Neoplasma 2021; 68(6): 1132–1138

doi:10.4149/neo_2021_210627N856

Research progress on the treatment of advanced prostate cancer with Olaparib

Minireview

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Received June 27, 2021 / Accepted October 7, 2021

Prostate cancer (PCa) is one of the most common malignancies in men worldwide, and metastatic castrate-resistant prostate cancer (mCRPC) has shown a poor prognosis. Although chemotherapy and androgen deprivation therapy (ADT) have improved clinical outcomes, the median survival (MS) of patients with mCRPC is still less than 2 years. With the development of poly adenosine diphosphate-ribose polymerase inhibitor (PARPi), the treatment strategy for patients with mCRPC has markedly evolved. Olaparib, a type of PARPi that can selectively induce synthetic lethality in cancer cells with homologous recombination (HR) deficiencies, was the first type of PARPi approved for treating patients with mCRPC harboring mutations in HR repair (HRR) genes. This review discusses and summarizes the latest progress on therapeutic mechanisms, monotherapy, combination therapy, and adverse events of Olaparib.

Key words: Olaparib, advanced prostate cancer, research progress, homologous recombination repair, synthetic lethality

According to the 2020 global cancer statistics [1], prostate cancer (PCa) ranks second in incidence and fifth in mortality among male malignant tumors worldwide. Besides, the incidence of PCa is the first among male malignant tumors, and its mortality rate ranks second according to the statistics released by the American Cancer Society [2]. To our knowledge, the treatment of localized prostate cancer (LPC) is mainly supported by radical surgery and radiotherapy, while 6% of patients have metastasis at the initial diagnosis [3], and androgen deprivation therapy (ADT) is given priority. However, after 2–3 years [4] of treatment, a patient may inevitably progress to castrate-resistant prostate cancer (CRPC). Although chemotherapy and ADT have improved clinical outcomes, the median survival of patients with metastatic CRPC (mCRPC) is still less than 2 years [5].

PCa is a highly heterogeneous malignancy, with variations in genetic mutations at different stages of the disease [6]. Abida et al. [6] performed targeted deep sequencing of tumor and normal DNA from patients with locoregional, metastatic non-castrate, and mCRPC. Their results showed that a large genomic dataset representing the clinical spectrum of PCa can provide mechanistic insight into possible genomic drivers of disease initiation, metastasis, and drug resistance. In addition, tumors that were profiled represented all three clinical classes of PCa: locoregional, metastatic non-castrate, and mCRPC. In total, 348 (77%) patients had mPCa, 53 (12%) had biochemical recurrence after definitive therapy, and 50 (11%) had a locoregional disease. It is noteworthy that PCa with DDR gene mutations is characterized by a remarkable invasion, a high level of malignancy, and a poor clinical prognosis [7]. A recent study reported that 22% of patients carried somatic alterations in the homologous recombination (HR) pathway, including BRCA (9.7%), ATM (5.9%), and other HR-associated genes (12.3%) [8], which were roughly consistent with the results of other clinical trials that explored key genes in mCRPC [9, 10].

The development of next-generation sequencing (NGS) technologies and targeted therapies have provided new insights into the treatment of PCa patients. Studies have shown that PCa is a highly heterogeneous malignancy, and with the progression of the disease, the probability of DNA damage response (DDR) gene mutations in mCRPC patients is increasing, while PCa with DDR gene mutations is characterized by a remarkable invasion, high level of malignancy,

and a poor prognosis [6, 7]. On December 19, 2018, the United States Food and Drug Administration (FDA) granted approval to Olaparib (OLA) monotherapy for the first-line maintenance treatment of BRCA-mutated (BRCAm) advanced ovarian cancer and, on May 8, 2020, expanded the indication of OLA to include its use in combination with bevacizumab for the first-line maintenance treatment of HR deficiency (HRD)-positive advanced ovarian cancer. Clinical trials have demonstrated that a single agent or in combination with endocrine therapy can be highly significant for patients with mCRPC. This review discussed and summarized the latest progress of therapeutic mechanisms, monotherapy, combination therapy, and adverse effects of OLA.

Therapeutic mechanisms

Genome stability is of great significance for cells to maintain physiological functions, whereas ionizing radiation, chemical poisons, and errors during DNA replication may cause DNA damage, highlighting the necessity of timely and accurate identification and treatment [11]. In order to maintain genomic integrity, the cell has evolved a DDR pathway, a multitier signaling pathway involving multiple, functionally diverse proteins. The major pathway for DNA single-strand damage (SSB) repair consists of base excision repair (BER), mismatch repair (MMR), etc. DNA double-strand breaks (DSBs) are repaired by non-homologous end-joining (NHEJ) and HR, and defects in these pathways cause genome instability and promote tumorigenesis [12]. DSBs are generated in a programmed manner as part of important cellular processes, such as the maturation of lymphoid cells or gametogenesis during meiosis. In both cases, specific enzymes are involved in the production of DSBs that are generated under stringent control, mostly at pre-defined locations in the genome. In cancer therapy, the lethal effects of randomly induced DSBs are exploited to eliminate actively proliferating tumor cells [13].

PARP was first identified in 1963 as a nuclear enzyme responsible for the majority of poly(ADP-ribosyl)ation activity. It is a critical enzyme involved in DNA repair and several other cellular processes [14]. Among all the 17 members of the PARP family, PARP-1 accounts for 90% of PARP activity and plays a significant role in SSB repair by the BER pathway [15]. Upon binding to damaged DNA, PARP-1 forms homodimers that activate PARP-1 catalytic activity, and catalyze the cleavage of nicotinamide adenine dinucleotide (NAD+) into nicotinamide and adenosine diphosphate ribose (ADPR). Using ADPR as a substrate, PARP-1 promotes the formation of poly (ADP-ribose) (PAR) polymer and exerts diverse biological effects, such as unraveling chromatin, recruiting several DNA repair proteins to repair damaged SSB, including X-ray repair complementing defective repair in Chinese hamster cells 1 (XRCC1) and DNA ligase III [16]. Besides, DNA repair proteins, e.g., ataxia telangiectasia-mutated (ATM) kinase, may cause inactivation of DNA-dependent protein kinase, stimulating HR/NHEJ pathways to repair DSB damage [17]. PARPi prevents SSB repair and results in DSBs by trapping PRRP protein on DNA. In cells with HRD, DSB cannot be accurately repaired and induces accumulation of DNA damage, contributing to synthetic lethality [18]. PARP pathway plays a pivotal role in DNA repair, and BRCA1 is an essential factor in the repair of DSBs via the HR pathway. Therefore, the use of PARPi can cause failure in DNA repair and eventually lead to the death of tumor cells. OLA [19] is the first approved type of PAPRi by the United States Food and Drug Administration (FDA) that has been exploited to target tumor cells using synthetic lethality.

Mechanisms of PARPi resistance

Although OLA has shown promising therapeutic efficacy in both monotherapy and combination regimens for PCa, it also faces drug resistance as other targeted therapies [20]. Distinct heterogeneous mechanisms underlying the resistance to PARPi have been previously described, including restoration of HR repair, decreased PARP trapping, increased drug efflux, and the protection of the replicative fork [21].

The most common mechanism of resistance to PARPi is the restoration of the functionality of BRCA1 or BRCA2 protein by secondary mutations [22]. Recently, the prevalence of BRCA reversion mutations in mCRPC was estimated. Using a large genomic database, 24 gBRCAm carriers were selected from 1,534 patients with mCRPC who underwent ctDNA testing. In this germline mutation-positive, platinum- or PARP-exposed cohort, the frequency of BRCA2 reversion mutations was 40% [23]. With the aid of liquid biopsy or circulating cell-free DNA, numerous BRCA reversion mutations (N1910_D1911del, L1908_S1917del) have been discovered to restore the open reading frame (ORF) of BRCA1/2 and confer the resistance to PARPi-based therapy [24]. Moreover, secondary somatic mutations restoring Rad51C and Rad51D were also demonstrated to be associated with acquired resistance to the PARPi [25]. As DNA end resection promotes HR repair and is dependent on the activity of cyclin-dependent kinases (CDKs), it is likely that CDKs play a key role in resistance to PARPi. It was reported that CDK12 was identified as a determinant of OLA in the models of high-grade serous ovarian carcinoma (HGSOC) by genome-wide synthetic lethal screen [26]. CDK5-silenced Hela cells were more sensitive to PARPi [27]. Accessory factors, including 53BP1, REV7, and RIF1 that can regulate DNA end resection, greatly contribute to resistance to PARPi [28–30].

The pharmacological alteration also modulates PARPi inhibitor response. PARPis are substrates of multidrug resistance protein (MDR1, P-gp), encoded by the ABCB1 gene [31]. The enhanced P-gp-mediated drug efflux promotes the acquired resistance to PARPi [32]. Moreover, overexpression of ACBA1 has been associated with resistance to PARPi in both *in vivo* and *in vitro* studies [32, 33]. The EVOLVE

Table 1. Results of completed and on-going clinical trials involving Olaparib for mCRPC patients.

Study Name	Date	Phase	Patients characteristics	Number of patients	Experimental group	Control group	RR (%)	Median rPFS (month)	OS (month)	PSA RR (%)
NCT01682772 (TOPARP-A) [46]	October 2015	II	mCRPC	50	Olaparib	none	88[a]	9.8[a]	13.8[a]	NR
NCT01682772 (TOPARP-B) [44]	January 2020	II	mCRPC with DDR gene aberrations	98	Olaparib 400 mg bid	Olaparib 300mg bid	54.3/39.1[b]	5.5/5.6[b]	14.3/10.1[b]	37/30.2[b]
NCT02987543 (PROfound) [8, 47]	May 2020	III	mCRPC with HRR gene aberrations	387	Olaparib	Enzalutamide /Abiraterone	Cohort A: 33 vs. 2; Cohort A+B: 22 vs. 4	Cohort A: 7.4 vs. 3.6; Cohort A+B: 5.8 vs. 3.5	Cohort A: 19.1 vs. 14.7; Cohort B 14.1 vs. 11.5; Cohort A+B 17.3 vs. 14.0	Cohort A: 43 vs. 8; Cohort A+B: 30 vs. 10
NCT01972217 (study08) [51]	July 2018	II	mCRPC	142	Olaparib and Abiraterone	Placebo and Abiraterone	27	13.8	22.7	48
NCT02861573 (KEYNOTE-365) [56]	2020	IB/II	mCRPC	84	Pembrolizumab and Olaparib	none	8	4.3	14.4	9
NCT02484404 [57]	December 2018	II	mCRPC	17	Durvalumab and Olaparib	none	NR	16.1	NR	53

Notes: [a]in patients with DDR mutations; [b]in 400/300 mg cohorts. Abbreviations: mCRPC-metastatic castrate-resistant prostate cancer; HRR-homologous recombination repair; DDR-DNA damage response; RR-response rate; rPFS-radiographic progression-free survival; OS-overall survival; PSA RR-PSA response rate; NR-not reported

study enrolled 34 patients with ovarian cancer who had progressed during PARPi maintenance therapy. ABCB1 expression was upregulated in 15% of patients, and patients had a poor response to re-treatment with OLA combined with Cediranib [34].

As PARP-1 protein is the main target of PARPi, the PARP1 expression level is positively correlated with PARP inhibitor sensitivity. For instance, a low expression level of PARP1 is a potential cause of resistance to PARP inhibitors in patient-derived xenograft (PDX) models [35]. Furthermore, cells with PARP1 mutations were 100-fold more resistant to PARP inhibitors than cells with wild-type PARP1 [36].

In addition to DNA repair, PARP1 and BRCA1/2 participate in DNA replication. Both BRCA1 and BRCA2 protect nascent DNA at stalled replication forks from MRE11/DNA2-dependent degradation [37]. In patients with platinum-sensitive recurrent serous ovarian cancer, ovarian cancer cells lacking replication fork-related factors (BRCA2, RAD51, FANCD2, and FANCA) were found to be more sensitive to PARPi [38]. Restoration of replication fork stability in MRE11-deficient cells can lead to resistance to PARPi in tumor cells [39]. Besides, epigenetic modification and restoration of PARylation also lead to resistance to PARPi. For instance, the increased expression level and N6-methylation modification of FZD10 were confirmed in resistant PEO1 cells. FZD10 contributed to PARPi resistance by upregulating the Wnt/β-catenin pathway [40].

In terms of PARPi resistance, although multiple potential resistance mechanisms have been identified, the therapy to overcome PARPi resistance is still in its infancy and further researches are required to eliminate the mentioned deficiency.

Clinical trials

The efficacy of OLA has been demonstrated in other solid tumors with BRCA mutations [41–43]. Consequently, clinical trials concerning the administration of OLA for HRR gene-mutated mCRPC have been carried out successively, and it was suggested that patients can also benefit from an effective therapy (Table 1) [8, 44]. In May 2020, OLA was approved as a second-line treatment for mCRPC patients with HR repair gene mutations and emerged as an attractive alternative to conventional therapies for the clinical management of PCa.

Monotherapy. In 2009, Fong et al. [45] conducted a phase I clinical trial on OLA and enrolled a total of 60 patients with advanced malignant tumors. Their results revealed that the maximum tolerated dose (MTD) was 400 mg bid, and OLA was shown to be clinically significant, particularly for patients harboring BRCA gene mutations. Furthermore, OLA exhibited a favorable safety profile, accompanied with the most common adverse events

(AEs), such as nausea (32%), fatigue (30%), vomiting (20%), taste disorders (13%), and anorexia (12%). A landmark phase I study on OLA reported a more than 50% reduction in the prostate-specific antigen (PSA) level and resolution of bone metastases after 58 weeks of treatment in an mCRPC patient with germline mutations in BRCA2.

In 2018, a phase II single-arm study (TOPARP-A) [46] included 50 patients who have received multi-line therapy and evaluated the efficacy and safety of OLA for mCRPC patients. The OLA showed an overall response rate (ORR) of 33% (16/49 patients) in patients who no longer responded to standard treatments, and radiographic progression-free survival (rPFS) was extended by 7.1 months (9.8 vs. 2.7 months, $p<0.001$). Further analyses confirmed that ORR in patients with mutated BRCA and ATM was 100% and 80%, respectively. As a result, FDA granted breakthrough therapy designation to OLA for monotherapy treatment of BRCA1/2 or ATM gene-mutated mCRPC in patients who received prior taxane-based chemotherapy and at least one newer hormonal agent. TOPARP-B aimed to clinically qualify a predictive biomarker for treating mCRPC. TOPARP-B also assessed different doses of OLA and correlated different genomic aberrations and anti-tumor activity. That study confirmed the anti-tumor activity of OLA against mCRPC with defective DNA repair secondary to either germline or somatic gene inactivation. The number of composite responses observed in the cohort of patients who received 400 mg tablets of OLA twice daily met the predefined criteria for success, validating the DDR biomarker identified in TOPARP-A as being predictive of response. Overall, it was suggested that both drug dose and the specific type of DDR gene aberration might influence anti-tumor activity [44].

Subsequently, Bono et al. conducted a randomized, open-label, phase III trial evaluating OLA in male patients with mCRPC who had disease progression while receiving a new hormonal agent (e.g., enzalutamide or abiraterone) [8, 47]. In cohorts A and B, patients were randomized in a 2:1 ratio to receive OLA or abiraterone/enzalutamide, and it was revealed that OLA prolonged rPFS (5.8 vs. 3.5 months, $p<0.001$) and OS (17.3 vs. 14.0 months). In cohort A, OLA improved ORR (33% vs. 2%), significantly prolonged OS (19.1 vs. 14.7 months, $p=0.02$) compared with the control group, and the risk of disease progression was reduced by 66%. They found that in male patients with mCRPC who had BRCA1, BRCA2, or ATM mutations and had disease progression while receiving a new hormonal agent, OLA led to a significantly longer imaging-based PFS than the physician's choice of enzalutamide or abiraterone. Besides, the most frequent adverse events with the administration of OLA were anemia and nausea. The NCCN guidelines have already listed OLA as a first-level recommended drug for the treatment of mCRPC patients with HRR mutations that would be advanced by endocrine drugs.

Further clinical trials on the administration of OLA for early-stage PCa patients are ongoing, including preoperative neoadjuvant therapy (Registration Nos. NCT03432897 and NCT02324998), OLA for male patients with high-risk biochemically-recurrent PCa following radical prostatectomy (Registration No. NCT03047135), and maintenance therapy (Registration Nos. NCT03263650 and NCT03434158).

Combination therapy. The efficacy of OLA monotherapy for patients with mCRPC was well documented. However, combination therapy, in form of OLA+endocrine therapy/immunotherapy/etc., has markedly attracted clinicians' and scholars' attention. Fundamental studies [48–50] reported that PARP-1 is recruited to sites of androgen receptor (AR) function, thereby promoting the occupancy and functionality of AR. Besides, AR plays a critical role in the development and metastasis of PCa. Thus, PARPi combined with ADT has a potentially synergistic effect on the treatment of CRPC patients. A randomized, double-blind, placebo-controlled, phase 2 trial [51] was conducted to assess the efficacy of OLA plus abiraterone for patients with mCRPC, regardless of HRR mutation status. For this purpose, 142 patients were randomly assigned to either OLA or placebo group with an allocation ratio of 1:1. Results showed that the OLA group increased rPFS by 5.6 months (13.8 vs. 8.2 months, $p = 0.034$), while it had a higher incidence of grade 3 or worse AEs (54% vs. 28%). This study, for the first time, demonstrated that OLA in combination with abiraterone provided a clinical benefit for patients with mCRPC compared with abiraterone alone. More serious adverse events were observed in patients who received OLA+abiraterone than abiraterone alone. Hence, a phase III clinical trial, namely PROpel [52], is ongoing to evaluate the feasibility of OLA+abiraterone as first-line agents for mCRPC.

PARPi has a potential synergistic effect in combination with immune checkpoint inhibitors (ICIs) [53]. It cannot solely induce upregulation of PD-L1 in tumor cells, while it can induce the production of type I interferon (IFN) by activating the STING/TBK1/IRF3 signaling pathways to upregulate CCL5 and CXCL10, thereby enhancing the efficacy of ICIs [54, 55]. In 2020, Professor Anthony Joshua published updated results of pembrolizumab combination therapy for patients with mCRPC [56]: patients with mCRPC who received pembrolizumab plus OLA had a median rPFS of 4.3 months and the median overall survival (OS) was 14.4 months. A PSA decline ≥50% was recorded in 9% of patients, while 35% reported AEs with grades 3–4. Another small sample-sized phase II clinical trial [57] investigated the efficacy of OLA plus duvarizumab for the treatment of mCRPC. A total of 17 patients were enrolled, and a median rPFS of 16.1 months was recorded, accompanied by a ≥50% decline in PSA level in 53% of patients. Furthermore, 12-month PFS was significantly higher in DDR-mutated mCRPC patients (83.3% vs. 36.4%). The most common AEs with grade 3–4 were anemia (24%), lymphopenia (12%); infection (12%), and nausea (12%). The above-mentioned studies indicated that although an improvement in OS was observed in combination immunotherapy, a small sample

size and high incidence of AEs are unneglectable. Therefore, it is highly essential to further explore effectively combined immunotherapy regimens with minimum adverse effects.

Adverse events. Concerning AEs of OLA, the TOPARP and PROfound trials confirmed the safety of OLA for mCRPC, which was consistent with the safety profile observed in other single-agent OLA-based trials [41, 43]. It was reported that AEs of OLA included gastrointestinal reaction, fatigue, and anemia. In the phase III PROfound clinical trial, the most common AEs were anemia (50%), nausea (43%), fatigue (42%), anorexia (31%), diarrhea (21%), and vomiting (20%). Besides, AEs with grades 3–4 were anemia (23%), fatigue (3%), decreased appetite (2%), and nausea (2%). In addition, anemia (9%) and pneumonia (4%) were detected as the most common serious AEs (SAEs). Treatment was discontinued due to anemia in 7% of patients, while it was canceled due to fatigue, neutropenia, thrombocytopenia, and nausea in 1% of patients. Therefore, hematological toxicity is a major concern for patients taking OLA.

Discussion

At present, PARPi is well-known to play a significant role in the treatment of PCa. There is also feasibility of formulating individual treatment for PCa patients according to the results of NGS, leading to improved survival benefits. OLA is well-known as standard second-line therapy for BRCA-mutated mCRPC, and clinical trials are ongoing in both monotherapy and combination therapy, which may hold promise for the therapy of PCa. However, a number of deficiencies need to be truly treated. Firstly, in the PROfound trial, there were no statistically significant differences in OS in cohort B, thus, further studies are warranted to better clarify the role of OLA-associated biomarkers that may expand the beneficiary population. Secondly, it is highly essential to explore efficacy, safety, and mechanisms of combination therapy using OLA. Last but not the least, the therapeutic feasibility of PARPi combined with other therapeutic strategies (e.g., radiotherapy, platinum drugs, and antiangiogenic therapy) that may cause DNA damage should be further explored for PCa patients. Altogether, improving the clinical efficacy of OLA accompanied by alleviating AEs for PCa patients is of great significance clinically.

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