Original Article

Serum Testosterone Level as Possible Predictive Marker for Prognosis in Metastatic Castration-Resistant Prostate Cancer Patients Treated With Enzalutamide

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Purpose: This study aimed to evaluate the impact of serum testosterone level before enzalutamide treatment in metastatic castration-resistant prostate cancer (mCRPC) for antitumor outcomes.

Materials and Methods: Single-center, retrospective study including patients that treated with enzalutamide for mCRPC before and after docetaxel chemotherapy. Clinicopathological parameters including serum testosterone at initial enzalutamide use were examined. Prostate-specific antigen (PSA) response, progression-free survival (PFS), and cancer-specific survival (CSS) were the outcomes of interest. Logistic-regression analysis was done for discovering odds for PSA response. Cox-proportional model was applied for risk stratification for progression and cancer-specific death.

Results: A total of 228 patients with mCRPC, treated with enzalutamide, both prechemotherapy and postchemotherapy, between 2011 and 2019 were included. One hundred sixty-two of patients (71.1%) experienced PSA decline over 50%. Median PFS and CSS were 5.4 and 13.2 months, respectively. Serum testosterone at initial enzalutamide use was the noble predictor for progression (hazard ratio [HR], 0.409; p=0.020) and cancer-specific death (HR, 0.454; p=0.033) in postchemotherapy group. No significant effect of serum testosterone in prechemotherapy group was detected. Time to CRPC, high-metastatic burden revealed as risk factors for PSA response, PFS, and CSS, both in prechemotherapy and postchemotherapy group.

Conclusions: High testosterone level at commencement of enzalutamide treatment was associated with a good prognosis in postdocetaxel setting, but not related to oncological outcomes in chemotherapy-naïve patients. **(Korean J Urol Oncol 2021;19:60-69)**

Key Words: Prostate cancer · Enzalutamide · Testosterone

INTRODUCTION

Prostate cancer is one of the most commonly diagnosed cancers in men, which has 2nd most prevalence in United States and 4th most prevalence in South Korea.[1,2] In metastatic disease, androgen-deprivation therapy (ADT) with or without abiraterone or docetaxel is the standard treatment on current guideline.[3,4] And most of these patients experience the progression in a castration-resistant prostate cancer

(CRPC), although consecutive ADT is maintained. In treatment of metastatic CRPC (mCRPC), taxane chemotherapies, androgen receptor (AR) axis-targeting agents including enzalutamide and abiraterone, and radio-isotope radium-223 have shown survival benefits.[5,6]

Enzalutamide is a small-molecule inhibitor of AR which can overcome resistance to nonsteroidal antiandrogens such as bicalutamide and flutamide. Previous clinical trials with enzalutamide have consistently shown improved overall survival (OS) in CRPC, whether before or after chemotherapy.[5,7,8]

Despite prostate cells in castration-resistant phase engage to survive in a low androgen environment, both residual androgen and AR play a central role to disease progression.[9] In addition, prostate cancer tissues cause *de novo* androgen synthesis which advances the progression to CRPC, resulting in increased testosterone level in CRPC.[10,11] Several attempts have been made to identify serum testosterone level as a biomarker for deciding treatment selection.[12,13] Recent studies observed that serum testosterone level affected therapeutic efficacy of abiraterone and enzalutamide.[14-16] However, the significance of pretreatment serum testosterone level on progression and survival in patients treated with enzalutamide for mCRPC remains limited.

Thus, the main purpose of this study is to reveal the association between serum testosterone level before enzalutamide treatment and oncologic outcomes.

MATERIALS AND METHODS

1. Study Design

This retrospective study based on medical records of prostate cancer patients is being reviewed by the Institutional Review Board of Asan Medical Center (S2020-2620-0001). From December 2011 to May 2019, the medical records of 266 patient who has been treated with enzalutamide for mCRPC were collected. Among these, 38 patients who treated with abiraterone before enzalutamide were excluded. At last, 228 men with mCRPC and treated with enzalutamide were enrolled. All patients were maintained androgen deprivation with added 160 mg of enzalutamide plus prednisolone 5 mg twice a day. The patients were divided into prechemotherapy group and postchemotherapy group.

2. Definition

In this study, PSA response was defined as a decrease in the level of PSA of at least 50% from initial enzalutamide use in a patient who received treatment. High-metastatic burden was defined as 4 or more bone metastasis with at least one outside the axial skeleton or presence of visceral metastases, according to the definition of CHAARTED trial.[17] Grade group was defined according to the International Society of Urological Pathology consensus.[18] Biochemical progression was defined as 2 serial rises in PSA level at least $\geq 25\%$ increase and ≥ 2 ng/mL increase from baseline beyond 12 weeks. Radiographic progression was defined as 2 or more new lesion in bone scintigraphy, or visceral progression and nodal progression according to RECIST (response evaluation criteria in solid tumors).

3. Statistical Analysis

Clinical variables such as PSA, testosterone, grade group, metastatic burden, time to CRPC of each group and duration of taxane chemotherapy of postchemotherapy group were analyzed. PSA response, progression-free survival (PFS), and cancer-specific survival (CSS) were the interest of antitumor outcome. Differences between patient groups were analyzed using independent sample t-test for continuous variables and Fisher exact test for categorical variables. Logistic-regression analysis was used to discover odds for PSA response. Cox-proportional model was applied in order to calculate hazard ratio of clinical variables for PFS and CSS. CSS following enzalutamide initiation was calculated using Kaplan Meier estimation and log-rank test. A p-value less than 0.05 indicated statistical significance. IBM SPSS Statistics ver. 25.0 (IBM Co., Armonk, NY, USA) was used for all statistical analysis.

RESULTS

The baseline patient characteristics are summarized in Table 1. PSA and testosterone of initial enzalutamide were 171.4±419.3 and 0.20±0.24. PSA response, progression (biochemical, radiographic, or both), cancer-specific death was observed in 162, 158, and 130 patients. There were 136 patients of prechemotherapy group and 92 patients of postchemotherapy group. Age (76 years vs. 71 years, p=0.004),

Table 1. Patient characteristics at initial enzalutamide use

Characteristic	Total (N=228)	Prechemotherapy (N=136)	Postchemotherapy (N=92)	p-value
Age (yr)	74 (68–79)	76 (70–80)	71 (66–77)	0.004
PSA (ng/mL)	38.9 (11.5–136.4)	33.7 (10.9–126.1)	47.5 (12.4–170.9)	0.564
Testosterone (ng/mL)	0.12 (0.07–0.23)	0.15 (0.09–0.23)	0.08 (0.04–0.21)	0.504
Grade group				0.016
2	3 (1.3)	1 (0.7)	2 (2.2)	
3	13 (5.7)	12 (8.9)	1 (1.1)	
4	41 (18.0)	29 (21.3)	12 (13.0)	
5	171 (75.0)	94 (69.1)	77 (83.7)	
Prior local therapy	63 (25.3)	43 (31.6)	20 (21.7)	0.102
Metastatic burden				<0.001
Low	80 (35.1)	62 (45.6)	18 (19.6)	
High	148 (64.9)	74 (54.4)	74 (80.4)	
Bone metastasis	198 (86.8)	111 (81.6)	87 (94.6)	0.005
Nodal metastasis	102 (44.7)	58 (42.6)	44 (47.8)	0.440
Visceral metastasis	32 (14.0)	11 (8.1)	21 (22.8)	0.002
Time to CRPC (mo)	26.2 (13.9–43.5)	27.0 (16.2–53.0)	22.4 (11.4–38.9)	0.002
Duration of chemotherapy (mo)			10.6 (6.0–16.4)	
Duration to progression				
Overall (mo)	5.4 (2.8–10.0)	6.6 (3.0–11.5)	4.4 (2.6–7.6)	0.006
Radiographic (mo)	6.0 (2.8–11.2)	6.8 (3.0–12.8)	4.5 (2.6–8.3)	0.007
Cancer-specific survival (mo)	13.2 (7.08–26.0)	15.8 (8.0–28.8)	10.7 (6.4–21.1)	0.014
PSA decline >50%	162 (71.1)	107 (78.7)	55 (59.8)	0.002
Cancer-specific death	130 (57.0)	59 (43.4)	71 (77.2)	<0.001

Values are presented as median (interquartile range) or number (%).
Median follow-up=10.3 months.
PSA: prostate-specific antigen, CRPC: castration-resistant prostate cancer.

number of patients of grade group 5 (69.1% vs. 83.7%, p=0.016), high-metastatic burden (54.4% vs. 80.4%, p<0.001), time to CRPC (27 months vs. 22.4 months, p=0,002), PSA response (78.7% vs. 59.8%, p=0.002), cancer-specific death (43.4% vs. 77.1%, p<0.001), PFS (median: 6.6 months vs. 4.4 months, p=0.006), and CSS (median: 15.8 months vs. 10.7 months, p=0.014) differed significantly between patients with prechemotherapy and postchemotherapy respectively.

The results of multivariable analysis for the prediction of PSA response in enzalutamide use are shown in Table 2. In multivariable analysis, Table 2 shows that grade group 5 (odds ratio [OR], 0.430; 95% confidence interval [CI], 0.191–0.965; p=0.041), and high-metastatic burden (OR, 0.337; 95% CI, 0.165–0.688; p=0.003) was the predictor of PSA response in overall population. In postchemotherapy group, high-metastatic burden (OR, 0.213; 95% CI, 0.054–0.835; p=0.027) was independent factor to predict PSA response.

Cox-proportional model for progression is presented in Table 3. In overall population, age (hazards ratio [HR], 0.974; 95% CI, 0.952–0.994; p=0.014), time to CRPC (HR, 0.991; 95% CI, 0.983–1.000; p=0.038), high-metastatic burden (HR, 1.949; 95% CI, 1.330–2.855; p=0.002) were the risk factors of progression. In prechemotherapy group, high-metastatic burden (HR, 1.787; 95% CI, 1.058–3.020; p=0.030) could predict progression. In postchemotherapy group, time to CRPC (HR, 0.985; 95% CI 0.972–0.999; p=0.034) and serum testosterone level at initial enzalutamide use (HR, 0.409; 95% CI, 0.192–0.871; p=0.020) were revealed as risk factors of progression, as can be seen from Table 3.

Table 4 provides summary of Cox-proportional model for cancer-specific death. Table 4 shows that time to CRPC (HR, 0.988; 95% CI, 0.980–0.997; p=0.008) and high-metastatic burden (HR, 2.291; 95% CI, 1.493–3.516; p<0.001) were the indicator for prediction of cancer-specific death. Same trends for cancer-specific death were found in pre

Table 2. Logistic-regression analysis for PSA response

Variable	Total				Prechemotherapy group				Postchemotherapy group			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	0.980 (0.946–1.016)	0.280	-	-	0.961 (0.913–1.012)	0.367	-	-	1.043 (0.990–1.098)	0.135	0.946 (0.896–0.999)	0.046
Grade group 5 vs. others	0.375 (0.172–0.818)	0.014	0.430 (0.191–0.965)	0.041	0.514 (0.192–1.376)	0.186	-	-	0.316 (0.083–1.211)	0.093	-	-
Prior local therapy	1.277 (0.662–2.464)	0.466	-	-	1.276 (0.514–3.167)	0.599	-	-	1.012 (0.368–2.780)	0.982	-	-
Time to CRPC	1.016 (1.003–1.029)	0.014	1.011 (0.998–1.024)	0.102	1.011 (0.996–1.026)	0.152	-	-	1.019 (0.996–1.042)	0.102	1.024 (0.999–1.049)	0.060
Duration of chemotherapy	-	-	-	-	-	-	-	-	0.995 (0.944–1.048)	0.837	-	-
High-metastatic burden	0.307 (0.153–0.618)	0.001	0.337 (0.165–0.688)	0.003	0.458 (0.191–1.098)	0.080	0.458 (0.191–1.098)	0.080	0.235 (0.063–0.882)	0.032	0.213 (0.054–0.835)	0.027
PSA at initial enzalutamide use	1.000 (0.999–1.000)	0.351	-	-	1.000 (0.999–1.000)	0.450	-	-	0.999 (0.998–1.001)	0.353	-	-
Testosterone at initial enzalutamide use	0.991 (0.307–3.194)	0.987	-	-	0.392 (0.022–7.008)	0.524	-	-	1.292 (0.368–4.539)	0.689	-	-

PSA: prostate-specific antigen, OR: odds ratio, CI: confidence interval, CRPC: castration-resistant prostate cancer.

**Table 3.** Cox-proportional model for progression

Variable	Total						Prechemotherapy group						Postchemotherapy group					
	Univariate			Multivariate			Univariate			Multivariate			Univariate			Multivariate		
	OR (95% CI)		p-value	OR (95% CI)		p-value	OR (95% CI)		p-value	OR (95% CI)		p-value	OR (95% CI)		p-value	OR (95% CI)		p-value
Age	0.972 (0.951–0.994)		0.011	0.973 (0.952–0.994)		0.014	0.979 (0.947–1.011)		0.198	-		-	0.982 (0.952–1.013)		0.246	-		-
Grade group 5 vs. others	1.524 (1.022–2.272)		0.039	1.451 (0.958–2.198)		0.079	1.359 (0.801–2.306)		0.255	-		-	1.285 (0.686–2.406)		0.433	-		-
Prior local therapy	1.117 (0.758–1.645)		0.576	-		-	1.286 (0.753–2.195)		0.357	-		-	1.268 (0.714–2.251)		0.418	-		-
Time to CRPC	0.987 (0.979–0.995)		0.001	0.991 (0.983–1.000)		0.038	0.991 (0.981–1.000)		0.052	-		-	0.987 (0.974–1.000)		0.055	0.985 (0.972–0.999)		0.034
Duration of chemotherapy	-			-		-	-		-	-		-	1.004 (0.972–1.038)		0.796	-		-
High-metastatic burden	2.108 (1.442–3.081)		<0.001	1.949 (1.330–2.855)		0.002	1.999 (1.200–3.329)		0.008	1.878 (1.105–3.191)		0.020	1.683 (0.934–3.034)		0.083	1.643 (0.908–2.972)		0.101
PSA at initial enzalutamide use	1.001 (1.000–1.001)		0.001	-		-	1.001 (1.000–1.001)		<0.001	1.001 (1.000–1.001)		0.002	1.001 (1.000–1.002)		0.147	-		-
Testosterone at initial enzalutamide use	0.677 (0.345–1.328)		0.256	-		-	1.776 (0.348–9.070)		0.490	-		-	0.490 (0.235–1.022)		0.057	0.409 (0.192–0.871)		0.020

PSA: prostate-specific antigen, OR: odds ratio, CI: confidence interval, CRPC: castration-resistant prostate cancer.

Table 4. Cox-proportional model for cancer-specific death

Variable	Total				Prechemotherapy group				Postchemotherapy group			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	0.999 (0.976–1.022)	0.920	-	-	1.003 (0.968–1.039)	0.859	-	-	1.024 (0.992–1.057)	0.139	-	-
Grade group 5 vs. others	1.482 (0.972–2.259)	0.067	-	-	1.108 (0.634–1.938)	0.719	-	-	2.150 (1.013–4.566)	0.046	-	-
Prior local therapy	0.900 (0.594–1.362)	0.618	-	-	0.806 (0.434–1.497)	0.495	-	-	1.109 (0.633–1.944)	0.717	-	-
Time to CRPC	0.986 (0.978–0.994)	0.001	0.988 (0.980–0.997)	0.008	0.982 (0.969–0.995)	0.008	0.985 (0.972–0.998)	0.020	0.991 (0.978–1.003)	0.149	0.988 (0.975–1.001)	0.079
Duration of chemotherapy	-	-	-	-	-	-	-	-	0.987 (0.955–1.020)	0.434	-	-
High-metastatic burden	2.589 (1.702–3.939)	<0.001	2.291 (1.493–3.516)	<0.001	2.099 (1.221–3.608)	0.007	1.809 (1.045–3.130)	0.034	2.208 (1.054–4.626)	0.036	2.084 (0.990–4.388)	0.053
PSA at initial enzalutamide use	1.001 (1.000–1.001)	0.001	1.000 (1.000–1.001)	0.053	1.001 (1.000–1.001)	0.012	-	-	1.001 (1.000–1.002)	0.004	1.001 (1.000–1.002)	0.003
Testosterone at initial enzalutamide use	0.799 (0.408–1.564)	0.513	0.589 (0.295–1.178)	0.134	1.016 (0.925–1.115)	0.740	-	-	0.607 (0.305–1.207)	0.155	0.454 (0.220–0.937)	0.033

PSA: prostate-specific antigen, OR: odds ratio, CI: confidence interval, CRPC: castration-resistant prostate cancer.
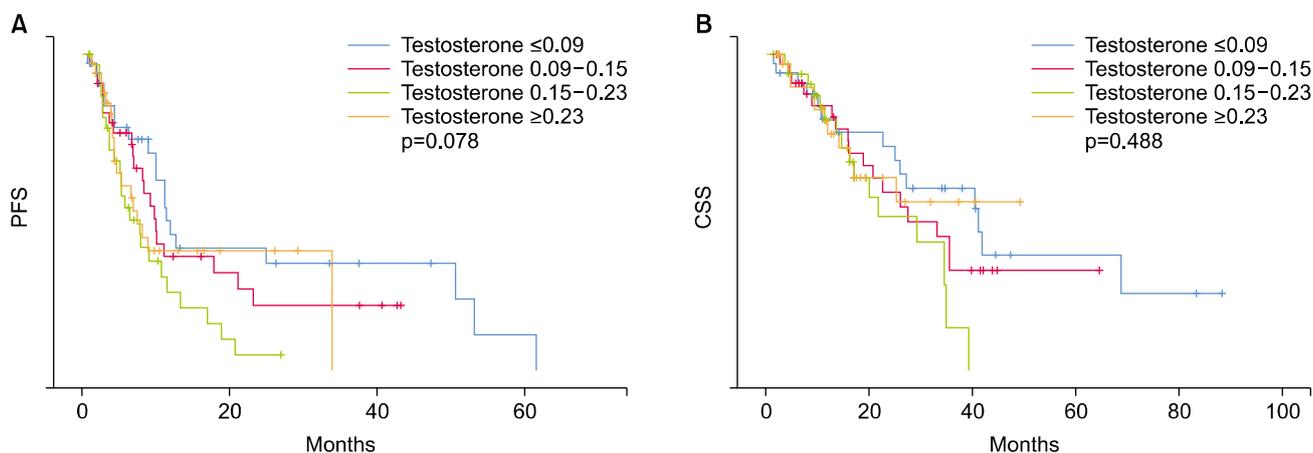
Fig. 1. Survival curve divided by the quartile of pretreatment serum testosterone levels in the prechemotherapy group. (A) Progression-free survival (PFS). (B) Cancer-specific survival (CSS).
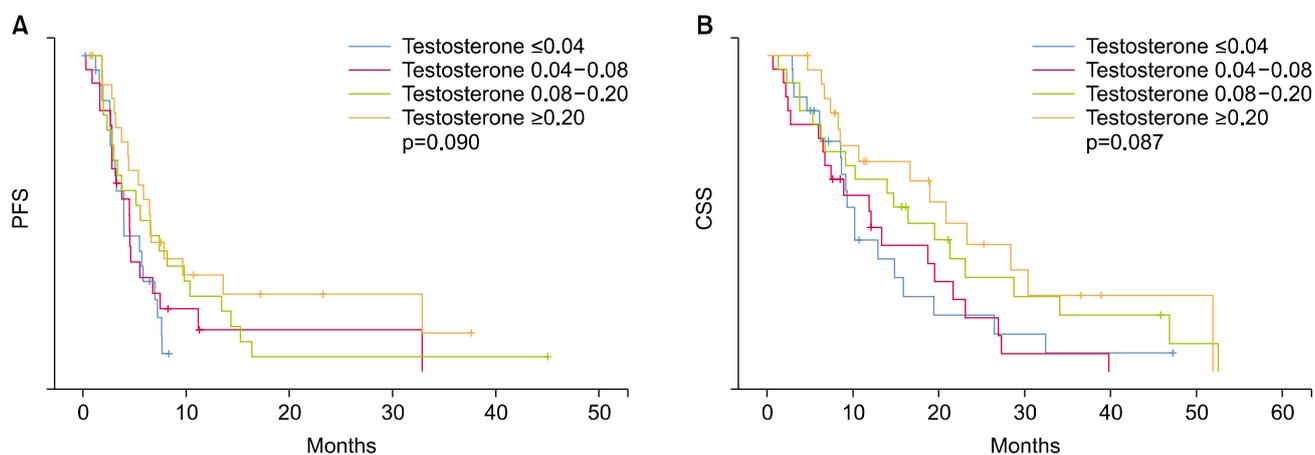
Fig. 2. Survival curve divided by the quartile of pretreatment serum testosterone levels in the prechemotherapy group. (A) Progression-free survival (PFS). (B) Cancer-specific survival (CSS).

chemotherapy group. Interestingly, serum testosterone level of initial enzalutamide use (HR, 0.454; 95% CI, 0.220– 0.937; p=0.033) was the noble predictor of cancer-specific death in postchemotherapy group, as shown in Table 4.

Survival curves for each ranges of quartiles of serum testosterone level, in prechemotherapy, are shown in Fig. 1. As shown in figure, there is no statistical relationship between serum testosterone level and PFS, CSS. In postchemotherapy group, patients with serum testosterone over the median (0.08 ng/mL) has shown better PFS and OS. Survival curves for each ranges of quartiles and median of serum testosterone level are highlighted in Figs. 2 and 3.

DISCUSSION

In our analysis, PFS and CSS were better in men with higher serum testosterone level when treated with enzalutamide following docetaxel, but PSA response could not be extrapolated to high serum testosterone. In prechemotherapy setting, serum testosterone was not associated with PSA response, PFS, and CSS. This provides new insights into establishing possible biomarker for prognosis of CRPC, and biomarker for efficacy of following enzalutamide use.

An subanalysis of the COU-AA 301 trial has shown that patients with lower testosterone level in postchemotherapy treatment with abiraterone have worse OS.[12] In this study, androstenedione and dehydroepiandrosterone sulfate also
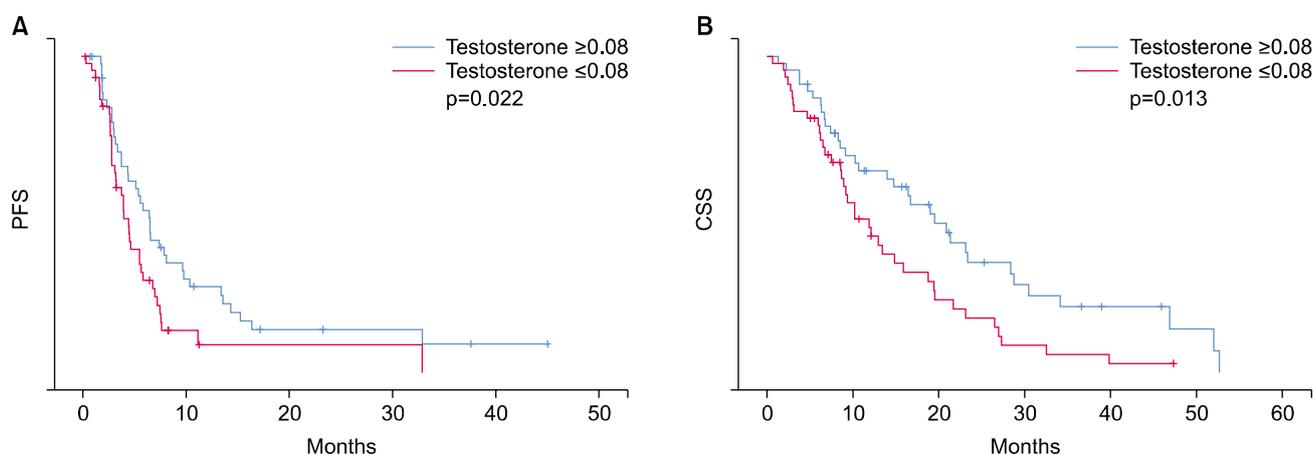
Fig. 3. Survival curve divided by the quartile of pretreatment serum testosterone levels in the postchemotherapy group. (A) Progression-free survival (PFS). (B) Cancer-specific survival (CSS).

has similar relationship was observed, in addition to testosterone. Authors explained it by the hypothesis that serum testosterone might reflect the activity of the AR, and tumor with amplified AR might be hypersensitive to androgens.[19] And they also adverted that it needs to be interpreted cautiously, because the relationship between serum androgens and intratumoral androgens remains poorly understood.

Recent retrospective study reported that low basal testosterone level and AR copy number gain is associated with worse PFS and OS, both abiraterone and enzalutamide treatment.[20] In this study, patient with testosterone below the median value experienced worse PFS and OS, with enzalutamide treatment. Also, the prognostic impact of testosterone showed better outcome in patients treated with docetaxel. Authors explained this result with mechanism of action of enzalutamide. Enzalutamide blocks the link between androgens and their receptor in prostatic cells. When serum testosterone is reduced, role of enzalutamide as an antagonist of ARs might be weakened. They also hypothesized that a progression with suppressed levels of testosterone could be more aggressive, independent of hormonal axis. Results of our investigation that higher serum testosterone is associated with better PFS and OS is supported by these studies, and we confirmed these knowledges again.

In our knowledge, no clinical trial or subanalysis of clinical trial has been conducted to analyze the effects of serum testosterone in patients using enzalutamide following docetaxel. But we know that antitumor activity of docetaxel

in CRPC is represented to the prohibition of the internalization of the activated AR. Therefore, residual activity of the androgenic signal could facilitate the activity of docetaxel in limited extent.[21]

Previous studies had argued that patients with higher serum testosterone levels associated with favorable PFS in mCRPC patients treated with enzalutamide and abiraterone acetate. A retrospective analysis of 115 patients of CRPC treated with abiraterone and enzalutamide showed longer biochemical PFS in serum testosterone of 5–50 ng/dL group than serum testosterone of 0–5 ng/dL group.[14] Another retrospective study of 107 patients treated with enzalutamide and/or abiraterone, 13 ng/dL or higher serum testosterone was correlated with PFS, and not with OS.[15] The other single-center retrospective study declares that PFS among men with serum testosterone level over 0.05 ng/mL was superior to that among men with testosterone level under 0.05 ng/mL when treated with enzalutamide.[16] These reports notwithstanding, our study showed contradictory results.

None of the 3 studies described above statistically demonstrated the relationship between serum testosterone levels and OS in chemotherapy-naïve patients with CRPC that treated with enzalutamide, and our research also failed. It can be assumed that the impact of serum testosterone on survival may change with secondary, tertiary, or more treatment after enzalutamide. In our cohort, of 136 patients of prechemotherapy group, 41 treated with docetaxel after enzalutamide due to progression, 17 patients treated with abiraterone following enzalutamide due to progression or ad-

verse effect of enzalutamide. Inhibition of androgen biosynthesis (mechanisms of action of abiraterone acetate), interactions with docetaxel and subsequent treatment may alter the effects of serum testosterone on survival.

Our analysis did not derive significant association between serum testosterone level and PSA response and PFS in prechemotherapy group. Although our results are presented as continuous values of serum testosterone, the statistical results were the same when using cutoff values based on quartiles. such as 0.09 ng/mL or 0.15 ng/mL. Survival curves according to quartiles of serum testosterone level did not demonstrated clear trend for PFS and CSS. This may be due to differences in the way testosterone levels are measured, or differences in patient characteristics, or poor patient randomization.

In our institution, serum testosterone level was measured with the radioimmunoassay kit (Cisbio Bioassays, Codolet, France), and the lowest testosterone level could be tested was 0.04 ng/mL. In above-mentioned studies, the chemiluminescent microparticle immunoassay device (The Architect Testosterone II, Abbot Diagnostics, Lake Forest, IL, USA) was used to determine testosterone levels. So, it is possible that our device did not accurately measure the very low testosterone level which is regarded as serum testosterone $<$ 0.05 ng/mL.

The previous studies and the distribution of serum testosterone in this study also differed from previously reported results. In Japanese population, the median nadir PSA of patients treated with ADT is known to be 0.16 ng/mL, and the mean maximum testosterone level of ADT-treated patients has been reported to be about 0.2 ng/mL.[22,23] In Korean population, the mean serum testosterone level in patients who treated with Goserelin for 9 months was reported at 0.13 ng/mL recently.[24] In a paper analyzing the prognosis of serum testosterone and CRPC patients published by Shiota et al.,[16] median pre-ART testosterone showed 0.03 ng/mL, and Sakamoto et al.[15] had a median testosterone before abiraterone or enzalutamide of 0.13 ng/mL. This is lower than known previously. In our data, median testosterone was 0.15 ng/mL, mean serum testosterone was 0.19 ng/mL (95% CI, 0.16-0.20) in prechemotherapy group, which is higher than recently reported in Korea. Due to the differences in the testosterone measurement and the distribution of serum testosterone, the role of serum testoster-

one in prechemotherapy group in the previous studies and this study may be different.

It is also possible that progression by other variables is masking the influence of testosterone. When chemotherapy-naïve patients were divided into 3 groups following treatment after enzalutamide (41, 17, 78 as docetaxel, abiraterone, maintaining enzalutamide or salvage ADT), there was a difference in median PSA levels between these groups (51.1 ng/mL vs. 47.1 ng/mL vs. 21.0 ng/mL). This heterogeneity might be a disturbance factor of the analysis because higher PSA level is associated with shorter interval to progression and cancer-specific death, higher rate of death in our data.

Several limitations associated with this investigation are present. First, although we have the larger number of patients compared with other studies, a small number of patients and retrospective study design may have caused a selection bias. Second, limited follow-up periods can lead to inaccurate survival analysis. Third, the timing of serum testosterone measurement was varied, and follow-up and imaging interval also does. Fourth, only testosterone level was investigated, and no androgen other than testosterone was considered. Despite of these limitations, our study may have contributed in part to the relationship between outcome of enzalutamide treatment and serum androgen level.

CONCLUSIONS

In mCRPC patients who underwent docetaxel chemotherapy, high level of serum testosterone before enzalutamide use has important implications for good prognosis, as expressed as long PFS and CSS.

CONFLICT OF INTEREST

The authors claim no conflicts of interest.

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