Optimal Timing of Cabazitaxel Introduction for Japanese Patients With Metastatic Castration-resistant Prostate Cancer

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Abstract. *Background/Aim:* Limited information is available to help physicians decide when to introduce cabazitaxel for metastatic castration-resistant prostate cancer (mCRPC) patients. The objective of this study was to assess the optimal timing of cabazitaxel introduction. *Patients and Methods:* The clinical outcomes of 66 mCRPC patients receiving cabazitaxel following failure of docetaxel were retrospectively analyzed. *Results:* Among the parameters possibly affecting the timing of cabazitaxel introduction, only an increased prostate-specific antigen (PSA) value from the diagnosis of CRPC had a significant impact on overall survival (OS) after the introduction of cabazitaxel. Furthermore, there was a significant correlation between the increased PSA value from the diagnosis of CRPC and the baseline PSA value at cabazitaxel introduction. Multivariate analysis showed that only the baseline PSA value at cabazitaxel introduction is an independent predictor of OS. *Conclusion:* A comparatively low PSA value could be an alternative index suggesting the optimal timing for cabazitaxel introduction.

Until recently, treatment options of patients with metastatic castration-resistant prostate cancer (mCRPC) were limited to docetaxel-based regimens (1). Over the past few years, however, the therapeutic strategy for patients with mCRPC has markedly changed with the introduction into routine clinical practice of several effective agents with different mechanisms of action (2, 3). Despite significant progress in

the development of these novel agents, the prognosis of mCRPC patients is still unsatisfactory, and a number of clinical issues remain unresolved (4). Of these, it is particularly important to determine the optimal timing of introducing each agent against mCRPC during sequential therapy with multiple agents.

Cabazitaxel, a tubulin-binding taxane drug, has been widely accepted as a powerful chemotherapeutic for mCRPC patients based on the findings of the pivotal phase III TROPIC trial. This trial was performed targeting patients with mCRPC whose disease had progressed during or after docetaxel-based therapy and demonstrated the significant prognostic advantage of cabazitaxel compared with mitoxantrone (5). To date, there have been various studies investigating prognosis in mCRPC patients treated with cabazitaxel (6-9). For example, Belderbos *et al.* have analyzed data from 224 mCRPC patients receiving cabazitaxel therapy, and found that performance status (PS), baseline hemoglobin, alkaline phosphatase (ALP) and albumin (Alb) are significant predictors of overall survival (OS) in these patients (6). We have also recently reported that the lactate dehydrogenase (LDH) levels, De Ritis ratio and PS were independently associated with OS in Japanese mCRPC patients based on multivariate analysis (9). However, limited information is available to help physicians decide when to initiate treatment with cabazitaxel in daily clinical practice.

In this study, therefore, a total of 66 consecutive mCRPC patients who received cabazitaxel following the failure of docetaxel at our institutions were included. Patient data were retrospectively analyzed to clarify the optimal timing of cabazitaxel introduction during sequential therapy with multiple agents.

Patients and Methods

Patients. This study retrospectively reviewed the clinicopathological data of 66 consecutive Japanese patients with mCRPC who had progressive disease following treatment with docetaxel and subsequently received cabazitaxel therapy between January 2015

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and March 2018 in a routine clinical setting at four institutions, belonging to Tokai Urologic Oncology Research Seminar. The design of the present study was approved by the Research Ethics Committee at Hamamatsu University School of Medicine, Institutional Review Board at Aichi Medical University, Research Ethics Committee at Fujita Health University School of Medicine and Institutional Review Board at Nagoya City University Graduate School of Medical Sciences. The need to obtain informed consent from all patients included in this study was waived because of its retrospective design.

Treatment. All patients included in this study were diagnosed with prostatic adenocarcinoma by histopathological examination, and were initially treated with androgen-deprivation therapy (ADT) by medical or surgical castration. According to either the Prostate Cancer Working Group 2 (PCWG2) criteria (10) or the Response Evaluation Criteria in Solid Tumors (11), disease progression against primary ADT, indicating the emergence of CRPC, was defined as prostate-specific antigen (PSA) or radiographic progression, respectively, in patients maintaining a serum testosterone level <50 ng/dl.

After failure of primary ADT, several patterns of sequential therapy using abiraterone acetate, enzalutamide and/or docetaxel were provided until the introduction of cabazitaxel according to the preference of the physicians and patients without strictly regulated criteria. As a rule, abiraterone acetate and enzalutamide were administered according to the standard dosing schedules, as previously reported (12, 13), whereas docetaxel and cabazitaxel were generally given at doses of 70 and 20 mg/m², respectively, every 3 weeks considering the severe toxic profiles for Japanese patients (14, 15). In patients with treatment-associated adverse events (AEs) corresponding to grade ≥3, dose modification and/or treatment delay of either agent was permitted. The treatment with either agent was generally continued until the diagnosis of disease progression, which was judged based on the same definition as applied to the primary ADT.

Evaluation. The clinicopathological data of each patient were obtained from the medical records. Before initiating the treatment with cabazitaxel, the Eastern Cooperative Oncology Group (ECOG) PS was evaluated, and the number and location of metastatic lesions were assessed by radiological examinations using computed tomography and radionuclide bone scans. Standard clinical testing methods were used to measure all laboratory data, including PSA levels, in each patient prior to the introduction of cabazitaxel. After the administration of cabazitaxel, the PSA level as well as bone marrow, renal and liver functions were evaluated every 4-6 weeks, while radiological examinations were conducted based on the discretion of the treating physicians.

Statistical analysis. All statistical analyses were performed using Statview 5.0 software (Abacus Concepts, Inc., Berkley, CA, USA), and a *p*-value <0.05 was considered significant. OS rates were calculated by the Kaplan–Meier method, and differences were determined by the log-rank test. The associations of certain factors with OS were analyzed using the Cox proportional hazards regression model. Pearson’s correlation coefficient analysis was performed to assess the association between the baseline PSA value at the introduction of cabazitaxel and increased PSA value from the diagnosis of CRPC.

Table I. Patient characteristics prior to the introduction of cabazitaxel.

Age* (years, range)	74 (55-94)
ECOG performance status (%)	
0	19 (28.8)
1	29 (43.9)
2≤	18 (27.3)
Prostate-specific antigen* (ng/ml, range)	164.0 (1.7-4477.0)
Hemoglobin* (g/dl, range)	10.9 (6.1-14.8)
Albumin* (g/dl, range)	3.6 (2.2-4.5)
Alkaline phosphatase* (IU/l, range)	292.5 (91.0-2856.0)
Lactate dehydrogenase* (IU/l, range)	251.5 (131.0-2597.0)
Lymph node metastasis (%)	
Negative	32 (48.5)
Positive	34 (51.5)
Bone metastasis (%)	
Negative	14 (21.2)
Positive	52 (78.8)
Visceral metastasis (%)	
Negative	47 (71.2)
Positive	19 (28.8)

*expressed as median value of the 66 patients included in this study. ECOG: Eastern Cooperative Oncology Group.

Results

Patient characteristics. Table I summarizes the clinicopathological characteristics of the 66 patients at the introduction of cabazitaxel. In this series, the median cycles of cabazitaxel therapy were 3 (range=1-23). During the observation period of this study (median, 6 months; range=1–35 months), 38 (57.6%) of the 66 patients died, and the median duration of OS in the 66 patients was 9 months.

Parameters affecting the timing of cabazitaxel introduction. To assess the optimal timing of introducing cabazitaxel for mCRPC patients, we assessed the associations between OS and the following parameters potentially affecting this timing: the duration from the diagnosis of CRPC, increased PSA value from the diagnosis of CRPC, cycles of prior docetaxel therapy and numbers of previously administered agents against CRPC before cabazitaxel therapy. Among these 4 parameters, only the increased PSA value from the diagnosis of CRPC was shown to have a significant impact on OS in the 66 mCRPC patients (Table II).

Association between the baseline PSA value at cabazitaxel introduction and increased PSA value from the diagnosis of CRPC. The correlation between the baseline PSA value at the introduction of cabazitaxel and the increased PSA value from the diagnosis of CRPC was assessed to examine whether the baseline PSA value could be used as a simple alternative to the increased PSA value. As shown in Figure 1, there was a significant correlation between the baseline

Figure 1. Correlation between increased prostate-specific antigen (PSA) value from the diagnosis of castration-resistant prostate cancer (CRPC) and baseline PSA value at the introduction of cabazitaxel in 66 patients with metastatic CRPC.

Table II. Cox proportional hazards regression univariate analyses of associations between overall survival and various parameters affecting the timing of cabazitaxel introduction.

Variables*	Hazard ratio	p-Value
Duration from the diagnosis of CRPC (months) (<22 versus ≥ 22)	0.7	0.28
Increased PSA value from the diagnosis of CRPC (ng/ml) (<142 versus ≥ 142)	1.5	0.023
Cycles of prior docetaxel therapy (≤ 6 versus ≥ 7)	0.65	0.2
Numbers of previously administered agents against CRPC (≤ 2 versus ≥ 3)	0.96	0.9

*Cutoff point of each continuous variable was the median value among the 66 patients included in this study. CRPC: Castration-resistant prostate cancer; PSA: prostate-specific antigen.

PSA value at the introduction of cabazitaxel and the increased PSA value from the diagnosis of CRPC.

Prognostic impact of the baseline PSA value at cabazitaxel introduction. To evaluate the significance of the baseline PSA value at the introduction of cabazitaxel as a predictor of OS in the 66 mCRPC patients, uni- and multivariate analyses of several conventional prognostic factors were performed (Table III). Univariate analysis found that the baseline PSA value in addition to Alb, ALP and LDH values are significant predictors of OS. Of these 4 significant factors, only the baseline PSA value was shown to be independently associated with OS. Figure 2 presents the OS according to the baseline PSA value at the introduction of cabazitaxel therapy.

Discussion

Over the last decade, marked changes in the treatment of mCRPC patients have taken place following the approval of several novel agents, demonstrated to significantly improve the prognosis of these patients (2, 3). However, it remains difficult to effectively control the progression of prostate cancer after the acquisition of castration-resistant phenotypes (4). Moreover, the up-front use of some of the novel agents against mCRPC, such as abiraterone acetate and docetaxel, has been shown to provide a survival benefit for patients with castration-sensitive prostate cancer as well (16). Considering the complicated schemes regarding the current therapeutic strategy for advanced prostate cancer, particularly mCRPC, it has become very important to optimally administer cabazitaxel to

Figure 2. Overall survival of 66 patients with metastatic castration-resistant prostate cancer who were treated with cabazitaxel according to the baseline prostate-specific antigen (PSA) value at the introduction of cabazitaxel.

Table III. Cox proportional hazards regression analyses of associations between overall survival and various parameters.

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio	p-Value	Hazard ratio	p-Value
Age (years) (<75 versus ≥75)	0.94	0.84	–	–
ECOG performance status (≤1 versus ≥2)	1.95	0.53	–	–
PSA (ng/ml) (<164.0 versus ≥164.0)	3.57	<0.001	2.38	0.035
Hemoglobin (g/dl) (<10.9 versus ≥10.9)	0.65	0.19	–	–
Albumin (g/dl) (<3.6 versus ≥3.6)	0.5	0.035	0.7	0.35
Alkaline phosphatase (IU/l) (<292.5 versus ≥292.5)	2.48	0.0061	1.65	0.18
Lactate dehydrogenase (IU/l) (<251.5 versus ≥251.5)	2.26	0.014	1.68	0.14
Lymph node metastasis (negative versus positive)	1.28	0.44	–	–
Bone metastasis (negative versus positive)	1.59	0.3	–	–
Visceral metastasis (negative versus positive)	1.46	0.27	–	–

ECOG: Eastern Cooperative Oncology Group; PSA: prostate-specific antigen.

further prolong the survival of mCRPC patients, since cabazitaxel will be ultimately introduced during the long-term course of sequential treatment of advanced prostate cancer, irrespective of the previous therapeutic history with multiple agents (5-9). In this study, therefore, the data from a total of 66 mCRPC patients, who received cabazitaxel therapy at our institutions, were analyzed focusing on the optimal timing of initiating treatment of mCRPC patients with this agent.

To date, randomized clinical trials and routine clinical observations have shown that cabazitaxel shows excellent

effects against docetaxel-refractory mCRPC (5-9, 17). For example, the TROPIC trial demonstrated that cabazitaxel significantly improved the OS of patients with docetaxel-refractory mCRPC compared with mitoxantrone, with the relative risk of death reduced by 30% (5). Furthermore, Carles *et al.* have assessed data from 189 patients with mCRPC receiving cabazitaxel in clinical practice, and reported that the median OS, progression-free survival and time to treatment failure were 13.2, 5.6 and 4.4 months, respectively (17). However, it is still not uncommon to

encounter mCRPC patients who did not get the full benefits of cabazitaxel treatment because the optimal timing of its introduction had been missed. Optimal timing can be missed because little is known about clinical parameters and biomarkers, which can help selecting appropriate patients and timing of cabazitaxel therapy (18). Furthermore, novel androgen receptor axis-targeted agents, abiraterone acetate and enzalutamide, have also been shown to prolong survival in docetaxel-refractory mCRPC (3), and the Japanese health insurance system has not set restrictions regarding the cycles of docetaxel therapy against mCRPC (9).

In this study, we initially examined whether the OS of the 66 patients could be affected by the four factors possibly associated with the timing of initiating treatment with cabazitaxel. Of these factors, only the increased PSA value from the diagnosis of CRPC (<142 ng/ml *versus* ≥ 142 ng/ml) was shown to have a significant impact on OS. Based on this finding, it is very important to introduce cabazitaxel prior to elevation of PSA value to approximately 150 ng/ml from the baseline value at the diagnosis of CRPC in order to significantly prolong the OS in mCRPC patients receiving cabazitaxel. However, it is well-known that despite the lack of a marked increase in the PSA value, evident disease progression could be detected in a certain proportion of mCRPC patients (19). Accordingly, it is necessary to perform not only measurement of the PSA value but also additional assessments, including evaluation of symptoms and radiological examinations.

It is of interest to identify more simple parameters that could be used as an alternative to the increase in the PSA value from the diagnosis of CRPC. In this series, the baseline PSA value at the introduction of cabazitaxel was shown to be closely correlated with the increase in the PSA value from the diagnosis of CRPC. In fact, the PSA value at the diagnosis of CRPC was negligibly low compared with that prior to the initiation of cabazitaxel therapy in the majority of patients. Thus, it might be possible to simply determine optimal timing of initiation of cabazitaxel therapy based on the baseline PSA value.

Another point of interest is the significance of the baseline PSA value at the initiation of cabazitaxel therapy as a prognostic indicator in mCRPC patients receiving this agent. In this series, OS in the 66 mCRPC patients was significantly correlated with the baseline values of Alb, ALP, LDH and PSA. Of these, only the baseline PSA value had an independent impact on OS. These findings suggested that the baseline PSA value could be a useful index to consider the appropriateness of the timing of cabazitaxel introduction as well as a reliable prognostic indicator in mCRPC patients treated with this agent. To date, there have been several studies on the identification of prognostic indicators in mCRPC patients receiving cabazitaxel therapy (5-9). However, none of these factors have been routinely utilized in clinical practice (18), since the findings, including the significance of the baseline PSA value, were not consistent among these previous studies (5-9, 18).

Here, we would like to emphasize various limitations of this study. Firstly, this was a retrospective study including a small number of patients with heterogeneous characteristics from four different institutions. Thus, the findings presented in this study should be confirmed in a prospective study with a larger sample size. Secondly, baseline characteristics of the included patients at the initiation of cabazitaxel therapy were relatively poor compared with those in previous studies. Thirdly, only four parameters were analyzed as candidates possibly affecting the timing of cabazitaxel introduction. However, there might be some important parameters other than those examined in this study. Finally, this study was conducted in Japan, where treatment approaches for advanced prostate cancer may differ from those in Western countries. For example, the majority of patients in this series received complete androgen blockade as an initial ADT, which is uncommon in Western countries (20). Accordingly, such differences may have affected the present outcomes.

Conclusion

The increase in the PSA value from the diagnosis of CRPC, which may affect the timing of initiating cabazitaxel therapy for docetaxel-refractory mCRPC patients, was shown to be significantly correlated with OS following the introduction of this agent. Furthermore, the increase in the PSA value from the diagnosis of CRPC was closely associated with the baseline PSA value at the introduction of cabazitaxel, which was further identified as an independent indicator of OS in these patients. Collectively, these findings suggest that it should be recommended to introduce cabazitaxel to mCRPC patients with a comparatively low PSA value, which could be regarded as a useful alternative index to determine the optimal timing of cabazitaxel introduction during sequential therapy with multiple agents against mCRPC.

Conflicts of Interest

The Authors have no conflict of interest to declare regarding this study.

Authors' Contributions

The types of contribution by each author are as follows: Study conception and design, Takahiro Yasui, Ryoichi Shiroki, Makoto Sumitomo, Hideaki Miyake; Acquisition of data, Toshiki Ito, Kent Kanao, Kiyoshi Takahara, Ryosuke Ando; Analysis and interpretation of data, Toshiki Ito, Hideaki Miyake; Drafting of manuscript, Toshiki Ito, Hideaki Miyake.

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