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Outcome of Combination Chemotherapy with Docetaxel, Estramustine Phosphate, and Carboplatin after Docetaxel and Prednisolone Therapy in Patients with Metastatic Castration-Resistant Prostate Cancer

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Abstract

We retrospectively reviewed the outcome of docetaxel, EMP, and carboplatin (DEC) as second-line chemotherapy in castration-resistant prostate cancer (CRPC) patients previously treated with docetaxel-prednisolone (DP). Nineteen patients pretreated with DP received a DEC regimen which consisted of a 28-day cycle of docetaxel [60 mg/m² intravenously (IV) on day 1)], carboplatin (IV to an area under the curve of 5 on day 1), and EMP (560 mg orally daily). The DEC therapy was continued intermittently after two consecutive courses. End points were DEC effect on prostate-specific antigen (PSA), radiographic response, progression-free survival (PFS), and overall survival (OS). All patients received DP before DEC administration with a median of 6 cycles (range, 1 - 12). Mean follow-up duration was 19.0 months after starting DEC therapy; median total number of the therapy cycles was 2 (range, 1 - 11). Thirteen patients (68.4%) showed a PSA decrease; 6 (31.6%) showed a decrease in the PSA level of ≥50%, including 4 with no PSA response to DP. Grade 3/4 neutropenia and febrile neutropenia were observed in 13 (68.4%) and 2 (10.5%) patients, respectively. The median PFS following DEC was 3.7 months. The median OS was 18.0 months. In univariate analyses, patients with ≤12 months from CRPC to DEC had shorter PFS and OS, whereas PSA response to DP was not associated with PFS or OS in CRPC patients treated with

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DEC after DP. In conclusion, DEC retains some clinical benefits for CRPC patients pretreated with DP, even in patients without any response to DP. Therefore, they may be an effective and feasible treatment option for CRPC patients after first-line docetaxel therapy, particularly for those deemed unfit for novel endocrine and chemotherapeutic drugs.

Keywords

Chemotherapy, Carboplatin, Docetaxel, Estramustine Phosphate, Prostate Cancer

1. Introduction

Prostate cancer is the second leading cause of cancer mortality among men worldwide [1]. While it initially responds to androgen deprivation therapy, it eventually becomes castration-resistant in most patients. Docetaxel has been a standard first-line treatment in patients with castration-resistant prostate cancer (CRPC) for almost a decade; however, novel drugs have now become available, including enzalutamide, abiraterone acetate, and cabazitaxel, which can be used in pre- and/or post-docetaxel settings [2]. Several studies have indicated that the clinical cross-resistances between docetaxel and novel androgen receptor (AR) signaling-targeted drugs existed [3] [4]. Furthermore, a novel chemotherapy agent cabazitaxel, which has been suggested to have a little cross resistance to new AR signaling-targeted agents, is reported to be accompanied by severe toxicities in a substantial number of patients, particularly in Asian patients [5] [6].

Platinum compounds, which have historically been believed to have only modest activity for prostate cancer in monotherapy [7], have also been shown to be effective when combined with taxanes and estramustine phosphate (EMP) in phase I - II studies [8]-[11]. In its pooled analysis, the response of prostate-specific antigen (PSA) levels and 12-month survival estimate were reported to be 69% and 79%, respectively [12]. We previously demonstrated that intermittent chemotherapy with docetaxel, EMP, and carboplatin (DEC) was a feasible option for CRPC based on the outcome with a decrease in the PSA level by ≥30% with 65.7% of patients and the median overall survival (OS) of 17.8 months [13]. These studies only assessed the outcomes for taxanes, EMP, and carboplatin (TEC) in first-line settings; therefore, the efficacy and feasibility of TEC as second-line chemotherapy in patients with CRPC who previously received docetaxel remain unknown.

In this study, we retrospectively assessed the outcome of combination therapy with DEC as second-line chemotherapy in patients with CRPC who were previously treated with docetaxel-prednisolone (DP) therapy.

2. Patients and Methods

2.1. Patients

We included all patients with confirmed CRPC who were previously treated with DP therapy. The definition of CRPC was histologically confirmed adenocarcinoma of the prostate with PSA or radiographic progression despite surgical or medical castration, with a serum testosterone level of 50 ng/dL or less. All patients were pretreated with a 28-day cycle of DP therapy, which consisted of docetaxel (70 mg/m^2 on day 1) and oral prednisolone (10 mg/day) in more than 1 cycle. The treatment of DP therapy was applied as an intermittent protocol using our original regimen. Briefly, three consecutive administrations of docetaxel in a 28-day cycle were defined as one course of the DP therapy. If the patient achieved PSA or clinical response during a course of therapy, a treatment holiday was taken until the patient's PSA level returned to the baseline. The DP therapy was intermittently continued until treatment failure (as defined above), intolerable drug toxicities occurred, or the patient refused further treatment.

2.2. Procedure and Treatment

This study and the DEC protocol were approved by the institutional review board of Akita University School of Medicine. The patients were treated with a DEC regimen that consisted of a 28-day cycle of docetaxel [60 mg/m^2 intravenously (IV) on day 1)], carboplatin (IV to an area under the curve of 5 on day 1), and EMP (560

mg orally daily). Pre-medication was with dexamethasone (8 mg IV), which was 30 min before each docetaxel infusion. The detailed regimen has been previously described [13]. Briefly, two consecutive DEC therapies were performed, followed by the assessment of efficacy and toxicity. Before further therapy with the DEC therapy, a chemotherapy holiday was taken until the PSA levels increased to above baseline. Dose-reduction was allowed for elderly patients, those with a low performance status, and those with a history of severe adverse events. A luteinizing hormone-releasing hormone agonist was continued throughout the study. Treatment was stopped for any of the following reasons: progression of disease, severe adverse events, patient's refusal of further treatment, or at the physician's discretion. The administration of zoledronic acid or denosumab was allowed for patients with bone metastasis.

2.3. Outcome and Statistical Analysis

The study end points were the PSA response rate, radiographic response, progression free survival (PFS), and OS. PSA and radiographic progression were defined according to the criteria of the Prostate Cancer Clinical Trials Working Group 2 [14]. We measured PSA levels at least every 3 months after starting chemotherapy. A post-therapy PSA response was calculated using the maximum degree of change from baseline within 3 months. PSA response and PFS was defined as a decrease in the PSA level of ≥50% and the period from the initiation of DEC therapy to PSA progression and/or radiographic progression, respectively. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 4.0 (NCI-CTC v4.0).

Regarding statistical analyses, continuous variables are expressed as median values. OS and PFS were estimated using the Kaplan–Meier method. To identify risk factors for PFS and OS, univariate analysis was conducted using the following variables: patient age, Eastern Cooperative Oncology Group performance status, baseline PSA, baseline alkaline phosphatase, baseline lactate dehydrogenase, baseline hemoglobin, PSA response to the previous DP therapy, total cycles of previous DP therapy, duration from CRPC to the DEC therapy, visceral metastasis presence, and Gleason score at biopsy. All reported p values were two-sided, with statistical significance considered at $p < 0.05$.

3. Results

3.1. Patient Characteristics

In total, 19 patients received DEC therapy after first-line chemotherapy with DP from May 2010 to March 2014. **Table 1** summarizes the baseline patient characteristics before DEC therapy. The median age was 65 years (range, 51 - 79 years), and most patients (89.5%) had a performance status of 0 or 1. In addition, 73.7% of the patients had a Gleason score of ≥8, and the median baseline PSA level was 67.0 ng/mL (range, 9.1 - 1102 ng/mL). A total of 18 (94.7%) patients had bone metastasis, whereas visceral metastasis was observed in 5 (26.3%) patients. The median time from diagnosis to docetaxel administration was 27.0 months (range, 3.0 - 1313 months), whereas the median time from docetaxel administration to DEC therapy was 13 months (range, 4.0 - 29 months). The median time from CRPC to DEC was 17 months (range, 5.0 - 57 months). All patients received a median of 6 cycles (range, 1 - 12) of DP therapy before receiving DEC therapy. In addition, 12 (63.2%), 3 (15.8%), and 16 (84.2%) patients had previously received flutamide, chlormadinone acetate, and EMP, respectively.

3.2. Treatment Outcome

The mean follow-up period was 19.0 months, and patients received a median of 2 (range, 1 - 11) cycles of DEC therapy. The maximum response to DEC therapy is shown in **Figure 1** and **Table 2**. Of the 19 patients, 13 (68.4%) had a PSA decrease, with 6 (31.6%) having a decrease of ≥50%. All patients were withdrawn from DEC therapy during the study period because of disease progression, except for one patient who experienced grade 3 general fatigue as a side effect. The median PFS was 3.7 months (range, 0.5 - 20.4 months). In 10 patients (52.6%) with evaluable extraosseous metastases, 1 patient (10%) achieved partial response and 6 patients (60%) achieved stable disease according to the Response Evaluation Criteria in Solid Tumors. Ten patients (52.6%) survived to the end of the study period, and the median OS was 18.0 months (**Figure 2**). The 1- and 2-year survival rates were 55.2% and 46%, respectively.

Table 1. Patient characteristics.

		n	%
No. of patients		19	
Pt age (yr)	Median (Range)	65 (51 - 79)	
No. ECOG performance status	0	13	68.4
	1	4	21.1
	2	2	10.5
Gleason score at diagnosis	≤6	2	10.5
	7	2	10.5
	≥8	14	73.7
	unknown	1	5.3
Baseline PSA before DEC (ng/mL)	Median (Range)	67.0 (9.1 - 1102)	
Median time from diagnosis to ADT (m)	Median (Range)	1.0 (0.0 - 1062)	
Median time from diagnosis to docetaxel (m)	Median (Range)	27.0 (3.0 - 1313)	
Median time from DP to DEC (m)	Median (Range)	13.0 (4.0 - 29.0)	
Median time from CRPC to DEC (m)	Median (Range)	17.0 (5.0 - 57.0)	
Median cycles of docetacel before DEC		6 (1 - 12)	
Metastatic site	Bone	18	94.7
	Lymph nodes	13	68.4
	Visceral	5	26.3
	Other	1	5.3
Prior therapy	Surgery	4	21.1
	Radiation	2	10.5
	Medical castration	15	78.9
	Surgical castration	4	21.1
	Bicalutamide	19	100.0
	Flutamide	12	63.2
	Chlormadinone acetate	3	15.8
	EMP	16	84.2
	Other	2	10.5

ECOG = Eastern Cooperative Oncology Group, DEC = docetazel, estramustine phosphate, and carboplatin, DP = docetaxel and prednisolone, PSA = prostate specific antigen, EMP = estramustine phosphate.

Table 2. Clinical outcomes.

	Effective no. pts/total no. pts	%
PSA decrease		
≥30%	9/19	47.4
≥50%	6/19	31.6
≥75%	3/19	15.8
Measurable disease		
PR	1/10	10.0
SD	6/10	60.0

PSA = prostate specific antigen, PR = partial response, SD = stable disease, pts = patients.

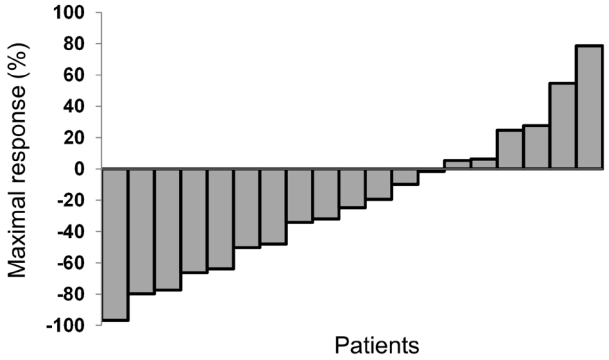

Figure 1. Waterfall graph of maximal changes in prostate-specific antigen levels after the administration of docetaxel, estramustine phosphate, and carboplatin in castration-resistant prostate cancer after first-line docetaxel and prednisolone therapy.

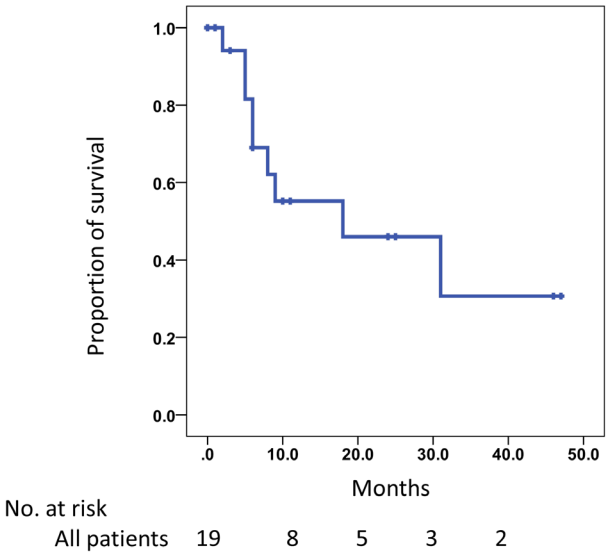

Figure 2. Kaplan-Meier curve for overall survival in patients with castration-resistant prostate cancer who were treated with docetaxel, estramustine phosphate, and carboplatin after docetaxel and prednisolone therapy.

3.3. Toxicity

A detailed toxicity profile during the study period is shown in **Table 3**. The most frequent grade 3 or 4 adverse events were neutropenia (68.4%), anemia (21.1%), thrombocytopenia (10.5%), and febrile neutropenia (10.5%). Non-hematologic adverse event exceeding grade 3 was observed in 2 patients (10.5%). There were no deaths due to treatment-related adverse event.

3.4. Pretreatment Variables for Clinical Outcome

We assessed the relationship between PSA response to DP therapy and treatment outcome from DEC therapy. Among the 13 patients without a PSA response to DP therapy, 4 (30.8%) achieved a PSA response to DEC therapy. In addition, among the 6 patients who had a PSA response to DEC therapy, 4 (66.7%) had no prior PSA response to DP therapy. On univariate analyses (**Table 4**), a duration from CRPC to DEC of ≤12 months was a significant risk factor of both PFS [hazard ratio (HR) = 3.055, $^{*}p = 0.047$] and OS (HR = 5.790, $^{*}p = 0.033$). Furthermore, the presence of visceral metastasis was significantly associated with a poor OS (HR = 6.139, $^{*}p = 0.027$). The PSA response to DP therapy had no statistically significant impact on PFS or OS in patients with CRPC receiving DEC therapy after DP therapy.

Table 3. Overall toxicities according to grade (CTCAE v4.0).

Grade (CTCAE v4.0)		1		2		3		4	
		n	%	n	%	n	%	n	%
Hematological	Neutropenia	2	10.5	4	21.1	8	42.1	5	26.3
	Anemia	1	5.3	11	57.9	4	21.1	0	0.0
	Thrombocytopenia	0	0.0	3	15.8	2	10.5	0	0.0
	Febril neutropenia	0	0.0	0	0.0	2	10.5	0	0.0
Nervous system	Peripheral sensory neuropathy	1	5.3	1	5.3	0	0.0	0	0.0
Gastrointestinal	Diarrhea	4	21.1	0	0.0	0	0.0	0	0.0
General	Anorexia	6	31.6	1	5.3	1	5.3	0	0.0
	Fatigue	0	0.0	0	0.0	1	5.3	0	0.0
	Nausea	1	5.3	0	0.0	0	0.0	0	0.0
	Alopecia	4	21.1	0	0.0	0	0.0	0	0.0
	Edema face	5	26.3	0	0.0	0	0.0	0	0.0
Skin and mucosa	Stomatitis	5	26.3	2	10.5	0	0.0	0	0.0
	Urticaria	1	5.3	0	0.0	0	0.0	0	0.0

Table 4. Univariate analysis for progression free survival and overall survival in patients with castration-resistant prostate cancer treated with docetaxel, estramustine phosphate and carboplatine therapy after docetaxel and prednisolone therapy.

Factors	Group	PFS			OS		
		HR	95% CI	p value	HR	95% CI	p value
Age	continuous	1.003	0.937 - 1.075	0.923	0.882	0.777 - 1.002	0.053
ECOG-PS	1.2 vs. 0	1.839	0.668 - 5.057	0.238	1.570	0.303 - 8.136	0.591
Baseline PSA (ng/dL)	continuous	1.001	0.998 - 1.003	0.499	1.002	0.998 - 1.006	0.276
	≥100 vs. <100	1.103	0.432 - 2.813	0.838	2.556	0.628 - 10.407	0.190
Baseline ALP (IU/l)	≥359 vs. <359	1.269	0.497 - 3.237	0.618	1.147	0.306 - 4.305	0.839
Baseline LDH (IU/l)	≥229 vs. <229	1.689	0.647 - 4.412	0.285	1.161	0.286 - 4.714	0.835
Baseline hemoblobin (g/dl)	<11.1 vs. 11.1<	1.566	0.608 - 4.028	0.353	2.227	0.526 - 9.436	0.277
Biopsy Gleason Score	≤8 vs. >8	1.214	0.389 - 3.790	0.738	1.261	0.313 - 5.082	0.744
Visceral metastasis	Yes vs. No	2.276	0.773 - 6.704	0.136	6.139	1.229 - 30.671	0.027*
PSA ≥ 50% decline in previous DP	No vs. Yes	1.637	0.563 - 4.763	0.365	3.743	0.455 - 30.800	0.220
Total cycles of previous DP	≤6 vs. >6	1.283	0.476 - 3.455	0.622	1.062	0.253 - 4.460	0.935
Duration from CRPC to DEC (month)	≤12 vs. >12	3.055	1.015 - 9.202	0.047*	5.790	1.148 - 29.215	0.033*

4. Discussions

Recently the outcomes have been reported for several combination chemotherapies and novel drugs as second-line treatment after docetaxel in CRPC [6] [15]-[20] (**Table 5**). Based on the large randomized trials, two novel drugs targeting AR signaling and chemotherapy with cabazitaxel achieved a PSA decrease of ≥50% in 29.4% - 54% of patients and a median OS of 15.1 - 18.4 months. Several combination chemotherapeutic regimens have also been reported to achieve a PSA decrease of ≥50% in 18% - 60% of patients and a median OS of 12.4 - 19

Table 5. Summary of the outcome of second-line therapy in patients with castration-resistant prostate cancer after docetaxel therapy.

Author	Year	No. of patient	Drug	PSA RR ≥ 50%	Tumor response rate%	Median PFS, mo	Median OS, mo
de Bono	2010	378	Cabazitaxel (TROPIC)	39.2	14.4	2.8	15.1
Fizazi	2012	797	Abiraterone acetate (COU-AA-301)	29.5	14.8	5.6	15.8
Scher	2012	800	Enzalutamide (AFFIRM)	54	29	8.3	18.4
Ross	2007	34	Docetaxel and carbopolatin	18	N/A	3	12.4
Loriot	2009	40	Etoposide, carboplatine with or without EMP	23	N/A	N/A	19
Sella	2009	15	Paclitaxel, estramustine, and carboplatin	60	40	4	14.6
Nozawa	2015	44	Cabazitaxel (Japanese phase I)	29.5	16.7	3.68	N/A
Current study		19	Docetaxel, estramustine phosphate and carbopolatin	31.6	10	3.7	18

EMP: estramustine phosphate, PFS: progression free survival, OS: overall survival, N/A: not assessed.

months [6] [15]-[20]. It is not valid to directly compare the outcomes between the previous reports and the current study because of the substantial differences in patient backgrounds and treatment regimens; however, we showed that DEC therapy is equivalent to other second-line treatments administered to patients after first-line docetaxel-based chemotherapy. Although the survival rate in some groups of the pateints in the current study seems to be worse than that in the previous study, most of the patients in the current study were previously heavily treated with second or thrid-line hormonal therapy (flutamide, 63.2%; chlormadinone acetate, 15.8%) and EMP (84.2%) in addition to docetaxel administration. Therefore, the outcomes in patients treated with our DEC therapy with a PSA decrease of ≥50% in 31.6% of patients and a median OS of 18.0 months could be feasible enough in this setting.

In a study evaluating the efficacy of second-line docetaxel-based chemotherapy, Nakabayashi *et al.* showed that docetaxel plus carboplatin had a modest effect, with PSA levels decreasing up to ≥50% in 20% of patients and a median OS of 14.9 months [21]. In another study of combination chemotherapy with TEC as second-line therapy, Sella *et al.* demonstrated the efficacy of combination paclitaxel, carboplatin, and EMP in 15 patients previously treated with docetaxel [18]. In the study, the PSA level decreased to ≥50% in 60% of patients, and a partial response was observed in 40%. Based on the results of the second-line taxane-based combination chemotherapies, including our result, the studies that included EMP and carboplatin in combination with a taxane appeared to have relatively better outcomes, potentially exploiting specific advantages of each drug for CRPC [18]. In vitro study has also shown the synergistic effect among these three drugs [22]. However, in the study using paclitaxel, one patient died due to brain hemorrhage following prolonged thrombocytopenia and four patients withdrawn from therapy due to toxicity [18]. Further study is warranted to determine which taxane is the best candidate partner for EMP and carboplatin to maximize the therapeutic effect and avoid severe adverse events.

Cabazitaxel is a promising second-line chemotherapeutic agent for patients with CRPC who fail to respond to first-line docetaxel chemotherapy. However, the problem with cabazitaxel treatment is the high incidence of severe side effects such as neutropenia and febrile neutropenia [5] [6]. Recent studies have shown that the rate of febrile neutropenia was extremely high in Asian patients (31% - 54.5%) [5] [6]. In our study, the incidence of febrile neutropenia was 10.5%, equivalent to the incidence in an international landmark trial of cabazitaxel (8%) [15] but lower than the rate in the phase I trial of cabazitaxel in Japanese patients (54.5%) [6]. Nevertheless, DEC therapy achieved a decrease in the PSA level of ≥50% in 31.6% of patients, which was not inferior to the outcomes of that phase I study (29.3%) [6]. These results indicate that patients who are expected to be unfit for cabazitaxel, particularly Asian patients, will be good candidates for the DEC therapy.

Another important issue in the treatment of patients with CRPC is to identify the best candidate for TEC therapy. Regan *et al.* conducted a meta-analysis that included seven trials using TEC and revealed that the absence of extra-skeletal metastases, a higher hemoglobin, and lower performance status, lactate dehydrogenase, alkaline phosphatase, and PSA at enrollment were associated with longer survival [12]. Our previous study also

showed that serum lactate dehydrogenase was an independent prognostic factor for OS in patients with CRPC who received DEC therapy [13]. As these trials examined the prognostic factors for TEC therapies in the first-line setting, these needed to be carefully applied to second-line settings, which we did in the current study. In second-line therapy, we showed that short duration from CRPC to DEC and the presence of visceral metastasis were significant risk factors of OS. Because these results imply that patients with these risk factors cannot achieve good response to current therapeutic options [23] [24], novel therapeutic approaches need to be developed for CRPC with these aggressive phenotypes.

We also focused on the impact of the PSA response to previous DP therapy on the PSA response to current DEC therapy. Our study revealed that the PSA response to previous DP therapy had no impact on any clinical outcomes, including the PSA response, PFS, and OS, in patients treated with the second-line DEC therapy. Therefore, it is possible that DEC therapy could be a feasible second-line chemotherapy option, even in patients with no PSA response to first-line docetaxel-based chemotherapy.

This study has some limitations, including a retrospective design, short follow-up duration, and small sample size. A Randomized trial should be needed to compare our results with those in the patients treated by classical methods. In addition, DP and DEC therapies were administered intermittently, according to our original protocol [13]. Therefore, the effect of continuous administration of DEC therapy, which is a more common protocol of taxane administration, remains unclear. Furthermore, none of the patients had received therapy from the new classes of drugs such as abiraterone acetate, enzalutamide, and cabazitaxel. The advantage of implementing DEC therapy before or after these novel drugs therefore also remains unclear and should be resolved in a future study.

5. Conclusion

We show that DEC therapy is feasible and beneficial in patients with CRPC after DP therapy. It produced relatively modest side effect and comparable response rates compared with previous studies evaluating the effects of second-line chemotherapy options. Thus, DEC may be an effective and feasible treatment option for patients with CRPC after the failure of first-line DP, particularly those deemed unfit for novel endocrine and chemotherapeutic drugs.

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