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Serum DHEA-S Is a Predictive Parameter of Abiraterone Acetate in Patients with Castration-resistant Prostate Cancer

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Abstract. *Background/Aim: There is no definitive biomarker that predicts the effectiveness of abiraterone acetate. The objective of this study was to investigate whether dehydroepiandrosterone sulfate (DHEA-S) predicts the effectiveness of abiraterone acetate. Materials and Methods: This study included a total of 28 consecutive patients. The optimal cutoff value of DHEA-S for predicting the PSA response was calculated by receiver operating characteristic (ROC) analysis. The Cox proportional hazards model was performed to determine the predictive factors for the susceptibility to abiraterone acetate. Results: Serum DHEA-S at baseline intercorrelated with the PSA response (correlation coefficient: –0.516). The optimal cutoff value of serum DHEA-S at baseline was 47.4 ug/dl in predicting >50% PSA decline. Serum PSA and serum DHEA-S at baseline were identified as significant factors for predicting PSA progression-free survival (p=0.010 and p=0.003, respectively). Conclusion: Serum DHEA-S at baseline may be a biomarker for predicting the prognosis of CRPC patients treated with abiraterone acetate.*

Prostate cancer that initially responds to treatment, but progresses despite suppression of serum testosterone is called castration-resistant prostate cancer (CRPC), and is invariably fatal (1, 2). The management of metastatic CRPC (mCRPC) involves sequential therapies, and five agents have shown a survival benefit in randomized clinical studies since 2010 (3-9).

Abiraterone acetate is a selective inhibitor of androgen biosynthesis that potently blocks cytochrome P450 c17 (CYP17), a critical enzyme in testosterone synthesis, has 17α-hydroxylase/17, 20-lyase inhibitory properties, and inhibits testicular, adrenal, and intratumor androgen synthesis (10, 11).

Although two randomized phase III trials (COU-AA-301 and COU-AA-302) have demonstrated that abiraterone acetate plus prednisone improves overall survival (OS) in patients with mCRPC, both pretreated with chemotherapy and chemotherapy-naïve, primary resistance to abiraterone acetate remains a clinical challenge (5, 9). Nevertheless, there is still no definitive biomarker for predicting patients with primary resistance to abiraterone acetate.

One important mechanism mediating CRPC is the intratumoral conversion of weak adrenal androgens, including dehydroepiandrosterone (DHEA), DHEA sulfate (DHEA-S), and androstenedione, into the androgen receptor (AR) ligands testosterone and dihydrotestosterone (DHT) (12). Abiraterone acetate blocks this conversion by blocking the production of DHEA. A retrospective analysis of COU-AA-301 demonstrated that DHEA-S at the induction of abiraterone acetate was prognostic for OS (13). However, the association of DHEA-S at baseline and the clinical response to abiraterone acetate is still unknown. Therefore, the objective of this study was to investigate whether DHEA-S at baseline could predict the effectiveness of abiraterone acetate in patients with CRPC.

Materials and Methods

Patients. This study included a total of 28 consecutive patients with CRPC treated with abiraterone acetate plus prednisone at the Kobe University hospital in Japan. All of these patients showed disease progression after the treatment with orchiectomy or medical castration. Patients were recruited between September 2014 and December 2016. Informed consent for performing the present study was obtained from all patients, and the study design was approved by the Research Ethics Committee of our institution (No.170217).

Treatment and procedures. Abiraterone acetate was administered orally in 28-day cycles at 1000 mg per day with prednisone at 10 mg per day until disease progression or unacceptable toxicity. Patients were assessed at the beginning of each 28-day cycle for safety and response. Computed tomography (CT) and bone scintigraphy were performed at baseline. PSA measurements were

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taken at baseline and with each cycle of treatment. DHEA-S measurements were taken at baseline.

The primary endpoint was PSA progression-free survival (PSA-PFS). PSA progression was defined as a 25% PSA increase and an absolute increase of 2 ng/ml from the nadir, or for patients without a PSA decline, a 25% PSA increase and an absolute increase of 2 ng/ml from baseline, according to Prostate Cancer Working Group (PCWG2).

Measurement of DHEA-S. DHEA-S was measured by chemiluminescent immunoassays on a Beckman Access Immunoassay system (UniCel DxI 800; Beckman Coulter, Inc., Brea, CA, USA). All blood samples were taken between 9 and 15 h to minimize the influence of daily DHEA-S variations.

Statistical analysis. The relationship between serum DHEA-S at the induction of abiraterone acetate and the PSA-PFS of abiraterone acetate were investigated. The optimal cut-off value of DHEA-S for predicting a PSA response, defined as ≥50% decline, was calculated by receiver operating characteristic analysis. Univariate analysis among the variables was assessed using a two-sample Student's t test and the χ^2 test, as appropriate. PSA-PFS was estimated by the Kaplan–Meier method and assessed with a log-rank test. The Cox proportional hazards model was used to determine the predictive factors for the susceptibility to abiraterone acetate.

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (14), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics. Each test was two-sided, and $p<0.05$ was considered significant.

Results

Demographic information and clinical characteristics of 28 patients are summarized in Table I. The median level of serum DHEA-S was 25.9 μg/dl, which was almost equivalent to that of a previous report (13).

The correlation between serum DHEA-S at baseline and PSA decline after treatment with abiraterone acetate was analyzed. There was a moderate correlation between these two factors (correlation coefficient: –0.516) (Figure 1). Then, we hypothesized that patients with a higher value of serum DHEA-S at baseline might have better PSA response, defined as a ≥50% decline.

Next, we investigated the optimal cutoff value of serum DHEA-S at baseline for predicting the PSA response in the receiver operating characteristic (ROC) analysis. The optimal cutoff value was 47.4 μg/dl (sensitivity: 0.727, specificity: 0.765) (Figure 2). Thus, the patients were divided into two groups, serum DHEA-S at baseline <47 μg/dl or ≥47 μg/dl. Demographic information and clinical characteristics of these two groups are summarized in Table II. There were no significant differences in baseline characteristics between the two groups including patient age, ECOG performance status, Gleason score of biopsy, serum PSA at baseline, site of disease, prior docetaxel treatment, and duration of prior androgen-deprivation therapy (ADT). The waterfall plots of PSA decline in treatment with abiraterone acetate showed that patients with ≥47 μg/dl of serum DHEA-S at baseline had a significantly better PSA response than patients with <47 μg/dl ($p<0.001$) (Figure 3).

Table I. *Patients' characteristics*.

n=28	
Periods of observation, median (range), months	18.5 (4.1-45.8)
Age, median (range), years	77.5 (61-88)
ECOG performance status, n (%)	
0	15 (53.6)
≥1	13 (46.4)
Gleason Score, n (%)	
≤7	4 (14.3)
≥8	24 (85.7)
PSA at baseline, median (range), ng/ml	12.5 (1.05-943)
Site of disease, n (%)	
None	5 (17.9)
Bone	20 (71.4)
Lymph node	4 (14.3)
Visceral	6 (21.4)
Post docetaxel, n (%)	
No	22 (78.6)
Yes	6 (21.4)
Duration of prior ADT ≥12 months, n (%)	24 (85.7)
Serum DHEA-S at baseline, median (range), μg/dl	25.9 (2.0-314.5)

ECOG: Eastern Cooperative Oncology Group; PSA: prostate-specific antigen; ADT: androgen deprivation therapy; DHEA-S: dehydroepiandrosterone sulfate.

The association between serum DHEA-S at baseline and the clinical outcome of treatment with abiraterone acetate were also evaluated. PSA progression-free survival (PSA-PFS) and OS curves based on serum DHEA-S stratified at 47 μg/dl are shown in Figure 4a, b. Although there was no significant difference in OS ($p=0.45$), patients with ≥47 μg/dl of serum DHEA-S at baseline had a significantly longer PSA-PFS than patients with <47 μg/dl (median PSA-PFS were 28.4 months and 3.4 months, respectively; $p=0.006$). As shown in Table III, serum PSA and serum DHEA-S at baseline were identified as significant factors for predicting PSA-PFS in the Cox proportional hazards model (hazard ratio 3.47 and 0.17; $p=0.010$ and $p=0.003$, respectively).

These results suggested that patients with a high value of serum DHEA-S at baseline may have a better PSA response and longer PSA-PFS when treated with abiraterone acetate.

Discussion

Here, it was demonstrated that patients with a high value of serum DHEA-S had a better PSA response and that a high value of serum DHEA-S and serum PSA at baseline

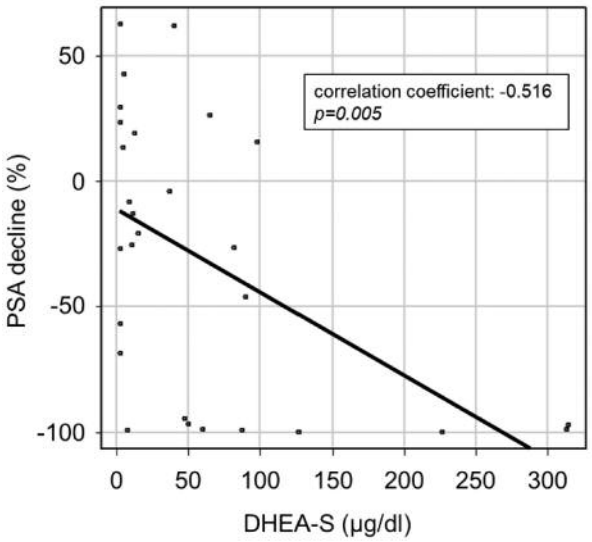

Figure 1. *Correlation analysis between the concentration of serum DHEA-S at baseline and the PSA response after induction of abiraterone acetate.*

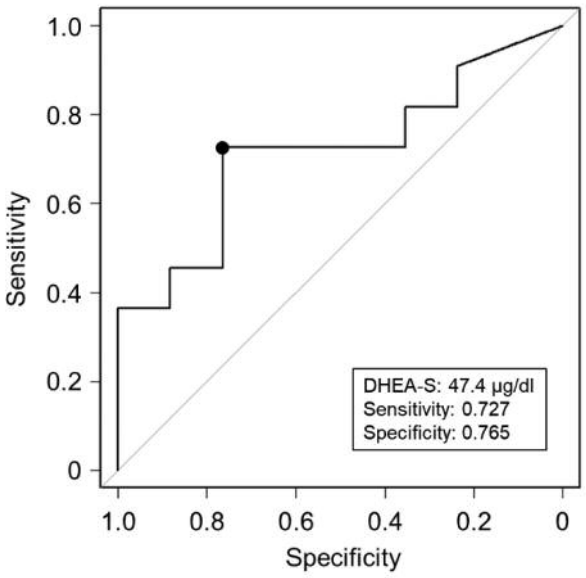

Figure 2. *Receiver operating characteristic curve (ROC) of the concentration of serum DHEA-S for predicting ≥50% PSA decline with the treatment of abiraterone acetate.*

correlated significantly with longer PSA-PFS in treatment with abiraterone acetate.

Although abiraterone acetate has commonly been used in androgen receptor-axis-targeted (ARAT) therapy with improvement of clinical outcomes of CRPC, primary resistance to this agent remains a clinical challenge. In a clinical trial with abiraterone acetate, 35% of patients, at most, showed radiographic progression and PSA progression within the first 3 months of these therapies (5, 9, 15, 16). Therefore, identification of a biomarker for predicting patients with primary resistance is an increasing clinical concern. Although the mechanisms of resistance to abiraterone acetate have been studied including intratumor androgen biosynthesis upregulation, increased expression of ligand independent AR splice variants (17, 18), and promiscuous activation of AR by alternative ligands (19, 20), resistance to abiraterone acetate is inevitable and identification of clinically validated predictive biomarkers remains elusive (21).

Adrenal androgen may be a biomarker for predicting the clinical outcome of treatment with abiraterone acetate. In CRPC patients previously treated with ketoconazole, patients with a high DHEA value at baseline had a better PSA response and longer PFS (22). A retrospective analysis of COU-AA-301 demonstrated that low serum DHEA-S at baseline was predictive of worse cancer-specific survival among metastatic CRPC (13). DHEA and DHEA-S are adrenal androgens that are converted into testosterone and

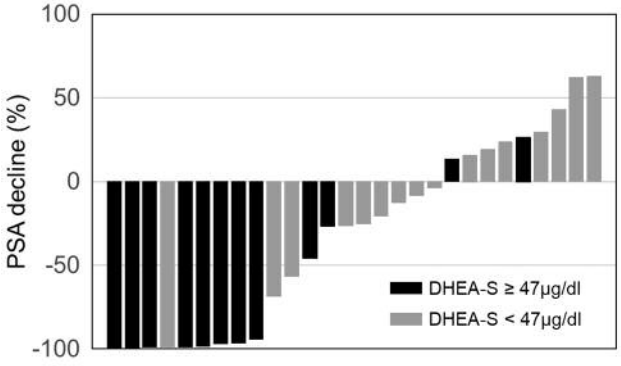

Figure 3. *Waterfall plot representing the percentage of the best response in PSA after the induction of abiraterone acetate.*

DHT in the prostate. DHEA is a product of de novo steroidogenesis, which begins with cholesterol and CYP17A1, the target of abiraterone acetate that regulates successive reactions to convert pregnenolone into DHEA (23). Tamae *et al*. found that although serum DHEA was significantly reduced in CRPC patients treated with abiraterone acetate, a significant amount of DHEA-S persisted and this persistent pool of DHEA-S could serve as a precursor for conversion into testosterone and DHT in prostate cancer (24), which suggests that DHEA-S may be a

Table II. *Patients' characteristics based on serum DHEA-S at baseline.*

	DHEA-S		
n=28	<47 μg/dl (n=16)	≥47 μg/dl (n=12)	*p*-Value
Periods of observation, median (range), months	18.5 (4.4-45.8)	15.8 (4.1-39.3)	0.345
Age, median (range), years	75.5 (61-87)	77 (61-88)	0.754
ECOG performance status, n (%)			
0	8 (50.0)	7 (58.3)	0.718
≥1	8 (50.0)	5 (41.7)	
Gleason Score, n (%)			
≤7	1 (6.3)	3 (25.0)	0.285
≥8	15 (93.7)	9 (75.0)	
PSA at baseline, median (range), ng/ml	13.6 (1.05-943)	9.4 (1.33-342)	0.473
Site of disease, n (%)			1.000
None	3 (18.8)	2 (16.7)	1.000
Bone	11 (68.8)	9 (75.0)	0.113
Lymph node	4 (25.0)	0 (0.0)	0.354
Visceral	2 (12.5)	4 (33.3)	
Post docetaxel, n (%)			
No	11 (68.8)	11 (91.7)	0.196
Yes	5 (31.2)	1 (8.3)	
Duration of prior ADT ≥12 months, n (%)	14 (87.5)	10 (83.3)	1.000

ECOG: Eastern Cooperative Oncology Group; PSA: prostate-specific antigen; ADT: androgen deprivation therapy; DHEA-S: dehydroepiandrosterone sulfate.

Table III. *Uni- and multivariate analyses of several parameters for predicting PSA-PFS.*

	Univariate analysis		Multivariate analysis	
n=28	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Age (≥70 *vs.* <70), years	1.35 (0.47-3.82)	0.576	-	-
ECOG performance status (≥1 *vs.* 0)	1.34 (0.54-3.33)	0.528	-	-
Gleason score (≥8 *vs.* ≤7)	3.47 (0.46-26.3)	0.228	-	-
PSA at baseline (≥20 *vs.* <20), ng/ml	3.67 (1.45-9.24)	0.006	3.47 (1.34-9.00)	0.010
Duration of prior ADT (≥12 vs <12), months	0.52 (0.14-1.92)	0.327	-	-
Post docetaxel (yes *vs.* no)	2.13 (0.79-5.71)	0.134	-	-
Bone metastasis at baseline (yes *vs.* no)	0.85 (0.30-2.40)	0.761	-	-
Visceral metastasis at baseline (yes *vs.* no)	0.86 (0.28-2.59)	0.783	-	-
Serum DHEA-S at baseline (≥47 *vs.* <47), μg/dl	0.17 (0.05-0.52)	0.008	0.17 (0.05-0.54)	0.003

PSA-PFS: Prostate-specific antigen progression free survival; ECOG: Eastern Cooperative Oncology Group; ADT: androgen deprivation therapy; DHEA-S: dehydroepiandrosterone sulfate; HR: hazard ratio; CI: confidence interval.

more optimal biomarker for predicting the clinical outcomes of treatment with abiraterone acetate than DHEA.

Yano *et al.* showed that low serum DHEA-S predicted poor responsiveness to hormone therapy in patients with hormone-naïve metastatic prostate cancer (25). Miyoshi *et al.* reported that a low DHEA level was associated with a higher Gleason score and more advanced clinical stage in patients with hormone-naïve prostate cancer (26). Interestingly, Lauren *et al.* demonstrated that statins block DHEA-S uptake into prostate cancer cells by competitively binding to SLCO2B1 *in vitro*, and that the use of statins during androgen-deprivation therapy (ADT) in a retrospective analysis was associated with a significantly longer time to progression (TTP) (27). These findings suggest that DHEA and DHEA-S may be biomarkers for predicting prognosis not only in CRPC but in hormone-naïve prostate cancer.

We demonstrated that a high value of serum DHEA-S at baseline correlated significantly with a longer PSA-PFS, but

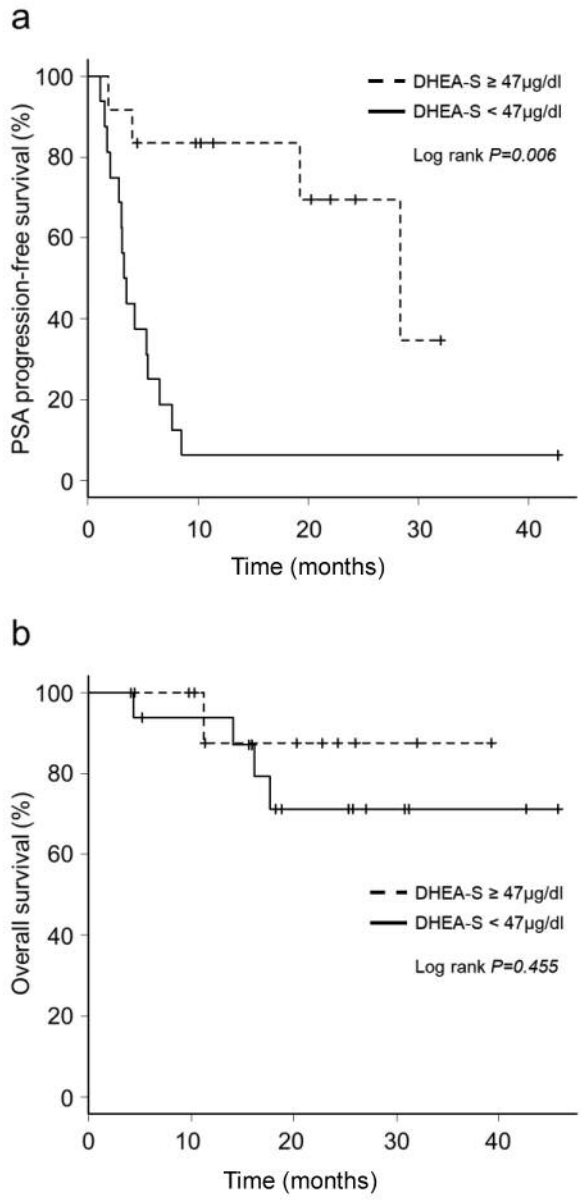

Figure 4. *Kaplan–Meier estimates of (a) PSA progression-free survival and (b) overall survival among castration-resistant prostate cancer patients with the indicated concentrations of DHEA-S at the induction of abiraterone acetate.*

a previous report demonstrated that there was no significant association between a baseline value of DHEA-S and PFS (28). This contradiction may be caused by the way of defining the cutoff value of serum DHEA-S. In general, because the value of serum DHEA-S decreases with age (29) and after prior ADT (30), there is no reference value of serum DHEA-S in our patients. Although the median value was defined as the cutoff value in this previous report, we defined 47 μg/dl as the cutoff value with ROC analysis to exactly reflect the PSA response, which was higher than the median value 25.9 μg/dl. This finding suggested that the cutoff value should be high enough to reflect the PSA response in future clinical applications, and further larger scale studies may provide a more predictive cutoff value.

Patients with a high value of serum PSA at baseline also had a significantly longer PSA-PFS in treatment with abiraterone acetate. Hiroshige *et al*. reported that a high value of serum PSA at baseline prior to treatment with abiraterone acetate was a prognostic factor of worse OS in patients with CRPC (31). A retrospective analysis of COU-AA 302 demonstrated that it was a prognostic factor of shorter radiographic progression-free survival (32). In addition, this factor has also been reported as a biomarker for predicting clinical outcomes of several therapeutic agents (33, 34), which suggests that serum PSA at baseline may be a biomarker for CRPC rather than for abiraterone acetate.

In sequential ARAT therapy for CRPC, several previous reports demonstrated that enzalutamide, a new non-steroidal antiandrogen, achieved only a modest response rate in patients progressing after abiraterone acetate (35-37). The impact of serum DHEA-S on subsequence enzalutamide is of great interest. More recently, abiraterone acetate has been used in various stage of therapeutic strategy for advanced prostate cancer, such as in metastatic hormone-naïve state (38) and in combination with radiotherapy (39-41). Serum DHEA-S may also be a biomarker for predicting the responses of these therapies.

The main limitations of the present study were the retrospective non-randomized analysis, the small cohort size including both docetaxel naïve and treated, and the relatively short follow-up time. There is a possibility that these limitations may have influenced our data on OS, which was contrary to the sub-analysis of COU-AA-301. Furthermore, the association between serum DHEA-S at baseline and radiographic progression were not evaluated. The CLEIA method was used to evaluate serum DHEA-S, but liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) was used in previous reports (13, 26), which may have resulted in differences in sensitivity to DHEA-S. In addition, we should more strictly manage the time to take blood samples because there is daily variation in DHEA-S.

In conclusion, patients with a high value of serum DHEA-S had a better PSA response and longer PSA-PFS in the treatment with abiraterone acetate, which suggests that serum DHEA-S at baseline may be a biomarker for predicting the effectiveness of abiraterone acetate in patients with CRPC.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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