Familial Breast Cancer – Targeted Therapy in Secondary and Tertiary Prevention

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**Introduction**

The identification of biomarkers with prognostic and predictive value enables oncologists to select a more efficient and less toxic therapy for their patients on the basis of individual tumor characteristics. Data from recent clinical trials point towards 2 agents for the targeted treatment of \textit{BRCA} mutation carriers with breast or ovarian cancer: platinum-containing chemotherapies and poly-ADP-ribose polymerase inhibitors (PARPi). In vitro both substances lead to apoptotic cell death of BRCA-deficient tumor cells albeit using different mechanisms. The shared drug target is the absence of homologous recombination in BRCA-deficient tumor cells. Homologous recombination is an error-free repair mechanism of DNA double-strand breaks (DSB) [1]. The absence of homologous recombination activates error-prone DSB mechanisms like non-homologous end joining resulting in genomic instability of the cells. Platinum compounds cause DNA crosslinks that lead to DSB. At the same time PARPi prevent single-strand break repair which is also followed by DSB [2].

**The Role of Platinum-Based Chemotherapy in Patients with \textit{BRCA}-Associated Breast Cancer**

Carboplatin acts on the Achilles heel of BRCA-deficient tumors; they are no longer capable of homologous repair which is the most reliable DNA repair mechanism in the presence of DSB caused by platinum adducts [3–5]. Whereas healthy body cells are heterozygous for the \textit{BRCA} germline mutation, in tumor cells due to a second hit the intact allele is lost and tumor cells are predominantly prone to apoptosis after treatment with carboplatin. Although there is not yet enough data from randomized controlled clinical trials to support platinum as standard treatment in \textit{BRCA}-associated breast cancer, in vitro and in vivo data indicate a particular sensitivity to platinum-based therapy. In \textit{BRCA1} carriers with...
breast cancer an amazing tumor response rate after neoadjuvant chemotherapy with cisplatin was reported [6–8].

Additionally a higher response to neoadjuvant chemotherapy with cisplatin was described in triple-negative breast cancers (TNBC) with germ line or somatic BRCA1/2 mutations compared to non-cisplatin chemotherapy [9]. The reason for the increased sensitivity of TNBC to platinum might be that about 15% of these heterogenous tumors are BRCA-associated with mostly BRCA1 and rarely BRCA2 harboring the underlying mutation [10, 11]. The histopathologic features of TNBC serve as surrogate marker for high genomic instability and response to DNA-damaging agents such as the DNA crosslinkers carboplatin and cisplatin [12].

Most recently GeparSixto, a prospective randomized controlled phase II clinical trial, reported that the addition of carboplatin (weekly carboplatin, area under the curve 2) to neoadjuvant chemotherapy significantly improved the pathologic complete response (pCR) rate in patients with TNBC (n = 315) from 44 to 64% irrespective of BRCA status and family history [15].

Furthermore the addition of carboplatin to standard neoadjuvant chemotherapy increased pCR rates in patients with TNBC in the CALGB 40603 study [13]. In this phase II trial patients with TNBC (n = 433) received paclitaxel with or without bevaxizumab and/or carboplatin. The 4 treatment arms were followed by dose-dense chemotherapy with doxorubicin and cyclophosphamide. A pCR rate of 54% was reported in patients receiving carboplatin and 41% in patients treated without carboplatin.

In addition Tutt et al. [14] at the San Antonio Breast Cancer Symposium 2014 presented the TNT trial, a phase III study in first-line treatment of patients with TNBC containing a subgroup of 43 BRCA1 of BRCA2 mutation carriers. After 6 cycles of carboplatin or docetaxel a longer progression-free survival (PFS) in carriers (6.8 months) compared to non-carriers (3.1 months) was demonstrated. In contrast to the data of von Minckwitz et al. [15] the TNT trial did not find a superior response with carboplatin compared to standard therapy in the whole group of TNBC patients. The reason might have been the different treatment settings comparing palliative to adjuvant therapy. Due to the intratumoral heterogeneity that derives from genomic instability and selection pressure under chemotherapy, the tumor might change its main features [11]. Even reconstitution of homologous repair in platinum-resistant ovarian cancer cells was described [16]. Advanced BRCA-associated breast cancer might therefore behave differently to primary early breast cancer.

**Platinum-Based Chemotherapy in Patients with BRCA-Associated Ovarian Cancer**

Moreover there is clinical evidence for the efficacy of platinum in patients with BRCA mutations derived from ovarian cancer trials. A pooled analysis of 26 observational studies on the survival of women with epithelial ovarian cancer (EOC) included data from 1,213 EOC cases with pathogenic germline mutations in BRCA1 (n = 909) or BRCA2 (n = 304) and from 2,666 non-carriers recruited and followed up at variable times between 1987 and 2010 [17]. Among patients with invasive EOC having a germline mutation in BRCA1 or BRCA2 was associated with improved 5-year overall survival (OS). BRCA2 carriers had the best prognosis. Irrespective of family history around 15% of non-mucinous ovarian carcinomas and 11–22% of high-grade serous ovarian cancers are BRCA1/2-associated [18, 19]. In the presence of a family history of breast or ovarian cancer mutation frequency rises to 40% and higher dependent on age of onset and number of affected relatives [20].

**Platinum-Based Chemotherapy So Far No Standard in BRCA-Associated Breast Cancer**

The above data lead to the presently observable tendency of oncologists to add platinum to chemotherapy regimens for BRCA mutation carriers with breast cancer outside of trial concepts, and this tendency will also increase for women with TNBC; therefore a prospectively planned randomized controlled trial is highly necessary. By means of a translational research program this trial will provide the rationale for further studies in sporadic breast cancers with a BRCA1/2 mutation that may account for up to 20% of all breast cancers [21]. These women may also benefit from the addition of platinum compounds and other agents targeting the BRCA signaling pathway (e.g. PARPi). Therefore the German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC) established the NeoFam trial (supported by the Deutsche Forschungsge- meinschaft) for comparison of weekly carboplatin with paclitaxel after standard anthracyline-containing neoadjuvant therapy of patients with BRCA1/2-positive early breast cancer (EudraCT number: 2014–004737–51).

**The Role of PARPi Inhibitors in Patients with BRCA-Associated Breast and Ovarian Cancer**

PARPi selectively produce cell death in BRCA-deficient tumor cells via ‘synthetic lethality’. This term describes the inactivation of 1 of the 2 most important alternative cell mechanisms in a cancer cell which prevent fatal cell damage in the first place. The additional inactivation of the residual ‘rescuing’ mechanism by a targeted drug finally induces tumor cell death. However further models try to explain the function of PARPi including not only the involvement in single-strand break repair but also the activation of another alternative DNA repair process, non-homologous end joining. Therefore PARPi are very promising drugs within treatment concepts against BRCA-associated cancers and may also be efficient in cancers associated with other mutated homologous recombination genes. 3 members of the 18-member PARP family (PARP1, 2, and 3) that have been identified in mammalian cells are linked to DNA repair [22]. Most preclinical and clinical data focuses on the role of PARP1 in DNA repair, regulation of genomic stability in the cell, or involvement in cellular energy mechanisms as a target of PARPi [23]. The different models describing the cel-
lular functions of PARP and the mechanisms of PARPi to selectively kill homologous recombination-deficient tumor cells might explain why some cancers respond to PARPi and others do not. Therefore further preclinical investigations and clinical trials are needed to analyze the different antitumoral effects of PARPi.

**Approval of PARPi Olaparib for BRCA-Associated Ovarian Cancer**

The PARPi which is currently developed furthest for clinical use is olaparib (Lynparza™, AstraZeneca, Wilmington, DE, USA). It is directed against PARP1, PARP2, and PARP3. In December 2014 the FDA and EMA granted accelerated approval for maintenance therapy after platinum chemotherapy for relapsed high-grade serous ovarian/fallopian/peritoneal cancer (HGSOC) in patients with a germline (FDA, EMA) or somatic (EMA) mutation in the breast cancer genes BRCA1 or BRCA2. Proof-of-concept phase I/II trials in BRCA1/2 mutation carriers with advanced breast and ovarian cancer extended first findings about the clinical effect of single agent activity of olaparib from phase I dose escalation trials [24, 25]. Recent data from a randomized, placebo-controlled, phase II trial in a maintenance setting with patients who are most likely to benefit from PARPi due to a BRCA mutation and platinum-responsive relapsed ovarian cancer lead to the approval in the US and the EU. The authors observed an increased median PFS of 8.4 versus 4.8 months after 2 or more lines of platinum-based therapy. This is the first new agent that brought such an improvement in ovarian cancer since bevacizumab in 2011 [26–28]. An interim analysis with 58% maturity showed differences between olaparib and placebo, in the BRCA1/2 mutation carriers with a hazard ratio (HR) of 0.18 (95% confidence interval 0.11–0.31) and a median PFS of 11.2 vs. 4.3 months, respectively. OS did not show a difference in this group, (HR = 0.74; median OS 34.9 vs. 31.9 months) probably due to the 22.6% of patients on placebo who switched to olaparib. Olaparib is an oral PARPi that is currently under further investigation e.g. within the SOLO1 and SOLO2 phase III trials. It is given after a platinum-containing chemotherapy. To be eligible SOLO1 patients have to display a good response to the first platinum-containing chemotherapy. For SOLO2 patients with platinum-sensitive relapse. At the same time accumulating data exists for prolongation of disease-free survival in HGSOC with and without mutations in BRCA1 or BRCA2 [29].

Two proof-of-principle trials with BRCA germline mutation carriers demonstrated similar response rates with olaparib in breast and ovarian cancer [24, 25]. In breast cancer current trials concentrate on palliative therapy of metastasized germline BRCA1/2-mutated breast cancer after several lines of chemotherapy. (Neo-)adjuvant trial concepts focus on maintenance therapy after chemotherapy and surgery (OlympiA trial and Brightness by German Breast Group). In the OlympiA trial patients with TNBC and elevated risk for recurrence receive treatment with olaparib versus placebo for 12 months after neoadjuvant chemotherapy and surgery or following adjuvant chemotherapy. Several other trials for patients with breast cancer in different therapy indications and with a variety of PARPi, e.g. veliparib, rucaparib, niraparib, are under way. Iniparib, originally assumed to be an active PARPi, in a phase III trial in combination with carboplatin/gemcitabine in patients with metastasized breast cancer failed and is no longer considered a PARPi [30–32].

Side effects of the different effective oral PARPi are consistent with mostly grade 2 toxicity for e.g. nausea, fatigue, anemia, diarrhea, dysgeusia, and thrombocytopenia. Rare side effects include myelodysplastic syndrome, acute myeloid leukemia (AML), and pneumonitis. Because of their seriousness these side effects could impede the development of PARPi in primary prevention [33]. Future development now aims to increase bioavailability for less tablet intake per day, which ranges at present between 2 × 8 and 1 × 1 tablets.

**Combined Therapy with PARPi and Carboplatin**

Current therapeutic concepts of multiple PARPi focus not only on PARPi as single agents but also in combination with various DNA-damaging agents. Optimal timing of therapy and selection of patients with highest benefit beyond BRCA mutation carriers is still the subject of research. Studies have shown clinical benefit and interactive adverse events, including bone marrow toxicity and fatigue [29, 34, 35]. Moreover PARPi might function as a sensitizer to platinum-based chemotherapy or radiation [36]. Therefore intermittent intake of oral PARPi starting a few days before platinum-containing chemotherapy is a very interesting approach. As a next step another phase III trial, PAOLA1, is investigating the concurrent use of olaparib versus placebo with first-line platinum-containing chemotherapy plus bevacizumab in advanced high-grade ovarian/fallopian/peritoneal cancer independent of a germline mutation. In breast cancer BROCADE3 offers treatment with carboplatin and paclitaxel in combination with intermittent application of veliparib versus placebo to BRCA1/2-associated advanced or metastasized disease.

**BRCAness: Treatment Options Beyond the Germline Mutation Status**

As mentioned before PARPi might be efficient in carcinomas with impaired repair mechanism of homologous recombination. Recent data indicate that up to 50% of HGSOC might be caused by homologous repair deficiency (HRD) [37]. HRD might be the result of germline BRCA1/2 mutations which are found in approximately 15% of EOC, somatic BRCA1/2 mutations (approximately 7% of HGSOC), mutations in other genes affecting proteins in homologous repair deficiency (e.g. RAD51C, RAD51D, ATM, CHEK2), and functional silencing of genes concerning the homologous recombination mechanism (10% of HGSOC) [11, 19–23]. This phenomenon is referred to as ‘BRCAness’, and different strategies are being followed to establish a routine test for its
detection in tumor tissue in paraffin material. So far preparation of
tumor DNA and sequencing of BRCA1/2 and other genes involved
in homologous recombination is the most reliable but also the
most costly strategy. Moreover mutations of unknown significance
cause difficulties in the interpretation of the analysis. Great efforts
are currently being made to establish a functional test for HRD. All
current trials are accompanied by large biomarker projects that re-
quire collection of blood and tumor material.

Similar to HER2-directed therapies indication for treatment with
PARPi might be dependent on a test which is performed on
tumor tissue in paraffin. If testing of tumor material is performed
first, genetic counselling is recommended for patients with somatic
BRCA1/2 mutations because a germline mutation will be found in
more than half of them. A germline mutation in BRCA1 or BRCA2
implies the known risk for secondary cancer and cancer risk for
consanguineous relatives [16].

**Outlook**

The inclusion of targeted agents such as platinum and PARPi in
anticancer therapy of BRCA1/2 mutation carriers and BRCAness
cancers has unleashed future challenges. There are a lot of unre-
solved questions: How can we select the patients who are most
likely to benefit? A deleterious germline mutation in the BRCA
genes is a predictive marker for the use of PARPi. Analysis cur-
rently involves various sequencing methods and screening for large
deletions or insertions by multiplex ligand probe analysis; however
are there other tools with which to identify susceptible patients
with methylation of BRCA genes or somatic mutations? Moreover
BRCA-like gene expression profiles in BRCA1/2-negative familial
and sporadic carcinomas (e.g. TNBC) may show the same response
rates to platinum or PARPi as carcinomas of BRCA mutation carri-
ers. Does the impairment of other homologous recombination
genes indicate potential drug response? What is the optimal tim-
ing, dosage, scheduling, and sequencing of PARPi? Could severe
adverse events like AML preclude the use of PARPi in primary pre-
vention? What are the mechanisms of resistance to PARPi, and
how can they be overcome?

**Conclusion**

Approval of PARPi in BRCA1/2-associated ovarian cancer gives
way to a new kind of medication that targets not only the germline
mutation but also the resulting deficiency, HRD, which is often
found in HGSOC and TNBC. Highly interesting trials with different
oral PARPi are ongoing for both tumor entities in various ther-
apy settings. Current trials with targeted agents are supported by
concepts of identifying and validating predictive biomarkers for
the stratification of patients. These data will further advance the
field of targeted therapy. Besides, chemotherapy with carboplatin is
becoming more and more important for the treatment of TNBC
with or without BRCA1 and BRCA2 mutations; however further
studies are needed.

**Disclosure Statement**

The authors have no conflicts of interest to declare.

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