Sequential Therapy with Docetaxel and Cabazitaxel Starting at Low PSA Levels was Associated with Longer Survival in Patients with Castration-Resistant Prostate Cancer

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Abstract

Background: This study investigated the optimal timing for starting docetaxel (DOC) and cabazitaxel (CBZ) by examining the correlation of their efficacy and evaluating factors associated with the prognosis of patients with castration-resistant prostate cancer (CRPC) receiving DOC-CBZ sequential treatment.

Methods: We retrospectively evaluated data for 146 patients who received DOC followed by CBZ. The correlations of prostate specific antigen (PSA) decrease rate and time to progression between DOC and CBZ treatment were examined. The association of parameters with progression-free survival (PFS) and overall survival (OS) were evaluated. Survival rates were compared between patients with high and low PSA levels at the start of DOC and CBZ treatment.

Results: No correlations of PSA decrease rate and time to progression were observed between DOC and CBZ. In multivariate analyses, higher PSA level at the start of DOC was significantly associated with shorter PFS ($P = 0.004$) and OS ($P = 0.001$). The OS of patients who started DOC and CBZ at low PSA levels was significantly longer than those that started at high PSA levels ($P = 0.002$ and $P = 0.003$). In patients who started DOC at high PSA levels, those who switched to CBZ at low PSA levels had longer OS than those who switched at high PSA levels ($P = 0.048$).

Conclusions: For patients for whom DOC was not effective, sequential CBZ might reduce PSA for a long duration. Starting DOC and switching to CBZ at low PSA levels might result in improved prognoses in CRPC patients.

Trial registration: This study was registered retrospectively.

Background

Prostate cancer is the second leading cause of cancer-related death in men in Western countries and its incidence in Japan is increasing rapidly. Androgen deprivation therapy (ADT) is an effective initial treatment for patients with advanced disease harboring distant metastasis. However, these lesions acquire therapeutic resistance within several years and progress to castration-resistant prostate cancer (CRPC). An increasing number of therapies for CRPC have become available, including androgen receptor axis–targeting agents (ARATs) and taxanes. Docetaxel (DOC) has been used to treat patients with CRPC since 2004. Cabazitaxel (CBZ) was reported to prolong the survival of patients with DOC-resistant cancers, and it became available in Japan in 2014. In 2015, primary DOC therapy combined with ADT was reported to prolong survival in patients with high volume metastatic hormone-naïve prostate cancer (HNPC). Subsequent studies showed that primary ARAT therapy prolonged survival in patients with HNPC, providing better quality of life than DOC. For patients with ARAT- and DOC-resistant CRPC, CBZ was reported to produce longer survival than alternative ARATs without reducing quality of life. Thereafter, sequential treatment with DOC-CBZ was established as standard treatment for ARAT-resistant patients. However, the optimal timing for starting DOC and switching to CBZ has not been elucidated.
We previously performed a retrospective multi-institutional study to evaluate the efficacy and safety of CBZ in Japanese patients with CRPC. In this study, we collected data for patients who received DOC and directly switched to CBZ in a larger number of institutes with a longer follow-up duration. We evaluated the correlation of the efficacy of DOC with that of CBZ and analyzed the association of parameters, including prostate-specific antigen (PSA) levels at the start of DOC and CBZ, with the prognosis of patients receiving DOC-CBZ treatment.

Patients And Methods

Study population

This retrospective study included patients with CRPC from 16 university and satellite hospitals in Japan who received DOC and CBZ between 2014 and 2019. This study was approved by the institutional review board of ethical committee in Miyazaki University (approval number: O-0538) and in each institute. The data were retrospectively obtained from patients’ medical records. All patients had pathologically proven adenocarcinoma of the prostate that was progressing to CRPC. CRPC was defined as either an increase in PSA levels of > 25% and > 2 ng/mL relative to the nadir PSA levels or radiological progression after initial ADT or ADT plus bicalutamide. This study included only patients with CRPC who had received DOC and directly switched to CBZ. The criteria for decision-making regarding the dose and timing of DOC and CBZ differed among the institutions and physicians.

Endpoints

To determine whether CBZ was effective in patients for whom DOC was not effective, the percent decrease in PSA levels and time to progression after DOC and CBZ treatment were calculated in each patient, and their correlation was evaluated. In calculating the time to progression, patients who changed treatment in response to adverse events or continued the treatment without progression were excluded. To identify parameters associated with the prognosis of patients receiving DOC-CBZ treatment, progression-free survival (PFS) and overall survival (OS) were calculated, and their associations with pre-treatment factors, including PSA levels at the start of DOC and CBZ treatment, were evaluated. Progression included PSA progression (defined as a >25% and >2 ng/ml increase in PSA levels relative to the nadir PSA level), radiological progression (defined as an increase in tumor size using RECIST 1.1 for nodal or visceral metastasis or the appearance of two new lesions for bone metastasis), symptomatic progression (defined as the worsening of pain or other symptoms), and death. The combined PFS for DOC-CBZ was determined as the time from the initiation of DOC to the failure of CBZ. OS was defined as the time from the initiation of DOC or diagnosis of CRPC to death from any cause.

Statistical analysis
The data are presented as the median and interquartile range (IQR) or 95% confidence interval (CI). The correlation between the percent PSA decrease and time to progression during DOC and CBZ treatment was evaluated using Pearson's correlation coefficient. PFS and OS were estimated using the Kaplan–Meier method. Patients were classified into subgroups using the clinicopathological variables of age; Gleason's score (GS); previous ARAT use; performance status (PS); PSA, hemoglobin (Hb), lactate dehydrogenase (LDH), and alkaline phosphatase (ALP) levels; the number of bone metastases; and the existence of visceral metastases. The associations of these variables with PFS or OS were assessed using univariate and multivariate Cox's proportional hazards regression models. The medians of continuous variables were used as cutoffs, and the patients were classified into subgroups. The differences of PFS and OS between patient subgroups according to PSA levels at the start of DOC and CBZ treatment were evaluated using the log-rank test. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria). P < 0.05 denoted statistical significance.

**Results**

In total, 146 patients were included in this study. Of them, 91 patients (62%) had de novo metastasis at prostate cancer diagnosis, 22 patients (15%) received radical prostatectomy and 37 patients (25%) received local radiation therapy. All the patients received ADT, the median (IQR) time to CRPC was 11 (6–27) months and 101 patients (69%) received previous ARAT therapy. The patients' backgrounds at the start of DOC and CBZ treatment are presented in Table 1. The median duration of follow-up was 16 months from the start of DOC treatment. The percent PSA decrease exceeded 50% in 52 patients (36%) during DOC treatment and 35 (24%) during CBZ treatment (Fig. 1A). The changes of PSA levels during DOC and CBZ treatment were not correlated ($R^2 = 0.0005$, Fig. 1B, C). The median (IQR) number of cycles of DOC and CBZ treatment were 6 (4–10) and 4 (3–8), respectively. The median (95% CI) PFS for DOC and CBZ were 4 (3–4) and 3 (2–3) months, respectively (Fig. 1D, E). The time to progression after DOC and CBZ treatment was not correlated ($R^2 = 0.0003$, Fig. 1F).

In univariate Cox proportional hazard analyses, the associations of PFS from the start of DOC and CBZ treatment with the following variables were examined: age > 70 years, PS ≥ 1, GS ≥ 9, previous ARAT use, PSA > 20 ng/mL at DOC or > 40 ng/mL at CBZ, Hb < 13 g/dL, LDH > 220 U/L, ALP > 280 U/L, and ≥ 4 bone metastases or visceral metastases. The existence of ≥ 4 bone metastases or visceral metastases was associated with shorter PFS of DOC, and LDH > 220 U/L was associated with shorter PFS of CBZ (Table 2). The median (95% CI) combined PFS for DOC-CBZ was 11 (10–13) months. Cox proportional hazard analyses were performed for the combined PFS of DOC-CBZ using the parameter levels at the start of DOC treatment. PSA > 20 ng/mL at the start of DOC treatment was significantly associated with shorter PFS in univariate and multivariate analyses (hazard ratio [HR] = 1.81, 95% CI = 1.20–2.72, $P = 0.004$, Table 3). The combined PFS of DOC-CBZ was compared between patients with PSA > 20 ng/mL and PSA ≤ 20 ng/mL at the start of DOC treatment. The combined PFS of DOC-CBZ was significantly longer in patients with PSA ≤ 20 ng/mL (median PFS = 12 months, 95% CI = 11–16) than in patients with PSA > 20
ng/mL (median PFS = 10 months, 95% CI = 8–11) at the start of DOC treatment (P = 0.003, Fig. 2A) and was significantly longer in patients with PSA ≤ 40 ng/mL (median PFS = 13 months, 95% CI = 11–16) than in patients with PSA > 40 ng/mL (median PFS = 9 months, 95% CI = 8–11) at the start of CBZ treatment (P = 0.017, Fig. 2B).

The median (95% CI) OS from the initiation of DOC was 22 (18–26) months. Cox proportional hazard analyses were performed for OS using the same parameters used for PFS. In univariate analyses, PSA > 20 ng/mL, Hb < 13 g/dL, and ALP > 280 U/L were significantly associated with shorter OS. In multivariate analyses, PSA > 20 ng/mL remained significantly associated with shorter OS (HR = 2.55, 95% CI = 1.45–4.48, P = 0.001, Table 4), together with Hb < 13 g/dL and LDH > 220 U/L. OS from the initiation of DOC treatment was significantly longer in patients with PSA ≤ 20 ng/mL (median OS = 31 months, 95% CI = 22–44) than in those with PSA > 20 ng/mL (median OS = 18 months, 95% CI = 15–25) at the start of DOC treatment (P = 0.002, Fig. 3A). OS from the initiation of DOC treatment was also significantly longer in patients with PSA ≤ 40 ng/mL (median OS = 34 months, 95% CI = 22–42) than in those with PSA > 40 ng/mL (median OS = 18 months, 95% CI = 15–22) at the start of CBZ treatment (P = 0.003, Fig. 3B). In patients with PSA ≤ 20 ng/mL and PSA > 20 ng/mL at the start of DOC treatment, the median PSA levels at the start of CBZ were 15 ng/ml and 100 ng/ml, respectively. In patients with PSA ≤ 20 ng/mL at the start of DOC treatment, OS from the initiation of DOC treatment was not significantly different between patients with PSA ≤ 15 ng/mL (median OS = 31 months, 95% CI = 16–not reached) and PSA > 15 ng/mL (median OS = 25 months, 95% CI = 22–47) at the start of CBZ treatment (P = 0.962). In patients with PSA > 20 ng/mL at the start of DOC treatment, OS from the start of DOC treatment was significantly longer in patients with PSA ≤ 100 ng/mL (median OS = 26 months, 95% CI = 13–37) than in those with PSA > 100 ng/mL (median OS = 16 months, 95% CI = 13–20) at the start of CBZ treatment (P = 0.048, Fig. 3C).

The patients starting DOC at lower PSA levels might include patients for whom primary ADT was more effective. However, time to CRPC was not significantly different between high PSA (median: 10 months) and low PSA (median: 12 months) at the start of DOC (p = 0.29). Starting DOC at lower PSA levels means that DOC was started earlier in disease progression. OS from the initiation of DOC seemed to be longer when DOC treatment was started earlier. To resolve the bias, the OS from the development of CRPC was examined. OS from CRPC was compared between patients with PSA > 70 ng/mL and PSA ≤ 70 ng/mL at the start of ADT, between patients with PSA > 20 ng/mL and PSA ≤ 20 ng/mL at the start of DOC treatment, and between patients with PSA > 40 ng/mL and PSA ≤ 40 ng/mL at the start of CBZ treatment. OS did not differ according to PSA levels at the start of ADT (median OS: 44 months vs. 48 months, P = 0.166, Fig. 4A), but it was significantly longer in patients with low PSA levels at the start of DOC (median OS: 55 months vs. 41 months, P = 0.030, Fig. 4B). In addition, OS tended to be longer in patients with low PSA levels at the start of CBZ (median OS: 70 months vs. 44 months, P = 0.064, Fig. 4C).

**Discussion**

The standard treatment strategy for metastatic prostate cancer has shifted to the use of life-extending therapies during earlier stages of disease. ARATs, including abiraterone, enzalutamide, and apalutamide,
in combination with ADT prolonged survival among patients with metastatic HNPC \textsuperscript{6–8}. These drugs also prolonged metastasis-free survival in patients with non-metastatic CRPC \textsuperscript{14–16}. For patients with metastatic CRPC that progressed during ARAT treatment, DOC was more effective than alternative ARATs and was considered the second-line treatment \textsuperscript{17}. CBZ is a next-generation taxane that has been approved for the treatment of metastatic CRPC in patients who previously received DOC \textsuperscript{4}. Research has suggested that CBZ retains activity in patients whose disease progressed during ARAT or DOC treatment \textsuperscript{18}. The CARD trial demonstrated that CBZ was superior to an alternative ARAT in patients previously treated with DOC and ARATs \textsuperscript{10,11}. These results indicate that DOC followed by CBZ might be the most appropriate treatment sequence for patients with metastatic CRPC resistant to ARAT. We previously reported that the number of life-prolonging agents such as ARAT, DOC, CBZ or Radium-223 was positively correlated with longer survival of CRPC patients\textsuperscript{19}. However, as far as USA real world data, only 11\% of patients received CBZ as a third line therapy for CRPC\textsuperscript{20}. To use CBZ at an appropriate timing after DOC might contribute to prolong the prognosis of CRPC patients.

The Prostate Cancer Clinical Trials Working Group 3 (PCWG3), an international expert committee of prostate cancer clinical investigators, established several definitions for disease progression including PSA, radiological, and clinical progression in the treatment for CRPC \textsuperscript{13}. However, the timing for starting second- or third-line treatment was not determined by PCWG3, and other guidelines did not provide clarification. In our study, individual physicians decided on the timing for starting DOC and CBZ and chose to start treatment at various PSA levels either without waiting for radiological progression or after radiological progression. In multivariate Cox proportional hazard analyses, lower PSA levels at the start of DOC treatment were significantly associated with longer PFS and OS from the initiation of DOC treatment. Moreover, the patients that started DOC at lower PSA levels had longer OS from CRPC. PSA is a useful serum marker for prostate cancer, and it can be easily measured because of its more dynamic changes compared with radiological changes during treatment. In cases in which PSA levels increase rapidly during ADT or ARAT treatment, starting DOC regardless of radiological progression might possibly prolong the prognosis of CRPC patients.

A previous study reported no significant association between the efficacy of DOC and CBZ treatment \textsuperscript{21,22}. Consistent with these reports, the percent PSA reduction and time to progression between DOC and CBZ was not correlated in our study, indicating that CBZ was effective in some patients for whom DOC was not effective. Patients with lower PSA levels at the start of CBZ had longer PFS and OS from the initiation of DOC. Moreover, in patients with higher PSA levels at the initiation of DOC treatment, OS from the start of DOC was significantly longer in those with lower PSA levels at the start of CBZ treatment. The TAXYNERGY study was a phase 2 trial that evaluated the clinical benefits of an early switch from DOC to CBZ or vice versa in patients with less than 30\% PSA reductions after four cycles of treatment \textsuperscript{23}. The early taxane switch strategy was associated with improved PSA response rates compared with the previous reported study of DOC treatment \textsuperscript{3}. However, the trial was not designed to definitively answer whether a taxane switch strategy was superior to waiting until disease progression. Such questions
should form the basis for future studies randomly assigning patients to a switch strategy versus a no switch strategy. Furthermore, CBZ has a different safety profile than DOC, including lower rates of alopecia, peripheral neuropathy, peripheral edema, and nail disorders\textsuperscript{24,25}. To elucidate the safety and efficacy benefits of an early switch from DOC to CBZ, a prospective study is needed to evaluate survival and patient-reported outcomes.

We focused on PSA levels at the start of DOC and CBZ treatment for the analyses in this study. Low Hb levels and high LDH levels were also significantly associated with shorter OS in multivariate analyses (Table 4). Many biomarkers have been reported and are clinically used to predict the prognosis of patients with prostate cancer\textsuperscript{26}. We previously reported that a high GS, high LDH levels, and the presence of visceral metastasis were associated with poor prognosis in patients with metastatic HNPC\textsuperscript{27}. In our previous study of the efficacy of CBZ, high PSA levels, low Hb levels, and a low initial CBZ dose were associated with OS from the initiation of CBZ\textsuperscript{12}. The initial dose or relative dose intensity of DOC and CBZ was not associated with PFS or OS in this study (data not shown). This finding contradicted that of a previous study, possibly because the follow-up duration was longer in the current study and only patients receiving sequential DOC-CBZ treatment were included in this study. The clinical utilization of these biomarkers combined with PSA levels helps guide clinical decision-making because of an improved understanding of the prognosis and the risk of progression in patients with CRPC.

This study had several limitations. First, most patients in this study received ADT alone or ADT and bicalutamide as a primary treatment. ADT combined with ARATs has been considered the standard primary treatment for patients with metastatic prostate cancer. PSA levels at the start of DOC and CBZ among patients with CRPC who are receiving ADT plus ARAT treatment might be lower, and the results might be different from those in the current study. Second, the number of patients was too small to permit precise statistical analyses. We used PSA levels as parameters for predicting PFS and OS. However, the nadir PSA level or PSA doubling time might be associated with the prognosis of CRPC. These parameters could not be included in the statistical analyses because of the small number of patients. Third, this study was retrospective, and it lacked a control group. In addition, the treatment protocol differed among institutions. Further prospective studies are needed to determine the optimal timing of starting DOC and switching to CBZ in patients with CRPC.

**Conclusions**

In conclusion, we evaluated the efficacy of DOC-CBZ sequential therapy for CRPC. In patients for whom DOC was not effective, sequential CBZ might effectively reduce PSA levels for a long duration. Starting DOC and switching to CBZ when PSA levels are lower might result in improved prognoses in patients with CRPC.

**Abbreviations**
DOC: docetaxel, CBZ: cabazitaxel, CRPC: castration-resistant prostate cancer, PSA: prostate-specific antigen, PFS: progression-free survival, OS: overall survival, ADT: androgen deprivation therapy, ARAT: androgen receptor axis–targeting agents, HNPC: hormone-naïve prostate cancer, IQR: interquartile range, CI: confidence interval, GS: Gleason's score, PS: performance status, Hb: hemoglobin, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, PCWG3: Prostate Cancer Clinical Trials Working Group 3,

Declarations

Ethics approval and consent to participate

This study was approved by the Yamagata University ethics committee and by the institutional review board of each university. Written informed consent was not necessarily required in this observational noninvasive retrospective study according to the local guidelines (the Ethical Guidelines for Medical and Health Research Involving Human Subjects by the Ministry of Health, Labour and Welfare of Japan).

Consent for publication

This manuscript contains no individual person's data.

Availability of data and materials

The datasets generated during the current study are not publicly available due to ethical restrictions, but are available from the corresponding author on reasonable request.

Competing interests

Dr. Narita received honoraria from Janssen. Dr. Masumori received honoraria from Astellas, Takeda, AstraZeneca, Janssen, Kissei, Daiichi-sankyo. Dr. Habuchi received honoraria from Janssen, Takeda, Astellas, AstraZeneca, Sanofi, and Bayer and research funding from Takeda, Astellas, Sanofi and Bayer. Other authors had no conflict of interest to declare.

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Authors’ contributions

TKa made substantial contributions to the conception and design, acquisition of data, and data analysis. NTe drafted the manuscript and approved the submitted version. He also made substantial contributions
All authors have read and approved the final manuscript.

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**Table**

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

**Figures**
Changes in prostate-specific antigen (PSA) levels and progression-free survival (PFS) by docetaxel (DOC) and cabazitaxel (CBZ) treatment. A. Waterfall plot of the changes of PSA levels during DOC (blue) and CBZ treatment (red). PSA levels declined by more than 50% in 36% (52/146) of patients during DOC treatment and 24% (35/146) of patients during CBZ treatment. B. The percent reduction of PSA levels in each patient during DOC (blue) and CBZ treatment (red). C. Correlation of PSA changes between DOC and CBZ (R² = 0.0005). D. Kaplan–Meier curve of PFS after DOC treatment. Median (95% CI) survival time was 4 (3–4) months. E. Kaplan–Meier curve of PFS after CBZ treatment. Median (95% CI) survival time was 3 (2–3) months. F. Correlation of time to progression between DOC and CBZ (R² = 0.0003).
Figure 2

Progression-free survival (PFS) for docetaxel (DOC)-cabazitaxel (CBZ) treatment according to the prostate-specific antigen (PSA) level at the start of DOC and CBZ (Kaplan–Meier curves and P in the log-rank test). A. PFS in patients with PSA ≤ 20 ng/mL (black) or PSA > 20 ng/mL (red) at the start of DOC (D). Median (95% CI) survival time: 12 (11–16) vs. 10 (8–11) months (P = 0.003). B. PFS in patients with PSA ≤ 40 ng/mL (black) or PSA > 40 ng/mL (red) at the start of CBZ (C). Median (95% CI) survival time: 13 (11–16) vs. 9 (8–11) months (P = 0.017).
Figure 3

Overall survival (OS) from the start of docetaxel (DOC) according to the prostate-specific antigen (PSA) level at the start of DOC and cabazitaxel (CBZ) (Kaplan–Meier curves and P in the log-rank test). A. OS in patients with PSA ≤ 20 ng/mL (black) or PSA > 20 ng/mL (red) at the start of DOC. Median (95% CI) survival time: 31 (22–44) vs. 18 (15–25) months (P = 0.002). B. OS in patients with PSA ≤ 40 ng/mL (black) or PSA > 40 ng/mL (red) at the start of CBZ. Median (95% CI) survival time: 34 (22–42) vs. 18 (15–22) months (P = 0.003). C. OS in patients with PSA ≤ 15 ng/mL (black) or PSA > 15 ng/mL (red) at the start of CBZ in patients with PSA ≤ 20 ng/mL at the start of DOC. Median (95% CI) survival time: 31 (16–not reached) vs. 25 (22–47) months (P = 0.962). OS in patients with PSA ≤ 100 ng/mL (green) or PSA > 100 ng/mL (blue) at the start of CBZ in patients with PSA > 20 ng/mL at the start of DOC. Median (95% CI) survival time: 26 (13–37) vs. 16 (13–20) months (P = 0.048).
Figure 4

Overall survival (OS) from confirmation of castration-resistant prostate cancer (CRPC) according to the prostate-specific antigen (PSA) level at the start of androgen deprivation therapy (ADT), docetaxel (DOC), and cabazitaxel (CBZ) (Kaplan–Meier curves and P in the log-rank test). A. OS in patients with PSA $\leq 70$ ng/mL (black) or PSA $> 70$ ng/mL (red) at the start of ADT. Median (95% CI) survival time: 44 (31–55) vs. 48 (37–76) months ($P = 0.166$). B. OS in patients with PSA $\leq 20$ ng/mL (black) or PSA $> 20$ ng/mL (red) at the start of DOC. Median (95% CI) survival time: 55 (43–not reached) vs. 41 (30–52) months ($P = 0.030$). C. OS in patients with PSA $\leq 40$ ng/mL (black) or PSA $> 40$ ng/mL (red) at the start of CBZ. Median (95% CI) survival time: 70 (34–76) vs. 44 (31–52) months ($P = 0.064$).

Supplementary Files

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