The cloning of the BRCA1 and BRCA2 breast cancer susceptibility genes two decades ago launched a new era of research focused on identifying patients most likely to benefit from targeted intervention due to an increased risk of developing cancer. The lifetime risk of developing breast cancer is 50-80% for individuals who carry the BRCA1 germline mutation. Additionally, the lifetime risk of developing ovarian cancer is approximately 40%. For BRCA2 carriers, the risks of breast and ovarian cancer are 40-70% and 15-20%, respectively. Risk can be modified by lifestyle factors, genetic factors (e.g., location of the gene and modifier gene allotypes), and hormonal interventions. Germline mutations also contribute to triple-negative breast cancer (TNBC) heterogeneity, independent of gene expression and somatic mutations. In one recent analysis of patients with TNBC unselected for family history of cancer, 14.6% harbored germline mutations associated with cancer susceptibility, including 11.2% who harbored BRCA1/2 mutations.

In addition to increasing cancer risk, susceptibility mutations appear to influence the likelihood of response to treatment. The randomized, phase 3 Triple Negative Breast Cancer Trial (TNT) compared platinum-based treatment with carboplatin versus docetaxel in 376 patients with locally advanced or metastatic TNBC. Patients were stratified by BRCA1/2 status at baseline. In the overall study population, no significant differences between carboplatin and docetaxel were observed in objective response rate (31% vs. 35.6%), median PFS (3.1 vs. 4.5 months), or median OS (12.4 vs. 12.3 months). However, subgroup analyses showed a significant interaction between treatment effect and BRCA1/2 status (p=0.01) relative to objective response (Table 1). Among patients who harbored a germline BRCA1/2 mutation, carboplatin significantly increased the objective response rate compared with docetaxel (68.0% vs. 33.3%; p=0.03). The interaction between PFS and BRCA1/2 status was also significant (p=0.03), with carboplatin prolonging the median PFS by 2 months compared with docetaxel (6.8 vs. 4.8 months) in patients who harbored a BRCA1/2 mutation.

One of the major challenges in metastatic TNBC management involves the lack of guideline recommendations specific for this patient population. The National Comprehensive Cancer Network (NCCN) breast cancer guidelines do not differentiate the preferred regimens for metastatic breast cancer (MBC) subtypes. Likewise, the Advanced Breast Cancer 2nd Consensus Conference (ABC2) guidelines do not specify treatment pathways for TNBC, although platinum agents “may be considered” for BRCA-associated TNBC. Although the dearth of effective therapies also limits TNBC management, new drug-development pathways may soon translate to novel treatment options. The U.S. Food and Drug Administration (FDA) has established an accelerated pathway for using neoadjuvant therapy and partial complete response (pCR) as surrogate endpoints in high-risk populations, including TNBC and HER2-positive breast cancer. No new therapies have been approved for the treatment of metastatic TNBC using this approval pathway to date, but several clinical trials are underway.

Understanding TNBC heterogeneity is key to identifying potential therapeutic targets. One emerging framework for evaluating TNBC heterogeneity involves intrinsic tumor subtypes (basal-like, Luminal A, Luminal B). Differences in intrinsic expression profiles may reflect distinct cells-of-origin for different breast cancer subtypes, with basal-like tumors associated with BRCA1 and Luminal B tumors associated with BRCA2. Among TNBC tumors, different intrinsic subtypes exhibit differential responses to neoadjuvant chemotherapy and varying degrees of susceptibility to different therapeutic classes (e.g., platinum-based chemotherapy, anti-androgen therapy, and PI3K/mTOR inhibition). The number and type of somatic mutations also characterizes TNBC heterogeneity, with basal-like tumors having a greater number of p53 mutations and total mutations than other intrinsic subtypes.
gation in BRCA1/2-associated cancers involves the poly (ADP-ribose) polymerase (PARP) enzyme pathway. Although the proteins encoded by the BRCA1 and BRCA2 genes are both involved in genome protection, the BRCA1 and BRCA2 proteins work at different stages of DNA damage response (DDR) and DNA repair.11 Whereas BRCA1 is a pleiotropic DDR protein, BRCA2 mediates the core mechanism of homologous recombination (HR).12 In the absence of BRCA1/2, a PARP-dependent pathway is required for DNA repair.13 PARP inhibitors have demonstrated selective efficacy in tumors that are deficient in HR-mediated repair by virtue of germline or somatic mutations in BRCA 1/2. In a phase II proof-of-concept trial, the oral PARP inhibitor olaparib 400 mg BID showed an overall response rate of 41% in patients with BRCA1 or BRCA2 mutations and advance breast cancer.14

Although germline BRCA1/2 mutations are relatively uncommon, it is now believed that a substantially larger group of tumors exhibits defects in the BRCA1/2 pathway. These tumors might similarly be treated successfully with PARP inhibitors or related agents. Unfortunately, identification of additional genes and mechanisms that cause a BRCA1/2 pathway defect has proven challenging and has hampered efforts to develop a clinically useful biomarker of the “BRCA-like” phenotype. Recent progress toward this goal has been made through genomic analyses comparing BRCA1/2-mutant and nonmutant tumors. This work has uncovered a group of related genomic rearrangement patterns, referred to collectively as a “genomic scar,” that reflects a selective deficiency in HR-mediated repair.15

To date, three DNA-based HR deficiency (HRD) scores have been developed that highly correlate with defects in BRCA1/2: the HRD-loss of heterozygosity (LOH) score, the HRD-telomeric allelic imbalance (TAI) score, and the HRD-large-scale state transition (LST) score.16 The HRD scores predict response to platinum-based chemotherapy in patients with TNBC and ovarian cancer. In the phase II prECOG O1015 trial of neoadjuvant carboplatin/cemcitabine/iniparib in patients with TNBC, higher HRD scores significantly predicted treatment response among all patients (p=0.0003) and in the subgroup of patients with intact BRCA1/2 (p=0.0006).17 Similarly, in the phase II TBCRCO09 trial of cisplatin or carboplatin in patients with metastatic TNBC, mean HRD scores differentiated between responding and nonresponding tumors (p=0.0089) tumors, including BRCA1/2 wild-type tumors (p=0.0318).17 The ongoing phase II TBCRCO30 trial will examine whether HRD scores distinguish platinum sensitivity from general chemosensitivity in patients with TNBC treated with cisplatin or paclitaxel.18

**Summary**

A growing body of evidence indicates that BRCA1/2-mutant tumors exhibit specific DNA repair defects that can be exploited therapeutically. A subset of BRCA1/2-intact tumors may exhibit a BRCA-like phenotype that is not reflected in traditional mutational and gene expression analyses. These BRCA-like tumors may be identifiable through empiric patterns of genomic aberrations. However, more robust assays for identifying the BRCA-like phenotype are needed. Additional subsets of tumors with distinct repair defects exist, and their identification may point to new therapeutic opportunities.

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