Short Communications

Editorial Process: Submission:07/09/2023 Acceptance:06/11/2024

Efficacy of Enzalutamide Rechallenge for Metastatic Castration-Resistant Prostate Cancer

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Abstract

Objective: There have been several reports on rechallenge with docetaxel, cabazitaxel, abiraterone acetate, or ethinylestradiol for metastatic castration-resistant prostate cancer (mCRPC). However, the efficacy of enzalutamide rechallenge for mCRPC has not been evaluated. **Methods:** We retrospectively reviewed 63 consecutive patients who received enzalutamide for mCRPC at our institution between 2014 and 2022. Eight of these patients underwent rechallenge with enzalutamide after disease progression on prior enzalutamide and other therapy and were the focus of this study. The prostate-specific antigen (PSA) response (PSA decrease >50%), PSA progression-free survival, treatment duration, overall survival (OS) after CRPC, and treatment-related adverse events were evaluated. **Results:** PSA decline to enzalutamide rechallenge was observed in 6 patients (75%), of which 2 patients had a PSA response. The median treatment duration was 4 months (range 1–12) and median PSA progression-free survival was 3 months (range 1–7). Median OS after CRPC was 41 months. OS after CRPC was not increased in patients with a PSA response. No toxicities were worse than grade ≥3. **Conclusion:** Enzalutamide rechallenge achieved a PSA response in a quarter of our patients with mCRPC after disease progression on prior enzalutamide. However, no improvement of OS was identified in these patients.

Keywords: Metastatic castration resistant prostate cancer- enzalutamide- rechallenge therapy- PSA response

Asian Pac J Cancer Prev, **25 (6)**, 1863-1867

Introduction

The standard initial treatment for advanced prostate cancer is androgen deprivation therapy (ADT). Although most patients respond initially to ADT via testosterone suppression, the disease often progresses to metastatic castration-resistant prostate cancer (mCRPC) 14–20 months later [1, 2] Patients with mCRPC are treated with chemotherapy, such as docetaxel or cabazitaxel, and androgen receptor-targeted therapy, such as abiraterone acetate or enzalutamide. However, mCRPC remains incurable and the prognosis is poor [3].

Rechallenge with docetaxel, cabazitaxel, abiraterone acetate, or ethinylestradiol has been reported to improve survival in patients with mCRPC [4-7]. Docetaxel rechallenge was found to achieve a prostate-specific antigen (PSA) response rate (PSA decrease >50%) of 35% and a median radiological progression-free survival (PFS) of 4.5 months [4]. Cabazitaxel rechallenge was reportedly associated with a PSA response rate of 60% and a median radiological PFS of 5.6–9.6 months [5], while ethinylestradiol rechallenge resulted in a PSA response rate of 33.3% and a median PSA PFS of 4 months [6]. With abiraterone acetate rechallenge, the PSA response rate was 46% and the median PSA PFS was 2.3 months, with limited benefit in patients who had a PSA response following first-line abiraterone acetate [7].

In the PRESIDE trial, continuing enzalutamide with docetaxel plus ADT delayed time to progression compared with docetaxel plus ADT alone in patients with mCRPC who progressed after first-line enzalutamide (hazard ratio 0.72, 95% confidence interval 0.53–0.96] [8]. These results supported the hypothesis that enzalutamide maintenance could control persistent androgen-dependent clones in men with mCRPC who progress after first-line enzalutamide. However, the efficacy of enzalutamide rechallenge has not been evaluated. The aim of this study was to investigate the efficacy and safety of enzalutamide rechallenge in patients with mCRPC after disease progression on prior enzalutamide and other therapy.

Materials and Methods

We reviewed 63 consecutive patients who were treated with enzalutamide for mCRPC at our institution between 2014 and 2022. Eight of these patients were identified to have undergone enzalutamide rechallenge (160 mg orally once daily) after disease progression on prior enzalutamide and other therapy and were the focus of this study. ADT was continued, and serum PSA was measured monthly

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during rechallenge with enzalutamide. Clinicopathological data were obtained, including age at first visit, initial PSA, biopsy Gleason score, clinical TNM stage, PSA nadir after ADT, time to CRPC, PSA doubling time, PSA reduction after first-line enzalutamide, history of treatment with docetaxel, PSA reduction after enzalutamide rechallenge, duration of enzalutamide rechallenge, overall survival (OS), OS after CRPC, and the prognosis (Table 1). Patient data were also obtained at the time of enzalutamide rechallenge, including age, Eastern Cooperative Oncology Group performance status, PSA, hemoglobin, albumin, lactate dehydrogenase, alkaline phosphatase, interval between first-line enzalutamide and enzalutamide rechallenge, number of treatment lines between cessation of first-line enzalutamide and enzalutamide rechallenge, and number of treatment lines between diagnosis of mCRPC and enzalutamide rechallenge (Table 2). The PSA response (PSA decrease >50%) after enzalutamide rechallenge, PSA PFS, duration of enzalutamide rechallenge, OS after CRPC, and treatment-related adverse events (AEs) were evaluated. PSA response was defined as a >50% decrease in serum PSA at least 4 weeks apart and PSA progression was defined as an increase of ≥25% above the nadir with an absolute increase of 2 ng/mL in accordance with the Prostate Cancer Clinical Trials Working Group 2 criteria [9]. AEs were graded according to the Common Terminology Criteria for Adverse Events version 4.0. Radiological PFS could not be evaluated because radiological assessments had not been performed at appropriate intervals. The study was approved by our institutional review board (No. 4-11).

Statistical analysis

Kaplan–Meier analysis was performed to calculate PSA PFS and OS after CRPC. All statistical analyses were performed using SPSS® version 27 (IBM Corp., Armonk, NY).

Results

Seven of the 8 patients had a PSA response after first-line enzalutamide (Table 1). The first-line enzalutamide was stopped because of PSA progression in all patients. Six patients (75%) who were treated with docetaxel before enzalutamide rechallenge. At the time of enzalutamide rechallenge median age was 81 years and median PSA was 75.8 ng/mL. The median time from first-line enzalutamide to enzalutamide rechallenge was 10 months. The median number of treatment lines between first-line enzalutamide cessation and enzalutamide rechallenge was 2 and that between diagnosis of mCRPC and enzalutamide rechallenge was 4. PSA decline to enzalutamide rechallenge was observed in 6 patients (75%), of which 2 patients had a PSA response (Table 1). Median PSA PFS was 3 months (range 1–7) and the median treatment duration was 4 months (range 1–12). Median OS after CRPC was 41 months (Figure 1A). The duration of OS after CRPC was not improved in patients with a PSA response to enzalutamide rechallenge (Figure 1B). Grade 1 toxicity was observed in 2 patients. No grade ≥3 toxicities occurred following enzalutamide rechallenge.

Table.1 Baseline Patient Characteristics and Outcome of Enzalutamide Treatment (first-line/rechallenge)

Patient number	Age at first visit (years)	iPSA (ng/mL)	bGS	T	N	M	PSA nadir (ng/mL)	Time to CRPC (months)	PSA DT (months)	PSA reduction after first-line Enz (%)	Docetaxel (yes/no)	PSA reduction after Enz rechallenge (%)	PSA PFS after Enz rechallenge (months)	Duration of Enz rechallenge (months)	OS (months)	OS after CRPC (months)	Prognosis
1	79	479	None	4	1	1b	2.28	8	2	-73.9	Yes	151	1	1	28	20	DOD
2	84	3040	5+4	3a	0	1b	99.2	5	3	-98	Yes	33	1	4	53	48	DOD
3	68	1876	4+5	4	1	1b	3.41	13	6	-92.1	Yes	-6	2	2	139	126	DOD
4	56	17.9	5+4	4	1	1b	0.1	22	5	10	Yes	-8.3	7	7	83	61	Dead from another cause
5	72	237.5	4+4	3a	1	1b	0.02	120	8	-59.4	No	-20.9	4	4	204	84	Alive
6	70	3837	4+3	3a	1	1b	0.02	89	4	-97	Yes	-35	2	3	216	127	Alive
7	65	1428	4+5	4	0	1b	8	12	2	-99	Yes	-84.8	4	8	53	41	DOD
8	80	67.8	4+5	4	1	1b	3.2	13	4	-82.3	No	-87.4	5	12	36	23	DOD

bGS, biopsy Gleason score; CRPC, castration-resistant prostate cancer; DOD, dead of disease; DT, doubling time; Enz, enzalutamide; iPSA, initial prostate-specific antigen; PSA, prostate-specific antigen; OS, overall survival

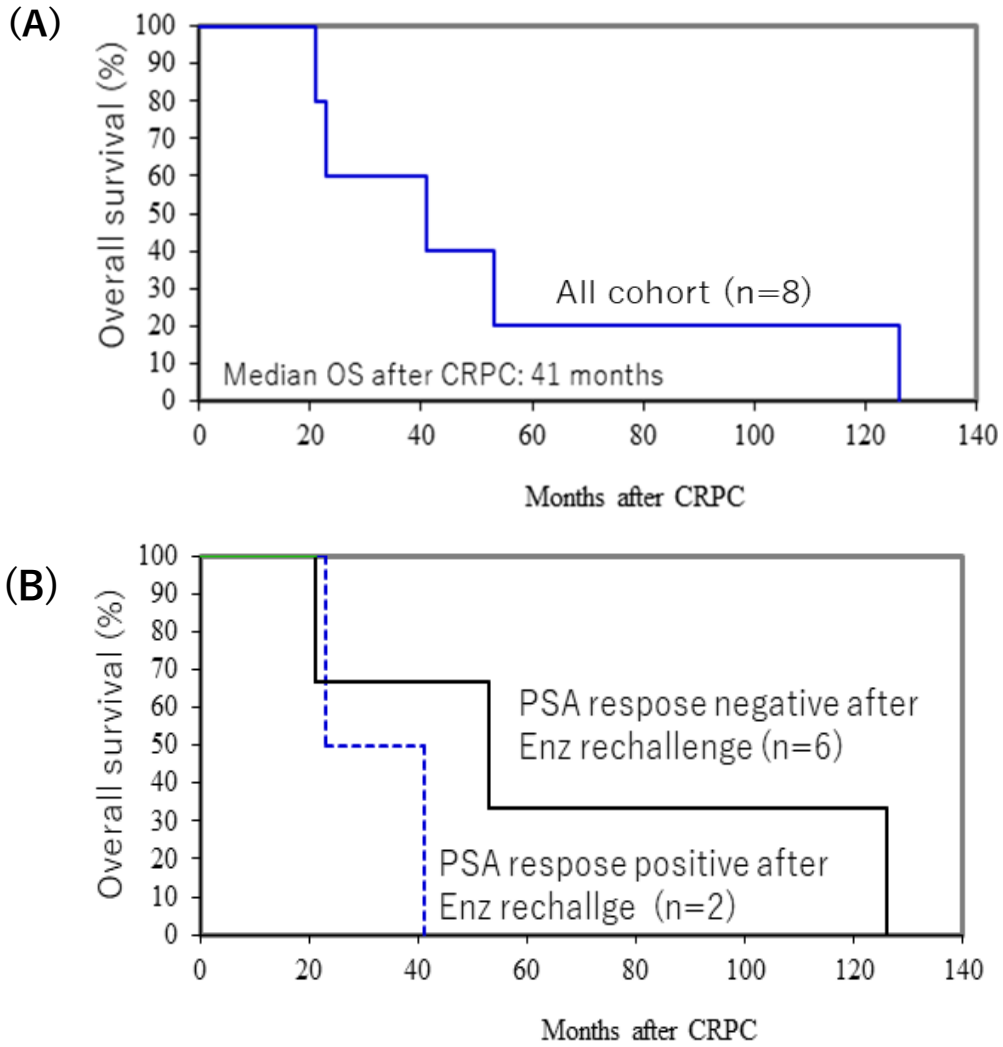

Figure 1. Kaplan–Meier Survival Curves. (A) Overall survival after CRPC and (B) Overall survival after CRPC stratified by PSA response to Enz rechallenge. CRPC, castration-resistant prostate cancer; Enz, enzalutamide; PSA, prostate-specific antigen

Discussion

A quarter of the patients with mCRPC in this study had a PSA response after enzalutamide rechallenge. The median treatment duration was 4 months and the median PSA PFS was 3 months. There was no improvement in OS after CRPC in patients with a PSA response. There were no severe toxicities following enzalutamide rechallenge.

There have been several reports of rechallenge therapy with docetaxel, cabazitaxel, abiraterone acetate, or

Table 2. Patient Data at the Time of Enzalutamide Rechallenge

Patients, n		8
Age, years, median (range)		81 (62–90)
ECOG PS, n (%)	1	5 (62.5%)
	2	3 (37.5%)
PSA, ng/mL, median (range)		75.8 (10.5–823)
Hemoglobin, g/dL, median (range)		11.7 (10.5–13.5)
Albumin, g/dL, median (range)		3.8 (2.3–4.1)
LDH, U/L, median (range)		205 (153–467)
Alkaline phosphatase, U/L, median (range)		90 (78–683)
Interval between first Enz and rechallenge, months (range)		10 (5–48)
Number of treatment lines between first Enz cessation and Enz rechallenge, median (range)		2 (1–3)
Number of treatment lines between mCRPC diagnosis and Enz rechallenge, median (range)		4 (2–5)

ECOG PS, Eastern Cooperative Oncology Group performance status; Enz, enzalutamide; LDH, lactate dehydrogenase; mCRPC, metastatic castration-resistant prostate cancer

ethinylestradiol in patients with for mCRPC [4-7, 10]. In patients with disease progression after first-line docetaxel, the role of docetaxel rechallenge remains unclear. However, docetaxel rechallenge was shown to retain anti-tumor activity in a selected population. Docetaxel rechallenge was a predictor of OS in patients with mCRPC who had disease progression after first-line docetaxel and subsequent abiraterone acetate or enzalutamide (hazard ratio 0.59, 95% confidence interval 0.32–0.99] [10]. Other predictors of OS in that study were Eastern Cooperative Oncology Group performance status score 2 (hazard ratio 2.46, 95% confidence interval 1.32–4.56], duration of hormone sensitivity (hazard ratio 0.99, 95% confidence interval 0.99–0.999], brain metastasis (hazard ratio 2.23, 95% confidence interval 1.26–5.46], and liver metastasis (hazard ratio 1.90, 95% confidence interval 1.04–3.47] [10]. Cabazitaxel rechallenge was performed in patients who responded well to first-line cabazitaxel and was associated with a PSA response rate of 60%. Median radiological PFS at first rechallenge was 9.6 months and 5.6 months at second rechallenge and it was suggested that cabazitaxel rechallenge may extend OS with no cumulative toxicitiy [5]. Ethinylestradiol rechallenge was reported to achieve a PSA response rate of 33.3% and a median PSA PFS of 4 months. A PSA response to rechallenge was observed even in patients who did not respond to initial treatment with ethinylestradiol. That study concluded that ethinylestradiol rechallenge can prolong disease control in selected patients [6]. In an abiraterone acetate rechallenge study, the PSA response rate was 46% and the median PSA PFS was 2.3 months. A PSA response to abiraterone acetate rechallenge was observed in patients with mCRPC who had a PSA response on first-line abiraterone acetate [7]. The role of rechallenge therapy remains unclear and rechallenge therapy including above drugs may be an option in patients with mCRPC who had a PSA response on first-line treatment.

Persistent androgen-dependent clones were found in patients with mCRPC who progressed after enzalutamide. In the PRESIDE trial, continuing enzalutamide with docetaxel plus ADT delayed time to progression compared with docetaxel plus ADT alone in patients with mCRPC who progressed after first-line enzalutamide (hazard ratio 0.72, 95% confidence interval 0.53–0.96] [8]. These results supported the hypothesis that enzalutamide maintenance could control persistent androgen-dependent clones in men with mCRPC who progress after first-line enzalutamide. In our study, PSA decline to enzalutamide rechallenge was observed in 6 patients (75%), of which 2 patients had a PSA response. Enzalutamide rechallenge may be effective against persistent androgen-dependent clones in mCRPC.

This study has several limitations. First, it was performed retrospectively and had a limited sample size, which could have introduced several types of bias. Second, the study was underpowered to determine the efficacy of enzalutamide rechallenge. Therefore, a validation study in a large population is needed to clarify the effect of rechallenge with enzalutamide.

In conclusion, enzalutamide rechallenge led to a PSA response in 25% of patients with mCRPC but without an improvement in OS. Further research in a larger cohort is necessary to identify the efficacy of enzalutamide rechallenge.

Author Contribution Statement

HS is the guarantor of the study. HS, YK, MU and YS conceived and designed it. HS wrote the first draft, and all contributed to subsequent drafts and the final paper.

Acknowledgements

None.

Approval of the research protocol by an institutional review board

The study was approved by the relevant ethics committee.

Informed consent

The requirement for informed consent was waived in view of the retrospective observational nature of the research and the anonymity of the data.

Conflicts of interest

None.

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