Editorial Commentary

Current status of circulating tumor cell androgen receptor splice variant-7 in metastatic castration-resistant prostate cancer

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In castration resistant prostate cancer (CRPC), the androgen receptor (AR) pathway remains activated through upregulation of AR, mutation, and paracrine/autocrine androgen synthesis (1). Clinical significance of AR variant 7 (AR-V7) in circulating tumor cells (CTCs) was first reported by Antonarakis *et al.*, which demonstrated a strong association with abiraterone and enzalutamide treatment resistance (2). On the other hand, due to the naïve nature of CTCs, detection of AR-V7 status by CTCs had some limitations includes reproducibility of AR-V7 positivity, heterogeneity between institutions. Furthermore, previous studies rarely attempt to compare the AR-V7 expression between tissue and CTCs. There have been several issues to be solved regarding the analysis of AR-V7 in CTCs.

In order to answer those questions, Sharp *et al.* conducted a multi-institutional study to prove the reproducibility as well as the clinical significance of AR-V7 in CTCs. They studied CTC AR-V7 status in 227 peripheral blood samples, from 181 metastatic CRPC (mCRPC) patients with CTC counts and matched mCRPC biopsies. They used AdonaTest for AR-V7 mRNA detection, and CellSearch systems for the CTC counts. Intralaboratory reproducibility was 92% between replicate. Between institutions, the overall interlaboratory agreement between London, UK, and JHU in Baltimore, USA, was as high as 86%. Among all cohorts, 35% of samples showed CTC+/AR-V7+. They demonstrated that CTC+/AR-V7+ samples had higher CellSearch CTC counts and biopsy AR-V7 protein expression than CTC+/AR-V7– samples. There was a positive correlation between AR-V7 mRNA expression and CTC counts. CTC+/AR-V7+ showed the worst survival, followed by CTC+/AR-V7–. On the other hand, CTC- showed the most favorable prognosis.

Another unique aspect of the article may be that they conducted a multivariate analysis of CTC AR-V7 and CellSearch CTC counts together with other clinical factors. Previous reports mainly looked at the role of AR-V7 status in CTCs in a univariate manner (2,3). Data demonstrated prognostic significance of CTC AR-V7 and CellSearch CTC counts (≥5) over the common clinical factors include prostate-specific antigen (PSA), lactate dehydrogenase (LDH), and even the presence of visceral metastasis. As Prostate Cancer Clinical Trials Working Group 3 (PCWG3) recommended serial biologic profiling using tumor samples from biopsies and blood-based diagnostics (4), current data confirmed the clinical significance of biological profiling through liquid biopsies.

Compare to recent published phase III clinical trial (ARMOR3-SV) using the same AdonaTest for detecting CTC ARV-7 (5), current article showed relatively high AR-V7 prevalence. AR-V7 prevalence was 8% in ARMOR3-SV, while 35% in the present study. The reason may be explained by the difference in patients' backgrounds. Median PSA in ARMOR3-SV trial was 72.0 ng/mL in enzalutamide arm and 96.15 ng/mL in galeterone arm. However, in the current study, the median PSA was >100 ng/mL among all the groups. It was also described that AR-V7+ was observed in 15% of patients with PSA

>31 ng/mL and 30% with >21 bone lesions in ARMOR3-SV (5). The heterogeneity observed between studies may be explained by the metastatic burden of prostate cancer patients enrolled in the studies.

In terms of detecting AR-V7, two major approaches are available, such as AdonaTest CTC AR-V7 mRNA assay and Epic Sciences (Epic; San Diego, CA, USA) CTC nuclear-specific AR-V7 protein assay. AdonaTest was first demonstrated by Antonarakis *et al.*, while CTC nuclear-specific AR-V7 assay was utilized by Scher *et al.* (2,6). Since heterogeneity of AR-V7 positivity between two tests and among institutions has been an issue, prospective multicenter validation of AR-V7 study (the PROPHECY study) was conducted. Twenty-four percent of samples were AR-V7 positive by the JHU mRNA assay, while 9% of samples were AR-V7 positive by the Epic protein-based assay. Clinical significance of AR-V7 status by two assays were similar among patients treated with Enzalutamide or Abiraterone (7).

One of the critical characteristics of AR-V7 may be the association between AR amplification. Previous reports demonstrated an overlapped expression pattern of AR-V7 and full-length AR (AR-FL) among CRPC patients (8). Compare to the primary tumor, AR-V7 increased 53 folds, while AR-FL also increased ten folds in CRPC (8). In biological aspects, AR-V7 was generated through RNA splicing factors. Under androgen deprivation therapy, the recruitment of several RNA splicing factors to the 3' splicing site for AR-V7 was increased. RNA splicing enhancers and their binding proteins (U2AF65 and ASF/SF2) play a critical role in splicing AR pre-mRNA into AR-V7 (9). In this aspect, the presence of AR-FL and AR-V7 may be a part of a common pathway. Del Re *et al.* investigated AR-FL and AR-V7 in association with resistance to the AR-directed therapy. Among 73 CRPC patients, AR-FL was detected in all patients, while AR-V7 was detected in 22% of patients. AR-FL expression was significantly higher in AR-V7+ patients compare to AR-V7– patients. There was a significant correlation between AR-FL and AR-V7 expression ($r=0.581$, $P<0.0001$). Presence of AR-V7 as well as high AR-FL copy numbers associated with poor prognosis (10).

Based on the next-generation sequence of biopsy samples of metastatic tissues, the detection of AR-V7 was 10% among CRPC patients (11). Among AR splicing variants, besides AR-V7, other variants exist, such as AR-V1, V3, and v567es (11). Tagawa *et al.* investigated the prognostic significance of AR-FL, AR-V7, and AR-567es in CTCs from patients receiving docetaxel or cabazitaxel in TAXYNERGY (NCT01718353) study. Of those CTCs were detected, 51.9% of the samples were CTC+/AR-V7+, and 26.9% were CTC+/AR-567es+. Presence of AR-V7 or AR-567es related to shorter PFS even among patients treated with taxane-based therapy. PSA response rate (>50%) was very similar between AR-V7+ (58%) and AR-567es+ (57%) patients. They concluded that the presence of AR-V7 might confer modest taxane resistance, although significantly less than that on AR targeted drugs (12).

Recently, Cucchiara *et al.* reported an interesting finding related to a gonadotropin-releasing hormone (GnRH) receptor antagonist. In mice bearing AR-V7 positive VCaP xenograft tumors, the size of tumors in degarelix-treated mice were 67% of those in the leuprolide-treatment group. Measurements of intratumoral steroids by LC/MS identified that degarelix significantly decreased the testosterone level and steroidogenesis pathway intermediates, comparable to surgical castration or leuprolide. The author described the potential clinical advantage of degarelix over GHRH agonists in AR-V7 harboring tumors (13).

A series of mechanisms exist during the development of CRPC. Resistance mechanisms independent of AR-V7 include AR gain or mutations, alternative AR variants, lineage plasticity, genomic structural rearrangements, and AR enhancer amplification (1,7). Furthermore, besides AR, compound genomic alterations of TP53, PTEN, and RB1 tumor suppressors are related to aggressive variant prostate cancer (AVPC) (14). The St Gallen Advanced Prostate Cancer Consensus Conference 2017 reported that the mutation in DNA damage response (DDR) genes, such as BRCA1, BRCA2, and ATM, should be reported in metastatic prostate cancer because that knowledge will likely influence management decisions (15). Treatment with the PARP inhibitor olaparib showed a high response rate (88%) in patients who had a homozygous deletion, deleterious mutations, or both in DNA repair genes, even after the development of resistance against the standard treatment (16). To investigate alteration in multiple target genes, it may be a practical approach to utilize the cfDNA in addition to CTCs (17).

As precision medicine is on the rise, the genomic analysis of individual patients is becoming more and more critical. As a series of retrospective and prospective trial identified, it is no doubt that the presence of AR-V7 in CTCs is related to treatment resistance to AR targeted therapy. However, alteration in tumor suppressor and DDR related genes are also involved during the development of CRPC (14,15). It may be the way to combine AR-V7 status in CTCs together

with the mutational landscape of AR and other prognostic genes in cfDNA to determine the optimal treatment sequence in CRPC patients. Based on biological profiling through the liquid biopsy, risk classification, and treatment strategy of metastatic prostate cancer may drastically change in the near future.

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None

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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