Consequences of an Early PSA Response to Enzalutamide Treatment for Japanese Patients with Metastatic Castration-resistant Prostate Cancer

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Abstract. *Background/Aim:* Recent studies have shown that an early prostate-specific antigen (PSA) response to androgen receptor (AR)-targeting agents in metastatic castration-resistant prostate cancer (mCRPC) is associated with a better prognosis. We analyzed early PSA response to enzalutamide and oncological outcomes to study their prognostic significance in the Japanese population. *Patients and Methods:* Fifty-one patients with mCRPC (26 of pre-docetaxel and 25 of post-docetaxel status) were treated with enzalutamide. The PSA progression-free survival (PFS), radiographic PFS (rPFS) and overall survival (OS) were assessed. The association of rPFS and OS in patients with an early PSA response at 4 weeks after commencement of enzalutamide was studied. *Results:* Early PSA responses were significantly associated with a longer rPFS (median of 47.9 vs. 20.1 weeks, $p<0.001$, in patients exhibiting a 50% PSA response; median of 40.9 vs. 20.1 weeks, $p=0.016$, in patients exhibiting a 30% PSA response). OS was also significantly associated with an early PSA response ($p=0.002$ for patients exhibiting a 50% PSA response, $p=0.003$ for patients exhibiting a 30% PSA response). Multivariate analysis showed that the predictors of a 50% PSA response were an interval to mCRPC and a docetaxel treatment history, while the predictor of a 30% PSA response was a docetaxel treatment history. Furthermore, a 50% PSA

response was independently prognostic of rPFS. *Conclusion:* An early PSA response to enzalutamide was significantly associated with a longer rPFS and OS. This information will aid in the management of patients treated with enzalutamide.

The treatment strategies for metastatic castration-resistant prostate cancer (mCRPC) have changed dramatically in time since new androgen receptor (AR)-targeting agents and a new class of taxane agents have been approved in Japan (1). Enzalutamide and abiraterone acetate are AR-targeting agents with proven survival benefits in patients of both pre- and post-docetaxel status (2-5). Enzalutamide is a second-generation anti-androgen exerting multiple inhibitory functions on androgen signal transduction (6). The pivotal clinical trials PREVEIL and AFFIRM showed that use of these drugs was associated with significantly better overall survival (OS), radiographic progression-free survival (rPFS), prostate-specific antigen (PSA) PFS, quality-of-life as assessed by the Functional Assessment of Cancer Therapy-Prostate questionnaire (FACT-P) and skeletal-related events (2, 3, 7, 8). Useful clinical effects of enzalutamide have been reported in Japanese patients (9).

Generally, the responses to AR-targeting agents are categorized into three patterns: continuous sensitivity, resistance acquisition and primary resistance (10). The mechanisms underlying drug resistance are multifactorial and biomarkers of drug resistance against AR-targeting agents are very important in the selection of patients suitable for treatment with such agents (11). The AR-V7 mutant, which lacks the ligand-binding domain of AR, has attracted attention in terms of resistance to AR-targeting agents (12). AR-V7 expression by circulating tumor cells (CTCs) was significantly associated with resistance to enzalutamide and abiraterone acetate (13, 14). However, no commercial method of detecting AR-V7 in CTCs is yet available. The prognostic significance of an early PSA response was recently evaluated in patients treated with AR-targeting

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Key Words: Castration-resistant prostate cancer, enzalutamide, early PSA response, radiographic progression-free survival, overall survival.

agents, including abiraterone acetate and enzalutamide (15-17). In the current study, we assessed PSA responses 4 weeks after initiation of enzalutamide in a Japanese population with mCRPC to determine whether such responses were associated with rPFS or OS.

Patients and Methods

Fifty-one patients with mCRPC treated with enzalutamide in Gunma University Hospital, Japan, from August 2014 through January 2015, were analyzed. The PSA levels, full blood counts and routine biochemical data were generally determined every 4 weeks, whereas radiographic analyses (computed tomography (CT)/bone scans) were generally performed every 3 to 5 months. Enzalutamide was basically discontinued after confirmation of radiographic progression, but not PSA progression, if no intolerable adverse events occurred. Docetaxel was administered with 70 mg/m² dose every 4 weeks in combination with 10 mg prednisolone or 1 mg dexamethasone. PSA PFS and rPFS were calculated according to the definitions of the Prostate Cancer Working Group 2 (PCWG2) (18). OS was defined as the time to death or the last follow-up of surviving patients. Clinical data collected to the end of March 2016 were analyzed.

Patients' characteristics were compared using Student's *t*-test or the Chi-squared test. PSA PFS, rPFS and OS were estimated using the Kaplan-Meier method and statistical significance was assessed with the aid of the log-rank test. Univariate and multivariate analyses estimating the effects of pretreatment factors on rPFS and OS were performed using Cox's proportional hazard models. Factors predicting an early PSA response were evaluated using logistic regression models. Laboratory data, including hemoglobin, alkaline phosphatase (ALP), lactate dehydrogenase (LDH) and C-reactive protein (CRP), were categorized in variables. Cut-off levels were determined by the median values of the aforementioned factors. SPSS software version 19 (IBM Corp., Armonk, NY, USA) was used in all analyses.

This study was approved by the institutional review board of Gunma University Hospital (No.1339).

Results

Patients' characteristics. Patients' characteristics are shown in Table I. The patients' ages ranged from 54 to 87 years (median=73). Most patients were of excellent performance status. All patients had radiographically confirmed metastases (bone only in 35.3%, bone + lymph node in 25.5%, lymph node only in 31.4% and viscera in 7.8%). The time to mCRPC ranged from 4 to 157 months with a median of 20 months. Twenty-six patients were docetaxel-naïve and 25 were of post-docetaxel status. We first administered enzalutamide at 160 mg/day with a dose reduction or interruption for patients who experienced intolerable adverse events. In the latter period of the study, we started with enzalutamide at 80 mg/day and generally increased the dose to 160 mg/day.

The post-docetaxel group was significantly younger, with their time to mCRPC being significantly shorter than that of patients in the pre-docetaxel group. In terms of the initial dose of enzalutamide, the rate of low-dose induction was

significantly higher in the pre-docetaxel group. The PSA levels were significantly lower in the pre-docetaxel than post-docetaxel group. No significant difference was evident in the baseline hemoglobin, ALP, LDH or CRP levels.

PSA PFS, rPFS and OS. A waterfall plot of the best PSA response rate is shown in Figure 1. A 50% PSA response was observed in 52.9%, 69.2% and 36.0% of patients in the entire, pre- and post-docetaxel groups, respectively. The PSA response in the pre-docetaxel group was significantly better than that in the post-docetaxel group ($p=0.024$). The PSA PFS (according to the PCWG2) is shown in Table II. The median PSA PFS was 16, 24 and 12 weeks in the entire, pre- and post-docetaxel groups, respectively. The PSA PFS of the pre-docetaxel group was significantly longer than that of the post-docetaxel group ($p=0.011$). The median rPFS was 37.7, 51.6 and 29.4 weeks in the entire, pre- and post-docetaxel groups, respectively. The OS of the entire and pre-docetaxel groups did not attain the median, while the median OS of the post-docetaxel group was 63.7 weeks. The OS of the pre-docetaxel group was significantly longer than that of the post-docetaxel group ($p=0.004$).

Early PSA response. Four weeks after initiation of treatment, a 30% and 50% PSA response was observed in 60.8% and 45.1% of patients, respectively, as shown in Table III. The pre-docetaxel group responded significantly better than did the post-docetaxel group ($p=0.023$ for a 30% PSA response, $p=0.025$ for a 50% PSA response).

In all patients, 30% and 50% PSA responses at 4 weeks were significantly associated with a longer rPFS (median of 40.9 vs. 20.1 weeks, $p=0.016$, for those with a 30% PSA response; median of 47.9 vs. 20.1 weeks, $p<0.001$, for those with a 50% PSA response) (Table IV; Figure 2a, b). OS was also significantly associated with 30% and 50% PSA responses at 4 weeks, with p -values of 0.003 and 0.002, respectively (Table IV; Figure 3a, b).

In the pre-docetaxel group, a 50% PSA response was significantly associated with a longer rPFS ($p=0.004$), as shown in Table IV. In patients treated with docetaxel, a 30% PSA response at 4 weeks was significantly associated with a longer rPFS ($p=0.042$). A 50% PSA response at 4 weeks exhibited a strong tendency to be associated with a longer rPFS ($p=0.066$) and OS ($p=0.096$), as shown in Table IV.

Pretreatment factors predicting an early PSA response. Factors predictive of a 30% or 50% PSA response were estimated using logistic regression models. The tested variables were a history of docetaxel use; the enzalutamide dose; performance status; LDH, hemoglobin, ALP and CRP levels; and times to mCRPC of less than 12 or 16 months. A history of docetaxel use and a time to mCRPC of longer than 16 months significantly predicted a 50% PSA response. A

Table I. *Patients' characteristics.*

		All patients	Pre-docetaxel	Post-docetaxel	<i>p</i> -Value
Number	51	26	25		
Age (years)	Median (range)	73 (54-87)	78(54-87)	71 (56-80)	0.02
PSA (ng/ml)	Median (range)	27.0 (1.6-847.8)	16.2 (1.61-247.0)	43.7 (4.72-847.8)	0.007
ECOG PS n (%)	0-1	46 (90.2)	25 (96.2)	21 (84.0)	0.69
	2	5 (9.8)	1 (3.8)	4 (6.0)	
Time to CRPC (months)	Median (range)	20 (4-157)	31 (4-157)	18 (5-150)	0.009
Metastases	Bone only	18 (35.3)	9 (34.6)	9 (36.0)	0.295
	Bone + LN	13 (25.5)	5 (19.2)	8 (32.0)	
	Bone + Vis*	2 (3.9)	0	2 (8.0)	
	LN only	16 (31.4)	11 (42.3)	5 (20.0)	
	LN + lung	2 (3.9)	1 (3.9)	1 (4.0)	
Laboratory data [#]					
Hb	g/dl	12.4 (6.5-14.9)	12.6 (8.1-14.9)	11.8 (6.5-14.2)	0.122
ALP	U/l	272 (119-1184)	273 (133-529)	249 (119-1184)	0.258
LDH	U/l	221 (107-1553)	202.5 (107-347)	236 (169-1553)	0.097
CRP	mg/dl	0.11 (0.0-9.66)	0.1 (0.0-4.0)	0.16 (0.01-9.66)	0.086
Docetaxel	course				
	Median (range)	-	-	11 (1-33)	
Initial dose	160 mg	22 (43.0)	7 (27.0)	15 (60.0)	0.017
n (%)	80 mg	29 (57.0)	19 (73.0)	10 (40.0)	

*One patient with lung and liver metastasis and the other patient with lung metastases. [#]Laboratory data are expressed as median values with range. PSA, Prostate-specific antigen; CRPC, castration-resistant prostate cancer; ECOG PS, Eastren Cooperative Oncology Group performance status; Hb, hemoglobin; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; CRP, C-reactive protein; LN, lymph node; vis, viscera.

Table II. *Median PSA PFS, rPFS and OS.*

	All patients	Pre-docetaxel	Post-docetaxel	<i>p</i> -Value
PSA PFS				
Week	16.0	24.0	12.0	0.011
95% CI	11.7-20.3	13.5-34.5	7.6-16.4	
rPFS				
Week	37.7	51.6	29.4	0.76
95% CI	31.9-43.6	26.4-76.8	11.2-47.6	
OS				
Week	Not reached	Not reached	63.7	0.004
95% CI			32.4-95.0	

PSA PFS, Prostate-specific antigen progression free survival according to PCWG2 criteria; rPFS, radiographic progression-free survival; OS, overall survival; CI, confidence interval.

history of docetaxel use was a significant predictor of the 30% PSA response (Table I).

Prognostic factors for rPFS and OS. For rPFS, univariate analysis using Cox proportional hazard models showed that early PSA30% response and 50% response were significantly associated with better rPFS. Multivariate analysis showed that early 50% PSA response was independently predictive of rPFS (Table VI).

Table III. *PSA responses at 4 weeks after treatment commencement.*

	All patients	Pre-docetaxel	Post-docetaxel	<i>p</i> -Value
30% PSA response				
%	60.8%	76.9%	44.0%	0.023
50% PSA response				
%	45.1%	61.5%	32.0%	0.025

PSA, Prostate-specific antigen.

For OS, univariate analysis showed that hemoglobin, ALP, CRP, time to CRPC with both 12 month and 16 month, a docetaxel treatment history, early PSA responses were significantly associated with better OS. Multivariate analysis showed that hemoglobin, ALP and a docetaxel treatment history were independently predictive of better OS (Table VII).

Discussion

The principal findings of the present study are the significant associations between the PSA responses 4 weeks after initiation of enzalutamide treatment and the improved

Table IV. Median rPFS and OS in terms of early PSA responses.

	PSA response	Responder	Non-responder	p-Value
rPFS				
All patients	30% response week (95% CI)	40.9 (35.2-46.5)	20.1 (13.8-28.5)	0.016
	50% response week (95% CI)	47.9 (28.7-67.1)	20.1 (10.0-30.3)	<0.001
Pre-docetaxel	30% response week (95% CI)	51.6 (28.1-75.0)	26.1 (0-65.3)	0.466
	50% response week (95% CI)	64.3 (35.4-93.2)	23.4 (11.9-34.9)	0.004
Post-docetaxel	30% response week (95% CI)	39.9 (24.8-54.9)	15.7 (9.8-21.6)	0.042
	50% response week (95% CI)	40.9 (35.4-46.3)	15.7 (13.8-17.6)	0.066
OS				
All patients	30% response week (95% CI)	not reached	62.9 (46.4-79.3)	0.003
	50% response week (95% CI)	not reached	63.7 (38.2-89.3)	0.002
Pre-docetaxel	30% response week (95% CI)	not reached	not reached	NA
	50% response week (95% CI)	not reached	not reached	NA
Post-docetaxel	30% response week (95% CI)	not reached	50.3 (38.5-62.1)	0.122
	50% response week (95% CI)	not reached	50.3 (38.5-62.1)	0.096

PSA, Prostate-specific antigen; NA, not applicable; rPF, radiographic progression-free survival; CI, confidence interval; OS, overall survival.

oncological outcomes. Overall, both the 50% and 30% PSA responses strongly predicted both rPFS and OS. When patients were stratified by docetaxel treatment history, the 50% PSA response still significantly affected rPFS and OS in patients without a history of docetaxel use. In patients of post-docetaxel status, such tendencies were consistently observed. Rescigno *et al.* (15) reported that a decline in the 30% PSA after 4 weeks of abiraterone acetate treatment was significantly associated with a better PFS and OS. Patients who did not achieve a 30% PSA decline showed significantly poorer OS. In a clinical trial, Fuera *et al.* (16) 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, abiraterone acetate and orteronel. The cohort of the Fuera's study included patients enrolled in clinical trials of cognate agents, with 78% being of post-docetaxel status. The authors confirmed the observations described above in patients treated with abiraterone acetate outside the clinical trial setting (16). A more recent study found that a very early PSA response (15 days after starting abiraterone acetate) was

Table V. Predictors estimating early PSA responses: multivariate analysis.

	OR	95% CI	p-Value
30% response			
Decetaxel treatment no vs. yes	4.03	1.201-13.526	0.024
50% response			
Time to CRPC 16>mo vs. <16mo	5.656	1.436-22.266	0.013
Decetaxel treatment no vs. yes	3.588	1.002-12.747	0.05

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

significantly associated with a better PFS and OS (17). Based on these findings, our current study is the first to show that the early PSA response is significantly associated with PFS and OS in patients with enzalutamide cohort.

Figure 1. Waterfall plots showing the best responses in terms of changes in prostate-specific antigen (PSA) levels from baseline in patients treated with enzalutamide. Left panels: pre-docetaxel group. Right panels: post- docetaxel group. A 50% PSA response was observed in 69.2% and 36.0% of patients in pre- and post-docetaxel groups, respectively ($p=0.024$).

Identification of pretreatment biomarkers predicting the responses to AR-targeting agents would allow optimal use of such agents and taxanes. The responses to primary androgen deprivation therapy are considered to be key when estimating responses to subsequent CRPC treatment. Chi *et al.* (19) proposed that 12 months was the key time at which to evaluate responses to AR-targeting agents and recommended that patients showing shorter times to CRPC should be considered for upfront use of docetaxel. Sonpavde *et al.* (20) proposed that a time of 16 months to CRPC should trigger upfront use of chemotherapy (20). In our present study, a time of 16 months to mCRPC significantly predicted a 50% PSA response. Other factors, including the Gleason score and the TMPRSS2-ERG translocation, did not appear to estimate the response to abiraterone acetate (21, 22). The baseline testosterone level was reported to be significantly prognostic of OS, but did not predict the response to treatment (23). In our current study, the baseline hemoglobin and ALP levels were significantly associated with the prognosis of OS. One of the potential pretreatment prognostic factors is the AR-V7 expression level in CTCs (12-14). Although the cohort studied was small, Antonarakis *et al.* (13) reported that the

AR-V7 expression level in CTCs was prognostic of the outcomes of CRPC treatment. Further studies using liquid biopsies that include CTCs and cell-free DNA are warranted to establish robust biomarkers, which were cited in PCWG3 (24).

PSA flare is an important feature of an early change in the PSA level. The clinical significance of an early PSA rise has been characterized in patients treated with docetaxel. PSA flares occurred in 7.6% to 13.8% of patients and four courses of docetaxel were, at least, recommended (25). In terms of AR-targeting agents, PSA flare has been reported in patients treated with abiraterone acetate (26), but in less than 10% percent, and did not affect prognosis. Since AR-targeting agents affect AR action by ligand depletion or interference with signal transduction, a transient rise in PSA would be expected to be rare. Nelson (27) categorized prostate cancer cells into molecular states based on ligand-AR interactions. Enzalutamide and abiraterone acetate act in state II; the cancer cells undergo ligand depletion or interference with AR signal transduction. Eventually, the AR becomes activated by mutation, splicing variation or aberrant stimulation by cytokines (state III). We suggest that an early

Figure 2. Radiographic progression-free survival of 51 patients treated with enzalutamide in terms of a (a) 30% prostate-specific antigen (PSA) response and a (b) 50% PSA response. Early PSA responder showed significantly better radiographic progression-free survival ($p=0.016$ for 30% PSA response; $p<0.001$ for 50% PSA response).

Figure 3. Overall survival of 51 patients treated with enzalutamide in terms of a (a) 30% prostate-specific antigen (PSA) response and a (b) 50% PSA response. Early PSA responder showed significantly better overall survival ($p=0.003$ for 30% PSA response; $p=0.002$ for 50% PSA response).

PSA response depends on the ratio of state II to state III cells. Further basic studies are required to prove this.

The labeled dose of enzalutamide is 160 mg/day; we used 80 mg/day at the start of treatment. Generally, the dose was rescheduled to 160 mg/day within the first 1 to 2 months. As mentioned in the Result section, the initial dose did not significantly predict the early PSA response, rPFS or OS. Based on these findings, we analyzed all data of the current cohort. We are now exploring safety aspects in the same cohort.

Limitations of the present study include its retrospective nature and the small number of patients; the powers of analyses of groups stratified by docetaxel use are rather low. We also noticed that two different initial doses of enzalutamide were adopted in this cohort. Both univariate

and multivariate analyses showed that initial doses were not predictive for rPFS or OS. In that sense, the clinical relevance in the current study would not be significantly affected by the initial doses of enzalutamide. However, an early PSA response was prognostically predictive in all patients treated with enzalutamide. The strong points of the study are the relatively uniform treatment strategy and follow-up featuring both regular PSA measurements and radiographic evaluation. Furthermore, this is the first report on the early PSA response in a Japanese mCRPC cohort treated with enzalutamide alone.

In conclusion, an early PSA response (4 weeks after initiation of enzalutamide) was significantly associated with a better rPFS and OS in a routine Japanese clinical setting.

Table VI. Univariate and multivariate analysis for radiographic progression-free survival.

Variable		Univariate analysis			Multivariate analysis		
		HR	95% CI	p-Value	HR	95% CI	p-Value
ECOG PS	1-2 vs. 0	1.54	0.72-3.29	0.27	-		
Hb	≤ 11.4g/dL vs. >11.4g/dl	1397.0	0.65-2.98	0.39	-		
LDH	≥ 221 U/l vs. <221 U/l	0.85	0.39-1.84	0.8	-		
ALP	≥ 278 U/l vs. <272 U/l	1.58	0.74-3.38	0.24	-		
CRP	≥ 0.11 mg/dl vs. <0.11mg/dl	1.6	0.75-3.44	0.23	-		
Time to CRPC	≤ 12 month vs. >12 month	1.14	0.46-2.87	0.78	-		
Time to CRPC	≤ 16 month vs. >16 month	1.45	0.65-3.21	0.36	-		
Dose	160 mg vs. 80 mg	0.96	0.65-1.42	0.85	-		
Docetaxel treatment	yes vs. no	1.97	0.92-4.24	0.08	-		
PSA 30% response	no vs. yes	2.73	1.17-6.35	0.02	-		
PSA 50% response	no vs. yes	3.98	1.79-8.88	0.001	3.84	1.72-8.55	0.001

ECOG PS, Eastren Cooperative Oncology Group performance status; Hb, hemoglobin; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; HR, hazard ratio; CI, confidence interval; CRP, C-reactive protein; PSA, prostate-specific antigen.

Table VII. Univariate and multivariate analysis for overall survival.

Variable		Univariate analysis			Multivariate analysis		
		HR	95% CI	p-Value	HR	95% CI	p-Value
ECOG PS	1-2 vs. 0	2.56	0.87-7.53	0.087	-		
Hb	≤ 11.4g/dl vs. >11.4g/dl	4.5	1.36-17.21	0.015	8.72	1.52-50.07	0.015
LDH	≥ 221 U/l vs. <221 U/l	2.5	0.85-7.32	0.095	-		
ALP	≥ 278 U/l vs. <272 U/l	3.19	1.09-9.36	0.035	13.41	2.38-75.55	0.003
CRP	≥ 0.11 mg/dl vs. <0.11mg/dl	5.01	1.41-17.79	0.013	-		
Time to CRPC	≤ 12 month vs. >12 month	4.91	1.73-13.92	0.003	-		
Time to CRPC	≤ 16 month vs. >16 month	4.11	1.4-12.08	0.01	-		
Dose	160 mg vs. 80 mg	1.1	0.64-1.88	0.73	-		
Docetaxel treatment	yes vs. no	6.77	1.52-15.44	0.012	5.87	1.11-31.19	0.038
PSA 30% response	no vs. yes	4.2	1.52-13.44	0.07	-		
PSA 50% response	no vs. yes	7.82	1.75-34.95	0.007	-		

ECOG PS, Eastren Cooperative Oncology Group performance status; Hb, hemoglobin; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; HR, hazard ratio; CI, confidence interval; CRP, C-reactive protein; PSA, prostate-specific antigen.

These findings will aid in the optimal use of enzalutamide by Japanese patients.

Conflicts of Interest

Kazuhiro Suzuki has served as an advisory board member of, spoken for, and received a research grant from Astellas.

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Received August 9, 2016

Revised August 22, 2016

Accepted August 23, 2016