

PSA declines and survival in patients with metastatic castration-resistant prostate cancer treated with enzalutamide

A retrospective case-report study

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Abstract

Rationale: PSA responses have been associated with a survival benefit in patients treated with enzalutamide in retrospective analyses.

Patient concerns: However the prognostic value of PSA declines in highly pretreated patients receiving enzalutamide remains to be defined.

Diagnoses and interventions: Medical records of patients with documented mCRPC treated with enzalutamide between September 2011 and August 2016 were reviewed at multiple participating centers and assessed for overall survival (OS), PSA variations, and other variables of interest. Univariable and multivariable analyses were conducted.

Outcomes: A total of 129 patients received enzalutamide. PSA response rates (>50% PSA declines) were 58/119 (48.7%), 58/115 (50.4%), 54/110 (49.1%), and 47/91 (51.7%) at weeks 4, 8, 12, and 16, respectively. Having a PSA response was a statistically significant prognostic factor of improved OS at 8 and 12 weeks in univariable analysis, whereas it was significant at 12 weeks in the multivariable analysis. Patients treated with enzalutamide had a median OS of 7.8 months.

Lessons: Our study supports the prognostic value of PSA declines in heavily treated patients receiving enzalutamide.

Abbreviations: AR = androgen receptor, CI = confidence interval, CRPC = castration-resistant prostate cancer, Hb = hemoglobin, OS = overall survival, PFS = progression-free survival, PS = performance status, rPFS = radiographic progression-free survival.

Keywords: castration-resistant setting, enzalutamide, prostate cancer, PSA

1. Introduction

Prostate cancer is the most prevalent malignancy in men, with an estimated 1,111,700 incident cases diagnosed in 2012 worldwide.^[1] After benefitting from androgen ablation treatment,

virtually all patients with recurrent/advanced disease develop castration-resistant prostate cancer (CRPC), which progresses despite androgen deprivation treatment.^[2] In most patients with CRPC, the androgen receptor (AR) pathway continues to drive

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tumor growth,^[3] which is consistent with the effectiveness of novel antiandrogen treatments abiraterone and enzalutamide, both in the predocetaxel and in the postdocetaxel setting.^[4-7] Despite both of these agents inhibit AR signaling, they have a different mechanism of action. Although abiraterone acetate inhibits the residual adrenal and intratumoral androgen synthesis by blocking the CYP17A activity,^[8] enzalutamide directly inhibits the AR with no agonist activity.^[9]

In patients with metastatic CRPC, PSA declines have been consistently associated with improved outcomes associated with systemic therapy, including docetaxel,^[10] cabazitaxel,^[11] and abiraterone.^[12] Recently, a retrospective analysis of the AFFIRM trial^[13] showed that PSA declines in men treated with enzalutamide after prior docetaxel were consistently associated with progression-free survival (PFS), overall survival (OS), and improvement of pain. In this retrospective review study, we aim to investigate the prognostic role of PSA declines recorded during the first 16 weeks of treatment by the use of multivariate analysis to account for potential confounding factors.

2. Patients and methods

2.1. Inclusion criteria

Medical records of patients with documented mCRPC treated with enzalutamide between September 2011 and August 2016 were reviewed at multiple participating centers (Azienda Ospedaliera Universitaria Federico II, Naples, Italy; Azienda Ospedaliera di Rilievo Nazionale ‘Antonio Cardarelli,’ Naples, Italy; Istituto Nazionale Tumori ‘Fondazione G. Pascale,’ Naples, Italy; Azienda Ospedaliera ‘G. Rummo,’ Benevento, Italy; Azienda Sanitaria Locale Napoli 3, Naples, Italy; Presidio Ospedaliero di Sapri, Sapri (Salerno), Italy; Ospedale di Vallo della Lucania, Vallo Della Lucania (Salerno), Italy; Casa Sollievo della Sofferenza, San Giovanni Rotondo (Foggia), Italy; the University of Alabama at Birmingham (UAB) Cancer Center, Birmingham, AL.

2.2. Retrieved data

Demographic data of eligible patients were retrieved along with information regarding known and previously recognized baseline prognostic factors (performance status [PS], hemoglobin [Hb], PSA, albumin, pain, neutrophil count, lymphocyte count, LDH, alkaline phosphatase, Gleason score, visceral metastasis status), previous local and systemic treatments and treatment with abiraterone/enzalutamide, statin use, early PSA declines at 4,8,12, and 16 weeks. All patients who received at least one dose of abiraterone were included in the abiraterone dataset, and all patients who received at least one dose of enzalutamide were included in the enzalutamide dataset. Patients receiving both abiraterone and enzalutamide could be included in analyses of both datasets. Approval of retrospective observational studies by the ethics committee is not required according to the existing law and regulations.

2.3. Data analysis

Summary statistics were used to describe the patient population and outcomes. In each subset, survival was computed from the start of enzalutamide to the time of death. Univariable Cox proportional hazards regression was used to evaluate PSA declines and other variables as potentially prognostic for OS.

Table 1

Baseline characteristics: patients treated with enzalutamide.

		N	All patients (n=129)
Age at diagnosis	Mean (SD)	129	66.3 (6.3)
PSA at diagnosis	Median (range)	120	12 (3.56, 1788)
Gleason Score	≤7	127	77 (60.6)
	8-10		50 (39.4)
Months, diagnosis to ADT	Median (range)	128	18.3 (-10.9, 259.1)
Months, diagnosis to metastatic Dz	Median (range)	123	26.6 (-1.3, 286.7)
Months, metastatic Dz to CRPC	Median (range)	120	16.8 (-26.0, 167.9)
Prior prostatectomy	N (%) Yes	129	63 (48.8)
Prior radiotherapy	N (%) Yes	129	62 (48.1)
Prior docetaxel	N (%) Yes	129	105 (81.4)
Prior cabazitaxel	N (%) Yes	129	61 (47.3)
Prior abiraterone	N (%) Yes	129	17 (13.2)
Months, diagnosis to enzalutamide	Median (range)	129	71.4 (18.0, 288.6)
Weeks, duration on enzalutamide	Median (range)	121*	18.6 (0, 94.6)
Visceral disease	N (%) Yes	129	22 (17.1)
Opiates	N (%) Yes	126	94 (74.6)
Alkaline phos. at enzalutamide	Median (range)	102	210 (41, 780)
Hemoglobin at enzalutamide	Median (range)	109	11.0 (8.7, 14.5)
LDH at enzalutamide	Median (range)	88	320 (160, 680)
Neutrophils at enzalutamide	Median (range)	85	3400 (1900, 5430)
Lymphocytes at enzalutamide	Median (range)	85	1500 (100, 2400)
Neutrophils/Lymphocyte ratio	Median (range)	85	2.16 (1.24, 29.00)
PSA at enzalutamide	Median (range)	129	120 (3.56, 1788)
PSA, change to week 4	Median (range)	118	-29.0 (-97.0, 127.8)
PSA, change to week 8	Median (range)	115	-30.0 (-99.0, 191.7)
PSA, change to week 12	Median (range)	110	-28.8 (-99.5, 455.3)
PSA, change to week 16	Median (range)	91	-33.3 (-99.6, 378.8)
Reason for discontinuation	1	119	85 (71.4)
	2		10 (8.4)
	3		22 (18.5)
	4		2 (1.7)
Time to death	N (%) Deaths	129	106 (82.2)
	Median (95% CI)		7.8 (6.9, 8.5)
	1-year (95% CI)		24.3 (17.0, 32.3)
	2-year (95% CI)		10.9 (5.5, 18.3)

CI = confidence interval, CRPC = castration-resistant prostate cancer.

*Excludes 8 patients still on enzalutamide.

Multivariable modeling was conducted by using the full model method, that is, including all potential factors in a multivariable model, regardless of whether they were statistically significant or not. The association of PSA response with survival was then assessed after adjusting for factors included in the multivariable model. Logarithmic transformation of factors was performed for statistical normalization purposes as necessary. All tests were 2-sided and a *P*-value of .05 or less was considered statistically significant. No statistical adjustments were made for multiple testing. OS was defined as the time between treatment initiation and either the date of death or of last follow-up for surviving patients.

3. Results

3.1. Cohorts' characteristics

A total of 129 patients starting enzalutamide between September 2011 and August 2016 were included in the enzalutamide cohort, as shown in Table 1. Eight patients remained on enzalutamide treatment at the time of analysis, with a median duration of

Table 2
Prognostic factors of overall survival: patients treated with enzalutamide.

	N	Hazard ratio (95% CI)	P
Age at diagnosis	/year	1.03 (1.00, 1.05)	.073
PSA at enzalutamide	Log-transformed	1.49 (1.23, 1.79)	<.001
Alkaline phosphatase at enzalutamide	Log-transformed	1.93 (1.35, 2.76)	.002
Hemoglobin at enzalutamide	/unit	0.69 (0.58, 0.82)	<.001
LDH at enzalutamide	Log-transformed	1.05 (0.55, 1.99)	<.001
Neutrophils at enzalutamide	Log-transformed	0.19 (0.08, 0.49)	<.001
Lymphocytes at enzalutamide	/unit	1.00 (1.00, 1.00)	.010
Neutrophils/Lymphocyte ratio	Log-transformed	1.02 (0.50, 2.10)	.95
Gleason score	≥8 vs ≤7	0.46 (0.30, 0.70)	<.001
Prior prostatectomy	Yes vs No	0.93 (0.64, 1.37)	.73
Prior radiotherapy	Yes vs No	1.00 (0.68, 1.47)	.99
Visceral disease	Yes vs No	0.56 (0.33, 0.97)	.038
Opiates	Yes vs No	8.60 (4.08, 18.12)	<.001
Prior docetaxel	Yes vs No	5.73 (2.73, 12.02)	<.001
Prior cabazitaxel	Yes vs No	2.35 (1.57, 3.52)	<.001
Prior abiraterone	Yes vs No	6.54 (3.63, 11.78)	<.001
Full model (n=77)			
Age at diagnosis	/year	1.05 (0.99, 1.11)	.080
PSA at enzalutamide	Log-transformed	0.96 (0.63, 1.46)	.83
Alkaline phosphatase at enzalutamide	Log-transformed	0.51 (0.19, 1.38)	.18
Hemoglobin at enzalutamide	/unit	0.84 (0.59, 1.19)	.32
LDH at enzalutamide	Log-transformed	1.29 (0.54, 3.10)	.57
Neutrophils/Lymphocyte ratio	Log-transformed	0.86 (0.39, 1.91)	.71
Gleason score	≥8 vs ≤7	1.08 (0.59, 1.98)	.80
Visceral disease	Yes vs No	0.51 (0.22, 1.16)	.11
Opiates	Yes vs No	3.58 (0.42, 30.30)	.24
Prior docetaxel	Yes vs No	0.12 (0.01, 1.00)	.050
Prior cabazitaxel	Yes vs No	2.33 (1.28, 4.25)	.006
Prior enzalutamide	Yes vs No	8.94 (2.73, 29.25)	<.001

CI = confidence interval.

enzalutamide treatment for the remaining patients of 18.6 (range = 0-94.6) weeks.

Patients in the enzalutamide cohort had an advanced disease at the time of treatment initiation, as shown consistently by multiple variables (Table 2), including time from diagnosis to initiation of enzalutamide therapy (71.4 months), prior cabazitaxel treatment (47.3%), use of opiates (74.6%), alkaline phosphatase levels (median, 210IU/L), and LDH levels (median, 320IU/L). As a result, median OS was 7.8 months in the cohort.

3.2. Variation of PSA levels

In the study cohort, PSA response rates (>50% PSA declines) were 58/119 (48.7%), 58/115 (50.4%), 54/110 (49.1%), and 47/91 (51.7%) at weeks 4, 8, 12, and 16, respectively. Having a PSA response was a statistically significant prognostic factor of improved OS at 8 and 12 weeks at univariable analysis, whereas it was significant at 12 weeks at multivariable analysis. Trends towards significance were observed after 8 and 16 weeks at multivariable analysis (see Table 3). Consistent results were

Table 3
PSA response information: patients treated with enzalutamide.

PSA Response at 4 weeks	n/N (%)	58/119 (48.7%)	
PSA Response at 8 weeks	n/N (%)	58/115 (50.4%)	
PSA Response at 12 weeks	n/N (%)	54/110 (49.1%)	
PSA Response at 16 weeks	n/N (%)	47/91 (51.7%)	
Landmark: univariable results			
	N	Hazard ratio (95% CI)	P
PSA Response at 4 weeks	117	0.73 (0.49, 1.09)	.12
PSA Response at 8 weeks	115	0.62 (0.41, 0.94)	.023
PSA Response at 12 weeks	108	0.40 (0.26, 0.62)	<.001
PSA Response at 16 weeks	88	0.66 (0.42, 1.05)	.079
Landmark: adjusted for multivariable			
PSA Response at 4 weeks	77	1.01 (0.60, 1.70)	.97
PSA Response at 8 weeks	76	0.62 (0.35, 1.12)	.11
PSA Response at 12 weeks	73	0.30 (0.16, 0.57)	<.001
PSA Response at 16 weeks	62	0.57 (0.29, 1.12)	.10

reported for 50% PSA declines and 25% increases (data not shown).

4. Discussion

In the retrospective study involving 1199 men enrolled in the AFFIRM trial reported by Armstrong et al,^[13] patients were grouped by maximal PSA decline during the first 3 months' treatment, with each PSA decline category being assessed for OS surrogacy using Prentice criteria. This analysis showed that patients with PSA declines of any, $\geq 30\%$, $\geq 50\%$, and $\geq 90\%$ with enzalutamide had a much longer OS, PSA, PFS, radiographic progression-free survival (rPFS) ($P < .001$), and better pain response ($P < .026$) versus PSA increase/no decline. In particular, the median duration of PSA PFS for men with PSA increase/no decline and confirmed PSA declines of $\geq 30\%$ and $\geq 50\%$ was 4.6 months (95% confidence interval [CI], 4.6–4.6), 11.1 months (95% CI, 11.0–13.8), and 11.1 months (95% CI, 11.1–14.0), respectively. The median duration of PSA PFS and rPFS had not been reached for men with confirmed PSA declines of $\geq 90\%$ and ≤ 0.2 ng/mL. The median rPFS duration for men with PSA increase/no decline and confirmed PSA decline of $\geq 30\%$ and $\geq 50\%$ were 5.5 months (95% CI, 5.3–5.6), 16.1 months (95% CI, 13.8–16.6), and 16.5 months (95% CI, 13.8–18.1). Confirmed PSA declines of $\geq 30\%$, $\geq 50\%$, and $\geq 90\%$ within 90 days of enzalutamide treatment were associated with a greater proportion of men with pain response (52.3%, 50.9%, and 63.2%, respectively) compared with increase/no decline in PSA levels (32.0%; $P < .026$ for all). Importantly, although patients who did not show any decrease or showed an increase of PSA values had a median survival of approximately 12 months, patients who had a greater than 30% presented a 12-month survival rate $> 80\%$.

In the patient population of our retrospective study, only approximately one fourth of patients were alive after 12 months, but we also found an association of early PSA declines with survival outcomes in patients receiving abiraterone and enzalutamide. As opposed to the patient population of the AFFIRM trial, our retrospective study has the merit to investigate a highly pretreated population of CRPC patients, with 47.3% of patients having received cabazitaxel and 13.2% of patients having received abiraterone. Of note, although a statistically significant or a trend were observed for 30% PSA declines at 8, 12, and 16 weeks at multivariable analysis, early 30% PSA decline after 4 weeks was not associated with survival in patients receiving enzalutamide. This result is consistent with those obtained by Conteduca et al^[14] who did not find an association of PSA declines at 4 weeks and OS in a cohort of patients receiving enzalutamide. Furthermore, we noted that the 30% PSA response rate was similar at 4, 8, 12, and 16 weeks in the enzalutamide cohort, which is also consistent with the results obtained by Conteduca et al, and suggests that enzalutamide patients who do not show early PSA declines may not be likely to have a PSA decline at all. Importantly, of the dozen of variables that were explored at multivariate analysis, including age, baseline PSA, alkaline phosphatase, Hb, and LDH levels, and other clinical variables such as the Gleason score, presence of visceral disease or

use of opiates, only PSA declines at 12 were significantly associated with OS.

Despite the limitations typical of retrospective studies, including the lack of sample size computation and missing/inaccurate data, we believe that the association reported here is of great importance to confirm the finding reported in the AFFIRM trial in a real-world setting of routine clinical practice. The lack of PSA declines during the first 3 months may prompt early radiological evaluation or re-assessment for Androgen-Receptor Splice Variant 7, which is known to confer resistance to novel hormonal treatments,^[15] or even change of the therapeutic strategy.

Novel prospective trials are required in order to assess the optimal treatment in CRPC patients receiving systemic therapy who do not achieve a PSA decline within the first 3 months of treatment.

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