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Review

Treatment of Metastatic Castration-resistant Prostate Cancer: Are PARP Inhibitors Shifting the Paradigm?

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Abstract. *Remarkable developments in the treatment of metastatic castration-resistant prostate cancer (mCRPC) have been achieved over the past decade. Although targeting the novel androgen receptor axis and using chemotherapeutic agents have improved survival, mCRPC is still a lethal disease. A better molecular characterization of cancer resulted in the determination of the important role of homologous recombination repair (HRR) genes in cancer development, and poly (ADP-ribose) polymerase (PARP) is one of the most attractive therapeutic targets. Recent clinical studies have demonstrated that PARP inhibitors significantly improve oncological outcomes in patients with mCRPC harboring BRCA mutations, and PARP inhibitors are becoming a standard of care for these patients. However, not only PARP inhibitors, but also chemotherapeutic agents such as platinum agents, taxanes, and radium-223 are active in HRR gene mutation carriers, and platinum sensitivity may predict the efficacy of PARP inhibitors for mCRPC. The combination of PARP inhibitors with other anti-cancer agents may overcome resistance mechanisms against PARP inhibitors and lead to survival benefits. Appropriate treatment sequences and combinations may change the therapeutic landscape of DNA repair deficient mCRPC.*

Prostate cancer is the most frequently diagnosed cancer in 105 of 185 countries (1), and the number of patients has been increasing worldwide, particularly in Asia and developing countries (2). Although localized prostate cancer has a favorable prognosis by definitive treatment such as surgery and radiation therapy, metastatic disease has a poor prognosis with five-year relative survival rate of only 30% (3). Despite the initial favorable response to androgen deprivation therapy, the vast majority of metastatic prostate cancers eventually progress to fatal disease, castration-resistant prostate cancer (CRPC), by overcoming low circulating levels of androgens (4).

Large-scale phase III clinical trials using novel agents for prostate cancer have demonstrated the improvement of oncological outcomes, and the treatment strategy of mCRPC has been dramatically changing. In 2004, the TAX327 trial showed prolonged overall survival (OS) in patients with metastatic CRPC (mCRPC) using the chemotherapeutic agent docetaxel. This was the first phase III trial to demonstrate a statistically significant prolongation of OS for mCRPC. Following this landmark study, the androgen receptor axis-targeted agents (ARATs) such as abiraterone acetate, enzalutamide, alpha-emitter radium-223, and immunotherapeutic sipleucel T demonstrated survival benefits for men with mCRPC (5). In fact, these agents improved OS by three–four months and OS for men with mCRPC was shorter than 3 years and still unfavorable (6). According to recent developments in molecular biology, precision medicine has been introduced, and molecular profiling can be used to select effective pharmaceuticals for each individual. Advances in the molecular characterization of cancer resulted in the determination of the important role of homologous recombination repair (HRR) genes in cancer development and progression, and poly (ADP-ribose) polymerase (PARP) is one of the most attractive therapeutic targets. PARP plays a pivotal role in single-strand DNA break repair *via* homologous recombination (7). Thus, in cells with pathogenic mutations in double-strand DNA repair

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genes such as *BRCA1* and *2*, *ATM*, and *PALB2*, PARP is required for survival and a PARP inhibitor is able to induce cell death.

Efficacy of PARP Inhibitors for mCRPC

PARP inhibitors have been approved for the treatment of breast, ovarian, and pancreatic cancers harboring *BRCA* mutations. PARP inhibitors have also shown promising efficacy in patients with mCRPC (8, 9).

The PROfound trial was a landmark phase III HRR alteration-driven study in mCRPC that evaluated for the first time the efficacy of the PARP inhibitor olaparib for mCRPC harboring HRR gene mutations (Table I) (8). This study enrolled mCRPC patients with progression while on ARATs and/or taxanes, such as docetaxel and cabazitaxel. All men had alterations in one or more HRR genes. Cohort A (n=245) patients had at least one mutation in *BRCA*1, *BRCA*2, or *ATM*, whereas cohort B (n=142) patients had mutations in 12 other HRR genes. Patients were randomized to olaparib or the physician's choice of abiraterone or enzalutamide (control arm). In cohort A, this study met the primary endpoint of radiological progression-free survival (rPFS) [median 7.4 *vs*. 3.6 months, hazard ratio (HR) for progression or death: 0.34, 95% confidence interval (CI)=0.25-0.47]. The objective response rate and time to pain progression were also better in the olaparib arm compared with the control arm. In cohort A, the median OS for patients treated with olaparib was significantly longer than that for those who received a control therapy (19.1 months *vs*. 14.7 months, HR=0.69; 95%CI=0.50-0.97, p=0.02) (10). In patients without *BRCA* mutations, olaparib was not effective in terms of rPFS, radiological response, or OS (8, 10, 11).

The efficacy of rucaparib, another PARP inhibitor, was evaluated in men with mCRPC harboring a *BRCA*1/2 mutation in the phase II TRITON2 study (9). The objective response rate (ORR), the primary endpoint, was 43.5% (27 of 62 patients; 95%CI=31.0%-56.7%), and the prostate specific antigen (PSA) response rate was 54.8% (63 of 115 patients, 95%CI=45.1%-64.1%). These results indicate the efficacy of rucaparib in mCRPC patients with *BRCA* mutations.

Olaparib and rucaparib are approved by the U.S. Food and Drug Administration (FDA) for patients with germline or somatic HRR gene-mutated mCRPC, who progressed following prior treatment with ARATs and/or taxane-based chemotherapy (12). The European Medicines Agency (EMA) approved olaparib for *BRCA* mutation carriers, and the updated AUA/ASTRO/SUO (13) and EAU guidelines (14) recommend PARP inhibitors for patients with HHR gene mutations. Other PARP inhibitors such as niraparib and talazoparib, were also shown to have anticancer activity in mCRPC patients with *BRCA* mutations and many clinical trials are evaluating efficacy and safety of PARP inhibitors for mCRPC (15). Treatment using a PARP inhibitor is becoming a standard of care for patients with DNA repair-deficient prostate cancer.

Are PARP Inhibitors Going to Dramatically Change the Treatment Landscape of mCRPC?

Frequency of BRCA mutations in prostate cancer. Germline mutations in HHR, *BRCA*1, and *BRCA*2 genes were noted in 11.8%, 0.87%, and 5.35%, respectively, of 692 men with metastatic prostate cancer (16). These mutations are thought to affect DNA repair efficiency (17). More recent analyses revealed that germline pathogenic and likely pathogenic variants of *BRCA*1 and *BRCA*2 were 0.8%-0.9% and 3.4%-4.8%, respectively, in African American and Caucasian men with metastatic prostate cancer (18, 19). Pathogenic mutations are generally more frequently somatic than germline. The prevalence of somatic *BRCA*1/2 mutations in CRPC was 14%-16% (20, 21). In bone and soft tissue biopsy samples from mCRPC, somatic HRR and *BRCA2* gene alterations were observed in 22.7% (34/150) and 12.7% (19/150) of patients, respectively (20). In the PROfound prospective study, only 141 of 2792 (5.1%) patients were found to carry a somatic and germline *BRCA* mutation, a prevalence that was less than that reported in previous studies (8).

The prevalence of HRR gene mutations may be different in selected populations. Some studies have demonstrated that HRR gene mutations are associated with higher Gleason scores, advanced stage, and poor oncological outcomes after treatment (16, 22-24). The first prospective trial PROREPAIR-B showed that germline *BRCA* mutations were an independent poor prognostic factor for cancer-specific survival (17.4 in *BRCA*2 mutation *vs*. 33.2 months in non-mutated patients, p=0.027) (25). More recently, Annala *et al*. (26) also demonstrated that HRR gene mutations were more frequently in men with metastatic castration-sensitive prostate cancer with aggressive and poor prognosis features than the unselected prostate cancer patient group (29% *vs*. 9% of patients, p<0.0001). In this population with higher HRR defects, however, the frequency of germline and/or somatic *BRCA*1/2 mutations was limited and observed in 0% and 11% of patients, respectively. These studies indicate an association between HRR deficiency and worse clinical features. However, conflicting results have been reported. For example, Mateo *et al*. (27) reported no difference in the PFS of patients treated with ARATs between patients carrying a germline HRR mutation and those who did not. Therefore, the association between HRR gene mutations and clinical features remains to be determined.

Kwon *et al*. (19) also suggested ethnic differences in patients with germline HRR gene mutations. African American men with prostate cancer were more likely to have germline pathogenic and likely pathogenic mutations of

Table I. *Cinical trials for mCRPC after ARAT and/or taxanes*.

Title, phase	PROfound (NCT02987543) (8), phase III						TRITON2 (NCT02952534) (9). phase II			CARD (NCT02485691) (30), phase III	
Previous therapy	ARAT and/or taxane						ARAT and taxane			ARAT and docetaxel	
Cohort	All		Group A (BRCA1/2m+ ATMm)		BRCA1/2m		All	BRCA1m	BRCA2m	All	
Intervention	Olaparib	ARAT	Olaparib	ARAT	Olaparib	ARAT	Rucaparib	Rucaparib	Rucaparib	Cabazitaxel	ARAT
N	256	131	162	83	88	52	115	13	102	126	129
PSA response (%)[1]	30	10	43	8	x	x	54,8	x	x	37.5 (p<0.001 *vs*. control)	13,5
Objective response (%)[2]	22	4	33	2	x	x	43,5	33,3	45,3	37	12
OR (95%CI), *vs*. control	5.39 (2.01-25.4)		20.86 (4.18-379.18), p<0.001							p=0.004	
Median rPFS (month)	5,8	3,5	7,4	3,6	9,8	3	9	8,7	9,7	8	3,7
HR (95%CI), *vs*. control	0.49 (0.38-0.63), p<0.001		0.34 (0.25-0.47), p<0.001		0.22 (0.15-0.32)					0.54; (0.40-0.73), p<0.001	
Median OS (months)	17,5	14,3	19.1*	14.7*	19,5	15,1	Immature	x	x	13,6	11
HR (95%CI), *vs*. control	0.67 (0.49-0.93), p=0.02		0.69 (0.50-0.97), p=0.02*		0.61 (0.37-1.01)					0.64 (0.46-0.89), p=0.008	
Discontinuation d/t AEs (%)	18	x	x	x	x	x	7,8	x	x	19,8	8,9

AEs: Adverse events; ARAT: androgen receptor axis targeting agent; CI: confidence interval; d/t: due to; HR: hazard ratio; m: mutation; mCRPC: metastatic castration-resistant prostate cancer; OR: odds ratio; OS: overall survival; PSA: prostate-specific antigen; rPFS: radiographic progression-free survival; x: not reported; wt: wild type. [1]PSA response (reduction >50% from base line); [2]Objective response: complete or partial response according to RECIST 1.1 criteria. *results in reference (10).

Table II. *Antitumor activity of platinum-based chemotherapy in prostate cancer patients with or without HRR mutations.*

Authors, year	Pomerantz *et al.* (40), 2017	Schmid *et al.* (41), 2020				Mota *et al.* (42), 2020			Sloolbeek *et al.* (43), 2021		
Cohort	BRCA2m	BRCA2wt	HRRm	BRCA2m	HRRwt	HRRm	BRCA2m	HRRwt	HRRm	BRCA2m	HRRwt
N	8	133	80	44	98	16	6	48	14	7	16
PSA response (%)[1]	75	17	47,1	63,9	36,1	50	67	13	71,4	100	31,3
Objective response (%)[2]	x	x	48,3	50	31,3	x	x	x	58,4	100	21,4
Time on treatment (median, months)	15 (weeks)	12 (weeks)	3,4	7,1	2,8	3	3,9	1,6	x	x	x
OS (median, months)	18,9	9,5	14	15	9,2	9	8,4	7,8	8,4	21	7

HRR: Homologous recombination repair; HR: hazard ratio; m: mutation; OS: overall survival; PFS: progression-free survival; rPFS: radiographic progression-free survival; x: not reported; wt: wild type. [1]PSA response (reduction >50% from base line); [2]Objective response: complete or partial response according to RECIST 1.1 criteria.

BRCA1 than Caucasian men (18). These studies raise the possibility that the frequency of *BRCA* mutations may be higher in selected populations than in unselected populations. *BRCA* mutations, however, are infrequent and have been found in a small population of patients with prostate cancer.

In addition to the limited prevalence of *BRCA* mutations, not all patients harboring *BRCA* mutations benefit from PARP inhibitors. The PROfound trial revealed that PSA and objective response rate to olaparib in patients in cohort A (alteration in *BRCA*1/2 or *ATM*) were 43% and 33%, respectively (8). PARP inhibitors, therefore, may be beneficial for a limited patient population with mCRPC.

Control arm in the landmark PROfound trial. The patients in the control arm of the PROfound trial received alternative ARAT after another ARAT; for example, they were switched from abiraterone to enzalutamide, and vice versa. The rPFS, objective response, and PSA response rate in the control arm were only 3.5 months, 4%, and 10%, respectively (8). Retrospective and prospective studies have indicated that cross-resistance between ARATs and the treatment efficacy of alternative ARATs is very limited (28-30). The CARD trial prospectively compared the efficacy and safety of cabazitaxel and alternative ARAT for men with mCRPC (Table I) (30). In the alternative ARAT arm, median rPFS, PSA response, and objective tumor response rate were only 3.7 months, 13.5%, and 11.5%, respectively. After progression on ARATs, most patients receive docetaxel in the real world (31). Although the PROfound trial showed the superiority of olaparib compared to the control arm of ARAT, this control arm may be suboptimal. PARP inhibitors should be compared with active and appropriate treatment for the individual patient. For example, the phase II clinical trial NCT04038502 is comparing the efficacy of carboplatin and olaparib in *BRCA*-deficient mCRPC.

Activity of platinum, taxane, and radium-223 in BRCA mutation carriers. BRCA mutation carriers are sensitive not only to PARP inhibitors, but also to platinum-based chemotherapy. Platinum binds directly to DNA, induces DNA double-strand breaks, and may be more effective in *BRCA* pathogenic mutation carriers. In ovarian, pancreatic, and breast cancers, *BRCA* carriers are more sensitive to platinum-based chemotherapy than non-carriers (32-37).

BRCA-associated prostate cancer may also be sensitive to platinum-based chemotherapy. Cisplatin and carboplatin were shown to exert moderate activity in men with mCRPC (38, 39). Retrospective studies revealed that platinum-based chemotherapy was more effective in patients with mCRPC harboring *BRCA* mutations (Table II) (40-43). The PSA responses (>50% decline) to platinum were 64%-100% and 17%-36% in *BRCA2* mutation carriers and non-carriers, respectively. Radiographic response rate and OS were also better in *BRCA2* mutation carriers compared to non-carriers. Some case series showed exceptional efficacy of carboplatin for mCRPC with DNA repair defects such as *BRCA*2 and *ATM* mutations (44, 45). An *in vivo* study demonstrated that suppression of functional *BRCA2* increased, but overexpression reduced the sensitivity of prostate cancer cells to carboplatin (40) These studies suggest that platinum is active in men with HRR gene alterations, including *BRCA* mutations.

To date, there are no data suggesting the superiority of a PARP inhibitor for HRR mutation carriers compared to platinum. In a small but real-world study, the efficacy of olaparib and carboplatin was identical for mCRPC with *BRCA* alterations (46). In this study, PFS for men with *BRCA*2 alterations who received olaparib and carboplatin was 4.9 months and 5.4 months, respectively (HR=0.71, 95%CI=0.45-1.11, p=0.13). No difference in PFS was also observed among men with *BRCA*2, *BRCA*1, or *ATM* alterations treated with olaparib and carboplatin (3.8 months

vs. 3.6 months, HR=0.80 95%CI=0.54-1.16, *p*=0.24). Taken together, platinum may have similar efficacy to PARP inhibitors and can be used for patients with HRR-mutated mCRPC. Clinical trials (NCT04038502, NCT03652493, NCT02598895, NCT02985021, and NCT03442556) are underway to assess the efficacy and safety of carboplatin with or without docetaxel for DNA repair-deficient mCRPC, and the results may provide promising clinical information.

HRR mutations have little impact on the efficacy of taxane chemotherapy. PFS of patients on docetaxel with and without HRR mutations was not significantly different (HR=0.86, 95%CI=0.61-1.20, *p*=0.37). PFS for patients with or without *BRCA* mutations was also identical (HR=0.96, 95%CI=0.64-1.43, *p*=0.83) (27). The PSA response to taxanes was 57% and 42% in *BRCA* mutation carriers and non-carriers, respectively. In breast cancer patients, docetaxel had the same activity regardless of *BRCA*2 mutation status (47). Therefore, taxanes are a valid option for patients with mCRPC, even though they have *BRCA* alterations.

Radium-223 may also be active in men with *BRCA* mutations. Alpha particles cause double-strand DNA breaks (48), and cells harboring DNA repair gene defects may be more susceptible to radium-223. van der Doelen *et al*. treated mCRPC patients with radium-223 (49). Twenty-six were pathogenic HHR mutation carriers (HRR+), and 67 were non-carriers (HRR–). The OS, the primary endpoint, was better in the HRR+ than in the HRR- cohort (36.3 months *vs*. 17.0 months, HR=2.29, 95%CI=1.21-4.32, *p*=0.011). PRORADIUM (NCT02925702) is a prospective observational biomarker study of patients with mCRPC treated with radium-223. In this study, 14 germline HRR mutation (five *BRCA*2, four *ATM*, one *BRCA*1, four other genes) carriers and 161 non-carriers were included. A significantly greater decline in alkaline phosphatase at 12 weeks was observed in HRR gene mutation carriers than in non-carriers (75% *vs*. 43%, *p*=0.036). OS was longer in HRR gene mutation carriers than in non-carriers, although the difference did not reach statistical significance (median 14.4 months *vs*. 10.6 months, *p*=0.066) (50). Taken together, not only PARP inhibitors, but also platinum, taxanes, and radium-223 may be promising treatment options for DNA repair-deficient prostate cancer.

Platinum Sensitivity Could be a Biomarker for Efficacy of a PARP Inhibitor

For patients with breast, ovarian, and pancreatic cancers harboring *BRCA* alterations, PARP inhibitors are used after chemotherapy. *BRCA* mutations predict the response of ovarian and breast cancers to platinum (51, 52). Niraparib and olaparib are recommended as maintenance therapies after platinum-based chemotherapy only for platinum-sensitive cancer (53-55).

In ovarian cancer patients with *BRCA* mutations, olaparib was more active in patients with platinum sensitivity than in others (56). In this study, platinum-sensitive and platinum-resistant patients were defined as those who showed disease progression in more and less than 6 months, respectively, after their last platinum chemotherapy. Platinum-refractory disease was defined as disease progression during platinum-based chemotherapy. Complete or partial responses were noted in 46.2%, 33.5%, and 0% of patients in the platinum-sensitive, platinum-resistant, and platinum-refractory groups, respectively. The clinical benefit rates determined by radiographic and tumor marker responses were 69.2%, 45.8%, and 23.1% in the platinum-sensitive, -resistant, and -refractory groups, respectively. These results suggest that platinum-insensitive cancer may be less sensitive to olaparib, and platinum sensitivity may be a useful biomarker for predicting the efficacy of olaparib in mCRPC with *BRCA* mutations.

Future Perspectives

Future studies may identify pharmacogenomic biomarkers that predict the efficacy of pharmaceuticals for HRR-deficient mCRPC. The expected results will improve the efficacy of PARP inhibitors. As the positive rate of the *BRCA* test is low among the unselected population, it is mandatory to identify patient groups with a higher frequency of HRR deficiency. Although the prognostic role of HRR gene mutations has not been determined yet, aggressive prostate cancer may be a suitable candidate for *BRCA* analysis because of the possibility of a higher rate of *BRCA* mutations (56).

Not all *BRCA* mutation carriers benefit from PARP inhibitors, and cancer cells harboring *BRCA* mutations exert primary and acquired resistance to a PARP inhibitor. Combination with other anticancer agents may overcome these resistance mechanisms. Many clinical trials investigating the efficacy of a combination of PARP inhibitors and ARATs, taxanes, molecular targeting, and immuno-oncology drugs for CRPC are ongoing (57) and show the efficacy of PARP inhibitors for mCRPC.

Platinum, taxanes, and radiopharmaceuticals are also active for mCRPC with *BRCA* mutations, and the clinical benefits of these agents should be determined.

Conclusion

PARP inhibitors are becoming the standard of care for mCRPC harboring HRR gene mutations. Clinical and molecular biomarkers that predict the patients who will benefit from PARP inhibitors should further improve treatment outcomes. DNA repair-deficient mCRPC patients respond not only to PARP inhibitors, but also to platinum, taxanes, and radium-223. Ongoing and future studies must determine which agent, either monotherapy or combination, is optimal for individual patients with mCRPC harboring HRR gene mutations.

Conflicts of Interest

Masaki Shiota received honoraria from Janssen Pharmaceutical, AstraZeneca, and Astellas Pharma, and research funding support from Daiichi Sankyo. Other Authors report no conflicts of interest regarding this work.

Authors' Contributions

Naohiro Fujimoto conceived the presented idea and wrote the manuscript. Kenichi Harada, Masaki Shiota, Ikko Tomisaki, Akinori Minato, Yujiro Nagata, Rieko Kimuro, Mirii Harada collected and selected the references. Masato Fujisawa supervised the work. All Authors discussed, verified and approved the final version of the manuscript.

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