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Original Article

Effects of etoposide combined with cisplatin on prognosis of patients with castration-resistant prostate cancer who failed castration treatment

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Abstract: Objective: To determine the influences of etoposide combined with cisplatin on prognosis of patients with castration-resistant prostate cancer (CRPC) who failed castration treatment. Methods: A total of 100 patients with metastatic CRPC who failed castration treatment in our hospital from January 2015 to January 2017 were retrospectively analyzed. The patients were divided into a control group (n=59) treated with docetaxel combined with prednisone and an experimental group (n=41) treated with etoposide combined with cisplatin (EP). The change in prostate-specific antigen (PSA) level was adopted as the evaluation criterion for efficacy, by which the total clinical effective rate of patients was calculated. The neurologic rating scale (NRS) was adopted to evaluate the pain of patients, and the incidence of adverse reactions was compared between the two groups. Cox regression was carried out to analyze independent prognostic factors impacting 3-year survival. Results: The experimental group showed a significantly better clinical improvement than the control group (P<0.05). According to further analysis, the experimental group had a significantly higher clinical efficacy rate than the control group (P<0.05). Life quality scores of the experimental group were higher than those of the control group (all P<0.05). The two groups were not greatly different in bone pain, or incidence of adverse reactions (both P>0.05). The median survival time of the control group was 15.9 months, while that of the experimental group was 18 months, and the control group experienced a greatly shorter median survival time than the experimental group (P=0.040). According to Cox regression analysis, Gleason score, clinical stage, and metastasis were independent factors impacting the patients' 3-year prognosis (all P<0.05). Conclusion: EP regimen can strongly improve the 3-year survival rate of patients, without increasing adverse reactions.

Keywords: Etoposide, cisplatin, metastatic castration-resistant prostate cancer, prognosis

Introduction

Prostate cancer (PCa) is a common male malignant tumor. One survey shows that in the USA, PCa ranks first among male malignant tumors in incidence (19%) and the third in fatality (8%) in recent years, second only to lung cancer and colorectal cancer [1]. In China, its incidence is also increasing annually. In 2015, China had approximately 60,300 new PCa cases and approximately 26,600 PCa-related deaths, and most PCa patients suffered metastasis at the time of first diagnosis [2]. Androgen deprivation therapy (ADT) is the standard treatment for metastatic prostate currently [3, 4]. Treatments preventing androgens from activating androgen receptors, including castration therapy, antiandrogen therapy, and combination therapy are now highly recognized and extensively adopted in clinical scenarios [5, 6]. Initial ADT is effective for the vast majority of patients, but almost all patients gradually develop castration-resistant prostate cancer (CRPC) after 18-24 months without ADT [7]. The treatment options for CRPC are still highly limited. According to one survey, the median survival time of CRPC is less than 2 years [8]. Therefore, it is urgent to search for a treatment regimen to prolong the survival of patients with CRPC.

Docetaxel chemotherapy has been verified to benefit the survival of patients with CRPC [9],

so it has become the primary treatment for it. Over the past few years, several other drugs have also been confirmed to benefit the survival of patients with CRPC, such as enzalutamide, cabazitaxel, radium-223, sipuleucel-T, and abiraterone [10]. However, as of now, only docetaxel and abiraterone are listed in China. Recent research has revealed that carboplatin combined with etoposide does not increase the toxicity in patients with metastatic CRPC while effectively improving their life quality [11]. Etoposide combined with cisplatin (EP) is a chemotherapy regimen for clinical treatment of small cell lung cancer, and can greatly prolong the survival of patients and improve their life quality [12, 13]. No relevant research has reported the difference between EP regimen and docetaxel combined with prednisone in treating CRPC.

Accordingly, this study retrospectively analyzed patients with CRPC who were treated with EP in our hospital to observe the influences of EP regimen on the prognosis and adverse reactions, with the goal of providing a reference regimen for clinical treatment.

Methods and materials

Clinical data

A total of 100 patients with CRPC whose castration treatment was failed in our hospital from January 2015 to January 2017 were retrospectively analyzed. The patients were divided into a control group (n=59) treated with docetaxel combined with prednisone and the experimental group (n=41) treated with EP based on treatment options. This study was approved by the Medical Ethics Committee of our hospital. The inclusion criteria were: Patients diagnosed with PCa by prostate biopsy or surgical specimens based on pathological examination, patients who met the diagnostic criteria of CRPC [14], patients who showed no remarkable efficacy or developed to disease progression after ADT, and those whose estimated survival was over 3 months. The exclusion criteria were: Patients who received EP treatment regimen before enrollment, patients with other comorbid malignancies, patients with a history of viral hepatitis or chronic liver disease, patients with blood system diseases before chemotherapy, and those with abnormal indicators that cannot be corrected. The ethics approval number was JL1904LL (approve) 048.

Primary materials and instruments

Dexamethasone (Guangdong South Land Pharmaceutical Co., Ltd., State Food and Drug, China, Administration (SFDA) approval no.: H44024618), docetaxel (Heng Rui Pharmaceutical Co., Ltd., Jiangsu, China, SFDA approval no.: H20030561), prednisone (Harbin Pharmaceutical Group Holding Co, China, SFDA approval no.: H23022389), etoposide (China, Sichuan Baojiantang Pharmaceutical Co., Ltd., National Medicine Standard H20-045483), and cisplatin (China, Guangdong Lingnan Pharmaceutical Co., Ltd., National Medicine Standard H20183341).

Therapeutic regimen

The two groups were given docetaxel combined with prednisone and EP regime, respectively. The control group was treated by docetaxel combined with prednisone. Specifically, the patient was ordered to orally take dexamethasone (0.75 mg/d) 1 day before chemotherapy for antiallergic treatment. Docetaxel was administered by intravenous drip at 75 mg/m^2 within 1 h, and one course spanned 3 weeks. In addition to these treatments, the patient was also required to orally take prednisone (5 mg/time, twice/d), and stop taking it one month after chemotherapy. The experimental group was treated with the EP regimen. Specifically, both etoposide and cisplatin were given by intravenous drip, among which etoposide (50-100 mg/m^2) was injected within 1-5 days of chemotherapy and injected completely within 2 hours, and cisplatin (10-15 d mg/m^2) was injected within the first 1-5 days of chemotherapy, and injected completely within 2-3 hours. Each course spanned 3 weeks. Both groups were treated continuously for at least 3 courses.

Outcome measures

Primary outcome measures: Changes in prostate-specific antigen (PSA) were adopted as the evaluation criteria for efficacy (**Table 1**) [15], from which the total clinical effective rate of patients was calculated. The total effective rate = (patients with complete remission combined with those with partial remission)/total

Table 1. Evaluation criteria for PSA

Efficacy grade	Assessment criteria
Complete remission	Serum PSA decreased to the normal range, i.e. lower than 4 ng/ml.
Partial remission	Serum PSA decreased to a level below 50% of baseline before chemotherapy.
Stable disease	Serum PSA decreased to a level not less than 50% of the baseline level, or increased to a level not more than 25% of the baseline level before chemotherapy.
Progressive disease	Serum PSA increased to a level more than 25% of the baseline level before chemotherapy.

Note: All indicators lasted for over 4 weeks.

Table 2. Comparison of clinical data

Factor	Control group (n=59)	Experimental group (n=41)	T/ X^2-value	*P*-value
Age (Y)			0.448	0.503
≥60	32	25		
<60	27	16		
BMI (kg/m^2)			0.575	0.448
≥22	29	17		
<22	30	24		
Gleason score	7.35±1.34	7.01±1.18	1.282	0.202
NRS score	3.56±1.13	3.60±1.00	0.070	0.944
ECOG score	1.81±0.47	1.71±0.32	0.504	0.615
Clinical staging			0.477	0.489
T2	15	8		
T3~T4	44	33		
Metastasis			0.360	0.835
No	10	7		
Bone metastasis	32	20		
Organ metastasis	17	14		

Note: The counted data were analyzed by chi-square test.

number of patients * 100%. The Functional Assessment of Cancer Therapy-Prostate (FACT-P) was adopted to evaluate the patients' quality of life before and after treatment. FACT-P covers five sections: physical condition, social/family condition, emotional condition, functional condition and others. A higher score indicates higher life quality [16]. Cox regression was carried out to analyze the independent prognostic factors impacting the 3-year survival of patients.

Secondary outcome measures: The neurologic rating scale (NRS) was adopted for evaluation of the patients' pain, with a total score of 0-10 points. Higher score indicates more severe pain. Gleason score was used for histological grading. A higher NRS score indicates worse situation. The ECOG score was used to evaluate the physical activity of patients. A higher ECOG score indicates worse movement ability of patients. The incidence of adverse reactions and clinical data were compared between the two groups. The electronic pathology files of patients who had received reexamination in our hospital in 3 years were collected to understand their 3-year survival.

Statistical analyses

In this study, SPSS20.0 (Chicago SPSS Company, USA) was adopted for statistical analysis of the collected data, and GraphPad Prism 8 (San Diego Graphpad Software Co., Ltd., United States) for visualization of the data into corresponding figures. The enumerated data were expressed as percentage (%) and analyzed using the chi-square test. Measured data were expressed by the mean ± SD. Intergroup comparison was performed by the independent-samples T test, and introgroup comparison was conducted by the paired t test. Ranked data were analyzed via the rank-sum test. Kaplan-Meier survival analysis was conducted to understand the 3-year survival of patients, and the log rank test was used to compare the survival between the two groups. Multivariate Cox regression test was adopted for multivariate analysis of survival. $P<0.05$ denoted a significant difference.

Results

Clinical data

According to comparison of clinical data between the control and the experimental groups, the two groups showed no notable difference in age, body mass index (BMI), Gleason score, NRS score, ECOG score, clinical stage, and metastasis (all $P>0.05$, **Table 2**).

Table 3. Evaluation of clinical efficacy

Group	Complete remission	Partial remission	Stable	Progress	Total effective rate
Control group	7	18	18	16	42.37%
Experimental group	10	16	8	7	63.41%
χ^2/Z-value		-2.108			4.286
P-value		0.035			0.038

Note: Ranked data were analyzed using the rank sum test, and non-ranked data were analyzed using the chi-square test.

Table 4. Comparison of bone pain

Group	Alleviated bone pain	Stable bone pain	Aggravated bone pain
Control group	14	8	2
Experimental group	6	7	1
χ^2/Z-value		-0.782	
P-value		0.501	

Note: Ranked data were analyzed using the rank sum test, and non-ranked data were analyzed using the chi-square test.

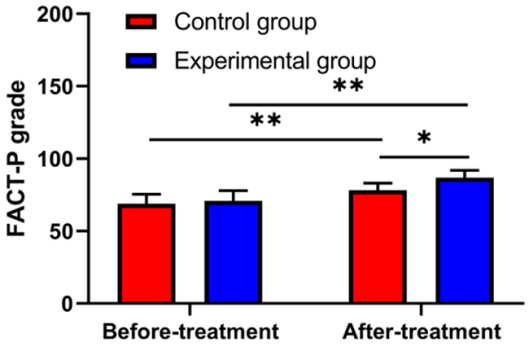

Figure 1. Comparison of FACT-P scores between two groups before and after treatment. *P<0.05; **P<0.01; The independent-samples t test was adopted for inter-group comparison; the paired t test was adopted for intra-group comparison.

Clinical efficacy evaluation

The change in PSA level was adopted as the evaluation standard for clinical efficacy in this study. According to comparison results, there were 7 cases with complete remission, 18 cases with partial remission, 18 cases with stable disease, and 16 cases with progressive disease in the control group, and there were 10 cases with complete remission, 20 patients with partial remission, 6 patients with stable disease, and 5 cases with progressive disease in the experimental group. The experimental group showed significantly better clinical efficacy improvement than the control group (P<0.05). According to further analysis, the experimental group showed a higher clinical efficacy rate than the control group (P<0.05, **Table 3**).

Comparison of bone pain

According to the evaluation results of bone pain in the two groups after therapy, there were 22 cases with bone pain in the control group, including 12 cases with alleviated bone pain, 2 cases with aggravated bone pain, and 8 cases with stable bone pain, and there were 14 cases with bone pain in the experimental group, including 6 cases with alleviated bone pain, 1 case with aggravated bone pain, and 7 cases with stable bone pain. The two groups were not significantly different in bone pain (P>0.05, **Table 4**).

Comparison of patients' life quality

The FACT-P was adopted to evaluate the life quality of patients before and after treatment. By comparison, we found that there was no difference in FACT-P scores between the control group and the experimental group before treatment (all P>0.05). After treatment, the FACT-P scores of the two groups significantly increased (all P<0.05), with higher FACT-P scores in the experimental group than those in the control group (**Figure 1**, all P<0.05).

Comparison of incidence of adverse reactions

The adverse reactions in patients were analyzed. The results revealed no notable difference between the two groups in fatigue, gastrointestinal reaction, hypokalemia, or myelosuppression (all P>0.05, **Table 5**).

Comparison of 3-year survival

The 3-year survival of the two groups was analyzed. The results revealed a median survival time of 15.9 months in the control group and a median survival time of 18 months in the experimental group. According to comparison results, the control group experienced a significantly shorter 3-year survival rate than the experimental group (P=0.040, **Figure 2**).

Table 5. Comparison of adverse reactions

Group	Hypodynamia		Gastrointestinal reaction		Hypokalemia		Myelosuppression	
	Grade I-II	Grade III-IV	Grade I-II	Grade III-IV	Grade I-II	Grade III-IV	Grade I-II	Grade III-IV
Control group	3	4	3	5	1	3	1	2
Experimental group	2	5	2	2	1	2	2	2
χ^2 value	0.311		0.171		0.058		0.194	
P-value	0.577		0.678		0.809		0.659	

Note: The data were analyzed using the chi-square test.

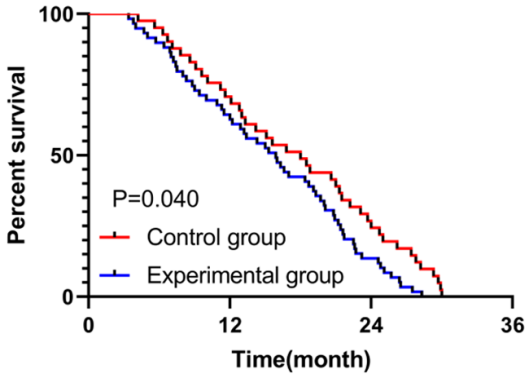

Figure 2. 3-year survival rate of the control group and experimental group. The K-M test was used to analyze the survival of patients.

Cox regression analysis

The clinical data of patients were collected (**Table 6**), and Cox regression was carried out to analyze the prognostic factors impacting the 3-year survival. According to univariate analysis, Gleason score, ECOG score, clinical stage, metastasis, and treatment regimen impacted prognosis (all P<0.05, **Table 7**). Significant factors were included for multivariate Cox regression analysis; and Gleason score, clinical stage, and metastasis were independent factors impacting the 3-year prognosis of patients (all P<0.05, **Table 8**).

Discussion

Over the past few years, the diagnosis rate of PCa in China has been increasing, and most patients have already suffered metastasis at the first time of diagnosis [17]. At the current stage, surgery is the primary clinical treatment for PCa [18]. However, patients in the middle or late stage have already missed the interval for surgery, so they can be only given drug treatment [19, 20]. ADT is the preferred choice for PCa patients who are not suitable for operation, and patients are sensitive to ADT at the initial stage, which greatly benefits disease control [21]. However, most patients under long-term ADT will develop CRPC [22]. Thus, searching for a strong treatment scheme is crucial to address this problem.

Docetaxel-based treatment is the preferred choice for patients with CRPC after ADT failure [23]. However, with docetaxel, patients face a high incidence of adverse reactions, and have an unfavorable tolerance, so docetaxel can hardly be extensively applied in clinical practice [24]. Caubet et al. [11] have revealed that platinum drugs combined with etoposide can improve the life quality of patients with CRPC during treatment. In our study, the EP regimen was adopted to treat patients with CRPC. Etoposide is a specific anti-tumor drug that mainly acts on DNA topoisomerase II to form a stable reversible drug-enzyme-DNA complex, which possesses the function of hindering DNA repair [25]. In addition, etoposide can be reversed with drug clearance, which can thus repair damaged DNA, reduce cytotoxicity, and prolong administration time to improve anti-tumor activity of drugs [26]. Cisplatin is a frequently adopted chemotherapy drug in clinic, which can suppress RNA transcription, prevent cells from entering division cycle, inhibit DNA replication and promote tumor cell apoptosis [27].

In our study, the EP regimen was adopted to treat patients with CRPC, and the change of PSA level was adopted for judgment of the clinical efficacy on patients after treatment. PSA is a secretion product of prostate epithelial cells, and its change can be adopted as one outcome measure of prostate injury severity and a crucial indicator for clinical diagnosis and prognosis evaluation of PCa [28, 29]. According to comparison results in this study, patients treated by the EP regime showed a significantly better clinical efficacy improvement

Table 6. Assignment

Factor	Assignment
Age (years)	≥60=0, <60=1
BMI	≥22=0, <22=1
Gleason score	≤6=0, 7=1, ≥8=2
NRS score	≤3=0, >3=1
ECOG score	≤1=0, >1=1
Clinical staging	T2=0, T3-T4=1
Metastasis	No metastasis =0, bone metastasis =1, internal organ metastasis =2
Therapeutic regimen	EP regimen =0, docetaxel combined with prednisone =1

Table 7. Univariate Cox regression analysis

Factor	β	S.E	χ^2 value	*P*-value	HR-value	95.0% CI	
						Upper	Lower
Age (years)	0.203	0.206	0.973	0.324	1.225	0.818	1.835
BMI	-0.217	0.205	1.119	0.290	0.805	0.538	1.204
Gleason score	0.362	0.129	7.924	0.005	1.436	1.116	1.847
NRS score	-0.047	0.203	0.053	0.818	0.954	0.641	1.420
ECOG score	0.688	0.256	7.203	0.007	1.989	1.204	3.288
Clinical staging	0.973	0.259	14.124	<0.001	2.645	1.593	4.394
Metastasis	0.595	0.145	16.773	<0.001	1.813	1.364	2.411
Treatment regimen	0.436	0.214	4.142	0.042	1.547	1.016	2.355

Note: All the indicators were separately included for Cox regression analysis, and the backward method was selected for testing.

Table 8. Multivariate Cox regression analysis

Factor	β	S.E	χ^2 value	*P*-value	HR-value	95.0% CI	
						Upper	Lower
Gleason score	0.270	0.134	4.063	0.044	1.310	1.007	1.702
ECOG score	0.194	0.276	0.497	0.481	1.215	0.707	2.086
Clinical staging	0.627	0.288	4.729	0.030	1.872	1.064	3.294
Metastasis	0.355	0.168	4.477	0.034	1.426	1.027	1.982
Therapeutic regimen	0.423	0.214	3.898	0.048	1.526	1.003	2.323

Note: Indicators with difference by univariate analysis were included for Cox regression analysis, and the backward LR was selected to test.

and a notably higher total effective rate than those treated by docetaxel combined with prednisone. This suggests an advantage of EP regimen in improving the clinical efficacy on patients with CRPC. Prior research has revealed the ability of docetaxel combined with cisplatin in effectively lowering PSA expression in patients with CRPC [30], which implies a certain effect of platinum drugs on patients with CRPC. Organ and bone metastases are common in patients with CRPC [31]. According to one study [32], most patients have severe bone pain during chemotherapy, which seriously disrupts their daily life. Our study compared the influences of the two regimens on patients' bone pain, and the results revealed no difference between patients under the two different regimens in bone pain, which suggested that the EP regimen would not increase patients' bone pain.

Adverse reactions are common after chemotherapy in clinic scenarios [33]. However, cisplatin is a broad-spectrum anticancer drug, that is likely to produce drug resistance in clinical application and bring many adverse reactions

[34]. In addition, etoposide also brings obvious adverse reactions, mainly including gastrointestinal reactions, bone marrow suppression, skin reactions, allergic reactions, and neurotoxicity [35]. However, recent research has revealed the advantage of combined medication in reducing the adverse reactions triggered by chemotherapy [35]. Accordingly, our study compared the influences of the two regimens on adverse reactions of patients. In our study, patients treated by the EP regimen and those by the docetaxel combined with prednisone regimen were not significantly different in adverse reactions, suggesting that the EP regimen would not increase adverse reactions. We believe that the long-term use of a single regimen can only improve the therapeutic effect by increasing the drug dose, which will inevitably increase the occurrence of adverse reactions, while the combination regimen can reduce the occurrence of adverse reactions triggered by increasing the drug dose. However, results of this study are different from previous studies, and we speculate that this may be due to our small sample size. Lastly, our study carried out a 3-year follow-up in the patients. According to analysis results, patients treated by the EP regimen showed a higher survival rate than those treated by docetaxel combined with prednisone. However, Cox regression analysis revealed that the treatment regimen had no obvious effect on the prognosis of patients. The results indicate that the EP regimen can improve the survival rate of patients but is still not an independent prognostic factor.

This study has confirmed the role of an EP regimen in patients with CRPC through experiments, though it still has some limitations. First of all, as a retrospective study, this study has obtained follow-up results of patients through electronic case inquiry, but has not conducted formal telephone follow-up survey. Secondly, we are unclear about the improvement of patients' life quality after treatment, so whether EP regimen can improve patients' life quality needs further exploration. Therefore, we hope to carry out forward-looking research to supplement our research results, so as to solidify the conclusions.

To sum up, EP regimen can strongly improve the 3-year survival rate of patients, without increasing adverse reactions.

Disclosure of conflict of interest

None.

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