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Docetaxel in Combination with Androgen Deprivation Therapy for Metastatic Hormone-Sensitive Prostate Cancer - A Single-Center Retrospective Study in Japan

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Abstract

We characterized the effects of docetaxel (DTX) therapy for patients with metastatic hormone-sensitive prostate cancer (mHSPC) at our institution. We retrospectively analyzed 348 patients with newly diagnosed metastatic prostate cancer treated with androgen deprivation therapy (ADT) between 2006 and 2018. In total, 313 patients were treated with ADT alone (control group). The remaining 35 patients received ADT plus five DTX (60 mg/m2) cycles every 4 weeks without steroids (DTX group). This group had significantly better prostate-specific antigen-progression-free survival (PSA-PFS) and overall survival (OS) rates than the control group (Hazard ratio (HR) = 0.398, 95% confidence interval (CI) = 0.258–0.613, p < 00001, HR = 0.442, 95% CI = 0.256–0.761, p = 0.0032, respectively), although treatments were not randomized. In multivariate Cox proportional hazard analyses, the DTX group was still significantly associated with longer PSA-PFS and OS rates (HR = 0.402, 95% CI = 0.258–0.625, p < 0.0001, and HR = 0.526, 95% CI = 0.302–0.916, p = 0.0233, respectively). Thus, DTX therapy is an effective treatment for mHSPC patients in Japan, like other countries.

Keywords: Prostate Cancer; Docetaxel Therapy; mHSPC; Japan

Introduction

Since the 1940s, androgen deprivation therapy (ADT) has been the standard care for patients with metastatic hormone-sensitive prostate cancer (mHSPC) [1]. However, in the modern era, many life-extending therapies have been developed in combination with ADT [2], e.g., docetaxel (DTX), abiraterone acetate, enzalutamide, and apalutamide [3-7].

Of these, DTX was the first to improve the overall survival (OS) of men with mHSPC [8]. Three pivotal randomized phase III trials (GETUG15, CHAARTED, and STAMPEDE) demonstrated progression-free survival (PFS) benefits with DTX [8-12]. While the GETUG15 study demonstrated no major OS benefit, the other two studies did.

Given these results, DTX chemotherapy combined with ADT for mHSPC is now indicated in European and American guidelines [13]. However, Japanese guideline 2016 edition simply state, "In large-scale clinical trials overseas, it was reported that the prognosis was improved by using DTX chemotherapy in combination with first-line hormone therapy for metastatic prostate cancer [14]."

Recently, benefit of docetaxel chemotherapy for mHSPC began to be reported also in Japan [15,16]. To clarify the effect of docetaxel chemotherapy for Japanese patients, we conducted this retrospective study examined cases during the period when androgen-receptor-axis-targeted agents (ARAT), i.e., abiraterone, enzalutamide, or apalutamide, were not used in our institution.

Material and Methods

Patients

We retrospectively analyzed clinicopathological and prognostic data from 348 patients with newly diagnosed metastatic prostate cancer treated with ADT at our institution between 2006 and 2018.

The study was approved by the institutional internal review board of Niigata Cancer Center Hospital (Niigata, Japan). The indication of DTX chemotherapy was determined by attending physicians, and treatment was performed for patients who provided written informed consent. All procedures conformed to the provisions of the Declaration of Helsinki.

Of the 348 patients, 35 received DTX chemotherapy in combination with ADT as a first-line therapy (DTX group) and the remaining 313 (control group) received ADT alone.

All patients were pathologically diagnosed using ultrasound-guided prostate biopsy or transurethral re-section. The disease stage was determined using digital rectal examination (DRE), abdominal pelvic computed tomography (CT), bone scans, and thoracic CT or chest roentgenography in accordance with the 8th edition tumor-node-metastasis classification of the Union for International Cancer Control and the American Joint Committee on Cancer [17].

Patients were also separated into a low metastatic burden (extra regional lymph node metastasis or < four bone metastases without visceral metastasis) group and a high metastatic burden (≥four bone metastases or visceral metastasis) group following the definition in the CHAARTED Trial [10].

Treatments

DTX group received five DTX (60 mg/m2) cycles every 4 weeks in combination with ADT. We did not use prednisone in DTX group, since we have concerns about the sequelae of chronic steroid use, such as glucose intolerance, osteopenia, fluid retention and peptic ulcers, among other risks. The control group received ADT alone. ADT included an LH-RH agonist (Leuprorelin or Goserelin) or surgical castration plus anti-androgen therapy (Bicalutamide 80mg per day).

No patients received ARAT as a first-line treatment during the study.

Adverse events were graded using the Common Terminology Criteria on Adverse Events version 5.0 of the National Cancer Institute [18].

Statistical analyses

Categorical variable data were compared between groups using the Fisher's exact test. Unpaired parameters were compared between groups using the Mann-Whitney U-test.

We defined OS and prostate-specific antigen-progression-free survival (PSA-PFS) as the period from treatment commencement to all-cause death, and PSA progression or death, respectively. PSA progression was defined as the earliest date where increased PSA ≥25% and ≥2 ng/mL values were observed.

Survival curves were generated using the Kaplan-Meier method and Log-rank tests were used for intertreatment comparisons. A Cox proportional hazards model was used for univariate and multivariate analyses to identify mortality risk factors. For multivariate analyses, we selected variables with p-value < 0.05 in univariate analyses. All tests were two-sided, and $p < 0.05$ was considered statistically significant. All statistical analyses were conducted using the Statview 5.0 software program (Abacus Concepts, Berkley, CA, USA).

Results

Baseline patient characteristics are shown (Table 1). The age at diagnosis was significantly lower in the DTX group than the control group ($p < 0.0001$).

Table 1: Baseline patient characteristics

	DTX group	Control group	P-value
Number of patients	35	313	
Months of follow-up, mean (range)	82.1 (8–152)	55.1 (1–180)	
Age, mean (range)	66.0 (46–77)	74.5 (47–101)	P < 0.0001
PS			
0	33	230	P = 0.0059
1 or greater	2	83	
PSA ng/ml, mean (range)	480.6 (3.21–3 416)	878.1 (1.24–19362)	P = 0.2240
Gleason score			
≤8	8	70	P = 0.9471
≥9	27	243	
cT			
≤T3a	19	149	P = 0.5674
≥T3b	16	164	
cN			
N0	12	119	P = 0.6655
N1	23	194	
cM			
M1a	4	50	P = 0.6464
M1b	25	223	
M1c	6	40	
Metastatic burden			
Low	14	135	P = 0.8611
High	21	178	

PS, Eastern Cooperative Oncology Group Performance Status; cT, clinical T-stage; cN, clinical N-stage; cM, clinical M-stage; PSA, prostate-specific antigen; DTX, docetaxel

Moreover, significantly more patients in the control group had an Eastern Cooperative Oncology Group performance status (PS) ≥1.

In total, 298 patients (85.6%) displayed PSA progression during primary treatment and the median PSA-PFS was 15 months. This period was significantly longer in the DTX group than the control group (Hazard Ratio (HR) = 0.398, 95% Confidence Interval (CI) = 0.258–0.613, p < 0.0001) (Figure 1).

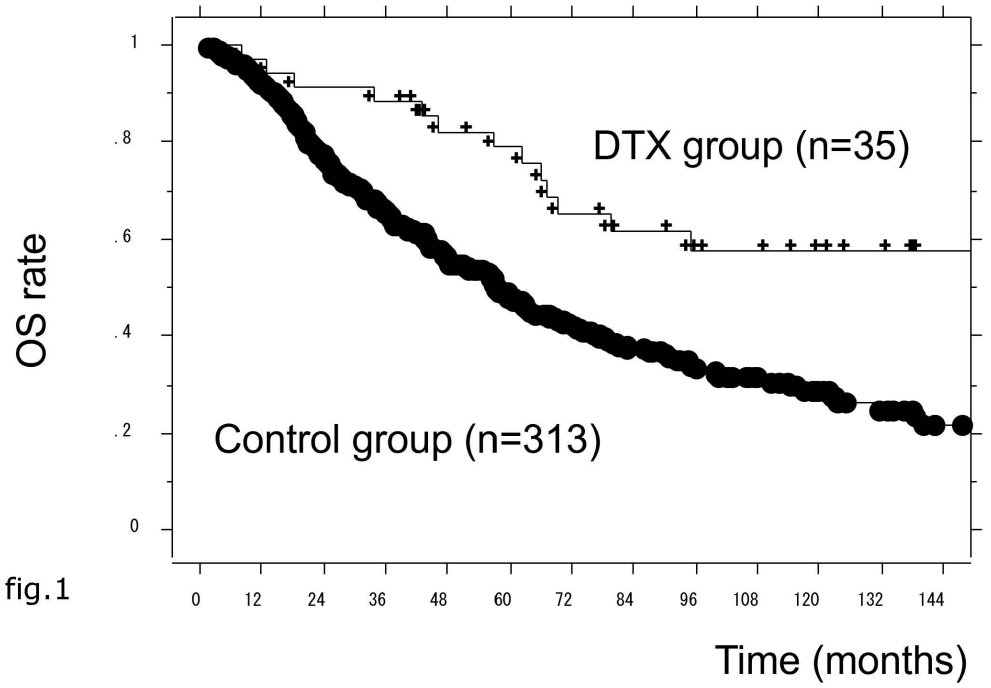

Figure 1: The prostate-specific antigen progression-free survival (PSA-PFS) in docetaxel (DTX) and control patient groups

In univariate Cox proportional hazard analyses, age <75 years, PS = 0, PSA <200 ng/mL, low metastatic burden, Gleason score (GS) <9, and DTX therapy were significantly associated with longer PSA-PFS periods. Moreover, in multivariate analyses, DTX therapy remained significantly associated with longer PSA-PFS periods (HR = 0.402, 95% CI = 0.25–0.625, p < 0.0001) (Table 2).

Table 2: Univariate and multivariate association analyses between different parameters and prostate-specific antigen-progression-free survival

	Univariate analysis			**Multivariate analysis**		
	Odds	*95% CI*	*P-value*	*Odds*	*95% CI*	*P-value*
Age (<75/≥75)	0.795	0.633–0.998	0.0481	0.918	0.726–1.161	0.4763
PS (0/≥1)	0.719	0.551–0.937	0.0147	0.869	0.661–1.141	0.3124
PSA (<200/≥200)	0.655	0.520–0.824	0.0003	0.793	0.623–1.011	0.0607
cT (≤T3a/≥T3b)	0.804	0.639–1.013	0.0639			
cN (N0/N1)	0.875	0.691–1.108	0.2668			
Met. burden (low/high)	0.569	0.450–0.718	<0.0001	0.570	0.448–0.726	<0.0001
GS (≤8/≥9)	0.762	0.578–1.006	0.0549			
DTX (y/n)	0.398	0.258–0.613	<0.0001	0.402	0.258–0.625	<0.0001

PS, Eastern Cooperative Oncology Group Performance Status; PSA, prostate-specific antigen; cT, clinical T-stage; cN, clinical N-stage; Met, Metastatic; GS, Gleason score; DTX, docetaxel

The median OS of all patients was 62 months, but this was significantly longer in the DTX group than the control group (HR = 0.442, 95% CI = 0.256–0.761, p = 0.0032) (Figure 2).

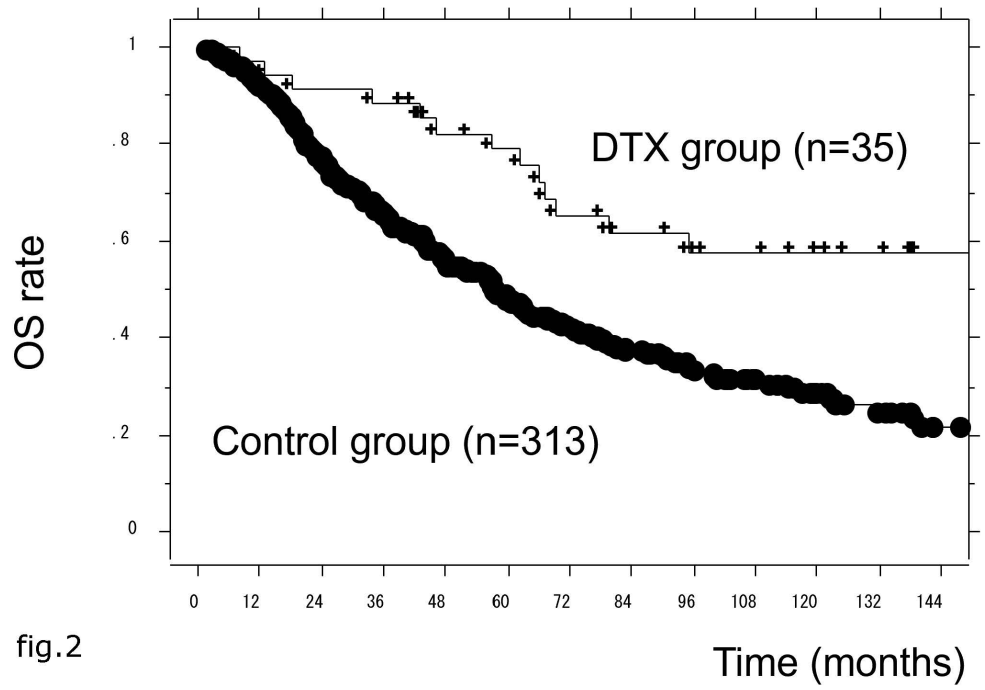

fig.2

Figure 2: The overall survival (OS) rate in docetaxel (DTX) and control patient groups

In univariate Cox proportional hazard analyses, age <75 years, PS = 0, low metastatic burden, GS <9, and DTX therapy were significantly associated with longer OS. In multivariate analysis, DTX therapy remained significantly associated with longer OS (HR = 0.526, 95% CI = 0.302–0.916, p = 0.0233) (Table 3).

Table 3: Univariate and multivariate association analyses between different parameters and overall survival

	Univariate analysis			**Multivariate analysis**		
	Odds	*95% CI*	*P-value*	*Odds*	*95% CI*	*P-value*
Age (<75/≥75)	0.513	0.388–0.676	<0.0001	0.556	0.417–0.741	<0.0001
PS (0/≥1)	0.541	0.400–0.731	<0.0001	0.688	0.503–0.940	0.0188
PSA (< 200/≥200)	0.839	0.638–1.104	0.2102			
cT (≤T3a/≥T3b)	0.838	0.636–1.105	0.2097			
cN (N0/N1)	0.839	0.630–1.117	0.2289			
Met. burden (low/high)	0.711	0.538–0.941	0.0170	0.698	0.526–0.927	0.0128
GS (≤8/≥9)	0.679	0.482–0.955	0.0260	0.660	0.468–0.930	0.0174
DTX (y/n)	0.442	0.256–0.761	0.0032	0.526	0.302–0.916	0.0233

PS, Eastern Cooperative Oncology Group Performance Status; PSA, prostate-specific antigen; cT, clinical T-stage; cN, clinical N-stage; Met, Metastatic; GS, Gleason score; DTX, docetaxel

Moreover, in subgroup analyses, PSA-PFS and OS were analyzed in high and low metastatic burden cohorts, respectively. PSA-PFS was significantly longer in the DTX group than the control group, as observed in both the high and low metastatic burden cohorts (Figures 3a and 3b).

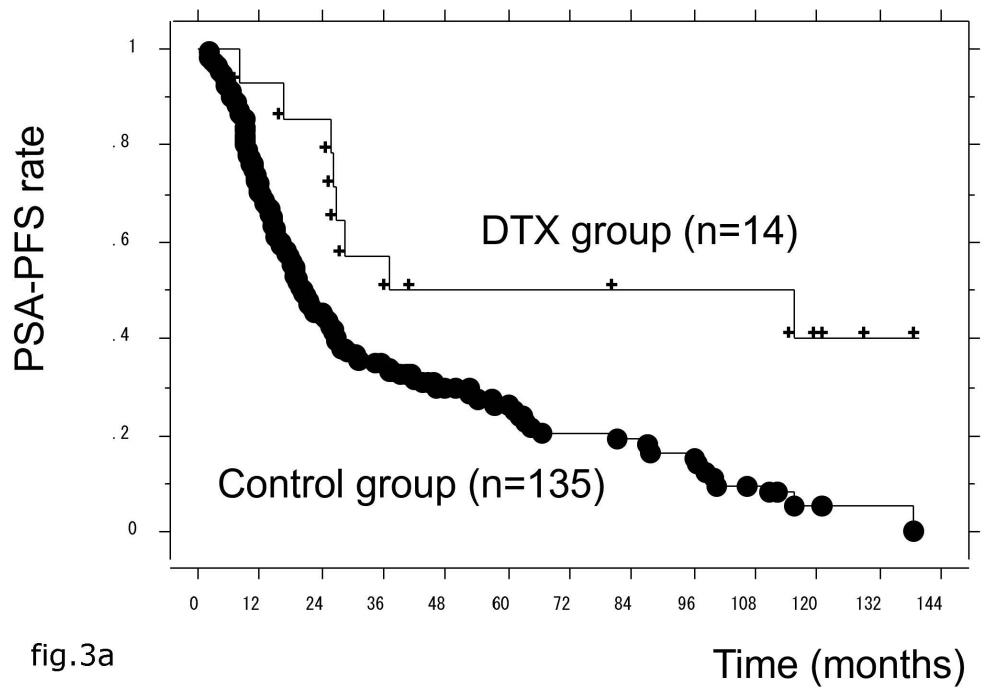

fig.3a

Figure 3a: The prostate-specific antigen progression-free survival (PSA-PFS) rate in docetaxel (DTX) and control patient groups in the low metastatic burden cohort

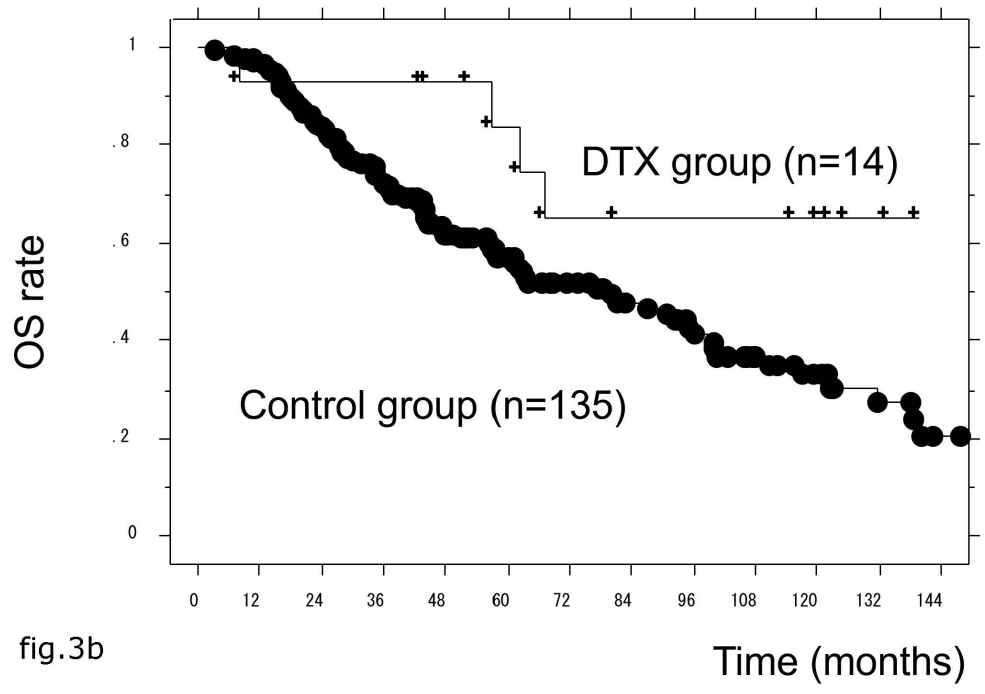

fig.3b

Figure 3b: The overall survival (OS) rate in docetaxel (DTX) and control patient groups in the low metastatic burden cohort

In multivariate analysis, DTX therapy remained significantly associated with longer PSA-PFS periods (Tables 4a and 4b).

Table 4a: Univariate and multivariate association analyses between different parameters and prostate-specific antigen progression-free survival in the low metastatic burden cohort

	Univariate analysis			**Multivariate analysis**		
	Odds	*95% CI*	*P-value*	*Odds*	*95% CI*	*P-value*
Age (<75/≥75)	0.837	0.584–1.200	0.3326			
PS (0/≥1)	0.710	0.455–1.109	0.1321			
PSA (<200/≥200)	0.907	0.626–1.316	0.6077			
cT (≤T3a/≥T3b)	0.647	0.447–0.938	0.0216	0.775	0.528–1.137	0.1922
cN (N0/N1)	0.803	0.546–1.180	0.2637			
GS (≤8/≥9)	0.631	0.404–0.986	0.0432	0.670	0.421–1.066	0.0910
DTX (y/n)	0.346	0.166–0.723	0.0048	0.366	0.173–0.776	0.0087

PS, Eastern Cooperative Oncology Group Performance Status; PSA, prostate-specific antigen; cT, clinical T-stage; cN, clinical N-stage; GS, Gleason score; DTX, docetaxel.

Table 4b: Univariate and multivariate association analyses between different parameters and prostate-specific antigen progression-free survival in the high metastatic burden cohort

	Univariate analysis			**Multivariate analysis**		
	Odds	*95% CI*	*P-value*	*Odds*	*95% CI*	*P-value*
Age (<75/≥75)	0.755	0.561–1.015	0.0630			
PS (0/≥1)	0.792	0.569–1.103	0.1680			
PSA (<200/≥200)	0.642	0.468–0.880	0.0059	0.702	0.511–0.964	0.0289
cT (≤T3a/≥T3b)	0.989	0.736–1.329	0.9406			
cN (N0/N1)	0.850	0.629–1.147	0.2873			
GS (≤8/ 9)	0.871	0.612–1.239	0.4412			
DTX (y/n)	0.396	0.232–0.677	0.0007	0.429	0.250–0.736	0.0021

PS, Eastern Cooperative Oncology Group Performance Status; PSA, prostate-specific antigen; cT, clinical T-stage; cN, clinical N-stage; GS, Gleason score; DTX, docetaxel

However, OS was significantly longer in the DTX group than the control group, as observed only in the high metastatic burden cohort (Figures 4a and 4b).

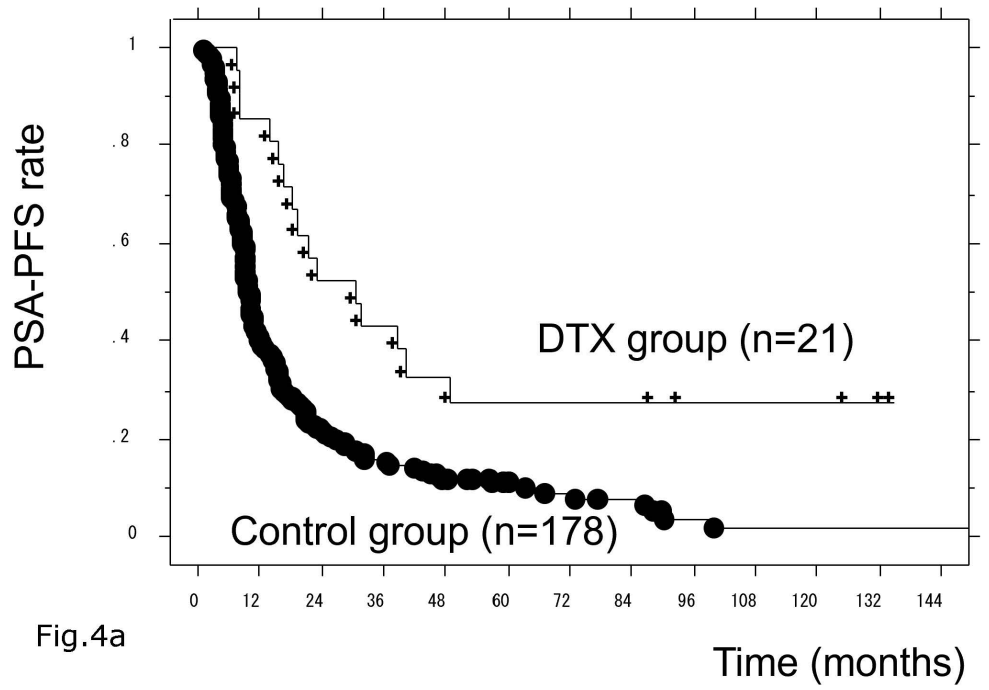

Figure 4a: The prostate-specific antigen progression-free survival (PSA-PFS) rate in docetaxel (DTX) and control patient groups in the high metastatic burden cohort

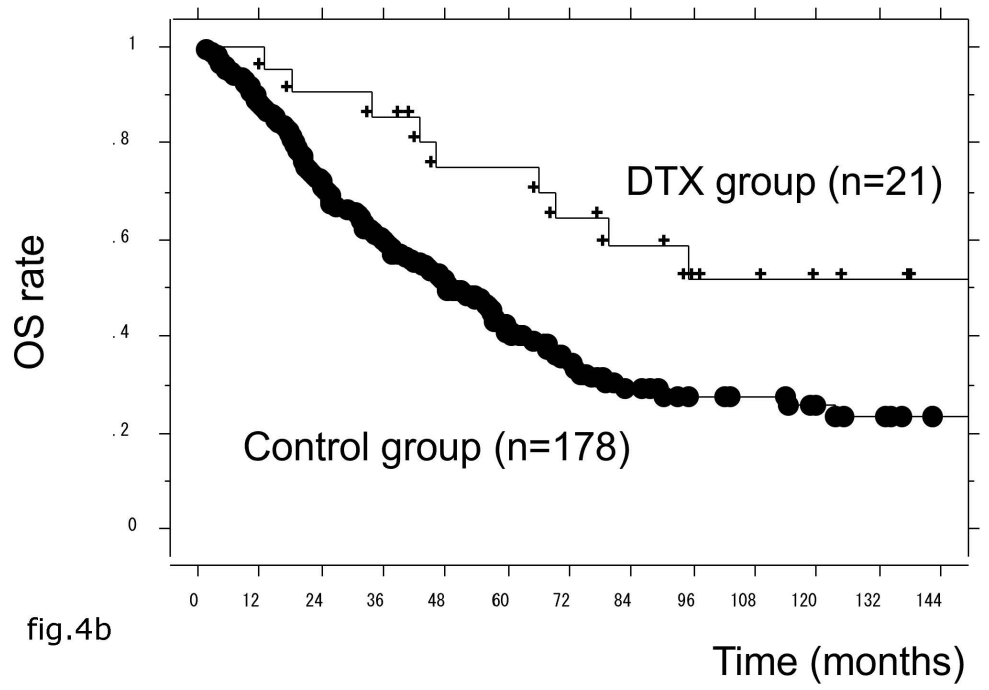

Figure 4b: The overall survival (OS) rate in docetaxel (DTX) and control patient groups in the high metastatic burden cohort

Moreover, in multivariate analysis, DTX therapy was not significantly associated with longer OS times, even in the high metastatic burden cohort (Tables 5a and 5b).

Table 5a: Univariate and multivariate association analyses between different parameters and overall survival in the low metastatic burden cohort

	Univariate analysis			Multivariate analysis		
	Odds	*95% CI*	*P-value*	*Odds*	*95% CI*	*P-value*
Age (<75/≥75)	0.427	0.272–0.670	0.0002	0.492	0.302–0.770	0.0022
PS (0/≥1)	0.434	0.263–0.715	0.0011	0.546	0.325–0.918	0.0224
PSA (<200/≥200)	0.953	0.604–1.502	0.8346			
cT (≤T3a/≥T3b)	0.378	0.436–1.056	0.0856			
cN (N0/N1)	0.786	0.488–1.266	0.3224			
GS (≤8/≥9)	0.618	0.355–1.075	0.0886			
DTX (y/n)	0.367	0.134–1.004	0.0509			

PS, Eastern Cooperative Oncology Group Performance Status; PSA, prostate-specific antigen; cT, clinical T-stage; cN, clinical N-stage; GS, Gleason score; DTX, docetaxel

Table 5b: Univariate and multivariate association analyses between different parameters and overall survival in the high metastatic burden cohort

	Univariate analysis			Multivariate analysis		
	Odds	*95% CI*	*P-value*	*Odds*	*95% CI*	*P-value*
Age (<75/≥75)	0.572	0.402–0.813	0.0019	0.613	0.428–0.877	0.0074
PS (0/≥1)	0.637	0.435–0.931	0.0200	0.740	0.502–1.091	0.1285
PSA (<200/≥200)	0.882	0.608–1.281	0.5105			
cT (≤T3a/≥T3b)	1.016	0.713-1.448	0.9308			
cN (N0/N1)	0.829	0.577–1.192	0.3115			
GS (≤8/≥9)	0.713	0.462–1.100	0.1258			
DTX (y/n)	0.462	0.241–0.884	0.0198	0.523	0.270–1.012	0.0542

PS, Eastern Cooperative Oncology Group Performance Status; PSA, prostate-specific antigen; cT, clinical T-stage; cN, clinical N-stage; GS, Gleason score; DTX, docetaxel

In the DTX group, the most common toxicity issue was neutropenia; grade 3 or 4 was observed in 16 patients and febrile neutropenia in one, but no grade 5 toxicity was observed. Adverse effects requiring discontinuation of docetaxel were observed in two patients. One discontinued after only one course of docetaxel due to bloody stools, and another patient after two courses due to arthritis.

Discussion

DTX is a first-line chemotherapy agent for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC), and was the first drug to demonstrate improved OS for mCRPC [19,20]. Following the establishment of DTX therapy for mCRPC, the pertinent question was whether to administer chemotherapy to patients who were sensitive to hormone therapy to improve patient outcomes.

Since prostate cancer cell growth is driven by androgens, ADT is the standard treatment for hormone naïve disease. However, despite reliable initial responses, disease progression is ultimately inevitable. The hypothesis that a subpopulation of prostate cancer cells may be hormone-resistant, and thus resistant to ADT from the beginning, formulated a rationale to combine ADT with chemotherapy in men with hormone-sensitive disease [21].

Indeed, many investigators have considered the early application of chemotherapeutic agents in combination with ADT. Three randomized clinical trials

conducted in the 1980s examined the role of early combined chemotherapy plus hormone therapy to treat mHSPC [22-24]. However, these studies did not demonstrate a survival benefit for patients on chemotherapy plus ADT. While these early cytotoxic therapy trials were continued with some alterations, a clear clinical benefit was not identified [25,26].

Previously, we reported promising results of chemo-endocrine therapy using a VIP (Vincristine, Ifosfamide, Pepleomycin) regimen [27], however, it was a non-randomized, retrospective study, and the conclusions were not definitive.

However, at that era, the clinical benefit of chemotherapy had not been established, even for mCRPC. Since then, DTX therapy has improved mCRPC patient survival [19,20], thus raising the possibility of early use with chemotherapy for mHSPC once more.

In this study, we began chemo-endocrine therapy using DTX for mHSPC with careful patient selection and informed consent based on our former experience with chemo-endocrine therapy using VIP regimen [27]. With respect to patient safety, we used a low DTX dose and a longer interval for the drug course.

Although our protocol included a low DTX dose and had one fewer course than the phase III clinical trials, the prognoses in patients receiving DTX chemotherapy were better than those receiving ADT alone. Since there was a significant difference in age and PS in the patient's background, we also performed a multivariate analysis. The results also show that this treatment improved survival.

A few studies have been reported on the results of docetaxel treatment for Japanese mHSPC patients [15,16], and the significance of this treatment has not been sufficiently verified because ARAT is currently often used for mHSPC in Japan,

Our results suggested that data from randomized phase III trials in other countries could also be applied to Japanese settings, indicating this treatment could be used as a standard therapy for mHSPC in Japan.

However, in these trials, high metastatic burden cases primarily benefited from this treatment [28]. Therefore, we also performed subgroup analyses in high and low metastatic burden groups.

Although in the low metastatic burden group, DTX therapy failed to show significant survival gain, in the high metastatic burden group, DTX showed significant survival benefits. These observations suggested that DTX therapy was more effective in high metastatic burden groups than low burden group, in agreement with these trials [10,11].

However, in our subgroup analyses, we failed to observe significant results in multivariate analyses, probably because case numbers were small. However, we believe this could be clarified by increasing case numbers in future studies.

Recently, ARAT was clinically used as an initial treatment for mHSPC and has rapidly spread across Japan. In June 2018, our institution commenced ARAT for mHSPC, and this has been increasing. To comprehensively clarify the effects of upfront DTX chemotherapy, we examined cases when ARAT was not used in our institution. Therefore, no patients receiving ARAT as an initial treatment were included in the control group in this study. However, whether chemotherapy or ARAT should be used as an initial treatment for mHSPC remains a perplexing issue.

A comparison of treatments used in this study were reported in a meta-analysis [29], but more data from randomized studies are required. In addition, combination therapy studies have begun elsewhere [30,31].

Currently, treatment options for mHSPC patients are increasing and patient benefits are emerging, however, there is no firm policy on drug selection so far.

Inevitably, our study included some bias because it was a retrospective, non-randomized study with relatively small cases at a single institution. Thus, a well-designed trial with more statistical power is required to confirm this approach is beneficial for newly diagnosed Japanese patients with mHSPC. However, we were able to show the local situation of prostate cancer treatment in Japan, which

is different from Western countries.

Conclusion

Our results suggest that DTX chemotherapy plus ADT improves the survival of Japanese patients with mHSPC. Further studies are warranted to confirm the efficacy and safety of this approach.

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Disclosure

The author reports no conflicts of interest in this work.

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