Translating Therapeutic Innovations into the Management of Metastatic Castration-Resistant Prostate Cancer

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EDITORIAL

Prostate cancer is the most commonly diagnosed cancer in men and the second leading cause of cancer-related deaths in the United States [1]. In 2016, the National Cancer Institute estimates there will be 180,890 cases diagnosed along with an estimated 26,120 estimated cancer-related deaths in 2016. 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). While therapeutic options for these patients have significantly improved, mCRPC remains a lethal disease.

Metastatic prostate cancer presents an appealing target for precision oncology because it is now recognized as a genetic disorder resulting from the accumulation of various genetic alterations [3]. In a Whole-exome gene analysis of a cohort of 150 patients with mCRPC, aberrations of androgen receptor (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. 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 [4]. (62.7% with aberrations in AR, 8% with actionable pathogenic germline alterations, 65% in other cancer-related genes).

DNA damage response (DDR) is an important mechanism to maintain genomic integrity. In advanced prostate cancer, the enrichment of genomic instability could be attributed to impaired ability of DNA repair [5]. BRCA2 alteration was identified in 12.7% of cases of mCRPC and the most frequent gene mutation [6]. 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 [6]. These findings of distinct molecular subtype of mCRPC have important implications for developing novel therapy.

Poly-(ADP-ribose) polymerase (PARP) is responsible for repairing single strand breaks in DNA. Inhibition of this enzyme leads to alterations in the ability of DNA replication to occur, causing cell death. 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 [7]. Similarly, a synthetic lethality using DNA-damage repair inhibitors has also been proposed to apply to the common PTEN-deletion CRPC tumors, which are reported to have defects in homologous recombination [8].

Multiple PARP inhibitors have entered in early clinical trials [9-12]. In a Phase I dose-escalation study of Niraparib 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. 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 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. In the TOPARP-A phase II trial, olaparib produced an impressive high RR in patients with previously heavily treated mCRPC with tumors exhibiting defects in DNA-repair genes [11]. 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 Food and Drug Administration (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 [13]. Larger clinical trials exploring the interaction between PARP inhibitors and DNA-repair defects in patients with mCRPC are currently ongoing.

Successful precision therapy is tailored based on examining the genomic alterations in tumor tissues. However, tissue biopsy in patients with mCRPC is very challenging because bone metastases are predominant. Biopsies are invasive, morbid, and are subject to sampling bias; biopsy of single site of metastatic lesion may not represent the overall tumor genetic changes. Since mCRPC is a progressive disease with accumulations of gene alterations during cancer progression, optimally, serial biopsies are required in order to identify genes that might contribute to disease recurrence, progression and resistance to therapy. Further, accurate next-generation sequencing in bone lesions-derived DNA is technically difficult and challenging. Cell-free DNA (cfDNA) is an appealing alternative as it is non-invasive and poses minimal risk to patients. cfDNA is derived from all tumor sites, therefore it may represent a more complete repertoire of tumor genome variations [14]. Recently, the results from a multi-institutional study [15] showed that DNA-based liquid biopsy has great potential to examine molecular alterations in advanced prostate cancer. Nearly all (94%) patients had at least one change detected in the cfDNA. A higher overall number of genetic changes (including changes in the AR gene) were associated with poorer treatment outcomes, such as a tendency towards shorter survival, although the difference in survival was not statistically significant.

CONCLUSIONS

With the advance of next generation sequencing technologies, we can now characterize individual mCRPC tumor sample and determine the driving mutations. Although the genomic knowledge available is ahead of our current ability to therapeutically target mCRPC, however, we are now able to offer patients genomic-driven clinical trials. We are finally beginning to see the potential of bringing molecular genomics into clinical decision-making for patients with mCRPC.

REFERENCES