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The Emerging Role of PARP Inhibitors in the Treatment of Prostate Cancer

Jue Wang, Brent B. Freeman and Paul Mathew

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Abstract

Poly (ADP-ribose) polymerase (PARP) is a critical DNA repair enzyme involved in DNA single-strand break repair through the base excision repair pathway. PARP inhibitors have been shown to sensitize tumors to DNA-damaging agents and selectively kill homologous recombination repair-defective cancers, such as those arising in BRCA1 and BRCA2 mutation carriers. In addition to its well-documented role in DNA damage repair (DDR), emerging evidence has indicated that PARP1 plays an important role in mediating the transcriptional activities of androgen receptor (AR) and ETS gene rearrangement in prostate cancer. Preclinical and clinical research suggested that the activity of PARP inhibitors is not limited to those with BRCA mutations. PARP inhibitors may have activity in cancers deficient in other DNA repair genes or signaling pathways that mitigate DNA repair.

Based on results of the TOPARP-A Phase 2 trial, the US Food and Drug Administration (FDA) has granted Breakthrough Therapy designation to olaparib (Lynparza) for monotherapy treatment of BRCA1/2 or ataxia telangiectasia mutated (ATM) gene mutated in patients with metastatic castration-resistant prostate cancer who received a prior taxane-based chemotherapy and at least one newer hormonal agent. Future research is needed to address the optimal timing, combination, and to identify predictive biomarker for PARP inhibition.

Keywords: prostate cancer, BRCA1, BRCA2, poly(ADP-ribose) polymerases, PARP inhibitors

1. Introduction

Prostate cancer is the most commonly diagnosed cancer in men and is the second leading cause of cancer-related deaths in men each year [1]. Androgen-deprivation therapy has been the gold standard of care for metastatic prostate cancer for decades. While this treatment strategy initially shows benefit, the disease inevitably progresses to metastatic castration-resistant prostate cancer (mCRPC) for which there is limited treatment options [2]. Although chemotherapies, immunotherapy, and novel androgen signaling pathway inhibitors therapies [3–7] have shown some benefit, mCRPC remain incurable with overall survival well under 5 years. Further development of novel agents is needed for the treatment of prostate cancer.

2. Poly(ADPribose) polymerase and DNA repair

Prostate cancer, like most other cancers, is a genetic disease resulting from the accumulation of genetic alterations that enable cancer cells to survive, proliferate, and metastasis [8, 9]. Such enrichment of genomic instability could be attributed to diminished DNA repair in mCRPC [8–11]. To maintain genomic integrity, there exists conserved checkpoint signaling pathways to facilitate cell cycle delay, DNA repair, and/or apoptosis in response to DNA damage [11].

BRCA1 and BRCA2 are the best characterized DNA repair genes associated with cancer development [12]. Germline-mutated prostate cancer is particularly frequent in young patients (<65 years), with BRCA2 more prevalent than BRCA1 (1.4 and 0.44% of all prostate cancer, respectively). Germline mutation carriers have higher Gleason scores, lower overall survival (OS) and cancer-specific survival, higher advanced stages, and globally a worse prognosis compared with noncarrier patients [13]. BRCA proteins have a crucial role in the regulation of homologous recombination (HR) repair, an accurate DNA double-strand break (DSB) repair process. In the absence of BRCA (and other HR proteins), DNA DSBs increase which induce the accumulation of DNA mutations and thereby promotes tumorigenesis. Although BRCA dysfunction promotes an oncogenic advantage, it also renders cancer cells reliant on alternative DNA repair pathways, such as base excision repair (BER).

Poly(ADPribose) polymerase (PARP) are a family of enzymes that catalyze Nicotinamide adenine dinucleotide (NAD) NAD⁺-dependent ADP ribosylation of DNA. PARP1 has been implicated in several DNA repair mechanisms, including DNA single-strand breaks (SSB) which repair through the BER pathway. PARP1 recognizes DNA SSB and orchestrates the recruitment and assembly of a DNA repair complex [14, 15]. As a result, PARP inhibition induces the accumulation of unrepaired SSB, which are subsequently converted into DSBs at fork replication. Cells with deficient HR repair systems (i.e., for BRCA1/2 mutations) treated with PARP inhibitors are overcome by DNA DSBs, which lead to further chromosomal instability, cell cycle arrest, and apoptosis [16]. Therefore, PARP-1 is an important therapeutic target in cancer therapy including prostate cancer, especially in patients harboring the BRCA mutations.

3. PARP-1 and prostate cancer

Several lines of evidence point to a potential role of PARP-1 in prostate cancer progression. PARP-1 expression is markedly elevated in prostate cancer relative to that in benign prostatic hyperplasia (BPH) tissues, which may imply the involvement of PARP-1 and PAR in the development of prostate cancer [17]. Augmented immunodetection of PARP-1 was associated with prostate cancer progression and biochemical recurrence [18].

In addition to its well-documented role in BER, emerging evidence has indicated that PARP1 plays an important role in mediating the transcriptional activities of androgen receptor (AR) and ETS gene rearrangement [19]. PARP inhibition results in antitumor activity in TMPRSS2-ERG rearranged cancer models and suppresses AR target gene expression and tumor proliferation [20]. PARP-1 regulates Smad-dependent responses to Transforming growth factor beta (TGF- β) signaling and potential AR activity, directing both toward epithelial-mesenchymal transition (EMT) in prostate cancer progression [21]. PARP-1 has also been implicated at the chromatin level in AR-mediated cell proliferation in the early and late-stage prostate cancer models [22], with suppression of PARP-1 resulting in reduced cell proliferation. In androgen-independent PC3 cells, PARP inhibition significantly decreased cell viability, migration, invasion, chromatin loop dimensions, and histone acetylation. Thus PARP could play a key role in the compartmentalization of chromatin and in the development of the more aggressive phenotype [23].

4. BRCAness and prostate cancer

McCabe et al. [24] demonstrated that deficiencies of several proteins in the HR DNA repair pathway, such as the DNA damage sensors ataxia telangiectasia mutated (ATM) and ataxia telangiectasia (ATR and RAD3-related protein), lead to HR deficiency and subsequent PARP inhibition sensitivity. This concept known as 'BRCAness' has been used to describe the phenotype arising in sporadic cancers that have intact BRCA1/2 genes but share features with the BRCA1/2 mutation-related tumors, such as profound platinum sensitivity [25]. For example, based on its high proliferation rate, sensitivity to platinum-based therapy and the rapid development of chemotherapy resistance [26], small cell/anaplastic prostate cancer clearly fits into the clinical phenotype of BRCAness. Studies of these tumor samples at the DNA level will likely reveal genetic alterations in DNA repair genes. Theoretically, PARP inhibitors may enhance the chemotherapy-induced DNA damage in anaplastic/small cell prostate cancer.

While only a minority of prostate cancer patients carry germline mutations, emerging data suggest that HR defects are common in prostate cancer, potentially conferring a BRCAness phenotype [26–29]. Recent genetic studies have shown somatic mutations of the DNA HR repair system in more than 20% of the patients with CRPC. The genes identified are involved in different steps and mechanisms of HR machinery [29]. In an extensive genome analysis, Robinson et al. compared genetic sequencing data of castration sensitive and CRPC. BRCA2

was the most frequent mutations occurring in 12.7% of cases. Interestingly, the analysis of other DNA repair genes showed overall DNA repair gene aberrations in 22.7% of patients, with ATM and BRCA1 alterations occurring most frequently (in 19.3% of patients). In addition, 3.4% of patients have CDK12, FANCA, RAD51B, and RAD51C mutations [29]. These patients represent a distinct subtype with unique clinical characteristics that have important implications for management.

5. Active clinical trials investigating PARP inhibitors in prostate cancer

The evidence correlating increased PARP-1 activity with tumor progression has opened a new avenue for the utilization of PARP inhibitors, which may impair the DNA repair machine. The clinical experiences with PARP inhibitors initially focused on patients carrying mutations of the BRCA1 or BRCA2 genes, which have been linked to increased sensitivity to PARP-1 inhibitors. Additional evidence has shown that tumors with other mechanisms of impaired DNA repair might benefit from treatment with PARP inhibitors. In addition to the use of single-agent, the PARP inhibitors have been studied in combination with a number of different agents in prostate cancer (Table 1) and other cancers (Table 2). Other areas of active investigation include the development of biomarkers that may predict clinical benefit from PARP inhibition, as well as the identification of resistance mechanisms to PARP inhibitor therapy.

Agent(s) [Phase]	Cancer	Identifier
Olaparib + Arbiraterone [II]	Metastatic castration-resistant prostate cancer	NCT01972217
Veliparib + Arbiraterone [II]	Metastatic castration-resistant prostate cancer	NCT01576172
Enzalutamide + Niraparib [I]	Metastatic castration-resistant prostate cancer	NCT02500901
Olaparib + Radical prostatectomy [I]	Intermediate/high-risk prostate cancer	NCT02324998

Table 1. Ongoing clinical trials (Phase I/II) with PARP-1 inhibitors combination for prostate cancers (www.clinicaltrials.gov).

5.1. PARP inhibitors as single-agent therapy

In a Phase I clinical trial with olaparib, 60 patients with various refractory caners were enrolled and treated. Objective antitumor activity was reported only in BRCA mutation carriers, all of whom had ovarian, breast, or prostate cancer and had received multiple treatment regimens. Three patients with mCRPC were recruited, and one of them had a BRCA2 mutation [30]. The patient with BRCA2 mutation had >50% decrease in serum prostate-specific antigen (PSA) levels and a complete response of bone lesions.

Niraparib was tested in a Phase 1 dose-escalation study of 21 mCRPC patients. The investigators reported 43% of the patients with stable disease, and a median duration of response of 254 days. In total, 30% of the patients had a decrease of circulating tumor cells (CTC), and one of the 21 patients enrolled had >50% PSA reduction. Importantly, the authors did not observe

the hypothesized correlation between ERG rearrangements or loss of PTEN expression and treatment response [31].

Agent(s) [Phase]	Cancer	Identifier
PET imaging of PARP activity in cancer [0]	Solid tumors	NCT02469129
Veliparib and SCH727965 (Dinaciclib) [I]	Advanced solid tumors	NCT01434316
Olaparib and AKT inhibitor AZD5363 [I]	Solid tumors	NCT02338622
Olaparib (AZD2281) alone and in combination with AZD1775, AZD5363, or AZD2014 [I]	Molecularly selected patients with solid tumors	NCT02576444
Anti-PD-1 monoclonal antibody BGB-A317 in combination with the PARP inhibitor BGB-290 [I]	Solid tumors	NCT02660034
Molecular profiling-based assignment of cancer therapy Everolimus/Afinitor (mTOR inhibitor), Trametinib DMSO (MEK inhibitor), Temozolomide and ABT-888 (PARP inhibitor), and Carboplatin and MK-1775 (Wee1 inhibitor) [I]	Solid tumors that are metastatic or cannot be removed by surgery and liver or kidney dysfunction	NCT01366144
Veliparib + Topotecan [I/II]	Solid tumor, ovarian, peritoneal cavity tumors	NCT01012817
Olaparib + AZD5363 [I]	Solid tumor	NCT02338622
Rucaparib [I/II]	Patients with gBRCA mutation solid tumor, breast cancer	NCT01482715
Fluzoparib [I]	Solid tumors	NCT02575651
E7449; E7449 + TMZ; E7449 + Carbo + Pacli [I/II]	Solid tumor, ovarian, breast, melanoma, B-cell malignancy	NCT01618136

Table 2. Ongoing clinical trials (Phase I/II/III) with PARP-1 inhibitors for other cancers (www.clinicaltrials.gov).

In a Phase II clinical trial evaluating the efficacy and safety of olaparib in a spectrum of BRCA1/2-associated cancers, the authors reported 50% response rate, 25% stable disease, and an overall median duration response of 327 days in eight previously heavily treated mCRPC patients with germline BRCA1/2 mutations. Median progression-free survival was 7.2 months with 62.5% of the patients still progression-free at 6 months. Moreover, the Overall Survival (OS) was 18.4 months, with 50% of the patients was still alive at 12 months [32].

The publication of the Phase II clinical trial, TOPARP-A, which tests the efficacy of olaparib in mCRPC patients [33] generated a lot of excitement in prostate cancer field. Fifty mCRPC patients previously treated with docetaxel, most of whom had also been previously treated with abiraterone (Zytiga®) or enzalutamide (Xtandi®), received oral olaparib 400 mg twice daily in 28 day-cycles until disease progression. All patients had received docetaxel; 98% had received abiraterone or enzalutamide; and 58% had received cabazitaxel. Patients underwent

biopsies at baseline and during therapy for whole-exome sequencing and transcriptome studies. The primary endpoint was response rate, PSA response, or conversion of the baseline circulating tumor cell count. Sixteen of the 49 patients who could be evaluated had a response rate of 33%, with 12 patients receiving the study treatment for more than 6 months. Median overall survival was 10.1 months. Next-generation sequencing identified homozygous deletions, deleterious mutations, or both in DNA-repair genes—including BRCA1/2, ATM, Fanconi's anemia genes, and CHEK2—in 16 of the 49 patients who could be evaluated (33%). Of these 16 patients, 14 (88%) had a response to olaparib, including all 7 patients with BRCA2 loss (four with biallelic somatic loss and three with germline mutations) and 4 of 5 with ATM aberrations. Anemia and fatigue were the major treatment-related adverse effects. The mutational status of the ERG oncogene and that of the PTEN tumor suppressor gene was not associated with olaparib responses. TOPARP-B, the second stage of this trial, is ongoing and aiming to validate findings of TOPARP-A. Part B of TOPARP (TOPARP-B) is open to the recruitment and aims to recruit a total of 88 patients. Potential participants will have their tumor tissue analyzed and only those with biomarkers predictive of olaparib response will go on to enter TOPARP-B. Forty-four patients will receive 300 mg twice daily, and 44 will receive 400 mg of olaparib twice daily. Part C (TOPARP-C) will be the subsequent Phase II randomized, double-blind, placebo-controlled evaluation of olaparib and is currently in development.

5.2. PARP inhibitors in combination therapy

5.2.1. *Combining the PARP inhibitor with cytotoxic chemotherapy*

Preclinical research has provided a strong rationale for employing PARP inhibitors as chemosensitizers in combination with cytotoxic agents. The PARP inhibitor veliparib has been shown to enhance the antitumor activity of Temozolomide (TMZ) in prostate cancer xenografts [34]. This formed the rationale for testing the safety and efficacy of veliparib and TMZ in 26 patients with mCRPC pretreated with docetaxel [35]. Despite the promising preclinical activity, this combination showed modest activity over TMZ monotherapy. Two patients had a confirmed PSA response and four patients had stable disease (SD) for at least 4 months. The median progression-free survival (PFS) and OS were 2.1 and 9.1 months, respectively. One patient had the TMPRSS2:ERG gene fusion, and this patient achieved stable disease with a progression-free survival of 70 days and overall survival of 277 days. Grade III/IV thrombocytopenia was noted in 15% of patients.

5.2.2. *Combining the PARP inhibitor with androgen deprivation therapy*

The preclinical findings of PARP1 in mediating transcriptional regulation by AR and the ETS fusion protein [20–23] and the potential preclinical synergy of targeting of the PARP and AR pathways provide a strong rationale for the clinical evaluation of combining of these two classes of anticancer drugs.

The primary objective of a multicenter randomized Phase II trial (NCT01576172) is to evaluate whether adding veliparib to abiraterone acetate and prednisone would improve the PSA response rate of the standard abiraterone acetate and prednisone regimen in patients with

mCRPC. Secondary and exploratory objectives include PSA decline rate, objective response rate, progression-free survival and toxicity. The investigators will evaluate ETS fusion status in metastatic tumor tissue, and a logistic model will be used to determine the association of TMPRSS2-ERG fusion status with the PSA response in the veliparib plus abiraterone and prednisone arm. This study will provide validation on the value of ETS gene rearrangement as a predictive biomarker for PARP inhibitor-based therapy for mCRPC.

Another Phase I trial evaluating the combination of PARP inhibitor niraparib and enzalutamide (NCT02500901) was recently activated. The primary goal of this study is to assess whether patients with AR-regulated CRPC can be assessed for synergistic clinical benefit from dual AR blockade and PARP-1 inhibition, with the combination of enzalutamide and niraparib. Secondary and exploratory objectives include PSA kinetics, progression-free survival, and objective response. Correlative studies using quantitative and qualitative measures of CTCs to identify a predictive biomarker of response to the combination. These include dynamic studies of AR and AR splice variant nuclear localization and feasibility studies aim to assess homologous repair deficiency in CTCs.

5.2.3. Combining the PARP inhibitors with radiotherapy

Preclinical study with prostate cancer cell lines reported that combining the PARP inhibitor rucaparib with radiation enhanced the DNA damage and antitumor effects compared with radiation alone. The strongest synergistic activities were observed in LNCaP and VCaP cells, which contain the TMPRSS2-ERG fusion gene [36–38]. However, no association was noted between the loss of PTEN expression and ETS rearrangements, with radiologic assessment of the antitumor activity of niraparib in a Phase I trial [31]. At the present time, there are no active clinical trials investigating the combination of radiation therapy with PARP inhibition in mCRPC.

The combination of a PARP inhibitor with radiation would be an attractive strategy for newly diagnosed ETS fusion-positive, locally advanced, high-risk prostate cancer in adjuvant or neoadjuvant setting, or nonmetastatic CRPC at recurrent setting. However, the risk of overtreatment and long-term safety are the main concerns of testing this strategy.

Combining PARP inhibitors with radiation or radiopharmaceuticals such like Xofigo® (radium 223) could be another reasonable combination for patients with mCRPC to the bone. Currently, there is no active trial testing the combination.

5.2.4. Combining the PARP inhibitors with molecularly targeted drugs

In a Phase II clinical trial (NCT02576444), the investigators evaluated the safety of combining the AKT inhibitor AZD5363 with olaparib. The authors reported that the novel combination of olaparib and AZD5363 was safe and yielded responses in patients with a variety of cancer types, including breast, ovarian, and prostate cancers, regardless of BRCA1/2 mutation status. One patient with BRCA1/2-mutant advanced prostate cancer had a sustained response both by MRI and PSA Working Group 2 response criteria at 11 months. The most commonly observed side effects were nausea, vomiting, fatigue, diarrhea, and anemia.

Several other trials combining the PARP inhibitor with other molecularly targeted drugs are ongoing (**Tables 1 and 2**).

5.2.5. *preoperative (neoadjuvant) studies of PARP1 inhibitors*

The testing of novel agents in the preoperative (neoadjuvant) setting approach offers a potentially rapid and efficient strategy for drug development. Neoadjuvant studies allow the assessment of drug effects on the target (pharmacodynamic response) and the development of predictive biomarkers of response.

A Phase I study investigating the feasibility and tolerability of a short course of neoadjuvant treatment with olaparib given prior to radical prostatectomy in men with localized intermediate-/high-risk prostate cancer is ongoing (NCT02324998). The primary objective is to determine the pharmacodynamic biomarker effects of olaparib in this patient population. Participants will receive either single-agent olaparib, or olaparib in combination with degarelix (androgen deprivation), for one week prior to routine radical prostatectomy. The degree of PARP inhibition will be measured by the change in immunohistochemistry (IHC) levels of biomarkers such as PAR, gamma H2AX, pH2A (s129), Rad51 foci, FancD2 foci, and ATM/ATR/CHK1/2 in tumor samples taken at baseline and following treatment with olaparib (either alone or in combination with degarelix). Secondary outcome measures include the incidence and severity of adverse events caused by treatment for 7 days with olaparib (either alone or in combination with degarelix) prior to radical prostatectomy [41].

5.3. Safety of PARP inhibitors

The toxicity profile of PARP inhibitor monotherapy appears to be similar to cytotoxic chemotherapeutic agents [30–33, 39]. The most frequently reported adverse events in published studies are grade 1–2 nausea, vomiting, diarrhea, fatigue, headache, and anemia. Grade 3 or 4 toxicities are rare in early phase clinical trials in patients with prostate cancer being treated with a single-agent. The most common grade 3–4 toxicities were nausea, vomiting, and hematological toxicity, with anemia, lymphopenia, and thrombocytopenia being the most common dose-limiting toxicities in dose-finding studies [31, 32]. In a Phase II trial, in which patients with mCRPC were treated with olaparib tablets at a dose of 400 mg twice a day, anemia (20%) and fatigue (12%) were the most common grade 3 or 4 adverse events. These findings are consistent with previous studies of olaparib [33].

Conversely, dose-limiting toxicities observed in trials of PARP inhibitors in combination with cytotoxic agents include primarily hematologic toxicities. For example, olaparib in combination with cisplatin and gemcitabine is associated with myelosuppression even at relatively low doses in a Phase I study of patients with advanced solid tumors [40]. An intermittent schedule of PARP inhibition instead of continuous dosing was investigated [41].

At this time, the long-term safety data on the PARP inhibitors is still lacking. Enhanced DNA damage with a PARP inhibitor and radiation may lead to genomic instability and more aggressive prostate cancer and secondary malignancy. Few cases of myelodysplastic syndrome and acute myeloid leukemia have been reported in PARP inhibitor trials; most of the

patients had been treated with DNA-damaging classic chemotherapeutic agents. Nonetheless, the potential increased risk of developing secondary cancer from DNA damage warrants close attention in future development of PARP inhibitors, especially in the neoadjuvant and adjuvant settings [42].

5.4. Biomarkers for PARP-directed therapy

The ultimate clinical need in the development of PARP-directed therapy is to identify biomarkers to enrich selection of patients who are most likely to respond to therapy [43]. As monotherapy, findings from clinical trials with olaparib showed that genetic biomarkers could be used to select the patients with mCRPC who will respond to PARP inhibitor therapy. The HR/PARP synthetic lethality model may be more widely applicable in prostate cancer with germline or somatic inactivating mutations in the HR DNA repair genes, CHK2, BRIP1/FANCD1, NBS1, BRCA1, and ATM, collectively estimated to occur in 20–25% of prostate cancer cases. Two of the most common genetic alterations in prostate cancer, TMPRSS2: ERG gene fusion, ETS gene rearrangement, and loss of PTEN, have also been linked to increased sensitivity to PARP inhibitor in preclinical models [37, 38]. However, this association has not been confirmed in clinical study [31]. Regardless, these results underscore the complexity and challenge in developing a biomarker for PARP inhibitor activity. Although additional synthetic lethal strategies have been explored in preclinical, or early clinical trial setting [44–47], development of a clinically validated biomarker (companion diagnostic) will depend on the results of well-designed and conducted Phase III clinical trials.

It is clear that the individual clinical response to PARP inhibition is varied and that currently accepted markers of response (progression-free survival, RECIST, PARP inhibition in peripheral blood mononuclear cells, or hair follicles) are not ideal [48]. The availability of direct imaging tests capable of measuring PARP inhibition locally would thus be of enormous value in such settings [49]. A new radiolabeled compound (^{18}F) FluorThanatrace ([^{18}F] FTT), has been generated which can be used to measure PARP1 activity noninvasively and quantitatively using positron emission tomography (PET). Preclinical models show that the uptake of this compound is specific for PARP1 activity and correlates with biochemically determined PARP1 activity. Additional data also suggests that decreased (^{18}F) FTT uptake predicts tumor response to PARP inhibition with olaparib. A Phase 0 study investigating the feasibility of PET imaging of PARP activity in cancer (NCT02469129) recently opened for enrollment. This technology provides both a biomarker for patient selection as well as a means of monitoring PARP activity during treatment.

6. Conclusion

Approximately 30% of mCRPC exhibit defective DNA repair via HR, representing a distinct subtype with unique clinical characteristics that have important implications for management. PARP inhibitors are an exciting new class of agents that have already demonstrated promising preclinical and clinical activity in mCRPC. Recent Phase I and II studies have reported single-

agent activities with favorable side effect profiles in sporadic and in BRCA-mutant prostate cancers. Based on results of the TOPARP-A Phase II trial, the US FDA has granted Breakthrough Therapy designation to olaparib (Lynparza) [50], for monotherapy treatment of BRCA1/2 or ATM gene mutated mCRPC in patients who received a prior taxane-based chemotherapy and at least one newer androgen signaling inhibitor. Currently, there are seven different PARP inhibitors in clinical development for cancer. As we learn more about these agents through ongoing trials, it will be important to identify biomarkers that predict patients who may benefit the most from PARP inhibitor therapy. In addition, it will be important to determine the optimal timing, sequence and clinical setting (neoadjuvant, adjuvant, or maintenance), either as monotherapy or in combination.

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