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Efficacy of Combination Chemotherapy With Docetaxel, Estramustine and Carboplatin in Men With Castration-resistant Prostate Cancer

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Abstract. *Background: The efficacy of docetaxel and carboplatin with oral estramustine was evaluated in patients with castration-resistant prostate cancer. Patients and Methods: Patients were treated with intravenous docetaxel at 30 mg/m2 on days 1, 8, 15, and 22 of a 28-day cycle. Intravenous carboplatin (area under the curve, 6 mg/ml/min) was administered on day 1. Patients received oral estramustine at 626.8 mg/day throughout the treatment protocol. Patients were evaluated for response, with treatment continued until cancer progression or onset of severe adverse events. Results: Twenty patients with castration-resistant prostate cancer were treated for a median of 3.5 cycles. Prostate-specific antigen decreased by more than 30% in 18 patients, including 14 patients with a decrease of more than 50%. Median overall survival was 11 months, prostate-specific antigen progression-free survival was 6.5 months, and radiographic progression-free survival was 7 months. Conclusion: Docetaxel and carboplatin with oral estramustine shows efficacy against castration-resistant prostate cancer.*

The number of patients diagnosed with prostate cancer (PC) has been increasing in recent years. The treatment of PC includes surgery, radiation therapy, and androgen deprivation therapy (ADT), each of which is useful for cancer control. For metastatic PC, ADT is generally the standard of care. ADT is a useful treatment for PC but disease in a certain percentage of patients becomes castration-resistant. For castration-resistant PC (CRPC), abiraterone, enzalutamide, apalutamide, darolutamide, docetaxel, and cabazitaxel have been used. Abiraterone was found to be effective in the COU-AA-301 and -302 trials, enzalutamide in the AFFIRM and PREVAIL trials, apalutamide in the SPARTAN trial, and darolutamide in the ARAMIS trial (1-6). Docetaxel was reported as useful by Tannock *et al*. and subsequently became the standard treatment for CRPC, but adverse events (AEs) such as peripheral neuropathy have also been reported (7). Use of cabazitaxel after docetaxel was reported by de Bono *et al*. and has been described as useful, but also leads to serious AEs such as myelosuppression, and particularly febrile neutropenia (8). In addition, no definitive treatment for CRPC after cabazitaxel has been reported. In recent years, therapies targeting mutations in breast cancer predisposition genes *BRCA1/2* have been implemented by testing for these genes but only a limited number of patients can be treated on this basis. A small number of platinum-based chemotherapies have been reported to be useful in patients with CRPC. Combination chemotherapy with docetaxel, estramustine and carboplatin (DEC therapy) was first reported by Urakami *et al*. in 2005 (9). Since 2012, we have been introducing DEC therapy for patients with CRPC whose disease has worsened after standard treatments such as docetaxel and cabazitaxel. The purpose of the present study was to evaluate the outcomes of DEC therapy.

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Key Words: Chemotherapy, metastatic castration-resistant prostate cancer, docetaxel, estramustine, cabazitaxel.

Patients and Methods

Ethics. This study was conducted at the Division of Urology at Tottori University Hospital, Tottori, Japan. The study protocol was

approved by the Ethics Committee at Tottori University (approval no. 20A063).

Patients. Patients who underwent DEC therapy between October 2012 and August 2020 at our Department for CRPC were included in the present study. Evaluations at the time of PC diagnosis included complete blood count, neutrophil-to-lymphocyte ratio (NLR), serum prostate-specific antigen (PSA), C-reactive protein (CRP), albumin (Alb), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH) levels, clinical stage, and Gleason score. Evaluations before initiation of DEC therapy included complete blood count, NLR, PSA, CRP, Alb, ALP, and LDH levels, local treatment, time to CRPC, time from CRPC to DEC therapy, sites of metastasis before DEC therapy, and previous treatments. Performance status (PS) was evaluated using Eastern Cooperative Oncology Group (ECOG) score. As outcome evaluations after DEC therapy, overall survival (OS), PSA progression-free survival (P-PFS), radiographic progression-free survival (R-PFS), PSA decrease post-DEC treatment, and AEs were analyzed. OS, P-PFS, and R-PFS were also examined in patients with and without visceral metastasis. All study data were analyzed retrospectively.

Treatment plan and evaluation of AEs. Patients were treated with intravenous docetaxel at 30 mg/m^2 on days 1, 8, 15, and 22 of a 28-day cycle. Intravenous carboplatin (area under the curve, 6 mg/ml/min) was administered on day 1. Patients received oral estramustine at 626.8 mg/day throughout the treatment protocol (days 1-28). Patients with cardiovascular disease, edema, or pleural effusion did not receive estramustine. AEs were evaluated using Common Terminology Criteria for Adverse Events version 5 (10). When myelosuppression of grade 4 or higher appeared, the doses of docetaxel and carboplatin were reduced to 80% for the next course. DEC therapy was continued until the cancer progressed or a severe AE was identified.

Definition of PSA progression. PSA progression was defined as at least three consecutive increases in serum PSA concentration from the baseline measurement at the start of DEC therapy.

Definition of radiographic progression. Imaging such as computed tomography or bone scintigraphy was performed every 3 months or at symptom progression. Progression was defined by radiographic progression according to Response Evaluation Criteria in Solid Tumours version 1.1 (11).

Statistical analysis. Data are presented as median values and interquartile ranges (IQRs). OS, P-PFS and R-PFS were analyzed using Kaplan–Meier methods. Statistical analyses were performed using EZR, which is a modified version of R Commander that has been designed to specifically add statistical functions that are frequently used in biostatistics (12).

Results

A total of 20 patients were eligible for this study. All patients were treated with bicalutamide and luteinizing hormone-releasing hormone agonists as initial therapy. At diagnosis, median patient age, body mass index, PSA and ECOG PS were 68 years (IQR=61-72 years), 21.5 kg/m^2 (IQR=19.7-24.8 kg/m^2), 144.9 ng/ml (IQR=22.9-855.0 ng/mL), and 0 (IQR=0-1), respectively. Clinical stage was D1 in one patient and D2 in 19 patients. Gleason score of biopsy was 9 or 10 in most patient (75%). Hematological and clinical chemistry examinations at diagnosis are shown in Table I. Before starting DEC therapy, the median PSA value and ECOG PS were 43.5 ng/ml (IQR=7.1-190.1 ng/ml), and 0 (IQR=0-1), respectively. As a local treatment, radiation therapy was performed for two patients. Median time to CRPC and time from CRPC to DEC therapy were 9 months (IQR=6-14 months) and 26 months (IQR=11-36 months), respectively. Sites of metastasis, hematological, and clinical chemistry examination are shown in Table II. The majority of patients had received three or more previous lines of treatment after CRPC. The details of the previous treatments are shown in Table II.

Table I. *Patient characteristics at diagnosis (n=20).*

Characteristic	Value
Age, years	
Median (IQR)	68 (61-72)
BMI, kg/m^2	
Median (IQR)	21.5 (19.7-24.8)
PSA, ng/ml	
Median (IQR)	144.9 (22.9-855.0)
ECOG performance status	
Median (IQR)	0 (0-1)
Clinical stage, n (%)	
D1	1 (5)
D2	19 (95)
Gleason score, n (%)	
8	2 (10)
9	7 (35)
10	8 (40)
Unknown	3 (15)
Hb, g/dl	
Median (IQR)	13.1 (10.4-13.9)
WBC, ×10^3/μl	
Median (IQR)	6.8 (5.1-8.6)
Plt, ×10^3/μl	
Median (IQR)	228 (202-395)
NLR	
Median (IQR)	2.5 (2.0-4.2)
Alb, g/dl	
Median (IQR)	4.1 (3.6-4.5)
ALP, U/l	
Median (IQR)	293 (196-587)
LDH, U/l	
Median (IQR)	218 (180-262)
CRP, mg/dl	
Median (IQR)	0.2 (0.1-1.6)

Alb: Albumin; ALP: alkaline phosphatase; BMI: body mass index; CRP: C-reactive protein; ECOG: Eastern Cooperative Oncology Group; Hb: hemoglobin; IQR: interquartile range; LDH: lactate dehydrogenase; NLR: neutrophil-to-lymphocyte ratio; Plt: platelets; PSA: prostate-specific antigen; WBC: white blood cells.

Table II. *Patient characteristics before therapy with docetaxel, estramustine and carboplatin (DEC) (n=20).*

Characteristic	Value
Median PSA, ng/ml	
Median (IQR)	43.5 (7.1-190.1)
ECOG performance status	
Median (IQR)	0 (0-1)
Local treatment, n (%)	
Prostatectomy	0 (0)
Radiation	2 (10)
Time to CRPC, months	
Median (IQR)	9 (6-14)
Time from CRPC to DEC, months	
Median (IQR)	26 (11-36)
Location of metastasis, n (%)	
Lung	9 (45)
Liver	4 (20)
Lymph node	20 (100)
Bone	20 (100)
Hb, g/dl	
Median (IQR)	10.8 (9.0-11.3)
WBC, $\times 10^3/\mu l$	
Median (IQR)	7.7 (5.7-10.0)
Plt, $\times 10^3/\mu l$	
Median (IQR)	247 (212-315)
NLR	
Median (IQR)	3.5 (3.0-8.5)
Alb, g/dl	
Median (IQR)	3.7 (3.5-4.0)
ALP, U/l	
Median (IQR)	234 (153-423)
LDH, U/l	
Median (IQR)	247 (204-479)
CRP, mg/dl	
Median (IQR)	0.8 (0.3-1.8)
Previous treatment after CRPC, n (%)	
Docetaxel plus prednisolone	17 (85)
Cabazitaxel plus prednisolone	8 (40)
Abiraterone	7 (35)
Enzalutamide	7 (35)
Flutamide	13 (65)
Radium 223	1 (5)
Lines of treatment after CRPC, n	
Median (IQR)	3.5 (3-5)
Docetaxel plus prednisolone courses, n	
Median (IQR)	6 (3-8)
Cabazitaxel plus prednisolone courses, n	
Median (IQR)	7 (2-8)

Alb: Albumin; ALP: alkaline phosphatase; CRP: C-reactive protein; CRPC: castration-resistant prostate cancer; ECOG: Eastern Cooperative Oncology Group; Hb: hemoglobin; IQR: interquartile range; LDH: lactate dehydrogenase; NLR: neutrophil-to-lymphocyte ratio; Plt: platelets; PSA: prostate-specific antigen; WBC: white blood cells.

In terms of treatment outcomes for DEC therapy, the median number of courses of DEC therapy was 3.5, with withdrawal of estramustine in 11 patients, and reduction of docetaxel or carboplatin dosage in five patients, respectively.

Table III. *Treatment outcomes and adverse events.*

Characteristic	Value	
No. of DEC courses		
Median (IQR)	3.5 (2-9)	
Withdrawal of estramustine, n (%)		
Yes	11 (55)	
Reduction of docetaxel or carboplatin, n (%)		
Yes	5 (25)	
Overall survival, months		
Median (IQR)	11 (8-30)	
P-PFS, months		
Median (IQR)	6.5 (4-16)	
R-PFS, months		
Median (IQR)	6 (4-14)	
PSA decrease, n (%)		
≥30%	4 (20)	
≥50%	10 (50)	
	Grade 1, 2	Grade 3-4
Adverse events, n (%)		
Anemia	8 (40)	12 (60)
Neutropenia	1 (5)	19 (95)
Thrombocytopenia	7 (35)	13 (65)
Febrile neutropenia	-	3 (15)
Heart failure	1 (5)	0 (0)
Hepatobiliary disorders	3 (15)	1 (5)
Peripheral sensory neuropathy	3 (15)	0 (0)
Nail changes	5 (20)	-
Nausea	5 (20)	0 (0)
Vomiting	2 (10)	0 (0)
Diarrhea	2 (10)	0 (0)
Malaise	3 (15)	1 (5)

DEC: Docetaxel; estramustine and carboplatin; IQR: interquartile range; P-PFS: prostate-specific antigen progression-free survival; PSA: prostate-specific antigen; R-PSF: radiographic progression-free survival.

Median OS, P-PFS, and R-PFS were 11 months (IQR=8-30 months), 6.5 months (IQR=4-16 months), and 6 months (IQR=4-14 months), respectively (Table III). OS, P-PFS, and R-PFS curves according to presence of visceral metastasis are shown in Figure 1, Figure 2 and Figure 3. No significant difference was seen between patients with and those without visceral metastasis. PSA decrease was 30% or more in 18 patients, including 14 patients with a decrease of at least 50%. Treatment after DEC therapy was carried out for seven patients, with cabazitaxel plus PSL in four, enzalutamide in two patients and ^{223}Ra in one. AEs associated with DEC therapy included anemia, neutropenia, and thrombocytopenia, which appeared in all patients, with grade 3 or 4 events 12, 19 and 13 patients. Other grade 3 or 4 events were febrile neutropenia in three patients, hepatobiliary disorders in one patient, and malaise in one patient (Table III).

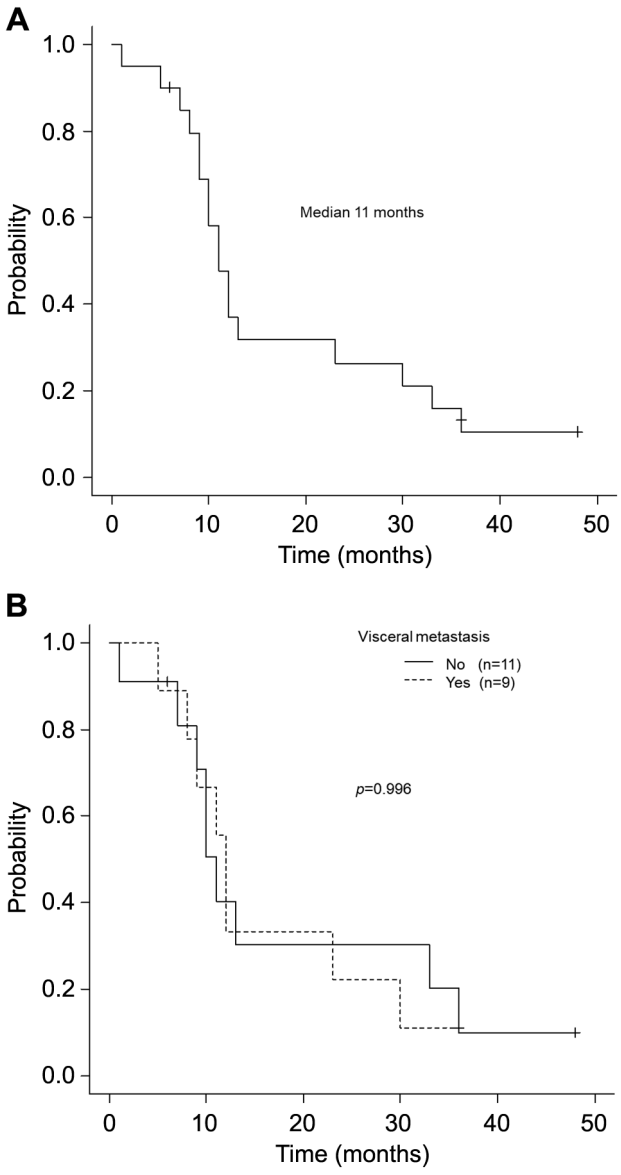

Figure 1. *A: Overall survival (OS) of patients who underwent therapy with docetaxel and carboplatin with oral estramustine (n=20), as determined by the Kaplan–Meier method. B: Comparison of OS between patients with and without visceral metastasis.*

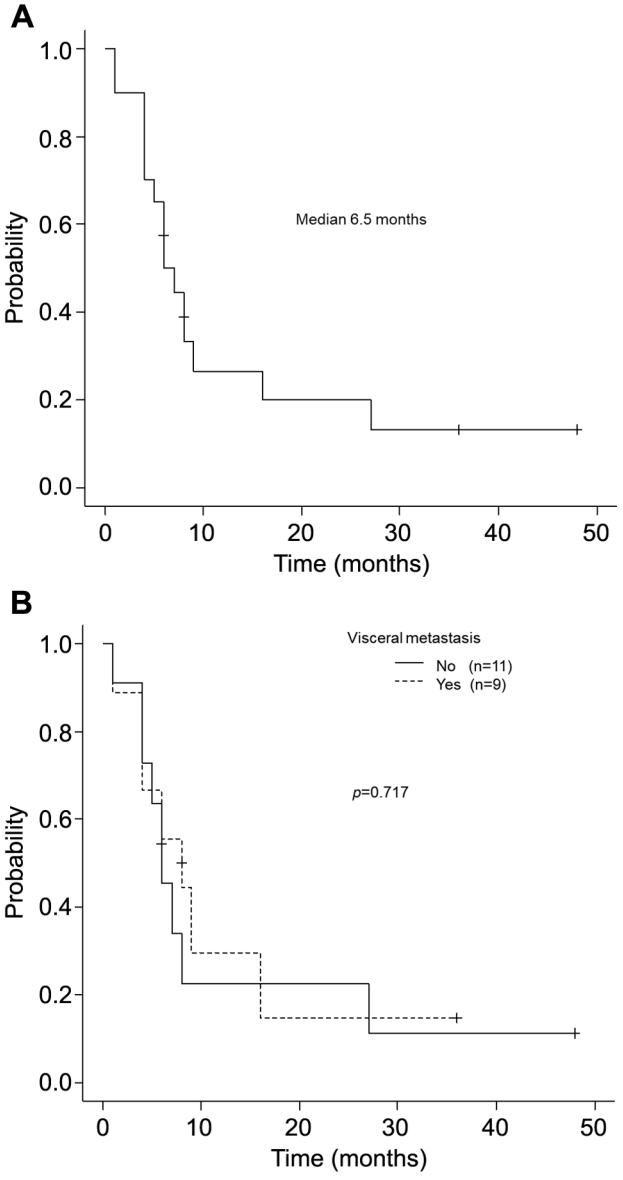

Figure 2. *A: Prostate-specific antigen progression-free survival (P-PFS) of patients who underwent docetaxel and carboplatin with oral estramustine therapy (n=20), as determined by the Kaplan–Meier method. B: Comparison of P-PFS between patients with and without visceral metastasis.*

Discussion

DEC therapy is a combination of docetaxel, estramustine, and carboplatin, and was first described by Urakami *et al*. in 2005 (9). Docetaxel is currently used as the standard treatment for CRPC, and its usefulness in combination with estramustine has been reported (9, 13, 14). In recent years, the combination of carboplatin with a taxane anticancer agent has been reported to provide a favorable treatment regimen for CRPC (14-17). In terms of results for DEC therapy, Kikuno *et al*. treated 40 patients with CRPC with DEC therapy and reported that the median time to progression was 12 months and median OS was 26.6 months (18). In our study, OS was 11 months and P-PFS was 6.5 months, worse than the results reported by Kikuno *et al*. However, in our study, the median number of treatment lines before DEC therapy was 3.5, and

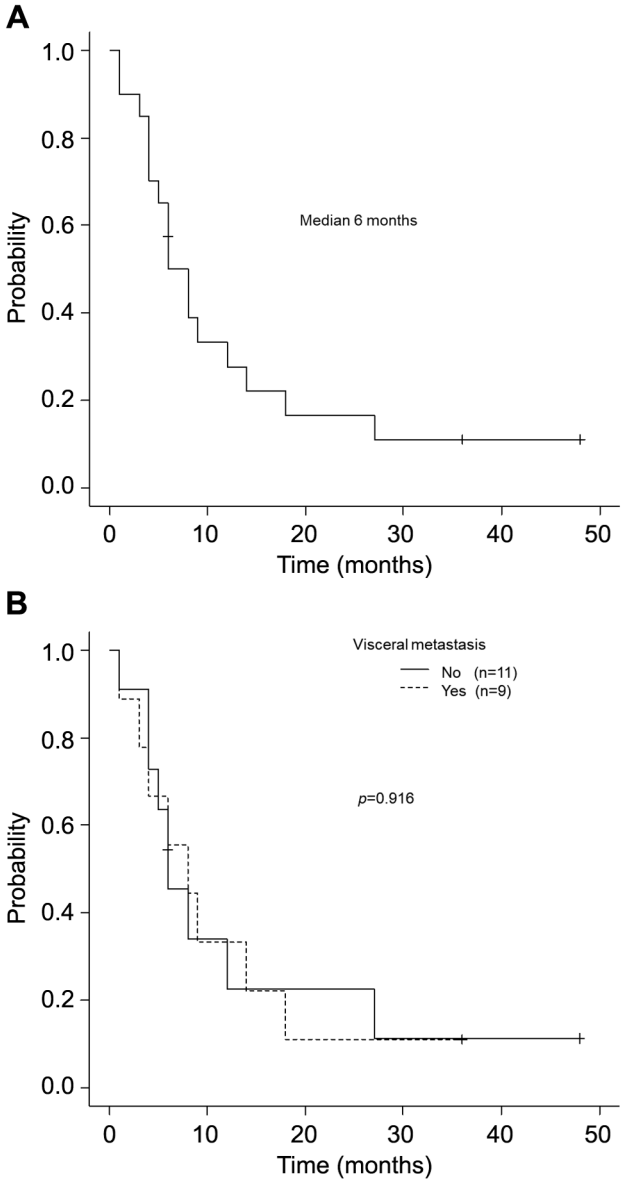

Figure 3. *A: Radiographic progression-free survival (R-PFS) of patients who underwent docetaxel and carboplatin with oral estramustine therapy (n=20), as determined by the Kaplan–Meier method. B: Comparison of R-PFS between patients with and without visceral metastasis.*

many treatment lines were performed before DEC therapy. In addition, the median time from CRPC to DEC therapy was also long, at 26 months. Although differences were observed in the drugs used and whether estramustine was used, Fujiwara *et al*. reported the therapeutic effects of taxanes and carboplatin after second-line therapy for CRPC (19). Fujiwara *et al*. reported that PFS after second-line was 1 month and OS was 6-11 months, similar to our results. Furthermore, Yasufuku *et al*. reported a median PFS of 6 months with paclitaxel or docetaxel in combination with estramustine and carboplatin, similar to our results (16).

Regarding the PSA response rate, Kikuno *et al*. reported that 95% of patients achieved a ≥50% reduction in PSA, but our results were worse than theirs (18). This may be due to differences in the number of lines performed and the fact that 55% of patients were not receiving estramustine, which may have influenced the results.

Recently, NLR has been reported as a useful prognostic predictor in PC. Nuhn *et al*. reported that pretreatment NLR affects the prognosis of PC. They divided patients into groups with NLR <3 and ≥3, and reported a significant difference in OS (20). They reported that patients with higher NLR had poorer cancer status and that the NLR may be useful in predicting OS in men with mCRPC. In the present study, at diagnosis the median NLR was 2.5 but it rose to 3.5 before the start of DEC, which was considered to be due to patients with poor prognoses.

Visceral metastasis is considered a poor prognostic factor. Median OS for men with liver metastases of PC who received docetaxel has been reported as 13.5 months, significantly worse than the 19.4-month OS for men with lung metastases (21). Our study was based on a small number of patients, and no significant difference in OS, P-PFS, or R-PFS was found between patients with and without visceral metastases. Because of the small number of patients, we were unable to perform multivariate analysis of factors that contribute to the efficacy of DEC therapy but some therapeutic benefit may be obtained for patients with visceral metastases.

Numerous reports have examined the usefulness of estramustine for CRPC, but a high frequency of AEs has also been described. Matsumoto *et al*. reported that 29.4% of patients with CRPC had a PSA decrease of ≥50% but 10.8% of patients discontinued estramustine due to AEs (22). We did not use estramustine in patients with cardiovascular disease, and discontinued estramustine in one patient who experienced heart failure after using estramustine. One possibility is that as 55% of patients were unable to use estramustine and therefore had a shorter OS and PFS than reported by Kikuno *et al*. (18).

In addition, our study showed that AEs also tended to be worse than in previous reports. Myelosuppression was highly prevalent. Kikuno *et al*. reported total frequencies of 77.5% for anemia, 75% for leukopenia, and 57.5% for thrombocytopenia, all of which were observed in all of the patients in this study (18). In addition, three patients had febrile neutropenia as a serious AE. This may have been related to the large number of treatment lines previously administered.

In our study, the OS, P-PFS, R-PFS, and PSA response rate all tended to be worse than past results of DEC therapy. However, the median number of treatment lines after PC became castration-resistant among patients in this study was 3.5 lines, suggesting that some benefit can be expected even

after multiple lines of treatments. In addition, patients with visceral metastases may also benefit to some extent. However, AEs are common, and caution should be exercised in treatment.

Limitations to this study were the extremely small number of cases, the retrospective design of the study, the differing number of pretreatments and treatment lines, and the fact that estramustine was not administered to 55% of patients. Further studies with a larger number of patients will allow better evaluation of the efficacy of DEC therapy in patients with CRPC.

Conflicts of Interest

There are no competing interests for this study.

Authors' Contributions

KH: Project development, data analysis, article writing; HI and SM: project development, data collection, data analysis; PT, ST, RS and TY: data analysis; MH and AT: project development, article revision. All Authors reviewed and approved the article.

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