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Risk Factors for Poor Survival in Metastatic Castration-resistant Prostate Cancer Treated With Cabazitaxel in Japan

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Abstract. *Background/Aim: Cabazitaxel (CBZ) is approved for docetaxel-resistant castration-resistant prostate cancer (CRPC). This retrospective study aimed at assessing the efficacy and prognostic markers of cabazitaxel treatment in Japanese CRPC patients. Patients and Methods: The medical records of 44 consecutive Japanese patients with CRPC who started cabazitaxel at our Institution between January 2011 and February 2019 were reviewed and statistically analysed. Results: The median follow-up period after cabazitaxel initiation was 13.2 [interquartile range (IQR)=6.9-21.5] months. The objective response rate, median progression-free survival period, and median overall survival period (OS) were 45.5%, 4.3 months, and 20.7 months, respectively. On multivariate analysis, higher prostate-specific antigen (PSA; >100 ng/ml), lower haemoglobin (<10 g/dl), and lower number of prior docetaxel therapy cycles (<10) were predictors for shorter OS. Conclusion: Patients with anemia, high PSA, and lower number of docetaxel therapy cycles might have shorter survival period from introduction of cabazitaxel therapy. In addition, PSA decline might still be a useful indicator as a predictor of prognosis of the metastatic CRPC patients treated with cabazitaxel.*

Prostate cancer is the most frequently diagnosed malignant disease and the sixth leading cause of cancer death among men in Japan (1, 2). According to the cancer statistics in Japan, it has been estimated that there are 92,600 newly-diagnosed prostate cancer patients each year, with an estimate of 12,300 prostate cancer-specific deaths (1, 2). Regarding patients with local disease, robot-associated radical prostatectomy has been the mainstay of surgical treatment in recent Japanese clinical practice. Approved radiation therapies for curative intent include intensity-modulated radiation therapy (IMRT) and particle therapies, including proton therapy and heavy particle therapy, which are also covered by medical insurance in Japan (1, 2).

However, between 10% and 15% of patients present with advanced disease at initial diagnosis, and these curative treatment modalities are not indicated for them (3). These patients with metastatic disease receive androgen-deprivation therapy as their initial treatment, but patients invariably develop progressive disease, which is called castration-resistant prostate cancer (CRPC). Docetaxel had been the only agent showing efficacy and prolonging the survival of CRPC patients (4). In recent years, several effective systemic agents for these CRPC patients have become available, such as the new androgen receptor targeted agents, abiraterone acetate (Zytiga, Jansen Pharmaceutical K.K.) and enzalutamide (Xtandi, Astellas), as well as the novel taxane chemotherapy agent, cabazitaxel (Jevtana, Sanofi), which were approved in 2014 (5-9). In addition, an alpha emitter, radium-223 dichloride (Xofigo, Bayer), was also approved for patients with bone metastatic CRPC in 2016 (10). Those drugs show promising anti-tumour efficacy and manageable safety profiles, as it was demonstrated in the respective international phase III clinical trials; thus, these agents are being rapidly introduced as CRPC therapy in clinical practice in Japan (5-11).

Of these newly-approved agents, cabazitaxel is a novel taxane drug with activity against docetaxel-resistant cancers (9). In the TROPIC phase III clinical trial, treatment with cabazitaxel plus prednisone demonstrated important clinical antitumour activity, improving overall survival (OS) in patients with metastatic CRPC, whose disease had progressed during or after docetaxel-based therapy (9). However, information regarding efficacy and adverse events with this treatment in real-world clinical practice is limited (12-16). In addition, the newly-approved life-prolonging

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agents described above are usually administered before or after cabazitaxel therapy. Therefore, the prognosis of patients with CRPC treated with cabazitaxel might be complicated. The present retrospective study examined the therapeutic outcomes, safety profiles, and prognostic factors of cabazitaxel for Japanese patients with CRPC after docetaxel chemotherapy in real-world clinical practice.

Patients and Methods

Patients. The medical records of patients with previous docetaxel chemotherapy for the treatment of metastatic CRPC who received cabazitaxel as second or later-line therapy at Cancer Institute Hospital Ariake between January 2011 and February 2019 were retrospectively reviewed. This study received the approval of the institutional review board of the Cancer Institute Hospital, Japanese Foundation for Cancer Research. Before the initial treatment, all patients gave their written informed consent.

Treatment and follow-up examination. Cabazitaxel (initial dose: 20 or 25 mg/m^2) was administered every 3 to 4 weeks, as previously described (9). Patients' medical history, including physical examination findings and Eastern Cooperative Oncology Group performance status (ECOG-PS), laboratory findings, and chest radiography data before starting treatment and during cabazitaxel therapy, as assessed based on the attending physician's discretion, were reviewed. The response to therapy was evaluated objectively by the serum prostate-specific antigen (PSA) level and computed tomography every 2 or 3 months using the Prostate Cancer Working Group 2 (PCWG2) response criteria (17). Toxicity was assessed by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Statistical analysis. The PSA-progression-free survival (PFS) and OS periods were defined as the periods from initial administration of cabazitaxel until PSA values reached 2 ng/ml and ≥25% relative to the nadir or the pre-treatment PSA value (or radiological progression according to the PCWG2 definition) and death from any cause, respectively (17). Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. All statistical analyses were performed using JMP software version 14.0 (SAS Institute Inc., Cary, NC), and p-values<0.05 were considered significant.

Results

Patient characteristics. The study included 44 consecutive patients diagnosed with metastatic CRPC, who started treatment with cabazitaxel after docetaxel chemotherapy at our hospital between January 2011 and February 2019. The characteristics of these patients are shown in Table I. The patients' median age was 70 years (range=41-83), and 11 (25%) were older than 75 years. Twelve patients (27%) had pain from metastatic disease and were administered analgesic agents. All patients had metastatic disease, with bone (n=35, 80%) and lymph nodes (n=17, 39%) as the most common metastatic sites. Of these patients, 32 (73%) and 25 (57%) had a history of prior enzalutamide and abiraterone therapies, respectively. The median number of prior docetaxel therapy cycles was 10 (range=1-29), and 24 patients (55%) had ≥10 cycles of docetaxel chemotherapy before cabazitaxel.

Efficacy of cabazitaxel after docetaxel therapy. The median observation period of the patients treated with cabazitaxel in this study was 13.2 months [interquartile range (IQR)=6.9-21.5]. During this period, 24 patients (54.5%) died from disease progression, whereas 21 patients were alive with disease. There were no treatment-related deaths. The objective PSA response rate (ORR) was 37% (Figure 1A). The estimated median PSA-PFS period was 4.3 (IQR=1.5-7.4) months, and the 3- and 6-month PSA-PFS rates were 58.8% and 35.8%, respectively (Figure 1B). The median OS period was 20.7 months (range=2.1-49.0), and the estimated 6-, 12-, and 24-month OS rates were 92.7%, 75.3%, and 39.7%, respectively (Figure 1C).

Haematological adverse events. The most clinically important adverse events of cabazitaxel are decreased neutrophils and consequent febrile neutropenia. Of the patients, 6 did not receive pegfilgrastim (G-Lasta, Kirin Pharma) because it was not available at that time. These 6 patients were excluded, and the remaining 38 patients who received pegfilgrastim for prophylaxis of the neutropenia were investigated. Of these 38 patients, the initial dose was 25 mg/m^2 for 25 patients and 20 mg/m^2 for 13 patients determined by the respective attending physicians. In this study, 57.9% (22/38) and 15.8% (6/38) of the patients still developed Grade 3/4 neutropenia and febrile neutropenia, respectively, with pegfilgrastim support. There was no difference in the frequency of Grade 3/4 neutropenia and febrile neutropenia between patients whose initial dose was 25 mg/m^2 [56.0% (14/25) and 20.0% (5/25), respectively] and those whose initial dose was 20 mg/m^2 [61.5% (8/13) and 7.7% (1/13), respectively]. In addition, there were no differences in Grade 3/4 neutropenia and febrile neutropenia between the patients >75 years old [55.6% (15/27) and 18.5% (5/27), respectively] and <75 years old [63.6% (7/11) and 9.1% (1/11), respectively].

Risk factors for short survival period at the induction of cabazitaxel therapy. Next, variables that could predict a shorter OS period for patients with metastatic CRPC treated with cabazitaxel as second or later-line therapy were investigated. On univariate analysis, few prior cycles of docetaxel (<10 cycles), worse PSA response (<50%) during prior docetaxel therapy, lower haemoglobin concentration (<10 g/dl), higher serum PSA level (>100 ng/ml), and higher serum C-reactive protein (CRP) level [>upper limit of the normal range (ULN)] were identified as factors predictive of a shorter OS. On multivariate analysis, few prior cycles of

Table I. *Patient characteristics (n=44).*

Variable	N (%)
Age (years)	70 (41-83)*
<75	33 (75%)
≥75	11 (25%)
Gleason score	
7	4 (9%)
8	5 (11%)
9	31 (71%)
10	4 (9%)
ECOG-PS	
≥0	41 (93%)
1	3 (7%)
Symptoms	12 (27%)
Pre-treatment PSA (ng/ml)	19.2 (0-4,262) *
<100	26 (59%)
≥100	18 (41%)
Prior prostatectomy	9 (21%)
Prior radiotherapy for primary lesion	15 (34%)
Metastatic sites	
Lung	3 (7%)
Liver	1 (2%)
Lymph node	17 (39%)
Bone	35 (80%)
Hb (mg/dl)	
≥10	38 (86%)
<10	6 (14%)
ALP (mg/dl)	
<300	32 (73%)
≥300	12 (27%)
CRP (mg/dl)	
<0.5	28 (64%)
≥0.5	16 (36%)
LDH	
<ULN	28 (64%)
≥ULN	16 (36%)
NLR	
<5	28 (64%)
≥5	16 (36%)
Prior 2nd androgen receptor targeted agents	
Enzalutamide	32 (73%)
Abiraterone	25 (57%)
Previous number of treatments for CRPC	
1	8 (18%)
2	15 (34%)
3	21 (48%)
Docetaxel therapy	10 (1-29)*
≥10 cycles	24 (55%)
<10 cycles	20 (45%)
Responder/	29 (66%)
Non-responder	15 (34%)
Initial dose of cabazitaxel (mg/m^2)	
25	31 (71%)/13 (29%)
20	

ECOG PS, Eastern Cooperative Oncology Group-performance status; PSA, prostate-specific antigen; Hb, haemoglobin; ALP, alkaline phosphatase; CRP, C reactive protein; LDH, lactate dehydrogenase; NLR, neutrophil-lymphocyte ratio; CRPC, castration-resistat prostate carcinoma. *Data presented as mean (range).

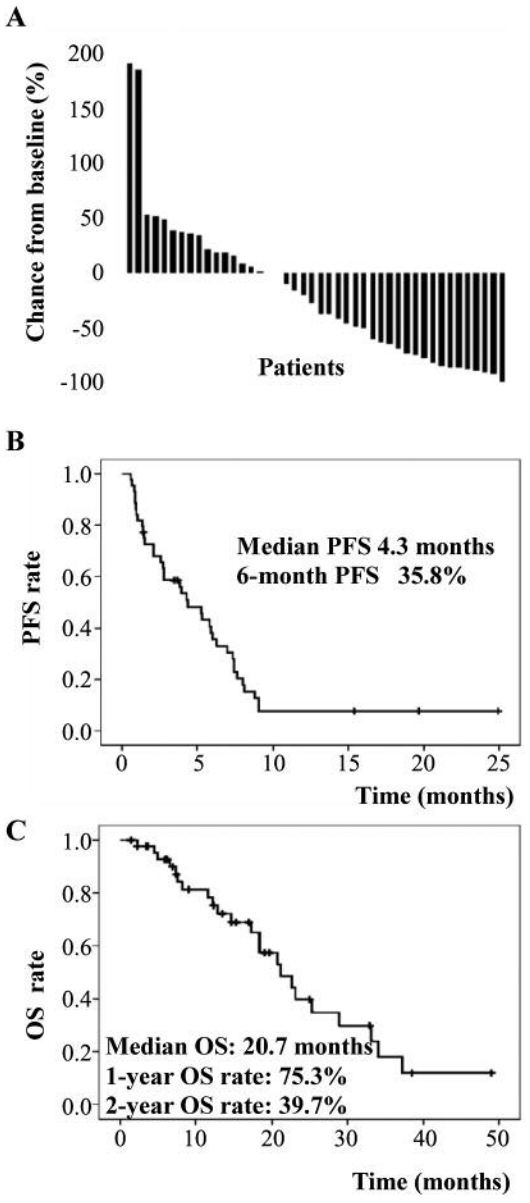

Figure 1. *Efficacy of cabazitaxel as second or later-line treatment for the studied Japanese patients (n=44) with docetaxel chemotherapy-resistant metastatic castration-resistant prostate cancer. Waterfall plots of the prostate-specific antigen (PSA) response (A). Progression-free survival (PFS) and overall survival (OS) curves for the study cohort are shown (B, C).*

docetaxel (<10 cycles) [hazard ratio (HR)=23.14, 95% confidence interval (CI)=6.57-111.40, p<0.0001], lower haemoglobin concentration (<10 g/dl) (HR=21.30, 95% CI=4.53-121.64, p=0.002), and higher serum PSA level (>100 ng/ml) (HR=3.65, 95% CI=1.39-10.60, p=0.0085) were identified as independent factors predictive of shorter OS (Table II). The median OS of the patients with few prior

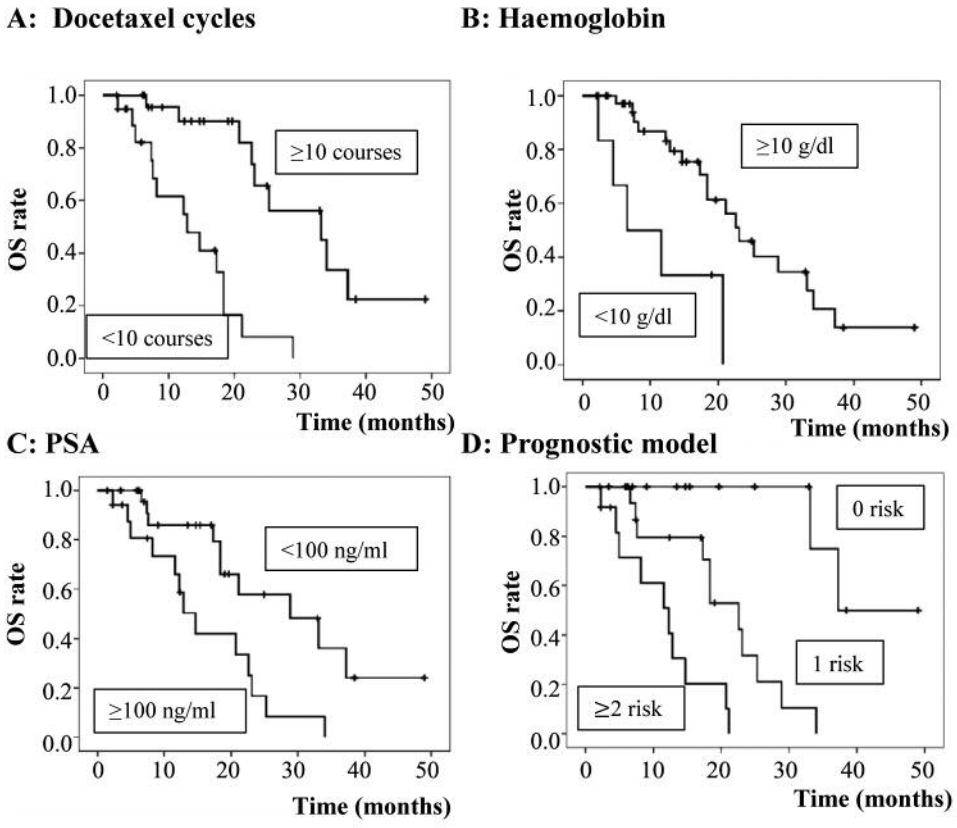

Figure 2. *Risk factors for short survival period at induction of cabazitaxel therapy. On multivariate analysis, <10 prior cycles of docetaxel (A), lower haemoglobin concentration (<10 g/dl) (B), and higher serum prostate-specific antigen (PSA) level (>100 ng/ml) (C) were shown as independent factors predictive of a shorter overall survival (OS) period. Our prognostic model, which includes 3 risk factors, namely poor performance status (≥2), presence of liver metastasis, and elevated C-reactive protein levels (>upper limit of the normal range), stratifies patients treated with cabazitaxel into three risk groups [good: 0 risk factors, n=14 (35%); intermediate: 1 risk factor, n=18 (45%); and poor: ≥2 risk factors, n=8 (20%)] (C).The prognostic model distinctly separates the OS curves of the three risk groups (p<0.001).*

cycles of docetaxel (<10 cycles) was 12.3 months, whereas that of patients with many prior cycles of docetaxel (≥10 cycles) was 32.9 months (Figure 2A). The median OS of the patients with lower haemoglobin concentration (<10 g/dl) was 6.6 months, whereas that of patients with normal haemoglobin concentration (≥10 g/dl) was 22.6 months (Figure 2B). In addition, the median OS of patients with higher serum PSA levels (≥100 ng/ml) was 12.9 months, whereas that of patients with lower serum PSA levels (<100 ng/ml) was 32.9 months (Figure 2C).

Next, a prognostic model was established using these three risk factors to stratify patients treated with cabazitaxel into three risk groups: good (0 risk factors, n=14), intermediate (1 risk factor, n=18), and poor (≥2 risk factors, n=12) risk groups. The median OS periods of patients in the good, intermediate, and poor risk groups were 49.0, 19.1, and 11.6 months, respectively. The 24-month OS rate of patients in the good risk group was 100%. In addition, the 12- and 24-month OS rates of patients in the intermediate risk group were 79.4% and 31.8%, respectively. Conversely, the 12- and 24-month OS rates of patients in the poor risk group were 40.7% and 0%, respectively. In this prognostic model, the OS curves of the three groups were significantly different (Figure 2D, good risk *vs*. intermediate risk $p<0.0005$, intermediate risk *vs*. poor risk $p<0.0033$, good risk *vs*. poor risk $p<0.001$).

Relationships between overall survival periods and response and adverse events of cabazitaxel therapy. Finally, the relationships between the response and OS periods of patients treated with cabazitaxel were investigated. The OS periods of patients who had a PSA response ≥50% were significantly longer (median OS=28.9 months, 95% CI=3.5-49.0) than those of patients who did not have a PSA response ≥50% (median OS=14.7 months, 95% CI=2.1-33.1, $p=0.0013$) (Figure 3). In addition, some investigators

Table II. *Univariate and multivariate analyses of prognostic factors for poor outcomes with cabazitaxel therapy.*

Subgroup	Univariate analysis HR (95% CI)	*p*-Value	Multivariate analysis HR (95% CI)	*p*-Value	Reference category
Age (years)	1.76 (4.68-0.57)	0.30			≥75/<75
ECOG PS	5.01 (40.66-0.24)	0.23			≥PS1/PS=0
Symptom	2.47 (7.24-0.75)	0.13			Yes/No
Prior docetaxel cycles	7.21 (21.13-2.77)	<0.0001	23.14 (6.57-111.40)	<0.0001	<10 cycles/≥10 cycles
Prior docetaxel PSA response	3.72 (9.44-1.51)	0.0048	1.49 (0.47-4.81)	0.50	<50%/≥50%
Visceral metastasis	0.48 (2.34-0.027)	0.42			Positive/Negative
Treatment line	1.98 (4.83-0.83)	0.12			4th-line/2nd,3rd-line
Start dose of cabazitaxel	0.96 (3.41-0.35)	0.95			20 mg/m^2/25 mg/m^2
Prior abiraterone	1.23 (2.99-0.54)	0.62			Yes/No
Prior enzalutamide	1.22 (3.10-0.52)	0.65			Yes/No
Haemoglobin (g/dl)	4.30 (12.16-1.33)	0.017	21.30 (4.53-121.64)	0.0002	<10/≥10
PSA (ng/ml)	3.42 (8.68-1.44)	0.0051	3.65 (1.39-10.60)	0.0085	≥100/<100
LDH (mIU/ml)	1.93 (4.69-0.77)	0.16			>ULN/normal range
CRP (mIU/ml)	2.79 (6.65-1.15)	0.024	3.13 (0.97-10.09)	0.062	>ULN/normal range
NLR	0.90 (2.07-0.37)	0.81			>2/≤2
ALP (mIU/ml)	1.54 (3.63-0.59)	0.36			>ULN/normal range

HR, Hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group-performance status; PSA, prostate-specific antigen; ULN, upper limit of the normal range; LDH, lactate dehydrogenase; CRP, C-reactive protein; NLR, neutrophil-lymphocyte ratio; ALP, alkaline phosphatase.

reported that the presence of these adverse events was a predictor of a long OS period (15). In the present study, however, there were no significant differences in OS periods between the presence and absence of Grade 3/4 neutropenia and between the presence and absence of febrile neutropenia.

Discussion

In this study, our initial experience with cabazitaxel for Japanese patients with metastatic CRPC patients after docetaxel was reported. The 50% PSA response rate was 37%, and the estimated median PFS and OS periods were 4.4 months and 20.4 months, respectively (Figures 1A, B, and C). The estimated 6-, 12-, and 24-month OS rates were 92.7%, 75.3%, and 39.7%, respectively. All these results are numerically better than those reported in the international phase III trial of cabazitaxel for patients with metastatic CRPC, *i.e.* the TROPIC trial, which included only relatively young patients (<75 years). On the other hand, since the present study was a real-world clinical practice retrospective study, it included 11 (25%) relatively old patients (>75 years).

In this study, few prior cycles of docetaxel (<10 cycles), lower haemoglobin concentration (<10 g/dl), and higher serum PSA level (>100 ng/ml) were identified as independent predictors of a shorter OS period (Table II). In addition, a prognostic model was established using these three risk factors, in which the OS curves of the three groups were distinctly different from each other (Figure 2D).

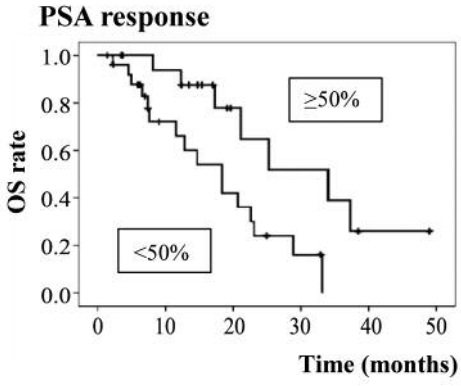

Figure 3. *Biomarkers for overall survival with cabazitaxel therapy. Median overall survival (OS) period of patients who had a prostate-specific antigen (PSA) response ≥50% is 30 months, whereas that of the patients whose PSA response was not ≥50% is 12 months (p=0.0013).*

Regarding the prognostic factors in the CRPC patients treated with second-line cabazitaxel, Halabi *et al*. reported nine risk factors from the TROPIC phase III clinical trial, which included ECOG PS, time since last docetaxel use, measurable disease, presence of visceral disease, pain, duration of hormone use, haemoglobin, PSA, and alkaline phosphatase (ALP) (18). Several distinct predictors of OS were identified as compared to this model, which was constructed from the TROPIC trial (9,18). The inconsistence between the identified variables in the final model from

Halabi *et al*. and the present cohort may be due to a different population and different pre- and post-treatment agents. As described previously, in recent years, several effective systemic agents other than cabazitaxel, including abiraterone acetate, enzalutamide, and radium-223, have become available for these CRPC patients. Indeed, in the present study, 32 (73%) and 25 patients (57%) had prior enzalutamide and abiraterone acetate therapy, respectively (Table I). These newly approved agents might alter the prognosis of CRPC patients after cabazitaxel.

Regarding the PSA response to cabazitaxel therapy, the patients with a PSA response ≥50% had a significantly longer OS period (median OS=30 months, 95% CI=5-40) than patients who did not have PSA response ≥50% (median OS=12 months, 95% CI=5-13, p=0.001) (Figure 3). In the era of chemotherapy for CRPC, PSA is not a prognostic factor, and relying on PSA changes in metastatic CRPC patients might mislead clinicians into continuing or changing a patient's treatment (4, 11). However, the present study suggested that a PSA decrease is still a useful predictor of prognosis for metastatic CRPC patients treated with cabazitaxel.

Since prophylactic administration of pegfilgrastim was not allowed at cycle 1, Grade 3/4 neutropenia and febrile neutropenia occurred in 100% and 54.5% of patients, respectively, in the phase I cabazitaxel clinical trial in Japanese patients with metastatic CRPC (19, 20). In addition, in the PROSELICA study, Grade 3/4 neutropenia was observed in 57.1% and 82.1% of patients treated with 20 mg/m^2 and 25 mg/m^2 of cabazitaxel, respectively, without altering efficacy (21). In the present study, 57.9% (22/38) and 15.8% (6/38) of the patients still experienced Grade 3/4 neutropenia and febrile neutropenia, respectively, with pegfilgrastim support. In addition, there were no differences in the frequencies of Grade 3/4 neutropenia and of febrile neutropenia between patients whose initial doses were 25 mg/m^2 and 20 mg/m^2. The lack of a significant difference was considered to be due to the retrospective design of this study and the patient selection bias based on the physicians' decisions.

This retrospective pilot study was conducted to clarify the efficacy and prognostic factors of cabazitaxel therapy in Japanese patients. The major limitations of the present study are its retrospective design and small cohort size. However, large, multi-institutional, and prospective or retrospective studies of cabazitaxel therapy have been limited in Japan (11-15, 19, 20). The present findings thus describe the features of cabazitaxel therapy for metastatic CRPC patients in current clinical practice in Japan.

Conclusion

In this study, a relatively better efficacy of cabazitaxel therapy for Japanese patients with metastatic CRPC in real-world clinical practice was demonstrated compared with the TROPIC trial. Patients with anaemia, high PSA, and fewer cycles of prior docetaxel therapy might have shorter survival periods from the start of cabazitaxel therapy. In addition, a PSA decrease might still be a useful predictor of prognosis for metastatic CRPC patients treated with cabazitaxel.

Authors' Contributions

Study Conception and Design: SY and TY; Manuscript writing: SY and TY; Statistical analysis: SY and TY; Coordination of the team and final corrections: JY and YK; Patient's management: TY, MO, YK, NN, SY and JY. All authors read and approved the final manuscript.

Conflicts of Interest

T. Yuasa received remuneration for lectures from Astellas (Tokyo, Japan), Sanofi Japan (Tokyo, Japan), Pfizer Japan (Tokyo, Japan), Novartis Pharma Japan (Tokyo, Japan), Ono Pharma (Osaka, Japan), Bristol-Myers Squibb Japan (Tokyo, Japan), MSD Japan (Tokyo, Japan), Janssen Japan (Tokyo, Japan), and Daiichi-Sankyo (Tokyo, Japan). The other authors have no conflicts of interest to declare.

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