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Homologous recombination deficiency in breast cancer

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Summary *BRCA* mutation-related DNA repair deficiencies increase the individual sensitivity to DNA-targeting agents. Therefore, the patient's *BRCA* mutational status is evaluated in clinical practice as a predictive marker in response to platinum salts and poly-ADP-ribose polymerase (PARP) inhibitors for breast cancer treatment. A substantial subset of *BRCA* wild-type breast cancer lesions, however, share both prominent molecular characteristics and clinical behavior patterns with cancer that harbors *BRCA* mutations, including DNA repair deficiencies. Also referred to as "BRCAness", this observation is related to aberrations of the homologous recombination (HR) repair pathway, which deprive cancer cells of the ability to adequately mend potentially lethal double-strand breaks and result in a *BRCA*-like genomic instability. Hence, HR deficiency is a promising target for related therapeutic options and the predictive potential of HR testing for treatment response has been increasingly studied. Several HR deficiency-testing assays have been proposed and prospectively validated for various cancer types; however, preliminary results in early breast cancer are inconsistent. As scientific evidence for a potential therapeutic benefit in breast cancer is scarce, HR testing remains highly experimental and should be limited to the boundaries of clinical studies until results of ongoing phase 3 trials are available.

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Abbreviations

DSB	Double-strand break
HR	Homologous recombination
ORR	Overall response rate
PARP	Poly-ADP-ribose polymerase
pCR	Pathological complete response
SSB	Single-strand break
TNBC	Triple-negative breast cancer

Introduction

Growing evidence supports the increased clinical efficacy of DNA-targeting therapies in breast cancers harboring *BRCA1* and/or *BRCA2* mutations as *BRCA* function is pivotal to DNA-damage response [1]. *BRCA* mutations are observed in approximately 5–10% of unselected breast cancers and 20–40% of all triple-negative breast cancers (TNBCs). Up to 15% more have been hypothesized to express non-*BRCA*-related alterations in the DNA repair pathway of homologous recombination (HR) repair [2–4]. TNBCs typically express few therapeutic targets; defining a predictive marker to identify patients that will most likely benefit from DNA targeting agents, such as platinum salts and poly-ADP-ribose polymerase (PARP) inhibitors, may therefore expand the therapeutic armamentarium for a clinically highly relevant subset of patients with breast cancer.

Homologous recombination deficiency as a marker for treatment response

The ability to adequately repair DNA double-strand breaks (DSBs) relies on HR repair, which reconstructs damaged DNA by copying the respective undam-

aged strand from the homologous sister chromatid. A complex set of proteins is required to interact within this procedure, including the gene products of *BRCA1, BRCA2, PALB2, RAD51, ATM,* and *CHEK2.* Any dysfunctional protein involved may impair the ability to adequately mend DSBs, thereby inducing a phenotypical cell behavior termed HR deficiency or "BRCAness." As HR repair fails, DSBs are frequently referred to non-homologous end joining (NHEJ) repair, an error-prone process of random end-to-end fusion of damaged strands, which inevitably leads to information loss, accumulation of genetic damage, and ultimately to cell death. Since the ability of HR-deficient cells to cope with DNA damage is therefore limited, phenotypical HR deficiency is associated with increased sensitivity to therapeutic agents targeting DNA integrity, particularly PARP inhibitors and platinum salts [1].

PARP inhibitors induce an excess of DNA single-strand breaks (SSBs) by inhibiting the activity of base excision repair and foster DSB by trapping PARP at the DNA, thereby blocking the replication fork [5]. A growing body of evidence, however, also indicates direct involvement of other DNA repair systems, as PARP can be trapped on DNA at sites of unrepaired SSBs, thereby directly contributing to lethal effects of PARP inhibitors [6]. Moreover, radiosensitization effects of PARP inhibition may be explained by interfering with HR-independent so-called PARP1-dependent end-joining [7]. In contrast, the principal effect of platinum salts relies on the induction of interstrand and intrastrand DNA cross-links. The repair of such cross-links depends on a complex interaction of manifold single- and double-strand repair systems including HR. Therefore, deficient cells often fail to restore proper DNA architecture. Moreover, cross-link-related distortions of the DNA double helix promote SSBs and DSBs [8, 9].

Defining and diagnosing homologous recombination deficiency

Several methodologically different approaches to test HR deficiency in breast cancer have been proposed. The so-called "genomic scarring" assays aim to quantify genomic aberrations by next-generation whole genome sequencing. The "myChoice" HR deficiency test (Myriad Genetics Inc., Salt Lake City, Utah, USA) calculates a score of sections of losses of heterozygosity, large-scale transitions, and telomeric allelic imbalance as three combined DNA-based measures of genomic instability [10]. The "CDx BRCA LOH" (Foundation Medicine, Cambridge, Massachusetts, USA) assesses deleterious *BRCA1* and/or *BRCA2* mutations. With the implementation of HR deficiency testing in treatment decision-making for epithelial ovarian cancer, recent comparative trials have focused on validating genomic scarring assays. Further, recent clinical studies have used genomic scarring assays to assess HR deficiencies in breast cancer [11–14].

Moreover, previously defined complex patterns of somatic mutations throughout the whole genome, so-called gene signatures, have been validated as predictors of HR-deficient tumors. The HRDetect test has been designed to detect HR deficiency with high sensitivity based on such gene signature analyses [15]. It has been hypothesized that such gene signature-based tests compensate a major shortcoming of genomic scarring assays, i.e., recognition of *BRCA* promoter hypermethylation-related HR deficiency. Such transcriptional deactivation of *BRCA* function is reversible and not predictive of therapy response, even though it is associated with higher "myChoice" HR scores. Large studies assessing different HR deficiency tests are urgently needed to clarify these findings [16, 17].

Lastly, protein function of crucial steps in HR such as *RAD51* can be assessed using DNA sequencing and immunostaining assays to predict HR deficiency.

Table 1 Clinical trials assessing homologous recombination deficiency in breast cancer patients

Study	Study design	Agent	No	Patients	pCR/ORR in HRd[a] patients with or without platinum
PrECOG0105/ pooled Cisplatin-1 and 2 [8]	Phase 2 single-arm	Carboplatin, gemcitabine, iniparib and cisplatin + bevacizumab	148	Neoadjuvant TNBC	pCR: 42% vs. 10% OR 6.52; [1.36–31.2]; $p < 0.01$ pCR: 27.5% vs. 0% OR 17; [1.91–2249]; $p < 0.01$
GeparSixto [17]	Phase 2 randomized open label	Paclitaxel, doxorubicin ± carboplatin	595	Neoadjuvant TNBC and Her2 positive	pCR: 63.5% vs. 33.9% OR 3.4 [1.7–6.9]; $p < 0.01$
GeparOLA (Abstract, NCT02789332)	Phase 2 randomized open label	Olaparib, paclitaxel versus carboplatin, paclitaxel	102	Neoadjuvant TNBC or Her2 negative	pCR: 20% vs. 56.2% OR not reported; $p < 0.01$
TNT [14]	Phase 3 randomized open label	Carboplatin versus docetaxel	376	Unselected advanced TNBC	ORR 38.2% vs. 40.4% OR not reported; $p = 1.0$

HR homologous recombination repair, *OR* odds ratio, *ORR* overall response rate, *pCR* pathological complete response, *TNBC* triple negative breast cancer
[a]HR deficiency (HRd) was defined by the "myChoice" HR (Myriad Genetics) assay for all studies listed

Broad availability and independence of commercial testing may favor this approach, especially in lower-income countries. However, its clinical applicability is limited as *RAD51* assays cannot be performed on formalin-fixed paraffin-embedded blocks, but they require viable tumor tissue [17].

Studies assessing homologous recombination deficiency in breast cancer patients

Despite promising preliminary results, published trials comprise heterogeneous populations and study designs, which hinder direct comparisons and limit drawing conclusions for clinical practice. Table 1 provides an overview of recent clinical studies evaluating the predictive value of HR assessment.

Results appear most promising for predicting therapy response to platinum salts in a neoadjuvant setting. Telli et al. [10] retrospectively assessed the predictive value of the "myChoice" HR test in three single-arm trials (PrECOG0105 and pooled cisplatin 1 and cisplatin 2) of neoadjuvant platinum therapy comprising 148 patients with TNBC. Patients with HR-deficient tumors achieved higher pathological complete response (pCR) rates with the addition of platin (PrECOG0105, pCR 42% versus 10%, OR 6.52; 95% CI 1.36–31.2, and cisplatin 1 and 2, pCR 27.5% versus 0%, OR 17; 95% CI 1.91–2249).

Moreover, a post-hoc analysis of the GeparSixto trial, a randomized phase 2 study assessing the additional benefit of carboplatin to anthracycline/taxane-based treatment for neoadjuvant chemotherapy regimens in 595 patients with primary, nonmetastatic TNBC and her2-positive breast cancer, reported higher pCR rates in patients with HR-deficient tumors with the addition of carboplatin (63.5% vs. 33.9%, OR 3.4, 95% CI 1.7–6.9) [18]. The long-term survival analysis, however, could not prove a correlation between HR deficiency and patient prognosis [19].

The ongoing randomized phase 2 trial TBCRC030 (NCT01982448) of neoadjuvant cisplatin versus paclitaxel in 140 patients with TNBC preliminarily reported that the pCR rate of patients with HR-deficient tumors was 21.1% in the carboplatin cohort and 19.4% in the paclitaxel cohort [20]. The also ongoing GeparOLA (NCT02789332) study, a randomized open-label phase 2 trial of paclitaxel/olaparib 100 mg BID versus paclitaxel/carboplatin both followed by epirubicin/cyclophosphamide as neoadjuvant treatment in 102 patients with her2-negative early breast cancer, preliminarily reported that pCR rate was not statistically significant different between the olaparib arm and the carboplatin arm. In the subgroup of patients with HR-deficient tumors, pCR rates were 52.6% in the olaparib arm and 20.0% in the carboplatin arm, whereas in the subgroup of patients with HR-proficient tumors, the rates were 56.0 and 59.3%, respectively [21].

The TNT trial, a randomized, open-label phase 3 study comparing carboplatin with docetaxel in 376 patients with unselected advanced TNBC, reported that patients with *BRCA*-mutated tumors achieved higher overall response rates (ORRs) after carboplatin treatment than after docetaxel treatment (68.0% versus 33.3%). There was no significant difference in ORR in patients with HR-deficient tumors after carboplatin and docetaxel treatment (38.2% versus 40.4%). This finding could partially be explained by the fact that the HR deficiency test was performed on archival samples of the primary tumor, which could result in lower positive predictive value as tumor evolution processes and inherent accumulation of genomic scars could not be depicted [22].

Future perspectives

As current evidence is limited, several ongoing clinical trials assessing treatment response to platinum salts and PARP inhibitors, stratified by HR assessment, are expected to further elucidate the role of HR for therapy decision-making in patients with breast cancer. A Chinese randomized phase 3 trial (NCT03876886) is studying dose-dense epirubicin/cyclophosphamide followed by paclitaxel and carboplatin/paclitaxel as adjuvant therapy of TNBC stratified by HR assessment. Moreover, a post-hoc HR deficiency analysis of the BrighTNess phase 3 trial, comparing veliparib plus carboplatin versus carboplatin alone, is currently underway and may provide insights into the predictive value of HR testing in this cohort [23].

The phase III trials OlympiAD and EMBRACA have proved that PARP inhibitors have the potential to increase PFS compared to standard chemotherapy in pretreated advanced *BRCA* mutated breast cancer [24, 25]. HR testing could greatly expand the scope of patients benefiting from these treatment options. To prove this hypothesis, several clinical phase 2 trials are currently ongoing, testing the efficacy of PARP inhibitors depending on the HR status; the agents involved in these studies include talazoparib in the TBB (talazoparib beyond *BRCA*) trial, olaparib in the NOBROLA trial, and rucaparib in the RUBY trial [26, 27]. In addition, a phase 2 three-armed trial (NCT03330847) is testing olaparib in combination with the DNA damage response inhibitors adavosertib and AZD6737, stratified by HR assessment.

Conclusions

The predictive value of the *BRCA* mutational status has been validated for platinum salt and PARP inhibitor therapy; however, published trials do not provide evidence of whether HR deficiency is an adequate marker for therapy decision-making in patients with breast cancer. Further studies and large comparative phase 3 trials are warranted to substantiate promising results of the currently published retro-

spective and early clinical studies. Similar to clinical routines of epithelial ovarian cancer, HR deficiency testing may identify subsets of breast cancer patients that are likely to benefit from platinum salt or PARP inhibition therapy in the future.

Take-home messages

- Homologous recombination (HR) deficiency may represent a valuable biomarker for therapy response to PARP inhibitors and platinum salts.
- The clinical use of HR deficiency could be of particular importance in women with TNBC.
- Ongoing trials are assessing the predictive value of commercially available "genomic scarring" assays that aim to quantify HR-related DNA-based measures of genomic instability.
- As there is no concrete evidence for the predictive value of HR deficiency, HR testing should currently be limited to clinical trials.

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