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Docetaxel rechallenge in metastatic castration-resistant prostate cancer: A retrospective, single-center study

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Purpose: To assess the efficacy and safety of docetaxel rechallenge in the salvage setting in metastatic castration-resistant prostate cancer (mCRPC) patients.

Materials and Methods: Clinicopathologic data from patients treated with docetaxel rechallenge were collected from a single-center cancer registry. Among 227 patients who received first-line docetaxel for mCRPC between January 2011 and June 2019, 23 undergo rechallenge docetaxel after failure to androgen receptor targeting agents and/or cabazitaxel treatment. Endpoints included radiologic progression-free survival (PFS), treatment duration, and prostate-specific antigen (PSA) response and safety.

Results: Overall, 30%, 44%, 13%, and 13% of patients received docetaxel rechallenge as either the third, fourth, fifth, or sixth-line therapy, respectively, at a median of 23.6 months after stopping first-line docetaxel. With first-line docetaxel and rechallenge, median treatment duration was 6.4 and 3.3 months, respectively. With docetaxel rechallenge, PSA response was 35% (95% confidence interval [CI], 15% to 54%) and median PFS was 4.5 months (95% CI, 1.9 to 7.1 months). The median OS was 24.3 months (95% CI, 4.6 to 44.0 months). There were 7 severe adverse events (grade 3 or more) including anemia (8.7%), neutropenia, thrombocytopenia, leukopenia, diarrhea, and nausea (4.3% each).

Conclusions: Docetaxel rechallenge showed meaningful anti-tumor activity with acceptable toxicity in heavily pretreated patients with mCRPC.

Keywords: Chemotherapy; Docetaxel; Prostate cancer

INTRODUCTION

In Korea, prostate cancer represents the fourth most common malignancy diagnosed in men, with an incidence of >10,000 cases annually [1]. If a patient with prostate cancer develops or is diagnosed with metastatic disease, androgen deprivation therapy (ADT) in conjunction with either a gonadotropin-releasing hormone (GnRH) agonist or antagonist that results in suppression of testosterone production in the testes or surgical castration would be considered. Although

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most patients initially respond to ADT, inevitably and despite effective suppression of testosterone, disease could progress to metastatic castration-resistant prostate cancer (mCRPC).

Docetaxel was the first systemic therapy to improve survival for men with mCRPC [2,3]. Furthermore, the treatment of mCRPC has expanded significantly over the last years as a result of the introduction of multiple novel agents including cabazitaxel [4], androgen receptor targeting agents (ARTAs) such as enzalutamide [5,6], and abiraterone acetate [7,8]. However, the optimal treatment sequence for mCRPC has yet to be determined, and an unmet need remains for mCRPC patients after treatment with docetaxel, cabazitaxel, and ARTAs.

Before ARTAs were available in the clinical setting, several studies investigated the efficacy of docetaxel rechallenge in selected mCRPC patients [9-11]. Docetaxel rechallenge provided modest efficacy with 25% to 48% of the prostate-specific antigen (PSA) response, especially in patients with good responses to first-line docetaxel. Here, we report the results from a retrospective study of mCRPC patients rechallenged with docetaxel after treatment with ARTAs and/or cabazitaxel.

MATERIALS AND METHODS

Current study is retrospective analysis of a prospectively collected patient population. Based on our cancer chemotherapy database, 227 consecutive mCRPC patients were identified who treated with first-line docetaxel between January 2011 and June 2019. Eligibility criteria was as follows: patients with confirmed metastatic prostate adenocarcinoma who were treatment with first-line docetaxel followed by one or more subsequent therapies, and then treatment with docetaxel rechallenge thereafter. Clinicopathologic data were obtained including age, gender, pathologic finding, Gleason score, PSA, docetaxel treatment duration, intervening therapies, and clinical outcomes. Analytical data with potential prognostic value, PSA decline, overall survival (OS) and progression-free survival (PFS) were collected for both first-line and rechallenge docetaxel treatments. All patients provided written informed consent according to institutional guidelines. Institutional Review Board of Samsung Medical Center (Seoul, Korea) approved current study (approval number: SMC 2020-05-072).

Treatment consisted of docetaxel 20 to 25 mg/m^2/week on a biweekly or tri-weekly regimen. Oral prednisone was given at a dose of 5 mg twice daily. Patients who had not undergone surgical castration were required to continue ADT. The adverse events (AEs) were recorded and graded according to the National Cancer Institute criteria (NCI-CTCAE). Endpoints of the present retrospective study included the PSA response, radiologic PFS, and OS in rechallenge. Radiologic response and progression were evaluated according to the Prostate Cancer Clinical Trials Working Group 2 (PCWG) criteria [12] using computed tomography scans and bone scintigraphy, or by the same tests that were used to initially stage the tumor. If a patient had no measurable lesions other than bone metastases, then the response was classified as no new lesions or disease progression. PSA response was defined as a >50% decline from baseline. Kaplan-Meier method was used to estimate treatment duration, PFS, and OS. Cox regression model was used to examine the impact of clinical and treatment variables on the PFS with covariates including age, performance status, treatment duration and the PFS with first-line docetaxel, line of prior therapies, and the presence of visceral metastases. All p-values were two-tailed with <0.05 indicating statistical significance.

RESULTS

Among 227 mCRPC patient received first-line docetaxel chemotherapy, 23 patients were identified as treated with docetaxel rechallenge during the study period. Table 1 summarizes patient characteristics and outcomes relating to their first-line docetaxel therapy. Most patients had metastases confined to bone and/or lymph nodes. PSA response rate to first-line docetaxel was 87.0% (95% confidence interval [CI], 73% to 100%) and the median PFS was 9.5 months (95% CI, 9.0 to 9.9 months). The chemotherapy-free interval after 4 to 6 months after starting docetaxel was the most common reason for treatment discontinuation.

1. Docetaxel rechallenge

Patient characteristics at the time of docetaxel rechallenge are listed in Table 2. The median time between discontinuation of first-line docetaxel and start of rechallenge was 23.6 months (95% CI, 6.3 to 84.0 months). Docetaxel rechallenge was given as either the third-, fourth-, fifth, or ≥sixth-line therapy to 30%, 44%, 13%, and 13% of patients, respectively. During the intervening period, 17 (73.9%) patients received enzalutamide, 13 (56.5%) received abiraterone acetate, and 7 (30.4%) patients were treated with cabazitaxel. The median treatment duration with docetaxel rechallenge was 3.3 months. Of note, six of 23 patients had a longer treatment duration with rechallenge than with first-line docetaxel.

Seven (30.4%) patients achieved a PSA response upon doce-

Table 1. Baseline patient characteristics and outcome of first-line docetaxel treatment (n=23)

Characteristic	Value
Age (y)	67.6 (52.1–77.9)
Gleason score	9 (7–10)
7 or 8	10 (43.5)
9 or 10	13 (56.5)
Prior treatment to primary tumor	
Prostatectomy	8 (34.8)
Radiotherapy	10 (43.5)
ADT duration to start of first-line docetaxel (mo)	16.1 (2.2–104.9)
≤12	10 (43.5)
>12	13 (56.5)
Performance status	
No symptoms	15 (65.2)
Symptomatic	8 (34.8)
Metastatic sites	
Bone	18 (78.3)
Lymph nodes	10 (43.5)
Lung	2 (8.7)
Liver	2 (8.7)
Treatment duration of first-line docetaxel (mo)	6.4 (1.3–18.6)
Reason for discontinuation	
Planned (chemotherapy-free interval)	16 (69.6)
Toxicity or decline	4 (17.4)
Disease progression	3 (13.0)
PSA (ng/mL)	
Baseline	521.19±1,290.00
Nadir	2.61±5.35
PSA response	20 (87.0)
Progression-free survival (mo)[a]	9.5 (9.0–9.9)

Values are presented as median (range), number (%), or mean±standard deviation.
ADT, androgen deprivation therapy; PSA, prostate-specific antigen.
[a]:Median (95% confidence interval).

Table 2. Baseline patient characteristics and outcome of docetaxel re-challenge (n=23)

Characteristic	Value
Age (y)	70.6 (55.1–80.2)
Docetaxel-free interval (mo)	23.6 (6.3–84.0)
≤24	12 (52.2)
>24	11 (47.8)
Performance status	
No symptoms	3 (13.0)
Symptomatic	20 (87.0)
Intervening systemic therapies	
Enzalutamide	17 (73.9)
Abiraterone acetate	13 (56.5)
Cabazitaxel	7 (30.4)
Mitoxantrone	6 (26.1)
Radium-223	3 (13.0)
Cisplatin-based	2 (8.7)
Treatment duration of rechallenge docetaxel (mo)	3.3 (0.5–17.5)
Reason for discontinuation	
Disease progression	18 (78.3)
Toxicity or decline	3 (13.0)
Planned (chemotherapy-free interval)	2 (8.7)
PSA (ng/mL)	
Baseline	446.94±804.35
Nadir	323.43±484.03
PSA response	7 (30.4)
Progression-free survival (mo)[a]	4.6 (1.4–7.7)

Values are presented as median (range), number (%), or mean±standard deviation.
PSA, prostate-specific antigen.
[a]:Median (95% confidence interval).

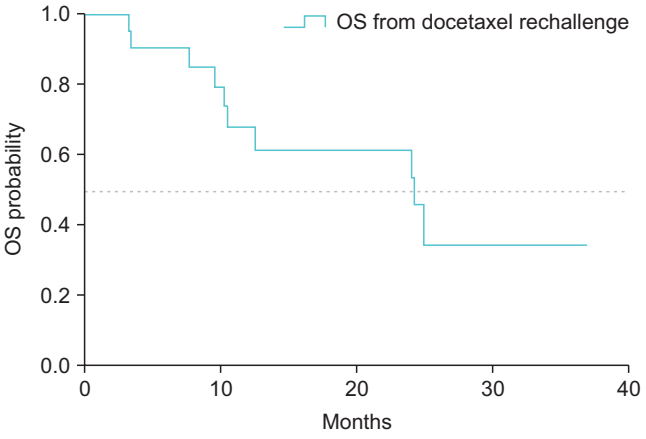

Fig. 1. Kaplan–Meier curves for overall survival from docetaxel re-challenge. OS, overall survival.

taxel rechallenge. As expected, the PSA response was significantly worse in the rechallenge docetaxel than in first-line setting (p=0.007). Among these seven responders, two patients showed no response to first line docetaxel treatment. PSA response to first-line docetaxel treatment, treatment duration of first-line docetaxel treatment (≤10 vs. >10 cycles), the interval between discontinuation of first-line docetaxel and the start of rechallenge (≤24 vs. >24 months) were not associated with response to docetaxel rechallenge treatment.

With a median follow-up of 31 months, the median OS was 24.3 months (95% CI, 4.6 to 44.0 months) (Fig. 1). The median PFS was 4.6 months (95% CI, 1.4 to 7.7 months), which was also shorter than that observed in first-line docetaxel (Fig. 2). To explore factors associated with PFS, ADT duration to the start of first-line docetaxel (≤12 vs. >12 months), Gleason score (≤8 vs. 9 or 10), and the presence of visceral metastases were analyzed either in first-line or rechallenge setting. We also analyzed PSA response to first-line docetaxel and the interval between discontinuation of first-line docetaxel and the start of rechallenge (≤24 vs. >24 months) as prognostic factors of rechallenge treatment. In the first-line docetaxel treatment, no variables were found as being associated with PFS. In the rechallenge setting, PFS was longer in patients with >24 months of interval (9.4 months)

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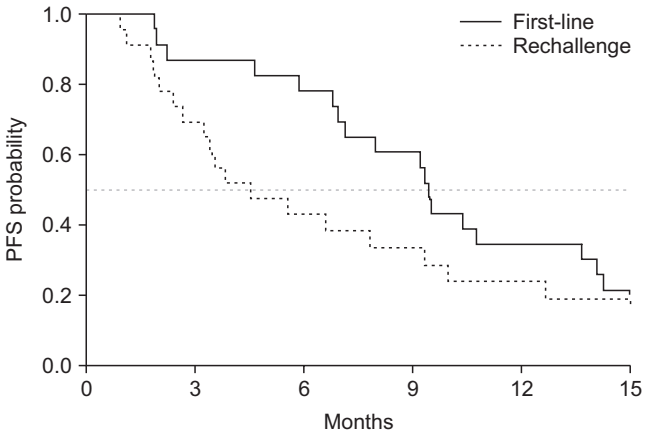

Fig. 2. Kaplan–Meier curves for progression-free survival comparing first-line to rechallenge docetaxel treatment. PFS, progression-free survival.

than in those with interval ≤24 months (3.3 months); however, the difference did not reach statistical significance (hazard ratio [HR], 0.55; 95% CI, 0.20 to 1.51; p=0.061). Likewise, PSA response to first-line docetaxel (HR, 0.73; 95% CI, 0.19 to 2.86; p=0.684) or the presence of visceral metastases (HR, 2.51; 95% CI, 0.64 to 9.88; p=0.189) did not have a significant effect on the PFS.

2. Safety

Adverse events recorded on docetaxel rechallenge are shown in Table 3. Anemia, fatigue, nail changes, leukopenia, and mucositis were the most commonly observed toxicities. In case of severe AEs, hematologic AEs were the most common (two Anemia grade 3, one thrombocytopenia grade 4, one neutropenia grade 4, and one leukopenia grade 3). Other severe AEs included one diarrhea grade 3 and one nausea grade 3. No AEs related death was observed.

Table 3. Adverse events

Adverse events	All grades	%	Grade ≥3	%
Anemia	14	60.8	2	8.7
Fatigue	12	52.2		
Nail change	7	30.4		
Leukopenia	7	30.4	1	4.3
Mucositis	6	26.1		
Thrombocytopenia	5	21.7	1	4.3
Pain	5	21.7		
Skin rash	4	17.4		
AST elevation	4	17.4		
ALT elevation	3	13.0		
Neutropenia	2	8.7	1	4.3
Anorexia	2	8.7		
Alopecia	2	8.7		
Diarrhea	2	8.7	1	4.3
Nausea	1	4.3	1	4.3
Vomit	1	4.3		
Localized Edema	1	4.3		
Lacrimation	1	4.3		
Nocturia	1	4.3		
Sensory neuropathy	1	4.3		
Prostatic obstruction	1	4.3		
Insomnia	1	4.3		
Hypersensitivity	1	4.3		
Dizziness	1	4.3		
Dyspnea	1	4.3		
Epistaxis	1	4.3		

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

DISCUSSION

The present study shows that docetaxel rechallenge is a feasible treatment option with potential therapeutic benefit for mCRPC patients who have failed multiple lines of therapy, including ARTAs, cabazitaxel, as well as first-line docetaxel. The finding is consistent with previous studies in which docetaxel rechallenge yielded a PSA response up to 48%, especially in patients with good response to first-line docetaxel, treatment-free interval more than 3 to 6 months, and the time from ADT to the development of mCRPC of more than 47 months [9-11]. Although the number of the patients and type of intervening therapies varied, the consequences of sharing is that some patients may benefit from docetaxel rechallenge.

During the past two decades, there have been major advances in the systemic treatment of prostate cancer, such as the incorporation of novel ARTAs and chemotherapeutic agents to ADT. However, mCRPC is remained as an incurable disease and the treatment goal is to prolong survival and to palliate the symptoms. The disease may respond to several types of therapy but eventually progression develops, and no established salvage treatment can be offered currently. In general, systemic therapy in mCRPC should focus on improving quality of life in patients, which is more important than prolonging OS in the salvage setting. Carefully selected chemotherapy regimen with anti-tumor efficacy and tolerability may provide an improvement of QOL and clinical outcome in subset of patients. Therefore, study of predictive and/or prognostic factors contributing to identify the patient population who are likely to benefit from salvage therapy, is warranted. Previous studies suggested that PSA response to first-line docetaxel was one of the factors when considering rechallenge [9,10]. In the present study, however, 26% of patients received longer duration of treat-

ment in rechallenge than in first-line treatment, suggesting the response to first-line docetaxel may not be an absolute indication for rechallenge.

As expected, patients in the present study had more disease-related symptoms at rechallenge than when chemotherapy-naïve, reflecting the more advanced status of their disease, and may explain the reduced PSA response rate (87% vs. 30%) and median PFS (9.5 vs. 4.6 months). In contrast, it is of note that the observed median OS of 24.3 months compared favorably with results of studies in the salvage setting [13,14]. In a retrospective study evaluating cabazitaxel rechallenge in mCRPC patients [14], rechallenge cabazitaxel resulted in a PSA response of 24% and a median PFS of 7.8 months. One may argue that rechallenge using cytotoxic chemotherapy may not be beneficial for all mCRPC patients. It is necessary to select patients who are likely to benefit from salvage chemotherapy because there is also the potential for treatment toxicity. When compared to cabazitaxel, the favorable toxicity profile with docetaxel rechallenge is of importance, as the primary objective of salvage treatment in mCRPC patients is palliative in nature. Although the results presented here are from a relatively small, retrospective study, our findings suggest that docetaxel rechallenge is feasible for heavily pretreated mCRPC patients, without compromising safety.

To the best of our knowledge, our study is the first attempt reporting the results of docetaxel re-challenge in Korean CRPC patients.

The major limitation of this study is its retrospective, non-comparative design. Patients received docetaxel rechallenge at the discretion of the treating medical oncologist. As a result, it may be that clinical judgment withheld the use of cytotoxic chemotherapy from patients at high risk of adverse events or those with poor performance status. However, given the paucity of clinical guidelines about treatment sequencing in mCRPC, these limitations could reflect our daily practice in the real-world setting. In addition, the small number of patients might have led to biases and a lack of significance in some calculations that otherwise would probably provide more consistent results. Further studies will be needed to establish the role of docetaxel rechallenge in prostate cancer treatment. Thus, we are planning the multicenter study investigating the efficacy of docetaxel rechallenge in Korean mCPRC patients.

CONCLUSIONS

In conclusion, we provide real world data of docetaxel rechallenge in mCRPC patients who had disease progression after first-line docetaxel and novel agent treatment. Further studies in larger cohorts will be necessary to support the present data and try to define an optimal patient population who may benefit from docetaxel rechallenge.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

AUTHORS' CONTRIBUTIONS

Research conception and design: Seonggyu Byeon and Se Hoon Park. Data acquisition: Seonggyu Byeon and Minsuk Kwon. Statistical analysis: Jinchul Kim. Data analysis and interpretation: Seonggyu Byeon and Se Hoon Park. Drafting of the manuscript: Seonggyu Byeon and Se Hoon Park. Critical revision of the manuscript: Hyun Moo Lee and Se Hoon Park. Administrative, technical, or material support: Hyera Kim, Jinchul Kim, Minsuk Kwon, Joon Young Hur, Hwang Gyun Jeon, and Seong Soo Jeon. Supervision: Se Hoon Park. Approval of the final manuscript: all authors.

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