



Use of docetaxel plus androgen deprivation therapy for metastatic hormone-sensitive prostate cancer in Korean patients: A retrospective study

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Purpose: We aimed to evaluate the efficacy and safety of the use of docetaxel plus androgen deprivation therapy (ADT) for metastatic hormone-sensitive prostate cancer (mHSPC) in Korean patients.

Materials and Methods: This study was conducted retrospectively. In total, 61 Korean patients with mHSPC who used docetaxel plus ADT were identified from medical records. Patients received docetaxel plus ADT at a dose of 75 mg/m² every 3 weeks for 6 cycles. We evaluated prostate-specific antigen (PSA) response, PSA progression, progression to castration-resistant prostate cancer (CRPC), clinical progression, and adverse events.

Results: Most of the patients had high volume disease (98.3%) and 83.6% had a Gleason score of 8 or higher. The median PSA level at the start of ADT was 131.4 ng/mL. The percentage of patients whose PSA levels decreased to less than 0.2 ng/mL at 3, 6, and 12 months were 28.3%, 41.0%, and 45.0%, respectively. During a median of 12.0 months after treatment, PSA progression occurred in 13.3% of patients. Clinical progression and progression to CRPC were observed in 15.1% and 14.8%, respectively. Neutropenia grade ≥ 3 and febrile neutropenia occurred in 63.5% and 11.5%, respectively.

Conclusions: Comparing our findings with those of the prior chemohormonal therapy versus androgen ablation randomized trial for extensive disease in prostate cancer (CHAARTED) study, in Korean patients, the use of docetaxel plus ADT for mHSPC showed similar results for early oncologic outcomes including PSA response and time to clinical progression. However, we observed a higher rate of adverse events, which should be considered seriously.

Keywords: Androgens; Docetaxel; Drug therapy; Prostatic neoplasms

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INTRODUCTION

Prostate cancer (PCa) is the second most common can-

cer in the world and is the fifth leading cause of cancer-related mortality worldwide [1]. Localized PCa can be successfully treated with radical prostatectomy or radiation

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therapy. It responds to various treatments, even if it is in a progressive or metastatic state. However, up to 40% of cases of detected PCa eventually progress to the metastatic stage [2,3]. For patients with such advanced PCa, the goal of treatment is increase survival while maintaining quality of life. Androgen deprivation therapy (ADT) is a common standard therapy for metastatic PCa (mPCa) because the androgen receptor (AR) pathway plays an important role in the development and progression of PCa cells [4]. Although ADT can induce biochemical and clinical responses in more than 90% of patients, testosterone levels remain low after a median of 24 to 36 months, but eventually progress to castration-resistant PCa (CRPC) [5]. It is currently known that the progression of CRPC is due to the manifestation of numerous resistance mechanisms induced by selective pressure during hormone therapy [6-10]. Castration can induce clonal selection and subsequent growth of androgen-independent cellular clones [11]. Accordingly, hormone-sensitive PCa (HSPC) should be considered a heterogeneous disease characterized by the coexistence of AR-positive and AR-negative tumor cells.

In this biological context, HSPC patients can benefit from chemotherapy in combination with hormone therapy, targeting AR-negative cells and delaying the development of resistance mechanisms. In the pre-docetaxel period, some randomized controlled trials have studied hormone therapy and other cytotoxic drug combinations in patients with

HSPC, but none of these studies have shown any significant and definitive benefit [12,13]. In the meantime, three large-scale phase 3 clinical trials in the past few years have begun to raise the possibility that chemohormonal treatment with docetaxel plus ADT may be clinically useful for mPCa (GETUGAFU15 [14], chemohormonal therapy versus androgen ablation randomized trial for extensive disease in prostate cancer [CHAARTED]-E3805 [15], and STAMPEDE [16]).

However, the results of the above studies are all based on Western populations. Korean are known to have very different PCa characteristics from those of Westerners [17-22]. Moreover, to the best of our knowledge there are no Korean studies on this subject. Therefore, the clinical usefulness of docetaxel plus ADT in Korean patients for metastatic HSPC (mHSPC) is largely unknown and requires further study. Accordingly, we here report the clinical results of the use of docetaxel plus ADT in Korean patients with mHSPC.

MATERIALS AND METHODS

This study was conducted retrospectively. Patient data were obtained from two institutions (Korea National Cancer Center and Asan Medical Center). The collection of session data used in the study was approved by the Institutional Ethics Committee after reviewing the adopted protocols and procedures (approval number: NCC2018-0038, AMC2018-0219).

Table 1. Baseline characteristics of the patients of this study and the CHAARTED trial

Characteristic	This study (n=61)	CHAARTED (n=397) [15]	p-value ^a
Age (y)	66.0 (47–79)	64 (36–88)	
ECOG PS			0.017
0	53 (86.9)	277 (69.8)	
1	7 (11.5)	114 (28.7)	
2	1 (1.6)	6 (1.5)	
Volume of metastasis			0.001
High	57/58 (98.3)	263 (66.2)	
Low	1/58 (1.7)	134 (33.8)	
Gleason score			0.105
6	1/55 (1.8)	21/358 (5.9)	
7	8/55 (14.5)	96/358 (26.8)	
8–10	46/55 (83.6)	241/358 (67.3)	
Missing	6	39	
PSA at start of ADT (ng/mL)	131.4 (1.7–3,372.0)	50.9 (0.2–8,540.1)	
Time from start of ADT to docetaxel (mo)	0.90 (0–8.90)	1.2 (0.03–3.9)	
Follow-up duration (mo)	12.0 (3.0–26.0)	28.9 (NA)	

Values are presented as median (range), number (%), number/total number (%), or number only.

CHAARTED, chemohormonal therapy versus androgen ablation randomized trial for extensive disease in prostate cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status; PSA, prostate-specific antigen; ADT, androgen deprivation therapy; NA, not applicable.

^a:Pearson's chi-square test was used.

In total, 61 Korean patients with mHSPC and who used docetaxel plus ADT were identified. Docetaxel plus ADT was administered to the following patients, who were enrolled in the present analysis: 1) PCa was diagnosed histologically and diagnosed as metastatic disease by imaging. 2) Eastern Cooperative Oncology Group (ECOG) performance status was less than 2. 3) Organ function was suitable for docetaxel treatment. High volume was defined as the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis.

All patients received ADT plus docetaxel at a dose of 75 mg/m² every 3 weeks for 6 cycles without daily prednisone. According to the organ system showing the greatest degree of toxic effects, dose adjustments were made and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, ver. 4.03). The use of growth factors was at the discretion of the researchers in case of hematologic adverse events, including grade ≥3 neutropenia or febrile neutropenia.

We evaluated prostate-specific antigen (PSA) response rate, PSA progression, clinical progression, progression to CRPC, and adverse events. A PSA response was defined as a serum PSA ≤0.2 ng/mL. We defined PSA progression according to the definition of the PSA Working Group [23].

For patients with measurable lesions, the clinical course was defined as the progression of a preceding lesion, as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST, ver. 1.0) [24] or the progression of the (new) bone lesion. We defined progression to CRPC as castrate serum testosterone <50 ng/dL, three consecutive rises in PSA 1 week apart resulting in two 50% increases over the nadir, and PSA >2 ng/mL or radiological progression.

Curves for the time to PSA progression-free survival, clinical progression-free survival, and progression to CRPC were estimated using the Kaplan–Meier method. We assessed adverse events using the CTCAE of the NCI (ver. 4.03). All statistical analyses were performed using PASW Statistics ver. 18.0 (IBM Co., Armonk, NY, USA).

RESULTS

Between January 2016 and April 2018, 61 patients were identified and analyzed. The median age was 66.0 years (range, 47–79 years), and 86.9% (53 out of 61) had an ECOG performance status score of 0.

Most of the patients had high volume disease (98.3%, 57 out of 58), and 83.6% (46 out of 55) had a Gleason score of 8 or higher. The median PSA level at the start of ADT was

Table 2. Efficacy profiles of this study and CHAARTED trial

Variable	This study (n=61)		CHAARTED (n=397) [15]		p-value ^a
	High volume disease (n=57, 98.3%)	Low volume disease (n=1, 1.7%)	High volume disease (n=263, 66.2%)	Low volume disease (n=134, 33.8%)	
RECIST criteria					
CR		0 (0.0)			
PR		22/53 (41.5)			
SD		25/53(47.2)			
PD		6/53 (11.3)			
Not evaluated yet		8			
PSA level <0.2 ng/mL at 3 mo		15/53 (28.3)			
PSA level <0.2 ng/mL at 6 mo		16/39 (41.0)		127/397 (32.0)	0.251
PSA level <0.2 ng/mL at 12 mo		9/20 (45.0)		110/397 (27.7)	0.095
PSA progression, yes		8/60 (13.3)			
Clinical progression, yes		8/53 (15.1)			
CRPC progression, yes		9/61 (14.8)			
Time to PSA progression		NR			
Time to clinical progression (mo) [25]		NR		33.0 (27.3–41.2)	
			27.3 (21.9–32.7)	42.5 (34.0–NR)	
Time to CRPC (mo) [25]		NR		19.4 (16.8–22.6)	
			14.9 (12.4–17.2)	31.0 (23.1–51.1)	

Values are presented as number/total number (%), number only, or median (95% confidence interval).

CHAARTED, chemohormonal therapy versus androgen ablation randomized trial for extensive disease in prostate cancer; RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PSA, prostate-specific antigen; CRPC, castration-resistant prostate cancer; NR, not reached.

^a:Pearson’s chi-square test was used.

131.4 ng/mL (range, 1.7–3,372.0 ng/mL). The median time from the onset of ADT to docetaxel administration was 0.9 months (range, 0–8.9 months). Compared with the CHAARTED trial, our cohort had a better ECOG performance status ($p=0.017$) and higher volume of metastasis ($p=0.001$). However, there was no statistical difference in Gleason score ($p=0.105$). Patient characteristics of the present study and the CHAARTED trial are shown in Table 1 [15].

Forty-one patients (67.2%, 41 out of 61) finished six cycles of docetaxel. Six patients (9.8%, 6 out of 61) stopped docetaxel because of treatment-related adverse events (4.9%, 3 out of 61) and follow-up loss (4.9%, 3 out of 61). Dose modification for docetaxel (60 mg/m² reduction) was observed in 18 patients (29.5%, 18 out of 61).

Among these 61 patients, there were 0 complete remission, 22 partial remission, 25 stable disease, and 6 progressive disease (8 patients were not yet evaluated and data for 2 patients were missing) according to the RECIST criteria. The percentage of patients whose PSA levels decreased

to less than 0.2 ng/mL at 3, 6, and 12 months were 28.3% (15 out of 53), 41.0% (16 out of 39), and 45.0% (9 out of 20), respectively (Table 2) [15,25]. The median follow-up period was 12.0 months (range, 3.0–26.0 months). PSA progression occurred in 13.3% (8 out of 60) and the PSA progression-free survival curve is shown in Fig. 1. Clinical progression occurred in 15.1% (8 out of 53), and the clinical progression-free survival curve is shown in Fig. 2. Finally, progression to CRPC occurred in 14.8% (9 out of 61), and the progression to CRPC-free survival curve is shown in Fig. 3.

Approximately 64% of the patients who received docetaxel plus standard ADT developed neutropenia grade ≥ 3 . Febrile neutropenia occurred in 11.5% of patients. The rates of neutropenia (69.2%), and neutropenia grade ≥ 3 of this study were higher than those of the CHAARTED trial, and febrile neutropenia was also more common but this difference was not statistically significant. Other common adverse events were anemia (88.5%), fatigue (28.8%), peripheral edema (11.5%), and sensory neuropathy (9.6%). Detailed data of the hematologic and non-hematologic adverse events are listed in Table 3.

DISCUSSION

The main goal of this study was to determine the efficacy and safety of the use of docetaxel plus standard ADT in Korean patients with mHSPC. Our data show similar early oncologic results as in previous Western trials, but with more adverse effects [15,16].

The 6-month PSA response in this study was 41.0%, and the 12-month PSA response was 45.0%. The 6- and 12-month PSA response of CHAARTED [15] were 32.0% and 27.7%, respectively. Regarding the higher PSA response in the present study, we hypothesize that this is mainly due to

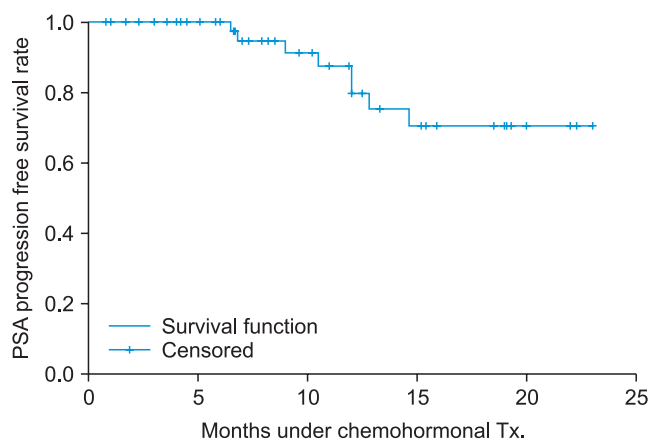


Fig. 1. Kaplan–Meier estimates of PSA progression-free survival rate. PSA, prostate-specific antigen; Tx., therapy.

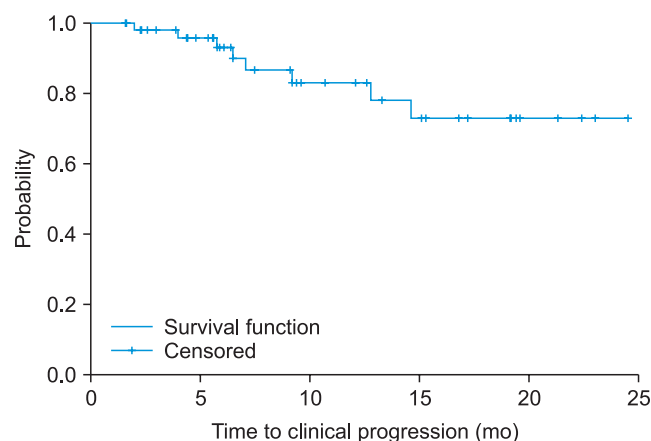


Fig. 2. Kaplan–Meier estimates of clinical progression-free survival rate.

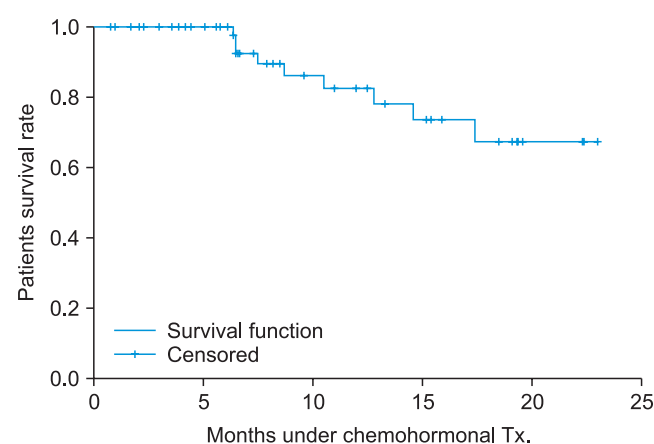


Fig. 3. Kaplan–Meier estimates of progression to CRPC-free survival rate. CRPC, castration-resistant prostate cancer; Tx., therapy.

Table 3. Adverse events of this study and CHAARTED trial

Event	This study (n=52)		CHAARTED (n=390) [15]		p-value ^a
	All	Grade ≥3	All	Grade ≥3	
Neutropenia	36 (69.2)	33 (63.5)		47 (12.1)	0.001
Febrile neutropenia	6 (11.5)	6 (11.5)		24 (6.2)	0.147
Anemia	46 (88.5)	0 (0.0)		5 (1.3)	
Fatigue	15 (28.8)	0 (0.0)		16 (4.1)	
Diarrhea	2 (3.8)	0 (0.0)		4 (1.0)	
Constipation	2 (3.8)	0 (0.0)			
Alopecia	1 (1.9)	0 (0.0)			
Sensory neuropathy	5 (9.6)	0 (0.0)		2 (0.5)	
Peripheral edema	6 (11.5)	0 (0.0)			
Mucositis	1 (1.9)	0 (0.0)			
Allergic reaction	2 (3.8)	0 (0.0)			
Others	15 (28.8)	0 (0.0)			
Total		39 (75.0)		114 (29.2)	0.001

Values are presented as number (%).

CHAARTED, chemohormonal therapy versus androgen ablation randomized trial for extensive disease in prostate cancer.

^a:Grade ≥3 vs. Grade ≥3, Pearson’s chi-square test was used.

differences in tumor characteristics between patients with and without high volume disease. The incidence of adverse events varies between Western and Asian (including Korean) patients. For example, 32% of patients in the TAX 327 study (docetaxel every third week) and 12.1% of patients with neutropenia of grade ≥3 in CHAARTED had adverse effects. On the other hand, in recent phase II clinical trials using docetaxel in Japan, 97.3% of patients had grade ≥3 neutropenia [26]. In the present trial, 63.5% of patients showed neutropenia of grade ≥3. In cases of febrile neutropenia, 0% of patients in TAX 327 and 6.1% of patients in CHAARTED had grade ≥3 adverse events. In a recent Phase II clinical trial in Japan, adverse events of grade ≥3 occurred in 4% of patients [26]. In the current study, 11.5% of patients had grade ≥3 febrile neutropenia. Anemia occurred in 88.5% of all cases in this study, similar to the recent Japanese phase II clinical trial [26]. In addition, Lavoie et al. [27] recently published a real-world population study with docetaxel for HSPC. One result of the study was that the clinical effects and hematologic adverse events of addition of docetaxel (DOC) plus ADT were worse than those reported in CHAARTED.

The National Comprehensive Cancer Network guidelines recommend that the DOC to standard ADT is a viable option for patients with metastatic hormone-naïve prostate cancer (mHNPC) [28]. The ESMO Clinical Practice Guidelines (2015) have recommended it as the first-line treatment for mHNPC, and men are well suited for chemotherapy [29]. Half of St. Gallen’s panelists recommended using docetaxel as an ADT therapy in most mHNPC patients with high-

volume disease [30]. However, when interpreting the above-mentioned guidelines, it is important to consider study findings showing that the aggressiveness of PCa varies between Korean and Western patients, and that higher grade, advanced stage PCa is more common in Koreans [17-19].

This study has some limitations. First, it is a single arm trial with a small sample size. A large randomized controlled trial is required to evaluate good PSA response. Second, the short-term follow-up period did not reveal the overall survival rate, time to clinical progression, or time to CRPC. Third, there is a possibility that bias could have occurred because data were collected from two institutions. Under this restriction, additional follow-up studies are underway to identify overall survival, additional treatment methods, and late adverse events.

However, to the best of our knowledge, this is the first study of the use of docetaxel plus ADT treatment in Korean patients with mHSPC. An additional strength of this study is that it is a real-world study with a large tumor volume in most patients (98.3%).

CONCLUSIONS

In conclusion, in this study of Korean patients, the use of docetaxel plus ADT for mHSPC showed similar results as in the CHAARTED trial for early oncologic outcomes, including PSA response and time to clinical progression. However, high rates of hematologic adverse events should be closely monitored. Moreover, dose adjustment and prophylactic granulocyte colony-stimulating factor need to be

considered.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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