alkylator. Differences in platinum dosing (weekly in GeparSixto vs every 3 weeks in 40603) or duration (18 vs 12 weeks, respectively) could also have had an impact. In addition, the improvements in pCR were associated with added toxicities, such as increased grade 3-4 neutropenia and thrombocytopenia, as well as required dosing adjustments of paclitaxel in the CALGB/Alliance trial.[30] It remains unclear how to incorporate platinum, and it is not known whether platinum could be used to substitute for anthracycline, taxane, or an alkylator rather than added to the current regimens.

Several ongoing phase III studies may provide additional insight regarding platinum. In the pre-operative setting, the ADAPT trial will evaluate nab-paclitaxel in combination with either carboplatin or gemcitabine for patients with TNBC.[34] The NRG BR003 study of adjuvant doxorubicin plus cyclophosphamide followed by weekly paclitaxel with or without carboplatin for node-positive or high-risk TNBC may provide additional insight on long-term outcomes, as well as on potential differences between neoadjuvant versus adjuvant setting. EA1131 is a randomized trial of 4 cycles of platinum chemotherapy versus observation for TNBC with residual disease after neoadjuvant chemotherapy. Given the complicating factors of toxicity and dosing, as well as unclear long-term benefit, platinum is not ready to be included in current standard neoadjuvant or adjuvant chemotherapy regimens for all patients with TNBC.

PARP Inhibitors in TNBC

Inhibitors of poly ADP ribose polymerase (PARP)1, a base excision repair enzyme, result in synthetic lethality in the context of altered *BRCA1* or *2*. PARP1 inhibitors have been explored in TNBC, which often have *BRCA* defects or deficiencies in other DNA repair participants.[35] In the I-SPY 2 study, patients with triple-negative and HR+ disease received veliparib and carboplatin in combination with paclitaxel as part of neoadjuvant therapy. The pCR rate for patients with TNBC in the arm with the PARP inhibitor plus carboplatin was 52% with the addition of veliparib/platinum versus 26% for patients receiving therapy not containing platinum or PARP, respectively.[36] Based on the success of this phase II trial, there is an ongoing phase III clinical trial in which patients with TNBC are randomized to receive veliparib/carboplatin/paclitaxel, carboplatin/paclitaxel, or paclitaxel alone, all to be followed by doxorubicin/cyclophosphamide in the neoadjuvant setting (NCT02032277).

Another recent trial enrolled patients with TNBC or *BRCA* mutation and randomized those with residual disease after neoadjuvant therapy to either single-agent cisplatin or cisplatin in combination with rucaparib following preoperative chemotherapy. The addition of the PARP1 inhibitor did not affect the toxicity of the chemotherapy, but it also did not significantly improve 1-year DFS.[37] Despite no definitive study showing improvement in DFS and/or OS using PARP inhibitors, the neoadjuvant or adjuvant settings ongoing studies may give us further insight into the role of PARP inhibitors.

Vascular Endothelial Growth Factor Inhibitors in TNBC

TNBCs demonstrate high intratumor levels of VEGF, leading to investigation of bevacizumab, a VEGF-directed monoclonal antibody, in this group.[38] The NSABP B-40 trial evaluated additional chemotherapeutic agents (gemcitabine or capecitabine) to anthracycline/taxane neoadjuvant regimens, as well as the role of neoadjuvant bevacizumab in HER2-negative breast cancers.[39] The addition of either gemcitabine or capecitabine was not associated with improved outcomes.[39] Adding bevacizumab was associated with increased OS (HR, 0.65; 95% CI, 0.49-0.88; P = .004) but not DFS (HR, 0.8; 95% CI, 0.63-1.01; P = .06) with significantly more frequent grade 3-4 neutropenia, hand-foot syndrome, and hypertension.[39] In the GeparQuinto study, the addition of bevacizumab to neoadjuvant epirubicin/cyclophosphamide followed by docetaxel demonstrated increased pCR rates for TNBCs (39.3% vs 27.9%), but no significant improvement in DFS or OS.[40]

Bevacizumab has also been explored in the adjuvant setting for TNBC. BEATRICE was an open-label, multicenter, phase III trial with in patients with TNBC who were randomized to receive 4 cycles of standard chemotherapy with or without bevacizumab.[41] The DFS (82.7% vs 83.7%) and OS (HR, 0.84; 95% CI, 0.64-1.12; P = 0.23) were not significantly different with the addition of bevacizumab. There was also a slight increase in cardiac events in patients receiving bevacizumab concomitantly with anthracyclines.[41] Given the added toxicities and lack of benefit in the adjuvant setting (ECOG 5103 and BEATRICE), bevacizumab is unlikely to have a role in the treatment of TNBC.

The Special Case of *BRCA*-Mutant TNBCs: Platinum and PARP

There is growing evidence that patients with *BRCA* mutations may have a distinct biology and disproportionately benefit from

platinums both in the neoadjuvant and adjuvant settings. In patients who develop breast cancer with an underlying *BRCA* mutation, 70% are classified as triple-negative and basal-like on intrinsic expression profiling.[15] In the neoadjuvant setting, a study of 107 women with breast cancer and *BRCA1* mutation, treated with 4 cycles of cisplatin, had a pCR of 61%.[42] The TBCR009 study, a nonrandomized, phase II trial using single-agent platinum in metastatic TNBC, had a response rate of 54.2% in *BRCA*-mutated patients versus only 19.7% in those with wild-type *BRCA*.[26] A study of neoadjuvant in TNBC suggested that biomarkers to platinum response were *BRCA1* mutation, low *BRCA1* expression, and high *BRCA1* methylation.[27] In the metastatic setting, subgroup analysis of patients in the TNT trial receiving carboplatin with *BRCA 1/2* mutations had significant improvement in progression-free survival.[28]

These data suggest that platinums are likely beneficial in patients with *BRCA*-mutant breast cancer. The ongoing INFORM trial (TBCRC 031) randomizes *BRCA* carriers to either 4 cycles of AC or 4 cycles of cisplatin followed by definitive breast surgery. Eventual results of this trial will examine pCR, long-term clinical response rate, and comparative toxicities of the 2 regimens and may provide more insight into how to incorporate platinum in this special subgroup.

While PARP inhibitors have not yet demonstrated a clear role in unselected TNBCs, their role in *BRCA*-mutant patients is of intense interest based on promising data in the metastatic setting.[27-29] A phase II trial enrolled women who had advanced, recurrent *BRCA*-mutated cancer and assigned them to receive either continuous maximum dose or lower dose olaparib. The overall response rate was higher for those on maximum dosing (41% vs 22%) with an acceptable toxicity profile.[43] The ongoing OlympiA study, which evaluates 1 year of adjuvant PARP inhibitor in patients with *BRCA*-mutant breast cancer, may give us further insight into the role of PARP inhibitors in this special patient population.

Looking Ahead: Better Biomarkers and Intriguing Immunotherapy

The development of specific biomarkers may help identify a subset of patients with TNBC who benefit from platinum beyond *BRCA*-mutant patients. In the CALGB/Alliance trial, the overall pCR rate did not differ between basal-like (54%) and the relatively small number of nonbasal-like cancers (52%).[30] A single-arm neoadjuvant phase II study of gemcitabine, carboplatin, and iniparib for TNBC found that a high homologous recombination deficiency (HRD) score predicted favorable pathologic response to cisplatin therapy.[44] Expression of various immune signatures that reflected tumor-infiltrating lymphocytes was associated with higher pCR rates, but was not specific to basal-like subtypes.[30] Continued investigation of biomarkers that indicate DNA repair deficiency and predict platinum responsiveness is ongoing.[45,46]

Recent impressive results of immune checkpoint inhibitors in melanoma and non-small cell lung cancer have led to evaluation of this class of agents across tumor types. In breast cancer, most work to date has focused on TNBC given greater frequency of tumor infiltrating lymphocytes (TILs) and an association of TILs with both response to neoadjuvant chemotherapy and long-term outcomes.[47-49] Three early-phase studies of immune checkpoint inhibitors demonstrated promising response rates of 8.3% to 19% in patients with metastatic disease.[50-52] This has led to the initiation of multiple studies of checkpoint inhibitors in combination with chemotherapy in the neoadjuvant setting for TNBC: pembrolizumab plus nab-paclitaxel with or without carboplatin followed by pembrolizumab + doxorubicin + cyclophosphamide (KEYNOTE-173; NCT02622074); MEDI4736 with weekly nab-paclitaxel and dose-dense doxorubicin/cyclophosphamide for stage I-III TNBC (NCT02489448); and MEDI4736 with taxane-anthracycline (GeparNuevo; NCT02685059).

Conclusions

The standard of care for neoadjuvant and adjuvant therapy in TNBC remains chemotherapy. While platinums show promise with increased pCR rates in the neoadjuvant setting, lack of consistent data regarding long-term outcomes limits widespread incorporation into routine care. PARP inhibitors have shown some promise, particularly in *BRCA*-mutant breast cancer, and several ongoing trials will clarify the role of this class of agents in TNBC. Although bevacizumab may be associated with increased pCR in TNBC, the lack of benefit in the adjuvant setting coupled with increased toxicity have not led to widespread adoption. Patients with *BRCA* mutations may have additional benefit from platinum, but when and how to incorporate therapy remains unclear. Progress in predictive biomarkers, as well as incorporation of immunotherapy may be practice-changing in the future.

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