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Serum testosterone level is a useful biomarker for determining the optimal treatment for castration-resistant prostate cancer

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Abstract

Objective: Our aim was to evaluate the usefulness of serum testosterone to guide treatment decision for castration-resistant prostate cancer (CRPC).

Methods: We conducted a retrospective analysis of 115 patients with CRPC treated with either abiraterone ($n = 43$) or enzalutamide ($n = 72$). A serum testosterone level was measured at time of starting of abiraterone or enzalutamide. We determined whether serum testosterone influenced the outcomes of androgen receptor (AR)-targeted therapy.

Results: In the very-low testosterone group (<5 ng/dl), the rate of prostate-specific antigen (PSA) response was significantly higher among patients treated with abiraterone compared to enzalutamide (62 vs. 32%, respectively; $P = 0.033$), with no difference in the low testosterone group (5−<50 ng/dl) (93 vs. 81%, respectively; $P = 0.429$). During the median follow-up of 26 months, PSA progression-free survival was significantly longer in the low testosterone group than in the very-low testosterone group (12.2 vs. 4.5 months, $P<0.001$). In the very-low testosterone group, enzalutamide use (HR 3.07, 95% CI 1.36−6.94; $P = 0.007$), primary androgen deprivation therapy <12 months (HR 2.50, 95% CI 1.23−5.08; $P = 0.011$) and bone metastases (HR 2.60, 95% CI 1.20−5.64; $P = 0.015$) were significantly associated with PSA progression.

Conclusion: Patients with a serum testosterone level ≥5 ng/dl were more likely to receive therapeutic benefits from AR-targeted therapy compared to those with serum testosterone levels <5 ng/dl. However, even for those with a very low serum testosterone level, the efficacy of abiraterone was slightly higher than that of enzalutamide. Therefore, serum testosterone level is a useful biomarker for informing treatment selection for CRPC.

Keywords: Serum testosterone; Prostate cancer; CRPC; AR targeted; Abiraterone; Enzalutamide

1. Introduction

Therapeutic options for metastatic castration-resistant prostate cancer (mCRPC) have drastically changed following the approval of new agents such as the androgen receptor-targeted agents (ARTAs) abiraterone [1] and enzalutamide [2], cabazitaxel, a second-generation taxane [3], and radium-223 dichloride, which is an α-particle-emitting radionuclide [4]. These new agents prolong the overall survival of patients with mCRPC. Although docetaxel-based chemotherapy has been the standard therapy for mCRPC, several treatment options are now available, with algorithms having been designed based on performance status

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of the drug, presence or absence of visceral metastases, and symptoms to assist selection [5,6]. However, specific guidelines to determine the most appropriate treatment for a given patient remain unclear due the lack of trials, as discussed at the St. Gallen Consensus Conference [7]. Therefore, there is an urgent need to develop strategies to provide more precise patient-specific information to guide the treatment of mCRPC.

ARTAs, which include abiraterone and enzalutamide, provide better tolerability than taxanes such as docetaxel and cabazitaxel. Abiraterone is a selective inhibitor of 17α-hydroxylase and 17,20-lyase, depleting the supply of extragonadal androgens [8]. Enzalutamide, by contrast, is a competitive androgen receptor (AR) inhibitor that binds to the androgen receptor [9]. Therefore, both abiraterone and enzalutamide inhibit the activation of ARs by extragonadal androgens, but through different mechanisms. However, there is currently no available biomarker to determine which of these 2 agents should be used in patients to maximize the clinical benefits of AR-targeted therapy for CRPC.

In a previous study, we evaluated whether the serum testosterone level could predict the efficacy of antiandrogen drugs for CRPC [10]. In that study, we reviewed 30 patients with CRPC who received a delayed add-on of antiandrogen therapy (bicalutamide 80 mg daily or flutamide 375 mg daily) following androgen deprivation therapy (ADT). A serum testosterone level of <5 ng/dl was identified as an independent factor for predicting PSA progression (hazard ratio [HR] 5.99, 95% confidence interval [CI] 1.84−19.5; $P = 0.003$). Therefore, we hypothesized that serum testosterone had an effect on the outcomes of AR-targeted therapy. In addition, to clarify the benefits of using serum testosterone to inform the decision for selecting abiraterone or enzalutamide for CRPC, we evaluated the efficacy of each of these drugs as a function of the serum testosterone level.

2. Materials and methods

2.1. Study population and design

This study was retrospectively conducted using the clinical data of consecutive CRPC patients treated at our institution and its satellite hospitals between April 2013 and May 2016. Institutional review board approval was obtained for this study. CRPC was defined by disease progression despite castrate levels of serum testosterone (≤50 ng/dl). The 174 patients who received enzalutamide or abiraterone for CRPC were eligible for this study. Patients who did not undergo serum testosterone measurements at the initiation of treatment were excluded. Ultimately, 72 patients treated with enalutamide 160 mg daily and 43 treated with abiraterone 1000 mg daily formed our study cohort. All diagnoses of prostate cancer were confirmed by pathological examination. As treatment for CRPC, ARTA was selected based on the preference of the treating physician.

2.2. Outcomes

PSA progression was defined as per the criteria of Prostate Cancer Working Group 3: i.e., a 25% increase from the nadir (consisting a starting value of ≥1.0 ng/ml) with a minimum rise of 2 ng/ml [11]. Computed tomography (CT) and a bone scan using 99mTc-methylene-diphosphonate (bone scintigraphy), were conducted to identify soft tissue and bone metastases, respectively, when PSA progressed. Serum testosterone levels (ARCHITECT II CLIA assay) were measured just before ARTA. All blood samples were obtained in the morning. Abiraterone or enzalutamide was selected regardless of the serum testosterone value. A PSA response was defined by a PSA decrease ≥50% at any time. All patients were followed-up by PSA measurement every 1 month. CT and bone scintigraphy were conducted at need.

2.3. Statistical analysis

Fisher's exact test and the Mann−Whitney U-test were used, as appropriate, to evaluate between treatment group differences. PSA progression-free survival (PSA-PFS) and overall survival (OS) were evaluated using the Kaplan-Meier method, with the log-rank test used to evaluate differences between treatment groups. Multivariate Cox proportional hazards analysis was used to identify factors to predict treatment efficacy, after controlling for confounding variables. A P value of <0.05 was considered statistically significant for all analyses. All statistical analyses were performed using EZR (Jichi Medical University, Saitama, Japan).

3. Results

3.1. Patient characteristics

The characteristics of the patients in the abiraterone and enzalutamide groups were compared (Table 1). The median age in the abiraterone group was 76 years and that in the enzalutamide group was 77 years ($P = 0.882$). There was no significant difference in the PSA values just before ARTA between abiraterone and enzalutamide (12.5 vs. 14.4 ng/ml, $P = 0.848$). No metastasis of CRPC was observed in 14 patients (33%) with abiraterone and 26 (36%) with enzalutamide ($P = 0.840$). Patients treated with abiraterone were more likely to have a very low serum testosterone level (<5 ng/dl) just before ARTA than those with enzalutamide (67 vs. 35%; $P<0.001$). There was no significant difference in other clinical parameters between patients treated with abiraterone and enzalutamide. The same was true for patients treated with abiraterone and enzalutamide in both the very-low and the low testosterone groups (Supplementary Table 1).

3.2. Serum testosterone levels just before ARTA

The distribution of serum testosterone levels just before abiraterone or enzalutamide is shown in Fig. 1. All patients

Table 1
Characteristics of all patients.

	Abiraterone $n = 43$	Enzalutamide $n = 72$	P value
Age just befroe ARTA, *n* (%), years			0.945
<75	17 (40)	28 (39)	
≥75	26 (60)	44 (61)	
Gleason score, *n* (%)			0.792
≤7	19 (44)	30 (42)	
≥8	24 (56)	42 (58)	
PSA at diagnosis, *n* (%), ng/ml			0.755
<100	22 (51)	39 (54)	
≥100	21 (49)	33 (46)	
T stage at diagnosis, *n* (%)			0.458
≤T2	8 (19)	20 (28)	
T3	21 (49)	28 (39)	
T4	14 (32)	24 (33)	
Primary ADT, *n* (%)			0.360
Orchiectomy	3 (7)	11 (15)	
LHRH agonist	20 (47)	38 (53)	
LHRH antagonist	8 (19)	9 (13)	
LHRH agonist with bicalutamide	12 (28)	14 (19)	
Duration of primary ADT, *n* (%), months			0.291
<12	9 (21)	22 (31)	
≥12	33 (79)	50 (69)	
PSA just before ARTA, *n* (%), ng/ml			0.838
<10	14 (33)	22 (31)	
≥10	29 (67)	50 (69)	
Metastases at CRPC, *n* (%)			
Visceral	5 (12)	6 (8)	0.561
Bone	31 (72)	41 (57)	0.104
Treatment line in CRPC, *n* (%)			0.791
≤2nd	35 (81)	60 (83)	
≥3rd	8 (19)	12 (17)	
Prior treatment in CRPC, *n* (%)			
Docetaxel	10 (23)	21 (29)	0.490
Bicalutamide	10 (23)	15 (21)	0.817
Flutamide	8 (19)	10 (14)	0.598
Estramustine	3 (7)	3 (4)	0.670
Serum testosterone level just before ARTA			<0.001
Very-low: <5 ng/dl	29 (67)	25 (35)	
Low: 5- <50 ng/dl	14 (33)	47 (65)	

ADT, androgen deprivation therapy; ARTA, androgen receptor-targeted agent.

had testosterone levels of <50 ng/dl (median: 5 ng/dl), which was not significantly associated with the modality of primary ADT. The level was lower in patients treated with abiraterone than in those with enzalutamide (3 vs. 8 ng/dl; $P < 0.001$).

3.3. Prostate-specific antigen (PSA) response

Overall, PSA responses were observed in 31 (72%) of the 43 patients treated with abiraterone and in 46 (64%) of the 72 treated with enzalutamide ($P = 0.366$). The PSA response rate to each treatment was drastically different according to the serum testosterone level (Supplementary Table 2). In the very-low testosterone group (<5 ng/dl), PSA responses were observed in 18 (62%) of the 29 patients treated with abiraterone and in 8 (32%) of the 25 treated with enzalutamide ($P = 0.033$). By contrast, the PSA response rates were 93% with abiraterone and 81% with enzalutamide in the low testosterone group (5− <50 ng/dl) ($P = 0.429$). Overall, there was no significant difference between abiraterone and enzalutamide when there was no PSA response (21% vs. 17%, respectively; $P = 0.622$). The same was true for each testosterone subgroup.

3.4. Predictive factors for prostate-specific antigen (PSA) progression

During the median follow-up period of 25.7 months, 84 patients (73%) developed PSA progression. Overall, 60 (52%) died of prostate cancer and 10 (9%) of other causes. Multivariate analysis identified a very low serum testosterone level just before ARTA, a short duration of primary ADT, and the use of prior docetaxel as factors associated with PSA progression (Table 2). We investigated predictive factors for PSA progression in each testosterone subgroup to adjust for

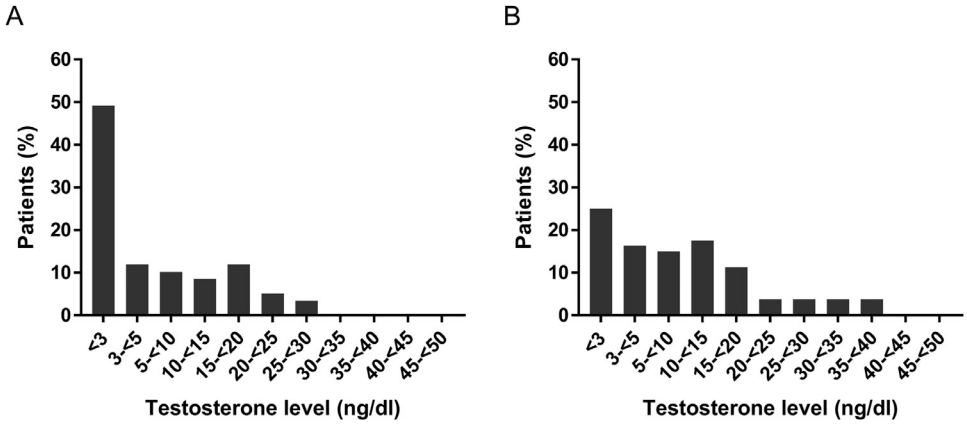

Fig. 1. Distribution of serum testosterone levels just before ARTA. (A) abiraterone, (B) enzalutamide. ARTA, androgen receptor-targeted agent.

Table 2
Factors to predict PSA progression of ARTA for CRPC.

Variable	Category	Univariate		Multivariate	
		HR (95%CI)	*P* value	HR (95%CI)	*P* value
Total					
Serum testosterone level, ng/dl	≥5 vs. <5	2.54 (1.60–4.02)	<0.001	3.33 (1.88–5.92)	<0.001
Treatment	Abiraterone vs. enzalutamide	1.17 (0.74–1.84)	0.506	1.66 (0.98–2.80)	0.059
Age just before ARTA	≤75 vs. ≥75	1.13 (0.55–1.43)	0.676		
Gleason score	≤7 vs. ≥8	1.20 (0.74–1.92)	0.464		
PSA at diagnosis, ng/ml	<100 ng/ml vs. ≥100 ng/ml	1.05 (0.53–1.64)	0.832		
Duration of primary ADT, months	≥12 vs. <12	2.19 (1.38–3.50)	<0.001	2.05 (1.26–3.35)	0.004
PSA just before ARTA, ng/ml	≤10 vs. ≥10	1.77 (1.05–2.97)	0.031	1.45 (0.85–2.49)	0.178
Visceral metastases	Absent vs. present	1.72 (0.91–3.27)	0.097	1.04 (0.55–2.00)	0.896
Bone metastases	EOD0 vs. ≥EOD1	1.59 (0.99–2.54)	0.053	1.46 (0.88–2.42)	0.140
Treatment line in CRPC	≤2nd vs. ≥3rd	1.03 (0.66–1.61)	0.897		
Prior docetaxel	Absent vs. present	2.24 (1.38–3.61)	0.001	1.81 (1.02–3.21)	0.041
Prior vintage hormonal agents	Absent vs. present	1.05 (0.66–1.67)	0.846		
Very-low testosterone subgroup (<5 ng/dl)					
Serum testosterone level, ng/dl	≥5 vs. <5	-	-	-	-
Treatment	Abiraterone vs. enzalutamide	2.69 (1.39–5.23)	0.003	3.07 (1.36–6.94)	0.007
Age just before ARTA	≤75 vs. ≥75	1.12 (0.76–1.77)	0.787		
Gleason score	≤7 vs. ≥8	1.45 (0.76–2.76)	0.261		
PSA at diagnosis, ng/ml	<100 ng/ml vs. ≥100 ng/ml	1.13 (0.61–2.10)	0.688		
Duration of primary ADT, months	≥12 vs. <12	3.16 (1.60–6.25)	<0.001	2.50 (1.23–5.08)	0.011
PSA just before ARTA, ng/ml	≤10 vs. ≥10	1.30 (0.66–2.55)	0.450	1.06 (0.51–2.20)	0.885
Visceral metastases	Absent vs. present	1.12 (0.47–2.70)	0.800	1.12 (0.44–2.91)	0.809
Bone metastases	EOD0 vs. ≥EOD1	1.54 (0.80–2.96)	0.197	2.60 (1.20–5.64)	0.015
Treatment line in CRPC	≤2nd vs. ≥3rd	1.30 (0.71–2.39)	0.398		
Prior docetaxel	Absent vs. present	2.05 (1.01–3.85)	0.024	1.58 (0.78–3.18)	0.201
Prior vintage hormonal agents	Absent vs. present	1.20 (0.64–2.25)	0.562		
Low testosterone subgroup (5– <50 ng/dl)					
Serum testosterone level, ng/dl	≥5 vs. <5	-	-	-	-
Treatment	Abiraterone vs. enzalutamide	1.18 (0.56–2.48)	0.666	1.00 (0.46–2.20)	0.993
Age just before ARTA	≤75 vs. ≥75	1.13 (0.47–2.03)	0.772		
Gleason score	≤7 vs. ≥8	1.15 (0.56–2.37)	0.707		
PSA at diagnosis, ng/ml	<100 ng/ml vs. ≥100 ng/ml	1.15 (0.61–2.16)	0.660		
Duration of primary ADT, months	≥12 vs. <12	1.94 (1.01–3.74)	0.047	1.74 (0.78–3.86)	0.174
PSA just before ARTA, ng/ml	≤10 vs. ≥10	2.63 (1.16–5.97)	0.021	2.34 (0.99–5.48)	0.051
Visceral metastases	Absent vs. present	1.34 (0.52–3.46)	0.542	1.11 (0.40–3.07)	0.840
Bone metastases	EOD0 vs. ≥EOD1	1.48 (0.77–2.85)	0.240	1.00 (0.45–2.23)	0.993
Treatment line in CRPC	≤2nd vs. ≥3rd	1.04 (0.55–2.00)	0.896		
Prior docetaxel	Absent vs. present	1.45 (0.61–3.46)	0.407	1.74 (0.63–4.79)	0.287
Prior vintage hormonal agents	Absent vs. present	0.96 (0.48–1.92)	0.905		

ADT, androgen deprivation therapy; ARTA, androgen receptor-targeted agent; CRPC, castration-resistant prostate cancer; EOD, extent of disease on bone scan.

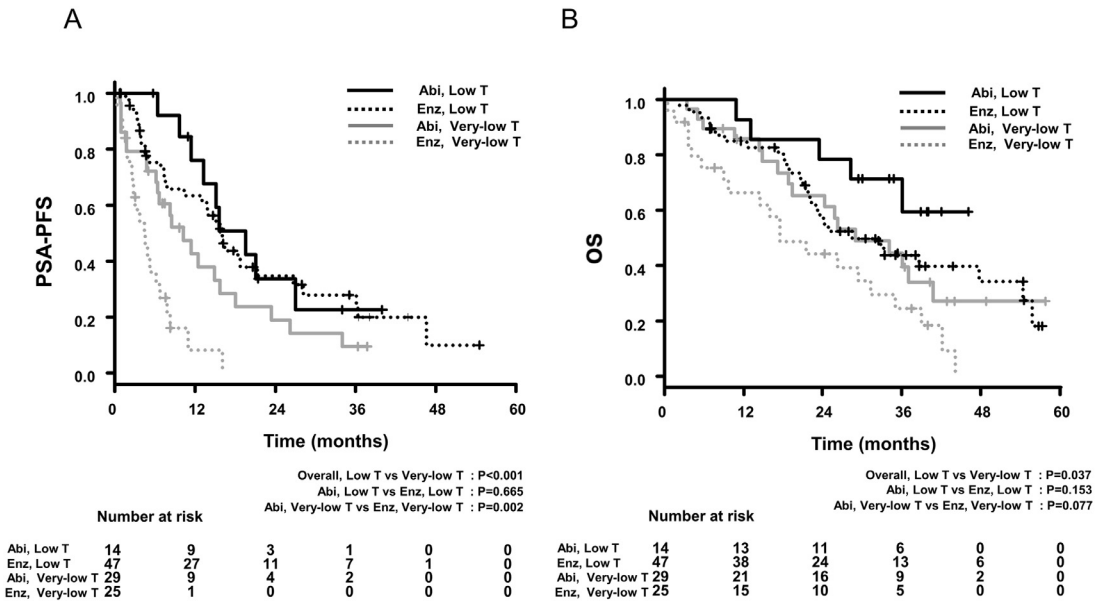

Fig. 2. Survival curves in combination with serum testosterone level and ARTA. (A) PSA progression-free survival (PSA-PFS), (B) overall survival (OS). Abi, abiraterone; ARTA, androgen receptor-targeted agent; Enz, enzalutamide; T, testosterone.

potentially confounding effects. In multivariate analysis, in the very-low testosterone group, enzalutamide use (HR 3.07, 95% CI 1.36−6.94; $P = 0.007$), primary ADT ≤12 months (HR 2.50, 95% CI 1.23−5.08; $P = 0.011$) and bone metastases (HR 2.60, 95% CI 1.20−5.64; $P = 0.015$) were significantly associated with PSA progression. No factor to predict PSA was identified in the low testosterone group.

3.5. Time to prostate-specific antigen progression and mortality

We assessed PSA-PFS and OS in combination with serum testosterone levels and AR-targeted therapy. For all patients, PSA-PFS and OS was significantly longer in the low testosterone group than in the very-low testosterone group (median, 12.2 vs. 4.5 months, 36.0 vs. 26.2 months, respectively; $P \leq 0.001$, $P = 0.037$). In the low testosterone group, there was no significant difference in PSA-PFS between the use of abiraterone or enzalutamide (median, 19.6 vs. 16.1 months, respectively; $P = 0.665$), whereas PSA-PFS was significantly longer with abiraterone than with enzalutamide in the very-low testosterone group (median, 10.3 vs. 4.5 months, respectively; $P = 0.002$; Fig. 2A). However, Kaplan-Meier probability curves did not reveal better OS for patients treated with abiraterone than for those treated with enzalutamide in the testosterone subgroups (Fig. 2B).

4. Discussion

Our findings indicated that serum testosterone was associated not only with the efficacy of AR-targeted therapy but also the prognosis of CRPC. A serum testosterone level of 5 to <50 ng/dl was a significant factor for predicting the efficacy of AR-targeted therapy. In the subgroup of patients with a serum testosterone level of <5 ng/dl, the efficacy was slightly higher for abiraterone than for enzalutamide, and led to improved survival. This indicated that serum testosterone would be an important marker when selecting either abiraterone or enzalutamide for CRPC treatment.

Serum testosterone levels of hormone-sensitive prostate cancer (HSPC) and CRPC might be quite different biologically [12]. Several studies have indicated that a nadir serum testosterone level of <20 ng/dl during primary ADT can be a favorable prognostic factor for HSPC [13,14]. Additionally, Perachino et al. reported that a low-serum testosterone level within 6 months of primary ADT was associated with a good prognosis for patients with metastatic prostate cancer [15]. In contrast, with CRPC, we found that a serum testosterone level ≥5 ng/dl was an independent significant factor to predict the efficacy of treatment with both abiraterone and enzalutamide. This result was consistent with our previous study, which indicated that CRPC patients with a serum testosterone level ≥5 ng/dl who were treated with delayed CAB using bicalutamide or flutamide were more likely to have a better treatment response and prognosis than those with a serum testosterone level of <5 ng/dl [10]. A subanalysis of the COU-AA 301 trial indicated that patients with a serum testosterone level of <5 ng/dl in the abiraterone arm and the control arm had worse OS than did those with a serum testosterone level ≥5 ng/dl [16]. Thus, the low-serum testosterone level achieved during primary ADT for HSPC could predict a better prognosis, whereas for CRPC it could be a risk factor for disease progression. Therefore, measurement of serum testosterone in patients with CRPC

might be required to reveal the correlation between intratumor androgen synthesis and the clinical response to AR-targeted therapy.

For CRPC, serum testosterone is thought to reflect a subset of extragonadal androgens from the adrenal gland and de novo steroidogenesis within tumors. A more recent study indicated that enzymes such as 3βHSD1 were overexpressed in tumors and accelerated intratumor androgen synthesis [17], indicating that AR activation contributed to CRPC progression and that AR-targeted therapy, which inhibits androgen synthesis or AR activation, should be considered as the main treatment strategy for CRPC. In our current study, we provide clear evidence that a serum testosterone level ≥5 ng/dl is a robust predictor of the therapeutic benefits of abiraterone and enzalutamide for the treatment for CRPC, with a higher serum testosterone level being associated with AR dependency in CRPC. This result was supported by a recent study indicating that a serum testosterone level ≥5 ng/dl was a predictor of treatment with enzalutamide [18].

Our findings do raise new questions on whether all patients with a serum testosterone level of <5 ng/dl have non-AR-driven tumor growth. If that is the case, then almost half of all CRPC patients will have a weaker response to AR-targeted therapy. However, substantial PFS benefits have been achieved in several clinical trials of AR-targeted therapy [19,20]. In our current study, patients treated with abiraterone, but not enzalutamide, had extended time to progression and a PSA response, even in patients with a serum testosterone level of <5 ng/dl. This is indicative of the potential to retain some AR activity in patients with CRPC, despite very low serum testosterone. Therefore, abiraterone could provide a possible treatment for CRPC progression among patients with very low serum testosterone levels.

Although the exact reason why patients with very low serum testosterone levels had more favorable results with abiraterone than with enzalutamide with respect to PFS is unclear. The benefits may be related to acquired resistance rather than primary resistance. In our cohort, there was no difference between the treatment groups with regard to the proportion of patients with no decrease in PSA. Several studies have shown that AR gain, amplification, mutation, or alternative splicing variants are associated with resistance against AR-targeted therapy [21,22]. Romanel et al. evaluated the AR gene copy number of plasma DNA at baseline and during CRPC progression in patients treated with abiraterone [23]. In that study, although 23% (of 22 patients) with no AR gain before treatment showed AR gain with progression, 23% (of 22 patients) with AR gain before treatment had no AR gain with progression. Because these proportions were offset by each other, it appeared clear that abiraterone did not result in AR gains. Moreover, an analysis of comparative genomic hybridization of 62 patients with mCRPC showed that AR amplification was significantly more common in patients with CRPC progression who were being treated with enzalutamide than in those treated using abiraterone or other agents (53% vs.17% and 21%, respectively; $P = 0.02$) [24]. Future analyses are required to clarify the effects of serum testosterone on AR aberration. In addition, the cooperativity between serum testosterone levels and loss of tumor suppressors such as PTEN, Tp53, and RB1, which are associated with aggressive variants for CRPC, needs to be clarified [25].

The limitations of our study should be acknowledged. Foremost are the retrospective design of our study, the short follow-up period, and the small number of patients. This might have substantially affected the results. However, the distribution of serum testosterone levels in our study was similar to that of the COU-AA-301 study cohort, and the overall outcomes of AR-targeted therapy were similar to those of other series involving Japanese CRPC patients [26–29]. This indicates that the selection bias in our study cohort was small, if any. Abiraterone, enzalutamide, and docetaxel are recommended by guidelines, along with radium-223 (if there is no visceral metastasis), as first-line treatments for mCRPC. We demonstrated that both abiraterone and enzalutamide exerted effects in patients who had CRPC progression and serum testosterone levels of 5 to 50 ng/dl, whereas abiraterone, but not enzalutamide, exerted effects even in those who had serum testosterone levels of ≤5 ng/dl. This new finding indicates that it is very important to measure serum testosterone to determine ARTAs in CRPC. Previous studies have shown that baseline cell-free DNA and circulating tumor cells, as well as changes during therapy, are prognostic factors for CRPC [22,30]; however, these factors are difficult to measure, which limits their broad availability. We believe that serum testosterone is a useful biomarker that can help in determining the treatment strategy for CRPC, with its ease of measurement providing greater clinical benefits.

5. Conclusions

We have provided evidence of the usefulness of serum testosterone as a biomarker for predicting CRPC treatment outcomes. Patients with a serum testosterone level ≥5 ng/dl were more likely to receive therapeutic benefits from AR-targeted therapy compared to those with serum testosterone levels <5 ng/dl. However, even for those with a very low serum testosterone level, the efficacy of abiraterone was slightly higher than that of enzalutamide. Based on our findings, the serum testosterone level should be considered to more precisely guide treatment selection for patients with CRPC.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.04.026.

References

[1] Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2012;13(10):983–92.

[2] Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367(13):1187–97.

[3] de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376(9747):1147–54.

[4] Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013;369(3):213–23.

[5] Cornford P, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: treatment of relapsing, metastatic, and castration-resistant prostate cancer. Eur Urol 2017;71(4):630–42.

[6] NCCN guidelines on prostate cancer, version 1.2019. Available at: http://www.nccn.org/progessionals/physician_gls/pdf/prostate.pdf.

[7] Gillessen S, Attard G, Beer TM, et al. Management of patients with advanced prostate cancer: the report of the advanced prostate cancer consensus conference APCCC 2017. Eur Urol. 2018;73(2):178–211.

[8] Ryan CJ, Smith MR, Fong L, et al. Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy. J Clin Oncol 2010;28(9):1481–8.

[9] Tran C, Ouk S, Clegg NJ, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science 2009;324(5928):787–90.

[10] Hashimoto K, Masumori N, Hashimoto J, et al. Serum testosterone level to predict the efficacy of sequential use of antiandrogens as second-line treatment following androgen deprivation monotherapy in patients with castration-resistant prostate cancer. Jpn J Clin Oncol 2011;41(3):405–10.

[11] Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the prostate cancer clinical trials working group 3. J Clin Oncol 2016;34(12):1402–18.

[12] Claps M, Petrelli F, Caffo O, et al. Testosterone levels and prostate cancer prognosis: systematic review and meta-analysis. Clin Genitourin Cancer 2018. https://doi.org/10.1016/j.clgc.2018.01.005:pii: S1558-7673(18)30032-6. Epub ahead of print.

[13] Yamamoto S, Sakamoto S, Minhui X, et al. Testosterone reduction of ≥ 480 ng/dL predicts favorable prognosis of Japanese men with advanced prostate cancer treated with androgen-deprivation therapy. Clin Genitourin Cancer 2017;15(6):e1107–15. https://doi.org/10.1016/j.clgc.2017.07.023. Epub 2017 Aug 3.

[14] Kamada S, Sakamoto S, Ando K, et al. Nadir testosterone after long-term followup predicts prognosis in patients with prostate cancer treated with combined androgen blockade. J Urol 2015;194(5):1264–70.

[15] Perachino M, Cavalli V, Bravi F. Testosterone levels in patients with metastatic prostate cancer treated with luteinizing hormone-releasing hormone therapy: prognostic significance? BJU Int. 2010;105(5):648–51.

[16] Ryan CJ, Molina A, Li J, et al. Serum androgens as prognostic biomarkers in castration-resistant prostate cancer: results from an analysis of a randomized phase III trial. J Clin Oncol 2013;31(22):2791–8.

[17] Mostaghel EA. Steroid hormone synthetic pathways in prostate cancer. Transl Androl Urol 2013;2(3):212–27.

[18] Shiota M, Kashiwagi E, Murakami T, et al. Serum testosterone level as possible predictive marker in androgen receptor axis-targeting agents and taxane chemotherapies for castration-resistant prostate cancer. Urol Oncol 2018. https://doi.org/10.1016/j.urolonc.2018.10.020:S1078-1439(18)30404-6.

[19] Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013;368(2):138–48.

[20] Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371(5):424–33.

[21] Silberstein JL, Taylor MN, Antonarakis ES. Novel insights into molecular indicators of response and resistance to modern androgen-axis therapies in prostate cancer. Curr Urol Rep 2016;17(4):29.

[22] Conteduca V, Wetterskog D, Sharabiani MTA, et al. Androgen receptor gene status in plasma DNA associates with worse outcome on enzalutamide or abiraterone for castration-resistant prostate cancer: a multi-institution correlative biomarker study. Ann Oncol 2017;28(7):1508–16.

[23] Romanel A, Gasi Tandefelt D, Conteduca V, et al. Plasma AR and abiraterone-resistant prostate cancer. Sci Transl Med 2015;7(312):312re10. https://doi.org/10.1126/scitranslmed.aac9511.

[24] Azad AA, Volik SV, Wyatt AW, et al. Androgen receptor gene aberrations in circulating cell-free DNA: biomarkers of therapeutic resistance in castration-resistant prostate cancer. Clin Cancer Res 2015;21(10):2315–24.

[25] Aparicio AM, Shen L, Tapia EL, et al. Combined tumor suppressor defects characterize clinically defined aggressive variant prostate cancers. Clin Cancer Res 2016;22(6):1520–30.

[26] Miyake H, Hara T, Ozono S, et al. Impact of prior use of an androgen receptor-axis-targeted (ARAT) agent with or without subsequent taxane therapy on the efficacy of another ARAT agent in patients with metastatic castration-resistant prostate cancer. Clin Genitourin Cancer 2017;15(2):e217–22. https://doi.org/10.1016/j.clgc.2016.07.005: Epub 2016 Jul 21.

[27] Terada N, Akamatsu S, Okada Y, et al. Factors predicting efficacy and adverse effects of enzalutamide in Japanese patients with castration-resistant prostate cancer: results of retrospective multi-institutional study. Int J Clin Oncol 2016;21(6):1155–61.

[28] Matsubara N, Yamada Y, Tabata KI, et al. Comparison of sequential treatment with androgen receptor-targeted agent followed by another androgen receptor-targeted agent vs androgen receptor-targeted agent followed by docetaxel in chemotherapy-naive patients with metastatic castration-resistant prostate cancer. Clin Genitourin Cancer 2017;15(6):e1073–80. https://doi.org/10.1016/j.clgc.2017.07.016:Epub 2017 Jul 26.

[29] Kato H, Furuya Y, Miyazawa Y, et al. Consequences of an Early PSA response to enzalutamide treatment for Japanese patients with metastatic castration-resistant prostate cancer. Anticancer Res 2016;36(11):6141–9.

[30] Antonarakis ES, Lu C, Luber B, et al. Clinical significance of androgen receptor splice variant-7 mRNA detection in circulating tumor cells of men with metastatic castration-resistant prostate cancer treated with first- and second-line abiraterone and enzalutamide. J Clin Oncol 2017;35(19):2149–56.