Editorial

Stem Cell INVESTIGATION

Personalized chemotherapy in triple-negative breast cancer: are we ready for prime time?

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Triple-negative breast cancer (TNBC) comprises a subgroup of breast tumors characterized by the absence of estrogen- and progesterone-receptor protein expression and human epidermal growth factor receptor-2 (*HER2*) gene amplification. Approximately 15–20% of all breast tumors are classified as TNBC. Clinically, patients with TNBC have been treated similarly. Because patients with TNBC are not candidates for endocrine or anti-HER2 therapy, chemotherapy remains their most important available systemic therapy and the outcomes are poor compared to other breast cancer subtypes, with median overall survival (OS) reaching fewer than 2 years (1-3).

At the molecular level, TNBC is a heterogeneous disease (4). While pivotal studies evaluating gene expression profiles of breast cancers have revealed that most (55–81%) immunohistochemically defined TNBCs are categorized as basal-like tumors, all the other intrinsic subtypes can be found in TNBC (5-8). Additionally, recent studies have shown that even the basal-like subgroup can be subclassified (9,10). Therefore, a better understanding of these different molecular entities may open new pathways of therapy and allow physicians to select patients who may benefit from more targeted approaches.

Of note, 10% of TNBCs arise in carriers of loss-of-function heterozygous mutations in the tumor suppressor genes *BRCA1* and *BRCA2* (6,11). Patients harboring these mutations are also at increased risk of developing ovarian, prostate and other cancers. These genes encode proteins involved in the repair of DNA double-strand breaks (DSB) by a process called homologous recombination (HR). Cancer cells with deficiency of BRCA1 or BRCA2 proteins cannot repair DNA damage through HR and, as a result, are more dependent on alternative mechanisms of DNA repair (12). Thus, such cells are more sensitive to cytotoxic agents that generate DSB, such as alkylating agents and platinum salts, triggering cell cycle arrest and apoptosis. HR-deficient cells are also very sensitive to poly ADP-ribose polymerase (PARP) inhibitors in part because these agents block important mechanisms for alternative repair. The recent successful clinical trials of olaparib and talazoparib for patients with breast cancer who carry germline *BRCA1/2* mutations have clinically validated the concept of synthetic lethality (13-15).

Although used to refer to any cytotoxic agent, the term chemotherapy is vague and does not account for the differences between cytotoxic drug classes. Recently, Tutt *et al.* reported the results of the Triple-Negative Breast Cancer Trial (TNT), which started to shed some light on the differences in activities of distinct chemotherapies according to specific biomarkers in patients with TNBC. The TNT study was a British multicenter randomized phase III trial designed to compare the activity of the standard-of-care microtubule-disrupting agent docetaxel versus the DNA-damaging agent carboplatin in patients with unselected advanced TNBC (16). A total of 376 patients were randomized 1:1 to receive docetaxel or carboplatin. Patients with a germline *BRCA1* or *BRCA2* mutation with any breast cancer subtype were also eligible

for inclusion in the study. Most patients (338 of 376) had TNBC with no known germline *BRCA1/2* mutation. Efficacy endpoints included objective tumor response rates (ORR), and time from randomization until disease progression [progression-free survival (PFS)] or until death (OS). After a median follow-up of 11 months, there was no significant difference in ORR, PFS or OS between treatment arms in the unselected population.

Notably, there are several phenotypic similarities between breast cancers raised in germline *BRCA1* carriers and sporadic basal-like breast tumors: both are commonly high grade, present with high genomic instability, and contain a high frequency of *TP53* mutations (17). Moreover, several other defects in the HR repair pathway have been identified in breast cancer (18). Altogether, these issues have raised the hypothesis that breast tumors with HR deficiency due to mechanisms other than *BRCA1/2* germline mutations could also have increased sensitivity to chemotherapy or biological agents targeting defective DNA-repair pathways (19), a concept called "BRACAness" (17). To better address this issue, the TNT study investigators prespecified different sub-analyses to evaluate whether there is a better activity of carboplatin over docetaxel in specific populations.

In the 43 patients with germline *BRCA1/2* mutations, there was a significant advantage in both ORR and PFS with platinum therapy compared with docetaxel (68% versus 33% ORR, P=0.03; and 6.8 versus 4.4 months PFS, P=0.002, respectively). There was no significant difference in OS, although this may have been affected by the fact that patients were allowed to crossover to the other treatment arm following disease progression.

In a subset of patients with available tumor tissue, additional tests were performed to assess the hypothesis that carboplatin has higher level of activity in patients with putative "BRCAness" due to DNA methylation at the *BRCA1* promoter and/or low *BRCA1* mRNA expression, as well as in patients with basal-like phenotype defined by gene expression (throughout PAM50 assay) or by protein expression (immunohistochemistry). *BRCA1* methylation was found in 33 (16%) of 212 cases, low mRNA expression was found in 31 (16%) of 191 cases, while 170 (83%) of 206 tumors were categorized as basal-like throughout the gene expression assay, and 132 (70%) of 189 tumors were classified as basal-like according to immunohistochemistry. In contrast to the authors' hypothesis, patients with tumors harboring epigenetic silencing of *BRCA1* through DNA methylation or with low expression of *BRCA1* mRNA achieved neither a better response rate to carboplatin compared with docetaxel nor better PFS or OS. These findings are in agreement with previous data from the multicenter single-arm Translational Breast Cancer Research Consortium (TBCRC) 009 trial in metastatic TNBC, in which *BRCA1* methylation was not associated with response to cisplatin (20). Moreover, the Myriad test for HR deficiency score used in the TNT study was not able to select patients more likely to achieve an objective response to or prolonged PFS with carboplatin over docetaxel.

Notably, one important confounder in the TNT analysis is that most of the patients included had been exposed to adjuvant chemotherapy containing agents that cause DNA lesions requiring HR for repair, and the status of *BRCA1* methylation and mRNA levels were measured in archival primary tumor specimens collected before starting adjuvant therapy. It has been recognized that reversal of DNA repair defects can occur relatively frequently following therapies that cause DNA damage (21). There is also interest in the utility of mutational signatures associated with HR deficiency in predicting benefit to platinum or PARP inhibitors in breast cancer (22,23). However, the fact that mutational signatures represent a permanent "scar" in the cell genome may prevent its utility in predicting HR-deficient tumors in real time, especially in patients who previously received systemic therapy. For these reasons, there is growing recognition that the HR status of tumors must be defined with a fresh biopsy at the time of treatment, coupled with a functional assay for the activity of the pathway. The presence or absence of RAD51 foci in tumor tissue is being explored as a measure of HR-proficiency or deficiency, respectively, and should provide ancillary and complementary information to genomic and epigenetic analyses (24,25).

Finally, the study also failed to find evidence that the presence of a basal-like tumor, defined either by gene or protein expression, predicts higher response to carboplatin than to docetaxel. On the other hand, the findings indicate that tumors categorized as non-basal by Prosigna–PAM50 had significantly lower response rates to carboplatin compared with docetaxel.

In summary, the results of the TNT study support the use of carboplatin as an active agent and fair alternative to docetaxel in unselected basal-like TNBC. Taxanes continue to be the standard-of-care in non-basal tumors. Furthermore, the results of the TNT study highlight the heterogeneity in TNBC. To date, germline *BRCA1/2* mutation is the only biomarker able to select patients with a

greater response and longer PFS to platinum over taxanes, validating its clinical utility for treatment selection in the first-line setting. Similarly, the PARP inhibitors olaparib and talazoparib have showed improved efficacy in germline *BRCA1/2*-mutated advanced HER2-negative breast cancers when compared with standard non-platinum chemotherapy, leading to FDA approvals (14,15). Importantly, additional research on both platinum salts and PARP inhibitors is needed to clarify whether differences in primary versus metastatic tumor specimens have influenced the results of the sub-analyses in this trial for patients who are not germline *BRCA1/2* carriers, but who have tumors with BRCA-ness features.

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Footnote

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