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ORIGINAL PAPER

Efficacy and safety of cabazitaxel for castration-resistant prostate cancer in patients with > 10 cycles of docetaxel chemotherapy: a multi-institutional study

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Abstract

This multi-institutional study aimed to investigate the efficacy and safety profiles of cabazitaxel after prior docetaxel chemotherapy in patients with castration-resistant prostate cancer (CRPC). This study included 63 Japanese patients with CRPC who were treated with cabazitaxel from 2014 to 2017. The oncological outcomes and adverse events (AEs) were documented, and prognostic factors for oncological outcomes and predictive factors for AEs were analysed. PSA decline was observed in 68.3% of patients, including 25.4% who achieved $a \geq 50\%$ decline. The median progression-free survival, treatment failure-free survival, and overall survival were 4.3, 4.1, and 9.0 months, respectively. More cycles of prior docetaxel therapy was identified as common favourable prognostic factors for progression-free survival, treatment failure-free survival, and overall survival. Severe neutropenia, febrile neutropenia, and severe non-haematological AEs were observed in 73.0%, 33.3%, and 23.8% of patients, respectively. However, > 10 cycles of docetaxel was not associated with increased incidence of AEs. In conclusion, cabazitaxel chemotherapy was still active in Japanese CRPC patients treated with > 10 cycles of docetaxel chemotherapy, with an acceptable risk of AE burden. Treatment with cabazitaxel after > 10 cycles of docetaxel may be an appropriate option when it can be administered.

Keywords Castration-resistant prostate cancer · Cabazitaxel · Docetaxel · Prognostic factor · Adverse event

Introduction

Prostate cancer is the most common non-cutaneous cancer and the second leading cause of cancer-related mortality among men in developed countries. For decades, androgen-deprivation therapy (ADT) has been the first-line therapy for recurrent or advanced prostate cancer [1, 2]. However, most cases of prostate cancer eventually relapse in a castration-resistant manner and then develop into castration-resistant prostate cancer (CRPC) [1–3]. To manage CRPC, several agents have emerged, including drugs targeting the androgen-receptor axis, chemotherapeutic agents, and

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radioisotopes [4]. In the phase 3 TROPIC trial, the next-generation taxane, cabazitaxel, showed survival benefit as well as pain relief for patients with CRPC after docetaxel chemotherapy [5, 6]. In addition, cabazitaxel showed comparable anticancer effects to docetaxel as first-line therapy for CRPC in the phase 3 FIRSTANA trial [7].

So far, several studies on clinical outcomes of cabazitaxel chemotherapy have shown its anticancer activity and adverse events (AEs) in early access programmes and real-world settings [8–13]. Clinical use of docetaxel chemotherapy has usually been limited to 10 cycles in most countries because the phase 3 TAX-327 trial demonstrated the survival benefit of up to 10 cycles of docetaxel chemotherapy [14]. Therefore, the data on anticancer activity and AEs of cabazitaxel among men heavily treated with docetaxel are limited.

In Japan, unlike other countries, docetaxel chemotherapy beyond 10 cycles has been approved for CRPC. In this multi-institutional study, we investigated the efficacy and safety profiles of cabazitaxel in Japanese patients with CRPC treated with prior docetaxel. We aimed to reveal the impact of number of cycles of prior docetaxel on oncological outcomes and severe AEs.

Patients and methods

Patients

We enrolled patients with CRPC treated with cabazitaxel chemotherapy from 2014 to 2017 in the following institutions: Kyushu University Hospital (Fukuoka), National Hospital Organization Kyushu Cancer Center (Fukuoka), Harasanshin Hospital (Fukuoka), Oita Prefectural Hospital (Oita), National Hospital Organization Kyushu Medical Center (Fukuoka), Kyushu Central Hospital (Fukuoka), Kitakyushu Municipal Medical Center (Kitakyushu), Japanese Red Cross Fukuoka Hospital (Fukuoka), JCHO Kyushu Hospital (Kitakyushu), and Miyazaki Prefectural Miyazaki Hospital (Miyazaki). This study was approved by each institutional review board (Kyushu University Hospital's Review Board, National Hospital Organization Kyushu Cancer Center's Review Board, Harasanshin Hospital's Review Board, Oita Prefectural Hospital's Review Board, National Hospital Organization Kyushu Medical Center's Review Board, Kyushu Central Hospital's Review Board, Kitakyushu Municipal Medical Center's Review Board, Japanese Red Cross Fukuoka Hospital's Review Board, JCHO Kyushu Hospital's Review Board, and Miyazaki Prefectural Miyazaki Hospital's Review Board). A waiver of informed consent was granted by institutional review board, on the condition that the right of opt-out was provided to all patients. The eligibility criteria included: (i) histopathologically diagnosed carcinoma of the prostate, (ii) confirmed failure of primary ADT, and (iii) age $\geq$ 20 years. Patients whose data on PSA response was not available were excluded.

Treatment

Cabazitaxel was given according to a 3- or 4-weekly (15–25 mg/m^2) regimen based on the schedule reported by the TROPIC [5] and PROSELICA [15] trials, in which 1, 19 and 43 patients were treated with 15, 20 and 25 mg/m^2 cabazitaxel. Prednisolone 5 mg was administered twice daily simultaneously with medical or surgical castration. The dose and schedule of cabazitaxel were modified according to the severity of AEs in each case. Treatment with cabazitaxel was continued according to the physician's judgement, based on disease progression and AEs, or patient refusal.

Endpoints

Progressive disease was defined as an increase in serum PSA of >2 ng/mL and a 50% increase over the nadir, and/or the appearance of a new lesion or progression of one or more known lesions classified according to the Response Evaluation Criteria in Solid Tumours (RECIST) [16]. Radiographic progression was defined as progression of measurable disease or bone scan progression. Treatment failure was defined as discontinuation of cabazitaxel chemotherapy. Progression, treatment failure, and all-cause mortality were defined as an event in the analyses of progression-free survival (PFS), treatment failure-free survival (TFFS), and overall survival (OS), respectively. Patients with no events were censored at the last follow-up visit. AEs were assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Clinically significant pain was defined by the daily consumption of narcotic or non-narcotic analgesics for pain derived from prostate cancer. Performance status (PS) was determined according to the Eastern Cooperative Oncology Group criteria.

Statistical analysis

All statistical analyses were performed using JMP version 13 software (SAS Institute, Cary, NC, USA). PFS, TFFS, and OS were determined by the Kaplan–Meier method and the log-rank test was used to compare survival duration between groups. Univariate analyses were performed using the Cox proportional hazards regression model. All tests were two-sided, and $P<0.05$ was considered significant.

Results

Patients' background

We enrolled a total of 63 Japanese patients who received a median five (interquartile range [IQR], 3–9) cycles of cabazitaxel therapy. The patient characteristics are listed in Table 1. The median age was 73 years (IQR 68–77 years). The patients had received a median seven (IQR 5–12) cycles of prior docetaxel chemotherapy. The median total number of cycles of docetaxel and cabazitaxel was 13 (IQR 9–21). Fifty-five (84.1%) and two (3.2%) men with CRPC were treated with abiraterone/enzalutamide and radium-223, respectively. PS was 0 in 35 (62.5%) patients, 1 in 13 (23.2%), and ≥ 2 in eight (14.3%). The median serum pre-treatment PSA level was 85.1 ng/mL (IQR 22.1–286.6 ng/mL). Most patients ($n = 58$, 92.1%) had metastatic lesions in lymph nodes ($n = 36$, 57.1%), bone ($n = 58$, 92.1%), and viscera, including liver and lung ($n = 17$, 27.0%).

Oncological outcomes of cabazitaxel chemotherapy

There was a decrease in PSA in 43 patients (68.3%); among whom, 29 (46.0%) and 16 (25.4%) had decreases of > 30% and > 50% from baseline, respectively (Fig. 1a). During a median observation period of 7.4 months (IQR

Table 1 Patients' characteristics according to number of cycles of docetaxel

Variables		Cycle number of docetaxel		
	All ($n = 63$)	≤ 10 ($n = 45$)	> 10 ($n = 18$)	*P* value
Median age, years (IQR)	73 (68–77)	73 (68–78)	71 (68–75)	0.14
Median PSA at diagnosis, ng/ml (IQR)	70.1 (21.8–403.8)	48.3 (19.5–309.6)	164.0 (24.6–981.0)	0.24
NA	2	1	1	
Biopsy Gleason score, *n* (%)				
≤7	12 (20.0%)	8 (18.6%)	4 (23.5%)	
8	9 (15.0%)	7 (16.3%)	2 (11.8%)	
≥9	39 (65.0%)	28 (65.1%)	11 (64.7%)	0.85
NA	3	2	1	
Prior local therapy, *n* (%)				
Absence	45 (71.4%)	32 (71.1%)	13 (72.2%)	
Presence	18 (28.6%)	13 (28.9%)	5 (27.8%)	0.93
Time to CRPC, years (IQR)	1.4 (0.7–2.5)	1.5 (0.6–2.6)	1.2 (0.8–2.3)	0.80
NA	6	2	4	
Cycle number of docetaxel	7 (5–12)	6 (4–8)	17 (12–26)	< 0.0001*
Prior treatment for CRPC, *n* (%)				
Abiraterone/enzalutamide	53 (84.1%)	39 (86.7%)	14 (77.8%)	0.40
Radium-223	2 (3.2%)	1 (2.2%)	1 (5.6%)	0.52
ECOG PS at pre-treatment, *n* (%)				
0	35 (62.5%)	25 (59.5%)	10 (71.4%)	
1	13 (23.2%)	11 (26.2%)	2 (14.3%)	
≥2	8 (14.3%)	6 (14.3%)	2 (14.3%)	0.62
NA	7	3	4	
Pain at pre-treatment, *n* (%)				
Absence	32 (50.8%)	22 (48.9%)	10 (55.6%)	
Presence	31 (49.2%)	23 (51.1%)	8 (44.4%)	0.63
Median PSA at pre-treatment, ng/ml (IQR)	85.1 (22.1–286.6)	85.1 (23.3–280.3)	80.4 (13.9–287.3)	0.79
Metastatic sites, *n* (%)				
Lymph node	36 (57.1%)	28 (62.2%)	8 (44.4%)	0.20
Bone	58 (92.1%)	40 (88.9%)	18 (100%)	0.060
Visceral	17 (27.0%)	12 (26.7%)	5 (27.8%)	0.93

IQR interquartile range, *NA* not available, *PS* performance status

*Statistically significant

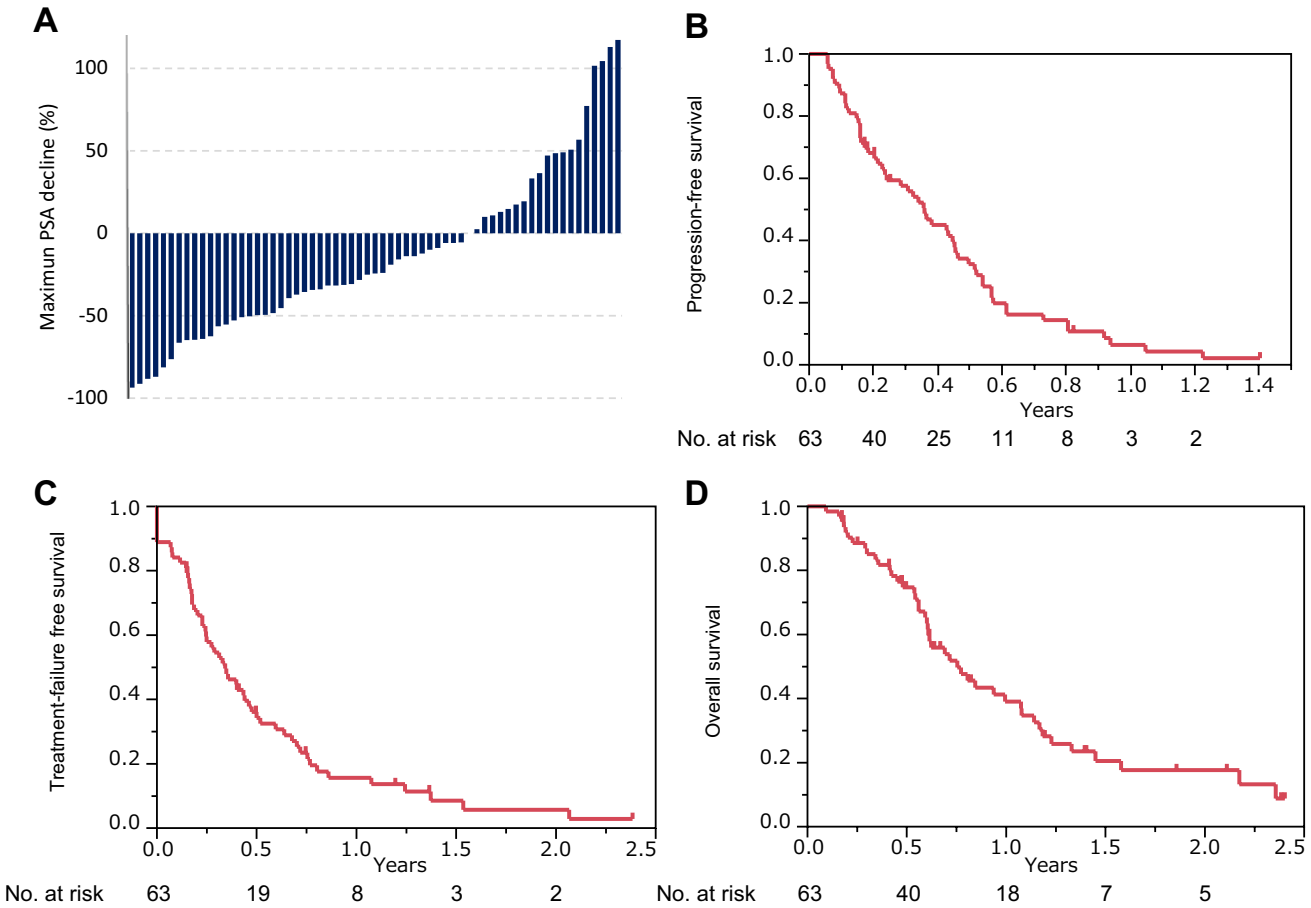

Fig. 1 Anticancer effects of cabazitaxel chemotherapy. Waterfall plots showing greatest decline in PSA levels from baseline (**a**), PFS (**b**), TFFS (**c**), and OS (**d**) in 63 patients with CRPC who received cabazitaxel chemotherapy

4.9–13.7 months), disease progression, treatment failure, and all-cause mortality were observed in 56 (88.9%), 55 (87.3%) and 44 patients (69.8%), respectively. Treatment failure occurred in 39 (61.9%), 9 (14.3%) and 7 (11.1%) patients because of disease progression, AEs and patient refusal, respectively, while cabazitaxel treatment was ongoing in 8 patients (12.7%). Median PFS, TFFS and OS were 4.3 months (95% CI 2.7–5.5 months; Fig. 1b), 4.1 months (95% CI 2.7–5.5 months; Fig. 1c) and 9.0 months (95% CI 7.2–12.9 months; Fig. 1d), respectively.

The impact of number of cycles of prior docetaxel on PFS, TFFS and OS in patients treated with cabazitaxel were investigated by univariate analysis. Higher number of cycles of prior docetaxel was significantly associated with lower risk of progression (hazard ratio [HR], 95% CI 0.19 [0.036–075], $P=0.016$), treatment failure (HR, 95% CI 0.12 [0.018–0.56], $P=0.0048$) and any-cause mortality (HR, 95% CI 0.10 [0.013–0.54], $P=0.0048$). However, prior abiraterone/enzalutamide and prior radium-223 were not associated with risk of progression, treatment failure and any-cause mortality (data not shown). PSA response and PFS were comparable between patients with ≤ 10 and >10 cycles of docetaxel (Fig. 2a, b). Meanwhile, TFFS and OS among patients with ≤ 10 cycles of docetaxel were significantly shorter than among those with >10 cycles (Fig. 2c, d). Patients with ≤ 10 and >10 cycles of docetaxel had comparable backgrounds, except number of cycle of docetaxel (Table 1).

Safety profiles of cabazitaxel chemotherapy

The pegylated form of recombinant human granulocyte colony-stimulating factor, pegfilgrastim, was utilized in 57 (90.5%) cases for prevention of febrile neutropenia. However, grade ≥ 3 neutropenia and febrile neutropenia were observed in 46 (73.0%) and 21 (33.3%) patients, respectively (Table 2). In addition to the haematological AEs, several non-haematological severe AEs were recognised, including one patient with pneumonia, and one with acute coronary syndrome, and one with intestinal perforation, which proved fatal despite intensive care (Table 2).

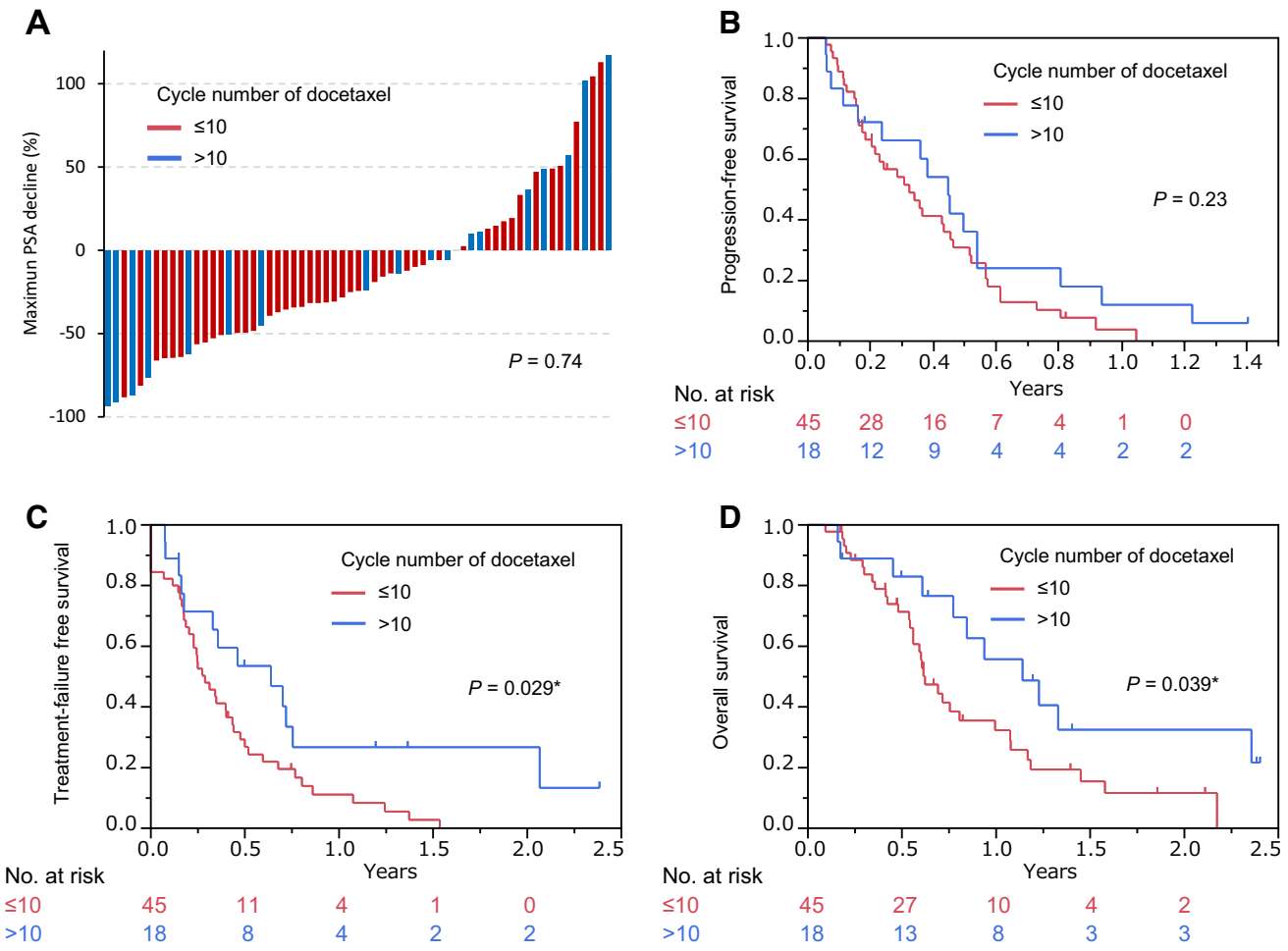

Fig. 2 Anticancer effects of cabazitaxel chemotherapy according to ≤10 and >10 cycles of prior docetaxel chemotherapy. Waterfall plots showing greatest decline in PSA levels from baseline (**a**), PFS (**b**), TFFS (**c**), and OS (**d**) in 63 patients with CRPC who received cabazitaxel chemotherapy after ≤10 and >10 cycles of prior docetaxel chemotherapy

Table 2 Grade ≥ 3 adverse events

	≥Grade 3
Hematological	
Neutropenia	46 (73.0%)
Febrile neutropenia	21 (33.3%)
Non-hematological	
Pneumonia	1 (1.6%)
Pulmonary embolism	1 (1.6%)
Acute coronary syndrome	1 (1.6%)
Elevated liver enzyme	2 (3.2%)
Nausea	1 (1.6%)
Diarrhea	1 (1.6%)
Gastroduodenal ulcer	3 (4.8%)
Intestinal perforation	1 (1.6%)
Peripheral neuritis	1 (1.6%)
Macular edema	1 (1.6%)
Urinary tract infection	1 (1.6%)
Sepsis	1 (1.6%)

Table 3 Grade ≥ 3 adverse events according to number of cycles of docetaxel

	Cycle number of docetaxel		
	≤10 ($n=45$)	>10 ($n=18$)	*P* value
Hematological			
Neutropenia (≥G3)	33 (73.3%)	13 (72.2%)	0.93
Febrile neutropenia (≥G3)	15 (33.3%)	6 (33.3%)	1.00
Non-hematological (≥G3)	12 (26.7%)	3 (16.7%)	0.39
Non-hematological (G5)	3 (6.7%)	0 (0.0%)	0.15

Moreover, grade 3 elevated liver enzymes and gastroduodenal ulcer were recorded in two (3.2%) and three (4.8%) patients, respectively (Table 2). However, severe AEs were comparable between patients who received ≤10 and >10 cycles of docetaxel (Table 3). Notably, fatal AEs were not observed in >10 cycles of prior docetaxel chemotherapy.

Discussion

In this study, cabazitaxel exerted its expected anticancer effects, even though most patients were treated with cabazitaxel in third-line or later settings. In 25.4% of patients, > 50% PSA decline was achieved. In addition, median PFS and OS were 4.3 and 9.0 months, respectively. In the TROPIC study, PSA response rate, median PFS, and median OS were 39.2%, 2.8 months, and 15.1 months, respectively [5]. A phase I study conducted in Japan showed similar oncological outcomes, with PSA response rate and median PFS of 29.3% and 3.7 months, respectively [17]. Compared with those prospective clinical trials, the patients in the present study showed comparable PSA response and PFS, but modest OS, which may be attributable to inclusion of patients with worse condition compared with the previous clinical trials. When compared with the previous studies in real-world settings, the oncological outcomes including PSA response (27–41%), PFS (2.8–8.5 months), and OS (8.2–20.3 months) appeared to be comparable [8–13].

The rates of severe neutropenia and febrile neutropenia were higher than those in previous reports from western countries [5, 15] while comparable with those in reports from Japan [17]. This suggests that this differential frequency of haematological toxicity after cabazitaxel treatment is attributable to racial difference, as it is after docetaxel chemotherapy. Notably, fatal AEs were recognized as high as 4.8%. Death within 30 days after last dose of cabazitaxel occurred in 5% in TROPIC trial as well as 2.1% of 20 mg/m^2 arm and 3.2% of 25 mg/m^2 arm in PROSELICA trial, suggesting comparative fatal AEs in cabazitaxel [5, 15]. Thus, careful patient inclusion and attention are required in cabazitaxel chemotherapy.

Our study showed persistent anticancer effects and less cumulative toxicity of cabazitaxel, even after > 10 cycles of docetaxel were administered. In the TROPIC trial, subgroup analysis showed excellent survival benefit among patients treated with ≥ 900 mg/m^2 docetaxel, although the number of patients was small [5], which supports the persistent anticancer effects of cabazitaxel even after > 10 cycles of docetaxel. Meanwhile, it was reported that insignificant difference of treatment response and prognosis in cabazitaxel chemotherapy regardless of the response and administered dose in prior docetaxel chemotherapy [12], warranting further investigation in the future. These data at least suggest that continuous administration of docetaxel for > 10 cycles until progression is suitable if docetaxel shows less cumulative toxicity, while switching from docetaxel to cabazitaxel is recommended if there is cumulative toxicity with docetaxel.

This study had some limitations. First, this was a retrospective study including a small number of cases. In addition, this study was conducted using the data from multiple institutions, which may have resulted in diagnostic and therapeutic variations among the institutions. However, despite these limitations, this study provided a valuable insight into clinical outcomes in cabazitaxel chemotherapy.

Conclusion

Our findings showed that cabazitaxel chemotherapy was still active in patients previously treated with > 10 cycles of docetaxel, with an acceptable risk of AEs. Finally, this study suggests that cabazitaxel after > 10 cycles of docetaxel chemotherapy is a therapeutic option when it can be administered.

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Compliance with ethical standards

Conflict of interest We declare no conflicts of interest.

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