Reduction of Initial Dose of Enzalutamide does not Decrease the Incidence and Severity of Adverse Events in Castration-Resistant Prostate Cancer

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Abstract

Background: There was no clear evidence whether the initial dose of enzalutamide affects the incidence of adverse events (AEs), and oncological outcome in patients with castration-resistant prostate cancer (CRPC).

Methods: The clinical chart of 233 CRPC patients treated with enzalutamide was reviewed retrospectively. After 1:3 propensity score matching (PSM), 124 patients were classified to whom introduced with full dose of enzalutamide or whom with reduced dose and the oncological outcomes were compared. To investigate the independent predictive factors with progression-free survival (PFS) and overall survival (OS), univariate and multivariate Cox regression analyses were performed.

Results: Of total, 190 CRPC patients initiated with full dose enzalutamide were younger and better performance status compared with 43 patients beginning with reduced dose. After PSM, the baseline characteristics were not different between full and reduced dose group. The incidence rate of patients with prostate specific antigen (PSA) decline of >90% in reduced dose group was significantly lower than that in full dose group (34.8% vs 46.2%) (p-value 0.03). The incidence rates of AEs were not statistically different between reduced dose group (22.6%) and full dose group (34.4%) (p-value 0.24). On multivariate analyses, initial enzalutamide dose was not a predictive factor of PFS and OS.

Conclusion: Initiating with reduced dose of enzalutamide did not significantly decrease the incidence rate of AEs, and it showed less PSA response rate. There is no clear rationale of treating with initial reduction of enzalutamide resulted in overcome incidence of AEs.

Background

Prostate cancer (PC) is the most common type of cancer among elderly men worldwide (1). Overall, 7%-15% of PC patients are initially diagnosed with metastatic PC and started with androgen deprivation therapy (ADT) (2). In addition, 20%-50% of non-metastatic PC patients treated with surgery or radiation experience biochemical recurrence (BCR) and are started with ADT (3). Finally, these patients receiving ADT develop castration-resistant prostate cancer (CRPC) within a couple of years.

Enzalutamide, a next-generation androgen receptor (AR)-targeted agent, was approved for CRPC based on the results of phase 3 double-blind, randomized trials (PREVAIL and AFFIRM) (4, 5). In these trials, enzalutamide significantly prolonged the survival of patients compared to placebo in, both, pre- and post-chemotherapy settings. On the other hand, a wide variety of adverse events (AEs), such as fatigue, decreased appetite, and hypertension, were reported. In both trials, > 90% of CRPC patients treated with enzalutamide experienced AEs of varying severity. A similar tendency was observed in the subgroup analysis of a Japanese cohort in the PREVAIL trial. In detail, approximately 95% of patients treated with enzalutamide had AEs of varying severity, with decreased appetite, weight loss, and fatigue being the commonly experienced AEs (6).

In real-world practice, patients are sometimes required to undergo dose reduction or discontinuation of enzalutamide because of severe AEs (7). A retrospective study reported the predictive factors for the occurrence of AE, which were as follows: older age, worse performance status (PS), and initially started with a full dose of enzalutamide (8). To minimize the occurrence of AEs and prolong the treatment period of enzalutamide, the initial starting dose is sometimes reduced for patients with such risk factors (i.e. older age and worse PS). Recently, inferiority of low-dose of enzalutamide in late-elderly patients over standard dose of enzalutamide has reported by retrospective study with 59 metastatic CRPC patients (9). However, there was no clear evidence whether the initial dose reduction of enzalutamide results in a longer treatment duration, thereby leading to the improvement of survival in these patients. Therefore, we aimed to investigate whether the initial dose of enzalutamide affects the incidence of AEs and oncological outcome in patients with CRPC.

Methods

This study was approved by the Ethics Committee of both The Jikei University School of Medicine ((30–390(9411)) and University of the Ryukyus, Graduate School of Medicine.

Patients and study design

We retrospectively reviewed the clinical records of CRPC patients who were treated with enzalutamide from June 2014 to December 2018 at The Jikei University Hospitals and University of the Ryukyus, Graduate School of Medicine and its affiliated institution. Patients were excluded from this study based on the following criteria: 1) lack of clinical information, 2) short follow-up periods (< 1 month) and 3) presence of prior treatment with abiraterone acetate. Eventually, 233 patients were enrolled for this study. The initial dose of enzalutamide was decided based on the discretion of the attending clinicians. Patients were classified to whom introduced with full dose of enzalutamide or whom with reduced dose and the efficacy and safety of enzalutamide treatment were compared. The treatment sequence for CRPC was basically decided according to the guidelines (10). CRPC was defined according to the guidelines of the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) (11). Prostate specific-antigen (PSA) progressions after enzalutamide treatment were defined according to the PCWG2 criteria (11). In this study, the discontinuation of enzalutamide treatment either temporally or permanently due to the occurrence of any AEs was used as the categorical variable in the Cox regression analyses.

Statistical analysis

The patients' characteristics between the full and reduced dose groups shown in Tables 1 and 2 were compared using the chi-square test and t-test. Propensity score for selecting the initial full dose of enzalutamide or the reduced dose of enzalutamide was calculated, thereafter 1:3 ratios of k-neighbor Propensity score matching (PSM) was performed to reduce the variance of the baseline characteristics in the full and reduced dose groups. The association of the initial dose of enzalutamide with PSA progression-free survival (PFS) and overall survival (OS) rates were estimated using the Kaplan-Meier method, and the log-rank test was used to compare the survival outcome. Univariate and multivariate Cox regression analyses were performed to identify the independent factors for PFS and OS. All data were analyzed using STATA 14 (Stata Corp., College Station, TX). Differences were considered significant if the two-sided p-values were < 0.05.

Table 1
Baseline characteristics of 233 CRPC patients based on initial dose of enzalutamide

Variables	Total Number (%)	Initial dose of Enzalutamide		P value
		40–120 mg Number (%)	160 mg Number (%)	
Number of patients	233	43 (18.5)	190 (81.5)	
Median age (IQR)	77 (70-81.5)	81 (76–84)	76 (69–80)	< 0.01
Median PSA(IQR)	14.4(6.2–52.4)	13.2(7.2–49.7)	14.9 (5.2–54.6)	0.55
GS				0.73
6–7	40 (17.2)	6 (14.0)	34 (17.9)	
8	38 (16.3)	11 (25.6)	27 (14.2)	
9–10	107 (45.9)	20 (46.4)	87 (45.8)	
NA	48 (20.6)	6 (14.0)	42 (22.1)	
PS				< 0.01
0–1	218 (93.6)	34 (79.1)	184 (96.8)	
2–4	15 (6.4)	9 (20.9)	6 (3.2)	
cT stage				0.92
Tx	33 (16.3)	6 (14.0)	27 (14.2)	
T1-2	108 (44.2)	19 (44.1)	89 (46.9)	
T3-4	92 (39.5)	18 (41.9)	74 (38.9)	
cN stage				0.94
0	158(67.8)	29 (67.4)	129 (67.9)	
1	75 (32.2)	14 (32.6)	61 (32.1)	
cM stage				0.66
0-1a	95 (40.8)	19 (44.2)	76 (40.0)	
1b-c	138 (59.2)	24 (55.8)	114 (60.0)	
Median time to CRPC (IQR)	18.5 (10–37)	16.5 (9.5–46.5)	19.5(10–36)	0.59
Prior DTX	60 (25.8)	7 (16.3)	53 (27.9)	0.09
With Steroid Therapy	43 (18.5)	10 (23.3)	33 (17.4)	0.38
With BMA	45 (23.6)	12 (27.9)	33 (17.4)	0.12
IQR = interquartile range NA = not available				

Table 2
Baseline characteristics of 124 CRPC patients after PSM

Variables	Total	Initial dose of Enzalutamide		P value
		40–120 mg	160 mg	
Number of patients	124	31	93	
Median age (IQR)	78.5 (74-82.5)	79 (74–82)	78 (74–83)	0.55
Median PSA(IQR)	14.7 (7.3–46.3)	13.6 (9.1–46.5)	14.9(7.1–45.0)	0.49
GS				0.95
6–7	19 (15.3)	4 (12.9)	15 (16.1)	
8	19 (15.3)	6 (19.4)	13 (14.0)	
9–10	59 (47.6)	16 (51.6)	43 (46.2)	
NA	27 (21.8)	5 (16.1)	22 (23.7)	
PS				0.50
0–1	117 (94.4)	30 (96.8)	87 (93.5)	
2–4	7 (5.6)	1 (3.2)	6 (6.5)	
cT stage				0.63
Tx	16 (12.9)	3 (9.7)	13 (14.0)	
T1-2	71 (60.5)	20 (64.5)	51 (54.8)	
T3-4	33 (26.6)	8 (25.8)	29 (31.2)	
cN stage				0.58
0	85 (68.5)	20 (64.5)	65 (69.9)	
1	39 (31.5)	11 (35.5)	28 (30.1)	
cM stage				0.34
0-1a	51 (41.1)	15 (48.4)	36 (38.7)	
1b-c	73 (58.9)	16 (51.6)	57 (61.3)	
Median time to CRPC (IQR)	19 (10–37)	10.5 (9–39)	20.5 (12-36.5)	0.58
Prior DTX	27 (21.8)	6 (19.4)	21 (21.5)	0.71
With Steroid Therapy	25 (20.2)	6 (19.4)	19 (20.4)	0.90
With BMA	30(24.2)	7 (22.6)	23 (24.7)	0.75
IQR = interquartile range NA = not available				

Results

The clinical characteristics before enzalutamide treatment of 233 patients are listed in Table 1. The patients' median age was 77 years (interquartile range [IQR]: 70-81.5 years), and PSA before enzalutamide treatment was 14.4 ng/ml (IQR: 6.20–52.4 ng/ml). Among the 233 patients, 42% had already undergone local therapies, such as prostatectomy or radiotherapy.

Approximately 70% of the patients were initially treated with ADT plus bicalutamide and the median time to CRPC was 18.5 months.

Regarding the allocation of patients based on the initial dose of enzalutamide, 190 (81.6%), 25 (10.7%), 15 (6.4%), and 3 (1.3%) patients received 160 (full dose), 120, 80 and 40 mg of enzalutamide, respectively.

When stratifying the patients to full or reduced dose groups, the patients in the reduced dose group were significantly older and had worse PS than those in the full dose group (Table 1).

The patients' baseline characteristics after PSM are shown in Table 2. After PSM, among the 124 patients, 31 and 93 patients received a reduced and a full dose of enzalutamide, respectively. The baseline characteristics were not significantly different between the full and reduced dose groups.

In the PSM cohort, the PSA reduction rates after enzalutamide treatment are shown in Table 3 and Fig. 1. The PSA response rate after enzalutamide treatment was significantly better in the full dose group (-87.4%) than in the reduced dose group (-66.3%). The proportion of patients with PSA decline of > 90% was significantly higher in the full dose group than in the reduced dose group (46.2% and 25.8%, respectively, p-value = 0.03). The median time to PSA nadir was 2 months, which was not significantly different between the two groups. There was no significant difference in the duration of enzalutamide treatment between the full (median: 8months) and the reduced dose group (median 7months).

Table 3
Efficacy of enzalutamide treatment based on initial dose of enzalutamide

Variables	Total	Initial dose of Enzalutamide		P value
		40–120 mg	160 mg	
Initial dose				< 0.01
40 mg	1 (0.8)	1 (3.2)	0	
80 mg	8 (6.5)	8 (25.8)	0	
120 mg	22 (17.7)	22 (71.0)	0	
160 mg	93 (75.0)	0	93 (100)	
Dose down				0.10
None	90 (72.6)	26 (83.9)	64 (68.8)	
Yes	34 (27.4)	5 (16.1)	29 (31.2)	
Discontinued *1				0.25
None	114 (81.9)	30 (96.8)	84 (90.3)	
Yes	10 (8.1)	1 (3.2)	9 (9.7)	
% PSA decline (IQR) *2	83.3(34.7–97.4)	66.3(24.1–94.9)	87.4(46.2–97.7)	0.02
50% PSA response *2	76 (61.3)	16 (51.6)	60 (64.5)	0.20
90% PSA response *2	51 (41.1)	8 (25.8)	43 (46.2)	0.03
Median time to PSA nadir(IQR)	2 (1–5)	2(1–5)	3(1–5)	0.10
Duration of enzalutamide (IQR)	7 (3-17.5)	7 (3–14)	8 (2–19)	0.17
Median time to PSA progression (range)	6 (1–58)	5 (1–24)	8 (1–58)	0.10
Median time to overall mortality (range)	N.R (1–58)	N.R (1–43)	N.R (1–58)	0.31
IQR = interquartile range, N.R = not reached, *1 due to any AEs, *2 at the best response				

During the follow-up period, the proportion of patients requiring a dose reduction due to AEs was not different between the full and reduced dose group (31.2% and 16.1%, respectively, p-value = 0.10. Moreover, the discontinuation rate of enzalutamide due to AEs was not significantly different between the full and reduced dose groups (9.7% and 3.2%, respectively, p-value = 0.25).

The median follow-up period was 17 months. Overall, 84 patients (67.7%) had PSA progression and 24 patients (19.4%) died due to any cause. The Kaplan-Meier curves of PSA PFS and OS according to the initial dose of enzalutamide are presented in Fig. 2. There was no significant difference in PSA PFS and OS between the full and reduced dose groups. In detail, the median time to PSA progression in the full and reduced dose groups was 8months and 6 months, respectively (p-value = 0.10) (Table 3).

The AE profile of the patients is presented in Tables 4 and 5. The incidence rates of AEs of any grade and of grades 3–5 were 30.2% and 8.9%, respectively, in the entire cohort. Fatigue and appetite loss were the most frequent AEs observed in this cohort. The incidence of AE of any grade was not significantly different between the full and reduced dose groups (34.4% and 22.6%, respectively, p-value = 0.24).

Table 4
Any grade of Adverse Events (AE) based on initial dose of enzalutamide

Variables	Total	Initial dose of Enzalutamide		P value
		40–120 mg	160 mg	
Number of patients	124	31	93	
Incidence of AE				
All grade	39 (31.5)	7 (22.6)	32(34.4)	0.24
Grade3-5	11 (8.9)	2 (6.5)	9 (9.7)	0.61

Table 5
Profile of Adverse Events (AE) based on initial dose of enzalutamide

Initial dose of enzalutamide	40–120 mg		160 mg	
Adverse Event	All grade	G3-5	All grade	G3-5
Fatigue	2 (6.5)	2 (6.5)	15(16.1)	4(4.3)
Appetite loss	4 (12.9)	0	10 (10.8)	3 (3.2)
Rush	0	0	1 (1.1)	0
AST/ALT increased	1 (3.2)	0	1 (1.1)	0
Nausea	0	0	5 (5.4)	0
Diarrhoea	0	0	3 (3.2)	0
Hypertension	0	0	1 (1.1)	1(1.1)
Dysgeusia	0	0	1(1.1)	0
Edema	0	0	2 (2.2)	0
Stiffness	0	0	1(1.1)	1(1.1)

Table 6

Univariable and multivariable Cox regression analyses for the prediction of PSA progression-free survival and overall survival (OS) in 124 CRPC patients treated with enzalutamide.

Variable	PSA progression				OS			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
Prior local therapy	0.91(0.71–1.17)	0.46			0.71(0.43–1.17)	0.18	-	-
Time to CRPC < 12 m	3.04(1.89–4.91)	< 0.01	2.55(1.53–4.23)	< 0.01	3.06(1.35–6.99)	0.01	2.24(0.79–6.39)	0.13
Age (continuous)	1.00(0.97–1.04)	0.80			0.99(0.94–1.05)	0.84		
PSA ^{#1} (continuous)	1.00(1.00–1.00)	< 0.01	1.00(0.99–1.00)	0.42	1.00(1.00–1.00)	< 0.01	1.00(0.99–1.00)	0.40
PS2-4 (ref:0–1)	0.74(0.18–3.02)	0.68			8.38(2.77–25.3)	< 0.01	4.97(0.98–25.3)	0.06
cT3-4 (ref:cTx-2)	1.23(0.87–1.73)	0.24			1.44(0.74–2.78)	0.28		
cN1 (ref:N0)	1.92(1.23–3.00)	< 0.01	1.55(0.96–2.51)	0.08	1.33(0.58–3.03)	0.50		
cM1b-c (ref: M0-1a)	1.15(0.75–1.77)	0.53			2.25(0.89–5.68)	0.09		
Prior DTX (ref:none)	2.16(1.31–3.54)	< 0.01	1.58(0.86–2.88)	0.14	3.79(1.68–8.51)	< 0.01	1.15(0.60–4.50)	0.33
Steroid (ref:none)	1.67(1.00–2.77)	0.05	1.28(0.72–2.26)	0.41	2.23(0.97–5.11)	0.06		
BMA (ref:none)	1.18(0.73–1.93)	0.49			1.08(0.44–2.65)	0.86		
Initial Enz dose (ref:full)	1.45(0.96–2.31)	0.12	-	-	1.59(0.65–3.89)	0.31	-	-
Dose down (ref:none)	0.76(0.46–1.24)	0.27			1.33(0.58–3.06)	0.41		
Discontinued due to any AEs (ref:none)					1.10(0.46–2.63)	0.82		
PSAdecline(continuous)					0.99(0.98–1.00)	< 0.01	0.99(0.98–1.00)	< 0.01
HR = Hazard Ratio; CI = Confidence Interval; #1: PSA @ before enzalutamide treatment, BMA = bone modifying agent, Enz: enzalutamide, DTX: docetaxel								

Finally, the univariate and multivariate Cox regression analyses were conducted to investigate the independent prognostic factors for PSA PFS and OS. The results are summarized in Table 6. We found that the initial dose of enzalutamide was not a predictive factor for PFS and OS. In the multivariate analyses, time to CRPC within 12 months (hazards ratio [HR]: 2.55) was the independent predictive factor for PSA progression. Lower PSA response rate (HR 1.00) was a significant predictive factor for worse OS.

Discussion

In the present study, we assessed the influence of the initial starting dose of enzalutamide on the survival outcome and incidence of AEs in CRPC patients. The results indicated that the rate of patients with PSA decline of >90% after enzalutamide treatment was lower in the reduced dose group than in the full dose group, despite the fact that the reduction of the initial dose was not significantly associated with worse PFS and OS in the multivariate analyses. On the other hand, the incidence and severity of AEs were not significantly different between the full and reduced dose groups.

A dose escalation study of enzalutamide (30–360 mg per day) was conducted in a previous preliminary and phase 1–2 trials, which found the dose-dependent increase of enzalutamide in the plasma (12, 13). In fact, the dose dependency of enzalutamide in the percentage change of PSA from baseline was analyzed in the phase 1–2 study (13). The proportion of patients with PSA decline of >50% was lower in the patients received 60 mg per day of enzalutamide than those received higher doses (>150 mg per day) (13). Likewise, the dose dependency of enzalutamide was observed on the incidence of AE in the phase 1–2 study. Patients administered $\leq$ 150 mg per day of enzalutamide did not complain of fatigue or required discontinuation of treatment due to AEs (13). Thus, the standard dose of enzalutamide was set as 160 mg per day.

However, at the start of its use in clinical practice, there were a number of patients with severe AEs after receiving 160 mg per day of enzalutamide in our study, even though the incidence was not higher than that of the previous phase 3 study (14). To minimize the incidence and severity of AEs and prolong the treatment period, some clinicians introduce enzalutamide with a reduced initial starting dose, even though reducing the dose might lead to insufficient treatment efficacy. The results of this study indicated that reducing the initial dose of enzalutamide might not decrease the incidence of AEs and might impair the PSA response.

The incidence of grade 3–5 AEs was generally very low in this study (9.7% and 6.5% in the full and reduced dose groups, respectively). Nevertheless, 8.1% of the patients preferred to discontinue the enzalutamide treatment due to any AEs. Regarding the median time to discontinuation of the enzalutamide treatment, no statistical difference was found between the full and reduced dose groups (7.0 and 6.5 months, respectively; p -value = 0.48), suggesting that the initial dose reduction of enzalutamide might not prolong its treatment duration.

In this study, the rate of patients with PSA decline of >90% was significantly higher in the full dose group than in the reduced dose group. The PSA response after enzalutamide was reported to be a predictor for radiographic PFS and OS of CRPC (15). The efficacy of enzalutamide might be impaired by reducing the initial dose, even though the OS and PFS were not significantly different possibly because of limited number of patients and events analyzed in this study. Thus, we considered that introducing the enzalutamide with a full dose might be more effective for disease control. Dose reduction or temporary discontinuation of enzalutamide should be considered if patients develop any AEs.

In this study, the multivariate analysis revealed that the time to CRPC within 12 months was the independent predictive factor for worse PSA PFS, and lower PSA response to enzalutamide treatment was an independent predictive factor for worse OS. These findings were consistent with those of previous reports (5, 16, 17), and suggested that enzalutamide might show strong effects if it was administrated at the early phase of CRPC treatment.

This study has several limitations. First, although we performed PSM, our research was a retrospective study with a small sample size; thus, a selection bias might have been introduced. Second, AEs were observed only in 31.5% of the patients, which might be due to the retrospective nature of this study. However, we were able to analyze the data of patients with AEs of grade 3 or higher. Third, the short follow-up period might have affected the results of the survival outcomes. Finally, due to the small number of patients analyzed, we did not divide the CRPC patients according to the history of prior chemotherapy. Despite these limitations, the present work is an original study that investigated the relation of the initial dose of enzalutamide to the survival outcomes and incidence of AEs. We believe that our data will be useful in daily clinical practice. Further external validation cohort and prospective study are warranted in the future.

Conclusions

Starting the enzalutamide treatment with a reduced dose did not significantly decrease the incidence rate of AEs and the PSA response rate after enzalutamide treatment was even lesser, thus, the full dose of enzalutamide might be the first choice. However, we should consider dose reduction or temporary discontinuation of treatment if the patients develop any AEs.

Abbreviations

AE

adverse event

PC

prostate cancer

CRPC

castration-resistant prostate cancer

PSM

propensity score matching

PFS

progression free survival

OS

overall survival

PSA

prostate specific antigen

ADT

androgen deprivation therapy

BCR

biochemical recurrence

AR

androgen receptor

PS

performance status

PCWG2

Prostate Cancer Clinical Trials Working Group 2

IQR

interquartile range

HR

hazards ratio

Declarations

■Ethics approval and consent to participate■All work on this analysis and publication was approved by the Ethics Committee of both The Jikei University School of Medicine ((30-390(9411)) and University of the Ryukyus, Graduate School of Medicine. As the analyses only used de-identified data, no additional approval from patients was required.

■Consent for publication■ Not applicable

■Availability of data and material■The de-identified datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests Shin Egawa is a paid consultant/advisor of Takeda, Astellas, AstraZeneca, Sanofi, Janssen, and Pfizer. Takahiro Kimura is a paid consultant/advisor of Astellas, Bayer, Janssen and Sanofi. Shunsuke Tsuzuki, Shotaro Nakanishi, Mitsuyoshi Tamaki, Takuma Oshiro, Jun Miki, Hiroki Yamada, Tatsuya Shimomura, Nozomu Furuta and Seiichi Saito declare no conflicts of interest.

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Author's contributions ST developed study design, analyzed and interpreted data and wrote the manuscript. SN, MT, TO, JM, HY and TS collected data. ST, TK performed statistical analysis. SN, KT and SS developed the study and interpreted data. All authors have read and approved the final manuscript.

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Figures

Figure 1

Waterfall plots of PSA response after enzalutamide according to initial dose of enzalutamide in 124 CRPC patients.

A.

B.

Figure 2

Kaplan-Meier curves for PSA progression-free survival (A) and overall survival (B) according to initial dose of enzalutamide in 124 CRPC patients.