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Original Article

Feasibility of classical secondary hormonal therapies prior to docetaxel therapy in Japanese patients with castration-resistant prostate cancer: Multicenter retrospective study

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ABSTRACT

Background: We retrospectively analyzed castration-resistant prostate cancer (CRPC) patients treated with secondary hormonal therapies (SHTs) prior to docetaxel therapy.
Methods: The cases of 73 CRPC patients who underwent docetaxel therapy in 2005–2011 at four hospitals in Ibaraki, Japan were analyzed. We determined the cause-specific survival (CSS) from the start of docetaxel therapy and the time point of CRPC diagnosis, and we compared the CSS achieved with/without prior classical SHTs, which were defined as low-dose steroid and estramustine phosphate.
Results: Of the 73 enrolled patients, 26 underwent docetaxel therapy (DOC group), and 47 underwent SHTs (SHTs-DOC group) as the initial treatment for CRPC. In the docetaxel therapy, the rate of prostate-specific antigen responses were higher in the DOC group compared with the SHTs-DOC group (76.9% vs. 44.7%, $P = 0.0066$). The median CSS from the docetaxel therapy initiation was not significant but longer in the DOC group than in the SHTs-DOC group (23.4 months vs. 16.6 months, $P = 0.0969$). However, the median CSS from the time of CRPC diagnosis did not significantly differ between the DOC and SHTs-DOC groups (23.4 months vs. 24.7 months, $P = 0.9233$). In a univariate analysis, pain and visceral metastasis appeared to be risk factors for the CSS in the SHTs-DOC group. The patients with pain and/or visceral metastasis had significantly poorer survival than those without these factors in the SHTs-DOC group (31.5 months vs. 16.8 months, $P = 0.0053$).
Conclusion: The induction of SHTs prior to docetaxel therapy is an acceptable treatment option with some survival benefits for CRPC patients without pain and visceral metastases.

1. Introduction

Among men in Western industrialized countries, prostate cancer (PC) is the most frequently diagnosed malignant disease and the second leading cause of cancer-specific mortality.[1] In Japan, the incidence of PC has markedly increased in recent years, and 21% of PC patients present with distant metastases; 19% present with locally advanced disease at diagnosis.[1,2] With this high incidence of advanced disease, androgen-deprivation therapy (ADT) is a mainstay of treatment for locally advanced and metastatic PC. ADT is reported to be effective for < 3–5 years as an average interval,[3,4] but cases of castrated PC eventually transform into castration-resistant PC (CRPC).

Docetaxel, which is the current standard first-line chemotherapeutic agent for CRPC, has shown survival and palliative benefits in the TAX327 and the Southwest Oncology Group 99-16 studies.[5,6] Several new agents such as abiraterone, enzalutamide, and

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cabazitaxel were shown to have a survival benefit against CRPC in Phase 3 trials.[7–11] However, the optimal sequencing of treatment for CRPC patients has not yet been established.

The classical secondary hormonal therapies (SHTs) such as corticosteroids and estramustine phosphate (EMP) are described as options for first-line systemic therapy for CRPC without visceral metastases in the National Comprehensive Cancer Network Clinical Practice Guidelines for Prostate Cancer, version 1.2015.[12] However, Armstrong et al[13] demonstrated that the prior use of EMP is a risk factor for the survival of CRPC patients undergoing docetaxel therapy. Although there is insufficient data supporting the classical SHTs as first-line systemic therapy for CRPC, it may be true that the majority of CRPC patients should be administered docetaxel therapy prior to SHTs before receiving any of the emerging new agents in Japan.

Therefore, in the present study we investigated whether classical SHTs could affect the response to docetaxel therapy and the survival of CRPC patients. We also analyzed the clinical factors that could be used to determine whether or not classical SHTs are feasible prior to docetaxel therapy in CRPC patients.

2. Materials and methods

2.1. Patients

Between 2005 and 2011, a total of 73 patients who received docetaxel therapy at four hospitals in Ibaraki prefecture, Japan were enrolled in this multi-institution retrospective cohort study. The eligible patients had histologically confirmed adenocarcinoma of the prostate, as clinically diagnosed CRPC. The Prostate Cancer Clinical Trials Working Group advises classifying tumors that are progressing with castration levels of testosterone as “castration-resistant”.[14] We defined CRPC by disease progression after the administration of ADT, because the serum levels of testosterone of some patients were not measured. Disease progression was defined by prostate-specific antigen (PSA) progression or by radiographic imaging studies. PSA progression was defined as an increase by $\geq$ 25% in serum PSA (at least 2 ng/mL) from the nadir value.

We evaluated the results of the patients' radiographic imaging studies using the Response Evaluation Criteria in Solid Tumors version 1.1. We excluded the patients who had prior treatment with cytotoxic agents other than EMP from this study. To analyze the differences in CRPC treatment types, we divided the patients into two groups. The patients who underwent docetaxel therapy as the initial treatment for CRPC were classified as the DOC group. After the initial docetaxel therapy, these patients underwent other treatment, e.g., with SHTs, other chemotherapy, and best supportive care. The patients who underwent docetaxel therapy after classical SHTs were classified as the SHTs-DOC group.

The data at the diagnosis of CRPC included the patient's age, performance status, presence of pain, laboratory evaluations (hemoglobin, alkaline phosphatase, and PSA), and site of metastases. The follow-up status data were collected in March 2016. The median duration of follow-up was 23.4 months (range, 1.53–101.2 months). The institutional review board of four hospitals approved this study, as the registry form was anonymous.

2.2. Evaluation of PSA doubling time

The PSA doubling time (PSADT) was defined as the time required for the PSA level to double. The PSADT was estimated according to the following formula:

$$\mathrm{PSADT} = \ln 2 \times \mathrm{T}/[\ln(\mathrm{PSA}_2) - \ln(\mathrm{PSA}_1)] \quad (1)$$

where ln is the natural log, and T is the number of months between two consecutive PSA determinations (PSA_1 and PSA_2).[15] PSA_1 is the value at the time of the diagnosis of CRPC, and PSA_2 is the value at the start of the initial treatment for CRPC. The PSADTs were determined by two measurements of the PSA value at least 4 weeks apart.

2.3. Treatment

The docetaxel therapy was given in a regimen of every 3 weeks docetaxel (70–75 mg/m^2) based on the schedule reported by Tannock et al,[5] and 5-mg prednisone was generally administered twice daily. The adjustment of the treatment schedule and any dose reduction in docetaxel therapy were determined by the treating physician's recommendation. The agent of classical SHTs was defined as low-dose steroid (prednisone 10 mg/d or dexamethasone 0.5–1.5 mg/d) and EMP.

2.4. Statistical analysis

The primary objective of this study was defined as the cause-specific survival (CSS) after either the induction of docetaxel therapy or the time point of the diagnosis of CRPC between the SHTs-DOC group and the DOC group. Survival curves were constructed using the Kaplan–Meier method, and the difference between the curves was evaluated using the Log Rank test. As the secondary objective, we analyzed prognosis-related risk factors in the SHTs-DOC group with univariate and multivariate analysis using Cox's proportional hazards model and the Log Rank test. We selected the known prognostic factors for multivariate analysis with the

Table 1
Baseline characteristics of the 73 patients with castration-resistant prostate cancer (CRPC).

	DOC group (n = 26)	SHTs-DOC group (n = 47)	P
Age (y)			
Median	68.0	70.0	0.3681
Range	39–81	54–83	
Gleason score > 7 (%)	83.3	86.1	0.7370
Prior treatment (%)			
Alternative anti-androgen	69.2	89.4	0.0527
Antiandrogen withdrawal	84.6	70.2	0.2575
ECOG performance status (%)			
0–1	96.2	89.4	0.4118
2	3.8	10.6	
Pain (%)	34.6	21.3	0.2685
Serum PSA (ng/mL)			
Median	42.0	26.5	0.5189
Range	2.24–2379	2.43–924	
Anemia, % (Hb < 12 g/dL)	50.0	31.0	0.1319
ALP (U/L)			
Median	310	331	0.9049
Range	164–4061	146–2789	
Extent of disease (%)			
Bone metastasis	73.1	78.7	0.5783
Visceral metastasis	19.2	10.6	0.3140
PSADT (mo)	1.04	1.30	0.2199
	0.01–7.38	0.02–10.7	
Time from starting PADT to CRPC (mo)			
Median	15.7	23.3	0.1313
Range	3.0–134.1	6.1–163.5	
Alive (%)	15.4	4.3	0.1775
Dead (%)	84.6	95.7	
Cancer/other causes (%)	73.1/11.5	95.7/0	

ALP, alkaline phosphatase; DOC, docetaxel; ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; PADT, primary androgen deprivation therapy; PSA, prostate-specific antigen; PSADT, PSA doubling time; SHTs, secondary hormonal therapies.

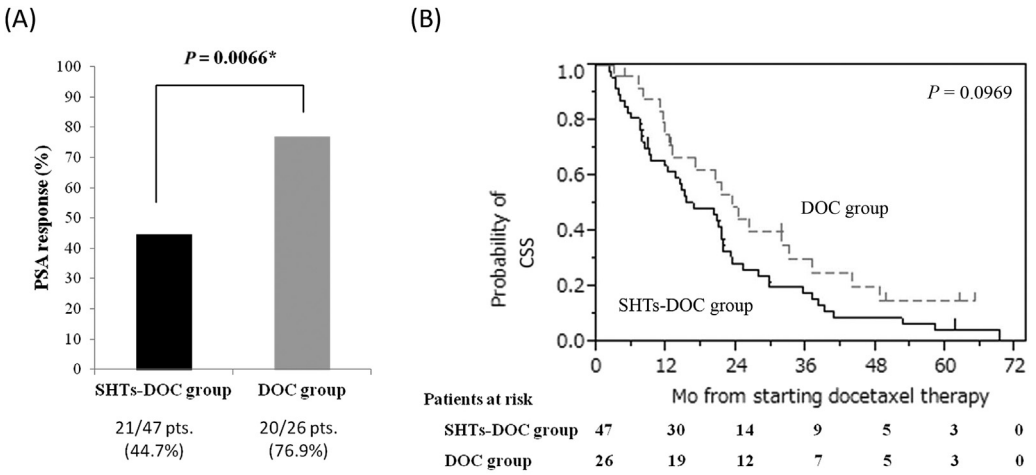

Fig. 1. Analysis of prostate-specific antigen (PSA) responses and cause-specific survival (CSS) following docetaxel therapy. (A) PSA responses [> 50% PSA decline compared with pretreatment PSA following docetaxel (DOC) therapy] and (B) CSS from the start of DOC therapy in the DOC group and secondary hormonal therapies (SHTs)-DOC group. * Statistically significant difference ($P < 0.05$). pts., patients.

following conditions, i.e., the factors could be assessed in all patients and were not confounder with the variables detected by univariate analysis. We then investigated the differences in the CSS from the time point of the diagnosis of CRPC classified by a combination of significant factors according to the above statistics. Additionally, we analyzed the difference in PSA responses between the DOC group and the SHTs-DOC group by Fisher's exact test. "PSA response" was defined as a > 50% decline following docetaxel therapy compared with the pretreatment PSA. Differences between the two patient groups in baseline characteristics were analyzed with the Chi-square test or Wilcoxon rank sum test. A probability (P) value < 0.05 was considered significant.

3. Results

3.1. Patient characteristics

Among the 73 enrolled patients, 26 patients underwent docetaxel therapy (the DOC group), and 47 patients underwent SHTs (the SHTs-DOC group) as the initial treatment for CRPC. The characteristics of the enrolled patients are summarized in Table 1. Most of the patients in this cohort undertook an alternative antiandrogen therapy and antiandrogen withdrawal. No significant difference in patient characteristics was observed between the DOC and SHTs-DOC groups.

3.2. Analysis of PSA responses and CSS following docetaxel therapy

The PSA responses to docetaxel therapy were significantly higher in the DOC group compared with the SHTs-DOC group (76.9% vs. 44.7%, $P = 0.0066$; Fig. 1A). Moreover, the median CSS from starting docetaxel therapy was longer in the DOC group than that in the SHTs-DOC group, but the difference was not significant (23.4 months vs. 16.6 months, $P = 0.0969$; Fig. 1B).

3.3. Analysis of CSS from time of diagnosis of CRPC

The median CSS from the time of diagnosis of CRPC was not significantly different between the two groups (DOC group 23.4 months, SHTs-DOC group 24.7 months, $P = 0.9233$; Fig. 2). The univariate analysis to analyze the prognosis-related risk factors in the SHTs-DOC group identified visceral metastasis and pain as significant factors associated with CSS (Table 2). There were no significant prognosis-related risk factors in multivariate analysis, but the hazard ratio of visceral metastasis and pain was still higher compared with the other factors.

The following statistics with risk classification, assessed by visceral metastasis and/or pain in the SHTs-DOC group, demonstrated that the median CSS form the diagnosis of CRPC was significant shorter in the high-risk group compared with the low-risk group (16.8 months vs. 31.5 months, $P = 0.0053$; Fig. 3). In low-risk group, the median CSS from the time of diagnosis of CRPC was not significantly different between the DOC group and SHTs-DOC group (31.5 months vs. 31.5 months, $P = 0.9139$; data not shown).

4. Discussion

Docetaxel-based chemotherapy showed a survival benefit for CRPC patients in the TAX327 and the Southwest Oncology Group 99-16 studies.[5,6] Although the efficacy of the new agents for CRPC has been demonstrated in recent years, docetaxel is still standard as a first-line chemotherapy agent for CRPC patients. However, there is no high-level evidence regarding which type(s) of patients with CRPC should be administered docetaxel-based chemotherapy

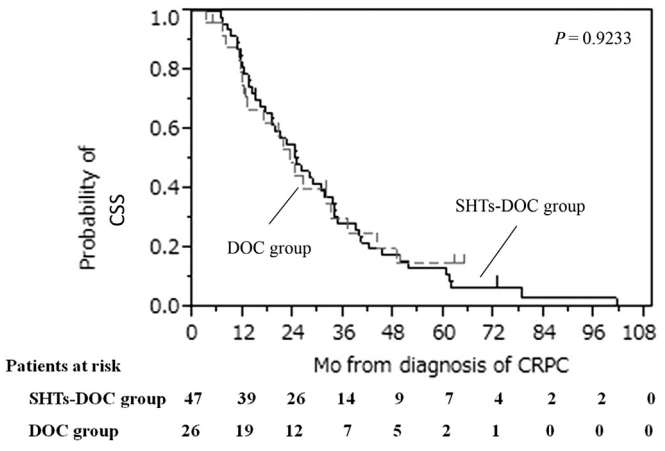

Fig. 2. Kaplan–Meier estimates of cause-specific survival (CSS) in the secondary hormonal therapies-docetaxel (SHTs-DOC) group and DOC group. CRPC, castration-resistant prostate cancer.

Table 2
The univariate and multivariate analysis of prognostic factors in the secondary hormonal therapies-docetaxel group.

	n	Cox proportional hazard model (univariate)			Log-rank test	Cox proportional hazard model (multivariate)		
		HR	95% CI of HR	*P*	*P*	HR	95% CI of HR	*P*
Age > 70 y	47	1.46	0.78–2.71	0.2318	0.2272	1.42	0.74–2.74	0.2959
ECOG performance status 2	47	0.98	0.34–2.28	0.9623	0.9624	0.87	0.25–2.43	0.8072
Gleason score > 7	43	1.00	0.45–2.68	0.9876	0.9876			
PSA > 100 ng/mL	46	0.82	0.37–1.64	0.5864	0.5928			
PSADT < 1.3 mo	43	1.52	0.81–2.86	0.1902	0.1857			
Anemia (Hb < 12g/dL)	42	0.73	0.39–1.40	0.3450	0.3410			
ALP > 700 U/mL	38	1.23	0.36–3.16	0.7022	0.6942			
Bone metastasis	47	1.69	0.82–3.94	0.1611	0.1781			
Visceral metastasis	47	3.27	1.09–8.05	0.0365*	0.0120*	1.94	0.49–6.64	0.3274
Pain	47	1.45	0.81–2.51	0.0638	0.0451*	1.90	0.65–5.37	0.2369
Time from starting PADT to CRPC < 24 mo	47	0.85	0.46–1.55	0.5919	0.5914	0.89	0.47–1.7	0.7294

ALP, alkaline phosphatase; CI, confidence interval; CRPC, castration-resistant prostate cancer; ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; HR, hazard ratio; PADT, primary androgen deprivation therapy; PSA, prostate-specific antigen; PSADT, PSA doubling time.
* Statistically significant difference ($P < 0.05$).

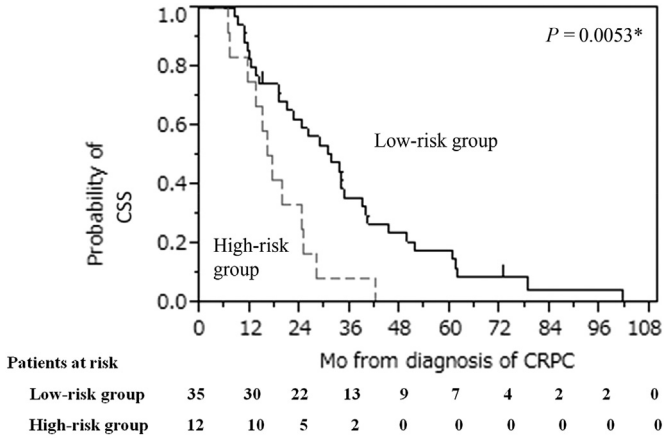

Fig. 3. Kaplan–Meier estimates of cause-specific survival (CSS) according to risk group classification in the secondary hormonal therapies-docetaxel (SHTs-DOC) group. CRPC, castration-resistant prostate cancer. * Statistically significant difference ($P < 0.05$).

earlier. In the present study, although survival after DOC therapy in the patients with prior SHTs was shorter than that of the patients without prior SHTs, the initial treatment by docetaxel or SHTs did not result in a significant difference in CSS from the diagnosis of CRPC.

Song et al[16] also assessed the efficacy of initial treatment in 384 CRPC patients by EMP, docetaxel, and mitoxantrone in Korea, and they found that the overall survival from the start of the initial treatment for CRPC was not significantly different among these initial treatments. Therefore, there might be survival benefits of classical SHTs as initial treatment for at least some Asian CRPC patients in clinical practice.

The recent use of AR-axis-targeted (ARAT) therapies, such as abiraterone and enzalutamide, provided improved survival in patients with metastatic CRPC who received prior docetaxel treatment and in those who were chemotherapy-naïve.[8,10] These clinical benefits of ARAT therapies have been shown in trials of asymptomatic or minimally symptomatic patients. In a systemic review of CRPC treatment, Chi et al[17] suggested the following treatment algorithm for CRPC patients based on prospective/retrospective data and clinical experiences. In their algorithm, ARAT therapies are preferred for patients without the following clinical characteristics: prior ADT response of < 1 year, symptomatic disease, or visceral disease.

In the present study, the median CSS achieved by administering classical SHTs prior to docetaxel was significantly longer in the CRPC patients who did not have pain and visceral metastases. CRPC is not curable, and so therapeutic strategies should be considered from a viewpoint of optimizing a patient's quality of life (QOL). We could not compare QOL between the DOC group and SHTs-DOC group in this retrospective study. However, the prechemotherapy phase is important because the adverse events of chemotherapeutic agents such as docetaxel and cabazitaxel reduce a patient's QOL. We thus speculate that SHTs including ARAT therapies are suitable for treating CRPC patients without pain and visceral metastases, particularly in Asian patients including Japanese. In classical SHTs, estrogen agents such as EMP and diethylstilbestrol are associated with cardiovascular and thromboembolic complications.[18,19] Notably, ARAT therapies are more than 10 times as expensive as classical SHTs in Japan.

The limitations of this study are that it was a retrospective study with a small sample size, and the heterogeneous background of the patients. Missing laboratory data may have influenced the results. In some patients, we were not able to determine whether the inclusion criteria for the CRPC definition were fulfilled because the serum level of testosterone was not checked. The patients in this study were treated upon their clinician's recommendation. Furthermore, we could not assess the measurements of patient's QOL in this cohort. A prospective study would be necessary to resolve these limitations in future studies.

In conclusion, the early administration of docetaxel improved the PSA response of CRPC patients and their survival after starting docetaxel therapy, but a significant difference in survival after the diagnosis of CRPC was not observed between the patients with early and late initiation of docetaxel therapy. Moreover, there was good survival outcome in the patients without pain and visceral metastases, even among those treated by classical SHTs prior to docetaxel.

Conflicts of interest

No potential conflicts of interest relevant to this article were reported.

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