Clinical Outcomes of Continuous Addition of Androgen Deprivation Therapy During Docetaxel Chemotherapy for Patients With Castration-Resistant Prostate Cancer

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Purpose: This study compared the oncologic results of docetaxel chemotherapy (DOC) in castration-resistant prostate cancer (CRPC) according to continuous addition of androgen deprivation therapy (ADT) during chemotherapy.

Materials and Methods: We retrospectively reviewed the medical records of 106 patients who received DOC in 6 medical institutes. Among them, 72 patients had a complete medical record: 28 patients with ADT (DOC+continuous ADT group) and 44 without ADT (DOC only group). We compared the progression-free survival of these groups after DOC.

Results: Docetaxel was administered an average of 28 months after primary ADT as the first treatment. A median number of 6 cycles of DOC was administered in both groups. In the DOC+continuous ADT group, orchiectomy was performed in 18 patients and luteinizing hormone-releasing hormone agonist was injected in 10 patients. During DOC treatment, prostate-specific antigen (PSA) progression-free survival was statistically different (6.0 ± 4.75 months in DOC+continuous ADT group vs. 4.8 ± 3.2 months in DOC only group, $p=0.024$), whereas radiologic progression-free survival was not statistically different (5.0 ± 3.12 months in DOC+continuous ADT group vs. 5.0 ± 2.79 months in DOC only group, $p=0.387$).

Conclusions: In our cohort, continuous addition of ADT showed a significant benefit in PSA progression-free survival during DOC in CRPC patients. Further prospective studies are needed to confirm these observations. (Korean J Urol Oncol 2017;15:59-65)

Key Words: Androgen deprivation therapy • Castration-resistant prostate cancer • Docetaxel chemotherapy

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INTRODUCTION

Prostate cancer (PCa) is the second most common cancer and the fifth leading cause of cancer-related death in males worldwide.¹ In Western countries, approximately 85% of newly diagnosed PCa cases remain localized to the prostate, whereas the remainder are advanced or metastatic.² In Korea, 21% of

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PCa patients present with distant metastases and 19% with locally advanced disease at diagnosis.³

For the advanced PCa patients, androgen deprivation therapy (ADT) has been the main treatment option. However, despite an initial favorable response, the majority of patients experience predictable resistance to ADT after 3–5 years, which is defined as castration-resistant prostate cancer (CRPC).^{4,5} Accumulating evidence has indicated docetaxel chemotherapy (DOC) as a standard modality after progression to CRPC.^{6,7} Studies have highlighted the need to maintain ADT because PCa growth remains dependent on androgen receptor signaling.⁸ However, it is not fully understood whether continuous addition of ADT therapy during DOC actually provides survival benefits compared with conventional DOC without ADT.

Under the current guidelines, concurrent administration of luteinizing hormone-releasing hormone (LH-RH) agonist for CRPC patients under DOC is reimbursed by the Korean National Health Insurance System. However, as mentioned above, the benefits of concurrent administration of ADT in CRPC patients under cytotoxic chemotherapy are still debatable due to the absence of tangible results from related studies.^{9,10}

The aims of this study were therefore to examine the effect of concurrent use of ADT during DOC on clinical outcomes in Korean CRPC patients.

MATERIALS AND METHODS

This multi-institutional retrospective cohort study involved 6 hospitals in Busan and Gyeongsangnam-do, Korea. The study cohort included data from a total of 106 patients with CRPC who received DOC at the Department of Urology in each hospital between 2006 and 2016. The eligible patient population had histologically confirmed locally advanced or metastatic prostate adenocarcinoma that were treated with ADT as primary therapy between 2002 and 2015. The study population was composed of men with PCa who demonstrated disease progression as indicated by increasing prostate-specific antigen (PSA) on 2 consecutive measurements or by radiographic imaging studies. All patients were confirmed as having CRPC defined by disease progression after ADT. Before initiation of DOC, a physical examination and baseline laboratory measurements were performed. Disease status was evaluated with abdomen/pelvic computed tomography or magnetic resonance imaging and a bone scan.

After the diagnosis of CRPC, all patients received docetaxel plus prednisone therapy with or without ADT. The regimen consisted of docetaxel (75 mg/m²), which was administered through intravenous infusion once on day 1 every 3 weeks, plus oral prednisolone 5 mg twice daily starting on day 1 and continuing throughout the treatment. DOC was continued until uncontrolled toxicity, disease progression, death, or treatment refusal by the patient. The National Cancer Institute Common Toxicity Criteria version 4.0 was used to evaluate the toxicity during each cycle.¹¹

We excluded patients who did not have a complete medical record including PSA response and radiologic response during DOC. The final study cohort comprised 72 patients. Among them, 28 patients received concurrent ADT as maintenance during DOC (DOC+continuous ADT group) and 44 patients did not receive ADT (DOC only group).

The primary endpoints were biochemical progression-free survival (bPFS) and radiographic progression-free survival (rPFS) during DOC according to concurrent ADT use. Biochemical progression was defined as a >50% increase from the PSA nadir, with a minimum increase of 5 ng/mL.¹² The PSA nadir was defined as the lowest PSA level achieved during DOC. The time to biochemical progression was defined as the interval from the day of treatment initiation to biochemical progression. The time to radiographic progression was defined as the interval from the day of DOC initiation to the first occurrence of progression on imaging studies. Progression on bone scans was assessed according to the Prostate Cancer Working Group-2 criteria,¹³ and soft tissue progression was evaluated with reference to the Response Evaluation Criteria in Solid Tumors version 1.1.¹⁴

Differences in baseline characteristics were compared between groups using a chi-square test or Fisher exact test for categorical variables and the Mann-Whitney U-test for continuous variables. bPFS and rPFS were calculated and analyzed using the Kaplan-Meier method and the log-rank test. All of the tests were 2-sided, and $p < 0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS ver. 18.0 (IBM Co., Armonk, NY, USA).

RESULTS

Baseline patient characteristics are presented in Table 1. Both groups were statistically similar in terms of age, PSA level,

Table 1. Baseline patient characteristics

Characteristic	DOC+continuous ADT group (n=28)	DOC only group (n=44)	p-value
Age at Dx (y)	65.7±6.9	65.7±8.1	0.980
PSA at Dx (ng/dL)	1,175±2,302	446±752	0.058
Gleason score at Dx			
≤7	2	5	0.146
8	14	12	
9–10	12	27	
Clinical stage			
cT2	5	3	0.348
cT3	9	16	
cT4	14	25	
Extent of disease			
Bone metastasis	19	34	0.377
Lymph node metastasis	10	26	0.169
Liver or lung metastasis	5	4	0.172
Nadir PSA after ADT (ng/mL)	6.8±15.8	10.7±31.1	0.502
Time to PSA nadir (mo)	8.9±7.1	8.2±6.8	0.705
Time to PSA progression (mo)	25.8±16.1	24.4±19.2	0.757
Time to image progression (mo)	29.0±19.2	27.7±21.5	0.801
Bone progression	22	33	0.728
Lymph node progression	2	7	0.378
Liver or lung progression	3	8	0.543

Values are presented as mean±standard deviation or number.

ADT: androgen deprivation therapy, DOC: docetaxel chemotherapy, Dx: diagnosis, PSA: prostate-specific antigen.

Table 2. Comparison of results of docetaxel chemotherapy in patients with CRPC according to concurrent ADT

Variable	DOC+continuous ADT group (n=28)	DOC only group (n=44)	p-value
Mean Ctx cycles	6.5	6.4	0.952
Time to CTx start (mo)	29.0±19.2	27.7±21.5	0.801
PSA level at CTx start (ng/mL)	126±284	208±353	0.301
Presence of Sx at CTx start	4	15	0.116
ADT during docetaxel			
Orchiectomy	18	-	
LH-RH only	20	-	
Time to PSA progression (mo)	6.0±4.75	4.8±3.2	0.554
Time to imaging progression (mo)	5.0±3.12	5.0±2.79	0.966
Increase in old lesion	8	17	
Development of new lesion	8	12	
Second-line HTx	15	13	
Enzalutamide	13	10	
Abiraterone	2	3	
Time to progression after 2nd ADT (mo)	10.0±4.62	3.4±2.55	0.005

Values are presented as mean±standard deviation or number.

CRPC: castration-resistant prostate cancer, ADT: androgen deprivation therapy, CTx: chemotherapy, Sx: symptoms, LH-RH: luteinizing hormone-releasing hormone, PSA: prostate-specific antigen, HTx: hormone therapy.

clinical stage and Gleason score, extent of metastasis at diagnosis, and biochemical/radiologic response to ADT.

Table 2 shows clinical results of DOC for the 2 groups. DOC

was administered for a median number of 6 cycles in both the DOC+continuous ADT group and DOC only group. The median time to DOC after initiation of primary ADT was

Fig. 1. Prostate-specific antigen (PSA) progression free survival and radiologic progression free survival after docetaxel chemotherapy according to concurrent androgen deprivation therapy. (A) PSA progression free survival. (B) Radiologic progression free survival. DOC: docetaxel chemotherapy, ADT: androgen deprivation therapy.

29.0±19.2 months and 27.7±21.5 months, respectively.

Among the DOC+continuous ADT group (n=28), 18 patients underwent surgical castration (orchiectomy) and 10 patients received LH-RH agonist. Median time to biochemical progression was 6.0±4.75 months versus 4.8±3.2 months (p=0.554), and time to radiologic progression was 5.0±3.12 months versus 5.0±2.79 months (p=0.966) for the DOC+continuous ADT group versus DOC only group. The main reason for discontinuing DOC was radiologic disease progression (57% of DOC+continuous ADT group and 52.2% of DOC only group). Other reasons included patient refusal (n=6) and chemotherapy-related toxicities (n=24).

Kaplan-Meier analysis revealed a significant association between concurrent administration of ADT and prolonged bPFS (log-rank p=0.024) (Fig. 1A). However, Kaplan-Meier analysis did not show a significant association between concurrent administration of ADT and prolonged rPFS (log-rank p=0.387) (Fig. 1B).

DISCUSSION

DOC has been demonstrated to be efficacious and well tolerated in Western patients with advanced CRPC.^{15,16} This therapy was also shown to be efficacious in Korean patients with CRPC, with toxicities within acceptable limits and similar to those observed in Western patients.^{17,18} However, concurrent use of ADT for CRPC patients who receive DOC is a still a topic of debate. The rationale for continuing ADT when starting

chemotherapy for CRPC is that cessation could lead to renewed release of testosterone and stimulation of the remaining androgen-sensitive elements of the tumor.

Regarding international guidelines, the European Association of Urology (EAU) guideline clearly states that, when CRPC develops, ADT should be continued indefinitely.¹⁹ In addition, the American Urological Association²⁰ and the National Comprehensive Cancer Network²¹ also mention the need to maintain ADT when CRPC develops. However, the EAU guidelines are based on the data of a single study in which 85 men with CRPC refractory to orchiectomy received a chemotherapy regimen that is no longer used.²² As a result, some investigators have doubts concerning this policy. Studies have shown that serum testosterone level remained under the castration level upon discontinuation of ADT within a certain period, and that second-line hormonal agents could replace the role of primary ADT even when disease progression was diagnosed after DOC. In fact, approximately 50% of men receiving ADT in the long term remain castrated for 2.5 years after stopping ADT,²³ although it should be noted that stopping ADT can reinduce hormone sensitivity.²⁴ These conflicting viewpoints are difficult to prove as there is a lack of well-designed prospective trials exploring this issue, and retrospective data are conflicting.^{25,26}

In fact, there is no strong evidence that the combination of ADT with chemotherapy is beneficial for CRPC patients. Recently, some pivotal trials of chemotherapy in PCa have stipulated that ADT should be continued when chemotherapy is initiated. To date, 2 studies have compared the clinical out-

comes of DOC according to concurrent ADT use in Korean patients. Lee et al.²⁶ reported that patients treated with concurrent ADT during chemotherapy did not show significant clinical differences in progression-free survival and overall survival compared with patients who received DOC without ADT use. The proposed explanation was that serum testosterone level did not recover to the noncastrated level during the period of chemotherapy despite ADT withdrawal. However, a recent published article drew the opposite conclusion. Jang et al.²⁷ reported that the combined use of ADT with DOC improved radiologic progression-free survival in chemotherapy-naïve patients with CRPC. They suggested that concurrent administration of ADT and DOC is superior to DOC alone and demonstrated that concurrent administration of ADT was the only significant predictor of radiologic progression-free survival using multivariable Cox regression analysis. However, they did not show a significant difference in overall survival according to concurrent use of ADT.

In the present study, our retrospective data analysis showed that biochemical recurrence-free survival was better in CRPC patients who received DOC with concurrent ADT than in those without ADT. Unfortunately, we could not prove a significant difference in radiologic-progression free survival; however, we believe that this is due to the different time interval of laboratory and imaging examinations. When CRPC patients received DOC, we usually performed laboratory examination including PSA every month, whereas radiologic examination was performed every 3 months according to Korean insurance guidelines. Moreover, most of enrolled patients in the early period of study underwent radiologic examination when the PSA level was checked in abruptly high. This could result in statistical bias. Furthermore, this was a retrospective study using patients who were diagnosed and treated more than 10 years ago, and we believe that if we used recently improved radiologic examinations including whole spine MRI, which is more sensitive than bone scan for detection of bone progression, we might detect radiologic progression earlier in patients who had treatment without concurrent ADT than in those with concurrent ADT.

In addition, we should discuss the role of concurrent ADT in second-line hormone therapy for CRPC patients. As all randomized prospective data for abiraterone use in CRPC include the continuation of backbone ADT and O'Donnell et al.²⁸ suggested that abiraterone monotherapy does not sustain testos-

terone suppression in noncastrated men, ADT should be maintained in men with CRPC when they start abiraterone treatment. Also, all phase III trial data of enzalutamide in CRPC include the continuation of backbone ADT. This, combined with the potential adverse effects of gynecomastia with enzalutamide monotherapy, suggests that ADT should be continued when initiating enzalutamide in men with CRPC. Based on these considerations, concurrent ADT should be maintained in CRPC patients treated with hormone therapy.

A recent pivotal trial of chemotherapy, the chemo-hormonal therapy versus Androgen Ablation Randomized Trial for Extensive Disease in PCa trial, recently reported that OS was improved and metastatic load was decreased in hormone-naïve men with metastatic PCa when treatment was initiated with ADT plus chemotherapy versus ADT alone.²⁹ This is the one of the strongest reasons why concurrent ADT should be maintained in CRPC patients.

Our current study had several limitations inherent to a retrospective study including a limited number of patients. First, our data were retrospectively collected at multiple institutes, causing the results to be sensitive to selection bias. Also, concurrent ADT use was performed in mainly one center. Second, many patients were excluded due to incomplete medical records. Third, we could not show overall survival data because only a small proportion of patients died, and these patients were all from the early part of the study period. Almost all of the included patients received DOC recently. This study does not have enough power to detect the potential benefit of ADT. Finally, we could not collect serum testosterone values because it was not measured for all patients. Despite these limitations, concurrent ADT use during DOC did show a benefit in biochemical recurrence-free survival in the present study. It appears that concurrent ADT use is not beneficial in all CRPC patients. As described above, it would be helpful for some patients who would experience reinduced hormone sensitivity upon stopping ADT. New and emerging clinical trials for CRPC offer the prospect of enhanced, multilayered hormonal therapies together with primary and second-line hormonal treatment, even though its effect remains unclear. Personalized/individualized management of PCa will become a reality as more treatment options/combinations that include concurrent ADT during DOC become available and are supported by clinical data.

CONCLUSIONS

Our study showed a statistically significant advantage of ADT in biochemical progression-free survival of patients with CRPC receiving DOC. The recent approval for concurrent administration of ADT for CRPC patients treated with DOC under the present guidelines of the Korean National Health Insurance system will provide an opportunity to prove the efficacy of ADT use by comparison with clinical data collected before its approval.

CONFLICT OF INTEREST

The authors claim no conflicts of interest.

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