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Effectiveness of Adding Docetaxel to Androgen Deprivation Therapy for Metastatic Hormone-Sensitive Prostate Cancer in Korean Real-World Practice

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Purpose: Evidence in favor of adding docetaxel in treatment of metastatic hormone-sensitive prostate cancer (mHSPC) has led to docetaxel in conjunction with androgen deprivation therapy (ADT) as standard therapy. The aim of this study was to examine the effectiveness of docetaxel with ADT for Korean patients with mHSPC in real-world practice.

Materials and Methods: A retrospective cohort study was performed at six Korean hospitals for patients with mHSPC treated with docetaxel plus ADT. Patients were treated every 3 weeks for up to six cycles with 75 mg/m^2 of docetaxel. The primary endpoint was time to castration resistant prostate cancer (CRPC).

Results: This study included 46 eligible patients from June 2016 to February 2021. Median age was 68.5 years (range, 52–84) and all patients present with de novo M1 with high-volume disease. The median prostate-specific antigen (PSA) level at ADT initiation was 205.4 (7.7–1933) ng/mL, and time from ADT to docetaxel was 2.4 months (0–5.3). All six planned cycles of docetaxel were delivered in 36 patients (78%), 7 patients (15%) discontinued treatment due to adverse events, and 3 patients (7%) discontinued due to progression. At the time of the analysis, CRPC had developed in 34 patients (74%), and the median time to CRPC was 18.0 (95% confidence interval, 14.1–21.9) months. PSA <0.2 ng/mL was achieved in 11 patients (24%) after 6 months of ADT and in 10 patients (22%) after 12 months. At last follow-up, 35 patients (76%) were alive; the median overall survival was not reached.

Conclusion: The effect of docetaxel combined with ADT for Korean patients with mHSPC is comparable with prior results in Western studies.

Key Words: Docetaxel, prostate cancer, hormone-sensitive, chemotherapy, prostatic neoplasms

INTRODUCTION

Although androgen deprivation therapy (ADT) has been the cornerstone in the management of metastatic hormone sensitive prostate cancer (mHSPC), progression to castration resistant prostate cancer (CRPC) occurs within a median of 18–24 months.[1] Many attempts have been made to delay the occurrence of CRPC and improve survival outcomes by early combination therapy of additional systemic agents with ADT, and several therapies have been approved for standard treatment of mHSPC.[1,2]

Three large randomized phase III trials (GETUG-AFU 15,[3] CHAARTED,[4] and STAMPEDE[5]) have investigated the efficacy of adding docetaxel to ADT in mHSPC. In terms of overall survival (OS), GETUG-AFU 15 was a negative study, while CHAARTED demonstrated a significant benefit in patients with high-vol-

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ume disease (either visceral involvement or ≥4 bone metastases including one outside the pelvis or spine). STAMPEDE demonstrated a significant benefit to all comers. Despite some differences between trials, long-term data follow-up[6] and a meta-analysis[7] showed that the weight of available evidence favors the use of docetaxel, supporting its incorporation in international guidelines.[8,9] Thus, adding docetaxel to ADT is now considered one of the standard options in mHSPC, and it has been introduced as a standard of care in Korea.

Although results from randomized controlled phase III trials are considered high-level evidence, the results can be difficult to generalize due to a few limitations, including "healthy patient" selection bias. Considering the increased incidence of prostate cancer (PCa) in elderly men,[10] real-world outcomes of adding docetaxel to ADT can provide clinicians with critical information to help in terms of decision-making. On the other hand, safety issues of docetaxel in Asians have been raised, including a pharmacokinetics study conducted in Japan,[11] and the belief that treatment tolerability is indispensable in the CRPC setting.[12,13] In Korean patients with mHSPC, there have been studies using a low dose regimen of docetaxel, that is, a 40 mg/m^2 biweekly regimen.[14,15] However, 75 mg/m^2 of docetaxel every 3 weeks is the current standardized dose until now.[2,16,17] Considering concerns for docetaxel tolerability in Asians and that docetaxel 75 mg/m^2 would remain a component of standard regimens, Asian real-world data about adding docetaxel 75 mg/m^2 to ADT is necessary.

While there are a few real-world Western studies,[18,19] the effectiveness of adding 75 mg/m^2 of docetaxel to ADT in an Asian real-world population is uncertain, with the exception of two studies, which did not provide sufficient long-term oncological outcome due to short follow-up periods.[20,21] Hence, this present study aims to assess the clinical outcomes in Korean men with mHSPC receiving docetaxel and ADT in routine practice.

MATERIALS AND METHODS

Study design and population

From June 2016 to February 2021, a retrospective cohort study was performed on patients treated with docetaxel in addition to ADT for mHSPC at six Korean hospitals (Pusan National University Yangsan Hospital, Keimyung University Dongsan Hospital, Gachon University Gil Medical Center, Kosin University Gospel Hospital, Chungnam National University Hospital, and Asan Medical Center). The subjects included patients who were not registered in previous research. Patient information included pathologic confirmation, radiological evidence of metastatic disease, and an Eastern Cooperative Oncology group (ECOG) performance status (PS) score of 0, 1, or 2. Patients were excluded if docetaxel treatment was performed for over 6 months, if confirmation of prostate-specific antigen (PSA) progression or radiologic progression preceded initiation of docetaxel, or if prior treatment apart from ADT was administered for mHSPC. Patients receiving novel androgen receptor-targeted agents (ARTA), such as abiraterone or enzalutamide, at mHSPC were also excluded. Patients were treated with up to six cycles of docetaxel (75 mg/m^2) given 3-weekly with or without prednisolone.

Data collection and outcomes

Data were retrieved from individual records for the following baseline patient characteristics: age, ECOG PS, Gleason score, pre-treatment PSA, number of bone metastases, presence of visceral disease, and previous PCa treatments. The volume of disease was defined according to the CHAARTED criteria: high-volume disease was defined as presence of visceral metastases and/or four or more bone metastases with at least one outside the vertebral column and pelvis or both based on CT of the abdomen and pelvis, the chest, and bone scan.[4] Treatment characteristics were reviewed, including time from ADT to the first cycle of docetaxel, number of cycles given, dose, and early discontinuation (and reason why). Dose intensity of docetaxel was calculated by dividing the total dose (mg/m^2) by the total administration period, and the value was expressed as a percentage based on the dose intensity of standard therapy (75 mg/m^2/3 weeks). Subsequent treatments for CRPC were also included.

Patients were evaluated every 3 weeks during docetaxel treatment and every 1 to 3 months thereafter. Radiologic disease assessments (CT of the abdomen and pelvis, X-ray or CT of the chest, and bone scan) were performed at baseline and as clinically indicated. Serum PSA concentrations were checked every visit. We specifically recorded PSA values at 6 and 12 months after initiation of ADT. CRPC was defined as either PSA progression, development of worsening symptoms, or radiographic progression, with a testosterone level of <50 ng/dL. PSA progression was defined as an increase in PSA level by >50% above nadir, which was confirmed by a consecutive increase at least 2 weeks later. For patients with a PSA nadir of <2 ng/mL, a PSA value of ≥2 ng/mL was required.

Statistics

Demographics, clinical presentation, perioperative clinical findings, pathologic information, and laboratory values were summarized using descriptive statistics, including median, mean, and range values. Continuous variables were described by medians, whereas categorical variables were described by absolute numbers and percentages. The primary endpoint was time from ADT to development of CRPC (time to CRPC). Secondary endpoints were OS, PSA response at 6 and 12 months, time to CRPC according to PSA response at 6 months, and dose intensity of docetaxel treatment. All time-based endpoints were defined with respect to the date of initiation of ADT, and analysis was performed using the Kaplan–Meier method. The log rank test was used to perform pairwise comparisons for Kaplan–

Meier estimates. All statistical tests were two-sided, and statistical significance was defined as $p<0.05$. Analyses were carried out using SPSS ver. 19 (IBM Corp., Armonk, NY, USA). This study was approved by the Institutional Review Board (Pusan National University Yangsan Hospital, 05-2022-034), which waived the requirement for informed consent due to the retrospective design of this study.

RESULTS

Patient and disease characteristics

In total, 46 patients were identified as having received docetaxel for mHSPC from June 2016 through February 2021. Patient characteristics are summarized in Table 1. The median age was 68.5 years (range, 52–84), 89% had an ECOG PS of 0–1, and 89% had a Gleason score of ≥8. Patients had a median PSA level of 205 ng/mL at the time of ADT. Of the 46 patients, none had prior local treatment for PCa, and all present with de novo M1 and high-volume disease. The median time from ADT start to initiation of docetaxel was 2.4 months (range, 0–5.3; interquartile range, 0.9–3.3).

Treatment delivery and outcomes

All six planned cycles of docetaxel were delivered in 36 patients (78%). However, 7 patients (15%) discontinued treatment due to adverse events (AEs), and 3 patients (7%) discontinued treatment due to disease progression. The causes of discontinuation due to AEs were as follows: asthenia in four, febrile neutropenia in two, and chemotherapy induced peripheral neuropathy in one. There was no treatment related death. Dose intensity of docetaxel was determined to be 87% (Table 2).

At the time of analysis (August 2021), with a median follow-up time of 34.4 months [95% confidence interval (CI), 23.9–44.9], CRPC developed in 34 patients (74%), with a median time to CRPC of 18.0 months (95% CI, 14.1-21.9). Thirty-six patients (78%) were alive at the last follow-up, and the median OS was not reached (Fig. 1).

With regard to PSA response, PSA of <0.2 ng/mL and PSA of 0.2–4.0 ng/mL were achieved in 11 patients (24%) and 25 patients (54%) after 6 months of treatment and in 10 patients (22%) and 17 patients (37%) after 12 months, respectively (Table 3). According to PSA response at 6 months, the median times to CRPC were 8.5 months (95% CI, 6.4–10.5) for the 11 patients with a PSA level of >4.0 ng/mL, 13.3 months (95% CI, 8.8–17.8) for the 25 patients with a PSA of 0.2–4.0 ng/mL, and 36.4 months for 10 patients with PSA <0.2 ng/mL. There was a statistically significant difference in time to CRPC between these groups ($p<0.001$) (Fig. 2).

Subsequent treatment of CRPC

At the time of analysis, 34 patients had progressed to CRPC, and all received subsequent systemic treatment for CRPC with

Table 1. Patient Characteristics (n=46)

Characteristics	Number (%)
Age (yr)	
Median (range)	68.5 (52–84)
IQR	63–72
ECOG performance status	
0	1 (2)
1	40 (87)
2	5 (11)
Volume of disease*	
Low volume	0
High volume	46 (100)
Visceral metastasis (n=18)	
Lung	13 (72)
Liver	3 (17)
Pleura	2 (11)
Bone metastases	
0	2 (4)
1–3	4 (9)
4–10	7 (15)
>10	33 (72)
Gleason score	
≤6	0
7	3 (7)
8–10	41 (89)
NA	2 (4)
PSA level at start of ADT (ng/mL)	
Median (range)	205.4 (7.7–1933)
IQR	(124.3–862.5)
≤20	2 (4)
≥20	43 (94)
NA	1 (2)
Time from ADT start to Docetaxel (months)	
Median (range)	2.4 (0–5.3)
IQR	(0.9–3.3)
PSA level at start of Docetaxel (ng/mL)	
Median (range)	9.8 (0.04–2238)
IQR	(1.5–119.3)
<4.0	18 (39)
4.0–20	11 (24)
≥20	17 (27)
Initial disease status	
Recurrent	0
Initially metastatic (de novo M1)	46 (100)
Initial definitive treatment	
Radical prostatectomy	0
Definitive radiotherapy	0
None	46 (100)
Primary ADT	
Surgical castration	2 (4)
LHRH-analogues	44 (96)

IQR, interquartile range; ADT, androgen deprivation therapy; ECOG, Eastern Cooperative Oncology Group; LHRH, luteinizing hormone-releasing hormone; PSA, prostate-specific antigen.
*Volume of disease was defined according to the CHAARTED criteria (high-volume disease was defined as presence of visceral metastases and/or four bone metastases with at least one outside of the vertebral column and pelvis).

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a median time to first subsequent systemic treatment of 20.8 months (95% CI, 14.1–27.5). The majority received either abiraterone with prednisone (55%) or enzalutamide (23%). Seven patients (15%) received docetaxel rechallenge, and among them, the rates of 30%, 50%, and 90% PSA decreasing responses were 86% (6/7), 43% (3/7), and 29% (2/7), respectively (Table 4).

Table 2. Treatment with Docetaxel (n=46)

Characteristics	Number (%)
Cycles of docetaxel treatment	
6 cycles	36 (78)
5 cycles	4 (9)
4 cycles	3 (7)
3 cycles	2 (4)
1 cycle	1 (2)
Causes of early docetaxel discontinuation	
Asthenia	4 (9)
Febrile neutropenia	2 (4)
Chemotherapy induced peripheral neuropathy	1 (2)
Disease progression during docetaxel	3 (5)
Treatment related death	0 (0)
Dose intensity of docetaxel (%, per 75 mg/m^2/3 week)	87%

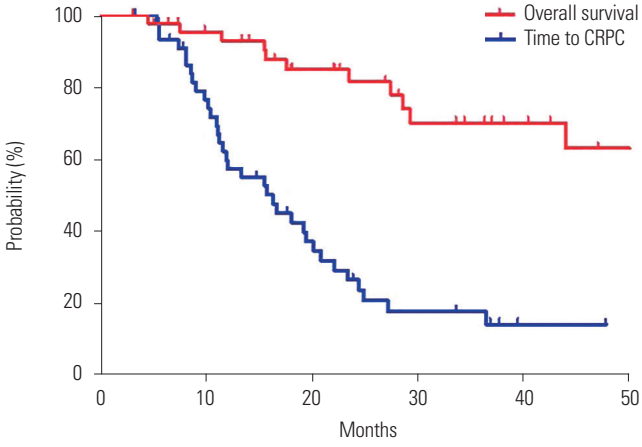

Fig. 1. Kaplan–Meier curve for time to castration-resistant prostate cancer (CRPC) and overall survival.

Table 3. Outcomes for All Patients (n=46)

Characteristics	Number (%)
PSA (ng/mL) at 6 months	
<0.2	11 (24)
0.2–4.0	25 (54)
>4.0	10 (22)
PSA (ng/mL) at 12 months	
<0.2	10 (22)
0.2–4.0	17 (37)
>4.0	9 (20)
Development of CRPC	34 (74)
Time to CRPC (months, median, 95% CI)	18.0 (14.1–21.9)
Survival rate at 1 year	43 (94)

PSA, prostate-specific antigen; CRPC, castration-resistant prostate cancer; CI, confidence interval.

DISCUSSION

This study showed that adding docetaxel to ADT in Korean patients with mHSPC resulted in 18.0 months of median time to CRPC, a PSA response of <0.2 ng/mL at 6 months in 24%, a completion rate of six planned cycles in 78%, and a docetaxel dose intensity of 87%. These results revealed that the efficacy and feasibility of adding 75 mg/m^2 of docetaxel to ADT in Korean are comparable not only to previous phase III trials,[5,6] but also to Western real-world data.[18,19] The current study is the first real-world report with sufficient follow-up duration and outcomes of adding docetaxel of the standard 75 mg/m^2 dose in Asian patients with mHSPC starting ADT.

This study demonstrates that the effectiveness of docetaxel in routine practice is in line with the CHAARTED[6] and STAMPEDE trials[5] and recent European real-word data.[18,19] When compared with the populations in the CHAARTED trial, this study population was skewed toward slightly older ages, higher Gleason scores, and a high metastatic burden. This is consistent with a bias toward fitter patients in clinical trials (Table 5). Furthermore, a notable difference between this study's cohort and that of other studies is that all patients in this cohort were newly di-

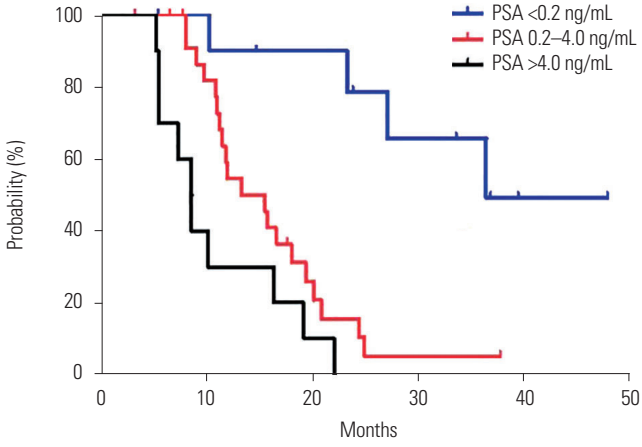

Fig. 2. Kaplan–Meier curve for time to castration-resistant prostate cancer according to prostate-specific antigen (PSA) level at 6 months.

Table 4. Subsequent Treatment in Castration-Resistant Prostate Cancer

Characteristics	1st line (n=34)	2nd line (n=17)	3rd line (n=5)
Abiraterone (+/- other treatment)	18 (55)	2 (12)	1/5 (20)
Enzalutamide	8 (23)	3 (17)	
Docetaxel	5 (14)	2 (12)	
Cabazitaxel	0	7 (41)	4/5 (80)
Observation	3 (8)	3 (17)	

Data are presented as n (%).

Table 5. Comparison of Baseline Characteristics of This Study vs. the CHAARTED and Denmark Real-World Studies

Characteristics	This study ADT plus Docetaxel (n=46)	Denmark real world ADT plus Docetaxel (n=173)	CHARRTED ADT plus Docetaxel (n=397)
Age (yr)			
Median (range)	68.5 (52–84)	68.8 (45–80)	64 (36–88)
ECOG performance status			
0–1	41 (89)	170 (98)	391 (98)
2	5 (11)	4 (2)	6 (2)
Volume of metastases			
Low	0	26 (15)	134 (34)
High	46 (100)	147 (85)	263 (66)
Visceral metastasis	19 (41)	29 (17)	57 (14)
Gleason score			
≤6	0	1 (1)	21 (5)
7	3 (7)	24 (14)	96 (24)
8–10	41 (89)	139 (80)	241 (61)
NA	2 (4)	9 (5)	39 (10)
PSA level at start of ADT			
Median (range)	205 (7.7–1933)	320 (1.6–10818)	51 (0.2–8540)
Time from ADT to Docetaxel (month)			
Median (range)	2.4 (0–5.3)	1.15 (0.1–4.6)	1.2 (0.03–3.9)
Initial definitive treatment			
Radical prostatectomy	0	4 (2)	81 (20)
Definitive radiotherapy	0	0	27 (7)
None	46 (100)	169 (98)	289 (73)

ADT, androgen deprivation therapy; ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.

Table 6. Comparison of Outcomes of Our Study vs. the CHAARTED and Denmark Real-World Studies

Characteristics	Our study ADT plus Docetaxel (n=46)	Denmark real world ADT plus Docetaxel (n=173)	CHAARTED (long-term follow-up) ADT plus Docetaxel (n=397)
Overall duration of follow-up (months)	34.4 (95% CI, 23.9–44.9)	42.0 (95% CI, 37.8–58.6)	53.7
Overall survival (months)	Not reached	51.6 (95% CI, 41.5–56.3)	57.6 (95% CI, 52.0–63.9)
Time to CRPC (high volume*)	18.0 (95% CI, 14.1–21.9)	15.8 (95% CI, 12.6–18.9)	14.9 (95% CI, 12.4–17.2)
Time to CRPC (overall)		15.6 (95% CI, 13.0–18.1)	19.4 (95% CI, 16.8–22.6)
PSA level <0.2 ng/mL at 6 months	11 (24)	26 (15)	127 (32)
PSA level <0.2 ng/mL at 12 months	10 (22)	33 (19)	110 (28)

ADT, androgen deprivation therapy; CRPC, castration-resistant prostate cancer; PSA, prostate-specific antigen; CI, confidence interval.
*Volume of disease was defined according to the CHAARTED criteria (high-volume disease was defined as presence of visceral metastases and/or four bone metastases with at least one outside of the vertebral column and pelvis).

agnosed with de novo M1 and high-volume disease: this group of patients has a different natural history compared with those presenting with metastatic disease after previous radical treatment.[22] Despite aggressive characteristics, our study showed a similar or numerically slightly more favorable time to CRPC (18.0 months), compared with the high-volume disease from the CHAARTED trial (14.9 months) or the European real-world data (15.8 months) (Table 6).

The favorable efficacy of adding docetaxel in this study was consistent in other single-arm phase 2 study (time to CRPC, 24.0 months).[15] These favorable outcomes in Korean patients with mHSPC cannot be concluded due to the limitation of a single-arm study. However, it can be presumed that cytotoxic chemotherapy might be more effective for Asian patients with PCa with aggressive feature, considering that characteristics of Korean patients with PCa are known to be more aggressive than those of Western patients.[23] Therefore, it is necessary to perform a future definitive study to confirm these favorable responses to cytotoxic chemotherapy in Asian patients.

All six planned cycles were completed in 78% of patients, which is similar to rates of 77% and 86% in the CHAARTED and STAMPEDE trials, respectively.[4,5] The dose intensity of docetaxel was 87%. There were seven cases (15%) of discontinuation due to AEs, and the others were non-serous AEs, such as asthenia or peripheral neuropathy, with exception of two cases of febrile neutropenia. There were no treatment-related deaths. These

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findings suggest that adding 75 mg/m^2 of docetaxel might also be tolerable in Asian patients.

A significantly different time was found to CRPC according to PSA levels at 6 months, which is consistent with previous Western data.[18,24] These results suggest varying outcomes and diverse tumor biology of mHSPC in Asian patients and that PSA response at 6 months could be a surrogate marker for discerning prognosis. PSA response at 6 months might help with individually tailoring therapy for patients with mHSPC. For example, even in patients with high-volume disease, if the 6 month PSA level is <0.2 ng/mL, the patient could be investigated for additional radiotherapy to the prostate, similarly with patients of low-volume disease.[25] Conversely, in favorable responders at the 6-month PSA level, it is also possible to plan a trial for omitting ARTAs from the ADT+docetaxel+ARTA regimen.

Following the introduction of adding docetaxel in the management of patients with mHSPC, other studies have demonstrated that the combination of ADT and abiraterone prolongs survival significantly.[26,27] A network analysis indicated that abiraterone may be more effective than docetaxel.[28] Furthermore, newly introduced second-generation antiandrogens in the ARCHES and TITAN studies, such as enzalutamide and apalutamide, respectively, demonstrated prolonged survival in the mHSPC setting.[29,30] No studies have as yet compared the different treatment strategies of ADT+docetaxel versus ADT+novel ARTAs, such as abiraterone, enzalutamide, and apalutamide, head-to-head. Indirect comparisons of docetaxel+ADT vs. abiraterone+ADT showed that there is a high likelihood that abiraterone+ADT is the preferred option and is associated with prolonged PFS and quality of life (QoL); however, survival advantages remain unclear.[31,32] ARTAs have to be maintained until CRPC, a period often lasting many years, which induces an economic burden, and trivial AEs, such as dyspepsia or dizziness, could occur continuously throughout the period. In the abiraterone, there is an additional inconvenience of taking concomitant prednisone from the early stage of mHSPC. Above all, adding ARTA in mHSPC settings would exhaust and leave limited options for CRPC. Conversely, adding docetaxel is in line with known properties of its cytotoxic chemotherapy-related toxicity, and QoL in docetaxel plus ADT has been shown to be significantly worse at 3 months (but better at 12 months, compared with those in ADT alone).[33] A network meta-analysis[31] and QoL comparison study within the STEMPEDE platform[34] showed decreased QoL in patients treated with adding docetaxel, compared to those treated with adding abiraterone, during the first 3 to 6 months. However, the difference in QoL was attenuated, and there was no significant difference after 1 year. Docetaxel is given for only 18 weeks, and all CRPC treatment options can be preserved. Triplet regimens composed of adding novel ARTAs to ADT+docetaxel in the PEACE-1 study (ADT+Docetaxel+Abiraterone) and the ARASENS study (ADT+Docetaxel+Darolutamide) have been found to achieve improved OS, compared with a doublet regimen (ADT+Docetaxel).[16,17] Docetaxel would constitute a standard of care in the future, and this study summarizing the data of adding 75 mg/m^2 of docetaxel in Asian patients with mHSPC can be a useful reference. On the other hand, it is necessary to confirm whether it is useful to add docetaxel to ADT+ARTAs as a triplet regimen, and appropriate target patients using a comparative design study between ADT+ARTA+docetaxel and ADT+ARTA groups.

This present study has the inherent limitations of a retrospective chart review, as outcome documentation was not protocol prescribed. The reliability of our estimates is challenged by missing data, ascertainment bias, and attribution bias. For the same reason, clinical responses, such as pain and radiologic response, could not be assessed. However, through a retrospective study, PSA values can be clearly reviewed, so the possibility of distracted data related with time to CRPC and PSA response is low. Many studies have consistently revealed a significant correlation between PSA response and time to CRPC and OS.[24,35] In addition, detailed AEs and information about docetaxel dose modification and its causes could not be assessed. However, the dose intensity (87%) of docetaxel was clearly assessed, and the incidence and causes of docetaxel discontinuation were also clearly identified. Thus, the safety of adding docetaxel can be estimated in some aspects.

Considering the efficacy and feasibility of adding 75 mg/m^2 of docetaxel in this study, adding docetaxel could be a worthwhile option for the treatment of Asian patients with mHSPC, even in the current era of novel ARTAs, particularly for some subpopulations, such as those with good toleration of cytotoxic chemotherapy and those with aggressive features, such as both de novo and high volume mHSPC.

AUTHOR CONTRIBUTIONS

Conceptualization: Jae Lyun Lee. Data curation: all authors. Formal analysis: Kwonoh Park. Investigation: Kwonoh Park and Jae Lyun Lee. Methodology: Kwonoh Park, Jin Young Kim, and Jae Lyun Lee. Project administration: Kwonoh Park and Jae Lyun Lee. Resources: all authors. Software: Kwonoh Park, Seong Hoon Shin, and Jae Lyun Lee. Supervision: Inkeun Park, Hyo Jin Lee, and Jae Lyun Lee. Validation: Hyo Jin Lee and Jae Lyun Lee. Visualization: Kwonoh Park and Jae Lyun Lee. Writing—original draft: Kwonoh Park. Writing—review & editing: Inkeun Park, Hyo Jin Lee, and Jae Lyun Lee. Approval of final manuscript: all authors.

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