PARPi: Efficacy in Hereditary Breast Cancer

19

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Abstract

Breast cancer (BC) with germline pathogenic variants of *BRCA1* or *BRCA*2 is found in approximately 5% of Japanese BC patients. *BRCA1/2*-associated BC with homologous recombination (HR) deficiency is potentially sensitive to DNA damage agents, including platinum agents and PARP (poly(ADP-ribose) polymerase) inhibitors. In this chapter, we will summarize the clinical evidence supporting the efficacy of chemotherapy and PARP inhibitors (PARPis), as single agents or in combination, in the (neo)adjuvant setting or in the advanced setting of *BRCA1/2*-associated BC. Moreover, we will discuss resistance to PARPi and the development of further approaches to improve the therapeutic efficacy of PARPi.

Keywords

BRCA · Breast cancer · Efficacy · Platinum · PARP inhibitors · Drug resistance

19.1 Introduction

Pathogenic germline variants of *BRCA1* or *BRCA*2 have been found in 1.4% and 2.7%, respectively, of Japanese breast cancer (BC) patients [1].

The prognosis of *BRCA1/2*-associated BC patients who received traditional standard treatment was similar to that of sporadic breast cancer patients after adjustment for age, tumor stage, nodal status, and hormone receptors, based on the literature [2, 3]. The result of a meta-analysis also showed that the status of

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germline *BRCA1/2* (g*BRCA1/2*) pathogenic variants does not influence the prognosis [4].

The *BRCA1* and *BRCA*2 proteins play a role in the repair of DNA double-strand breaks (DSBs) by intervening in homologous recombination (HR).

In functional HR repair-deficient cells, nonconservative forms of DNA repair such as nonhomologous end joining (NHEJ) became dominant [5]. Therefore, *BRCA1/2*-deficient BC is potentially sensitive to DNA damage agents such as platinum agents and PARP (poly(ADP-ribose) polymerase) inhibitors (PARPis) [6, 7].

19.2 Traditional Anthracycline- and Taxane-Based Regimens

The anthracyclines used in the treatment of BC are either epirubicin or doxorubicin. The commonly used anthracycline-containing regimens include cyclophosphamide. Anthracyclines can induce DSBs by inhibiting the enzyme topoisomerase II. Anthracyclines stabilize the topoisomerase II complex after the enzyme has induced a break in the DNA chain for replication, thus preventing the DNA double helix from being resealed; this inhibits the process of replication. In vitro data suggest that cells without functional *BRCA1* or *BRCA*2 proteins are particularly sensitive to agents causing DSBs including doxorubicin, with a subsequent increased level of apoptosis [8, 9].

On the other hand, taxanes are anti-microtubule agents which work by inhibiting the depolymerization of the mitotic spindle and by inhibiting the polymerization of tubulin during cell division. Several preclinical studies showed that the inhibition of *BRCA1* leads to increased chemoresistance to microtubule-interfering agents [10, 11]. The *BRCA1* protein is involved in facilitating apoptosis in cells with disrupted mitotic spindle formation. Deficiency of the *BRCA1* protein may lead to paclitaxel resistance through premature inactivation of the spindle checkpoint in BC cells [12].

19.2.1 Neoadjuvant Setting

Studies conducted at the MD Anderson Cancer Center (MDACC) have reported on the pathological complete response (pCR) rate after anthracycline- and taxane-based regimens in *BRCA1/2* pathogenic variant carriers and noncarriers. Twenty-six (46%) of 57 *BRCA1* carriers achieved a pCR, compared with 3 (13%) of 23 *BRCA*2 carriers and 53 (22%) of 237 *BRCA* noncarriers ($P < 0.001$). *BRCA1* status and ER negativity were independently associated with a higher pCR rate in patients with BC [13].

In a retrospective study involving triple-negative breast cancer (TNBC) patients receiving neoadjuvant AC (doxorubicin and cyclophosphamide) followed by paclitaxel, 34 *BRCA1* carriers had pCR rate of 68%, compared with that of 37% among 43 noncarriers ($P = 0.01$). However, this did not translate into superior survival [14].

More recently, another prospective cohort study from MDACC reported the pCR rate after AC or AC-T (AC followed by taxane) in TNBC with and without g*BRCA*

pathogenic variants. The pCR rates in *BRCA*-associated tumors and non-*BRCA*-associated tumors were 58.3% (28/48) and 51.1% (43/84), respectively [15].

Furthermore, the GeparQuinto phase III trial evaluated the efficacy of the addition of bevacizumab on neoadjuvant EC-docetaxel for 493 TNBC patients.

Germline *BRCA1/2* pathogenic variants were detected in 18.3% of patients with TNBC. Overall, the pCR rate was higher in *BRCA1/2* pathogenic variant carriers than in noncarriers (50% vs. 31.5%, $P = 0.001$), and the pCR rate among patients treated with bevacizumab was 61.5% for *BRCA1/2* pathogenic variant carriers and 35.6% for those without pathogenic variants ($P = 0.004$). Disease-free survival (DFS) was also better in those without the *BRCA1/2* pathogenic variants (HR, 0.644; $P = 0.047$) [16].

19.2.2 Advanced or Metastatic Setting

Kriege et al. investigated the sensitivity to standard first-line chemotherapy of 121 metastatic *BRCA1/2*-associated BC patients (93 with *BRCA1* and 28 with *BRCA*2 pathogenic variants), compared to 121 matched sporadic BC patients in a retrospective study from the Family Cancer Clinic database. The chemotherapy regimens most frequently used were anthracycline-based ($n = 147$) and also included cyclophosphamide, methotrexate, and fluorouracil (CMF) ($n = 68$). As compared to sporadic patients, *BRCA*2-associated BC patients had a significantly higher OR (89% vs. 50%; $P < 0.001$) and a longer PFS (HR, 0.64; $P = 0.04$) and OS (HR, 0.53; $P = 0.005$) after start of first-line chemotherapy for metastatic breast cancer (MBC). Statistically significant increase in sensitivity was not observed for *BRCA1*-associated BC [17].

Kriege et al. also assessed the efficacy of either paclitaxel or docetaxel for 48 MBCs with g*BRCA1/2* pathogenic variants (35 with *BRCA1* and 13 with *BRCA*2 pathogenic variants), compared to 95 sporadic MBCs. *BRCA1*-associated, hormone receptor-negative MBC patients were less sensitive to taxane chemotherapy than sporadic HR-negative patients (OR 23% vs. 38%, PD 60% vs. 19%, $P < 0.001$; PFS 2.2 vs. 4.9 months, $P = 0.04$). The sensitivity of *BRCA1*- and *BRCA*2-associated, HR-positive MBC patients to taxane chemotherapy was similar to that of sporadic MBC patients [18].

Clinical data suggest that breast cancer with g*BRCA1/2* pathogenic variants may be more sensitive to anthracyclines and may be less sensitive to taxane monotherapy, which supports preclinical studies. However, these data are not definitive.

19.3 Alkylating Agents

Cyclophosphamide affects the alkylation of DNA and inhibits DNA replication by cross-linking guanine nucleobases in DNA double-helix strands.

Byrski et al. reported that pCR was observed in only 1 patient (7%) among 14 g*BRCA1* pathogenic variant carriers receiving neoadjuvant CMF [19].

From a retrospective study, the status of g*BRCA1/2* pathogenic variants did not influence the sensitivity to first-line CMF for MBC [17]. The specific impact of cyclophosphamide also remains unclear in *BRCA1/2*-associated BC.

19.4 Platinum Agents

Recent evidence suggests that *BRCA*-related BC is particularly sensitive to treatment with inter-strand cross-linking agents such as platinum-based chemotherapy [20, 21].

The cytotoxic actions of platinum drugs involve the binding of platinum to DNA, which interferes with DNA replication and transcription. It seems likely that cross-links cause replication fork stalling when encountered by the DNA replication machinery; this may result in DSBs. *BRCA1/2* are critical genes in the HR repair of DSBs. Hence, *BRCA1/2*-deficient BC may be more sensitive to platinum drugs [22, 23].

Representative clinical trials of platinum agents in *BRCA1/2*-associated BC are summarized in Table 19.1.

19.4.1 Neoadjuvant Setting

Byrski et al. in a retrospective study conducted in 2010 were the first to report a greater sensitivity of g*BRCA1* pathogenic variant carriers to neoadjuvant platinum agents [19]. Among 102 patients with g*BRCA1* pathogenic variants including 12 patients who received cisplatin from the Poland registry, a higher rate of pCR (83%) was seen after treatment with cisplatin (75 mg/m^2 every 3 weeks for 4 cycles) compared to the pCR (22%) for AC (doxorubicin and cyclophosphamide) or FAC (fluorouracil, doxorubicin, and cyclophosphamide). In a larger study of 107 patients with *BRCA1*-related BC treated with neoadjuvant cisplatin, pCR was observed in 65 patients (61%) [24].

On the other hand, the GeparSixto trial assessed the efficacy of adding neoadjuvant carboplatin to a regimen consisting of anthracycline, taxane, and bevacizumab for 291 patients with TNBC including 50 g*BRCA1/2* pathogenic variant carriers. Under the nonstandard GeparSixto polychemotherapy regimen, the high pCR rate observed in *BRCA1/2* pathogenic variant carriers in the non-carboplatin arm (66.7%) was not increased further by adding carboplatin (65.4%) [20, 25].

A secondary analysis of the GeparOcto trial reported an association of germline variant status with therapy response. For TNBC, a positive g*BRCA1/2* variant status was associated with therapy response in both the PMCb arm (74.3% vs. 47.0%; OR, 3.26; 95% CI, 1.44–7.39; $P = 0.005$) and the iddEPC arm (64.7% vs. 45.0%; OR, 2.24; 95% CI, 1.04–4.84; $P = 0.04$). Differences between treatment arms were not significant (74.3% vs. 64.7%; OR, 1.58; 95% CI, 0.56–4.43; $P = 0.39$). Interaction between the g*BRCA1/2* variant and the study arm was not significant ($P = 0.51$). In g*BRCA1/2*-associated TNBC, iddEPC also appears to be effective, though with a

Table 19.1 Clinical trials of platinum agents

Clinical trial	Type of study	Patients	Platinum treatment regimen	Result
Neoadjuvant setting				
Byrski 2010 [19]	Retrospective	12 pts with *gBRCA1* pathogenic variant	CDDP (75 mg/m2 every 3 weeks for 4 cycles)	pCR = 83% (10/12)
Byrski 2014 [24]	Retrospective	107 pts with *gBRCA1* pathogenic variant	CDDP (75 mg/m2 every 3 weeks for 4 cycles)	pCR = 61% (65/107)
Hahnen 2017 GeparSixto [20, 25]	Ph. II RCT Ancillary analysis	TNBC (n = 146) including 50 pts with *g BRCA1/2* pathogenic variant	Adding CBDCA (AUC1.5–2.0 weekly for 18 weeks) with paclitaxel/doxorubicin/ bevacizumab	Additional CBDCA pCR =66.7% (16/24) Non-CBDCA pCR = 65.4% (17/26)
Pohl-Rescigno 2020 GeparOcto [26]	Ph. II RCT Secondary analysis	TNBC (n = 393) including 69 pts with gBRCA1/2 pathogenic variant	CBDCA (AUC1.5 weekly for 18 weeks) with paclitaxel/doxorubicin (PMCb) Intensive-dose-dense epirubicin/paclitaxel/ cyclophosphamide (iddEPC)	PMCb pCR = 74.3% (26/35) iddEPC pCR = 64.7% (22/34)
Tung 2020 TBCRC031 [27]	Ph. II RCT	117 pts (HER2-neagtive) with gBRCA1/2 pathogenic variant	CDDP (75 mg/m2 every 3 weeks for 4 cycles) Doxorubicin-cyclophosphamide (AC)	CDDP pCR = 18%, RCB 0/1 = 33% AC pCR = 26%, RCB 0/1 = 46%
Advanced or metastatic setting				
Byrski 2012 [28]	Ph. II Single arm	20 pts with gBRCA1 pathogenic variant	CDDP (75 mg/m2 every 3 weeks for 6 cycles)	ORR = 80% mPFS = 12 months

(continued)

Table 19.1 (continued)

Clinical trial	Type of study	Patients	Platinum treatment regimen	Result
Isakoff 2015 TBCRC009 [29]	Ph. II Single arm First or second line	mTNBC (n = 86) including 11 pts with gBRCA1/2 pathogenic variant	CDDP (75 mg/m2) or CBDCA (AUC6) once every 3 weeks	BRCA-associated BC ORR = 54.5% mPFS = 3.3mo Non-BRCA-associated BC ORR = 19.7% mPFS = 2.8 mo
Tutt 2018 TNT trial [30]	Ph. III RCT for TNBC First line Subgroup analysis	mTNBC(n = 376) including 43pts with gBRCA1/2 pathogenic variant	CBDCA (AUC 6 every 3 weeks) Docetaxel (100 mg/m2 every 3 weeks)	CBDCA ORR = 68% (17/25) mPFS = 6.8mo Docetaxel ORR = 33% (6/18) mPFS = 4.4mo
Zhang 2020 CBCSG006 [31]	Phase III RCT for TNBC First line Biomarker assessment	mTNBC(n = 236) including 12pts with gBRCA1/2 pathogenic variant	Cisplatin+gemcitabine (GP) Paclitaxel +gemcitabine (GT)	GP ORR = 83.3% (5/6) mPFS = 8.9mo GT ORR = 37.5% (3/8) mPFS = 3.2mo

gBRCA germline *BRCA*, *CDDP* cisplatin, *CBDCA* carboplatin, *pCR* pathological complete response, *Ph* phase, *RCT* randomized clinical trial, *TNBC* triple-negative breast cancer, *mTNBC* metastatic TNBC, *pts* patients, *ORR* overall response rate, *mPFS* median progression-free survival

pCR rate approximately 10 percentage points lower than that observed in the PMCb arm. Whether this difference is associated with survival outcome is yet unclear [26].

A randomized phase II study of neoadjuvant cisplatin (CDDP) versus doxorubicin-cyclophosphamide (AC) in g*BRCA* pathogenic variant carriers with HER2-negative BC (TBCRC 031) demonstrated that the pCR or residual cancer burden (RCB) 0/1 was not significantly higher with CDDP than with AC in *BRCA* carriers for both TNBC and ER+/HER2-negative disease [27].

A meta-analysis showed that the addition of platinum to chemotherapy regimens in the neoadjuvant setting increases the pCR rate in *BRCA*-associated (58.4%, 93/159) as compared to wild-type TNBC patients (50.7%, 410/808). However, this trend did not achieve statistical significance [21].

19.4.2 Advanced or Metastatic Setting

In a phase II single-arm study, 20 patients with *BRCA1*-asscoated MBC, 55% of whom had prior chemotherapy for MBC, were treated with cisplatin at 75 mg/m^2 every 3 weeks for 6 cycles [28]. The overall response rate (ORR) was 80%, including complete clinical response (45%) and partial response (35%). A complete response was achieved in 8 of 15 ER-negative patients (53%), compared to only 1 of 5 ER-positive patients (20%). The median time to progression was 12 months.

The TBCRC009 trial was also a single-arm phase II clinical trial of single-agent platinum for 86 metastatic TNBC patients, including 11 patients with g*BRCA1/2* pathogenic variants. Patients received either cisplatin (75 mg/m^2) or carboplatin (AUC6) as first- or second-line therapy by physician's choice once every 3 weeks. Individuals with *BRCA1/2* mutations were more likely to achieve a response than were those without mutations (54.5% vs. 19.7%, $P = 0.022$). However, PFS was not significantly different between carriers and noncarriers (median 3.3 vs. 2.8 months; $P = 0.92$) [29].

Although there are no randomized controlled trials investigating the efficacy of platinum alone in patients with *BRCA1/2*-associated advanced breast cancer, the randomized phase III CBCSG006 and TNT trials conducted in TNBC patients included patients with g*BRCA1/2* pathogenic variants.

The TNT trial compared first-line carboplatin (AUC6 every 3 weeks) with docetaxel (100 mg/m^2 every 3 weeks) in *BRCA1/2*-associated BC or TNBC patients [30]. In 376 patients, carboplatin was not more efficacious than docetaxel (ORR, 31.4% vs. 34.0%; $P = 0.66$). In subgroup analysis by patients with g*BRCA1/2* pathogenic variants ($n = 43$), carboplatin showed double the ORR compared to docetaxel (68% vs. 33%, $P = 0.03$). PFS also favored carboplatin (6.8 months vs. 4.4 months, interaction $P = 0.002$), but no difference was found in overall survival, which may be due to the crossover design. This trial provided evidence that the platinum agent was better than the current standard chemotherapies for a selected population in whom g*BRCA1/2* pathogenic variants were detected early.

The CBCSG006 trial reported the superior efficacy of cisplatin plus gemcitabine (GP) regimen compared to the paclitaxel plus gemcitabine (GT) regimen (HR. 0.692;

95% CI, 0.523–0.915) as first-line treatment of metastatic triple-negative breast cancer (mTNBC) [31]. In additional biomarker assessment, patients with g*BRCA1/2* mutations (n = 12) had numerically higher ORR and prolonged PFS in the GP arm than in the GT arm (83.3% vs. 37.5%, P = 0.086; 8.90 vs. 3.20 months, P = 0.459).

In summary, the efficacy of platinum in patients with *BRCA1/2*-associated MBC is promising, but there are no randomized controlled trials of platinum limited to patients with *BRCA1/2* germline pathogenic variants; this needs to be studied further.

19.5 PARP Inhibitors

As described in Chap. 18, several PARP inhibitors have been developed based on the concept of "synthetic lethality" and with the expectation of an antitumor effect based on PARP trapping. PARP inhibitors including olaparib, talazoparib, veliparib, niraparib, and rucaparib have undergone clinical investigation for the treatment of BC.

PARPi, either as monotherapy or in combination with cytotoxic chemotherapy, improved efficacy compared to conventional chemotherapy. However, PARPi combination therapy showed increased hematological toxicity as well as fatigue and gastrointestinal toxicities. Adverse events have been a challenge for further development.

Here, we briefly review the clinical data of PARPi in *BRCA1/2*-associated BC (Table 19.2).

19.5.1 Olaparib

Olaparib, a PARP-1, PARP-2, and PARP-3 inhibitor, is the first FDA-approved PARPi for the treatment of *BRCA*-associated ovarian cancer.

In Japan, olaparib was approved in 2018 for maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer and was subsequently approved for MBC patients with a g*BRCA* pathogenic variant based on the results of the OlympiAD study [36].

19.5.1.1 Neoadjuvant Setting

The GeparOLA study was a randomized phase II trial conducted to assess the efficacy of paclitaxel and olaparib (PwO) in comparison to paclitaxel and carboplatin (PwCb) followed by EC as neoadjuvant chemotherapy in patients with HER2-negative early BC with homologous recombination deficiency (HRD). Here, HRD was defined as score high tumors +/− germline (g) or tumor (t) *BRCA* pathogenic variants. The pCR rate with PwO was 55.1% (90% CI, 44.5%–65.3%) vs. that of PwCb which was 48.6% (90% CI, 34.3%–63.2%). An analysis of the stratified subgroups showed higher pCR rates with PwO in the cohorts of patients aged <40 years and hormone receptor-positive tumors [32].

Table 19.2 PARP inhibitors

Clinical trial	Type of study	Patients	PARP inhibiter treatment regimen	Result
1. Olaparib				
Neoadjuvant setting				
Fasching 2019 GeparOLA [32]	Ph. II	102 HER2-negative BC pts with HRD high tumors +/− germline (g) or tumor (t) BRCA1/2 pathogenic variant	Paclitaxel and olaparib (PwO) followed by EC(n = 65) Paclitaxel and CBDCA(PwCb) followed by EC(n = 37) ※Olaparib 100 mg tablets twice daily for 12 weeks	PwO pCR = 55.1% PwCb pCR = 48.6%
Adjuvant setting				
OlympiA (NCT02032823)	Ph. III RCT Post-(neo)adjuvant chemotherapy	1500pts (high risk HER2-negative) with gBRCA1/2 pathogenic variant	Olaparib 300 mg tablets twice daily or placebo for 12 months	Active, not recruiting
Advanced or metastatic setting				
Fong 2009 [33]	Ph. I dose-escalation study	60 pts with advanced solid tumors including 22 pts with gBRCA1/2 pathogenic variant	Olaparib 10–600 mg twice daily	Maximum tolerated dose as 400 mg twice daily
Tutt 2010 [34]	Ph. II Nonrandomized	54 MBC pts with gBRCA1/2 pathogenic variant	Olaparib 400 mg twice daily Olaparib 100 mg twice daily	ORR = 41% ORR = 22%
Kaufman 2015 [35]	Single arm Prior three chemotherapy regimens for MBC	298 solid tumor pts (62 BC) with gBRCA1/2 pathogenic variant	Olaparib 400 mg twice daily	RR = 12.9%(8/62) in MBC
Robson 2017 OlympiAD [36, 37]	Ph. III RCT No more than two prior chemotherapy regimens for MBC Anthracycline and taxane pretreated	302 MBC pts with gBRCA1/2 pathogenic variant	Olaparib 300 mg twice daily Chemotherapy of the physician's choice (capecitabine, eribulin, vinorelbine)	Olaparib ORR = 59.9% mPFS = 7.0mo Chemotherapy ORR = 28.8% mPFS = 4.2mo
2. Niraparib				

(continued)

Table 19.2 (continued)

Clinical trial	Type of study	Patients	PARP inhibiter treatment regimen	Result
Advanced or metastatic setting				
Sandhu 2013 [38]	Ph. I dose-escalation study	100 solid tumors including 22 MBCs	Niraparib 30–400 mg daily	Maximum tolerated dose as 300 mg daily
3. Rucaparib				
Advanced or metastatic setting				
Drew 2016 [39]	Ph. II dose escalation IV and subsequently oral study	78 solid tumor pts including 23 MBCs with gBRCA1/2 pathogenic variant	Rucaparib IV 4–18 mg → oral 92–600 mg twice daily	Well-tolerated doses as oral 480 mg daily No responders by ORR in BC
Wilson 2017 [40]	Ph. I dose-escalation study in combination with chemotherapy	85 pts with advanced solid tumors including 7 pts with gBRCA pathogenic variant	Rucaparib IV 12–24 mg → oral 80–360 mg + chemotherapy	Maximum tolerated dose for the combination was oral 240 mg daily rucaparib and CBDCA
Miller 2015 [41]	Ph. II RCT	128 pts with TNBC or BRCA-associated BC (n = 22) with residual tumor post-neoadjuvant chemotherapy	Cisplatin 75 mg/m2 ± Rucaparib 25–30 mg IV days 1 to 3 (4 cycles) → oral rucaparib 100 mg weekly	Cisplatin alone 2 yr DFS = 58.3% Cisplatin+rucaparib 2 yr DFS = 63.1%
4. Talazoparib				
Neoadjuvant setting				
Litton 2020 [42]	Ph. II	20 HER2-negative BC pts with gBRCA1/2 pathogenic variant	Talazoparib 1 mg once daily for 6 months	RCB0 (pCR) = 53% RCB 0–1 = 63%
Advanced or metastatic setting				
Litton 2018 EMBRACA [43]	Ph. III RCT No more than three cytotoxic regimens for MBC Anthracycline or taxane pretreated	431 advanced/metastatic BC pts with gBRCA1/2 pathogenic variant	Talazoparib 1 mg once daily Chemotherapy of the physician's choice (capecitabine, eribulin, gemcitabine, or vinorelbine)	Talazoparib arm ORR = 62.6% mPFS = 8.6 mo Chemotherapy arm ORR = 27.2% mPFS = 5.6mo
5. Veliparib				

Neoadjuvant setting				
Rugo 2016 I SPY2 [44]	Ph. II adaptive randomized trial	Veliparib group 72 pts with Stage 2–3 BC including 12 BRCA-associated BCs Control group 74 pts with Stage 2–3 BC including 3 BRCA-associated BCs	Weekly paclitaxel+ veliparib 50 mg twice daily + CBDCA followed by AC Weekly paclitaxel followed by AC	Veliparib group pCR = 51% Control group pCR = 26%
Lobi 2016 Brightness [45]	Ph. III RCT	Stage 2–3 TNBC (n = 634) including 92 pts with gBRCA1/2 pathogenic variant	Weekly paclitaxel 12 doses Weekly paclitaxel + CBDCA (AUC6, q3weeks, 4 cycles) Weekly paclitaxel + CBDCA +veliparib (50 mg BID) All patients received followed by AC	Paclitaxel pCR = 31% Paclitaxel + CBDCA pCR = 58% Paclitaxel +CBDCA +veliparib pCR = 53%
Advanced or metastatic setting				
Han 2018 BROCADE [46]	Ph. II RCT	290 advanced/metastatic BC pts with gBRCA1/2 pathogenic variant	Carboplatin/paclitaxel (CP) Carboplatin/paclitaxel veliparib (VCP) Veliparib 120 mg daily plus temozolomide (VT)	CP ORR = 61.3% mPFS = 12.3mo VCP ORR = 78% mPFS = 14.1mo VT ORR = 28.6% mPFS = 7.4mo

g*BRCA* germline *BRCA*, *CBDCA* carboplatin, *pCR* pathological complete response, *Ph* phase, *RCT* randomized clinical trial, *TNBC* triple-negative breast cancer, *MBC* metastatic BC, *pts* patients, *ORR* overall response rate, *mPFS* median progression-free survival

19.5.1.2 Adjuvant Setting

The presence of residual invasive disease after neoadjuvant chemotherapy is a strong predictive factor for survival in TNBC.

A study evaluating the benefit of experimental postoperative PARPi therapy in patients with a high risk of recurrence is being planned.

The OlympiA (NCT02032823) study is a randomized, placebo-controlled phase III trial enrolling *BRCA1/2*-associated, high-risk HER2-negative BC, after completion of local treatment and (neo)adjuvant chemotherapy. Patients were randomized between olaparib (300 mg) and placebo for 12 months. The primary endpoint is invasive DFS. Approximately 1500 patients were randomized, and recruitment was closed in 2019. The result of this study is awaited.

19.5.1.3 Advanced or Metastatic Setting

The first phase 1 trial of the clinical evaluation of olaparib in humans was reported in 2009 [33] and was conducted in 60 patients with advanced solid tumors including 22 g*BRCA1/2* pathogenic variant carriers. The olaparib dose and schedule were increased from 10 mg daily for two of every 3 weeks to 600 mg twice daily continuously. The manifestations of dose-limiting toxicity led to the establishment of a maximum tolerated dose of 400 mg of olaparib twice daily. Clinical response according to three MBC patients with g*BRCA1/2* pathogenic variants was as follows: one patient had CR, and another showed PR.

Tutt et al. assessed the efficacy of olaparib monotherapy in 54 MBC patients with g*BRCA1/2* pathogenic variants in a phase II trial. The first cohort (27 patients) was treated with 400 mg twice daily, and the second cohort (27 patients) was treated with 100 mg twice daily [34]. Most patients had already received anthracycline and taxane regimens. The overall response rate was 41% in the first cohort and 22% in the second cohort.

Kaufman et al. reported that the ORR was 12.9% (8/62) in heavily pretreated *BRCA1/2*-associated MBC. The most common adverse events (AEs) were fatigue, nausea, and vomiting. Severe anemia (grade > 3) was seen in 17% of the patients [35].

In 2017, Robson et al. reported the first randomized, open-label, phase III OlympiAD trial which compared olaparib monotherapy with standard single-agent chemotherapy (eribulin, capecitabine, or vinorelbine) of the physician's choice in patients with HER2-negative MBC carrying g*BRCA1/2* pathogenic variants [36, 37]. Patients had received no more than two previous chemotherapy regimens for MBC and had received anthracycline and a taxane for (neo)adjuvant or metastatic disease. A total of 302 patients were randomized, 205 being assigned to receive olaparib and 97 to receive standard therapy. Olaparib was clinically superior to the standard therapy with mPFS (7.0 months vs. 4.2 months; HR, 0.58; $P \leq 0.001$) and RR (59.9% vs. 28.8%).

While there was no statistically significant improvement in OS with olaparib compared to TPC, a trend of meaningful OS benefit among patients who had not received chemotherapy for metastatic disease was observed. The rate of grade 3 or higher AEs was 36.6% in the olaparib group and 50.5% in the standard-therapy group; the quality of life data were significantly better in the olaparib group. Olaparib was generally well-tolerated.

19.5.2 Niraparib

Niraparib, a high-selective PARP-1 and PARP-2 inhibitor, was approved by the FDA for unselected platinum-sensitive recurrent ovarian cancer patients. It has recently been approved in Japan for ovarian cancer.

In a phase 1 dose-escalation trial evaluating niraparib in 100 solid tumors including 22 MBC patients, 2 MBC patients had PR among 4 MBC patients with g*BRCA* pathogenic variants. The maximum tolerated dose was established to be 300 mg/day [38].

19.5.3 Rucaparib

Rucaparib, a PARP-1, PARP-2, and PARP-3 inhibitor, is a second FDA-approved PARPi for the treatment of patients with *BRCA* (germline and/or somatic)-associated advanced ovarian cancer.

19.5.3.1 Advanced or Metastatic Setting

A phase II trial of rucaparib was conducted in proven *BRCA1/2* mutation carriers with advanced breast and/or ovarian cancer [47]. Rucaparib was well-tolerated in patients up to doses of 480 mg per day. There were no responders to rucaparib as per ORR among the BC patients.

A phase I dose-escalation trial of rucaparib in combination with standard chemotherapy (carboplatin, carboplatin and paclitaxel, cisplatin, and pemetrexed, or epirubicin and cyclophosphamide) has been conducted for the treatment of 85 solid tumors including 22 MBC cases. Maximum tolerated dose for the combination was 240 mg per day of oral rucaparib and carboplatin. Clinical activity (one CR and one PR) was observed among seven cases of heavily pretreated MBC with g*BRCA* pathogenic variants. Neutropenia and thrombocytopenia were the most common grade ≥ 3 toxicities [39].

A randomized phase II trial assessed the efficacy of cisplatin with or without low-dose rucaparib after preoperative chemotherapy (anthracycline and/or taxane) in 128 patients with TNBC or *BRCA*-associated BC ($n = 22$) with residual disease. The addition of rucaparib did not improve the 2-year DFS (58.3% with cisplatin vs. 63.1% with cisplatin and rucaparib, $P = 0.43$). The variant status had no impact, which was thought due to the low-dose schedule of rucaparib [40].

19.5.4 Talazoparib

Talazoparib is an inhibitor of PARP-1 and PARP-2 and shows powerful PARP trapping.

An in vitro comparison of the effects of talazoparib, olaparib, and rucaparib on PARP-1 and PARP-2 showed that talazoparib has the highest efficacy in trapping the PARP-DNA complex [41]. Clinical data supports that the strength of DNA-PARP trapping effect may be associated with enhanced toxicity.

19.5.4.1 Neoadjuvant Setting

In the neoadjuvant setting, the use of the PARPi as a single-agent was reported to minimize toxicity. Litton et al. evaluated the pathologic response and tolerance of talazoparib alone for 6 months in patients with g*BRCA* pathogenic variants [48]. A total of 20 patients were enrolled, including 16 patients with g*BRCA1* and 4 patients with g*BRCA*2 pathogenic variants. Fifteen patients had TNBC. The rate of pCR was 53%, and the RCB 0/1 was 63%. Eight patients (40%) had grade 3 anemia and required a transfusion, three patients had grade 3 neutropenia, and one patient had grade 4 thrombocytopenia. Common grade 1 or 2 toxicities were nausea, fatigue, neutropenia, alopecia, dizziness, and dyspnea. Toxicities were managed by dose reduction and transfusions. Nine patients required dose reduction. Neoadjuvant single-agent oral talazoparib at 1 mg once per day for 6 months without chemotherapy produced a substantial RCB-0 rate with manageable toxicity. Talazoparib monotherapy may be a novel strategy for developing and de-escalating therapy in the neoadjuvant setting.

19.5.4.2 Advanced or Metastatic Setting

The EMBRACA was a randomized, open-label, phase III trial which compared talazoparib (1 mg once daily) or standard single-agent therapy of the physician's choice (capecitabine, eribulin, gemcitabine, or vinorelbine in continuous 21-day cycles) in MBC patients with g*BRCA1/2* pathogenic variants. The median PFS was significantly longer in the talazoparib arm than in the chemotherapy arm (8.6 months vs. 5.6 months; HR, 0.54; $P < 0.001$). The ORR was also better in the talazoparib arm compared to the chemotherapy arm (62.6% vs. 27.2%; $P < 0.001$). Hematologic grade 3–4 AEs occurred in 55% of participants in the talazoparib arm and in 38% of participants in the chemotherapy arm. Patient-reported outcomes favored the talazoparib arm [42].

The results of two RCTs (the OlympiAD and EMBRACA studies) were assessed in a meta-analysis. A total of 733 patients were included, of whom 492 received single-agent PARPi therapy (olaparib in the OlympiAD trial and talazoparib in the EMBRACA trial) and 241 received mono-chemotherapy as per the physician's choice [43]. As compared with mono-chemotherapy, single-agent PARPi therapy significantly improved PFS (HR, 0.56; 95% CI, 0.45–0.70) and ORR (OR, 4.15; 95% CI, 2.82–6.10), with no difference in OS (HR, 0.82; 95% CI, 0.64–1.05). Patients treated with PARPi therapy experienced a significant delayed time to QoL deterioration (HR, 0.40; 95% CI 0.29–0.54). Single-agent PARPi therapy was observed to be an effective, well-tolerated, and useful treatment in maintaining the QoL of patients with *BRCA*-mutated HER2-negative MBC.

19.5.5 Veliparib

Veliparib is an inhibitor of PARP-1 and PARP-2, with the weakest PARP trapping among the clinically tested PARPis, and has been considered as the weakest PARPi. Therefore, this drug has been essentially developed for use in combination

with platinum-based chemotherapy, which is more feasible and is more advantageous.

19.5.5.1 Neoadjuvant Setting

The I-SPY2 trial was the first trial to assess carboplatin-veliparib therapy in a neoadjuvant setting. I-SPY2 is an open-label, adaptive randomized phase II trial for the evaluation of new agents combined with standard neoadjuvant therapy for the treatment of BCs that have a high risk of recurrence. Patients were randomized to combined veliparib-carboplatin and standard chemotherapy (paclitaxel, followed by AC) or standard chemotherapy alone. A total of 72 patients were randomly assigned to receive veliparib-carboplatin including 17% with a deleterious variant in *BRCA1* or *BRCA*2. The rate of pCR in the TNBC population was 51% in the veliparib-carboplatin group, versus 26% in the control group. The toxicity of veliparib-carboplatin was greater than that of the control. This trial showed that veliparib-carboplatin added to standard therapy resulted in higher rates of pCR than standard therapy alone, specifically in TNBC [49].

Based on these results, in the same population, the phase III BrighTNess trial evaluated the addition of carboplatin with and without veliparib to the standard neoadjuvant combination of paclitaxel followed by AC in 634 TNBC patients including 92 patients with a deleterious g*BRCA* mutation [44]. The pCR rates for patients treated with paclitaxel alone, those treated with paclitaxel plus carboplatin, and those treated with paclitaxel plus carboplatin plus veliparib were 31%, 58%, and 53%, respectively. Addition of carboplatin to standard chemotherapy increased the pCR, while veliparib had no further benefit to pCR. The subgroup analyses of patients with a deleterious g*BRCA* mutation showed the pCR rates for paclitaxel alone, paclitaxel plus carboplatin, and paclitaxel plus carboplatin plus veliparib were 41%, 50%, and 57%, respectively.

19.5.5.2 Advanced or Metastatic Breast Cancer

A randomized phase II study (BROCADE) examined the safety and efficacy of carboplatin/paclitaxel (CP) with or without veliparib (VCP) or a third arm with veliparib plus temozolomide (VT) in 290 g*BRCA*-associated advanced/metastatic breast cancer patients. The median PFS and OS were similar for VCP and CP (PFS, 14.1 months vs. 12.3 months, respectively, $P = 0.227$; OS, 28.3 vs. 25.9 months, respectively, $P = 0.156$). The ORR was higher for the VCP regimen compared to that for the CP regimen (77.8% vs. 61.3%; $P = 0.027$). The VT arm was inferior to the CP arm in PFS, OS, and ORR [45].

19.5.6 Potential Mechanisms of Resistance to PARP

Germline *BRCA1/2* pathogenic variants are predictive biomarkers for PARPi response in BC patients; however, the majority of patients had primary and acquired resistance to PARPi. It is essential to identify the mechanism of resistance, to help overcome such resistance.

Several studies have suggested the potential mechanisms of resistance to PARPi in preclinical models and clinical reports. One of the resistance mechanisms in HRR-deficient tumors is associated with a reversion mutation which can cancel the HRR deficiency and restore HRR function. Moreover, increased gene activity such as that of RAD51 that restores the HRR mechanism and genes involved in resistance to PARPi without restoration of the HRR has also been reported. However, we will not describe the mechanisms in detail here, though further information is available in other publications [46]. Combination therapies would be the next options to overcome such resistance.

19.5.7 Combination with Immune Checkpoint Inhibitors

PARPi upregulated PD-L1 expression in *BRCA1/2*-associated BC cell lines and xenograft models. The combination of PARPi and anti-PD-L1 therapy compared with each agent alone significantly increased the therapeutic efficacy in vivo [50].

Meanwhile, *BRCA1*-associated tumors frequently exhibit a triple-negative phenotype with extensive lymphocyte infiltration, with the increased expression of immunomodulatory genes including PD-1 and CTLA4, when compared to TNBCs from *BRCA1* wild-type patients [51].

In these contexts, trials of combination PARPi and immune checkpoint inhibitors (ICIs) have been conducted (Table 19.3).

19.5.7.1 Advanced or Metastatic Setting

The results of two preliminary phase II studies for MBC are already available, and there are several ongoing studies. The phase II, single-arm MEDIOLA basket trial evaluated the efficacy and safety of olaparib in combination with durvalumab (anti-PD-L1 inhibitor) in patients with solid tumors, including ovarian cancer, breast cancer, and gastric cancer. In *BRCA*-associated HER2-negative MBC (n = 30), the 12-week DCR (disease control rate) was 24/30 (80%), and the 28-week DCR was 15/30 (50%). The ORR was 63%. The most common AEs of ≧grade 3 were anemia, neutropenia, and pancreatitis [52].

Another phase II, single-arm TOPACIO trial assessed the clinical activity and safety of niraparib combined with pembrolizumab (anti-PD-1 inhibitor) for TNBC (n = 55), irrespective of *BRCA* status or PD-L1 expression. In patients with *BRCA* pathogenic variants (n = 15), the ORR was 47% (7/15), DCR was 80% (12/15), and the median PFS was 8.3 months. In 27 patients with *BRCA* wild-type tumors, the ORR was 11% (3/27), DCR was 33% (9/27), and the median PFS was 2.1 months. Numerically higher response rates in *BRCA*-associated tumors were observed in a BC cohort. The most common treatment-related AEs of grade 3 or higher were anemia (18%), thrombocytopenia (15%), and fatigue (7%). Immune-related adverse events were reported in 15% (grade 3 in 4%) of patients [53].

Table 19.3 Clinical trials of combinations of PARPi and ICIs

Clinical trial	Type of study	Patients	PARPi and ICIs combination regimen	Result
Advanced or metastatic setting				
Domchek 2019 MEDIOLA [52]	Ph. II Single arm	30 HER2-negative BC pts with gBRCA pathogenic variant	Olaparib 300 mg twice daily Durvalumab (1500 mg) once every 4 weeks	12-week DCR = 80% 28-week DCR = 50% ORR was 63% mPFS = 8.2mo mOS = 20.5mo
Vinayak 2019 TOPACIO [53]	Ph. II Single arm	mTNBC (n = 55) including 15 pts with tBRCA pathogenic variant 27 pts with tBRCA wild type 5 pts with tBRCA unknown	Niraparib 200 mg once daily Pembrolizumab (200 mg) once every 3 weeks	BRCA-associated BC ORR = 47% DCR = 80% mPFS = 8.3mo BRCA wild-type BC ORR = 11% DCR = 33% mPFS = 2.1 mo

PARPi PARP inhibiter, *ICIs* immune checkpoint inhibitors, *gBRCA* germline *BRCA*, t*BRCA* tumor *BRCA*, *Ph* phase, *mTNBC* metastatic triple-negative breast cancer, *pts* patients, *ORR* overall response rate, *DCR* disease control rate, *mPFS* median progression-free survival, *mOS* median overall survival

19.6 Future Direction

In HER2-negative *BRCA*-associated BC, the benefit of PARPi has been validated, and further combination trials are ongoing. In contrast, in HER2-positive *BRCA*-associated BC, the efficacy of PARPi is still unclear. Although data on HER2 expression in *BRCA*-associated tumors vary from series to series, Honrado et al. reported that HER2 positivity was 7% in tumors with *BRCA1* variants and 6% in those with *BRCA*2 variants. Using data from the Japanese hereditary breast and ovarian cancer syndrome registry, we confirmed that HER2 positivity was 4.6% in tumor with *BRCA1* pathogenic variants and 11.3% in those with *BRCA*2 pathogenic variants.

Han et al. reported the efficacy of the combination of olaparib and neratinib in HER2-positive, *BRCA* wild-type ovarian cell lines and xenografts in the 2019 SGO Annual Meeting. Olaparib is approved for the treatment of HER2-negative *BRCA*-associated BC, and neratinib is approved for HER2-positive BC. The effectiveness of PARPi for the treatment of HER2-positive, *BRCA*-associated BC needs to be assessed [54].

Combinations of PARPi with other targeted therapies have the potential to further increase their benefit. PARPis are associated with several oncogenic pathways such as EGFR, IGF, VEGF, or PI3K, and trials evaluating the combination of PARPi with inhibitors of these pathways have been initiated [55].

PARPis are also known to act as radiosensitizing agents, and combination therapy with radiation has been validated in various preclinical models [56].

Moreover, PARPi may potentially have the ability to penetrate the blood-brain barrier, which increases their possible clinical utility in patients with brain metastases [57].

Lastly, pathogenic variants of g*BRCA1/2*, as well as ER, PR, and HER2, have become major, indispensable biomarkers for treatment decisions in BC. In the coming years, further developments in this field will greatly improve the prognosis of hereditary BC and may also lead to improvements in the prognosis of sporadic breast cancer.

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