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REVIEW

Role of Olaparib in the Management of Metastatic Castration-Resistant Prostate Cancer: A Japanese Clinician's Perspective

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Abstract: Several studies have identified various targetable genomic alterations in prostate cancer, which accumulate during carcinogenesis and cancer progression. Genomic alterations in genes involved in DNA damage repair by homologous recombination repair may predict increased sensitivity to poly-ADP ribose polymerase (PARP) inhibitors. The Phase 3 PROfound trial has shown that treatment with the PARP inhibitor olaparib was associated with an improved radiographic progression-free survival and overall survival among patients with homologous recombination repair-deficient metastatic castration-resistant prostate cancer (mCRPC) after the treatment with androgen receptor targeting therapy, especially in men with *BRCA1* or *BRCA2* mutation. In Japan, olaparib was approved in December 2020 for the treatment of mCRPC with *BRCA1* or *BRCA2* mutation. In addition, genetic tests to detect *BRCA1* or *BRCA2* mutation to select patients who are likely to benefit from olaparib were also approved. This review summarizes the status of olaparib treatment for mCRPC, focusing on the situation in Japan.

Keywords: olaparib, metastatic castration-resistant prostate cancer, Japanese, BRCA, companion diagnosis, genomic profile

Introduction

Prostate cancer (PCa) is an androgen-sensitive disease that requires testosterone for its development and proliferation.[1] Standard treatment for metastatic PCa is androgen deprivation therapy, which suppresses androgen receptor (AR) signaling.[2] These interventions result in low testosterone levels and initially are highly effective in the relief of cancer-related symptoms, tumor marker decline, and tumor shrinking. However, the disease inevitably progresses to castration-resistant PCa (CRPC).[3]

Recent studies for molecular profiling, including the Stand Up to Cancer-PCF (SU2C-PCF) for metastatic CRPC (mCRPC) project and The Cancer Genome Atlas (TCGA) for primary localized PCa study, have identified various genomic alterations in PCa, which accumulate during carcinogenesis and cancer progression.[4–6] Interestingly, some of them were potentially targetable alterations that occur somatically as well as in the germline.[4–6] In particular, genomic alterations in genes involved in DNA damage repair by homologous recombination repair (HRR) may predict increased sensitivity to platinum-based therapy and poly-ADP ribose polymerase (PARP) inhibitors.[7,8] The PROfound trial has shown that treatment with the PARP inhibitor olaparib was associated with an improved radiographic progression-free survival (rPFS) among patients with HRR-deficient mCRPC before treatment with AR axis-targeting therapy (ARAT), especially in men with *BRCA1* or *BRCA2* mutation.[9,10] Accordingly, the Food and Drug Administration (FDA) approved olaparib, in the United States (US) in May 2020, for the treatment of mCRPC with HRR gene mutations (HRRm). In Japan, olaparib was approved by the Pharmaceutical and Medical Devices Agency (PMDA) in December 2020 for the treatment of mCRPC with *BRCA1* or *BRCA2* mutation, and companion diagnostic tools for the indication of olaparib in PCa have also been approved accordingly. This review summarizes the status of olaparib treatment for mCRPC, focusing on the situation in Japan.

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PCa Incidence and Mortality in Japan

PCa is the most frequently diagnosed cancer in 112 countries and the leading cause of cancer death in 48 of them.[11] The number of PCa cases diagnosed in the US in 2020 was 209,512, with an age-standardized incidence rate of 72 per 100,000, and the number of PCa deaths was 32,438, with an age-standardized mortality rate of 8.2 per 100,000. On the other hand, in Japan, the number of PCa cases was 106,139 with an age-standardized incidence rate of 51.8 per 100,000, and the number of deaths was 13,426 with an age-standardized mortality rate of 4.5 per 100,000.[12] Thus, morbidity and mortality rates in Japan are lower than those in the US, as race in addition to age and family history of PCa are well-known risk factors for PCa. In addition, total energy intake, obesity, and intake of dairy products have also been suggested as risk factors, which may affect different morbidity and mortality rates between the US and Japan.[13–15]

HRR Genes and PCa Risk

As the disease progresses from hormone-sensitive PCa to mCRPC, various genomic alterations accumulate, including pathways related to AR signaling, PI3K/AKT, cell cycle, and DNA repair.[5,16–19] Single-strand breaks are repaired by several mechanisms involving PARP, while two systems including HRR or non-homologous end joining (NHEJ) repair a DNA double-strand break (DSB).[20,21]

Tumor suppressor genes *BRCA1, BRCA2*, and *ATM* are involved in HRR, which can repair DSB accurately with few errors. However, when there is a HRR deficiency due to HRRm, the DSB is repaired by the NHEJ, which is prone to make compensatory repair errors.[21] Therefore, genetic mutations in *BRCA1* and *BRCA2* lead to accumulating genomic abnormalities, making them susceptible to a variety of cancers, including breast, ovarian, prostate, and pancreatic cancer.[22–24]

So far, retrospective studies have shown the association between *BRCA* mutation and PCa incidence rate.[25] In addition, the prospective EMBRACE study from the United Kingdom and Ireland has recently reported that germline *BRCA1* and *BRCA2* mutations were associated with an accumulative risk of developing PCa. The risk comorbid with PCa by age 85 years was 29% and 60% in germline *BRCA1* and *BRCA2* mutations, respectively.[26] Another study found that in Japanese with pathogenic variants (PVs) of the *BRCA2* gene, the accumulative risk of developing PCa was 24.5% by age 85 years, suggesting relative lower risk of PCa incidence related to *BRCA* mutation in Japanese, compared with Caucasian.[27]

Olaparib Treatment Outcomes in Japanese

PARP inhibitors block PARP-mediated repair of single-strand breaks, leading to the generation of more deleterious DNA.[5,28–32] During DNA replication, cancer cells attempt precise repair of DSBs by HRR. However, in the presence of HRR deficiency, NHEJ repairs DSBs caused by PARP inhibition, resulting in intolerable genomic alterations, ultimately leading to cancer cell death.[33]

The PROfound trial, a randomized, open-label, phase 3 study, evaluated the efficacy and safety of olaparib (n=256) compared to enzalutamide or abiraterone acetate (n=131) as alternative ARAT, in patients with HRRm-deficient mCRPC who had failed ARAT.[10] The median rPFS as the primary endpoint was 7.4 months (95% CI, 6.2–9.3 months) and 3.6 months (95% CI, 1.9–3.7 months) in the olaparib and alternative ARAT arms among men harboring *BRCA1/2* or *ATM* mutation (cohort A, HR 0.34; 95% CI, 0.25–0.47; p<0.001), respectively. Moreover, a significantly longer rPFS was also observed in all HRRm (cohort A+B, HR 0.49; 95% CI, 0.38–0.63; p<0.001). The incidence of grade ≥3 adverse events was higher with olaparib than with alternative ARAT. The most common adverse events of any grade with olaparib were anemia, nausea, and fatigue or asthenia, while those with alternative ARAT were fatigue or asthenia.

Based on these results, the FDA approved olaparib for patients with 11 HRRm in addition to *BRCA1/2* and *ATM* in May 2020, where the FDA excluded *PPP2R2A* gene, a regulator of phosphorylation of *ATM*, among 15 HRR genes due to unfavorable risk-benefit.[34,35] Meanwhile, the HR of rPFS in the olaparib arm was 0.41 (95% CI, 0.13–1.39) in *BRCA1*-mutated subgroup and 0.21 (95% CI; 0.13–0.32) in *BRCA2*–mutated subgroup. However, no benefit was observed in *ATM*–mutated subgroup (HR, 1.04; 95% CI, 0.61–1.87).[10] Based on these results, in December 2020, olaparib was

approved only for mCRPC with *BRCA1* or *BRCA2* mutation in Japan by the PMDA,[36] and also by the European Medicines Agency.[37]

Additional reports of the PROfound trial showed a median overall survival (OS) of 19.1 months with olaparib and 14.7 months with alternative ARAT (HR, 0.69; 95% CI, 0.50–0.97; p=0.02) in cohort A. When adjusting for crossover to olaparib, the HR for OS was 0.42 (95% CI, 0.19–0.91) in cohort A, 0.83 (95% CI, 0.11–5.98) in cohort B, and 0.55 (95% CI, 0.29–1.06) in the overall cohort.[9] Thus, the patients initially assigned to olaparib with *BRCA1*-, *BRCA2*-, or *ATM*–mutated mCRPC after disease progression during prior treatment with AR significantly had longer OS than those assigned to enzalutamide or abiraterone acetate plus prednisone, despite significant crossover from control therapy to olaparib. In addition, the objective response rate (ORR) was higher in the olaparib group (43.9% vs 0%), with a PSA response rate of 56.9%.[10] Olaparib therapy was also associated with reduced pain burden and maintenance of the health-related quality of life.[38]

An subgroup analysis of 101 Asians (including 57 Japanese) in the PROfound study showed the greatest improvement of rPFS (9.3 vs 3.5 months; HR, 0.17; 95% CI 0.06–0.49; p=0.0003) with olaparib in patients with *BRCA1* or *BRCA2* mutation, and similar trend of OS improvement (26.8 vs 14.3 months; HR, 0.62; 95% CI, 0.24–1.79; p=0.34) was shown.[39] In patients with *BRCA1, BRCA2*, or *ATM* mutation, rPFS was longer in the olaparib arm than in the alternative ARAT arm (7.2 vs 4.5 months, HR, 0.58; 95% CI, 0.29–1.21, p=0.14) although statistical significance was not obtained due to less statistical power. Thus, in Asians with mCRPC accompanied with *BRCA1* or *BRCA2* mutation and disease progression during prior ARAT, rPFS was significantly longer with olaparib than with enzalutamide or abiraterone acetate and prednisone.

In addition, Phase 2 TRITON2 study (NCT02952534), an ongoing multicenter, single-arm clinical trial, evaluated the efficacy and safety of the PARP inhibitor rucaparib in men with mCRPC harboring a *BRCA1* or *BRCA2* gene alteration.[30,40] The confirmed ORR by independent radiology review was 44% (95% CI, 31–57%), and safety profile was favorable. Based on the results, the FDA announced in 2020 the expedited approval of the PARP inhibitor rucaparib for advanced PCa with germline or somatic *BRCA* mutation and a history of ARAT and taxane-based therapy. However, rucaparib has not been approved in Japan.

Frequency of HRR Gene Mutations

As genetic variations differ among ethnics, the frequency of germline and somatic mutations in HRR gene can vary. Actually, it has recently been reported that Black men with prostate cancer exhibited a lower frequency and narrower spectrum of germline PVs and a higher frequency of variants of uncertain significance (VUS) in DNA repair genes compared with White men.[41]

The frequency of *BRCA1* and *BRCA2* mutations in advanced PCa globally was 0.9% and 8.6% in germline mutation, and 0.9% and 7.7% in somatic mutation, respectively (Table 1).[42] Meanwhile, in the study from Japan on the frequency

Table 1 Comparison of Germline and Somatic Mutations of BRCA1/2 Between Overseas and Japan

	Overseas				**Japan**			
	Advanced Prostate Cancer				**Prostate Cancer**		**mCRPC**	
	Germline Mutation		**Somatic Mutation**		**Germline Mutation**		**Germline/Somatic Mutation**	
	n=221		**n=221**		**n=7636**		**n=143**	
	n	%	n	%	n	%	n	%
BRCA1	2	0.9	2	0.9	14	0.2	1	0.7
BRCA2	19	8.6	17	7.7	83	1.1	18	12.6
ATM	5	2.3	10	4.5	37	0.5	NA	NA
Reference	Abida et al[42]				Momozawa et al[24]		Uemura et al[46]	

of germline *BRCA1* and *BRCA2* PVs in 7636 PCa cases and 12,366 non-carcinoma patients, 64 (1.3%) had germline *BRCA1* or *BRCA2* PVs, accounting for 0.2% and 1.1% of the prevalence rate among patients with PCa, respectively.[24] In another study from Japan germline *BRCA1* or *BRCA2* mutation rates were 0% and 3.4% in advanced PCa (n=562), respectively.[43] Thus, the frequency of germline mutation of *BRCA1* and *BRCA2* seems higher in Caucasians than Asians, which may be attributable to the frequency of VUS, at least in part. Since few genetic studies have been conducted in Asians, abnormalities in *BRCA1* and *BRCA2* genes among this population are associated with a high frequency of VUS.[44] Functional assays to determine the pathological value of VUS are needed to provide clinical guidance regarding cancer risk and treatment options.[45] As well, further studies on the clinical significance of genetic abnormalities unique to Asians, including Japanese are needed.

In addition, several results were reported on somatic mutations of *BRCA1* or *BRCA2*. In the ZENSHIN study, the mutation rates of *BRCA1* or *BRCA2* including germline and somatic mutation in Japanese patients with mCRPC were 0.7% or 12.6%, respectively, and the rate of the 15 HRRm genes was 35.7% in total.[46] Consistently, the frequency of HRRm in the PROfound study in global population and Japanese showed that the frequency of *BRCA1* or *BRCA2* mutation was comparable between global population (1.3% or 9.7%) and Japanese subset (2% or 8.3%), respectively (Table 2).[39,47] Furthermore, comparable frequency of *BRCA1* somatic mutation was observed among Asian, White, and Black men, despite differences of genomic alteration signatures, including HRR genes in PCa among ethnics.[48] Thus, accumulating evidence suggested no large difference in the frequency of somatic mutation in *BRCA1* and *BRCA2* genes between global population and Japanese with mCRPC.

BRCA Mutations in Tissue and Liquid Biopsy

A biopsy from soft tissues may be difficult in most cases with mCRPC, where a blood-based liquid biopsy using circulating tumor DNA (ctDNA) may detect the mutations. When comparing ctDNA alterations with tumor DNA from matched tissue, all somatic mutations identified in the tumor were simultaneously present in the ctDNA.[49] Furthermore, variant allele frequencies and copy number profiles of common mutations showed a high correlation between ctDNA

Table 2 Comparison of Homologous Recombination Repair Mutation Between Global and Japan in PROfound Trial

		Germline/Somatic Mutation			
		mCRPC			
		Global (n=2793)		**Japan (n=302)**	
Cohort	Gene	n	%	n	%
Cohort A	*BRCA1*	35	1.3	6	2
	BRCA2	272	9.7	25	8.3
	ATM	177	6.3	28	9.3
Cohort B	*CDK12*	199	7.1	37	12.3
	CHEK2	44	1.6	0	0
	PPP2R2A	41	1.5	2	0.7
	PALB2	15	0.5	1	0.3
	BRIP1	14	0.5	0	0
	RAD54L	11	0.4	0	0
	BARD1	11	0.4	1	0.3
	RAD51B	10	0.4	1	0.3
	RAD51D	6	0.2	1	0.3
	CHEK1	4	0.1	0	0
	FANCL	2	0.1	0	0
	RAD51C	1	0.04	0	0
	Total	842	30.1	101	33.4

and tissue.[49] Therefore, those data support that ctDNA-based genomic profiling is useful as DNA biomarkers in mCRPC.

The rates of *BRCA1* and *BRCA2* mutations in circulating tumor DNA (ctDNA) among 3334 men with mCRPC in the US were 1.4% and 7.5%, respectively.[50] Although the concordance rate of gene alterations between tumor tissue and ctDNA was 93%, ctDNA contained several *BRCA1* and *BRCA2* alterations that were not identified in tumor tissues.[50] This inconsistent detection between tumor tissue and ctDNA may be due to spatiotemporal heterogeneity or clonal hematopoiesis of indeterminate potential (CHIP).[51] Meanwhile, a study among 100 Japanese with CRPC treated with abiraterone acetate or enzalutamide found 1% and 6% of somatic *BRCA1* and *BRCA2* mutations in ctDNA, respectively.[52] Similarly, a preliminary analysis from the SCRUM-JAPAN MONSTER SCREEN project demonstrated 6% of *BRCA2* mutation in ctDNA among 95 patients with unresectable PCa at pretreatment.[53] Therefore, the rates of *BRCA1* and *BRCA2* mutations in ctDNA were comparable between the residents in the US and Japan, but less frequent compared with those in tissues.

However, there is a concern that liquid biopsy may detect CHIP of leukocytes with genetic abnormalities.[54] Analysis of ctDNA from 69 advanced PCa cases detected four *BRCA1* and *BRCA2* mutations, and one of them was derived from CHIP.[55] Therefore, current ctDNA testing has a high risk of misdiagnosis as an indication for PARP inhibitor therapy, and a test using genomic DNA from white blood cells that distinguish between CHIP mutants and PCa is ideal.

Companion Diagnostics and Comprehensive Genome Profiling

Companion diagnostics is a clinical test to predict the efficacy and side effects of treatment. Conventional genetic or genomic testing can detect alterations in a single gene, while comprehensive genome profiling test can reveal the alterations in hundreds of genes using next-generation sequencer. In Japan, on 31 May 2022, BRACAnalysis®, FoundationOne® CDx Cancer Genome Profile (F1CDx), and FoundationOne® Liquid CDx Cancer Genome Profile (F1L) are available for reimbursement as companion diagnostics (Table 3). In addition, F1CDx, F1L, and OncoGuide™ NCC OncoPanel System (NCC OncoPanel) are also available as comprehensive genome profiling (CGP) test. BRACAnalysis® is a test for germline mutations in *BRCA1* and *BRCA2* genes using leukocyte-derived DNA. F1CDx and F1L are CGP tests using tumor tissue and ctDNA in the blood, respectively, and provide gene alteration profiles in 324 genes without distinguishing between germline and somatic mutations. The NCC OncoPanel, which uses DNA derived from cancer tissue and leukocytes to distinguish germline from somatic mutations and detect alterations in 124

Table 3 Companion Diagnosis Devices in the US and Japan

	Japan	**US**		
Device	BRACAnalysis® FoundationOne® CDx FoundationOne® Liquid CDx	BRACAnalysis®	FoundationOne® Liquid CDx	FoundationOne® CDx
Gene	*BRCA1* *BRCA2*	*BRCA1* *BRCA2*	*BRCA1* *BRCA2* *ATM*	*BRCA1* *BRCA2* *ATM* *BARD1* *BRIP1* *CDK12* *CHEK1* *CHEK2* *FANCL* *PALB2* *RAD51B* *RAD51C* *RAD51D* *RAD54L*

genes has been approved as CGP by insurance in Japan. As well, Guardant360®, which tests for germline and somatic mutations using ctDNA in blood, has been approved as CGP by PMDA in Japan.

In the US, companion diagnostics for olaparib include BRACAnalysis®, F1CDx, and F1L.[56] Similarly, F1CDx, F1L, and Guardant360®are approved by the FDA as CGP. In addition, the FDA approved F1CDx as companion diagnostic for rucaparib based on TRITON2 trial results.[30] Thus, although there are a few differences in the availability of diagnostic tests for *BRCA1* and *BRCA2* mutations, similar tests are available in the US and Japan.

Issues related to olaparib treatment in Japan and beyond

Olaparib is expected to show high efficacy in Japanese patients, as shown by the results from the Asian subgroup in the PROfound trial. However, in Japan, olaparib is approved only for *BRCA1* and *BRCA2* mutations, in contrast to the FDA's approval for 14 HRRm. Although the frequency of somatic *BRCA1* and *BRCA2* mutations is comparable between Japan and worldwide, the frequency of germline *BRCA1* and *BRCA2* PVs in Japanese is suggested to be lower than other races. Therefore, the number of patients who can be treated with olaparib for mCRPC could be relatively limited in Japan compared to the US.

The phase 3 PROpel trial (NCT03732820) compared the effect of olaparib plus abiraterone acetate versus placebo plus abiraterone acetate in patients with untreated mCRPC.[57] An interim analysis showed that olaparib treatment improved the rPFS compared to abiraterone acetate alone in the HRRm group (HR 0.54, 95% CI 0.36–0.79) and the non-HRRm group (HR 0.76, 95% CI 0.59–0.97). On the other hand, the MAGNITUDE phase 3 trial (NCT03748641) compared the PARP inhibitor niraparib plus abiraterone acetate (combination therapy) versus placebo plus abiraterone acetate in mCRPC, in which study up to 4 months of prior abiraterone plus prednisone for mCRPC was allowed. The HRRm group showed an improvement in rPFS with the combination therapy, whereas no benefit was observed in the HRR-nonmutant group.[32] Thus, the results of PARP inhibitors combined with ARAT for non-HRR deficiency are conflicting, which might be due to the difference of eligibility whether prior abiraterone plus prednisone was allowed or not. It is necessary to discuss the optimal use of PARP inhibitor, depending on the results from further investigations.

In addition, phase 3 TALAPRO-3 (NCT04821622) is currently testing the effect of enzalutamide plus the PARP inhibitor talazoparib versus enzalutamide plus placebo in patients with metastatic castration-sensitive PCa carrying DNA damage response gene mutation.[58] Moreover, phase 3 AMPLITUDE (NCT04497844)[59] is testing the effect of abiraterone acetate plus the PARP inhibitor niraparib, in metastatic castration-sensitive PCa with HRRm.

As well, platinum-based anticancer drugs, radioisotope radium-223, and bipolar androgen therapy have also been suggested to be effective for PCa with HRR deficiency, including *BRCA1* and *BRCA2* mutations.[60–63] Then, HRR deficiency may be a predictive biomarker of efficacy with those treatments.

Conclusion

Olaparib treatment is currently available for treatment of mCRPC in Japan although there are several differences such as frequency of *BRCA* gene mutation and the genes for olaparib indication between the US and Japan. Despite some challenges, there is no doubt that olaparib has opened the door to precision medicine for PCa. Several PARP inhibitors are also under investigation, and further clinical applications in PCa are expected based on the results of future clinical trials.

Disclosure

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