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Delivering on the promise: PARP inhibition as targeted anti-cancer therapy

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Abstract

Purpose of the review—Authors present the rationale, clinical development, and current status of Poly (adenosine diphospohate [ADP]) ribose polymerase (PARP) inhibitors (PARPi) as anticancer agents.

Recent Findings—The recent approval of olaparib in heavily pre-treated patients with advanced ovarian cancer carrying a *BRCA1/2* mutation represents a significant therapeutic advance for patients with this difficult to treat disease. Though olaparib is the first agent in this class to be approved, multiple PARPis are in various stages of clinical development, including in combination with other treatment modalities such as radiation, anti-angiogenic agents, and cytotoxic chemotherapies.

Summary—Clinical benefit has been observed with PARPis in patients with advanced *BRCA1/2* mutant ovarian and breast cancers. Various PARPis, either as single agents or in combination, are being evaluated in the neoadjuvant, adjuvant and metastatic settings.

Keywords

BRCA 1/2; ovarian cancer; DNA damage repair; combination strategies; chemopotentiation; radiation sensitizer

Introduction

Cellular DNA damage must be repaired to preserve the integrity of the human genome. DNA damage can present as single-strand breaks, double strand breaks or stalling of the replication fork (1). Multiple pathways and mechanisms are involved in DNA damage repair (DDR), including the Base Excision Repair (BER), Nucleotide Excision Repair (NER), single strand annealing, mismatch repair (MMR) as well as homologous recombination (HR) and non-homologous end joining (NHEJ) (2) pathways. The Poly (adenosine diphospohate [ADP]) ribose polymerase (PARP) super-family of enzymes plays a crucial role in DDR, controlling both enzymatically and structurally the mechanism of BER to repair single-strand DNA breaks (SSBs) (3). Following PARP inhibition, single-strand DNA

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breaks progress to double-strand breaks due to the collapse of the replication fork, requiring either HR or NHEJ pathways for repair(4).

The super-family of PARP proteins is a branch of ADP-ribosyltransferases that are activated by DNA damage, and include 17 enzymes of which PARP-1 is the most abundant and best described (5, 6). PARP enzymes are recruited to DNA damage sites, and after binding to these undergo ADP-ribosylation together with histones H1/H2B leading to uncoiling of chromatin and permitting DNA repair with consumption of NAD+ and release of nicotinamide (1, 7). PARPis have been reported to inhibit the catalytic activity of PARP-1, and hypothesized to potentiate the effect of chemotherapeutic agents because of the accumulation of SSBs from delayed DNA damage repair (8). PARPis are also postulated to enable 'trapping' of PARP-1 and 2 at DNA repair sites, which precludes accessibility of other repair proteins and inhibits catalytic repair thus exerting their anti-tumor effect (1, 9). Additionally, pre-clinical work suggests that trapped PARP-DNA complexes are cytotoxic in their own right, which may contribute to their mechanism of action (9).

Cells carrying *BRCA 1* and *2* deleterious mutations were noted to have an increased sensitivity to cell death following treatment with PARPi (10). In the presence of *BRCA1* and *2* mutations, inhibition of BER pathway following administration of PARPi results in accumulation of unrepaired double-strand DNA breaks, leading to cell death, a phenomena referred to as 'synthetic lethality'. Defects in the HR pathway can also occur due to aberrations in genes other than the *BRCA* genes, referred to as 'BRCA-ness', such as mutations in *ATM, RAD51, RAD54, CHK2, PTEN* and *PALB2* or due to epigenetic silencing of *BRCA 1* and *2*(2, 7, 11). Presence of mutations/or epigenetic changes resulting in defects in the HR pathway may also sensitize cells to PARP inhibition.

Granting of accelerated approval to the PARPi, olaparib (Lymparza®, AstraZeneca, Maryland, USA), by the US Food and Drug Administration in December 2014 for the treatment of *BRCA* defective advanced ovarian cancer further validates the modulation of the DDR pathway as a successful therapeutic strategy in the cancer armamentarium (12). This approval was granted together with a companion *in vitro* diagnostic test, BRACAnalysis CDX™ (Myriad Genetics, Inc., Utah USA), to detect for the presence of germline mutations in the *BRCA* gene (g*BRCA*m), identified by PCR/Sanger sequencing of whole blood specimens.

Clinical experience with PARP inhibitors: Current inhibitors in Development

Currently five PARPis are undergoing evaluation in cancer: olaparib, rucaparib, niraparib, veliparib and talazoparib).

Olaparib—Given the pre-clinical data suggesting marked sensitivity of BRCA-deficient tumors to PARPi, a proof-of-concept phase I clinical trial was performed to test olaparib (AZD2281, Ku-0059436, PARP1/2 IC_{50} 5nM/1nM (13), AstraZeneca, London, UK) in patients with refractory solid tumors. This trial enriched its target population for g*BRCA*m 1 and 2, which was the main patient group to benefit from therapy (clinical benefit seen in 63% of g*BRCA*m 1/2 carriers). The maximum tolerated dose (MTD) was identified at 400 mg twice daily by mouth, which was well tolerated with mild fatigue and gastrointestinal

side effects as the main toxicities(14). An additional 50 ovarian cancer patients with g*BRCA*m 1/2 showed correlation between platinum sensitivity and PARP response (clinical benefit rate 69%, 45% and 23% for the platinum sensitive, resistant and refractory groups respectively)(15).

Two separate phase II trials confirmed the efficacy and minimal toxicity of olaparib in patients with g*BRCA*m advanced breast and ovarian cancers, respectively, at an oral dose of 400 mg twice daily(16, 17). A follow up phase II trial evaluated olaparib as a treatment for high grade serous ovarian cancer (HGSOV) and triple negative breast cancer, with a reported 41% response rate (RR) in g*BRCA*1/2m patients with ovarian cancer(18). Olaparib was also compared to pegylated doxorubicin (PLD) in g*BRCA*m 1/2 platinum-resistant ovarian cancer. Median progression-free survival (PFS) was 6.5 months, 8.8 months and 7.1 months for the olaparib 200 mg, olaparib 400 mg, and PLD groups, respectively. There was no difference in PFS (hazard ratio, 0.88; 95% CI, 0.51 to 1.56; P = .66) for the combined olaparib doses versus PLD (19). There were also no differences in the RR between patients treated with olaparib at a higher/lower dose and PLD. It's important to note that though this trial was negative, this well-tolerated oral PARPi generated a similar outcome as intravenous chemotherapy (19).

A placebo-controlled phase II maintenance trial was initiated in patients with HGSOC with or without g*BRCA*m. The PFS in this trial was 8.4 months for patients treated with olaparib 400 mg twice daily compared to 4.8 months for patients taking placebo. These results were not expected to translate into a significant overall survival (OS) benefit, and plans to continue development were tentatively shelved. This decision was reversed following a retrospective review of the trial, which revealed that patients carrying g*BRCA*m 1/2 showed an improvement in PFS (11.2 months compared to 4.3 months) in favor of olaparib treatment (4). Interestingly, accelerated approval was not granted for olaparib in the maintenance setting but rather as a single agent in patients with g*BRCA*m 1/2-associated ovarian cancer (three or more prior lines of therapy) based on the published results of phase III SOLO2 trial, where 34% of patients had objective responses that lasted an average of 7.9 months (4). This approval is contingent on the results of the SOLO3 phase III trial (olaparib versus physicians' treatment of choice); primary outcome is PFS.

Veliparib—Veliparib (ABT-888, PARP1/2 IC_{50}5.2nM/2.9nM (13), AbbVie, Illinois, USA) is an oral PARP 1 and 2 oral inhibitor. The single agent phase I/II study has been presented, with reported greater clinical activity in the g*BRCA*m patients compared to WT (ORR=23% combining all dose levels: 50 to 500mg twice daily) with a tolerable toxicity profile (20). This agent has the broadest clinical development plan in combination trials at this time.

Rucaparib—This IV PARPi (PF-01367338, PARP1 IC_{50}1.4nM (13), Clovis Oncology, Colorado, USA) was the first to enter clinical trials (6, 21) though has lagged behind in therapeutic development. It was evaluated in combination with temozolomide in refractory solid tumors in a phase I setting (22); this same combination in the first-line setting for metastatic melanoma reported significant bone marrow toxicity (23). Phase II trials are underway including as a single agent in g*BRCA*m breast and ovarian cancer (ARIEL2, Table

1) and in the phase III ARIEL 3 maintenance trial, where patients with or without g*BRCA*m 1/2 will be stratified according to HR status.

Niraparib—Niraparib (MK-4827, PARP1/2 IC_{50}3.2nM/4.0nM (13), Tesaro, Massachusetts, USA) is a selective PARP-1/2 inhibitor, currently available in an oral formulation. It is being evaluated in phase II trials either as a single agent or in combination with standard of care chemotherapy in advanced solid tumors (2). It has also entered phase III trial evaluation, NOVA, to determine its clinical activity as a single agent in the maintenance setting for g*BRCA*m 1/2 or sporadic platinum-sensitive recurrent ovarian cancer (4).

Talazoparib—Talazoparib (BMN 673, PARP1/2 IC_{50}1.2nM/0.9nM (13), BioMarin, California, USA) is currently undergoing both single and combination clinical trials and is being evaluated in phase I, II and III trials to date (Table 1). It is a selective PARP-1/2 inhibitor that has been reported to have antitumor effects at lower concentrations than other inhibitors (8). Since myelosuppression was the DLT in the single agent trial, there was concern about the feasibility of safely administering the combination of talazaparib with full dose cytotoxic chemotherapy. Preclinical data supports the antitumor benefit of combining low doses chemotherapy with talazoparib (8). Phase I trials in pediatric and adult patients are ongoing with results awaited.

Combination Treatment Strategies with PARP inhibitors

PARP inhibitors in combination: Chemotherapy and Radiation—Pre-clinically the combination of PARP inhibitors with cytotoxic chemotherapy has been shown to potentiate DNA damage by inhibiting ongoing repair; however this is associated with an increase in the toxicity of the combination compared to single agent chemotherapy. Chemotherapy agents that induce single strand DNA breaks, such as temozolomide and topoisomerase inhibitors, have been previously evaluated in combination with PARPi, however it is the combination with platinum agents that has shown the most significant anti-tumor activity (5). This is postulated to be secondary to platinum agents inducing DNA crosslinks, which are usually repaired by HR or BER.

A phase I study of olaparib, cisplatin and gemcitabine in solid tumors reported grade 4 myelosuppression at the first dose level, and needed de-escalation to determine the MTD (24). Veliparib in combination with topotecan administered over 5 days was also associated with significant myelosuppression, limiting the doses of veliparib that could be safely administered (25). However, the combination was better tolerated when topotecan was administered weekly along with veliparib, with veliparib successfully given at doses ≥ 200mg BID (26). However, various encouraging, and effective, veliparib combination trials have been presented or reported in 2015. Promising preliminary results have been reported in combination with irinotecan (27) and along with carboplatin/paclitaxel (28) in patients with triple negative breast cancer (TNBC). Preliminary phase I results of veliparib in combination with intravenous and intraperitoneal paclitaxel/cisplatin +/- bevacizumab in the adjuvant setting have achieved safe recommended phase II dose of Veliparib at 150mg BID (29). In a phase I study of irinotecan and veliparib with an expansion cohort in TNBC

patients, 7/8 *BRCA* mutation patients had PR and 7/10 non *BRCA* mutation patients had SD (27). Veliparib in combination with temozolomide is being evaluated in the ongoing precision medicine trial Molecular Profiling based Assignment of Cancer Therapy (MPACT), for the treatment of patients carrying genetic defects in the DNA repair pathway, other than g*BRCA*m. This trial will explore role of PARPis in the treatment of tumors carrying mutations in DDR genes other than BRCA genes (Table 2).

In comparison to the plethora of combination studies evaluating PARPi with chemotherapy, there are fewer trials evaluating PARPis as radiosensitizers. Recently a trial evaluating low dose radiotherapy with veliparib in patients with peritoneal carcinomatosis reported prolonged disease stabilization, particularly in patients with ovarian/fallopian tube cancer (30). A phase I trial of olaparib with radiotherapy for inoperable breast cancer (NCT02227082); and a phase I study of olaparib and radiotherapy for stage II-III laryngeal and HPV-negative oropharyngeal squamous cell carcinomas (NCT02229656), are ongoing. A trial of radiotherapy, paclitaxel and carboplatin with or without veliparib in non-small cell lung cancer (stage III) is also currently ongoing (Table 2).

PARP inhibitors with Targeted Agents

The most significant trial to date of this combinatorial approach has been the randomized phase II trial of olaparib with cediranib, an anti-angiogenic agent with demonstrable activity against the VEGF receptor 1,2 and 3(31). The combination of these two oral agents significantly increased PFS and the ORR compared to olaparib alone in recurrent, platinum-sensitive ovarian, primary peritoneal or fallopian tube cancer, with and without deleterious g*BRCA*1/2m. Median PFS, the primary endpoint of the trial, in the intent-to-treat population was 17.7 months (95%CI 14.7-not reached) with the combination of olaparib and cediranib compared to 9 months (95%CI 5.7-16.5, HR 0.42, 95% CI 0.23-0.76; p=0.005) for those treated with olaparib alone. There was a greater incidence of grade 3/4 adverse events, including hypertension, fatigue and diarrhea in the combination arm (31). Importantly, 77% of patients in the combination arm required a dose reduction compared to 27% in the olaparib arm (5, 31). Intriguingly, the improvement in PFS was more marked in the *BRCA* WT patients receiving the combination than in those with g*BRCA*m(5, 31). OS survival data is awaited.

Aberrations in the PI3K/AKT/mTOR pathway, such as loss of *PTEN* or *PI3K* activating mutations and sensitivity to PARP inhibition has been controversial, though preliminary xenograft data has demonstrated improved anti-tumor activity for dual PARP and PI3K inhibition (5). Other key regulators of DDR such as ataxia-telangiectasia mutated (ATM) and ataxia-telangiectasia Rad3 related (ATR) kinases, are feasible targets given their role in DNA repair (32). It has also been reported that ATM or ATR defects are synthetically lethal when combined with PARPi, suggesting a potential therapeutic strategy for tumor cells with these intrinsic deficiencies or with acquired DDR defects, and independent of gBRCAm status (32). Trials of these new combination approaches are in progress (Table 2).

Future Directions

The successful development of PARPi for the treatment of g*BRCA*m ovarian cancer, as evidenced by the FDA approval of olaparib is a welcome addition to the anti-cancer therapeutic armamentarium. There is extensive ongoing research exploring additional roles for PARPi in other tumors associated with mutations in the BRCA genes as well as those carrying defects in other genes involved in the DNA damage repair cascades. Combinatorial strategies with chemotherapy, radiation, and other targeted agents are being evaluated. The clinical benefit of combining PARPi with traditional cytotoxic agents will need to be balanced with the associated toxicities.

Recognition of the human immune system's capability to identify tumor-associated antigens and generate specific lymphocytes in response to them has been a crucial building block in the development of cancer immunotherapy. Specifically, the programmed death pathway (PD-1), is postulated to suppress the cytotoxic immune response to many tumors which can occur in response to tumoural neoantigens (33). The recently positive phase II trial of pembrolizumab, which reported a clinical benefit in tumors with mismatch repair deficiency (34), would theoretically support the premise of synergic cytotoxic effect for the combination of PARPi and immunotherapy agents, with possibly non-overlapping toxicities.

Conclusions

The approval of olaparib marks the creation of a new class of active anti-cancer agents and another step towards mainstreaming of precision medicine: tailoring of therapy to a specific subgroup of patients to obtain greater efficacy while limiting exposure to patients that will experience little benefit. Though the major development focus of these agents has been in g*BRCA*m-associated tumors, a growing understanding of other integral HR repair pathways will undoubtedly lead to evolving areas of therapeutic intervention. Significant progress in identifying additional predictive biomarkers will further improve patient selection, clinical benefit, inform combinations, and lead to a broader application of PARPi as anticancer therapies.

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Key Points

1. Olaparib, a first-in-class PARPi, has been FDA approved for use in heavily pre-treated, gBRCA1/2m ovarian cancer with a companion BRCA gene-detection test.
2. PARPi, as monotherapy or in combination with other agents, are in advanced stages of clinical development for both wild type and gBRCA1/2m tumors.
3. The combination of cediranib and olaparib has shown clinical activity in recurrent platinum-sensitive ovarian cancer.

Table 1

Selected ongoing clinical trials evaluating PARP inhibitor monotherapy

Tumor type/eligibility	Experimental Agent	Molecular Target	Randomized	Phase	NCT number
Solid tumors (metastatic)	BMN 673 (talazoparib)	Deleterious *BRCA1/2*	No	Phase I	NCT01989546
Prostate cancer (Pre-surgery)[π]	olaparib vs olaparib+degarilix intermediate/high risk disease	none	Yes	Phase I	NCT02324998
Solid tumors (advanced, unresectable, metastatic)	veliparib vs veliparib+mitomycinC	Deficient Fanconi Anemia pathway on FATSI	Yes	Phase I	NCT01017640
Solid tumor Expansion: ovarian cancer	rucaparib	Expansion cohort only: deleterious *gBRCA1/2m*	No	Phase I/II	NCT01482715
Breast cancer [B] (locally advanced/metastatic)	BMN 673 (talazoparib) ABRAZO study	*gBRCA1/2m*	No	Phase II	NCT02034916
Breast cancer (metastatic /recurrent)	BMN 673 (talazoparib)	*BRCA1/2* WT, Triple neg or HER2 neg HR deficiency, germ/som MT*	No	Phase II	NCT02401347
Advanced malignancy	BMN 673 (talazoparib)	multiple[α]	No	Phase II	NCT02286687
Non-small cell lung cancer (chemo-responsive)	Olaparib vs placebo	None	Yes	Phase II	NCT01788332
Endometrial cancer (inoperable, advanced)	BMN 673 (talazoparib) PANDA study	Retrospective PTEN, MSI and MRE11 analysis	No	Phase II	NCT02127151
Ovarian/PP/Fallopian [X] (platinum-sensitive, relapsed)	Rucaparib ARIEL2 study	Tumor HRD status	No	Phase II	NCT01891344
Ovarian cancer (≥3 prior lines Rx)∞	niraparib	None	No	Phase II	NCT02354586
Breast Cancer (stage III or IV)	ABT-888 (veliparib)+/-carboplatin	Deleterious *gBRCA1/2m*	Yes	Phase II	NCT01149083
Ovarian cancer (received prior PARPi)	BMN 673 (talazoparib)	Deleterious *gBRCA1/2m*	No	Phase II	NCT02326844
Ovarian/PP/Fallopian (After CR/PR to platinum)	olaparib vs placebo	Deleterious *BRCA1/2m*	Yes	Phase III	NCT01874353
Ovarian/PP/Fallopian (After CR/PR to platinum, maintenance)	rucaparib vs placebo ARIEL3 study	Tumor HRD status	Yes	Phase III	NCT01968213
Ovarian cancer FIGO III-IV (after first-line platinum)	olaparib vs placebo	Deleterious *BRCA1/2m*	Yes	Phase III	NCT01844986
Breast cancer (metastatic/recurrent)	talazoparib vs Physician's choice EMBRACA study[φ]	*gBRCA1/2m*	Yes	Phase III	NCT01945775
Breast cancer** (metastatic)	olaparib vs Physician's choice OLYMPIAD study	*gBRCA1/2m*	Yes	Phase III	NCT02000622
Breast cancer[ɤ] (HER2 negative)	niraparib vs physician's choice	*gBRCA1/2m*	Yes	Phase III	NCT01905592

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Table 2
Selected ongoing combination clinical trials with a PARP inhibitor

Tumor type/eligibility	Experimental Combination	Randomized	Phase	NCT number
Solid tumors (metastatic)[1]	olaparib and AZD5363	No	Phase I	NCT02338622
Triple (-) Breast cancer or Ovarian cancer	olaparib+BKM120 or BLY719	No	Phase I	NCT01623349
Ewing's sarcoma (previously treated)	niraparib+temozolomide	No	Phase I	NCT02044120
Breast cancer (inoperable/inflammatory/metastatic)	Olaparib+radiotherapy	No	Phase I	NCT02227082
Triple (-) Breast cancer or Ovarian cancer[2]	Olaparib+mTORC1/2i or AZD5363 (AKTi)[3]	No	Phase Ib	NCT02208375
Triple (-) Breast Cancer or Ovarian Cancer	cediranib+olaparib vs olaparib	Yes	Phase I/II	NCT0116648
Non-small cell lung cancer (stage III)	Veliparib+paclitaxel/carbo (VPC) +XRT followed by VPC consolidation	Yes	Phase I/II	NCT02412371
Refractory solid tumors[4] (Phase II: Ewing's and ALL)	BMN 673 (talazoparib)+/-temozolomide	No	Phase I/II	NCT02116777
Small Cell lung cancer	Veliparib+carboplatin/etoposide	Yes	Phase I/II	NCT02289690
Advanced Solid tumors	NCI-MPACT[5] veliparib + temozolomide	Yes	Phase II	NCT01827384
Glioblastoma Multiforme (newly diagnosed)	Temozolamide+/-veliparib[6]	Yes	Phase II/III	NCT02152982
Breast cancer (HER2neg or g*BRCA*m)	Carboplatin+paclitaxel with veliparib or placebo	Yes	Phase III	NCT02163694