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Research Article

Olaparib outcomes in metastatic castration-resistant prostate cancer: First real-world experience in safety and efficacy from the Chinese mainland

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ABSTRACT

Background: Olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, has been approved for use in breast cancer susceptibility gene (BRCA)-mutated metastatic castration-resistant prostate cancer (mCPRC) patients. Our aim was to evaluate the adverse events (AEs) and efficacy of Olaparib in the treatment of mCRPC patients from the Chinese mainland.

Methods: We retrospectively included mCPRC patients treated with Olaparib more than for 28 days. Patients with alterations in 15 homologous recombination repair (HRR) genes were defined as the HRRmt group, and the rest were defined as the HRRwt group. The efficacy was analyzed by prostate-specific antigen (PSA) decreased rate and PSA progression-free survival (PFS). The partial response, good response, and high response of PSA were defined as a reduction of between 0% and 50%, greater than 50%, and greater than 90% from baseline.

Results: A total of 43 patients were enrolled in this study, including 26 HRRmt group patients and 17 HRRwt group patients. Two HRRwt patients received additional abiraterone therapy. A partial response, good response, and high response were achieved in 89% (23/26), 59% (15/26), and 15% (4/26) of HRRmt group patients, respectively. In HRRwt group, 59% (10/17), 35% (6/17), and 12% (2/17) of patients met the criteria of partial response, good response, and high response, respectively. Median PFS was 8.0 months in the HRRmt group and 3.0s months in the HRRwt group (HR, 0.61; 95% CI, 0.24–1.14; $p = 0.148$), respectively. All the 20 patients had AEs during Olaparib treatment. Ten episodes of grade 3 or 4 AEs were observed in four patients. The most common all-grade AEs were fatigue or asthenia (70%), anemia (65%), and decreased appetite (55%).

Conclusions: Most of the AEs were tolerated, and Olaparib was effective in mCRPC patients with HRR deficiency. In addition, the underlying mechanism of the efficacy of Olaparib observed in HRRwt group patients remained explored.

1. Introduction

Prostate cancer (PCa) is the most common cancer malignancy and the eighth leading cause of death among men worldwide[1]. PCa has been an important disease threatening the health of Chinese men, with 115,426 new cases and 51,094 deaths nationwide in 2020[1]. Even though localized PCa may be cured with radiotherapy or surgery, virtually most patients will eventually develop metastases and become androgen-independent, despite the suppression of gonadal androgens, which are considered to be incurable[2,3].

Tumors in up to 30% of patients had deleterious aberrations DNA damage repair genes[4–6]. Among these genes, *BRCA1* (*breast cancer susceptibility gene*), *BRCA2*, and other genes also act a direct or indirect role in activating homologous recombination repair (HRR)[7]. Tumors with loss-of-function alterations in these genes are sensitive to poly (ADP-ribose) polymerase inhibition (PARP)[8]. When DNA damage occurs in patients with HRR mutation (HRRm), tumor cells rely on other DNA repair mechanisms to prevent excessive

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DNA damage from leading cell to death. At this moment, the application of PARP could inhibit PARP-mediated DNA repair resulting in the lethal synthesis of tumor cells[9]. Olaparib is a highly effective oral PARP that has been approved for the treatment of prostate and other cancer[10–13]. The randomized phase III PROfound trial enrolled metastatic castration-resistant prostate cancer (mCRPC) patients with HRRm who had failed prior AR targeted therapy (abiraterone or enzalutamide). They found median overall survival (OS) was 17.3 vs. 14.0 months (hazard ratio [HR] = 0.79, 95% CI, 0.61-1.03) with Olaparib and the other AR targeted agent, respectively[14,15].

Although data from various studies had shown that Olaparib monotherapy is effective and safe in the treatment of mCRPC patients[14,15], there remains a question that whether already established data sources of Olaparib could be used to generate real-world evidence for mCRPC patients from the Chinese mainland. First, the efficacy of Olaparib in clinical trials could be different from its efficacy in the real world as the patient population from the clinical trials is a selected population that includes participants with more favorable prognostic factors than unselected general clinical practice population in the real world. Second, the PROfound trial did not include mCRPC patients from the Chinese mainland[16]. In this study, the adverse events (AEs) and efficacy of Olaparib for mCRPC patients in the real world were retrospectively analyzed.

2. Subjects and methods

2.1. Study population

This retrospective study was performed after the approval of the Human Ethics Committee of Fudan University Shanghai Cancer Center (FUSCC) and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all included participants for the use of clinical data. Patients with or without HRRm who had received Olaparib between December 2018 to February 2021 at FUSCC were enrolled. All patients took Olaparib for more than 28 days and were monitored until August 2021 for survival and discontinuation of Olaparib. Clinical information including basic information (such as age at diagnosis, Gleason score, clinical/pathological stage of the tumor, history of treatment, etc.), imaging findings, and prostate-specific antigen (PSA) level were collected.

All patients had undergone gene sequencing of primary PCa tissue including 15 HRR genes (*BRCA1*, *BRCA2*, *ATM*, *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*). Tumor testing was conducted centrally with the use of archival biopsy tissue from the primary disease. Patients with deleterious or suspected deleterious alterations in 15 HRR genes were defined as the HRRmt group, and the rest were defined as the HRRwt group.

2.2. Treatment plan

During the study period, Olaparib was approved by the Food and Drug Administration (FDA) for use as monotherapy for the maintenance treatment of mCRPC patients with HRRm. Treatment decisions of the HRRmt group patients were made at the discretion of the physician. HRRwt group patients who were not applied in the scope of indications by the FDA purchased the Olaparib on their own to explore the efficiency of Olaparib after being informed of how the drug worked and what potential side effects would happen. All patients orally received the standard dose of Olaparib tablets (300 mg twice daily) and two HRRwt patients received additional abiraterone (1000 mg once daily, plus prednisone at a dose of 5 mg twice daily) therapy. If patients experienced grade 3 or above AEs, the dose was adjusted to 150 mg twice daily; discontinuation was considered if the AE remained unrelieved.

2.3. Study assessments

During the period of drug administration, patients were instructed to visit every month for symptom check-ups and laboratory tests (complete blood cell count, liver and kidney function, electrolytes, blood lipids, and PSA) and three months for tumor assessment (imaging studies, mostly computed tomography scan) until objective disease progression or intolerable toxicities. Safety

Table 1
Baseline characteristics of patients.

Characteristic	Overall	HRRmt	HRRwt
	$n = 43$	$n = 26$	$n = 17$
Age, year (IQR)	60 (64-68)	63 (59-67)	66 (61-70)
Age $\geq$ 65 yr at baseline, *n* (%)	19 (44)	10 (38)	9 (53)
PSA at baseline, ng/ml (IQR)	83 (7.7-299.3)	38 (3.9-276.7)	100.2 (42.3-466.4)
Gleason score[a)]			
<8	5 (12)	3 (12)	2 (12)
≥8	34 (79)	19 (73)	15 (88)
M1 or N1 at diagnosis, *n* (%)	35 (81)	21 (81)	14 (82)
Metastatic site, *n* (%)			
Viscera: liver or lung	10 (23)	4 (15)	6 (35)
Bone, no viscera	31 (72)	21 (81)	10 (60)
Lymph node only	2 (5)	1 (4)	1 (6)
Metastases volume, *n* (%)			
High	36 (84)	20 (77)	16 (94)
Low	7 (16)	6 (23)	1 (6)
Prior new hormonal agent, *n* (%)			
Enzalutamide only	0 (0)	0 (0)	0 (0)
Abiraterone only	34 (79)	20 (77)	14 (82)
Enzalutamide and abiraterone	5 (12)	3 (12)	2 (12)
Prior docetaxel use, *n* (%)	27 (63)	15 (54)	13 (76)
Prior RP	13 (30)	6 (23)	7 (41)
Prior RT	8 (19)	7 (27)	1 (6)

PSA: prostate-specific antigen; IQR: interquartile range; mCRPC: metastatic castration-resistant prostate cancer; RP: radical prostatectomy; RT: radiation therapy.
[a)] Gleason score was not available for four patients.

Table 2
Prevalence of qualifying gene alterations.

Patients, *n* (%)	Overall	Germline mutation	Somatic mutation
	(*n* = 26)	(*n* = 13)	(*n* = 15)
BRCA2	13 (50)	11 (85)	2 (13)
CDK12	9 (35)	0 (0)	9 (60)
ATM	3 (12)	1 (8)	2 (13)
BRCA1	1 (4)	0 (0)	1 (7)
PALB2	1 (4)	0 (0)	1 (13)
RAD51D	1 (4)	1 (8)	0 (0)

Patients with multiple genes are included across more than one gene.
HRR: homologous recombination repair.

and tolerability were monitored throughout the follow-up period by recording patients, chief complaint, vital signs, AEs (graded using CTCAE v5.0), as well as physical examination results and clinical laboratory findings. The primary objective of the study was to describe the efficiency and safety of Olaparib in a real-world setting. The endpoints of this study included PSA response, safety, progression-free survival (PFS), and OS. The baseline of PSA was used as the reference value. The efficiency of the Olaparib was evaluated based on the dynamic of PSA levels, with a partial response defined as a reduction of between 0% and 50% from baseline, and a good response defined as a reduction of greater than 50%. In addition, we also evaluated the rate of high PSA response defined as a reduction of greater than 90% from baseline. PFS was defined as the interval between the day Olaparib was started and the first progressive disease with rising PSA defined by PCWG3 criteria (sequence of 2 rising values above a baseline at a minimum of one-week intervals) or last follow-up[17].

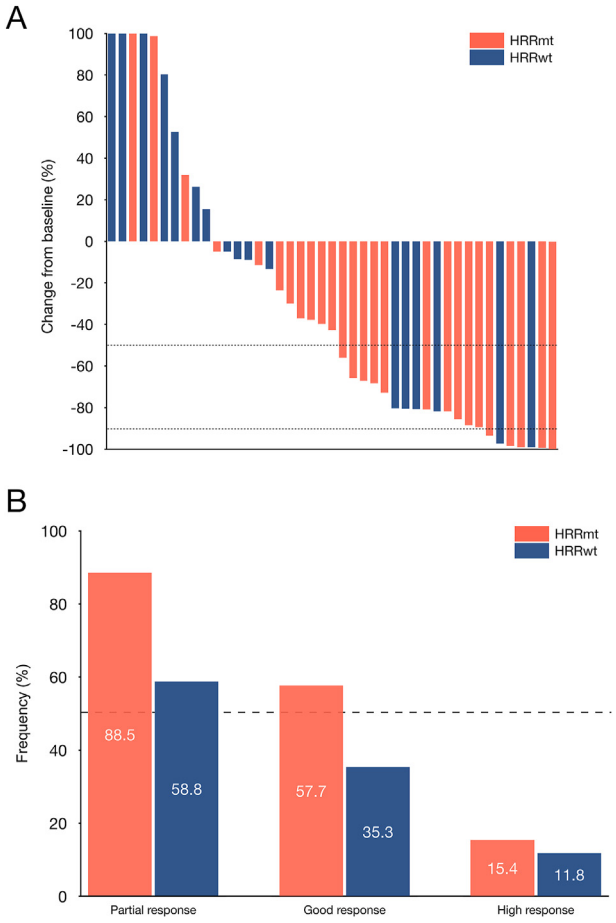

Fig. 1. (A) Waterfall plot of maximal change in PSA from baseline. (B) The percentage of patients with different PSA decrease rate in all patients. PSA: prostate-specific antigen; HRR: homologous recombination repair.

2.4. Statistical analysis

Categorical data were shown as frequencies and percentages, and continuous data were shown as medians and interquartile ranges (IQR). Median follow-up was calculated according to the inverted Kaplan–Meier technique. All other statistical analyses were performed using SPSS 22.0 (IBM Corp., Armonk, NY, 12 USA), with a two-sided $p < 0.05$ considered statistically significant.

3. Results

3.1. Patient characteristics

Patient characteristics before Olaparib administration are summarized in Table 1. A total of 43 patients were enrolled in this study, including 26 HRRmt group patients and 17 HRRwt group patients. Among HRRmt group patients, 13 (50%) had germline HRRm, while 15 (58%) had somatic HRRm. The distribution of pathogenic mutation genes was as follows: *BRCA2*, 13 patients; *ATM*, three patients; *BRCA1*, one patient; *PALB2*, one patient; *RAD51D*, one patient (two patients had two mutations, with one had both *BRCA2* and *ATM* mutations, and one had both *BRCA2* and *BRCA1* mutations). The detailed HRRm types and locations in this cohort were shown in Table 2.

The median age at baseline was 60 years (IQR 46.6–59.4), while there were 19 patients older than 65 years. Median PSA at baseline was 83 ng/ml (IQR 7.7–299.3). Most patients (81%) developed metastases at diagnosis. The analysis of baseline metastasis site showed that ten patients (23%) had visceral metastasis only, two patients (5%) had distant lymph node only metastasis, while 31 patients (72%) had both bone and lymph node metastasis. Thirty-four patients had a Gleason score ≥8. Thirty-six and seven patients were diagnosed with high burden and low burden metastatic disease, respectively[18]. Most patients (91%, 39/43) progressed after abiraterone or enzalutamide, and five patients had received both treatments. Twenty-seven (63%) patients had docetaxel experience.

3.2. Efficacy

The median duration of follow-up was 8.5 months (range, 2.0–29.0 months), and the median treatment duration with Olaparib was 3.0 months (1.0–16.5 months). Despite the short follow-up period, we derived Kaplan–Meier estimates of PFS from the start of Olaparib maintenance therapy. Median PFS from the start of Olaparib maintenance therapy was 8.0 months in the HRRmt group and 3.0s months in the HRRwt group (HR, 0.61; 95% CI, 0.24–1.14; $p = 0.148$), respectively (Fig. 1). A partial response, good response, and high response were achieved in 89% (23/26), 59% (15/26), and 15% (4/26) of HRRmt group patients, respectively. In HRRwt group, 59% (10/17), 35% (6/17), and 12% (2/17) of patients met the criteria of partial response, good response, and high response, respectively (Fig. 2).

3.3. Adverse events

AEs are shown in Table 3. A complete record of AEs was available for a total of 20 of the 43 patients in this study, while unavailable for the remaining due to lost to follow-up. All the 20 patients had AEs in various severities during treatment. We did not identify AEs that have never been reported previously. The most common all-grade

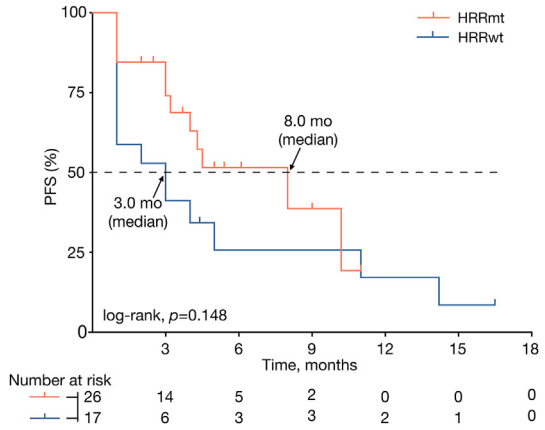

Fig. 2. Kaplan–Meier curves of median PFS of patients. PFS: progression-free survival; HRR: homologous recombination repair.

AEs were fatigue or asthenia (70%), anemia (65%), decreased appetite (55%), constipation (55%), nausea (40%), and vomiting (40%). Most patients (80%, 16/20) had grade 1 or 2 AEs. Ten episodes of grade 3 or 4 AEs were observed in four patients: three cases (15%) of anemia, two cases of diarrhea (10%), two cases of arthralgia (10%), one case of fatigue (5%), one case of decreased appetite (5%), one case of nausea (5%), and one case of vomiting (5%). AEs were usually managed by dose discontinuation or dose reduction (DR), rather than an interruption. DR, drug interruption, and drug discontinuation were performed in 6, 1, and 5 cases, respectively. The most common AEs that led to discontinuation were anemia and decreased blood pressure. One HRRwt patient died during the follow-up period due to grade 4 anemia.

4. Discussions

Our real-world experience showed Olaparib was a safe and effective treatment choice in the maintenance treatment of mCRPC patients. Good PSA response was achieved in 57.7% and 35.3% of HRRmt and HRRwt patients, respectively. In the HRRwt group, two patients even had high PSA responses after Olaparib treatment. In addition, the toxicity profile in the current study was in concordance with prior findings[14] as an overall incidence of fatigue, anemia, decreased appetite, and constipation similar to prior studies. Overall, the most common AE was fatigue followed by anemia. The incidence of grade ≥3 events for decreased appetite tended to be higher than prior reports, while the incidence of grade ≥3 events for fatigue, anemia, and constipation was relatively rare.

Since the approval of Olaparib for men with mCRPC, the era of precision treatment of mCRPC has come. To our knowledge, this was the first population-based study of Olaparib's real-world use and outcomes in mCRPC patients from the Chinese mainland. In our study, we were not able to determine the radiographic PFS. However, we found the median PSA-PFS of the HRRmt group was promising when taking the short follow-up into account. In addition, unlike the PROfound trial[14], we also accessed the outcome of Olaparib in HRRwt patients. More than half (58.8%, 10/17) of HRRwt group patients had PSA response to Olaparib which had not been reported before. We were not able to explain the underlying mechanism. And until an integral biomarker-driven trial is conducted, the targeted use of Olaparib on clinical outcomes in HRRwt group patients will be unknown. However, in ovarian cancer, PARP maintenance therapy was approved by FDA for the use in the setting of recurrent disease regardless of HRR gene status, despite low clinical efficacy in HRRwt group patients.

There was a recommended schedule of dose modifications that allows for continued use when toxicity occurred. Olaparib was continued for patients with grade 1 AEs. For grade 2 or higher AEs, dose interruptions and reductions were recommended. Discontinuations would be recommended when grade 3 or 4 AEs occurred and lasted more than 28 days at the lowest Olaparib dose[19–22]. While we had higher AEs rates and interruptions than the PROfound trial, we had lower rates of reductions, discontinuations, and grade 3 or 4 AEs. Our results indicated that while it was common for patients to experience AEs—particularly fatigue, anemia, and decreased appetite—the AEs of Olaparib were manageable, and the drug was well tolerated.

There are several potential limitations to the current study. First, the results should be interpreted cautiously, and the selection bias should not be ignored due to the retrospective nature. Secondly, due to expensive genetic testing methods, the majority of mCPRC patients may not opt for genetic tests for the identification of HRR gene

Table 3
Adverse events

Event	Overall (n = 20)		HRRmt (n = 13)		HRRwt (n = 7)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
	number (percent)					
AEs						
Any	20 (100)	6 (30)	13 (100)	1 (8)	7 (100)	5 (71)
Fatigue or asthenia	14 (70)	1 (5)	9 (69)	0 (0)	5 (71)	1 (14)
Anemia	13 (65)	3 (15)	9 (69)	1 (8)	4 (57)	2 (29)
Decreased appetite	11 (55)	1 (5)	8 (62)	0 (0)	3 (43)	1 (14)
Constipation	11 (55)	0 (0)	6 (46)	0 (0)	5 (71)	0 (0)
Nausea	8 (40)	1 (5)	4 (31)	0 (0)	4 (57)	1 (14)
Vomiting	8 (40)	1 (5)	4 (31)	0 (0)	4 (57)	1 (14)
Dyspnea	7 (35)	0 (0)	6 (46)	0 (0)	1 (14)	0 (0)
Diarrhea	6 (30)	2 (10)	3 (23)	0 (0)	3 (43)	2 (29)
Back pain	6 (30)	0 (0)	4 (31)	0 (0)	2 (29)	0 (0)
Peripheral edema	6 (30)	0 (0)	3 (23)	0 (0)	3 (43)	0 (0)
Cough	6 (30)	0 (0)	4 (31)	0 (0)	2 (29)	0 (0)
Arthralgia	6 (30)	2 (10)	4 (31)	0 (0)	2 (29)	2 (29)
Urinary tract infection	1 (5)	0 (0)	0 (0)	0 (0)	1 (14)	0 (0)
Drug interruption due to AEs	1 (5)	NA	1 (8)	NA	0 (0)	NA
Dose reduction due to AEs	6 (30)	NA	5 (38)	NA	1 (14)	NA
Discontinuation due to AEs	5 (25)	NA	2 (15)	NA	3 (43)	NA
Death due to AEs	1 (5)	NA	0 (0)	NA	1 (14)	NA

AEs: adverse events; HRR: homologous recombination repair.

alterations, thereby resulting in a limited sample size; meanwhile, the collection of safety data was uncompleted. Finally, follow-up time was not long enough to determine PFS and OS outcomes, as we can see one-third (38.5%, 10/26) of HRRmt patients who showed PSA response to Olaparib had $\leq$ 6 months treatment duration. Additional follow-up is needed to explore the impact of Olaparib in real-world settings on survival outcomes and quality of life and assess how the integration of Olaparib in the frontline setting will impact treatment patterns in mCRPC patients. Notwithstanding these drawbacks, we believed it to have contributed to the current understanding of mCRPC treatment by providing the first real-world data regarding the efficiency and safety of Olaparib in unselected mCRPC patients from Chinese mainland. We also could demonstrate that Olaparib was a feasible option in some HRRwt patients. These data, although provocative, need to be confirmed in further studies with a bigger population and longer follow-up time, and adding translational studies to explain the efficacy of Olaparib observed in HRRwt patients.

5. Conclusion

In conclusion, our study evaluated the AEs and short-term efficacy in mCRPC patients who were treated with Olaparib in the real-world setting. The toxicity profiles we observed were similar to the prior conducted clinical trials and tolerable. In addition, HRRmt patients can benefit from Olaparib.

Author contributions

Study concept and design: DY and YZ. Acquisition of data: JP. Analysis and interpretation of data: JP. Drafting of the manuscript: JP. Critical revision of the manuscript for important intellectual content: DY and YZ. Statistical analysis: JP. Obtaining funding: YZ. Administrative, technical, or material support: DY and YZ. Supervision: DY and YZ. All authors contributed to the article and approved the submitted version.

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Ethics approval

This clinical trial received approval from the Human Ethics Committee of Fudan University Shanghai Cancer Center (FUSCC) and was conducted in accordance with the Declaration of Helsinki.

Consent of participate

This clinical trial obtained informed consent from all participating subjects.

Consent for publication

Not applicable.

Availability of data and material

The datasets generated and analyzed during the current study are included in this publication and are available from the corresponding author on reasonable request.

Conflict of interest

The authors have no conflicts of interest that are directly relevant to the content of this article.

Acknowledgments

It is no applicable.

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