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ORIGINAL ARTICLE

Early PSA response to antiandrogen therapy in metastatic castration-resistant prostate carcinoma patients: A predictive marker for progression-free survival?

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Summary

Purpose: *Enzalutamide and abiraterone acetate (AA) are the main therapeutic approaches for the treatment of metastatic castration-resistant prostate cancer (mCRPC) after the failure of androgen deprivation therapy during or following docetaxel-based chemotherapy. The aim of the present study was to investigate the role of early prostate-specific antigen (PSA) decline (four weeks after anti-androgen therapy) in predicting long-term progression-free survival (PFS).*

Methods: *In this retrospective study, we evaluated 65 patients who had histologically confirmed metastatic prostate cancer and were treated with AA or enzalutamide in the post-docetaxel period. Serum PSA levels were evaluated at 4th and then 12th week. The main goal of this study was to demonstrate that an early PSA decline predicts PFS.*

Results: *Between May 2015 and June 2019, the medical records of 65 patients were collected. Of these patients, 38 (58.5%) received AA and 27 (41.5%) enzalutamide. Early PSA response rate (RR; ≥ 30% and ≥ 50% from baseline at the 4th week) was identified in 38.5% (n=25) and 15.3% (n=10) of the patients, respectively. In multivariate analysis, we found that PSA RR≥ 30% in patients had a statistically significant advantage in terms of PFS (HR: 0.38, 95% CI (0.13-0.71;p=0.03).*

Conclusion: *In conclusion, 30% PSA RR was significantly associated with a better PFS.*

Key words: *metastatic castration-resistant prostate cancer, abiraterone acetate, enzalutamide, PSA response, early PSA response, predictive biomarker*

Introduction

Prostate cancer is the most common malignancy among men and the second leading cause of cancer death in Western countries [1]. One-third of men for whom radical treatment fails develop incurable metastatic prostate cancer [2]. Castration-induced androgen deprivation therapy is the first-line treatment for these patients, and nearly 90% initially respond. Unfortunately, this status does not last, and aproximately 75% of patients progress to a castration-resistant state within a median of 18-24 months and are defined as having metastatic castration-resistant prostate carcinoma MCRPC [3]. There is a remarkable diversity among mCRPC patients in terms of clinical condition, ranging from asymptomatic patients diagnosed with PSA increase to severely symptomatic patients [4].

Docetaxel-based chemotherapy was the only approved regimen for mCRPC until recently, and it modestly improved survival rates [5]. New treatment options became available during the last decade, including abiratorene asetate (AA), enzalutamide, cabazitaxel, radium-223, and sipuleucel-T

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[6-8]. Although androgen receptor (AR) inhibitors such as enzalutamide and AA have been shown to improve PFS and overall survival (OS), one-third of patients treated with AA and one-quarter of patients treated with enzalutamide show primary resistance to the therapies, defined as progression within the first 3 months of treatment [9].

The aim of the present study was to investigate the role of very early PSA decline (4 weeks after AA or enzalutamide therapy) in predicting long-term PFS. The identification of non-responders may lead to early changes in the therapeutic strategies, and this situation may affect treatment costs.

Table 1. PSA value and response

Baseline PSA (ng/ml), median (min-max)	*9.0 (0.9-48.9) n (%)*
≥ 30% PSA RR at 4th week	25 (38.5)
≥ 50% PSA RR at 4th week	10 (15.3)
≥ 30% PSA RR at 12th week	54 (83)
≥ 50% PSA RR at 12th week	26 (40)

Methods

In this retrospective study, we evaluated 65 patients who had histologically confirmed metastatic prostate cancer and were treated in School of Health Science, University Umraniye Training and Research Hospital and Acibadem University Medical Oncology Outpatient Clinic between May 2015 and June 2019 with AA or enzalutamide in the post-docetaxel period. The definition of mCRPC was biochemical or radiological progression, in accordance with the criteria of the Prostate Cancer Working Group (PCWG) [8], in patients with blood testosterone levels < 50 ng/dl. Patients who did not have mCRPC or progressive disease, who did not receive first-line docataxel-based therapy and were not treated with antiadrogen therapy were excluded from the study.

AA and enzalutamide were initially administered as full doses, in keeping with previously published regimens [6,10]. AA (1000 mg/day) (in combination with prednisone 10 mg/day) and enzalutamide (160 mg/day) were administered in a 28-day cycle. All patients maintained androgen deprivation, with a serum testosterone level ≤ 50 ng/dL (≤ 2.0 nmol/L).

During AA and enzalutamide therapies, hematological parameters were checked monthly. PSA value was recorded on the 4th week and 12th week after the start of

Table 2. Comparison of baseline demographic and clinical patient characteristics between early responders and non-responders

Variables	*All Patients n=65*	*PSA Response Rate ≥ 30 %*			*PSA Response Rate ≥ 50%*		
	n (%)	Responders n=25 n (%)	Non-responders n=40 n (%)	p	Responders n=10 n (%)	Non-responders n=55 n (%)	p
Age, years (min-max)	68 (55-85)	66 (19-75)	68 (29-78)	0,7	65 (56-82)	68 (55-85)	0.3
Age-groups (years)				0.5			0.3
<75	52 (80)	21(84)	31 (77)		9 (90)	43 (78)	
≥75	13(20)	4 (16)	9 (21)		1 (10)	12 (22)	
ECOG PS				0,1			0.5
0-1	54 (83)	23 (92)	31 (78)		9 (90)	45 (82)	
2-4	11 (17)	2 (8)	9 (12)	0.6	1 (10)	10 (18)	0.5
PSA (median) (min-max) (ng/ml)	9 (0.9-48.9)	9 (1.2-48.9)	8.5(0.9-47.2)		13.1 (2.8-32.4)	8.8 (0.9-48.9)	
Gleason score				0,2			0.1
≤ 8	37(57)	18 (72)	19 (48)		8 (80)	29 (53)	
>8	28 (43)	7 (28)	21 (52)		2 (20)	26 (47)	
Metastatic regions				0,2			0.48
Visceral	26(69)	12 (48)	14 (35)		5(50)	21(38)	
Non-visceral	39 (40)	13 (52)	26(65)		5(50)	34(62)	
Treatment				0.7			0.9
Enzalatumide	27(60)	11 (44)	16(40)		4 (40)	23 (42)	
Abiraterone acetate	38(59)	14 (56)	24 (60)		6 (60)	32 (58)	
Progression				**0.04**			**0.03**
Yes	33 (51)	7(28)	26(65)		2(20)	31(56)	
No	32 (49)	18 (72)	14(35)		8 (80)	24 (44)	

Bold numbers denote statistical significance

therapy date. Bone scan and/or computed tomography were performed before the start of treatment and every 3 months or as clinically indicated. Electrocardiography and echocardiography were also performed before the treatment and repeated in any clinical suspicion of cardiac involvement. Prostate Cancer Working Group 2 (PCWG-2) criteria, death, or unacceptable toxicity were used to define disease progression.

Early PSA response rate (RR) was assessed 4 weeks after the start of treatment. Also, PSA response was evaluated according to PCWG2 in the 12th week. Early PSA response was defined as a 30% and 50% decline in PSA at 4th week relative to baseline. Early and 12-week PSA declines were also calculated as continuous variables, expressed as the percentage decline relative to baseline PSA.

Statistics

Continuous variables are shown as median and interquartile range (IQR), and categorical variables are shown in percentages. One sample Kolmogorov-Smirnov test was carried out to evaluate the normality of continuous variables, and Kaplan-Meier method was used to estimate survival and log-rank test to estimate significant differences. The association between PSA changes (response and/or progression) and survival were evaluated with univariate and multivariate Cox regression models. Only variables significantly associated with outcome ($p \leq 0.05$) in univariate analysis were selected for testing in multivariate models. Statistical analyses were performed using SPSS version 21 (IBM, Armonk, NY, USA).

Results

Between May 2015 and June 2019, the medical records of 65 patients were collected. Median follow up period was 18 months (min 6-max 45 months). Of these patients, 38 (58.5%) received AA, and 27 (41.5%) enzalutamide. Median serum PSA value at baseline was 9.0 ng/ml (min 0.9-max 48.9). Thirty percent early PSA response rate showed 38.5% (n=25) of the patients. Thirty percent PSA response on the 12th week was identified in 81.5%

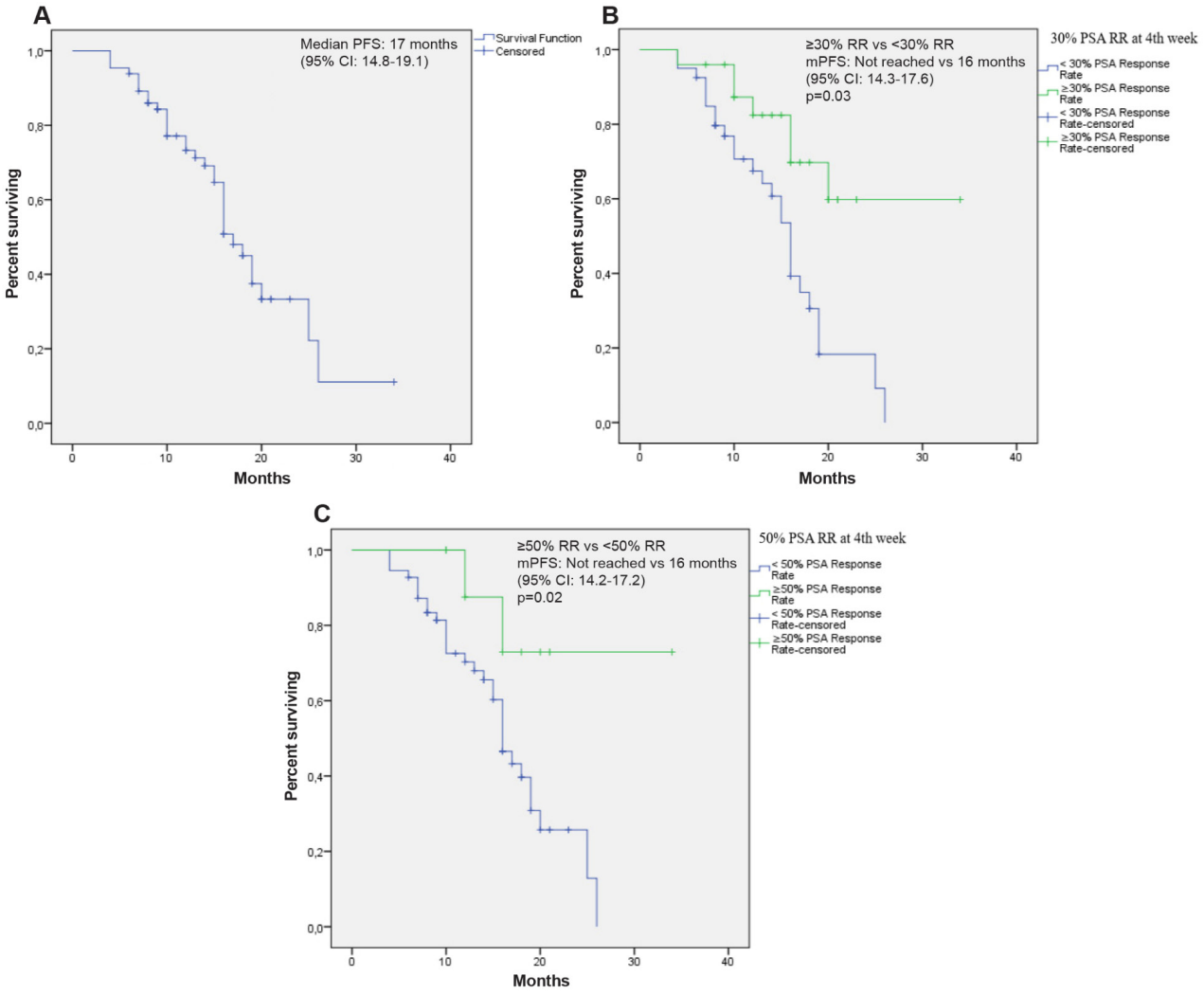

Figure 1. A: progression-free survival according of the whole cohort by Kaplan-Meier method. **B:** progression-free survival according to 30% PSA RR groups by Kaplan-Meier method. **C:** progression-free survival according to 50% PSA RR groups by Kaplan-Meier method.

(n=53) of the patients. Fifty percent early PSA response rate was identified in 15.3% (n=10) of the patients, and 50% PSA response rate was identified in 40% (n=26) of the patients in the 12th week (Table 1).

Comparison of baseline clinical and demographic parameters of patients with early responses and non-responders are shown in Table 2. Age, Eastern Cooperative Oncology Group performance status (ECOG PS), Gleason score, median PSA value, extent of disease and androgenic receptor antagonist choice (abireterone vs enzalutamide) were similar between groups.

During the follow-up period, 33 (51%) of 65 patients progressed. For the whole cohort, median PFS was 17 months (Figure 1A). According to PSA response groups, survival outcomes are given in Table 3 (Figure 1B and C). ECOG PS, age, 30% PSA RR and 50% PSA RR at fourth week, Gleason score, and AR antagonist group (AA or enzalutamide) were investigated as prognostic factors for PFS by Cox regression analysis. In univariate analysis, Gleason score and 30% and 50% PSA RR at 4th week predicted prolonged PFS (p ≤0.05). In multivariate analysis, only 30% PSA RR at 4th week was found to be independent prognostic factors for

Table 3. Survival outcomes according to PSA response rates

	All patients (n=65)	*≥30% PSA RR**			*≥50% PSA RR**		
		Responders (n=25)	Non-responders (n=40)	p	Responders (n=10)	Non-responders (n=55)	p
Median PFS (months)	17 (95%CI:14.8-19.1)	Not reached	16 (95%CI:14.3-17.6)	0.03	Not reached	16 (95%CI:14.2-17.2)	0.02
1-year PFS (%)	73	82	67		87	70	
2-year PFS (%)	33	59	18		72	25	

*PSA response at 4th week, CI: confidence interval, PFS: progression-free survival, RR: response rate

Table 4. Cox regression model of progression-free survival (PFS) in mCRPC

	Univariate analysis				*Multivariate analysis*			
	HR	*95% CI*		*p*	*HR*	*95 % CI*		*p*
		Lower	Upper			Lower	Upper	
Age, years								
<75	0.48	0.7	3.5	0,2				
≥ 75								
ECOG PS								
0-1	1.2	0.55	2.8	0.59				
2-4								
Gleason score								
≤8	2.42	1.21	4.89	**0.01**				
>8								
Visceral metastastasis								
Yes	0.6	0.3	1.38	0.26				
No								
Treatment								
Enzalutamide	1.44	0.65	3.19	0.36				
Abiraterone acetate								
PSA response PSA response ≥30% at 4th week								
Yes	0.31	0.13	0.72	**0.007**	0.38	0.13	0.71	**0.03**
No								
PSA response ≥50% at 4th week								
Yes	0.23	0.05	1	**0.05**				
No								

Bold numbers denote statistical significance

PFS (HR: 0.38, 95% CI 0.13-0.71, p=0.03). Univariate and multivariate analysis results are shown in Table 4.

Discussion

The main findings of our study were the significant associations between the PSA decline 4 weeks after initiation of enzalutamide or AA treatment and improved PFS. In our analysis, 30% PSA reduction strongly predicted PFS. Although our cohort was not large enough to compare the effects of AA with those of enzalutamide, our results did not show any differences in PFS between the two AR antagonists.

AR have an important role during mCRPC progression. The continuation of AR signaling has been explained by several mechanisms [11]. While mCRPC patients had very few and weak therapeutic options during the last decade, AA, enzalutamide and cabazitaxel have recently been shown to improve survival in this population. Unfortunately, not all patients respond to these therapies. Consequently, it is very important to determine clinical or biological markers for the early identification of non-responding patients who will benefit from other therapeutic options, which also will protect patients from unnecessary treatment-related toxicities and countries from the high costs of these medications [12,13].

While visceral metastases, anemia, progression on bone scan, performance status, and PSA progression have been shown to predict OS after docetaxel treatment, none of these parameters are useful markers of response in this new era of hormonal therapy [14]. Rather, PSA and symptom assessment are the main tools used to predict PFS and guide the therapeutic approach [15]. In our trial, ECOG PS, age and Gleason score did not vary between patients with or without progression. None of these parameters independently predicted PFS in Cox regression analysis.

It is well-known that PSA can reflect tumor burden in mCRPC patients. A decline in PSA value can indicate a reduction in disease burden and a potential clinical benefit with cytotoxic chemotherapy or novel hormonal agents. The existence of a direct relationship between AR activity and PSA production has been documented [14,16]. Rescigno et al [17] investigated the predictors of PFS and OS among mCRPC patients treated with AA in the post-docetaxel setting, reporting that 30% PSA decline from baseline at 4 weeks significantly predicted OS. Albumin, baseline PSA, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and hemoglobin were other predictors of OS in a multivariate analysis. Consistent with that study, our patients also were treated with docetaxel before enzalutamide or AA, and 30% decline in PSA levels compared with baseline predicted PFS. In another clinical trial, Fuerea et al [18] showed that a 50% PSA decline after 4 weeks of treatment was significantly associated with a longer PFS and OS in patients on various AR-targeting therapies, including enzalutamide, AA and orteronel. This cohort included patients enrolled in trials, with 78% in a post-docetaxel setting. In our study population, a 50% decline in PSA at 4th week did not predict PFS.

The present study has several limitations, including its retrospective nature and the small number of patients, and requires further validation in large prospective studies. Secondly, this was a single-center study, and, thirdly, although we had enzalutamide and AA groups, we did not have enough patients to compare the effectiveness of these agents.

Conclusion

In conclusion, an early PSA response was significantly associated with a better PFS. This study was a retrospective analysis with a limited number of patients, so further investigations with a larger cohort and in a prospective setting should be performed to confirm our findings.

Authors' contributions

A.D: drafted the manuscript. A.G.M: designed of the writing and searched the literature. O.A: designed the writing and searched the literature. S.K: designed of the writing and editing English.

Ethics approval and consent to participate

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all participants included in the study.

Ethics/institutional review board approval of research: Faculty of Medicine, Acibadem University, Istanbul, Turkey, Number: 2018-17, Date: 08.11.2018.

Conflict of interests

The authors declare no conflict of interests.

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