Correlation Between Trough Level of Abiraterone and Prostate-Specific Antigen (PSA) Response in Metastatic Hormone-Sensitive Prostate Cancer

Zin W. Myint, Jill M. Kolesar, Joseph Robert McCorkle, Jianrong Wu, Carleton S. Ellis, Danielle E. Otto, Peng Wang

Background: Prostate cancer growth is primarily driven by testosterone and 5α-dihydrotestosterone. Abiraterone is an irreversible inhibitor of CYP17, and CYP17 inhibition is a required step in testosterone biosynthesis. Previous studies have shown that abiraterone trough levels are predictive of prostate-specific antigen (PSA) response in metastatic castrate-resistant prostate cancer (mCRPC). It has not been demonstrated if this association exists for patients with metastatic hormone-sensitive prostate cancer (mHSPC). In this study, we aimed to explore the correlation and association between abiraterone trough levels and PSA levels in patients with mHSPC.

Material/Methods: This was a single-center, prospective, observational study of patients with mHSPC being treated with abiraterone acetate (AA) 1000 mg once daily. Abiraterone trough levels (22-26 h after drug administration) were drawn at 1, 3, and 7 months after treatment initiation.

Results: Thirteen patients with mHSPC were enrolled, and complete pharmacokinetic data were available for 8 patients. The mean trough levels at 1 month, 3 months, and 7 months were 34.49 ng/mL (3.36-240.46), 13.82 ng/mL (2.91-29.96), and 15.7 ng/mL (3.58-26.86), respectively. The correlation between the 1-month abiraterone trough level and 1-month PSA was 0.29 (P=0.38), between 3-month abiraterone trough and 3-month PSA was -0.61 (P=0.08), and between 7-month abiraterone trough and 7-month PSA was -0.31 (P=0.54).

Conclusions: This study demonstrated a trend toward a negative correlation between 3-month abiraterone trough levels and PSA levels, but the correlation was not statistically significant. A study with a larger prospective sample size is needed to validate these findings.

Keywords: Abiraterone Acetate • Prostate-Specific Antigen

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Prostate cancer cell growth is mainly controlled by testosterone and 5α-dihydrotestosterone, which are driven from the androgen receptor-signaling pathway (80-90%) and the adrenal steroidal pathway (10-20%) [1]. Abiraterone acetate (AA) in combination with androgen-deprivation therapy demonstrated survival benefit in men with metastatic hormone-sensitive prostate cancer (mHSPC) [2] and in men with metastatic castrate-resistant prostate cancer (mCRPC) prior to [3] or after docetaxel treatment [4]. AA, a prodrug of abiraterone, is metabolized by hydroxyl-delta-5-steroid dehydrogenase, 3 beta and steroid delta-isomerase 1 (HSD3B1) into Δ4-abiraterone, which irreversibly inhibits the CYP17 enzyme, thereby blocking the conversion from dehydroepiandrosterone (DHEA) to testosterone and 5α-dihydrotestosterone in prostatic tissue [5]. The 3β-hydroxysteroid dehydrogenase isoenzyme 1 (3βHSD1), encoded by the gene HSD3B1, is the initial rate-limiting step in androgen biosynthesis [5,6]. The correlation between plasma progesterone level and abiraterone treatment response was studied in mCRPC and mHSPC [7]. The study showed that an increased level of progesterone within 3 months of starting abiraterone could be a predictive biomarker for poor abiraterone response, and thus resulted in poor clinical outcomes [7].

Previous studies have evaluated the plasma trough abiraterone level as a predictive factor for prostate-specific antigen (PSA) response in mCRPC. Carton et al performed a prospective observational study of the relationship between the abiraterone plasma trough concentration and 3-month PSA response (≥50% reduction) in mCRPC [8]. They found that there was a correlation with PSA response at 3 months if the abiraterone concentration was above 8.4 ng/mL. In those patients with levels higher than 8.4 ng/mL, a prolonged progression-free survival (PFS) was observed compared with that in patients whose abiraterone concentration was below 8.4 ng/mL (PFS 12.2 months vs 7.4 months, HR: 0.55) [8]. Stein et al determined that maintenance of abiraterone trough levels above 8.4 ng/mL was consistent with sustained testosterone suppression to <50 ng/dL and PSA ≥50% reduction through day 84 [9]. This led us to question whether the correlation of plasma abiraterone trough levels above 8.4 ng/mL and attainment of PSA 0.2 ng/mL or less after treatment remain predictive in the setting of mHSPC.

Based on this rationale, in the present study, we aimed to explore the correlation and association between steady-state trough abiraterone plasma concentrations and 3-month and 7-month PSA levels in patients with mHSPC.

**Background**

**Material and Methods**

The study protocol was approved by the local institutional review board (approval no. 51840). Written informed consent was obtained from each participant.

**Study Population**

This was a single-center, prospective, observational study in patients with newly diagnosed mHSPC who were treated with AA and recruited from July 2019 to October 2021 in the Medical Oncology Clinic at University of Kentucky, Markey Cancer Center. Abiraterone trough levels were measured at 1 month, 3 months, and 7 months after starting AA for routine therapeutic drug monitoring. Trough levels were collected between 22 and 26 h after AA was taken. Eligible patients included men with mHSPC (either de novo or with failure after definitive localized prostate therapy), pathological diagnosis of prostate cancer, PSA elevation, radiologic evidence of metastatic disease, and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2. Prior adjuvant androgen-deprivation therapy was allowed if progression had occurred more than 12 months after completion of therapy. Patients were excluded if they were not eligible to take AA as their first-line therapy for any reason or if they did not meet the above inclusion criteria. Patients’ baseline characteristics (age, race, body mass index, documented metastases as either low volume vs high volume, PSA values, AA dosing, adverse effects, and clinical outcomes) were collected prospectively by reviewing electronic patient records. The definition of high volume was defined by the CHAARTED criteria: the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis [10].

**Treatment**

Participating patients were treated with combined androgen-deprivation therapy and AA/prednisone. All patients were treated with AA at 1000 mg once daily on an empty stomach. A pharmacist checked the potential drug-drug interactions on all patients before initiation of AA. Medication diaries completed by the patients were reviewed by treating physicians for adherence. All adverse events were graded using the National Cancer Institute Common Toxicity Criteria version 6.0. PSA level was monitored at baseline, 1 month, 3 months, and 7 months. Radiologic evaluation was performed at 3 to 4 months after starting AA.

**Pharmacokinetic Analysis**

Plasma samples were obtained from enrolled patients for analysis of AA at 1, 3, and 7 months after the start of treatment. AA was quantified from EDTA-plasma using methods described.
by Alyamani et al [11], with modifications. Briefly, 100 μL plasma samples were spiked with 50 ng/mL abiraterone-d4 (internal standard) then combined with 400 μL methyl tertiary butyl ether and vortex-mixed for 5 min. Samples were centrifuged 5 min at 15,000×g, and 250 μL of the supernatant was transferred to a 96-well polypropylene plate and then evaporated to dryness at 40°C under a stream of nitrogen gas. Dried residues were reconstituted in a 100-μL 2:1 mixture (v:v) of 0.1% formic acid in water: acetonitrile: methanol. Abiraterone and abiraterone-d4 were separated on a 1260 Infinity II LC system (Agilent) with an InfinityLab Poroshell 120 HPH-C18 column (Agilent), 2.1×100 mm, 2.7 μm. Mobile phase A consisted of 0.1% formic acid in water, and mobile phase B was 1:1 (v:v) acetonitrile: methanol. The flow rate was set to 0.4 mL/min and started with 0.5-min 50% mobile phase A, 50% mobile phase B, then the mobile phase B increased to 80% over the next 1 min, was maintained for additional 1.5 min, then returned back to 50% over the next 0.5 min. Abiraterone and abiraterone-d4 were quantified using an Agilent Ultivo triple quadrupole mass spectrometer operating in positive ion mode with an electrospray ionization source. Multiple reaction monitoring was used to quantify mass to transition ions of 350.2 to 156 for abiraterone and 354.3 to 160.1 for abiraterone-d4. The abiraterone standard curve was linear from 1 to 1000 ng/mL, with r² >0.99.

**HSD3B1 Genotyping**

Genomic DNA was extracted from 750 μL of whole blood samples for each enrolled patient using QIAamp DNA blood midi kits (Qiagen) according to the manufacturer’s instructions. DNA was eluted from columns using 200 μL AE buffer and stored at 4°C. TaqMan SNP genotyping assay (Applied Biosystems), C__8695674_10, was used to genotype 20 ng of genomic DNA at the HSD3B1 polymorphic site rs1047303 (c.1245A>C) with TaqMan genotyping master mix (Applied Biosystems) using a QuantStudio 3 real-time PCR system (Applied Biosystems). Positive control samples from the International HapMap Project were obtained from the NIGMS Human Genetic Cell Repository via the Coriell Institute for Medical Research and included samples from individuals CEPH 13291 (NA06986; A/A), CEPH 1341 (NA07048; A/C) and CEPH 13292 (NA07051; C/C).

**Study Endpoints**

We examined (1) the correlation between steady-state trough abiraterone plasma concentrations and PSA levels in patients with mHSPC and (2) the association between abiraterone trough levels and 3-month PSA levels ≤1 ng/mL and 7-month PSA levels ≤0.2 ng/mL in patients with mHSPC. The language of correlation and association can be interchangeable; however, they are technically different. Correlation refers to 2 variables that are correlated in a linear relationship; whereas, association refers to a general relationship between 2 variables [12]. In addition, we measured the germline HSD3B1 (1245 C) allele at baseline and its association with clinical outcomes. We also analyzed the correlation between HSD3B1 and abiraterone trough concentrations.

**Statistical Analysis**

Trough plasma concentrations of abiraterone were correlated with PSA levels by the Spearman correlation coefficient. Abiraterone levels were associated with 3-month PSA levels (categorized as PSA ≤1 ng/mL vs >1 ng/mL) and 7-month PSA levels (categorized as PSA ≤0.2 ng/mL vs >0.2 ng/mL) by logistic regression. Germline HSD3B1 (1245 C) allele at baseline was associated with overall survival (OS) status (alive vs dead) and response (yes vs no) by the Mantel-Haenszel chi-square test. The SAS statistical package (version 9.4; SAS Institute, Inc, Cary, North Carolina) was used for all data analyses. All hypotheses testing was conducted at a 5% significance level.

**Results**

**Patient Baseline Characteristics**

Thirteen patients were enrolled from July 2019 to October 2021. Among them, 8 patients had complete pharmacokinetic (PK) data, 4 patients did not complete the study due to disease progression, and 1 patient refused 1 PK blood draw. Patients with mHSPC who had at least 1 abiraterone plasma trough concentration level were included in this study. Patient demographic and baseline characteristics are listed in Table 1. The median age was 64 (56-83) years; 11 patients were White and 2 were African-American. Ten patients presented with de novo mHSPC, while 3 patients received prior local therapy (2 had a prostatectomy and 1 had prostate radiation) and later developed mHSPC. Ten patients had high-volume disease and 3 had low-volume disease, as defined per CHAARTED [10]. Most patients had an ECOG performance status of 0 or 1 and only 3 patients had an ECOG performance status of 2. The median PSA at diagnosis was 132 (57-4279). The median body mass index was 30.1 (20.7-38.7). At a median of 11 months (3-14) of follow-up, 9 patients were still alive; 1 patient had a complete response, 5 had a partial response, 3 had stable disease, and 4 had disease progression and died from prostate cancer. At the cut-off in November 2021, nine patients were still being treated with AA.

**Pharmacokinetics**

There was high inter-patient variability in abiraterone trough levels; the mean abiraterone trough levels at 1 month, 3 months, and 7 months were 34.49 ng/mL (3.36-240.46), 13.82 ng/mL (2.91-29.96), and 15.7 ng/mL (3.58-26.86), respectively (Table 2).
adverse events. Most of the adverse events were mild and did not require dose reduction; however, 2 patients required dose reduction due to moderate to severe fatigue. However, these 2 patients were removed from the study when the dose reduction was initiated, and thus, the reduced dose did not contribute to PK variability. The most frequently reported adverse events were fatigue (56%), hypertension (22%), and abnormal liver function tests (11%).

**Discussion**

In the present study, we reported the plasma steady-state trough abiraterone levels at 1 month, 3 months, and 7 months in patients with mHSPC. The trough levels were highly variable: 1-month abiraterone trough levels >8.4 ng/mL were seen in 62% of patients; 3-month abiraterone trough levels >8.4 ng/mL were seen in 55% of patients; and 7-month abiraterone trough levels >8.4 ng/mL were seen in 75% of patients. A total of 8 patients had all 3 PK time points; among them, 4 of 8 patients (50%) had their abiraterone trough levels maintained at >8.4 ng/mL at the 3 time points. As a result, achieving abiraterone levels >8.4 ng/mL within 3 months of initiation was somewhat similar between our study cohort with mHSPC and historical mCRPC cohorts. In our study, all 4 patients with a trough level >8.4 ng/mL were still alive at the time of data cut-off; 2 patients had partial response, and 2 patients had stable disease.

We studied the correlation between steady-state trough abiraterone plasma concentrations and PSA levels in patients with mHSPC. We found a trend toward a negative correlation between the 3-month plasma steady-state trough concentration of abiraterone and 3-month PSA level but not with the 1-month or 7-month time points. Higher abiraterone trough levels were associated with a lower 3-month PSA for all patients, although it did not meet statistical significance. Patients with mHSPC are androgen-dependent, and most patients are sensitive to hormonal therapy at the beginning of their treatments. Therefore, not surprisingly, we saw a significant drop in the patients’ PSA levels at 3 months, which negatively correlated with higher abiraterone trough levels in our study. Nakanishi et al retrospectively studied the early percent change in PSA level after 3 months of starting hormonal therapy to determine if that parameter could be used as a predictive biomarker in patients with mHSPC. They found a 3-month PSA that was >1% higher than a pre-treatment PSA correlated with poor prognosis, including shorter time to CRPC and shorter OS [13]. Therefore, our findings may support the use of percent change in PSA >1% as a prognostic marker. However, further studies are warranted to confirm this finding.

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**Table 1. Patient baseline characteristics.**

| Characteristics                        | # (Range) | %    |
|----------------------------------------|-----------|------|
| Total patients enrolled                | 13        |      |
| Median age, years (range)              | 64 (56-83)|      |
| Ethnicity                              |           |      |
| White                                  | 11        | 85%  |
| African-American                       | 2         | 15%  |
| Median body mass index, kg/m² (range)  | 30.1 (20.7-38.7)|  |
| Obese                                  | 8         | 62%  |
| Non-obese                              | 5         | 38%  |
| ECOG performance status                |           |      |
| 0                                      | 4         | 31%  |
| 1                                      | 6         | 46%  |
| 2                                      | 3         | 23%  |
| Received previous treatment            |           |      |
| Yes                                    | 3         | 23%  |
| No                                     | 10        | 77%  |
| Median PSA (ng/mL) (range)             | 132 (57-4279)|  |
| Volume of disease                      |           |      |
| High                                   | 10        | 77%  |
| Low                                    | 3         | 23%  |

ECOG – Eastern Cooperative Oncology Group; PSA – prostate-specific antigen; # – number.

We removed patient 5 and patient 12 from Table 2 in the analyses due to extremely high trough levels (240 and 81.1 ng/mL) to avoid sampling error. The correlation between the 1-month abiraterone trough and 1-month PSA levels was 0.29 ($P=0.38$), between the 3-month abiraterone trough and 3-month PSA was -0.61 ($P=0.08$), and between the 7-month abiraterone trough and 7-month PSA was -0.31 ($P=0.54$) (Table 3). We did not find any correlation between abiraterone trough and PSA levels even when stratified by body mass index (obese vs non-obese) (Table 4). There was no significant correlation between abiraterone trough levels and PSA alteration (from baseline to 1 month of abiraterone treatment) (Table 5). There was no significant association between abiraterone trough and 3-month PSA ($P=0.25$) and 7-month PSA ($P=0.56$) (Table 6). Six patients carried the germline HSD3B1 (1245 C) allele, and among those, 2 patients had stable disease, 2 had a partial response, and 2 had disease progression (Table 2). We did not observe an association between HSD3B1 genotype and abiraterone trough levels (Table 7). There was no significant association between 1245 C allele and OS status ($P=0.5$) (Table 8).

**Safety and Tolerability**

Safety data were collected for all patients who received at least 1 dose (n=13). Nine of 13 patients did experience AA-related adverse events. Most of the adverse events were mild and did not require dose reduction; however, 2 patients required dose reduction due to moderate to severe fatigue. However, these 2 patients were removed from the study when the dose reduction was initiated, and thus, the reduced dose did not contribute to PK variability. The most frequently reported adverse events were fatigue (56%), hypertension (22%), and abnormal liver function tests (11%).

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Primary resistance is defined as the absence of ≥50% PSA reduction within the first 3 months after initiation, with or without radiographic progression [15]. Therefore, a predictive biomarker is needed to maximize clinical outcomes and minimize unnecessary toxicities. Several biomarkers have been studied to predict or correlate with abiraterone response or to identify potential mechanisms of resistance. Androgen-receptor splice variant 7 messenger RNA (AR-V7) detection in circulating tumor cells has been shown to be associated with resistance to abiraterone and enzalutamide [16]. Two prospective studies using RNA seq found that detectable levels of KLK3 mRNA and miR-375 at baseline and 1 month after the start of either abiraterone or enzalutamide in patients with mCRPC were associated with from primary or acquired resistance [14].

| Patient | bPSA<sup>a</sup> | PSA<sup>a</sup> Trough AA<sup>b</sup> | PSA<sup>b</sup> AA<sup>b</sup> | PSA<sup>a</sup> Trough AA<sup>b</sup> | PSA<sup>b</sup> AA<sup>b</sup> | BMI<sup>c</sup> | Status<sup>c</sup> | Risk allele copy | HSD3B1<sup>d</sup> | DS<sup>e</sup> | SS<sup>f</sup> |
|---------|-----------------|-----------------|--------------------|-----------------|--------------------|----------|--------------|----------------|----------------|--------------|---------|
| 1       | 57.65           | 34.56           | 28.50              | 16.11           | --                 | 22.5     | DP           | Dead           |                |              |         |
| 2       | 132.5           | 3.07            | 5.51               | 0.55            | 20.93              | 0.02     | Refused      | 35.8           | Homo (A/A)    | 0             | CR      |
| 3       | 246.0           | 1.65            | 7.89               | 0.23            | 12.50              | 1.25     | 26.86        | 31.7           | Hetero (C/A)  | 1             | SD      |
| 4       | 1536.0          | 7.44            | 4.55               | 1.66            | 7.09               | 0.41     | 3.58         | 32             | Homo (A/A)    | 0             | PR      |
| 5       | 735.6           | 3.78            | 240.46             | 1.95            | 18.22              | 0.84     | 21.37        | 31.5           | Homo (A/A)    | 0             | PR      |
| 6       | 73.56           | 3.06            | 9.01               | 0.25            | 16.28              | 0.08     | 14.68        | 23.5           | Homo (A/A)    | 0             | PR      |
| 7       | 150.2           | 18              | 3.36               | 11.90           | 2.91               | 5.86     | 4.60         | 35             | Hetero (C/A)  | 1             | PR      |
| 8       | 62              | 0.38            | 4.36               | 0.24            | 7.48               | 0.20     | 10.09        | 38.7           | Hetero (C/A)  | 1             | PR      |
| 9       | 1160            | 165.40          | 12.25              | 49.20           | 6.52               | --       | --           | 20.8           | Homo (A/A)    | 0             | DP      |
| 10      | 4279            | 4317            | 11.96              | Off study       | Off study          | Off study | Off study    | 30.1           | Hetero (C/A)  | 0             | DP      |
| 11      | 121.7           | 6.92            | 21.63              | 0.42            | 25.48              | 0.04     | 22.94        | 28.3           | Hetero (C/A)  | 1             | SD      |
| 12      | 122             | 5.86            | 81.82              | 0.27            | 29.96              | 0.03     | 21.80        | 31.4           | Homo (A/A)    | 0             | SD      |
| 13      | 68              | 1.92            | 17.25              | 0.65            | 4.84               | --       | --           | 27.2           | Hetero (C/A)  | 1             | DP      |

**Table 2.** Summary of abiraterone trough concentration levels, prostate-specific antigen levels, germline HSD3B1, and survival data of all patients.

| Correlation (PSA, AA) | Spearman rank correlation | P value |
|-----------------------|----------------------------|---------|
| 1 Month               | 0.29                       | 0.38    |
| 3 Months              | -0.62                      | 0.08    |
| 7 Months              | 0.31                       | 0.54    |

**Table 3.** Correlation between 1-month, 3-month, and 7-month abiraterone trough levels and prostate-specific antigen levels.

PSA – prostate-specific antigen; AA – abiraterone acetate.
shorter PFS and OS than that in patients with non-detectable levels [17]. Pal et al studied the resistant clones by measuring RNA seq in circulating tumor cells and compared responders vs non-responders to either abiraterone or enzalutamide [18]. They found an upregulation of transforming growth factor β, SMAD family member 3, and cyclin D1 signaling pathways in non-responders [18].

However, to date, there is no biomarker to provide an early prediction (prior to 3 months) of which patients will be AA responders or which will be AA non-responders in mHSPC. Our aim was to evaluate whether abiraterone trough levels predicted early resistance or response to AA therapy. We found that the plasma trough concentrations of abiraterone were neither predictive of PSA response nor of discontinuation due to resistance [19].

### Table 4. Correlation between 1-month, 3-month, and 7-month abiraterone trough levels and prostate-specific antigen levels stratified by obesity vs non-obesity.

| Correlation (PSA, AA) | Spearman rank correlation | P value | Spearman correlation | P value |
|-----------------------|---------------------------|---------|----------------------|---------|
|                       | Obese (BMI >30) | Non-obese (BMI <30) |
| 1 Month               | 0.2 | 0.7 | 0.2000 | 0.75 |
| 3 Months              | -0.7 | 0.19 | -0.6000 | 0.40 |
| 7 Months              | -0.00 | 1.0 | – |

BMI – body mass index, PSA – prostate-specific antigen; AA – abiraterone acetate.

### Table 5. Correlation between 1-month, 3-month, and 7-month abiraterone trough levels and prostate-specific antigen alteration (change from baseline to 1 month of starting treatment).

| Correlation (PSA alternation, AA) | Spearman rank correlation | P value |
|-----------------------------------|---------------------------|---------|
| 1 Month                           | 0.372 | 0.259 |
| 3 Months                          | 0.183 | 0.637 |
| 7 Months                          | 0.200 | 0.704 |

PSA alteration, change of PSA from baseline to 1 month after treatment; AA – abiraterone acetate.

### Table 6. Logistic regression between 3-month abiraterone trough level and 3-month prostate-specific antigen ≤1 ng/mL and 7-month abiraterone trough level and 7-month prostate-specific antigen ≤0.2 ng/mL.

| PSA | N  | mean (tABI)a | P value |
|-----|----|--------------|---------|
| 3 months |    |              |         |
| PSA ≤1 | 6  | 14.59 | 0.25 |
| PSA >1 | 3  | 5.51  |       |
| 7 months |    |              |         |
| PSA ≤0.2 | 4  | 15.90 | 0.56 |
| PSA >0.2 | 4  | 11.5  |       |

a tABI, trough abiraterone; PSA – prostate-specific antigen.

### Table 7. Association between HSD3B1 genotype risk allele and 1-month, 3-month, and 7-month abiraterone trough levels.

| HSD3B1 genotype | N  | Mean (tABI)a | P value |
|-----------------|----|--------------|---------|
| 0h             | 1  | 11.07        | 0.398   |
| 1h             | 6  | 7.83         |         |
| 0h             | 4  | 5            |         |
| 1h             | 5  | 12.71        | 0.678   |
| 0h             | 2  | 9.13         | 0.386   |
| 1h             | 4  | 16.12        |         |

HSD3B1, hydroxyl-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1.

### Table 8. Association between HSD3B1 genotype risk-allele and survival outcomes (overall survival and response).

| Risk allele | Alive | Yes | No | P value |
|-------------|-------|-----|----|---------|
| Yes         | 4     | 35  |    | 0.79    |
| No          | 2     | 1   |    |         |

| Survival response | Yes (CR, PR) | No (SD, PD) | P value |
|-------------------|--------------|-------------|---------|
| Yes               | 2            | 3           | 0.22    |
| No                | 4            | 1           |         |

OS – overall survival; CR – complete response; PR – partial response; SD – stable disease; PD – progressive disease.

OS – overall survival; CR – complete response; PR – partial response; SD – stable disease; PD – progressive disease.
to adverse events; however, our study demonstrated a trend toward a negative correlation between 3-month abiraterone trough levels and 3-month PSA levels. We also did not replicate the association between abiraterone trough levels >8.4 ng/mL and 3-month and 7-month PSA reduction by ≥50%, as previously reported in a mCRPC population [8]; however, our study was not powered to validate these findings in mHSPC.

The germline HSD3B1 (1245C) allele has been associated with poor prognosis and poor clinical outcomes in mHSPC and mCRPC in retrospective and prospective studies [19-22]. Studies reported that genotype of the HSD3B1 gene can serve as a predictive biomarker for men treated with androgen-deprivation therapy [19], AA (steroidal CYP17A1 inhibitor) [20], ketoconazole (nonsteroidal CYP17A1 inhibitor) [21], and enzalutamide (androgen receptor blocker) [20] in mCRPC and in mHSPC with low-volume disease [22]. A preclinical study has shown that increased expression levels of 3βHSD1 were seen in VCaP-enz cells (enzalutamide-resistant cell lines) due to a gain of function mutation of HSD3B1 (A1245C), suggesting that steroidogenesis has an important role in abiraterone and enzalutamide drug resistance [23]. Targeting 3βHSD1 might reduce drug resistance [5,7,23]. In this study, we correlated the HSD3B1 gene and abiraterone trough levels and associated it with OS. We did not find any correlation or association; however, our sample size was small for making a meaningful conclusion.

**Strength and Limitation**

The strength of this study is that it was a prospective observational study; however, it had some limitations. This was a single-center and not a multi-center study. The main limitation of the study was a small sample size, which reduced the power of the study. Also, the standardization of sampling was not always feasible. Other limitations were (1) assessment of compliance: we instructed patients to take AA 22-26 h prior to blood draw; however, we could not confirm whether all patients followed this instruction; (2) lack of record of time points of patients taking AA; and (3) only patients with metastatic disease on AA were eligible.

**Conclusions**

AA showed a high inter- and intra-patient variability in PK but is currently utilized as a standard fixed dose. Despite the lack of support in utilizing AA trough levels in predicting PSA changes as a prognostic or predictive marker in mHSPC in our study, we found a trend toward a negative correlation between abiraterone trough levels and PSA levels 3 months after treatment initiation. A prospective study with a larger sample size is needed to validate these findings. Additional prospective clinical trials are indicated to assess the clinical outcomes or PSA changes by increasing and decreasing AA doses based on targeted trough plasma concentrations (for example, to maintain 8.4 ng/mL) in a population with prostate cancer.

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