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REVIEW

Clinical efficacy of PARP inhibitors in breast cancer

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Abstract

BRCA1 and BRCA2 are key tumor suppressor genes that are essential for the homologous recombination DNA repair pathway. Loss of function mutations in these genes result in hereditary breast and ovarian cancer syndromes, which comprise approximately 5% of cases. BRCA1/2 mutations are associated with younger age of diagnosis and increased risk of recurrences. The concept of synthetic lethality led to the development of PARP inhibitors which cause cell cytotoxicity via the inhibition of PARP1, a key DNA repair protein, in cells with germline BRCA1/2 mutations. Although still poorly understood, the most well-acknowledged proposed mechanisms of action of PARP1 inhibition include the inhibition of single strand break repair, PARP trapping, and the upregulation of non-homologous end joining. Olaparib and talazoparib are PARP inhibitors that have been approved for the management of HER2-negative breast cancer in patients with germline BRCA1/2 mutations. This review article highlights the clinical efficacy of PARP inhibitors in patients with HER2-negative breast cancer in early and advanced settings.

Keywords PARP inhibitors · Breast cancer · Olaparib · Talazoparib · HRD breast cancer

Introduction

Poly (ADP-ribose) polymerases, also known as PARP, are a versatile group of 17 proteins involved in a myriad of cellular processes ranging from cellular stress response to chromatin remodeling, DNA repair, and apoptosis [1]. In a typical cell, DNA single-strand break repair (SSBR) pathways and double-strand break repair (DSBR) pathways are the means through which damaged DNA is uncovered and repaired [2]. PARP1 is the most heavily involved of this family of 17 proteins in such DNA repair [1, 2], participating in both SSBR and DSBR pathways. SSBR pathways include DNA mismatch repair (MMR), nucleotide excision repair (NER), and the detection and repair of single-stranded DNA breaks, while DSBR pathways include homologous recombination (HR) and non-homologous end joining (NHEJ) [1, 2].

Normal HR repair is highly dependent on PARP1 and PARP2 activity as well as adequate BRCA1 and BRCA2 function. Mutations in BRCA1/2 lead to HR deficiency [3, 4] and indirectly increase cellular reliance on PARP1 and PARP2. While PARP proteins are able to largely detect ensuing DNA damage and recruit the appropriate repair proteins, over time these homologous recombination-deficient (HRD) cells have increased malignant potential. Specifically, deficiencies in the HR repair pathway increase the likelihood of developing various epithelial malignancies, including the hereditary breast and ovarian cancer syndromes [3]. Among those at higher risk of harboring this autosomal dominant mutation are patients of Ashkenazi Jewish descent, male patients with breast cancer, patients with a strong family history of breast cancer, and patients with breast cancer who are less than 30 years old [3, 4].

In BRCA1/2 mutated HRD cells, despite the loss of functionality in BRCA1/2, the cell remains viable, due to the role of PARP. Cell death only occurs with the simultaneous loss of function in both BRCA1/2 and PARP, a concept known as synthetic lethality. This synthetically lethal relationship between the inhibition of PARP and mutated or depleted BRCA was first observed in 2005 [1]—namely, when both SSBR and HR repair pathways are simultaneously inhibited

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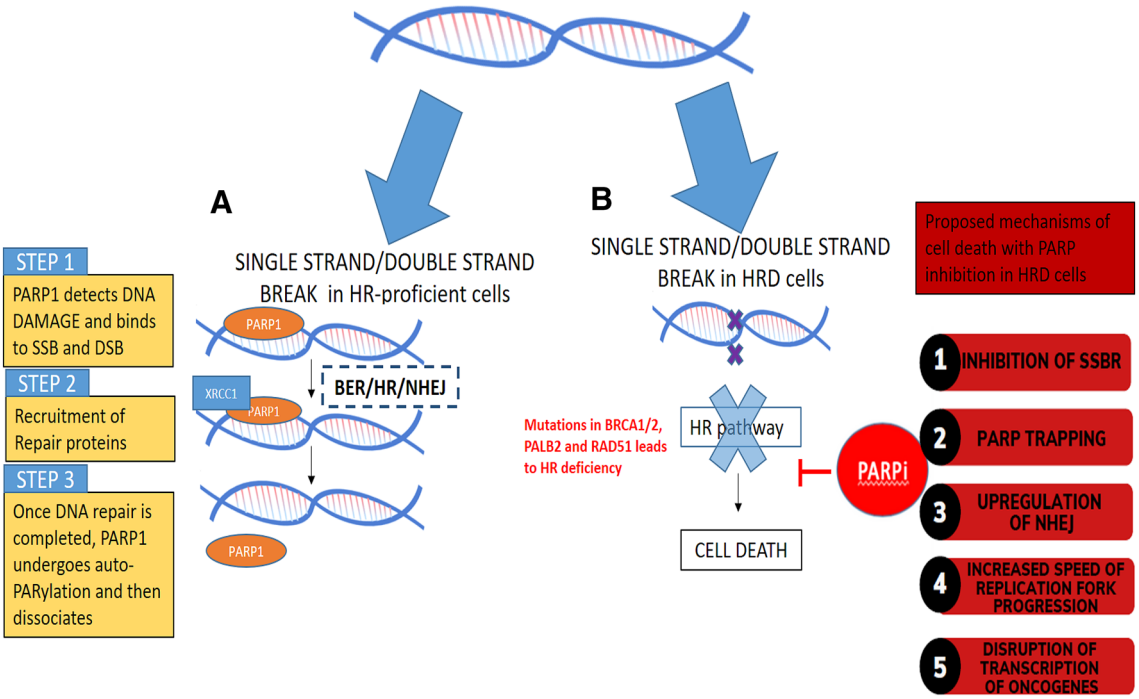

Fig. 1 A: DNA repair mechanism with functional PARP and DNA repair proteins. B: Cell Death in HRD cells with PARP inhibitors. HRD cells are able to remain viable due to the role of PARP. Cell death occurs with simultaneous loss of both BRCA 1/2 and PARP. *BER* base excision repair; *HR* homologous recombination; *NHEJ* non homologous end joining

and the more error-prone NHEJ pathway is upregulated, a cell's survival would be greatly inhibited [1, 2]. Nearly a decade later, olaparib became the first PARP inhibitor to be approved for clinical use [1]. In breast cancer, olaparib and talazoparib have been approved for the treatment of breast cancer in women with BRCA1/2 mutations.

Since its initial approval, the use of PARP inhibitors has greatly expanded. In this article, we will briefly review the role of PARP inhibitors in early-stage and metastatic breast cancers.

Mechanism of action

PARP1 is integral to both SSBR and DSBR pathways. In the SSBR pathway, PARP detects DNA damage and then quickly binds itself to the single strand breaks (SSB) [1, 2, 5]. Subsequently, the auto-inhibitory domain of PARP1 is suppressed while the ADP-ribosyltransferase catalytic domain of PARP1 is activated [1, 2]. This activation promotes rapid SSBR component recruitment and/or stabilization at the SSB [5]. One essential protein in SSBR is XRCC1, a scaffold protein for other SSBR proteins including DNA ligase 3, DNA polymerase β, and PNKP. It is through the recruitment of such proteins that DNA repair is stimulated [5]. Once DNA repair is complete, PARP1 undergoes auto-PARylation resulting in the dissociation of PARP1 from DNA and the restoration of PARP1's auto-inhibitory state [1, 2] (Fig. 1).

While PARP inhibitors have demonstrated clinical benefit in numerous tumor types, their mechanism is not well understood. Multiple mechanisms have been postulated, all of which ultimately induce synthetic lethality. SSBR inhibition and PARP trapping represent the most commonly accepted mechanisms of PARP inhibition [1, 6]. By hampering the repair process of DNA SSB, an accumulation of damaged DNA results and hence the replication fork collapses [1]. In a HRD state, such as that seen in BRCA-mutated cells, a cell is unable to use its HR repair pathway to effectively repair DNA DSB [2, 7]. Thereby, in such a cell, a damaged replication fork cannot be repaired and thus apoptosis results. Meanwhile, PARP trapping is the action PARP inhibitors take in preventing the dissociation of PARP1 from damaged DNA, creating a DNA–protein complex (DPC) which acts as a replication barrier [2, 5, 6]. As PARP1 is involved in both protecting and restarting stalled replication forks, PARP1 trapping results in fork collapse via both the formation of DPC replication barriers as well as via the destabilization of replication forks by preventing fork restart. In a HRD state, BRCA-deficient cells cannot repair such DNA breaks, resulting in cell death [5].

Alternative means by which PARP inhibitors induce synthetic lethality are being actively explored. Among these, NHEJ upregulation has been postulated [1]. As PARP1

typically acts to inhibit NHEJ, when PARP1 is inhibited, NHEJ is upregulated, and thus genomic instability and subsequent cell death ensue [1]. Another theory implicates PARP inhibition in increasing the speed of replication fork progression, resulting in both a higher frequency of DSB as well as single-stranded DNA gaps [1]. It is also hypothesized that PARP1 is involved in regulating the transcription of p53 and other proteins integral to cancer cell survival, and thereby PARP inhibition may prevent oncogenic expression and, by extension, carcinogenesis [1].

Clinical activity of PARP inhibitors

The clinical development of PARP inhibitors stemmed from two key preclinical studies, in which BRCA-mutated cells demonstrated up to 1000-fold increased susceptibility to PARP inhibition [8, 9]. These discoveries, demonstrating proof-of-concept of synthetic lethality, paved the way for the first in-human phase I trial of olaparib, an orally active potent PARP inhibitor. In this trial, 9 of 19 patients in a cohort of BRCA-mutated advanced solid tumors achieved a complete or partial response to the maximally tolerated dose of 400 mg twice daily [10]. In a subsequent phase II study of 54 patients with germline BRCA mutated breast cancer, those receiving olaparib 400 mg twice daily had a 41% overall response rate (ORR), while those receiving olaparib 100 mg twice daily still had a 22% ORR [11].

Today, two PARP inhibitors, olaparib and talazoparib, are approved in BRCA mutated breast cancer. Talazoparib has shown excellent PARP-trapping potential in preclinical models, with 100-fold increased cytotoxic activity as compared to olaparib [12]. In a phase I trial of 18 patients with germline BRCA mutated advanced breast cancer, talazoparib demonstrated a 50% ORR and 86% clinical benefit rate at 24 weeks [13], and in the phase II ABRAZO study, talazoparib showed 21% ORR in a cohort of germline BRCA mutated metastatic breast cancer patients who previously had a response to platinum chemotherapy, and a 37% ORR in another germline BRCA mutated metastatic breast cancer cohort that had received at least three prior cytotoxic therapies [14].

Role of PARP inhibitors in metastatic breast cancer

Early phase trial results of both olaparib and talazoparib have prompted investigative phase III studies in germline BRCA mutated breast cancers. These orally available agents were both initially evaluated in the metastatic setting.

The OLYMPIAD trial sought to compare the efficacy of olaparib with that of standard single-agent chemotherapy among patients with germline BRCA-mutated metastatic HER2-negative breast cancer. This randomized, open-label, international multicenter phase III trial assigned just over 300 eligible patients from April 2014 to November 2015 in a 2:1 ratio to receive olaparib or physician's choice of single-agent chemotherapy [15]. Patients were stratified based on hormone receptor status, prior exposure to platinum-based therapy, and whether they had received prior chemotherapy for metastatic disease [15]. At the time of initial analysis, the primary end point of median progression-free survival (PFS) was 7 months in the olaparib group, significantly longer than the 4.2 months in the standard therapy group, with those receiving olaparib having an overall response rate twice that of the standard therapy group [15]. There was a general trend toward improved outcomes across all subgroups with olaparib, and even suggestion at initial analysis that olaparib benefited patients with triple negative breast cancer (TNBC) more than patients with hormone-receptive positive breast cancer (HR+BC) [15]. No significant overall survival benefit was noted at the interim or final analysis, and though subgroup analysis showed no difference in survival amongst the TNBC and HR+BC cohorts, there was a potentially meaningful benefit for olaparib in patients who had not received chemotherapy for metastatic disease [15, 16]. Based on these results, olaparib received FDA approval for use with germline BRCA-mutated, HER2-negative metastatic breast cancer for patients previously treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting.

The EMBRACA trial, designed similarly to the OLYMPIAD trial, compared the efficacy of talazoparib with that of standard single-agent chemotherapy among patients with germline BRCA-mutated metastatic HER2-negative breast cancer. This randomized, open-label, international multicenter phase III trial, enrolled 431 patients from October 2013 to April 2017, with 2:1 randomization to receive talazoparib or physician's choice of single-agent chemotherapy, with stratification according to hormone-receptor status, number of prior chemotherapy regimens received for advanced disease, and prior history of CNS metastasis [17]. As in the OLYMPIAD study, the primary end point of median PFS was significantly longer with talazoparib (8.6 months) as compared to standard therapy (5.6 months) [17]. The risk of disease progression in all clinically relevant subgroups was lower with talazoparib than with standard therapy [17]. Though this study, unlike OLYMPIAD, was powered to identify a difference in OS, talazoparib did not significantly improve OS over chemotherapy at final OS analysis [18]. Furthermore, no significant OS benefit was noted amongst clinically relevant subgroups [18]. Based on these results, talazoparib received FDA approval for use in germline BRCA-mutated, HER2 negative, advanced or metastatic breast cancer (Table 1).

Owing to their deficient HR repair pathway, prior studies have shown that BRCA-mutated tumors are more genomically unstable than HR-proficient tumors, particularly when treated with PARP inhibition [19, 20]. These tumors may

Table 1 Key trials of PARP inhibitors in breast cancer

Drug	Trial	Setting	Phase	Design	Study population	Results
Olaparib	OlympiAD [15]	Advanced/metastatic	III	Olaparib vs PCT	gBRCA, 0–2 lines of prior therapy	PFS: 7 mo (Olaparib) vs 4.2 mo (Placebo); ORR: 59.9% (Olaparib) vs 28.8% (Placebo); OS: 19.3 mo (Olaparib) vs 19.6 mo (Placebo)
	MEDIOLA [20]	Advanced/metastatic	I/II	Olaparib followed by Durvalumab	gBRCA, 0–2 lines of prior therapy	PFS: 8.2 mo; ORR: 63.3%; OS: 20.5 mo
	TBCRC 048 [28]	Advanced/metastatic	II	Olaparib	Germline non-BRCA HRR pathway mutant or somatic HRR pathway mutant	ORR: 33% (germline non-BRCA HRR pathway mutant), 31% (somatic HRR pathway mutant); among PALB2 mutations, ORR 82% with PFS 13.3 mo; among sBRCA, ORR 50% with PFS 6.3 mo
	OlympiA [24]	Adjuvant	III	Olaparib vs placebo	Early-stage gBRCA, after SOC adjuvant therapy	IDFS: 85.9% (Olaparib) vs 77.1% (Placebo); DDFS: 87.5% (Olaparib) vs 80.4% (Placebo); OS: 89.8% (Olaparib) vs 86.4% (Placebo)
	GeperOLA [29]	Neoadjuvant	II	Olaparib + P vs C + P	s/gBRCA or high HRD	pCR: 55.1% (Olaparib + P) vs 48.6% (C + P)
	PARTNER [31]	Neoadjuvant	II	C + P + Olaparib vs C + P, followed by anthracycline-based regimen	Basal TNBC and/or gBRCA	Acceptable toxicity
Talazoparib	EMBRACA [17]	Advanced/metastatic	III	Talazoparib vs PCT	gBRCA, 0–3 lines of prior therapy	PFS: 8.6 mo (Talazoparib) vs 5.6 mo (Placebo)
	JAVELIN [23]	Advanced/metastatic	I/II	Talazoparib + Avelumab	TNBC or gBRCA, 0–2 lines of prior therapy	Antitumor activity, manageable safety profile
	NEOTALA [26]	Neoadjuvant	III	Talazoparib f/b breast surgery	Early-stage gBRCA	pCR: 49.2% (ITT population); 45.8% (evaluable)
Veliparib	BROCADE3 [41]	Advanced/metastatic	III	C + P + Veliparib vs C + P	gBRCA, 0–2 lines of prior therapy	PFS: 14.5 mo (C + P + Veliparib) vs 12.6 mo (C + P) OS: 33.5 mo (C + P + Veliparib) vs 28.2 mo (C + P)
	BrighTNess [36]	Neoadjuvant	III	C + P + Veliparib vs C + P vs P, all followed by AC	TNBC	4-year EFS: 78.2 mo (C + P + Veliparib) vs 79.3 mo (C + P) vs 68.5 mo (P) HR: 0.63 (C + P + Veliparib vs P); 1.12 (C + P + Veliparib vs C + P); 0.57 (C + P vs P)

PCT physician's choice chemotherapy; *g* germline; *s* somatic; *PFS* progression free survival; *ORR* overall response rate; *OS* overall survival; *HRR* homologous recombination repair; *SOC* standard of care; *IDFS* invasive disease free survival; *DDFS* distant disease free survival; *HRD* homologous recombination repair deficiency; *pCR* pathologic complete response; *TNBC* triple negative breast cancer; *C* carboplatin, *P* paclitaxel; *ITT* intention to treat; *EFS* event free survival; *HR* hazard ratio

also be more immunogenic, as preclinical models have indicated that PARP inhibitors might elicit an antitumor immune response [21, 22]. As such, combining PARP inhibition with immunotherapy represents a novel and promising approach to treatment.

The MEDIOLA trial was a phase I/II study assessing the efficacy of olaparib combined with the anti-PDL1 inhibitor durvalumab in patients with advanced solid malignancies [20]. Prior anthracycline or taxane therapy was required, and prior platinum-based chemotherapy was allowed, unlike OLYMPIAD or EMBRACA. Of the 30 patients enrolled with HER2-negative, germline BRCA-mutated advanced breast cancer, the primary endpoint of 12-week disease control rate was 80%, with median OS (21.5 months) and ORR (63%) similar to those reported in OLYMPIAD (19.3 months and 60%, respectively) [20]. The combination was overall well tolerated, without increase in immune-related adverse events, grade > 2 nausea or neuropathy, or incidence of pneumonitis, myelodysplastic syndromes, or second malignancies [20].

The JAVELIN phase I/II trial, designed similar to the MEDIOLA trial, sought to assess the activity of talazoparib combined with the anti-PDL1 inhibitor avelumab in patients with germline BRCA-mutated advanced or metastatic breast cancer. Talazoparib 1 mg daily was administered in combination with avelumab 800 mg every 2 weeks until disease progression or unacceptable toxicity. Preliminary results showed antitumor activity and manageable safety profile [23].

Role of PARP inhibitors in early-stage breast cancer

The clinical benefit seen with PARP inhibition in patients with germline BRCA-mutated metastatic breast cancers spurred investigation of these therapies in those with earlier stage disease, where presence of BRCA1/2 mutations also portents increased risk of disease recurrence with aggressive features.

The OLYMPIA study was a phase III double-blinded randomized clinical trial investigating adjuvant olaparib after completion of local treatment and either neoadjuvant or adjuvant chemotherapy in high-risk HER2-negative germline BRCA mutated early-stage breast cancers. High-risk disease connoted at least pathologic T2 or nodal disease, or incomplete pathologic response to neoadjuvant therapy in the TNBC cohort, and at least four positive lymph nodes or an incomplete pathologic response to neoadjuvant therapy in the HR+ BC cohort [4]. In total, over 1800 patients, stratified by hormone-receptor status, BRCA1 versus BRCA2 mutation, neoadjuvant versus adjuvant prior chemotherapy, and prior platinum chemotherapy, were randomized 1:1 to receive either 1 year of adjuvant olaparib or placebo [4]. The primary end point of invasive disease-free survival was 85.9% at 3 years in those receiving olaparib, significantly longer than the 77.1% invasive disease-free survival in the placebo group [4]. Distant disease-free survival, a secondary end point, was also longer at 3 years in the olaparib group as compared to the placebo group (87.5% vs 80.4%, respectively) [4]. Treatment effect was consistent, without evidence of significant heterogeneity across major subgroups [4, 24]. At the second planned interim analysis, at a median follow up of 3.5 years, adjuvant olaparib demonstrated overall OS benefit with limited manageable toxicity [24]. Based on these results, olaparib received FDA approval for use as adjuvant treatment in germline BRCA-mutated, HER2-negative high-risk early-stage breast cancer for patients previously treated with neoadjuvant or adjuvant chemotherapy.

While the OLYMPIA study investigated adjuvant olaparib in early-stage BRCA mutated breast cancer, the NEOTALA study explored neoadjuvant PARP inhibitor monotherapy with talazoparib in patients with early invasive HER2 negative breast cancer and germline BRCA mutation. In this non-randomized multicenter phase II study, 61 patients were treated with talazoparib 1 mg daily for 24 weeks prior to breast surgery, with primary endpoint being pathologic complete response (pCR) rate [25]. pCR rates approached 50% in both evaluable and intention-to-treat populations, comparable to those observed with combination anthracycline and taxane-based chemotherapy regimens [25]. Overall, this regimen was very well tolerated, with the most common toxicities being fatigue, nausea, and alopecia [25].

Role of PARP inhibitors in TNBC and breast cancers with high HRD scores

While germline BRCA mutated breast cancers have clinically demonstrated susceptibility to PARP inhibition, the role for PARP inhibition in other HR repair pathway genes is not fully elucidated [26]. The TBCRC 048 trial sought to better understand the role olaparib within this subpopulation. This single-arm phase II study assessed 54 metastatic breast cancer patients with either germline mutations in non-BRCA HR-related genes or somatic mutations within any HR-related genes, including BRCA1/2 [27]. Those eligible received olaparib 300 mg twice daily until disease progression [27]. While ORR in the germline non-BRCA HR-related gene mutation group was just 33%, all patients harboring germline PALB2 mutations responded to olaparib, with 82% ORR and PFS of 13.3 months [27]. Similarly, despite 31% ORR in the somatic HR-related gene mutation group, those with somatic BRCA1/2 mutations had 50% ORR and PFS of 6.3 months [27]. Meanwhile, no responses were observed in patients with either ATM or CHEK2 mutations [27]. Together, these results suggested efficacy of PARP inhibition in patients with germline PALB2 or somatic BRCA1/2 mutations, expanding the population of

breast cancer patients gaining benefit from PARP inhibition [27].

The GEPEROLA trial studied PARP inhibition in a similar subpopulation of early-stage breast cancer patients, through the utilization of a HRD score, created to quantify chromosomal structural instability and by extension help predict tumors with higher susceptibility to PARP inhibition in the absence of germline BRCA1/2 mutations [28]. This randomized phase II study investigated olaparib in combination with paclitaxel versus carboplatin/paclitaxel, in early-stage HRD, HER2-negative breast cancer [29]. Both arms received 12 weeks on therapy, followed by 12 weeks of standard-of-care epirubicin/cyclophosphamide, with primary endpoint being pCR rate [29]. Of the 107 total patients enrolled on study, those receiving olaparib plus paclitaxel had pCR rates of 55.1% compared to 48.6% in the carboplatin/paclitaxel control arm, with better overall tolerability [29].

The PARTNER trial also sought to expand the role of PARP inhibition in breast cancer, taking advantage of the fact that basal TNBCs show phenotypic and molecular resemblance to germline BRCA mutated breast cancers [30]. This randomized phase II/III trial offered neoadjuvant carboplatin and paclitaxel, with or without Olaparib, for 4 cycles followed by physician's choice standard-of-care anthracycline-based regimen to basal TNBC patients and/or germline BRCA mutated breast cancer patients [30]. The addition of olaparib to standard-of-care neoadjuvant chemotherapy showed an acceptable toxicity profile with efficacy data yet to come [30].

Other PARP inhibitors in development for breast cancer

While olaparib and talazoparib are the only PARP inhibitors with current FDA approval in breast cancer, a number of other PARP inhibitors are in development. Of these, veliparib and niraparib are presently most promising in breast cancer.

Veliparib is a PARP inhibitor which specifically inhibits PARP1 and PARP2 [31]. While its inhibitory effects on PARP catalytic activity are similar to olaparib, veliparib appears to have less "PARP trapping" potential; its overall decreased efficacy in PARP trapping allows for its use in combination with conventional chemotherapeutics without unmanageable toxicity [31]. Phase I studies of veliparib in germline BRCA mutated TNBC established a 400 mg twice daily monotherapy dose with 60% ORR [32], with a subsequent phase II study showing 14% and 36% ORR in patients with BRCA1 and BRCA2 mutations, respectively, with a PFS of 5.2 months [33].

Veliparib was first evaluated with chemotherapy in the I-SPY2 study, in which TNBC patients, independent of BRCA mutation status, received weekly paclitaxel with or without carboplatin and veliparib, followed by doxorubicin and cyclophosphamide in the neoadjuvant setting [34]. In this study, pCR rates were 51% in the Veliparib arm, compared to 26% in the control arm [34], leading to the randomized phase III BRIGHTNESS study. This study evaluated outcomes of TNBC patients in three groups: those receiving neoadjuvant veliparib, carboplatin, and paclitaxel, those receiving carboplatin and paclitaxel, and those receiving paclitaxel alone; each of these comparator arms went to receive standard doxorubicin and cyclophosphamide chemotherapy [35]. Ultimately, the addition of veliparib to carboplatin/paclitaxel failed to show pCR improvement (53.2% versus 57.5%, respectively) [35, 36].

Niraparib, another highly selective PARP1 and PARP2 inhibitor, has also shown promising efficacy in advanced or metastatic TNBC, particularly in those harboring BRCA mutations. In the single-arm phase II TOPACIO trial, among 47 patients eligible for efficacy evaluation, combination niraparib and pembrolizumab achieved 21% ORR and 49% disease control rate, with median duration of response still not having been met [37]. Meanwhile, several trial evaluating the role of niraparib in early-stage breast cancer are currently ongoing. The phase II TBCRC 056 trial is evaluating the role of preoperative niraparib combined with the anti-PD1 monoclonal antibody dostarlimab in early-stage BRCA-mutated or PALB2-mutated, HER2-negative breast cancers, while the phase III ZEST study is assessing the efficacy of niraparib in patients with either TNBC or BRCA-mutated, HER2-negative breast cancer with molecular disease based on the presence of circulating tumor DNA.

Toxicity profile

Although quite versatile, PARP inhibitors have many adverse effects, most commonly myelosuppression, gastrointestinal toxicities and fatigue [6, 38, 39]. While largely grade 1 or 2, higher grade toxicities can be seen, particularly hematologic [6, 39]. PARP inhibitors are additionally teratogenic [39] (Fig. 2).

Neurologic (headache, dizziness, and insomnia), respiratory (dyspnea, cough, pneumonitis), musculoskeletal (arthralgia and back pain), cutaneous (photosensitivity, pruritus, rash, and peripheral edema), and cardiovascular (hypertension, tachycardia, and palpitations) toxicities are infrequently seen [38, 39]. Rarely, the use of PARP inhibitors can lead to the development of secondary acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) [6]. These secondary malignancies have an incidence of 0.5–1.4% and typically occur after long-term treatment [39]. In the OLYMPIA trial, there was notably no difference in frequency of development of AML or MDS observed

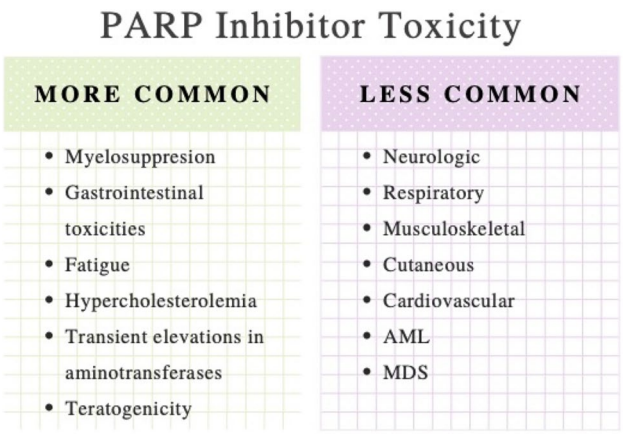

Fig. 2 Toxicity profile of PARP inhibitors

between the olaparib and placebo groups, though median follow-up was short (2.5 years) [4].

In comparing between PARP inhibitors, olaparib carries a higher risk of nausea and vomiting than talazoparib [38, 40], while talazoparib has a higher risk of hematologic events and alopecia than olaparib [38, 40]. Talazoparib, with greater PARP1 trapping ability and by extension increased cytotoxic potency [1, 2, 39], is initially dosed as a daily 1 mg capsule, while olaparib is initially dosed at 300 mg twice daily [6].

Conclusion

The inhibition of PARP1 in cells with defective HR repair mechanisms results in the accumulation of single and double-strand DNA breaks, creating genomic instability that leads to cell death. While the exact mechanism by which PARP inhibitors precipitate this cell death remains poorly understood, its efficacy in doing so has therapeutic relevance in the management of patients with BRCA mutations.

The OLYMPIAD and EMBRACA trials were groundbreaking in demonstrating the benefit of PARP inhibitors in advanced HER2-negative breast cancers in patients with germline BRCA1/2 mutations, highlighting the importance of germline mutation testing in all patients with recurrent or metastatic breast cancer. If present, strong consideration must be given to frontline PARP inhibition among those in the HR+ BC cohort who are refractory to endocrine therapy or in visceral crisis, and among the TNBC cohort with PDL1 combined positive score (CPS) less than 10, whereas second-line consideration, following chemoimmunotherapy, should be given to TNBC with PDL1 CPS greater than 10. The OLYMPIA study expanded the role for olaparib to early-stage disease as an adjuvant therapy. Meanwhile, the TBCRC 048 trial and others have attempted to elucidate the role for PARP inhibition in other HR repair pathway genes.

Presently, olaparib and talazoparib are the only FDA approved PARP inhibitors in breast cancer, though other PARP inhibitors, namely veliparib and niraparib, offer great promise. The toxicities associated with PARP inhibitors are generally manageable with supportive care but require close monitoring of hematologic parameters and gastrointestinal side effects; special consideration must be given considering their teratogenicity.

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Data availability Enquiries about data availability should be directed to the authors.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

References

1. Rose M et al (2020) PARP inhibitors: clinical relevance, mechanisms of action and tumor resistance. Front Cell Dev Biol 8:564601
2. Yi M et al (2019) Advances and perspectives of PARP inhibitors. Exp Hematol Oncol 8:29
3. Casaubon JT, Kashyap S, Regan JP (2022) BRCA 1 and 2. StatPearls, Treasure Island
4. Tutt ANJ et al (2021) Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer. N Engl J Med 384(25):2394–2405
5. RayChaudhuri A, Nussenzweig A (2017) The multifaceted roles of PARP1 in DNA repair and chromatin remodelling. Nat Rev Mol Cell Biol 18(10):610–621
6. Murthy P, Muggia F (2019) PARP inhibitors: clinical development, emerging differences, and the current therapeutic issues. Cancer Drug Resistance. https://doi.org/10.20517/cdr.2019.002
7. Stewart MD et al (2022) Homologous recombination deficiency: concepts, definitions, and assays. Oncologist 27(3):167–174
8. Bryant HE et al (2005) Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature 434(7035):913–917
9. Farmer H et al (2005) Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 434(7035):917–921
10. Fong PC et al (2009) Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 361(2):123–134
11. Tutt A et al (2010) Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet 376(9737):235–244
12. Murai J et al (2014) Stereospecific PARP trapping by BMN 673 and comparison with olaparib and rucaparib. Mol Cancer Ther 13(2):433–443
13. de Bono J et al (2017) Phase I, dose-escalation, two-part trial of the PARP inhibitor talazoparib in patients with advanced germline

BRCA1/2 mutations and selected sporadic cancers. Cancer Discov 7(6):620–629
14. Turner NC et al (2019) A phase II study of talazoparib after platinum or cytotoxic nonplatinum regimens in patients with advanced breast cancer and germline BRCA1/2 mutations (ABRAZO). Clin Cancer Res 25(9):2717–2724
15. Robson M et al (2017) Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med 377(6):523–533
16. Robson ME et al (2019) OlympiAD final overall survival and tolerability results: olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. Ann Oncol 30(4):558–566
17. Litton JK et al (2018) Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. N Engl J Med 379(8):753–763
18. Litton JK et al (2020) Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial. Ann Oncol 31(11):1526–1535
19. Lyons TG, Robson ME (2018) Resurrection of PARP inhibitors in breast cancer. J Natl Compr Cancer Netw 16(9):1150–1156
20. Domchek SM et al (2020) Olaparib and durvalumab in patients with germline BRCA-mutated metastatic breast cancer (MEDIOLA): an open-label, multicentre, phase 1/2, basket study. Lancet Oncol 21(9):1155–1164
21. Chabanon RM et al (2016) Mutational landscape and sensitivity to immune checkpoint blockers. Clin Cancer Res 22(17):4309–4321
22. Jiao S et al (2017) PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression. Clin Cancer Res 23(14):3711–3720
23. Yap TA et al (2020) Abstract P1–19–03: JAVELIN PARP Medley, a phase 1b/2 study of avelumab plus talazoparib: results from advanced breast cancer cohorts. Cancer Res 80:P1-19-03-P1-19–03
24. Tutt A et al (2022) VP1-2022: pre-specified event driven analysis of overall survival (OS) in the OlympiA phase III trial of adjuvant olaparib (OL) in germline BRCA1/2 mutation (gBRCAm) associated breast cancer. Ann Oncol 33(5):566–568
25. Litton JK et al (2021) Neoadjuvant talazoparib in patients with germline BRCA1/2 (gBRCA1/2) mutation-positive, early HER2-negative breast cancer (BC): results of a phase 2 study. J Clin Oncol 39(15_suppl):505–505
26. Takamatsu S et al (2022) Utility of homologous recombination deficiency biomarkers across cancer types. JCO Precis Oncol 6:e2200085
27. Tung NM et al (2020) TBCRC 048: phase II study of olaparib for metastatic breast cancer and mutations in homologous recombination-related genes. J Clin Oncol 38(36):4274–4282
28. Telli ML et al (2016) Homologous recombination deficiency (HRD) Score predicts response to platinum-containing neoadjuvant chemotherapy in patients with triple-negative breast cancer. Clin Cancer Res 22(15):3764–3773
29. Fasching PA et al (2021) Neoadjuvant paclitaxel/olaparib in comparison to paclitaxel/carboplatinum in patients with HER2-negative breast cancer and homologous recombination deficiency (GeparOLA study). Ann Oncol 32(1):49–57
30. Alba KP et al (2020) Abstract P3–10–05: Preliminary safety data from stage 1 and 2 of the phase II/III PARTNER trial: Addition of olaparib to platinum-based neoadjuvant chemotherapy in triple negative and/or germline BRCA mutated breast cancer patients. Cancer Res 80(4_Supplement):P3-10-05-P3-10–05
31. Wagner LM (2015) Profile of veliparib and its potential in the treatment of solid tumors. Onco Targets Ther 8:1931–1939
32. Puhalla S, Beumer J, Pahuja S (2014) Final results of a phase 1 study of single-agent veliparib (V) in patients (pts) with either BRCA1/2-mutated cancer (BRCA+), platinum-refractory ovarian, or basal-like breast cancer (BRCA-wt) [abstract]. J Clin Oncol 32(Suppl):2570
33. Somlo G, Frankel P, Arun B (2017) Efficacy of the PARP inhibitor veliparib with carboplatin or as a single agent in patients with germline BRCA1- or BRCA2-associated metastatic breast cancer: California Cancer Consortium Trial NCT01149083. Clin Cancer Res 23:4066–4076
34. Rugo HS et al (2016) Adaptive randomization of veliparib-carboplatin treatment in breast cancer. N Engl J Med 375(1):23–34
35. Loibl S et al (2018) Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. Lancet Oncol 19(4):497–509
36. Geyer CE et al (2022) Long-term efficacy and safety of addition of carboplatin with or without veliparib to standard neoadjuvant chemotherapy in triple-negative breast cancer: 4-year follow-up data from BrighTNess, a randomized phase III trial. Ann Oncol 33(4):384–394
37. Vinayak S et al (2019) Open-label clinical trial of niraparib combined with pembrolizumab for treatment of advanced or metastatic triple-negative breast cancer. JAMA Oncol 5(8):1132–1140
38. Madariaga A et al (2020) Manage wisely: poly (ADP-ribose) polymerase inhibitor (PARPi) treatment and adverse events. Int J Gynecol Cancer 30(7):903–915
39. LaFargue CJ et al (2019) Exploring and comparing adverse events between PARP inhibitors. Lancet Oncol 20(1):e15–e28
40. McCrea C, Hettle R (2019) Indirect treatment comparison of the efficacy and safety of olaparib 300 mg tablets BID and talazoparib 1 mg once daily in the treatment of patients with germline BRCA-mutated (gBRCA) HER2-negative metastatic breast cancer. J Clin Oncol 37(15):e12570–e12570
41. Diéras V et al (2020) Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 21(10):1269–1282. https://doi.org/10.1016/S1470-2045(20)30447-2