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ORIGINAL ARTICLE

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Enzalutamide Maintenance Following Docetaxel in Metastatic Castration-Naive Prostate Cancer: A Pilot Feasibility Study

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Purpose: To assess the feasibility and short-term efficacy of maintenance enzalutamide following first-line docetaxel plus androgen deprivation therapy (ADT) in patients with high-volume, metastatic castration-naive prostate cancer (mCNPC).

Materials and Methods: The present study included 38 consecutive patients with mCNPC who did not have disease progression with ADT plus docetaxel between October 2022 and October 2023. Patients received a switch maintenance therapy with enzalutamide until progression, unacceptable toxicity, or patient withdrawal. Endpoints included time to prostate-specific antigen (PSA) progression and safety.

Results: Among the 38 patients, the median age was 68 years, and the most frequently observed metastatic site was bone (n=36), followed by lymph nodes (n=28), lung (n=8), and liver (n=1). The median duration of first-line docetaxel was 2.8 months (range, 2.7–5.0 months). At the time of commencing maintenance enzalutamide, the median PSA was 3.2 ng/mL (range, 0.01–258 ng/mL). Maintenance enzalutamide was generally well-tolerated. A total of 11 patients (28%) discontinued enzalutamide, and the main reasons included adverse events (prolonged fatigue of grade 1 or 2, n=6), disease progression (n=3) and financial burdens (n=2). Median time to PSA progression was not reached, and 93% were PSA progression-free at 12 months.

Conclusions: Maintenance enzalutamide is a feasible treatment option with potential clinical benefit for patients with high-volume mCNPC who were progression-free after first-line ADT+docetaxel.

Key Words: Enzalutamide, Prostatic neoplasms, Castration-naive

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- **Research Ethics:** The study protocol was approved by the Institutional Review Board of Samsung Medical Center (IRB No. 2023-07-103), and all patients provided a written informed consent prior to both starting docetaxel and switch to enzalutamide.
- **Conflicts of Interest:** The authors have nothing to disclose.

INTRODUCTION

In Korea, prostate cancer is one of the greatest growing cancers, 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), which includes bilateral orchiectomy or medical castration with gonadotropin-releasing hormone agonists/antagonists

can provide palliation of symptoms and prolong survival [2]. More recently, based on findings from clinical trials [3-8], guidelines have established the addition of docetaxel or novel androgen receptor targeting agents (ARTAs; i.e., abiraterone acetate, enzalutamide, or apalutamide) to ADT as the standard of care for those with metastatic castration-naive prostate cancer (mCNPC) [9].

Although the long-term follow-up of clinical trials confirmed the benefit of adding docetaxel to ADT persisted regardless of metastatic burden [10], it is suggested that docetaxel might be under-used in clinical practice [11]. Use of docetaxel plus ADT in mCNPC setting is limited to patients with high-volume disease, provided they are willing and fit enough to receive cytotoxic chemotherapy. A major challenge with docetaxel is balancing the toxicity with clinical benefit. Duration of first-line docetaxel is limited to 4 to 6 months [3,4]. Therefore, there is a growing interest in switch maintenance therapy as a strategy for prolonging the benefit with first-line docetaxel while minimizing toxicity. In phase III trials involving first-line enzalutamide in mCNPC (ENZAMET and ARCHES) [6,7], prior treatment with docetaxel was permitted. Based on these considerations, from Oct 2022, we adopted a maintenance therapy with enzalutamide following 6 to 8 cycles of docetaxel as an institutional standard regimen for patients with high-volume, high-risk mCNPC. The present study was conducted to evaluate the feasibility of the regimen in anticipation of initiating a prospective, formal phase II study.

MATERIALS AND METHODS

We retrospectively collected and reviewed the medical records of 38 men with mCNPC who did not have disease progression with first-line ADT plus 6 to 8 cycles of docetaxel between Oct 2022 and Oct 2023. Enrolled patients had histologically confirmed prostate adenocarcinoma, documented metastatic disease before the receipt of ADT and first-line docetaxel for high-volume disease, no disease progression (i.e., no prostate-specific antigen [PSA] elevation and no evidence of progression on imaging studies) after 6 to 8 cycles of docetaxel chemotherapy, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and acceptable major organ functions to receive enzalutamide. High-volume disease was defined as bone metastases beyond the axial skeleton and/or visceral involvement, regardless of PSA level. The choice of first-line docetaxel was determined by a multidisciplinary urologic oncology team composed of urologists, radiologists, pathologists, radiation and medical oncologists.

Patients and initial tumor characteristics, docetaxel treatment duration, intervening therapies, and clinical outcomes were recorded. Analytical data with potential prognostic value, PSA decline and time to PSA progression were collected for both first-line docetaxel and maintenance enzalutamide treatments. First-line treatment consisted of docetaxel 20–25 mg/m^2/week biweekly or tri-weekly regimen. Oral prednisone was given at a dose of 5 mg twice daily. After 6 to 8 cycles of docetaxel, clinical response was evaluated with PSA level, computed tomography scans, bone scans, or by the same tests that were initially used to stage the tumor. Patients without evidence of disease progression were eligible to switch to maintenance enzalutamide 160 mg orally per day. At the same time, patient who had not undergone surgical castration were required to continue ADT. The adverse events were recorded and graded according to the National Cancer Institute criteria (NCI-CTCAE). Endpoints of the present retrospective study included the PSA and radiologic responses, and safety during maintenance enzalutamide. PSA response and progression were defined as a >50% decline from baseline, and as an increase >25% and >2 ng/mL, respectively. Radiologic response and progression were evaluation according to the PCWG (Prostate Cancer Clinical Trials Working Group 2) criteria [12]: if a patient had no measurable lesions other than bone metastases, then the response was only classified as stable disease or disease progression. All statistical analyses were performed using R for Windows v2.11.1 (https://www.r-project.org).

RESULTS

The baseline patient characteristics and outcomes relating to prior docetaxel therapy are listed in Table 1. The duration of first-line docetaxel was 2.8 months (range, 2.7–5.0 months). All 38 patients had a PSA response with docetaxel, and radiologic responses were seen in 21 patients (58%). With ADT plus docetaxel, their PSA value was decreased

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Table 1. Baseline patient characteristics and outcome of first-line docetaxel (N=38)

Characteristic	Value
Age (yr)	68 (46–82)
Gleason score	9 (7–10)
7 or 8	18 (47)
9 or 10	20 (53)
Prior treatment to primary tumor	
Prostatectomy	5 (13)
Radiotherapy	2 (5)
PSA (ng/mL)	
Prior to ADT	222.0 (3.3–10,000.0)
Prior to docetaxel	147.0 (0.2–4,580.0)
Prior to enzalutamide	3.2 (0.01–258.0)
Performance status	
No symptoms	20 (53)
Symptomatic	18 (47)
Metastatic sites	
Bone	35 (92)
Lymph nodes	28 (74)
Lung	8 (21)
Liver	1 (3)
Treatment duration of first-line docetaxel (mo)	2.8 (2.7–5.0)

Values are presented as median (range) or number (%).
PSA, prostate-specific antigen; ADT, androgen deprivation therapy.

Table 2. Maximum grade adverse events per patient

Adverse event	Grade 1	Grade 2
Anemia	19 (50)	4 (11)
Fatigue	20 (53)	4 (11)
Pain	10 (26)	2 (8)
Nail changes	8 (21)	0 (0)
Sensory neuropathy	8 (21)	0 (0)
Anorexia	15 (40)	0 (0)
Nausea	4 (11)	0 (0)
Stomatitis	4 (11)	0 (0)
Edema	11 (29)	0 (0)
Urinary tract symptoms	16 (42)	1 (3)

Values are presented as number (%).

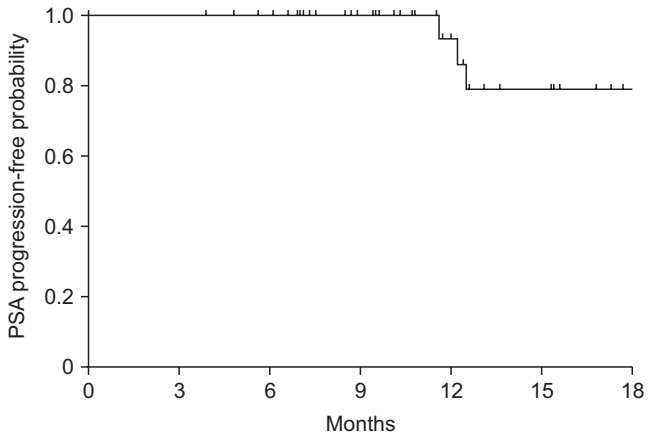

Fig. 1. Kaplan-Meier curve for time to prostate-specific antigen (PSA) progression.

from a median of 222.0 ng/mL (range, 3.3–10,000 ng/mL) to 3.2 ng/mL (range, 0.01–258.0 ng/mL). Most patients had metastases confined to bone and/or lymph nodes. Nine patients (24%) had visceral metastases (lung and/or liver). At the start of enzalutamide, their median age was 68 years (range, 46–82 years) and 47% had symptomatic (i.e., ECOG performance status of 1) disease.

With a median follow-up duration of 10 months (95% confidence interval, 9–12), 27 patients (71%) were still receiving maintenance enzalutamide. The main reasons for discontinuation of enzalutamide included adverse events (prolonged fatigue of grade 1 or 2, n=6), disease progression (n=3) and financial burdens (n=2). Two patients received a subsequent anticancer therapy: rechallenge docetaxel (n=1) and cabazitaxel (n=1). Maintenance enzalutamide was generally well-tolerated: adverse events of any grade occurred in 34 patients (90%) (Table 2) but none of the adverse events were grade 3 or higher. Two patients discontinued enzalutamide due to prolonged grade 1 or 2 fatigue but they are on ADT alone without evidence of disease progression. Eight patients (21%) demonstrated PSA response, and there was no radiologic response during enzalutamide therapy. PSA and/or radiologic progression was noted in 3 patients, thereby 93% were PSA progression-free at 12 months (Fig. 1).

DISCUSSION

The present study shows that maintenance therapy with enzalutamide is a feasible treatment option with potential therapeutic benefit for patients with high-volume mCNPC, progression-free following first-line docetaxel plus ADT. The finding is consistent with previous studies [6,7] in which the effect of enzalutamide for mCNPC was substantial regardless of early docetaxel treatment. Although the number of patients and follow-up duration are limited in the present study, baseline characteristics were generally consistent with those seen in these phase III studies, with the only exception that we included high-volume disease.

Although there are more than a few newly developed treatment options for mCNPC [5,8], it is not possible to replace ADT plus docetaxel, for high-volume disease in

particular. It is suggested that the high tumor burden is a poor prognostic factor, and patients are suffering from symptoms of metastatic disease. The addition of docetaxel to ADT is often preferred in patients with mCNPC based on a high-volume of disease and potentially the symptomatic burden [13]. On the other hand, considering most cases are diagnosed in elderly patients, hematologic toxicities of docetaxel can be a major hurdle for general application to mCNPC. In general, the safety profile of ARTAs seems more tolerable than docetaxel [13], although a direct comparison has never been made. Another difference between docetaxel and other ARTAs is the treatment duration. Patients with mCNPC receive ADT plus either <6 months of docetaxel or long-term (i.e., until progression or unacceptable adverse events) ARTAs [3,5-7]. The omission of excessive docetaxel cycles may avoid unnecessary cumulative toxicity which may sometimes be severe. Conversely, the majority of patients will progress after the cessation of first-line therapy. In our prospective phase II study involving first-line docetaxel plus ADT in mCNPC patients [14], the median PFS was 26 months.

Despite major advancements in prostate cancer treatment, mCNPC remains an incurable condition where the aim of treatment is to improve survival and to palliate symptoms. In general, systemic therapy in mCNPC should be focused on prolongation of time to PSA progression, as well as preserving the quality of life of the patients. Most patients are elderly, and usually a frail population with multiple comorbidities and poor tolerance to cytotoxic chemotherapy. Switch maintenance therapy with an active and tolerable treatment regimen in a well-selected patient population may have a beneficial effect on quality of life, as a direct effect of the improvement in clinical outcome. The major limitation of this study is its retrospective, noncomparative design. Patients received maintenance enzalutamide following first-line docetaxel 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. The definition of high-volume disease was not well-defined but judged by treating physicians. In general, guidelines included the presence of extensive bone metastases and/or visceral disease as a predictor for poor prognosis [9,15]. Patients included men with newly diagnosed metastatic disease and a small proportion of patients with recurrent disease. It seems unlikely to look for statistically different results in patients with recurrent disease, as the estimates of the effect of docetaxel were consistent with that seen in the whole population in previous trials [3,4]. In addition, the small number of patients led to biases and lack of significance of some considerations that otherwise would probably provide more consistent results. These questions are currently being addressed in our prospective study (ClinicalTrials.gov, NCT06015321; CRIS.nih.go.kr, KCT0009086), which aims to assess treatment outcomes with enzalutamide first-line maintenance, following 6 to 8 cycles of ADT plus docetaxel.

CONCLUSIONS

In conclusion, our data provide the evidence of feasibility and tolerable safety of enzalutamide first-line maintenance in patients with high-volume mCNPC, who were progression-free following ADT+docetaxel. The findings warrant further investigation and the prospective study is under way.

NOTES

- **Author Contribution:** Conceptualization: SHL, SWC, SHP; Data curation: JHJ, WS, MK, HHS, HGJ, BCJ, SIS, SSJ, SHP; Formal analysis: SHL, SWC; Methodology: SHP; Project administration: SHP; Visualization: SWC, SHP; Writing - original draft: SHL, SWC; Writing - review & editing: All authors.
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REFERENCES

1. Han SH, Yuk HD. Epidemiology of urologic cancer in Korea: nationwide trends in the last 2 decades. J Urol Oncol 2023; 21:32-44.
2. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. Lancet 2000;355:1491-8.
3. Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015;373: 737-46.
4. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016;387:1163-77.
5. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017;377:352-60.
6. Davis ID, Martin AJ, Stockler MR, Begbie S, Chi KN, Chowdhury S, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. N Engl J Med 2019;381:121-31.
7. Armstrong AJ, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, Villers A, Azad A, et al. ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. J Clin Oncol 2019;37:2974-86.
8. Chi KN, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med 2019;381: 13-24.
9. Schaeffer E, Srinivas S, Antonarakis ES, Armstrong AJ, Bekelman JE, Cheng H, et al. NCCN guidelines insights: prostate cancer, version 1.2021. J Natl Compr Canc Netw 2021;19:134-43.
10. Clarke NW, Ali A, Ingleby FC, Hoyle A, Amos CL, Attard G, et al. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial. Ann Oncol 2019;30:1992-2003.
11. Kwon WA, Joung JY, Lee JE, Choi SY, Kim SH, Seo HK, et al. Use of docetaxel plus androgen deprivation therapy for metastatic hormone-sensitive prostate cancer in Korean patients: a retrospective study. Investig Clin Urol 2019;60:195-201.
12. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008; 26:1148-59.
13. Vale CL, Fisher DJ, Godolphin PJ, Rydzewska LH, Boher JM, Burdett S, et al. Which patients with metastatic hormone-sensitive prostate cancer benefit from docetaxel: a systematic review and meta-analysis of individual participant data from randomised trials. Lancet Oncol 2023;24:783-97.
14. Byeon S, Kim H, Jeon HG, Seo SI, Jeon SS, Lee HM, et al. A prospective phase-II trial of biweekly docetaxel plus androgen deprivation therapy in patients with previously-untreated metastatic castration-naive prostate cancer. BMC Cancer 2021;21:1281.
15. Kim IH, Shin SJ, Kang BW, Kang J, Kim D, Kim M, et al. 2020 Korean guidelines for the management of metastatic prostate cancer. Korean J Intern Med 2021;36:491-514.