Examining HSD3B1 as a possible biomarker to detect prostate cancer patients who are likely to progress on ADT

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ABSTRACT
The Chemohormonal Therapy vs Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) was a randomized phase III trial that evaluated the outcomes of men with metastatic prostate cancer who received castration with or without docetaxel. Patients from this trial were genotyped in a recent study to detect HSD3B1 variance and to determine 2-y freedom from castration-resistant prostate cancer as well as overall survival. The results of this study identified HSD3B1 as a possible biomarker that can be used to predict response to therapy in patients with metastatic disease.

Men with clinically advanced prostate cancer commonly develop metastatic castration-resistant prostate cancer (mCRPC), despite initial efficacy with androgen deprivation therapy (ADT). Progression is driven by androgen receptor reactivation through various mechanisms, one of which involves intratumoral androgen synthesis originating from adrenal precursor steroids. It has been proposed that progression could also be related to an inherited single-nucleotide polymorphism in the HSD3B1 gene. This gene encodes 3β-hydroxysteroid dehydrogenase-1 (3βHSD1), an enzyme that is responsible for dihydrotestosterone (DHT) generation through catalyzed synthesis of adrenal androgen precursors. The identified polymorphism inhibits 3βHSD1 from undergoing degradation, leading to downstream increases in intratumoral DHT and early onset of castration-resistant prostate cancer (CRPC). Retrospective studies have suggested that the inheritance of the variant allele, HSD3B1(1245 C), is linked to decreased progression-free survival (PFS) and overall survival (OS) when compared to individuals with the wild-type allele, HSD3B1(1245 A).

The Chemohormonal Therapy vs Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) examined the clinical benefit of castration with or without docetaxel in men with metastatic prostate cancer. A 2020 study published in JAMA Oncology determined the HSD3B1 germline genotype in 475 white men who participated in the CHAARTED trial to explore clinical outcomes in relation to the determined genotype. If a patient had no HSD3B1(1245 C) alleles, they were defined as adrenal restrictive. Adrenal permissive was defined as one or more HSD3B1(1245 C) alleles. Of the 475 white men included in the trial, the adrenal-permissive genotype was present in 56.8% of them. Patients in the trial were randomized 1:1 to ADT or ADT plus docetaxel.

Surgical or medical castration through luteinizing hormone-releasing hormone antagonist or agonist with or without an antiandrogen was provided to all patients. Patients who required antiandrogen therapy received bicalutamide or flutamide, and docetaxel was administered at a dose of 75 mg/m² every 3 weeks for six cycles. Inclusion criteria required a confirmed prostate cancer diagnosis or a clinical presentation of prostate cancer with an elevated prostate-specific antigen (PSA). Patients had evidence of metastatic disease, confirmed by imaging and an Eastern Cooperative Oncology Group (ECOG) performance score of 0, 1, or 2. Patients already receiving ADT were included as long as therapy was started within 120 d of randomization. Past ADT use was allowed if ADT was given as adjuvant therapy and the duration of use was 24 months or less with a progression-free interval of at least 12 months following therapy. Patients with high-volume disease were defined as those with visible metastases or four or more bone metastases, with one or more lesion(s) beyond the vertebral bodies and pelvis. This trial investigated 5-y OS including death from any cause and 2-y freedom from CRPC.

In men with low-volume disease and the adrenal-permissive genotype, freedom from CRPC at 2 y was significantly worse when compared to those with the adrenal-restrictive genotype (51% vs. 70.5%, p = .01). After adjusting for prognostic factors within the multivariate analysis, the adrenal-permissive genotype continued to show a higher risk for CRPC (hazard ratio [HR]: 1.89, 95% confidence interval [CI]: 1.13–3.14, p = .02). There was no significant difference in freedom from CRPC at 2 y in men with high-volume disease when comparing the adrenal-permissive genotype to the adrenal-restrictive genotype (26.6% vs. 27.3%, p = .89). In patients with high-volume disease, both the adrenal-permissive and adrenal-restrictive genotypes showed meaningful benefit from docetaxel (p = .003, p < .001).
while the patients with low-volume disease did not regardless of genotype in relation to freedom from CRPC at 2 y.

Survival was worse in men with low-volume disease with the adrenal-permissive genotype at 5 y when compared to those with the adrenal-restrictive genotype (57.5% vs 70.8%, \( p = .03 \)). Following adjustment for prognostic factors in the multivariate analysis, the adrenal-permissive genotype remained associated with a higher risk of death at 5 y (HR: 1.74, 95% CI: 1.01–3, \( p = .045 \)). Men with high-volume disease showed no significant difference at 5 y in OS when comparing the adrenal-permissive to the adrenal-restrictive genotypes (37.3% vs. 33.1%, \( p = .65 \)). However, in men with high-volume disease, both adrenal-restrictive and adrenal-permissive genotypes benefited from the addition of docetaxel (\( p = .008, p = .02 \)); conversely, men with low-volume disease regardless of genotype did not have improved OS with the addition of docetaxel.

The results of this study demonstrate the role of the adrenal-permissive genotype in patients with low-volume disease. The inheritance of the variant allele, HSD3B1(1245 C), is linked to the early development of CRPC and decreased OS at 5 y in patients treated with ADT, with or without docetaxel. Furthermore, in patients with high-volume disease, the inheritance of the variant allele was not associated with inferior clinical outcomes, demonstrating that low-volume and high-volume disease follow courses that are distinct from one another. Patients with high-volume disease also benefited from the addition of docetaxel, while those with low-volume did not. This suggests that patients with low-volume disease will likely require an alternative treatment as previous studies have demonstrated the same tendency.

Previously, Hearn et al. hypothesized in a multi-cohort study that men who inherited the variant allele would show signs of intrinsic resistance when treated with ADT. All patients in this study had undergone prostatectomy prior to the initiation of ADT due to a rising PSA. The results of the primary cohort showed that PFS was decreased depending on the number of variant alleles that were inherited. Median survival was 6.6 y in homozygous wild-type men, 4.1 y in heterozygous men, and 2.5 y in homozygous men (\( p = .011 \)).

Results of the Mayo SPORE cohort revealed a median PFS of 3.3 y in homozygous wild-type men, 2.8 y in heterozygous patients, and 0.9 y in homozygous variant patients (\( p = .0022 \)). The same trend existed in the third metastatic cohort, and distant metastasis-free survival was lowest in homozygous men when compared to homozygous wild-type and heterozygous patients (\( p = .022 \)). Relative to OS, all three cohorts showed that inheritance of two copies of the variant allele led to significantly worse OS when compared to homozygous wild-type men.

A validation study in 102 patients showed that the variant allele (1245 C) was associated with a shorter PFS in metastatic hormone-sensitive prostate cancer patients on ADT, where men who were homozygous variant had a shorter median PFS than those who were homozygous wild-type (11 vs 21 months, 95% CI: 1.01–4.58, \( p = .046 \)). A retrospective study demonstrated that the gain-of-function resulting from HSD3B1 variance was coupled with adverse outcomes for homozygous variant patients following ADT therapy. All of the patients with a variant allele progressed to CRPC, whereas 64.7% of patients that were homozygous wild-type developed CRPC (\( p = .003 \)). Furthermore, an additional study looked at outcomes associated with HSD3B1 in men treated with ADT in the context of recurrence following radiotherapy. They found no difference in median time to progression or median OS; however, median time to metastasis was diminished in homozygous variant patients when compared to heterozygous and homozygous wild-type patients (4.4 vs 5.8 vs 7.4 y, \( p = .03 \)).

Men who have inherited two variant alleles progress on ADT sooner than those with the homozygous wild-type genotype. Hearn et al. have demonstrated this in their recent results using a population derived from the CHAARTED trial, and previous studies have alluded to this. Current data support the idea of HSD3B1 as a predictive biomarker of progression on ADT therapy. The downside of this possible biomarker is that it is not applicable to all races. The allele itself presents much higher in white men; therefore, its role as a biomarker is currently limited to that population. More studies in other races need to be conducted to determine if this trend extends past white males.

Prior studies should encourage researchers to examine strategies to overcome HSD3B1 variance to prolong PFS and OS in homozygous variant patients as recent data show that appropriate therapy has yet to be determined. Hahn et al. concluded that the duration of response to abiraterone did not correlate with HSD3B1 genotype in CRPC, suggesting that it is a poor biomarker to guide abiraterone treatment in patients who have already progressed. However, a retrospective study in Japanese patients demonstrated a favorable response to abiraterone therapy in patients with the variant genotype. In the setting of ketoconazole without prior abiraterone use in CRPC, patients who were homozygous for the variant allele displayed a longer duration of response compared to wild-type individuals.

While Hearn et al. have strengthened the evidence that patients with the variant allele have diminished outcomes, it is now important that we are able to pinpoint the appropriate treatment options for these patients. Further research will help identify what therapy is best in this subset of patients to improve therapeutic outcomes.

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No potential conflicts of interest were disclosed.

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