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Therapeutic Outcome of >10 Cycles of Cabazitaxel for Castration-resistant Prostate Cancer: A Multi-institutional Study

MASAKI SHIOTA[1], MOTONOBU NAKAMURA[2], AKIRA YOKOMIZO[3], TOSHIHISA TOMODA[4], NAOTAKA SAKAMOTO[5], NARIHITO SEKI[6], SHUJI HASEGAWA[7], TAKAKAZU YUNOKI[8], MASAHIKO HARANO[9], KENTARO KUROIWA[10] and MASATOSHI ETO[1]

[1]*Department of Urology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan;*
[2]*Department of Urology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan;*
[3]*Division of Urology, Harasanshin Hospital, Fukuoka, Japan;*
[4]*Department of Urology, Oita Prefectural Hospital, Oita, Japan;*
[5]*Department of Urology, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan;*
[6]*Department of Urology, Kyushu Central Hospital, Fukuoka, Japan;*
[7]*Department of Urology, Kitakyushu Municipal Medical Center, Kitakyushu, Japan;*
[8]*Department of Urology, Japanese Red Cross Fukuoka Hospital, Fukuoka, Japan;*
[9]*Department of Urology, JCHO Kyushu Hospital, Kitakyushu, Japan;*
[10]*Department of Urology, Miyazaki Prefectural Miyazaki Hospital, Miyazaki, Japan*

Abstract. *Background/Aim: Cabazitaxel use has usually been limited to up to 10 cycles in most countries according to the protocol in the TROPIC trial. Therefore, clinical data on cabazitaxel use beyond 10 cycles is limited. The aim of this study was to report the therapeutic outcome of cabazitaxel chemotherapy administered for >10 cycles. Patients and Methods: This study included 74 Japanese patients with prostate cancer between 2014 and 2017. Patients background, and treatment outcomes including PSA decline, progression-free survival, treatment-failure-free survival, overall survival, and adverse events were investigated, comparing patients treated with ≤10 and >10 cycles. Results: Patients characteristics were favorable as indicated by the higher number of cycles of prior docetaxel chemotherapy, absence of pain, and absence of bony and visceral metastases among men who received >10 cycles of cabazitaxel. PSA response, progression-free survival, treatment-failure-free survival and overall survival were better among patients treated with >10 cycles of cabazitaxel compared to those treated with ≤10 cycles. The incidence of severe adverse events was similar between the two groups. Conclusion: Taken together, this study suggested that continuous chemotherapy with cabazitaxel beyond 10 cycles may be beneficial.*

Correspondence to: Masaki Shiota MD, Ph.D., Department of Urology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. Tel: +81 926425603, Fax: +81 926425618, e-mail: shiota@uro.med.kyushu-u.ac.jp

Key Words: Castration-resistant prostate cancer, cabazitaxel, outcome, adverse event.

The phase III TROPIC trial has shown that cabazitaxel, the next-generation taxane, after docetaxel chemotherapy, prolongs survival of patients suffering from castration-resistant prostate cancer (CRPC) and provides pain relief (1, 2). Usually, clinical use of cabazitaxel has been limited to up to 10 cycles in most countries according to the protocol in the TROPIC trial (1). However, it can be hypothesized that cabazitaxel use beyond 10 cycles may be more beneficial to patients with CRPC if antitumor effects are sustained and toxicities are tolerable. In Japan, cabazitaxel is being used for more than 10 cycles. Therefore, in this study, we aimed to reveal the therapeutic outcome of long-term cabazitaxel chemotherapy, comparing patients treated with ≤10 and >10 cycles.

Patients and Methods

Patients. This study retrospectively enrolled Japanese men treated with cabazitaxel between 2014 and 2017 at the following institutions: Kyushu University Hospital (Fukuoka), National Hospital Organization Kyushu Cancer Center (Fukuoka), Harasanshin Hospital (Fukuoka), Oita Prefectural Hospital (Oita),

Table I. *Patients' characteristics according to number of cycles of cabazitaxel.*

Variables	Cycle number of cabazitaxel			
	All (n=74)	≤10 (n=62)	>10 (n=12)	*p*-Value
Median age, years (IQR)	72 (67-76)	72 (67-76)	74 (64-77)	0.81
Median PSA at diagnosis, ng/ml (IQR)	48.3 (19.4-376.8)	46.2 (18.4-349.7)	192 (34.0-645.7)	0.21
NA	2	2	0	
Biopsy Gleason score, n (%)				
≤7	12 (16.9%)	9 (15.3%)	3 (25.0%)	
8	12 (16.9%)	10 (16.9%)	2 (16.7%)	
≥9	47 (66.2%)	40 (67.8%)	7 (58.3%)	0.71
NA	3	3	0	
Prior local therapy, n (%)				
Absence	53 (71.6%)	43 (69.4%)	10 (83.3%)	
Presence	21 (28.4%)	19 (30.6%)	2 (16.7%)	0.33
Time to CRPC, years (IQR)	1.3 (0.7-2.4)	1.3 (0.7-2.3)	1.7 (0.7-4.2)	0.31
NA	7	7	0	
Cycle number of prior docetaxel	8 (5-12)	7 (5-10)	13 (7-20)	0.0092*
Prior treatment for CRPC, n (%)				
Abiraterone/enzalutamide	62 (83.8%)	52 (83.4%)	10 (83.3%)	0.96
Radium-223	4 (5.4%)	4 (6.5%)	0 (0.0%)	0.37
ECOG PS at pre-treatment, n (%)				
0	43 (65.2%)	33 (61.1%)	10 (83.3%)	
1	15 (22.7%)	13 (24.1%)	2 (16.7%)	
≥2	8 (12.1%)	8 (14.8%)	0 (0.0%)	0.12
NA	8	8	0	
Pain at pre-treatment, n (%)				
Absence	37 (50.0%)	27 (43.5%)	10 (83.3%)	
Presence	37 (50.0%)	35 (56.5%)	2 (16.7%)	0.012*
Median PSA at pre-treatment, ng/ml (IQR)	72.3 (18.0-240.6)	93.1 (17.3-293.2)	38.8 (28.8-77.6)	0.22
Metastatic sites, n (%)				
Lymph node	43 (58.1%)	37 (59.7%)	6 (50.0%)	0.53
Bone	66 (89.2%)	58 (93.5%)	8 (66.7%)	0.0061*
Visceral	20 (27.0%)	20 (32.3%)	0 (0.0%)	0.021*

*Statistically significant. IQR: Interquartile range; NA: not available; PS: performance status.

Table II. *Grade ≥3 adverse events according to number of cycles of cabazitaxel.*

	Cycle number of cabazitaxel			
	All (n=74)	≤10 (n=62)	>10 (n=12)	*p*-Value
Hematological				
Neutropenia (≥G3)	54 (73.0%)	45 (72.6%)	9 (75.0%)	0.86
Febrile neutropenia (≥G3)	23 (31.1%)	20 (32.3%)	3 (25.0%)	0.62
Non-hematological (≥G3)	17 (23.0%)	14 (22.6%)	3 (25.0%)	0.86
Non-hematological (G5)	5 (6.8%)	5 (8.1%)	0 (0.0%)	0.31

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). The Institutional Review Boards approved this study. Inclusion criteria are as follows: (i) histopathological diagnosis as carcinoma of the prostate; (ii) age ≥20 years; and (iii) progression despite primary androgen-deprivation therapy.

Treatment. Cabazitaxel (20-25 mg/m^2) was administered as a 3- or 4-weekly regimen according to the physician's preference (1, 3),

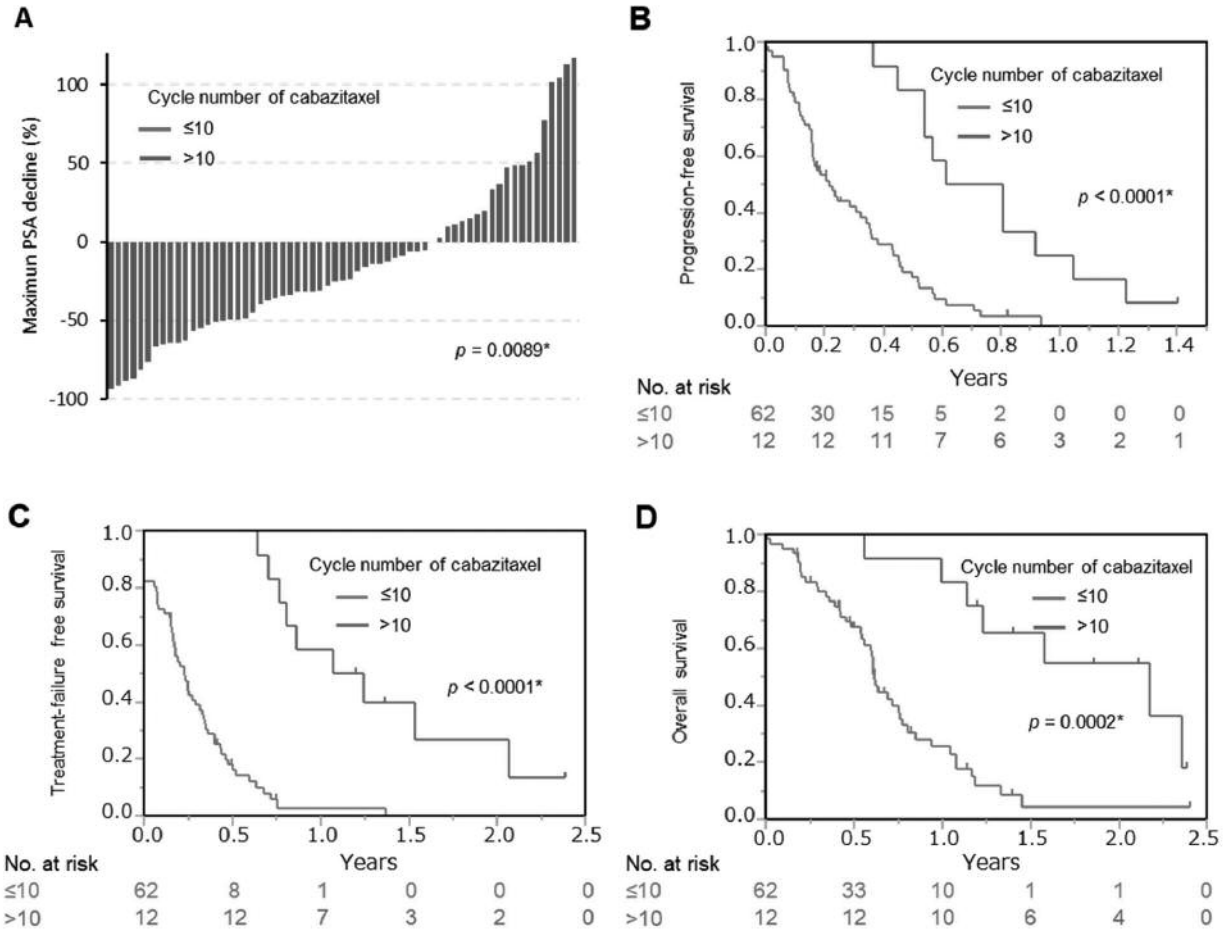

Figure 1. *Anticancer effects of cabazitaxel chemotherapy administered in ≤10 or >10 cycles. Waterfall plots showing greatest decline in PSA levels from baseline (A), progression-free survival (B), treatment-failure-free survival (C), and overall survival (D) in 74 patients with CRPC who received ≤10 or >10 cycles of cabazitaxel chemotherapy.*

and only one case was treated with 15 mg/m^2 cabazitaxel. Prednisolone 5 mg was given twice daily simultaneously with medical or surgical castration.

Measurements. Disease progression was defined according to PCWG2 (4). Treatment failure was defined as discontinuation of cabazitaxel, which was determined by disease progression and adverse events (AEs), or patient refusal. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Pain and performance status were determined by the prescription of analgesics for the symptom and according to the Eastern Cooperative Oncology Group criteria, respectively.

Statistical analysis. All statistical analyses were performed using JMP13 (SAS Institute). The differences of categorical and continuous variables were examined by Pearson's chi square test and Wilcoxon rank sum, respectively. The Kaplan–Meier method and log-rank test were used for survival analyses. $p<0.05$ was considered significant.

Results

A median of four (interquartile range=2-8) cycles of cabazitaxel therapy were administered to 74 patients according to the physician's judgement and patient's preference. Patients' backgrounds are shown in Table I. More cycles of prior docetaxel chemotherapy, absence of pain, and absence of bony and visceral metastases were recognized among men treated with >10 cycles of cabazitaxel (Table I), which suggested more favorable characteristics. Not surprisingly, PSA response, progression-free survival, treatment-failure-free survival and overall survival were all better among patients treated with >10 cycles compared to those treated with ≤10 cycles of cabazitaxel (Figure 1). The incidence of Grade ≥3 AEs was similar between patients treated with ≤10 and >10 cycles of cabazitaxel (Table II). Notably, lethal AEs did not occur in patients with >10 cycles of cabazitaxel, while pulmonary emboli, peripheral neuritis,

and macular edema were observed in each case, leading to discontinuation of cabazitaxel chemotherapy.

Discussion

In the present study, more cycles of prior docetaxel, absence of pain, and absence of bony and visceral metastases were associated with >10 cycles of cabazitaxel chemotherapy, suggesting that they are favorable prognostic factors for cabazitaxel chemotherapy and lead to successful long-term cabazitaxel treatment. Consistently, Halabi *et al*. have previously reported several prognostic factors for overall survival using data from the TROPIC trial, and pain and short response to docetaxel were identified as adverse prognostic factors (5).

Our study showed cabazitaxel also exerted excellent anticancer activity and modestly increased cumulative toxicity even when >10 cycles were administered. Intriguingly, therapeutic outcomes of cabazitaxel re-challenge have been reported, showing moderate anticancer effects with PSA response in 24% of cases and 13.7 months survival without cumulative toxicity (6, 7). This agrees with the excellent outcomes among patients who received >10 cycles of cabazitaxel in the present study.

Conclusion

These results support continuous chemotherapy with cabazitaxel for >10 cycles if disease control is achieved, there is less cumulative toxicity and patients wish to continue cabazitaxel chemotherapy.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

MS designed the study, analyzed the data, and wrote the draft of the manuscript. All other authors have contributed to data collection and interpretation, and critically reviewed the manuscript. EM supervised the study.

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