Survival outcomes of concurrent treatment with docetaxel and androgen deprivation therapy in metastatic castration-resistant prostate cancer

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by Author

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ABSTRACT

Survival outcomes of concurrent treatment with docetaxel and androgen deprivation therapy in metastatic castration-resistant prostate cancer

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(Directed by Professor Byung Ha Chung)

Introduction: Docetaxel-based chemotherapy (DTX) improves overall survival (OS) of men with metastatic castration-resistant prostate cancer (mCRPC). Considering the potential existence of androgen receptors that remain active at this stage, we aimed to assess the impact of combined use of androgen deprivation therapy (ADT) with DTX for mCRPC.

Materials and Methods: We performed a single-institutional retrospective analysis of patients with mCRPC who received either DTX alone (DTX group, n=21) or concurrent DTX and ADT (DTX+ADT group, n=26) between August 2006 and February 2014. All patients received DTX dosed 75 mg/m2 every three weeks for at least three cycles. In the DTX+ADT group, all patients used luteinizing hormone releasing hormone agonist continuously as a concurrent ADT.

Results: The median follow-up period was 24.0 months (IQR 12.0–37.0) for the entire cohort. The median radiographic progression-free survival (rPFS) was 9.0

months and 6.0 months in the DTX+ADT and DTX groups, respectively (log-rank p=0.036). In multivariable Cox regression analysis, concurrent administration of ADT was the only significant predictor of rPFS (HR=0.525, 95% CI 0.284-0.970, p=0.040). The median OS was 42.0 and 38.0 months in the DTX+ADT and DTX groups, respectively (log-rank p=0.796). On multivariable analysis, Hb level at the time of DTX initiation was associated with OS (HR=0.532, 95% CI 0.381-0.744, p<0.001).

Conclusions: In chemotherapy-naive patients with mCRPC, the combined use of ADT with DTX improved rPFS. Our result suggests that the concurrent administration of ADT and DTX is superior to DTX alone.

Key words : prostatic neoplasms, castration-resistant; neoplasm metastasis; disease-free survival; docetaxel; drug therapy, combination; gonadotropin-releasing hormone

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I. INTRODUCTION

Prostate cancer (PCa) is the second most common cancer and the fifth leading cause of cancer-related deaths in males worldwide.[1] Death from PCa is typically the result of castration-resistant prostate cancer (CRPC), a clinical state in which disease progression occurs despite maintenance of castrate serum testosterone levels.[2,3] According to recent analysis, approximately 84 % of CRPC patients present with metastatic disease at time of diagnosis,[4] and patients with metastatic CRPC (mCRPC) are expected to survive up to 18 to 19 months.[5]

CRPC was once regarded as androgen-insensitive or hormone-refractory; however, it is now widely accepted that androgen receptor (AR) signaling activity is persistent in the prostate in CRPC, and that residual androgens continue to drive AR signaling

activity.[6-10] Various molecular studies have shown that tumor progression in CRPC is related to AR-associated signaling mechanisms.[11] Reported mechanisms include AR overexpression and amplification, AR mutations, and increased AR ligand expression in the surrounding stroma. According to these mechanisms, the increase in AR protein sensitizes prostate cancer cells to respond to low levels of ligand,[12,13] and AR mutations are associated with production of a receptor that is more sensitive to native ligand.[14] In this regard, discontinuation of ADT in patients with CRPC who have not undergone surgical castration could result in tumor growth and proliferation. However, there are drawbacks to maintaining ADT. It has been reported that continuation of ADT is associated with serious health problems – coronary heart disease, myocardial infarction, fracture, anemia, and diabetes – and thus can affect the survival outcomes of patients.[15-18]

In terms of survival advantage, the benefits of concurrent administration of ADT in CRPC patients under cytotoxic chemotherapy are debatable. Retrospective reviews of trials by the Eastern Cooperative Oncology Group (ECOG) and the South West Oncology Group (SWOG) have been performed, and they provided conflicting results with regard to survival.[19,20] Due to the absence of tangible results from related studies, concurrent administration of luteinizing hormone-releasing hormone agonist (LHRHa) for CRPC patients under cytotoxic chemotherapy cannot be reimbursed by the Korean National Health Insurance system under the present guidelines. Considering the potential presence of androgen receptors that remain active at this stage of the disease, we sought to assess the impact of the combined use of ADT with

cytotoxic chemotherapy, especially docetaxel-based chemotherapy (DTX) for mCRPC.

II. MATERIALS AND METHODS

1. Study sample

This retrospective study included data from a total of 199 consecutive patients with mCRPC who received DTX at the Department of Urology, Yonsei University Health System (Seoul, Korea), between August 2006 and February 2014. Collection of retrospective data of the study was approved by the Institutional Ethics Committee after review of the protocol and procedures employed (2009-0131-001). The study was carried out in lieu of a formal ethics committee and followed the principles of the Helsinki Declaration.

Patients with the following criteria were included in the present analysis: (1) histologically confirmed adenocarcinoma of the prostate with clinical or radiologic evidence of metastatic disease and defined as CRPC according to the European Association of Urology guideline 2011,[21] (2) ECOG performance status ≤ 2, (3) computed tomography or magnetic resonance imaging, and radionuclide bone scans performed every three cycles of DTX, (4) serum prostate specific antigen (PSA) levels measured each cycle, and (5) adequate bone marrow and organ function. Patients were excluded if they received cytotoxic chemotherapy or radioisotope therapy before administration of docetaxel, had incomplete follow-up, had administered reduced dose of docetaxel, had serious or uncontrolled concomitant

medical illness, had history of other cancer within the five years, or had evidence of central nervous system metastasis. And patients who received less than three cycles of DTX were excluded because of the possibility of a PSA surge.

Of 199 mCRPC patients who received DTX, 47 patients fulfilled the criteria described above. 152 patients were excluded for the following reasons: prior cytotoxic chemotherapy (n=23), dose reduction of docetaxel (n=82), combination with immunotherapy or other cytotoxic chemotherapy agents (n=25), and received less than three cycles of DTX (n=22). 47 patients were divided into two groups: those who had received DTX with ADT (DTX+ADT group, n=26), and those who received DTX without ADT (DTX group, n=21).

Medical records were reviewed for the following characteristics: patient age, body mass index (BMI), Gleason score, tumor-node-metastasis (TNM) classification of the American Joint Committee on Cancer,[22] neoadjuvant treatments, response to prior antiandrogen therapies, ECOG performance status, baseline hemoglobin (Hb), neutrophil-to-lymphocyte ratio (NLR), albumin, PSA levels, presence of visceral metastases, and extent of the disease.

2. Treatment

All patients received docetaxel plus prednisone therapy with or without ADT. The regimen consisted of docetaxel (75 mg/m^2), which was administered through intravenous infusion once on day one every three weeks, plus oral prednisolone 5 mg twice daily starting on day one and continued throughout the treatment.

DTX continued until uncontrolled toxicity, disease progression, planned

termination of individual patient, death, or refusing treatment of a patient. The National Cancer Institute Common Toxicity Criteria version 4.0 was used to evaluate the toxicity during each cycle.[23]

3. Study end points

The primary endpoints were biochemical progression-free survival (bPFS) and radiographic progression-free survival (rPFS). Secondary endpoint was overall survival (OS). Biochemical progression was defined as a >50% increase from the PSA nadir, with a minimum increase of 5 ng/mL.[24] The PSA nadir was defined as the lowest PSA level achieved during DTX. The time to biochemical progression was assessed between the day of treatment initiation and biochemical progression. The time to radiographic progression was defined as the time interval from the day of DTX initiation to the first occurrence of either progression by imaging studies. Progression from bone scan was assessed according to the Prostate Cancer Working Group (PCWG)-2 criteria,[25] and soft tissue progression was evaluated with reference to Response Evaluation Criteria in Solid Tumors criteria version 1.1.[26] OS was calculated from the date of DTX initiation to that of death from any cause. For all patients, survival and cause of death were investigated based on the National Cancer Registry Database or institutional electronic medical records.

4. Statistical analysis

The descriptive values of the variables are expressed as the median and interquartile range (IQR) according to the results of normality testing. Differences in baseline characteristics were compared between groups using the chi-square test or the Fisher exact test for categorical variables, and the Mann-Whitney U test for

continuous variables.

rPFS, OS, and bPFS were calculated and analyzed using the Kaplan–Meier method and the log-rank test. Univariable and multivariable analyses used Cox proportional hazards models. Factors associated with progression or mortality with a P value of less than 0.20 in the univariable analysis were entered in the multivariable model, and nonsignificant factors were removed by means of a backward-elimination procedure. The hazard ratio (HR) and the 95 % confidence intervals (CI) were estimated for each variable.

All of the tests were two-sided, and $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 18 (SPSS Inc., Chicago, IL, USA).

III. RESULTS

Patient demographics are presented in Table 1. Both groups had comparable age, BMI, pretreatment laboratory values, stage and grade, extent of metastasis, duration of ADT prior to DTX, response of previous ADT, and number of DTX cycles received. As shown in Table 2, there was no difference between the two groups in adverse events. The reasons for discontinuation of treatment are outlined in Table 3.

The median follow-up period was 24.0 months (IQR 12.0–37.0) for the entire cohort, 23.0 months (IQR 13.5–32.5) for the DTX+ADT group, and 24.0 months (IQR 11.5–40.0) for the DTX group. Overall, 22 patients expired at last follow-up, and the reason for patient mortality was PCa-related death in all patients.

The median bPFS was 8.0 months (95% CI 6.854–9.146) in the DTX+ADT group

and 5.0 months (95% CI 4.128–5.872) in the DTX group. Kaplan–Meier analysis revealed a significant association between concurrent administration of ADT and prolonged bPFS (log-rank p=0.044; Fig. 1). In univariable and multivariable Cox regression analyses, the number of DTX cycles was the only significant predictor of bPFS (Table 4).

The median rPFS was 9.0 months (95% CI 4.003–13.997) in the DTX+ADT group and 6.0 months (95% CI 4.206–7.794) in the DTX group. Kaplan–Meier analysis revealed a significant association between concurrent administration of ADT and prolonged rPFS (log-rank p=0.036; Fig. 2). In univariable Cox regression analysis, the number of DTX cycles and concurrent administration of ADT were significantly associated with rPFS, and concurrent administration of ADT was the only significant predictor in multivariable analysis (Table 5).

The median OS was 42.0 months (95% CI 19.677–64.323) and 38.0 months (95% CI 7.752–68.243) in the DTX+ADT and DTX groups, respectively (log-rank p=0.796; Fig. 3). On multivariable analysis, Hb level at the time of DTX initiation was associated with OS (Table 6).

Table 1. Patient demographics

	DTX	DTX+ADT	*p*
Number of patient	21	26	*NS*
Age (years)	69 (67-74)	68 (63-72)	*0.459*
BMI (kg/m^2)	24.0 (22.5-25.4)	24.2 (23.3-26.6)	*0.708*
ECOG PS ≥1	8 (38.1%)	15 (57.7%)	*0.181*
Gleason score at diagnosis			
≤ 8	8 (38.1%)	8 (30.8%)	*0.598*
≥ 9	13 (61.9%)	18 (69.2%)	*0.598*
Clinical T stage at diagnosis			
≤ T3	14 (66.7%)	15 (57.7%)	*0.529*
T4	7 (33.3%)	11 (42.3%)	*0.529*
Clinical N stage at diagnosis			
N1	13 (61.9%)	14 (53.8%)	*0.579*
Prior treatment			
Radical prostatectomy	5 (23.8%)	6 (23.1%)	*1.000*
Definitive EBRT	0 (0.0%)	1 (3.8%)	*1.000*
Palliative EBRT	7 (33.3%)	9 (34.6%)	*0.927*
Duration of ADT prior to DTX	12 (7-32.5)	10.5 (7-31.5)	*0.464*
Response to primary ADT			
PSA nadir (ng/ml)	2.3 (0.4-14.5)	0.7 (0.2-7.8)	*0.380*
PSA velocity (ng/ml/year)	28.9 (6.7-252.1)	33.5 (14.6-158.9)	*0.906*
PSA doubling time (ng/ml/year)	0.16 (0.11-0.42)	0.18 (0.09-0.30)	*0.700*
Laboratory values			
PSA at diagnosis (ng/ml)	68.9 (29.7-449.0)	85.2 (25.4-262.0)	*0.881*
PSA at CRPC diagnosis (ng/ml)	41.5 (26.9-112.0)	42.2 (28.8-173.4)	*0.966*
Hb (g/dL)	11.6 (10.8-12.9)	11.9 (10.9-13.0)	*0.676*
NLR	2.06 (1.39-3.64)	2.28 (1.57-4.13)	*0.341*

Albumin (g/dL)	4.1 (3.8-4.6)	4.2 (3.6-4.4)	*0.772*
Number of DTX cycles	7 (6-11)	9.5 (5-12)	*0.643*
Extent of disease at CRPC diagnosis			
Bone metastasis	18 (85.7%)	25 (96.2%)	*0.311*
Lymph node metastasis	15 (71.4%)	17 (65.4%)	*0.659*
Lung or liver metastasis	1 (4.8%)	1 (3.8%)	*1.000*

Data are median (IQR) and number (%).

DTX, docetaxel-based chemotherapy; ADT, androgen deprivation therapy; IQR, interquartile range; BMI, body mass index; ECOG, eastern cooperative oncology group; PS, performance status; PCa, prostate cancer; EBRT, external-beam radiation therapy; PSA, prostate specific antigen; CRPC, castration-resistant prostate cancer; Hb, hemoglobin; NLR, neutrophil-to-lymphocyte ratio

Table 2. Adverse events during DTX.

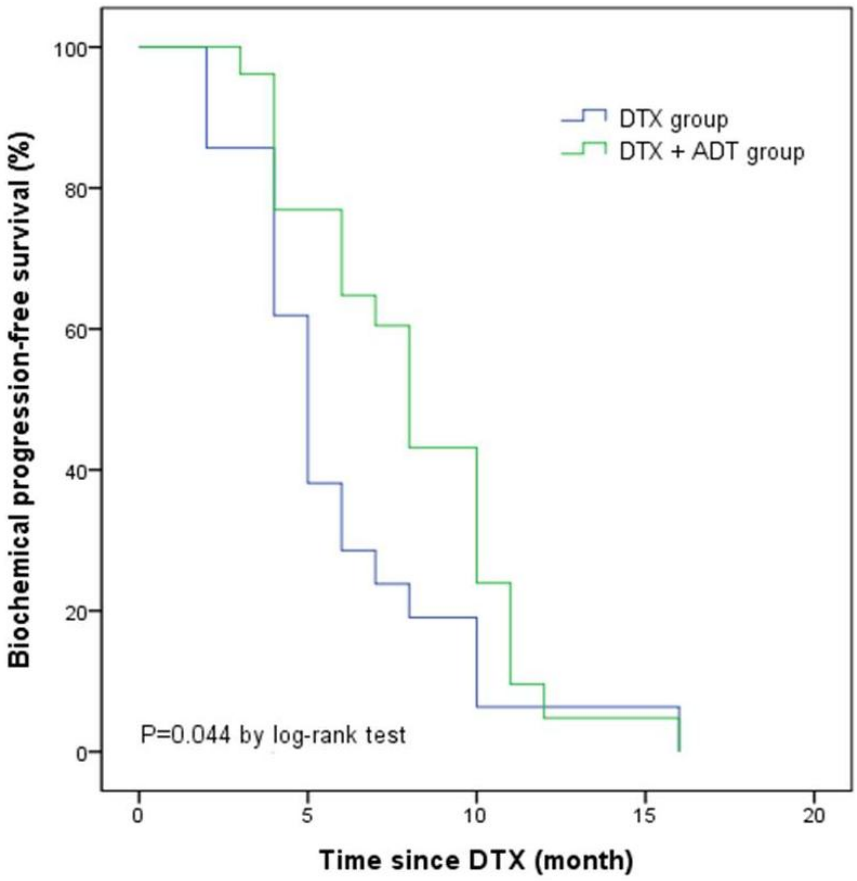
	Overall	DTX	DTX+ADT	*p*
CTCAE Grade ≤ 2				
Thrombocytopenia	1 (2.1%)	1 (4.8%)	0 (0.0%)	0.266
Anemia	8 (17.0%)	3 (14.3%)	5 (19.2%)	0.657
AST/ALT increased	14 (29.8%)	5 (23.8%)	9 (34.6%)	0.426
Nausea & vomiting	29 (61.7%)	15 (71.4%)	14 (53.8%)	0.223
Diarrhea	9 (19.1%)	6 (28.6%)	3 (11.5%)	0.144
Constipation	13 (27.7%)	8 (38.1%)	5 (19.2%)	0.155
Peripheral neuropathy	7 (14.9%)	3 (14.3%)	4 (15.4%)	0.917
Dry mouth	14 (29.8%)	8 (38.1%)	6 (23.1%)	0.268
Dry eye	12 (25.5%)	7 (33.3%)	5 (19.2%)	0.275
Edema limbs	6 (12.8%)	2 (9.5%)	4 (15.4%)	0.554
Myalgia	11 (23.4%)	6 (28.6%)	5 (19.2%)	0.457
CTCAE Grade ≥ 3				
Febrile neutropenia	8 (17.0%)	4 (19.0%)	4 (15.4%)	0.742
Anemia	1 (2.1%)	0 (0.0%)	1 (3.8%)	0.369
Nausea & vomiting	2 (4.3%)	2 (9.5%)	0 (0.0%)	0.112
Peripheral neuropathy	2 (4.3%)	0 (0.0%)	2 (7.7%)	0.199
Fatigue	2 (4.3%)	1 (4.8%)	1 (3.8%)	0.878

CTCAE, common terminology criteria for adverse events; DTX, docetaxel-based chemotherapy; ADT, androgen deprivation therapy; AST, aspartate aminotransferase; ALT, alanine aminotransferase

Table 3. Reasons for discontinuation of DTX.

	Overall	DTX	DTX+ADT	*p*
Treatment toxicity	15 (31.9%)	7 (33.3%)	8 (30.8%)	0.851
Neutropenia	8 (17.0%)	4 (19.0%)	4 (15.4%)	
Anemia	1 (2.1%)	0 (0.0%)	1 (3.8%)	
Nausea & vomiting	2 (4.3%)	2 (9.5%)	0 (0.0%)	
Peripheral neuropathy	2 (4.3%)	0 (0.0%)	2 (7.7%)	
Fatigue	2 (4.3%)	1 (4.8%)	1 (3.8%)	
Disease progression	19 (40.4%)	10 (47.6%)	9 (34.6%)	0.366
Planned	9 (19.1%)	3 (14.3%)	6 (23.1%)	0.711
Death	2 (4.3%)	0 (0.0%)	2 (7.7%)	0.495
Patient refusal	2 (4.3%)	1 (4.8%)	1 (3.8%)	1.000

DTX, docetaxel-based chemotherapy; ADT, androgen deprivation therapy



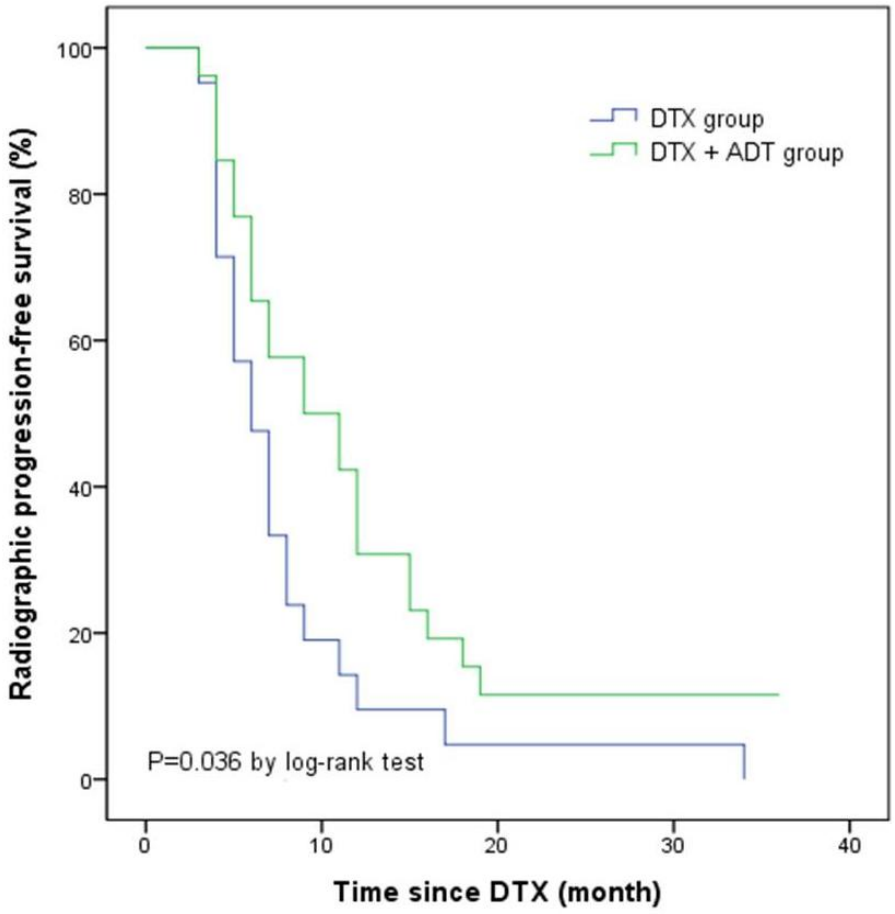
Number at risk					
DTX	21	12	2	1	0
DTX+ADT	26	19	8	1	0

Fig. 1. Kaplan-Meier curve of biochemical progression-free survival.

Table 4. Associated baseline factors of biochemical progression-free survival by univariable and multivariable analysis.

	Univariable analysis			Multivariable analysis		
	HR	**(95% CI)**	***p***	**HR**	**(95% CI)**	***p***
Age	1.009	(0.968-1.052)	0.680			
BMI	0.938	(0.831-1.059)	0.302			
ECOG PS ≥1	1.042	(0.572-1.898)	0.893			
Gleason score						
≤ 8	1.356	(0.697-2.638)	0.370			
≥ 9	0.738	(0.379-1.436)	0.370			
Clinical T stage						
≤ T3	0.907	(0.484-1.699)	0.760			
T4	1.103	(0.589-2.065)	0.760			
Clinical N stage						
N1	0.736	(0.392-1.382)	0.340			
PSA at diagnosis	1.000	(1.000-1.000)	0.647			
PSA at CRPC diagnosis	1.000	(1.000-1.001)	0.307			
Hb	0.904	(0.738-1.107)	0.328			
NLR	1.027	(0.944-1.117)	0.534			
Albumin	1.732	(0.797-3.765)	0.165			
Prior Radical prostatectomy	0.728	(0.355-1.494)	0.387			
Prior Palliative EBRT	1.292	(0.675-2.472)	0.439			
DTX+ADT	0.583	(0.316-1.075)	0.084			
Number of DTX cycles	0.876	(0.796-0.964)	0.007	0.876	(0.796-0.964)	0.007
Extent of disease						
Bone metastasis	0.855	(0.303-2.414)	0.767			
Lymph node metastasis	1.087	(0.563-2.096)	0.804			
Lung or liver metastasis	0.788	(0.188-3.304)	0.745			

HR, hazard ratio; CI, confidence intervals; DTX, docetaxel-based chemotherapy; ADT, androgen deprivation therapy; IQR, interquartile range; BMI, body mass index; ECOG, eastern cooperative oncology group; PS, performance status; PCa, prostate cancer; EBRT, external-beam radiation therapy; PSA, prostate specific antigen; CRPC, castration-resistant prostate cancer; Hb, hemoglobin; NLR, neutrophil-to-lymphocyte ratio



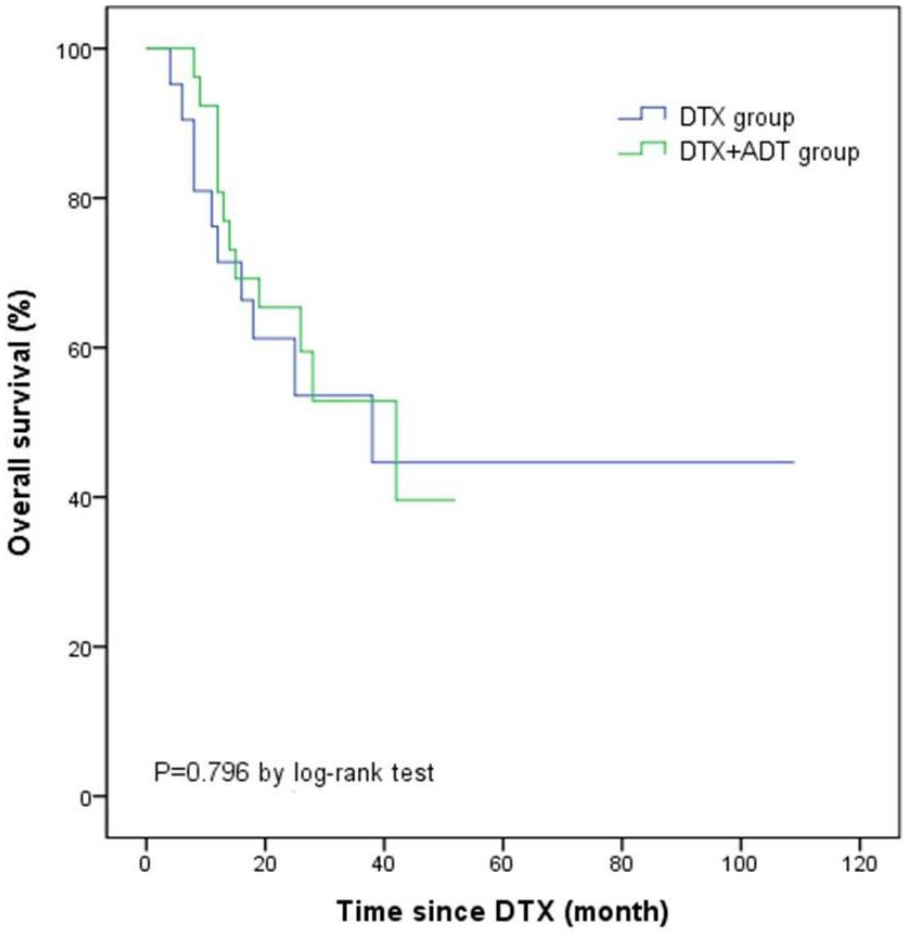
Number at risk				
DTX	21	4	1	0
DTX+ADT	26	13	2	1

Fig. 2. Kaplan-Meier curve of radiographic progression-free survival.

Table 5. Associated baseline factors of radiographic progression-free survival by univariable and multivariable analysis.

	Univariable analysis			Multivariable analysis		
	HR	**(95% CI)**	***p***	**HR**	**(95% CI)**	***p***
Age	1.024	(0.979-1.070)	0.301			
BMI	0.995	(0.879-1.127)	0.938			
ECOG PS ≥1	0.720	(0.394-1.317)	0.287			
Gleason score						
≤ 8	1.363	(0.725-2.559)	0.336			
≥ 9	0.734	(0.391-1.379)	0.336			
Clinical T stage						
≤ T3	1.620	(0.861-3.048)	0.134			
T4	0.617	(0.328-1.161)	0.134			
Clinical N stage						
N1	0.788	(0.435-1.429)	0.433			
PSA at diagnosis	1.000	(1.000-1.000)	0.695			
PSA at CRPC diagnosis	1.001	(1.000-1.001)	0.120			
Hb	0.913	(0.737-1.131)	0.406			
NLR	0.955	(0.879-1.039)	0.283			
Albumin	0.853	(0.403-1.808)	0.679			
Prior Radical prostatectomy	1.189	(0.596-2.372)	0.623			
Prior Palliative EBRT	1.306	(0.696-2.452)	0.406			
DTX+ADT	0.550	(0.300-1.007)	0.053	0.525	(0.284-0.970)	0.040
Number of DTX cycles	0.948	(0.884-1.017)	0.134	0.940	(0.872-1.013)	0.104
Extent of disease						
Bone metastasis	1.136	(0.349-3.700)	0.832			
Lymph node metastasis	1.349	(0.708-2.572)	0.363			
Lung or liver metastasis	1.385	(0.331-5.796)	0.656			

HR, hazard ratio; CI, confidence intervals; DTX, docetaxel-based chemotherapy; ADT, androgen deprivation therapy; IQR, interquartile range; BMI, body mass index; ECOG, eastern cooperative oncology group; PS, performance status; PCa, prostate cancer; EBRT, external-beam radiation therapy; PSA, prostate specific antigen; CRPC, castration-resistant prostate cancer; Hb, hemoglobin; NLR, neutrophil-to-lymphocyte ratio



Number at risk						
DTX	21	12	5	3	3	1
DTX+ADT	26	17	5	0	0	0

Fig. 3. Kaplan-Meier curve of overall survival.

Table 6. Associated baseline factors of overall survival by univariable and multivariable analysis.

	Univariable analysis			Multivariable analysis		
	HR	**(95% CI)**	***p***	**HR**	**(95% CI)**	***p***
Age	1.036	(0.969-1.109)	0.301			
BMI	0.950	(0.806-1.120)	0.543			
ECOG PS ≥1	1.121	(0.485-2.592)	0.789			
Gleason score						
≤ 8	0.772	(0.301-1.980)	0.590			
≥ 9	1.295	(0.505-3.322)	0.590			
Clinical T stage						
≤ T3	0.910	(0.391-2.118)	0.826			
T4	1.099	(0.472-2.558)	0.826			
Clinical N stage						
N1	1.302	(0.545-3.113)	0.552			
PSA at diagnosis	0.999	(0.997-1.000)	0.130	0.999	(0.997-1.000)	0.138
PSA at CRPC diagnosis	1.001	(1.000-1.003)	0.012			
Hb	0.610	(0.453-0.822)	0.001	0.532	(0.381-0.744)	< 0.001
NLR	1.039	(0.938-1.151)	0.465			
Albumin	0.391	(0.144-1.056)	0.064			
Prior Radical prostatectomy	0.656	(0.222-1.945)	0.447			
Prior Palliative EBRT	1.842	(0.779-4.355)	0.164			
DTX+ADT	1.116	(0.481-2.591)	0.798			
Number of DTX cycles	1.012	(0.938-1.092)	0.759			
Extent of disease						
Bone metastasis	0.487	(0.143-1.656)	0.249			
Lymph node metastasis	1.946	(0.716-5.281)	0.192			
Lung or liver metastasis	1.175	(0.156-8.878)	0.876			

HR, hazard ratio; CI, confidence intervals; DTX, docetaxel-based chemotherapy; ADT, androgen deprivation therapy; IQR, interquartile range; BMI, body mass index; ECOG, eastern cooperative oncology group; PS, performance status; PCa, prostate cancer; EBRT, external-beam radiation therapy; PSA, prostate specific antigen; CRPC, castration-resistant prostate cancer; Hb, hemoglobin; NLR, neutrophil-to-lymphocyte ratio

IV. DISCUSSION

DTX has been one of the standard chemotherapy treatments for CRPC since 2004, the SWOG 99-16 study and the Taxanes (TAX) 327 study demonstrated the superiority of DTX over mitoxantrone.[27,28] The patients enrolled in both the SWOG 99-16 and TAX 327 trials continued on ADT because of the possible detrimental effects of its discontinuation. AR activation and enzymatic androgen synthesis are potential mechanisms of CRPC, and these mechanisms can increase the sensitivity of neoplastic cells to very low concentration of testosterone.[6-14] A study related to abiraterone acetate revealed that reducing serum testosterone to undetectable levels was correlated with extended survival for patients with mCRPC.[29] Organizations such as the American Society of Clinical Oncology, the National Comprehensive Cancer Network, and others also recommend that ADT should be continued in nonorchiectomized CRPC patients during clinical trials for the same reason.

There have been several studies on the effectiveness of continued ADT in CRPC patients under cytotoxic chemotherapy, but the results have been inconsistent. Taylor et al. examined data from 341 patients enrolled in ECOG trials, patients who maintained castrate levels of testosterone had a longer median survival of two months.[19] On the other hand, Hussain et al. analyzed data from 205 patients with CRPC enrolled in SWOG phase II chemotherapy trials, and there was no difference in median survival between patients who maintained castrate levels of testosterone and those who did not.[20] Recently, a retrospective study was published on patients with CRPC who were treated with DTX, and clinical outcomes were not significantly

different between patients who received concurrent ADT and those who did not.[30]

In our study, the rPFS and bPFS rates were significantly better in the DTX+ADT group than the DTX group; however, did not show efficacy for OS. OS has been considered the most important endpoint for evaluation of new treatments in oncology.[31] Death is clinically important, objective, and easily defined. However, OS is associated with some drawbacks, which can in turn lead to inappropriate conclusions. First, it requires long-term follow-up and a large number of patients to detect realistic OS. It may not be appropriate to evaluate the superiority of treatment in small-scale retrospective studies. Second, potential differences in OS between the experimental and the control groups could be masked by the use of second-line therapy after tumor progression on first-line therapy. In our study, except expired patients, various type of secondary line chemotherapies were administrated to the disease progressed patients. Third, OS can be influenced by survival postprogression. According to a study of Broglio et al., lack of statistical significance in OS does not imply lack of improvement in OS for clinical trials with a PFS benefit, especially for diseases with long median survival postprogression.[32] If there is long survival after disease progression, with the opportunity for multiple additional treatments, which can dilute treatment effect. They suggested longer periods of survival postprogression, such as longer than 12 months, make statistical significance in OS decreasingly likely. The median survival postprogressions were 13.0 and 18.0 months (radiographic and biochemical, respectively) in our study, and these long periods have potential to affect OS. Therefore, it is not appropriate to evaluate the efficacy of continuing ADT solely

by OS in our study.

As described above, use of OS as the primary endpoint is often limited, and it may be helpful to use an appropriate surrogate endpoint in that case. PFS is an attractive endpoint as a surrogate of survival. PFS can use in studies with small sample sizes, because the definition of PFS produces a higher number of events than that of OS. And progression of disease occurs before survival can be measured, so PFS is not confounded by the effect of intrim treatments. Because of its advantages, the European Agency for the Evaluation of Medical Products accepts a prolongation in time to progression as a primary requirement for new drug registration in the European Union.[33] Particularly in recent years, radiographic progression defined using the PCWG-2 criteria has emerged as a feasible surrogate endpoint of OS. Sonpavde et al. showed that rPFS was significantly associated with OS in patients with mCRPC who received first-line docetaxel-based chemotherapy or post-docetaxel therapy.[34] Kendall's τ was 0.50 ($p < 0.001$) in the setting of docetaxel-based therapy and 0.34 ($P < 0.001$) in the post-docetaxel setting for association between rPFS and OS. Unlike radiographic progression, PSA response has not demonstrated robust results as a surrogate endpoint of OS in studies of the survival outcomes of mCRPC after chemotherapy. PSA cannot differentiate variability in tumor response across different disease sites.[35] Besides, PSA surge or flare-up phenomena, which lead to transient PSA elevation following chemotherapy, are not uncommon in patients with CRPC who respond to chemotherapy.[36-38] It is reported that these phenomena occur between one and eight weeks following a drop in the level of serum PSA.[39] For this

reason, we only included patients who continued for at least three cycles of DTX in this study.

The PCWG2 recommends that early rising PSA levels not be used as the sole criterion for discontinuing treatment on the basis of the description above.[24] The Advanced Prostate Cancer Consensus Conference, held in 2015, there was consensus (82% of the panel) that at least two of three criteria (PSA progression, radiographic progression and clinical deterioration) should be fulfilled to stop treatment of patients with advanced PCa.[40] In this study, there was no patient that stopped DTX for PSA progression alone, and there was no significant difference in the respective reasons for discontinuing DTX between the two groups (Table 2). There was also no patient who stopped DTX due to adverse effects of continuing ADT, such as coronary heart disease, myocardial infarction, a bone fracture, or diabetes, in the DTX+ADT group.

The present study was primarily designed to assess the impact of concurrent administration of ADT and DTX in patients with mCRPC using rPFS as a primary endpoint. None of the patients in this study had received cytotoxic chemotherapy before DTX, so it is considered that our study can provide more accurate result. However, there are some limitations to this study: 1) our data were retrospectively collected at a single center, therefore the results are sensitive to selection bias; 2) serum testosterone measurements were not performed for all patients, and the limited number of sample precludes a meaningful analysis; and 3) this study includes a small sample size due to the relative rarity of chemotherapy-naive patients without dose reduction of docetaxel. The limited sample size may preclude a strong conclusion.

V. CONCLUSION

In this study involving men with mCRPC, the combined use of ADT with DTX improved rPFS and bPFS. Mentioned previously, there are some limitations on using OS to evaluate the efficacy of treatment in our study, and rPFS could be a clinically meaningful surrogate of survival for several reasons. Therefore, the results of our study suggest that the combined use of ADT with DTX is superior to DTX alone.

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ABSTRACT(IN KOREAN)

Docetaxel 치료를 받는 전이 거세저항성 전립선암 환자에서 남성호르몬 박탈치료 유지의 효과

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I. 서론

Docetaxel 기반 항암화학요법 (docetaxel-based chemotherapy, DTX)이 전이 거세저항성 전립선암 (metastatic castration-resistant prostate cancer, mCRPC) 환자의 생존기간을 연장시킨다는 결과가 보고된 바 있다. 거세저항성 전립선암 상태에서도 남성 호르몬 수용체의 반응이 유지된다는 연구 결과들을 고려하여, 이 연구에서는 DTX를 받는 mCRPC 환자들을 대상으로 남성 호르몬 차단 치료 (androgen deprivation therapy, ADT)를 유지할 경우 효과에 대해서 알아보고자 한다.

II. 재료 및 방법

2006년 8월부터 2014년 2월까지 단일 기관에서 DTX를 받은 mCRPC 환자를 ADT 병용유무에 따라서 DTX 군 (n = 21)과 DTX + ADT 군 (n = 26)으로 나누어 후향적으로 분석하였다. 분석에 포함된 모든 환자들은 DTX를 매 3주마다 3 회 이상 받았으며, 매 회 마다 75 mg/m^2 용량의 docetaxel을 정맥 투여 받았다. DTX + ADT 군에서는 지속적 ADT 로서 황체 형성 호르몬 분비 호르몬 작용제(luteinizing hormone- releasing hormone agonist)가 사용되었다.

III. 결과

전체 코호트의 추적 관찰 기간에 대한 중위값은 24.0 개월 (IQR 12.0-37.0) 이었다. 방사선학적 무진행 생존 (radiographic progression-free survival, rPFS) 의 중위값은 DTX + ADT 군에서 9.0 개월, DTX 군에서 6.0 개월이었다 (log-rank p = 0.036). 콕스 다변량 생존 분석을 통해 ADT의 병용투여 유무가 rPFS와 유의하게 연관된 예후인자임을 확인할 수 있었다 (HR = 0.525, 95% CI 0.284 – 0.970, p = 0.040). 전체 생존 (overall survival, OS) 의 중위값은 DTX + ADT 군에서 42.0 개월, DTX 군에서 38.0 개월이었다 (log-rank p = 0.796). 콕스 다변량 생존 분석을 통해 DTX 시작 시점의 혈색소 (hemoglobin) 수치가 OS와 유의하게 연관된 예후인자임을 확인할 수

있었다 (HR = 0.532, 95% CI 0.381 – 0.744, p < 0.001).

IV. 결론

이전에 항암화학요법을 받은 적이 없는 mCRPC 환자에서 DTX와 ADT의 병용요법은 향상된 rPFS을 보여주었으며, 본 연구의 결과들은 DTX와 ADT의 병용요법이 DTX 단독 요법에 비해 생존 측면에서 우수함을 시사한다.

핵심 되는 말 : 거세저항성 전립선암; 방사선학적 무진행 생존; 황체형성호르몬 분비호르몬 유사체; 남성 호르몬 차단 치료

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