

The Efficacy and Safety of a Low Relative Dose Intensity of Cabazitaxel in Patients With Metastatic Castration-resistant Prostate Cancer

FUMIHIKO URABE^{1#}, DAIGO KOBAYASHI^{1#}, KOSUKE IWATANI¹, YU IMAI¹,
HAJIME ONUMA¹, KOICHI AIKAWA¹, TAKAFUMI YANAGISAWA¹, KOJIRO TASHIRO¹,
HIROSHI SASAKI¹, JUN MIKI^{1,2}, KENTA MIKI¹ and TAKAHIRO KIMURA¹

¹Department of Urology, The Jikei University School of Medicine, Tokyo, Japan;

²Department of Urology, The Jikei University School of Medicine, Kashiwa Hospital, Chiba, Japan

Abstract. *Background/Aim:* Clinical trials have shown that the efficacy of a reduced dose of cabazitaxel (20 mg/m² every 3 weeks) was not inferior to that of the standard dose (25 mg/m² every 3 weeks). However, the efficacy of even lower relative dose intensities, such as 20 mg/m² every 4 weeks, have not been evaluated conclusively. The aim of this study was to investigate the efficacy and safety of a low relative dose intensity of cabazitaxel in patients with metastatic castration-resistant prostate cancer in the real world. *Patients and Methods:* We retrospectively analyzed 101 consecutive patients treated with cabazitaxel for docetaxel-refractory metastatic castration-resistant prostate cancer. The progression-free and overall survival after introduction of cabazitaxel and prostate-specific antigen response rate were assessed as oncological outcome measures. *Results:* The patients were divided into two groups (relative dose intensity >60%, n=74 and ≤60%, n=27). Both progression-free and overall survivals were significantly better in the >60% group than in the ≤60% group (median 5 and 2 months, $p<0.01$, and 15 and 6 months, $p<0.01$, respectively). In multivariate analyses, visceral metastasis and relative dose intensity ≤60% were prognostic factors for shorter progression-free and overall survivals ($p=0.04$, $p<0.01$, respectively). The incidence of adverse events was not significantly different between groups. *Conclusion:* The cabazitaxel relative dose

intensity ≤60% group had significantly shorter progression-free and overall survivals than the >60% group, whereas the incidence of adverse events was not significantly different. The results suggested that reducing the relative dose intensity of cabazitaxel to ≤60% may not be recommended.

Prostate cancer is a highly prevalent cancer in men worldwide. It is the second most frequently diagnosed cancer and the fifth leading cause of cancer-related deaths among men worldwide (1). During the last decade, major advances have been made in the treatment of metastatic castration-resistant prostate cancer (mCRPC) (2). Although 80-90% of the patients with metastatic prostate cancers respond to initial androgen deprivation therapy (ADT), most develop mCRPC (3, 4). To date, several approved treatment options are available for mCRPC either in the pre- or post-docetaxel setting or in both, including androgen receptor axis-targeted (ARAT) agents (abiraterone or enzalutamide), a radiopharmaceutical agent (radium-223), and a new taxane chemotherapy (cabazitaxel) (5). In the phase 3 TROPIC trial, cabazitaxel plus prednisone improved overall survival (OS) compared to mitoxantrone plus prednisone (6).

Hematotoxicity, such as neutropenia and febrile neutropenia (FN), is a serious adverse event (AE) of cabazitaxel. The incidence is reported to be higher in Asian men than in Western men. The incidences of grade ≥3 neutropenia and FN in the global TROPIC trial were 82% and 8%, respectively, whereas those in a phase 1 study involving Japanese patients were 100% and 54.5%, respectively, even though both trials did not allow primary prophylaxis with granulocyte colony-stimulating factor (6, 7). An open-label study in Japan revealed that primary prophylaxis with pegfilgrastim at least 24 hours after administration of cabazitaxel (25 mg/m²) reduced the rate of FN to 9.5% (8). The phase 3 trial, PROSELICA, compared the efficacy and safety of standard and reduced doses of

#These Authors contributed equally to this study.

Correspondence to: Takahiro Kimura, Department of Urology, The Jikei University School of Medicine, 3-25-8 Nishi-Shimbashi, Minato-ku, Tokyo, Japan. Tel: +81 0334331111, Fax: +81 0354001387, e-mail: tkimura@jikei.ac.jp

Key Words: Metastatic castration-resistant prostate cancer, cabazitaxel, relative dose intensity.

Table I. Patient characteristics.

	Total (n=101)	RDI ≤60% (n=27)	RDI >60% (n=74)	p-Value
Age, years, median (range)	73 (47-86)	76 (51-86)	71 (47-82)	0.02
ECOG, PS, n (%)				0.66
0-1	85 (84.2)	22 (81.5)	63 (85.1)	
2	16 (15.8)	5 (18.5)	11 (14.9)	
Gleason score, n (%)				0.09
≤7	22 (41.6)	9 (33.3)	13 (17.6)	
≥8	79 (58.4)	18 (66.7)	61 (82.4)	
Site of metastasis, n (%)				
Bone	91 (90.1)	23 (85.2)	68 (91.9)	0.32
Visceral	25 (24.8)	10 (37.0)	15 (20.3)	0.08
Time to CRPC, n (%)				0.29
≤1 year	40 (39.6)	13 (48.1)	27 (36.5)	
>1 year	61 (60.4)	14 (51.9)	47 (63.5)	
Use of ARAT agent, n (%)	78 (77.2)	23 (85.2)	55 (74.3)	0.25
Number of cycles of docetaxel therapy, median (range)	6 (1-41)	6 (1-41)	7 (1-20)	0.38
Maximum PSA change during docetaxel therapy, %, median (range)	-33 (-100-469.2)	-36 (-93.8-76.9)	-35.3 (-100-469.2)	0.64
Initial dose of cabazitaxel, n (%)				<0.01
≤20 mg/m ²	61 (60.4)	27 (100)	34 (45.9)	
>20 mg/m ²	40 (39.6)	0 (0)	40 (54.1)	
Interval of cabazitaxel, n (%)				<0.01
Every 3 weeks	54 (53.5)	1 (3.7)	53 (71.6)	
Every ≥4 weeks	47 (46.5)	26 (96.3)	21 (28.4)	
Number of cycles of cabazitaxel, n (%)	5 (1-27)	3 (1-10)	5.5 (1-27)	<0.01
Treatment line of cabazitaxel, n (%)				0.49
2 nd or 3 rd	58 (57.4)	14 (51.9)	44 (59.5)	
≥4 th	43 (42.6)	13 (48.1)	30 (40.5)	
Median PSA, ng/ml, median (range)	54.2 (0-1,528.4)	115 (0.0-1,528.4)	48.8 (0-1,443.7)	0.12
RDI, %, median (range)	75 (45-100)	60 (45-60)	80 (61.4-100)	<0.01

ECOG PS: Eastern Cooperative Oncology Group Performance Status; CRPC: castration-resistant prostate cancer; ARAT: androgen receptor-axis-targeted; PSA: prostate specific antigen; RDI: relative dose intensity.

cabazitaxel (25 mg/m² vs. 20 mg/m² every 3 weeks) in mCRPC patients and showed that OS and progression-free survival (PFS) were not significantly different between the groups even though the prostate-specific antigen (PSA) response was better in the standard-dose group (9). In addition, the study revealed that the incidences of grade ≥3 neutropenia and FN were lower in the reduced-dose group than in the standard-dose group (41.8% and 2.1% vs. 73.3% and 9.2%, respectively).

In real-world practice, patients are sometimes administered an even lower relative dose intensity (RDI) of cabazitaxel by reducing the dose or implementing a 4-week regimen due to the frailty of the patients or their restricted visiting schedule. RDI is typically defined as the ratio of the actual delivered chemotherapy dose to the planned dose (10). As for cabazitaxel therapy, RDI 100% means dose of 25 mg/m² every 3 weeks. Even though the reduced dose of cabazitaxel to 20 mg/m² every 3 weeks (RDI 80%) was not inferior to the standard dose, the efficacy of an even lower RDI of

cabazitaxel, for instance, 20 mg/m² dose every 4 weeks (RDI 60%), has not been evaluated. The aim of this study was to investigate the efficacy and safety of a low RDI of cabazitaxel in patients with mCRPC in real-world practice.

Patients and Methods

Study design, patients, and treatment. This study was approved by the Institutional Review Board of the Jikei University School of Medicine, Tokyo, Japan (approval no.: 31-478(10060)). We retrospectively analyzed 101 consecutive patients who were treated with cabazitaxel for docetaxel-refractory mCRPC between January 2015 and December 2020 at the Jikei University and its affiliated hospitals. Patients had histologically confirmed adenocarcinoma of the prostate and previously received ADT in the form of medical or surgical castration. CRPC status was defined as PSA and/or radiographic progression despite the maintenance of castration levels of serum testosterone (11). The clinical stage was evaluated using computed tomography, magnetic resonance imaging, and bone scintigraphy. Generally, cabazitaxel was administered at an initial dose of 25 or 20 mg/m² every 3 or 4 weeks. Five milligrams of

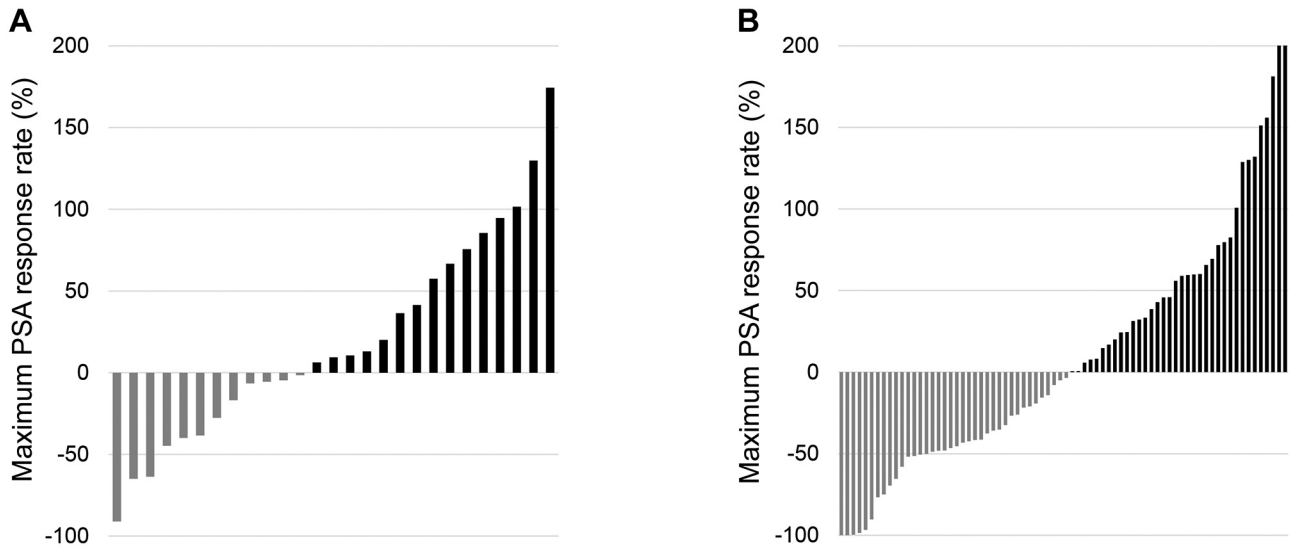


Figure 1. Maximum PSA response rate of patients. A) Waterfall plot of maximum PSA response rate in the relative dose intensity (RDI) $\leq 60\%$ group. B) Waterfall plot of maximum PSA response rate in the RDI $>60\%$ group.

prednisone were administered twice daily. Primary prophylaxis with pegfilgrastim was administered to all patients except nine who were administered cabazitaxel before its approval in Japan. ADT was maintained throughout the study period. Cabazitaxel was continued until PSA or radiographic progression, emergence of other events related to cancer progression, occurrence of AEs, or patient refusal. AEs were classified according to the Common Terminology Criteria for Adverse Events, version 5.0 (12). The dose reduction and interval of cabazitaxel administration were at the discretion of the clinicians. The number of cycles of cabazitaxel was not limited.

Outcome measures. The PFS, OS, and PSA response rate of cabazitaxel after the introduction of cabazitaxel were assessed as oncological outcome measures. All patients were assessed according to the Prostate Cancer Working Group 2 criteria (13). Generally, PSA assessments were performed once every month and imaging assessments by computed tomography and bone scintigraphy were done every 3 months.

Statistical analysis. Descriptive statistics for categorical variables are presented as frequencies and percentages, whereas continuous variables are reported as medians and ranges. The patients were stratified according to the RDI of cabazitaxel (RDI $\leq 60\%$ or $>60\%$). The patients' clinical characteristics, presented in Table I, were compared using the chi-square test and *t*-test. The PFS and OS after the introduction of cabazitaxel were calculated and analyzed using the Kaplan-Meier method and log-rank test. Cox proportional hazards regression analyses were also conducted to investigate the association between PFS or OS and clinical predictive factors, such as age, Eastern Cooperative Oncology Group performance status, Gleason score, RDI, use of cabazitaxel as third-line therapy for CRPC treatment, presence of visceral metastasis, and serum PSA. All analyses were conducted using Stata® 16 for Windows (StataCorp LLC, College Town, TX, USA) and R package (R Foundation for Statistical Computing, Vienna, Austria). The statistical significance was defined as a 2-sided *p*-value of <0.05 .

Results

Patient characteristics. The patients' clinical characteristics are shown in Table I. Among 101 patients, the initial dose of cabazitaxel was ≤ 20 mg/m² in 61 patients (60.4%) and >20 mg/m² in 40 patients (39.6%). Cabazitaxel was administered every 3 weeks in 54 patients (53.5%) and every 4 weeks in 47 patients (46.5%). The median number of cycles of cabazitaxel was five (range=1-27). In the mCRPC treatment sequence, cabazitaxel was introduced as third-line therapy in 58 patients (57.4%) and fourth-line therapy or later in 43 patients (42.6%). The median RDI was 75% (range, 45-100%). The patients were divided into two groups (RDI $>60\%$, *n*=74 and RDI $\leq 60\%$, *n*=27). Thirty-four of the 74 patients in the RDI $>60\%$ group (45.9%) were administered cabazitaxel at ≤ 20 mg/m², whereas all patients in the RDI $\leq 60\%$ group were administered ≤ 20 mg/m² cabazitaxel (*p* <0.01). Fifty-three of the 74 patients in the RDI $>60\%$ group (71.6%) were administered cabazitaxel every 3 weeks, whereas only one patient in the RDI $\leq 60\%$ group (3.7%) was administered cabazitaxel every 3 weeks (*p* <0.01). The median age at which cabazitaxel was started was significantly lesser in the RDI $>60\%$ group than in the RDI $\leq 60\%$ group (71 and 76 years old, respectively, *p*=0.02).

PSA response. Waterfall plots of the maximum PSA response rate in the RDI $>60\%$ and RDI $\leq 60\%$ groups are shown in Figure 1. There was no significant difference between the RDI $>60\%$ and RDI $\leq 60\%$ groups in terms of the number of patients observed $>50\%$ and any PSA reduction.

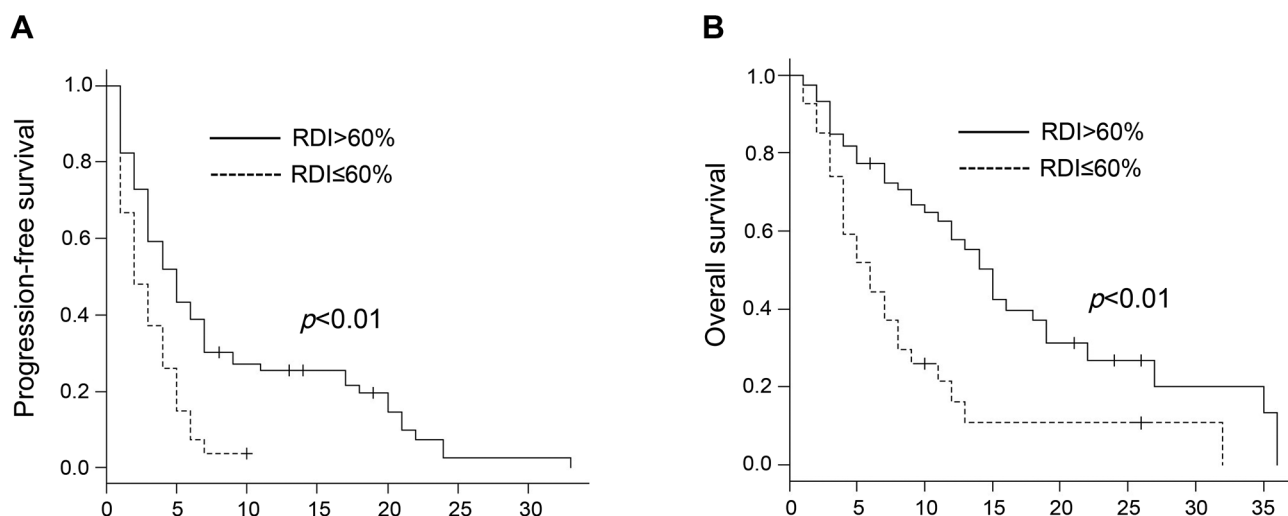


Figure 2. Oncological outcomes of patients. A) Kaplan-Meier curves of progression-free survival (PFS) after initiating cabazitaxel treatment stratified by relative dose intensity (RDI) >60% and RDI ≤60%. The solid and dotted lines indicate a PFS of patients in the RDI >60% and RDI ≤60% groups, respectively. The median PFS of patients in the RDI >60% and RDI ≤60% groups were 5 months and 2 months, respectively ($p<0.01$). B) Kaplan-Meier curves of overall survival (OS) after initiating cabazitaxel treatment stratified by RDI >60% and RDI ≤60%. The solid and dotted lines indicate OS of patients in the RDI >60% and RDI ≤60% groups, respectively. The median OS of patients in the RDI >60% and RDI ≤60% groups were 15 months and 6 months, respectively ($p<0.01$).

Progression-free and overall survival. The median PFS and OS after administration of cabazitaxel were 4 and 12 months, respectively. According to the Kaplan-Meier analysis, PFS was significantly better in the RDI>60% group than in the RDI≤60% group (median 5 and 2 months, respectively, $p<0.01$, Figure 2A). According to the univariate analysis, visceral metastasis [hazard ratio (HR)=1.9; 95% confidence interval (CI)=1.2-3.1; $p=0.01$] and RDI ≤60% (HR=2.1; 95%CI=1.3-3.4; $p<0.01$) were significantly associated with shorter PFS. According to the multivariate analysis, visceral metastasis (HR=1.7; 95%CI=1.0-2.8; $p=0.04$) and RDI ≤60% (HR=1.9; 95%CI=1.2-3.1; $p=0.01$) were also significantly associated with shorter PFS (Table II).

According to the Kaplan-Meier analysis, OS was significantly better in the RDI>60% group than in the RDI≤60% group (15 and 6 months, respectively, $p<0.01$, Figure 2B). According to the univariate analysis, visceral metastasis (HR=2.6; 95%CI=1.5-4.7; $p<0.01$) and RDI ≤60% (HR=2.5; 95%CI=1.5-4.2; $p<0.01$) were prognostic factors for shorter OS. Multivariate analysis also demonstrated that visceral metastasis (HR=2.2; 95%CI=1.2-4.0; $p<0.01$) and RDI ≤60% (HR=2.1; 95%CI=1.3-3.7; $p<0.01$) were prognostic factors for shorter OS (Table III).

Adverse events. The incidence of AEs was not significantly different between the groups. FN occurred in 18.9% (14/74) and 7.4% (2/27) of the patients in the RDI >60% and ≤60% groups, respectively ($p=0.16$). Grade ≥3 neutropenia occurred in 31.0% (23/74) and 33.3% (9/27) of the patients

in the RDI >60% and ≤60% groups, respectively ($p=0.83$). Grade ≥3 AEs occurred in 32.4% (24/74) and 37.0% (10/27) of the patients in the RDI >60% and ≤60% groups, respectively ($p=0.66$).

Discussion

Cabazitaxel prolongs survival in patients with mCRPC. The phase 3 TROPIC trial showed that administering 25 mg/m² cabazitaxel every 3 weeks significantly improved OS in docetaxel-refractory mCRPC patients compared to mitoxantrone (6). Subsequently, two phase 3 studies, the PROSELICA and FIRSTANA trials, prospectively evaluated the efficacy and safety of the reduced dose of cabazitaxel (20 mg/m² every 3 weeks) compared to the standard dose (25 mg/m² every 3 weeks). Both studies concluded that PFS and OS were not significantly different between the groups, and the incidence of grade 3 or 4 treatment-emergent AEs was lower in the reduced-dose group than in the standard-dose group (9, 14). Therefore, 20 mg/m² cabazitaxel every 3 weeks, with an RDI of 80% of the standard dose, can be recommended for patients with risk factors for FN (15). However, doses of cabazitaxel that were reduced further to achieve lower RDI are sometimes administered because of the frailty of the patients or their restricted visiting schedule in real-world practice. The aim of this retrospective study was to assess the efficacy and safety of reducing the RDI of cabazitaxel further, such as by administering 20 mg/m² every 4 weeks (RDI 60%).

Table II. Univariate and multivariate analysis of clinical factors associated with progression-free survival.

	Univariate HR (95%CI Lower-Upper)	p-Value	Multivariate HR (95%CI Lower-Upper)	p-Value
Age (continuous)	1.0 (1.0-1.0)	0.36		
ECOG PS (0,1 vs. 2-)	1.2 (0.6-2.1)	0.6		
Gleason score (≤ 7 vs. > 8)	1.0 (0.6-1.6)	0.92		
Baseline RDI ($\leq 60\%$ vs. $> 60\%$)	2.1 (1.3-3.4)	< 0.01	1.9 (1.2-3.1)	0.01
Treatment line of cabazitaxel ($\leq 3^{\text{rd}}$ vs. $\geq 4^{\text{th}}$)	1.0 (0.6-1.5)	0.9		
Visceral metastasis or not	1.9 (1.2-3.1)	0.01	1.7 (1.0-2.8)	0.04
Baseline PSA (≤ 55 ng/ml vs. > 55)	1.4 (0.9-2.1)	0.14		

HR: Hazard ratio; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; RDI: relative dose intensity; PSA: prostate specific antigen.

Table III. Univariate and multivariate analysis of clinical factors associated with overall survival.

	Univariate HR (95%CI Lower-Upper)	p-Value	Multivariate HR (95%CI Lower-Upper)	p-Value
Age (continuous)	1.0 (1.0-1.0)	0.54		
ECOG PS (0,1 vs. 2-)	1.0 (0.5-2.2)	0.92		
Gleason score (≤ 7 vs. ≥ 8)	0.9 (0.5-1.6)	0.63		
Baseline RDI ($\leq 60\%$ vs. $> 60\%$)	2.5 (1.5-4.2)	< 0.01	2.1 (1.3-3.7)	< 0.01
Treatment line of cabazitaxel ($\leq 3^{\text{rd}}$ vs. $\geq 4^{\text{th}}$)	0.9 (0.6-1.5)	0.7		
Visceral metastasis or not	2.6 (1.5-4.7)	< 0.01	2.2 (1.2-4.0)	< 0.01
Baseline PSA (≤ 55 ng/ml vs. > 55)	1.5 (0.9-2.5)	0.11		

HR: Hazard ratio; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; RDI: relative dose intensity; PSA: prostate specific antigen.

The results of the present study indicated that the RDI $\leq 60\%$ group had significantly shorter PFS and OS than the RDI $> 60\%$ group, even though the PSA response rate was not significantly different. In the RDI $\leq 60\%$ group, all patients were administered cabazitaxel at an initial dose ≤ 20 mg/m², and 96.3% were treated with a four-week regimen. This suggests that administration of cabazitaxel at 20 mg/m² every 4 weeks might be less effective than the standard dose.

Several reports have investigated the efficacy and safety of reduced doses or longer intervals of cabazitaxel administration in real-world practice. In a post-marketing surveillance study of 662 Japanese patients with docetaxel-refractory CRPC, the safety and efficacy were compared between patients who received cabazitaxel at initial doses of 25 and 20 mg/m² (16). Both OS and time to treatment failure were significantly longer in patients who received cabazitaxel at an initial dose of 25 mg/m². The results were not consistent with those of the phase 3 PROCELICA and FIRSTANA trials. We suggest that the discrepancy might be caused by the difference between the patients' backgrounds in clinical trials and real-world settings. In this study, the median RDI with initial doses of 25 and 20 mg/m² were 79.2% and 64.6%, respectively, suggesting that several

patients were administered these doses every 4 weeks. Although the difference in the treatment interval might have influenced the outcomes, it was not assessed in this study.

A retrospective study involving 62 Japanese CRPC patients compared the efficacy and safety of three- and four-week cabazitaxel regimens (17). The results indicated that the oncological outcomes, including PSA response, PFS, time to treatment failure, and OS, were not significantly different between the regimens. These results are not consistent with those of our study. Possible explanations for this discrepancy are the limited number of patients in both studies, and the difference in focus between the studies, the interval of administration in the former study, and the RDI in our study.

The incidence of AEs was not statistically different between the groups, even though it was lower in the RDI $\leq 60\%$ group. The incidence of hematological AEs might be associated with the initial dose of cabazitaxel. Among 92 patients who received primary prophylaxis with pegfilgrastim in our study, the incidence of FN was significantly higher in patients who were administered 25 mg/m² cabazitaxel than in those administered a reduced dose (25.8% and 8.2%, respectively, $p=0.021$, chi-square

test). Overall, reducing the initial dose of cabazitaxel to 20 mg/m² may decrease the incidence of AEs; however, reducing the RDI to less than 60% may impair the efficacy of cabazitaxel.

The difference in patient backgrounds between the groups might have influenced the results. In particular, the patients in the RDI ≤60% group were significantly older than those in the RDI >60% group, which might have influenced the initial dose and the duration of each regimen decided. Such biases of patients' background might have caused the difference in OS, even though the RDI was significantly associated with OS according to the results of the multivariate analysis. The PSA response was not significantly different between the RDI ≤60% and >60% groups despite the significant difference in PFS and OS. However, the significance of the PSA response as a surrogate of oncological outcomes after chemotherapy remains controversial (16). According to the multivariate analyses, the presence of visceral metastasis was significantly associated with shorter OS and PFS, which corroborated the results of previous studies (18-21).

This study has some limitations. First, this was a retrospective study with a limited number of patients. The follow-up protocol and criteria for discontinuing cabazitaxel were not standardized. Second, as mentioned above, there might be biases in patient backgrounds between the groups. Finally, detailed information on AEs might not have been sufficiently collected from the medical records. Further prospective studies are required to validate the results of this study.

In conclusion, the RDI≤60% group had significantly shorter PFS and OS than the RDI>60% group, whereas the incidence of AEs was not significantly different between the groups. The results suggested that reducing the RDI of cabazitaxel to ≤60% may not be recommended for patients with mCRPC.

Conflicts of Interest

Takahiro Kimura is a paid consultant/advisor of Astellas, Bayer, Janssen and Sanofi. Daigo Kobayashi, Hajime Onuma, Fumihiko Urabe, Takafumi Yanagisawa, Hiroshi Sasaki, Jun Miki, and Kenta Miki declare no conflicts of interest.

Authors' Contributions

FU and DK: Project development, data collection, data analysis, manuscript writing. KI, YI, and HO: Project development, manuscript writing. TY: Data collection; manuscript writing. AK, KT, and HS: Data collection. JM, KM, and TK: Project development, data analysis, manuscript writing.

Acknowledgements

This research was supported by The Jikei University Research Fund.

References

- 1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 68(6): 394-424, 2018. DOI: 10.3322/caac.21492
- 2 Bracarda S, Logothetis C, Sternberg CN, Oudard S: Current and emerging treatment modalities for metastatic castration-resistant prostate cancer. *BJU Int* 107 Suppl 107: 13-20, 2011. DOI: 10.1111/j.1464-410X.2010.10036.x
- 3 Small EJ, Vogelzang NJ: Second-line hormonal therapy for advanced prostate cancer: a shifting paradigm. *J Clin Oncol* 15(1): 382-388, 1997. DOI: 10.1200/JCO.1997.15.1.382
- 4 Oh WK, Kantoff PW: Management of hormone refractory prostate cancer: current standards and future prospects. *J Urol* 160: 1220-1229, 1998.
- 5 Kapoor A, Wu C, Shayegan B, Rybak AP: Contemporary agents in the management of metastatic castration-resistant prostate cancer. *Can Urol Assoc J* 10(11-12): E414-E423, 2016. DOI: 10.5489/auaj.4112
- 6 De Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels J, Kocak I, Gravis G, Bodrogi I, Mackenzie MJ, Shen L, Roessner M, Gupta S, Sartor AO: Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 376(9747): 1147-1154, 2010. DOI: 10.1016/S0140-6736(10)61389-X
- 7 Nozawa M, Mukai H, Takahashi S, Uemura H, Kosaka T, Onozawa Y, Miyazaki J, Suzuki K, Okihara K, Arai Y, Kamba T, Kato M, Nakai Y, Furuse H, Kume H, Ide H, Kitamura H, Yokomizo A, Kimura T, Tomita Y, Ohno K, Kakehi Y: Japanese phase I study of cabazitaxel in metastatic castration-resistant prostate cancer. *Int J Clin Oncol* 20(5): 1026-1034, 2015. DOI: 10.1007/s10147-015-0820-9
- 8 Kosaka T, Uemura H, Sumitomo M, Harada K, Sugimoto M, Hayashi N, Yoshimura K, Fukasawa S, Ecstein-Fraisse E, Sunaga Y, Oya M: Impact of pegfilgrastim as primary prophylaxis for metastatic castration-resistant prostate cancer patients undergoing cabazitaxel treatment: an open-label study in Japan. *Jpn J Clin Oncol* 49(8): 766-771, 2019. DOI: 10.1093/jjco/hyz051
- 9 Eisenberger M, Hardy-Bessard A, Kim CS, Géczi L, Ford D, Mourey L, Carles J, Parente P, Font A, Kacso G, Chadja M, Zhang W, Bernard J, De Bono J: Phase III study comparing a reduced dose of cabazitaxel (20 mg/m²) and the currently approved dose (25 mg/m²) in postdocetaxel patients with metastatic castration-resistant prostate cancer—PROSELICA. *J Clin Oncol* 35(28): 3198-3206, 2017. DOI: 10.1200/JCO.2016.72.1076
- 10 Crawford J, Denduluri N, Patt D, Jiao X, Morrow PK, Garcia J, Barron R, Lyman GH: Relative dose intensity of first-line chemotherapy and overall survival in patients with advanced non-small-cell lung cancer. *Support Care Cancer* 28(2): 925-932, 2020. DOI: 10.1007/s00520-019-04875-1
- 11 Mottet N, Van Den Bergh RC, Briers E, Van Den Broeck T, Cumberbatch MG, De Santis M, Fanti S, Fossati N, Gandaglia G, Gillessen S, Grivas N, Grummet J, Henry AM, Van Der Kwast TH, Lam TB, Lardas M, Liew M, Mason MD, Moris L, Oprea-Lager DE, Van Der Poel HG, Rouvière O, Schoots IG,

- Tilki D, Wiegel T, Willemsse PM, Cornford P: EAU-EANM-ESTRO-ESUR-SIOG Guidelines on prostate cancer—2020 update. Part 1: Screening, diagnosis, and local treatment with curative intent. *Eur Urol* 79(2): 243-262, 2021. DOI: 10.1016/j.eururo.2020.09.042
- 12 U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf [Last accessed on February 7, 2021]
- 13 Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, Eisenberger MA, Higano C, Bubley GJ, Dreicer R, Petrylak D, Kantoff P, Basch E, Kelly WK, Figg WD, Small EJ, Beer TM, Wilding G, Martin A, Hussain M, Prostate Cancer Clinical Trials Working Group: Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol* 26(7): 1148-1159, 2008. DOI: 10.1200/JCO.2007.12.4487
- 14 Oudard S, Fizazi K, Sengeløv L, Daugaard G, Saad F, Hansen S, Hjalms-Eriksson M, Jassem J, Thiery-Vuillemin A, Caffo O, Castellano D, Mainwaring PN, Bernard J, Shen L, Chadja M, Sartor O: Cabazitaxel *versus* docetaxel as first-line therapy for patients with metastatic castration-resistant prostate cancer: a randomized Phase III trial—FIRSTANA. *J Clin Oncol* 35(28): 3189-3197, 2017. DOI: 10.1200/JCO.2016.72.1068
- 15 Boyle H, Alibhai S, Decoster L, Efstathiou E, Fizazi K, Mottet N, Oudard S, Payne H, Prentice M, Puts M, Aapro M, Droz J: Updated recommendations of the International Society of Geriatric Oncology on prostate cancer management in older patients. *Eur J Cancer* 116: 116-136, 2019. DOI: 10.1016/j.ejca.2019.04.031
- 16 Matsuyama H, Matsubara N, Kazama H, Seto T, Tsukube S, Suzuki K: Real-world efficacy and safety of two doses of cabazitaxel (20 or 25 mg/m²) in patients with castration-resistant prostate cancer: results of a Japanese post-marketing surveillance study. *BMC Cancer* 20(1): 649, 2020. DOI: 10.1186/s12885-020-07131-6
- 17 Shiota M, Nakamura M, Yokomizo A, Tomoda T, Sakamoto N, Seki N, Hasegawa S, Yunoki T, Harano M, Kuroiwa K, Eto M: Efficacy and safety of 4-weekly cabazitaxel for castration-resistant prostate cancer: a multi-institutional study. *Cancer Chemother Pharmacol* 84(3): 561-566, 2019. DOI: 10.1007/s00280-019-03874-7
- 18 Bando Y, Hinata N, Terakawa T, Furukawa J, Harada K, Nakano Y, Fujisawa M: Activity of cabazitaxel in patients with metastatic castration-resistant prostate cancer after treatment with single or dual regimens of novel androgen receptor-targeting agents. *Med Oncol* 34(9): 163, 2017. DOI: 10.1007/s12032-017-1024-0
- 19 Yokom DW, Stewart J, Alimohamed NS, Winquist E, Berry S, Hubay S, Lattouf JB, Leonard H, Girolametto C, Saad F, Sridhar SS: Prognostic and predictive clinical factors in patients with metastatic castration-resistant prostate cancer treated with cabazitaxel. *Can Urol Assoc J* 12(8): E365-E372, 2018. DOI: 10.5489/cuaj.5108
- 20 Kosaka T, Shinojima T, Morita S, Oya M: Prognostic significance of grade 3/4 neutropenia in Japanese prostate cancer patients treated with cabazitaxel. *Cancer Sci* 109(5): 1570-1575, 2018. DOI: 10.1111/cas.13556
- 21 Uemura K, Miyoshi Y, Kawahara T, Ryosuke J, Yamashita D, Yoneyama S, Yokomizo Y, Kobayashi K, Kishida T, Yao M, Uemura H: Prognostic value of an automated bone scan index for men with metastatic castration-resistant prostate cancer treated with cabazitaxel. *BMC Cancer* 18(1): 501, 2018. DOI: 10.1186/s12885-018-4401-y

Received July 5, 2023

Revised July 27, 2023

Accepted July 28, 2023