

Applying precision medicine approach to metastatic castration-resistant prostate cancer: urgent education need on genomic oncology.

Jue Wang*

University of Arizona Cancer Center at Dignity Health St. Joseph's, Phoenix, AZ, USA

Abstract

Metastatic castration-resistant prostate cancer (mCRPC) remains a therapeutic challenge. As a result of advances in genomic sequencing technology, “next-generation sequencing” (NGS) is increasingly incorporated into clinical trials and routine oncology clinical practice. Molecular profiling of mCRPC can be a valuable way of defining molecular alterations that might contribute to optimal treatments while reduce risk of adverse effects. To effectively apply cutting edge research to daily patient care, oncologists must grasp the fundamentals of genomic oncology, molecular testing and interpretation. There is an urgent need for health professional education to allow implementation of these novel precision medicine tools.

Keywords: Metastatic castration-resistant prostate cancer (mCRPC), Personalized medicine, Next-generation sequencing, Genomic oncology, Professional education, Cancer genomics, DNA damage response (DDR), Homologous recombination (HR), BRCA1, BRCA2, Poly(ADP-ribose) polymerases (PARP), PARP inhibitors, Cell-free DNA (cfDNA).

Accepted on 04 December, 2017

Prostate Cancer Overview

Prostate cancer is the most commonly diagnosed cancer in men and the second leading cause of cancer-related deaths in the United States [1]. Androgen-deprivation therapy (ADT) has been the standard first line therapy for metastatic prostate cancer for last six decades. While ADT initially shows clinical benefit for the majority of patients, prostate cancer inevitably progresses to metastatic castration-resistant prostate cancer (mCRPC) [2]. In the last six years, five novel treatments have been approved by U.S. Food and Drug Administration (FDA). These novel treatments have distinct mechanisms of action: novel microtubule-targeted agent (cabazitaxel); first-of-type immunotherapy (sipuleucel-T); steroidal CYP17A1 inhibitor (abiraterone); androgen receptor (AR) blockade (enzalutamide); and alpha particle-emitting radiopharmaceutical agent (radium-223) [3,4]. While therapeutic options for these patients have significantly improved, mCRPC remains a lethal disease.

Genomics Alterations in Prostate Cancer

Prostate cancer is now recognized as a genetic disorder resulting from the accumulation of various genetic alterations [5]. In a study of Whole-exome gene analysis of a cohort of 150 patients with mCRPC, aberrations of AR, ETS genes, TP53, and PTEN were identified in 40%–60% of cases, with TP53 and AR alterations enriched in mCRPC compared to primary prostate cancer [6-8]. Aberrations of BRCA2, BRCA1, and ATM were observed at much higher frequencies (19.3% overall) compared to those in primary prostate cancers. Clinically actionable alterations were identified in 89% individuals with aberrations in AR, 8% with actionable pathogenic germline alterations, 65% in other cancer-related genes [9,10].

The current progress on mCRPC genomic analysis can be summarized into two aspects: the identification of clinically actionable targets; and novel mutations in mCRPC genomes. Incorporation of practice NGS technology into clinical trials and routine clinical will hopefully advance our understanding of aggressive biological behavior of mCRPC, which will in turn lead to personalized therapy for mCRPC [9-11]. The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for metastatic disease now include a reference to molecular profiling as a permissible consideration for treatment decision making. The reduced cost and faster turn-around-times, clinical applications for genomic testing likely continue to increase.

DNA Repair Defect in Prostate Cancer

Genomic DNA is constantly exposed to various genotoxic insults from both internal and external environments that can lead to different types of distinct DNA damage. Unrepaired DNA damage can impact the integrity of the genome, creating genomic instability and leading to accumulation of further genomic aberrations that support cancer cell growth, proliferation and survival [8,9].

DNA damage response (DDR) are important mechanism to maintain genomic integrity [12,13]. The single-strand breaks (SSB_s) are repaired primarily through the base excision repair (BER) pathway. SSBs may accumulate because of damaged repair pathways, resulting in the formation of a double-strand break (DSB). One of the major pathways of DSB repair is homologous recombination (HR).

In advanced prostate cancer, the enrichment of genomic instability could be attributed to impaired ability of DNA repair [14]. BRCA2 alteration was identified in 12.7% of cases of

mCRPC and the most frequent gene mutation [15]. Overall DNA repair gene aberrations were found in 22.7% of patients, with ATM and BRCA1 alterations occurring in 19.3% of patients. In addition, 3.4% of patients have CDK12, FANCA, RAD51B and RAD51C mutations [16]. These findings of distinct molecular subtype of mCRPC have important implications for developing novel therapy.

Poly-(ADP-ribose) Polymerase and DNA Repair

Poly-(ADP-ribose) polymerases (PARP) are DNA damage repair enzymes activated by DNA single-(SSB) or double strand breaks (DSB) [17-20]. In the situation of PARP inhibition, cells switch over to homologous recombination (HR) for DNA repair. BRCA1- and BRCA2-mutated cells, which are HR deficient, are hypersensitive to PARP inhibition through the mechanism of synthetic lethality [21]. Similarly, HR deficient cancer cells also show increased sensitivity to PARP inhibitor.

Clinical Trials Investigating PARP Inhibitors in mCRPC

Several PARP inhibitors have entered in early clinical trials. In a multi-center, Phase I clinical trial with PARP inhibitor olaparib (Lynparza), sixty patients with various refractory cancers were enrolled. Antitumor activity was observed in patients of BRCA mutation carriers, who had ovarian, breast, or prostate cancer. Among the three patients with mCRPC recruited, only one had a BRCA2 mutation [22]. This patient had a partial prostate-specific antigen (PSA) response and a complete radiographic response of bone metastases.

In a Phase I dose-escalation study of Niraparib (MK-4827) in BRCA mutation carriers and patients with sporadic cancer, 30% of 21 mCRPC patients had a decrease of circulating tumor cells (CTC) counts and one patient had partial PSA response [23]. In addition, stable disease (SD) was reported in 43% of patients.

In a Phase II clinical trial of olaparib in BRCA1/2-associated cancers, 50% response rates (RR), 25% SD were reported in eight previously heavily treated mCRPC patients with germline BRCA1/2 mutations. Median progression-free survival and the Overall Survival (OS) were 7.2 and 18.4 months, respectively, with 50% of patients were still alive at 12 months [24].

In the TOPARP-A phase II trial reported in The New England Journal of Medicine by investigators from the Institute of Cancer Research (ICR) and The Royal Marsden Hospital in London, olaparib produced an impressive high RR in patients with previously heavily treated mCRPC with tumors exhibiting defects in DNA-repair genes [25]. Overall, sixteen of 49 evaluable patients had a RR of 33%. Median OS was 10.1 months. In 16 of 49 (33%) evaluable patients, DNA-repair genes defects (BRCA1/2, ATM, Fanconi's anemia genes, and CHEK2) were identified by Next-generation sequencing. 88% of those patients with identifiable DNA-repair defects had a response to olaparib. Based on the impressive results of this trial, the FDA has granted Breakthrough Therapy designation to olaparib for patients with BRCA1/2 or ATM gene mutated

mCRPC, who had taxane-based chemotherapy and at least one androgen signaling pathway inhibitor [26]. Larger clinical trials exploring the interaction between PARP inhibitors and DNA-repair defects in patients with mCRPC are currently ongoing (Table 1).

Table 1. Ongoing Clinical Trials (Phase I/II/III) with PARP-1 inhibitors for metastatic castration-resistant prostate cancer.

Agent(s) [Phase]	Identifier
Rucaparib [II]	NCT02952534
Olaparib+Arbiterone [II]	NCT01972217
Olaparib with or without cediranib [II]	NCT02893917
Veliparib+Arbiterone [II]	NCT01576172
Rucaparib versus Abiraterone acetate or Enzalutamide or Docetaxel [III]	NCT02975934
Olaparib versus Enzalutamide or Abiraterone Acetate [III]	NCT02987543

Challenges of Precision Therapy

Successful precision therapy is tailored based on examining the genomic alterations in tumor tissues. However, tissue biopsy is very challenging because bone metastases are predominant in patients with advanced prostate cancer. Biopsies are invasive, morbid, and are subject to sampling bias, biopsy of single site metastatic lesion may not represent the overall tumor genetic changes. mCRPC is a progressive disease with accumulations of gene alterations during disease progression. Serial biopsies are required in order to identify genes might contribute to disease recurrence and resistance to therapy. Further, accurate next-generation sequencing in metastatic bone lesions-derived DNA is technically challenging.

There has been an increasing interest in developing liquid biopsies test such as cell-free DNA (cfDNA) as a predictive biomarker for monitoring therapeutic response, and detecting recurrence. cfDNA is a blood-based test is an appealing alternative as it is non-invasive and poses minimal risk to patients. It is easy to perform, can be repeated at the time of recurrence. cfDNA is derived from all tumor sites, therefore it may represent a more complete repertoire of tumor genome variations [26-29]. It has been shown that tumor genomic abnormalities are well reflected in cfDNA during cancer progression [30-33].

Urgent Education Need on Genomic Oncology

The advances in genomics and expansion of molecular testing likely pave the way for precision cancer medicine for prostate patients in the near future. With more cancer-specific genetic information available, patients can be directed toward to appropriate therapies or clinical trials. There is clearly increasing availability of molecular profiling tests in recent years (Table 2). Commercial laboratories have begun to market such genomic tests to oncologists. Patients express willingness to get those tests [34]. However, genomic oncology has not typically been part of the training for oncology fellowship.

Citation: Wang J. Applying precision medicine approach to metastatic castration-resistant prostate cancer: urgent education need on genomic oncology. *J Mol Oncol Res.* 2018;2(1):6-10.

Even for physicians with substantial expertise in genitourinary oncology, NGS based tests are new term to them, which provide so much information and so many possible uses for it, in some cases, not actionable at all. A recent study showed there is no consensus on how physicians to use molecular assays for personalized cancer care and suggest an urgent need for health professional education to allow implementation and optimal use of these novel personalized medicine tools [35]. In the future, evidence-based genomic tests may help guide the optimal utilization of these tests.

Table 2. Examples of current available molecular tests from commercial laboratories.

Test	Company	Source	Platform	Gene panel
FoundationOne	Foundation Medicine	Tissue, blood	Next Generation Sequencing	236 genes
Caris Molecular Intelligence®	CarisLife Sciences	Tissue	IHC, FISH, Next Generation Sequencing	40 genes
Paradigm Diagnostic test	Cancer (PCDX) Paradigm	Tissue	IHC, Next Generation Sequencing	131 genes
Guardant360	Guardant Health	Blood	Next Generation Sequencing	54 genes

University of Arizona Cancer Center (UACC) Experience

We have applied next generation sequencing using both tumor tissue and cfDNA in patients with mCRPC. As part of a multi-

Table 3. Summary of University of Arizona Cancer Center (UACC) experience on the application of next generation sequencing in the management of patients with metastatic castration-resistant prostate cancer. ECOG: Eastern Cooperation Oncology Group; RB: retinoblastoma gene; BRCA1: breast cancer 1; BRCA2: breast cancer 2; cfDNA: Cell-free DNA; PSA: Prostate-specific antigen (PSA); CR: Complete remission; PR: Partial response; SD: stable disease; PCR: Pathological complete remission; CR: Complete remission.

Patient ID	Age	ECOG	Gleason	Gene alterations	Source	Treatment	Best response
1	85	2	4+5	BRCA1	cfDNA	Olaparib	PSA response
2	62	0	5+4	BRCA2	tumor tissue	DOCETAXEL	PSA CR
3	63	1	5+4	BRCA2, TMPRSS2-ERG gene fusion, and TP53	tumor tissue and cfDNA	Olaparib	PR
4	78	1	4+5	BRCA2	cfDNA	Enzalutamide	SD
5	67	1	5+4	PTEN, RB, TMPRSS2-ERG gene fusion, and TP53	tumor tissue	Olaparib	PCR

Looking Forward

Since genomics-guided therapy will be integrated into treatment paradigm of mCRPC (Table 4), there is a critical need for education in genomics among oncology professionals. In order to take full advantage of valid and clinically useful genomic tests, oncologists must become knowledgeable about indications and interpretation, limitations of current available tests. In addition, they need aware that the survival benefits of

disciplinary molecular tumor board at UACC, specialists meet together to discuss patient cases and findings from molecular profiling tests. The genomic testing is appropriate for a given patient of pursuing these tests are usually made at our Molecular Tumor Board for those refractory patients who have run out of standards options. Recently, we and others reported the results from a multi-institutional study showed that DNA-based liquid biopsy has great potential to examine molecular alterations in advanced prostate cancer [36].

Based on the molecular profiling findings of DNA repair defects, several heavily pretreated, refractory mCRPC patients were found eligible and treated with olaparib. One patient with BRCA 2 deletion who had partial response lasting eight months. Another patient with TMPRSS2-ERG fusion and PTEN loss had complete pathological response (Table 3). Olaparib monotherapy at the dose of 400 mg bid was generally well tolerated in our patients, with the majority of adverse events being of mild to moderate severity. Further studies are ongoing to examine the utility of cfDNA as a predict biomarker for treatment response and clinical outcomes. There are numerous challenges that need to be surpassed before delivering on the promise of personalized cancer therapy. These include tumor heterogeneity, the requirement of tissue sample for Next-generation sequencing, potential morbidity of biopsies, technical limitations of current available molecular tests, costs, and reimbursement hurdles.

genomic guided therapy largely have not been proved and the perceived benefit may be overestimated [37]. Continued critical evaluation of emerging NGS and other new technologies, their clinical utility, interpretation, and indications for the use of such tests are necessary to ensure the optimal integration into appropriate patient care. At UACC genitourinary oncology division, we are developing case based approach on genomic medicine education for our oncology

providers, resident physicians, oncology trainees, and community oncologists.

Table 4. Current available and emerging therapies for the patients with metastatic castration-resistant prostate cancer.

Agent	Mechanisms of action	Genomic guided therapy
Lupron	Androgen-deprivation therapy (ADT)	No
Docetaxel	Microtubule-targeted agent	No
Cabazitaxel	Novel microtubule-targeted agent	No
Sipuleucel-T	Immunotherapy	No
Abiraterone	Steroidal CYP17A1 inhibitor	No
Enzalutamide	Androgen receptor (AR) blockade	No
Radium-223	Alpha particle-emitting radiopharmaceutical agent	No
Olaparib (Lynparza)	PARP inhibitor	Yes

Conclusion

Precision medicine shows great promise in the management of mCRPC, but it is still in the very early stages. Advancement in mCRPC precision medicine is dependent on continuous research in prostate cancer genomics and enrolling patients into clinical trials. Given the rapid integration of genomics into genitourinary oncology, health care providers for prostate cancer should be educated in genomic medicine.

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Citation: Wang J. Applying precision medicine approach to metastatic castration-resistant prostate cancer: urgent education need on genomic oncology. *J Mol Oncol Res.* 2018;2(1):6-10.

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***Correspondence to**

Jue Wang
University of Arizona Cancer Center
Dignity Health St. Joseph's
Phoenix AZ, USA
E-mail: jue.wang@dignity health.org