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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.
Materials and 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:

$$PSADT = \ln 2 \times T/[\ln(PSA_2) - \ln(PSA_1)] \quad (1)$$

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

Table 1
Baseline characteristics of the 73 patients with castration-resistant prostate cancer (CRPC) Q6

	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	2.43–924.5	
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.

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