Efficacy and Safety Profile of Enzalutamide for Japanese Patients with Castration-resistant Prostate Cancer

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Abstract. *Enzalutamide is a novel, non-steroidal anti-androgen that was approved for the treatment of patients with castration-resistant prostate cancer (CRPC) in 2014 in Japan. To assess the potency of enzalutamide treatment in Japan, we performed a pilot retrospective study. Among 91 patients who received treatment in our Institution between May 2014 and July 2015, 51 patients with docetaxel-naïve CRPC (56.0%) underwent enzalutamide therapy. The median progression-free survival (PFS) and overall survival (OS) were 10.2 months and 27.9 months, respectively. The remaining 40 patients with CRPC (44.0%) underwent enzalutamide therapy after docetaxel. The median PFS and OS were 4.4 months and not reached, respectively. Among patients with docetaxel-naïve CRPC, 12 (24%) experienced adverse events, whereas 16 (40%) experienced adverse events after docetaxel. Fatigue (15%) and appetite loss (13%) were the most common. We partially clarified the characteristics of enzalutamide therapy in Japan. The PFS associated with enzalutamide might be shorter in Japanese patients.*

Androgen deprivation therapy (ADT) is the mainstream treatment paradigm for metastatic prostate cancer. Maintenance of serum testosterone at the castration level (<0.5 ng/ml) has been the fundamental strategy, with or without blockade agents for the androgen receptor. The initial efficacy of ADT is excellent; however, it is time-limited and most patients eventually experience relapse. Treatment modalities for these patients with classical ADT-resistant prostate cancer, so-called castration-resistant prostate cancer (CRPC), have since long been limited (1, 2). Until recently, docetaxel was the only agent demonstrated to provide a significant survival benefit to patients with CRPC (3, 4). In recent large international prospective clinical studies, three novel agents (two androgen-signal targeting agents and one taxane-line chemotherapeutic agent) have shown improved overall survival (OS) and quality of life for patients with CRPC (3-7). In 2014 in Japan, all three agents were approved for clinical use by the Ministry of Health, Labour and Welfare.

Among them, enzalutamide is a novel, non-steroidal anti-androgen that demonstrated excellent antitumor activity both for patients previously treated with docetaxel in the phase III AFFIRM trial and for chemotherapy-naïve patients in the phase III PREVAIL trial (5, 6). To date, however, there is only limited information regarding the efficacy, as well as safety profile, for Japanese patients. To assess the potency of enzalutamide treatment in Japan, we performed this pilot retrospective study.

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Patients and Methods

Patients and treatment. The medical records of 91 consecutive Japanese patients with CRPC who received enzalutamide (160 mg orally once daily as four 40 mg capsule) at our Institution between May 2014 and July 2015 were reviewed. This retrospective study was conducted after obtaining approval from the Institutional Review Board of the Cancer Institute Hospital, Japanese Foundation for Cancer Research (approval 2012-1008). The schedule of radiological evaluation, including bone scan and computed tomography, depended on the attending physicians. Prostate-specific antigen (PSA) was measured a minimum of every 1 to 3 months. Toxicity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 criteria (8).

Statistical analysis. Time-to-event distributions were estimated using Kaplan–Meier curves. Univariate and multivariate analyses were performed by the log-rank test and the Cox proportional hazards model, respectively. Progression-free survival (PFS) and OS were defined as the period from initial administration of enzalutamide until diagnosis of progressive disease and until death from any cause, respectively. Poorer performance status (≥2), higher biopsy Gleason score (≥8), presence of visceral metastases, higher serum PSA level (≥median), lower hemoglobin level [<lower limit of

Table I. *Characteristics of patients treated with enzalutamide (n=91).*

Characteristic	Median (IQR) or n (%)
Age (years)	74 (70-77)
Body weight (kg)	65.4 (58-70)
Body height (m)	1.67 (1.62-1.69)
Body mass index (kg/m2)	23.7 (21.3-25.6)
ECOG PS ≥2 (%)	19 (21%)
Gleason score ≥8 (%)	73 (80%)
PSA (ng/ml)	14.2 (6.1-67.7)
Prior anti-androgen use (%)	91 (100%)
Prior use of two anti-androgens (%)	80 (88%)
Prior radical prostatectomy (%)	20 (22%)
Bone metastasis (%)	63 (69%)
Visceral metastasis (%)	13 (14%)
Lymph node metastasis (%)	23 (25%)

n: Number of patients, IQR: interquartile range, ECOG PS: Eastern Cooperative Oncology Group performance status, PSA: prostate-specific antigen.

normal (LLN)], lower serum albumin (>LLN), higher serum lactate dehydrogenase (LDH) [>upper limit of normal (ULN)], higher serum alkaline phosphatase (ALP) (>ULN), higher serum C-reactive protein (CRP) (>ULN), and the duration of the beginning of the ADT to enzalutamide start (≥ or <median value) were investigated as the predictive factors for shorter PFS. All statistical analyses were performed using SPSS software version 9.0 (SAS Institute Inc., Cary, NC, USA) and a *p*-value of less than 0.05 was considered significant.

Results

Patients' characteristics. Among the patients with prostate cancer attending our institution during the study period, 91 patients with CRPC underwent enzalutamide therapy. Patients' characteristics and demographic data are shown in Table I. All 91 patients underwent ADT with luteinizing-hormone releasing hormone (LH-RH) agonist, LH-RH antagonist, or surgical castration, and were treated by the anti-androgen agent, bicalutamide. Moreover, as the second-line anti-androgen, flutamide was administered to almost 90% of these patients and one-fifth of the patients demonstrated poor PS (≥2) (Table I).

Clinical outcome of docetaxel-naïve CRPC patients treated by enzalutamide. Among the 91 patients, 51 patients with docetaxel-naïve CRPC (56.0%) underwent enzalutamide therapy (Table II). The median observation period was 3.5 months [interquartile range (IQR)=1.8-7.3 months]. The median treatment duration between the beginning of the systemic hormonal therapy and the beginning of enzalutamide treatment was 45.8 months (IQR=32.9-83.7 months). Eighteen patients (35.3%) stopped enzalutamide therapy, mainly because

Table II. *Baseline variables of the patients with docetaxel-naïve disease treated with enzalutamide and patients treated with enzalutamide after docetaxel treatment.*

Characteristic	Docetaxel naïve (n=51) Median (IQR) or n (%)	After docetaxel (n=40) Median (IQR) or n (%)
Age (years)	74 (71-79)	73 (67-76)
ECOG PS ≥2 (%)	7 (14%)	12 (30%)
Gleason score ≥8 (%)	40 (78%)	33 (83%)
Visceral metastasis (%)	7 (14%)	6 (15%)
PSA (ng/ml)	11.2 (4.9-40.9)	23 (8.7-70.2)
Hemoglobin (g/dl)	12.7 (11.4-13.3)	11.6 (10.7-12.5)
Albumin (g/dl)	3.9 (3.6-4.2)	3.7 (3.5-4.0)
LDH (IU/l)	207 (178-236)	222 (182-294)
ALP (IU/l)	253 (199-344)	226 (159-315)
CRP (mg/dl)	0.08 (0.04-0.34)	0.23 (0.06-1.04)
Prior radical prostatectomy	10 (20%)	10 (25%)
Duration of hormonal therapy (months)	45.8 (32.9-83.7)	Not analyzed
Number of prior anti-androgen therapies		
0	0 (0%)	0 (0%)
1	9 (18%)	2 (5%)
2	42 (82%)	38 (95%)
Prior estramustine phosphate use	8 (16%)	20 (50%)
Prior abiraterone acetate use	9 (18%)	4 (10%)
Cycles of docetaxel treatment	0 (0)	8 (4.75-13)
Use of corticosteroids >7 days	18 (35%)	35 (88%)

n: Number of patients, IQR: interquartile range, ECOG PS: Eastern Cooperative Oncology Group performance status, PSA: prostate-specific antigen, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, CRP: C-reactive protein.

due to disease progression, whereas 33 patients (64.7%) continued on this novel anti-androgen therapy. In addition, five patients died from disease progression and one died from another cause. A total of six patients (11.8%) died during the study period. Regarding the PSA response, as shown in Figure 1A, 70.8% and 62.5% of patients demonstrated a 30% and 50% PSA decline, respectively. The median PFS and OS were 10.2 months [95% confidence interval (CI)=4.0-16.4 months) and 27.9 months (95% CI=18.0-29.1 months), respectively (Figure 1B and C).

Next, we searched for the variables predicting shorter PFS for patients with docetaxel-naïve CRPC treated with enzalutamide. Univariate analysis demonstrated that worse PS (≥2) (p=0.002) and short hormonal therapy treatment duration (<45.8 months) (p=0.046) were extracted as the factors predictive of shorter PFS. In addition, only worse PS [hazard ratio (HR)=3.82, 95% CI=1.27-11.55, p=0.017] was also extracted as the factor predictive of shorter PFS by multivariate analysis.

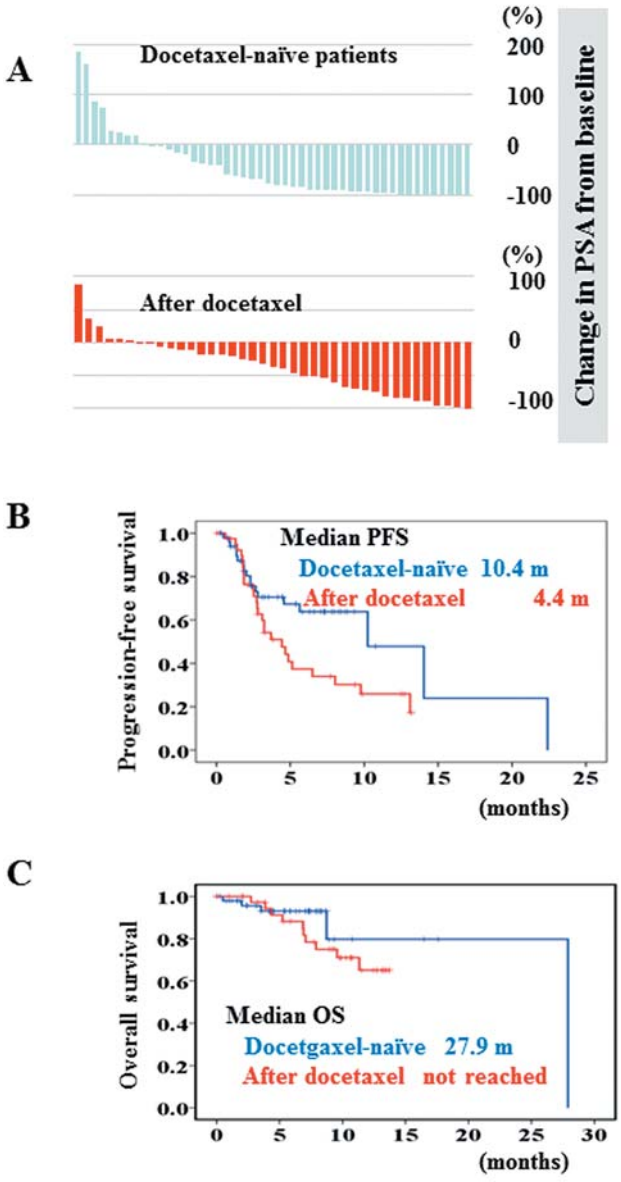

Figure 1. *Efficacy of enzalutamide treatment for Japanese patients with castration-resistant prostate cancer. A: Waterfall plots of the kinetics of serum prostate-specific antigen level of patients treated with enzalutamide. B: Progression-free survival (PFS) period of patients treated with enzalutamide. C: Overall survival (OS) period of patients treated with enzalutamide.*

Clinical outcome of patients with CRPC treated by enzalutamide after docetaxel. The remaining 40 patients with CRPC (44.0%) underwent enzalutamide therapy after docetaxel (Table II). The median observation period was 9.3 months (IQR=5.0-11.8 months). Twenty-six patients (65.0%) stopped enzalutamide therapy due to disease progression, whereas 14 patients (64.7%) continued on this novel anti-androgen therapy. In addition, nine patients died from disease progression and one from another cause. In total, 10 patients (25.0%) died during the study period. Regarding the PSA response, as shown in Figure 1A, 53.8% and 43.6% of patients demonstrated a 30% and 50% PSA decline, respectively. The median PFS and OS were 4.4 months (95% CI=2.8-6.1 months) and not reached, respectively (Figure 1B and C).

Next, we searched for the variables for predicting shorter PFS for patients with CRPC treated with enzalutamide after docetaxel. Univariate analysis demonstrated that worse PS (≥2) (p=0.033) and lower hemoglobin (<LLN) (p=0.027) were extracted as the factors predictive of shorter PFS. By multivariate analysis, only lower hemoglobin (HR=3.38, 95% CI=1.01-11.36, p=0.049) was extracted as a factor of predictive shorter PFS.

Treatment efficacy after enzalutamide. Among these patients, 20 underwent abiraterone acetate therapy. Abiraterone acetate is another novel androgen signal inhibitor. Sixteen patients had already been administered docetaxel and four had not. When the median observation period was 4.8 months, the estimated median PFS of the 16 patients treated with abiraterone acetate after docetaxel and enzalutamide was 2.3 months (95% CI=1.6-3.8 months).

Adverse events in patients treated with enzalutamide. The adverse events of patients treated with enzalutamide are presented in Table III. Among the 51 patients with docetaxel-naïve CRPC, 12 (24%) experienced adverse events. Sixteen patients (40%) experienced adverse events among the 40 patients with CRPC after docetaxel. One patient had repeated syncope attacks 3 months after the start of enzalutamide. These syncope attacks stopped after the patient discontinued the enzalutamide therapy. Two patients showed decreased platelet counts two weeks after administration (grade 2). Both patients successfully re-started enzalutamide treatment without dose modification after a one-week break.

Table III. *Adverse events of patients treated with enzalutamide (n=91).*

	Grade 1/2		Grade 3/4		
	n	(%)	n	(%)	Total (%)
Syncope	0		1	1	1%
Fatigue	14	15%	0	0	15%
Decreased appetite	12	13%	0	0	13%
Constipation	3	3%	0	0	3%
Diarrhea	2	2%	0	0	2%
Decreased platelet count	2	2%	0	0	2%
Hypertension	2	2%	0	0	2%
Headache	1	1%	0	0	1%

Discussion

Whether or not racial differences have an impact on the efficacy of enzalutamide therapy has not yet been clarified. The sub-group analysis of Japanese patients from the PREVAIL trial of enzalutamide demonstrated some differences in patient characteristics (9). There were apparent differences in the body weight and body mass index (BMI) between the overall population of that study and the Japanese sub-group. The median body weight and BMI of the study population overall were 83.1 kg and 27.5 kg/m2, respectively, whereas they were 64.8 kg and 23.5 kg/m^2, respectively in the Japanese sub-group (6,9). The trough values of enzalutamide at week 5 for non-Japanese patients (n=724) and Japanese patients (n=25) were different [13.2 μg/ml (95% CI=12.9-13.4 μg/ml) and 15.9 μg/ml (95% CI=14.5-17.2 μg/ml), respectively]. Body weight and BMI in this study were similar to those of the Japanese sub-group in the PREVAIL trial (Table I). In addition, the higher proportion of patients with a high Gleason score (≥8) also seems characteristic of Japanese patients with CRPC. The percentage of such patients in the PREVAIL and AFFIRM studies was 50.6% and 50.4%, respectively (5, 6). On the contrary, the percentage of patients with a high Gleason score in this study and the PREVAIL Japanese sub-group was 80.2% and 82.1%, respectively (9). Therefore, the treatment efficacy and safety profile of Japanese patients may be different from those of the patients in other countries.

In our study, 62.5% of docetaxel-naïve patients demonstrated a 50% PSA decline and the PFS of these patients was 10.2 months (Figure 1A and B). Out of the patients in the PREVAIL trial, 78.0% demonstrated a 50% PSA decline and the median biochemical PFS was 11.2 months (6). Our results are comparable or slightly worse than those of the PREVAIL trial. The worse results may be due to the higher proportion of patients with a high Gleason score (≥8: 78.4% *vs*. 50.6%), the existence of patients with a poor performance status (PS=13.7% *vs*. 0%), a higher number of patients with an anti-androgen regimen (until second-line: 84.3% *vs*. 18.9%), the existence of a history of estramustine phosphate (15.7% *vs*. 0%) or abiraterone acetate (18.0% *vs*. 0%) use, and the higher proportion of corticosteroid use (35.3% *vs*. 4.0%).

For patients treated with enzalutamide after docetaxel, 43.6% demonstrated a 50% PSA decline and the PFS of these patients was 4.4 months (Figure 1A and B). Of the patients in the AFFIRM trial, 54.0% demonstrated a 50% PSA decline and the median biochemical PFS was 8.3 months, respectively (5). Our results might be worse than those of the AFFIRM trial. This may be because of the higher proportion of patients with a high Gleason score (≥8: 82.5% *vs*. 50.4%) and poor performance status patients (PS= 30.0% *vs*. 8.8%) or the history of abiraterone acetate use (10%). After enzalutamide, the activity of abiraterone was very limited. This result was similar to those of previous small foreign retrospective studies (10, 11).

The safety profile was generally consistent with or slightly better than that previously reported for enzalutamide in patients in large international clinical phase III trials (5, 6), although the concentration of enzalutamide in our patients, which may be similar to that in the Japanese patients in the PREVAIL study, can be predicted to be higher as described above (9). We did not observe seizures in any patients, as has been previously observed in enzalutamide therapy (5, 6). However, syncope attacks (grade 3) were observed in one patient (1%). As enzalutamide crosses the blood–brain barrier, adverse events of the central nervous system can occur. Fatigue and appetite loss were the most common adverse events. These events might also be caused by the crossing of the blood–brain barrier.

We conducted this retrospective study to clarify the characteristics of enzalutamide for Japanese patients. The major limitations of our study are that the design is retrospective in nature and that the study cohort had a small size. However, for enzalutamide therapy, no large, multi-institutional, and prospective or retrospective studies have been published from Japan. These results reflect the characteristics of enzalutamide therapy for patients with CRPC in current clinical practice in Japan.

In conclusion, we partially clarified the characteristics of enzalutamide therapy in Japan. The treatment efficacy of enzalutamide might be worse in Japanese patients with CRPC and higher numbers of prior treatment regimens and a higher proportion of patients with a high Gleason score might be one of the reasons for this. Japanese urologists should consider the ideal or most suitable treatment schedule of hormonal/chemotherapeutic treatment for prostate cancer at the beginning of therapy in the hormone-sensitive state.

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