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Original Research Article

Treatment efficacy of carrelizumab in metastatic castration-resistant prostate cancer, and the significance of circulating tumor DNA fraction

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Abstract

Purpose: *To explore the efficacy of carrelizumab in the treatment of metastatic castration-resistant prostate cancer (mCRPC), and the significance of circulating tumor DNA (ctDNA) fraction in the process.*
Methods: *100 mCRPC patients who were treated in the Oncology Department of Harbin Medical University Cancer Hospital in a time frame of January 2018 to January 2019 were enrolled and assigned (1:1) into control and study groups and were given a regimen consisting of a combination of docetaxel and prednisone. Prognosis of patients with high and low ctDNA fractions relative to baseline ctDNA level, was compared.*
Results: *The study group obtained considerably higher objective response rate (ORR) in relation to the control group ($p < 0.05$). Serum levels of prostate-specific antigen (PSA) and testosterone (TTE) were significantly lower in the study group versus control group. Better quality of life and bladder function were witnessed in the study group when compared to control group ($p < 0.05$). The proportion of patients with ctDNA fraction < 2 % in the study group significantly increased, but there was no significant change in ctDNA in the control group. The clinical prognosis of patients with low ctDNA fraction was significantly better than that of patients with high fraction ($p < 0.05$).*
Conclusion: *Combined use of carrelizumab and docetaxel-prednisone regimen for mCRPC patients substantially improved clinical efficacy, quality of life, and long-term prognosis, while reducing ctDNA levels. Thus, the combination regimen has promise for the treatment of mCRPC patients.*

Keywords: *Metastatic Castration-Resistant Prostate Cancer, Camrelizumab, PD-1 inhibitors, Circulating tumor DNA, Clinical outcomes*

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INTRODUCTION

Prostate cancer is an epithelial malignant tumor in the prostate, the morbidity of which shows an increasing trend after 55 years of age, with a peak incidence between 70 and 80 years [1]. Prostate cancer is often asymptomatic at the early stage. However, as it develops, it compresses the urethra, resulting in progressive dysuria, or it may invade the bladder, seminal vesicles, and vascular nerve bundles, thereby

triggering complications such as hematuria, bloody sperm, and impotence [2,3].

Androgen deprivation therapy, the mainstay of prostate cancer treatment, results in castration-resistant prostate cancer (CRPC) in most cases as the disease progresses [4,5]. Castration-resistant prostate cancer (CRPC) is associated with continuous increase in prostate-specific antigen (PSA) and/or progressive prostate cancer confirmed through imaging, with patient's serum testosterone reaching castrated level (< 50 ng/dL) after treatment or surgical castration. Metastatic castration-resistant prostate cancer (mCRPC) refers to bone metastases and distant metastases during CRPC [6]. Patients with mCRPC suffer poor prognosis, with an average median survival of only about 2 years [7].

The docetaxel-prednisone combination is the standard chemotherapy regimen for mCRPC. However, only 44 - 76.8 % of patients achieved decreases in PSA and prolonged overall survival after chemotherapy, due to tumor drug resistance and primary drug resistance [8]. Carrelizumab is a humanized anti-PD-1 monoclonal antibody which inhibits and kills tumor cells by activating anti-tumor, thereby providing a new direction for immunotherapy of prostate cancer [9]. Circulating tumor DNA (ctDNA), a cell-free extracellular DNA, is composed of single-stranded or double-stranded DNA and a mixture of single-stranded and double-stranded DNA. It exists in two forms: DNA-protein complex or free DNA. The ctDNA is a tumor marker with broad application prospects, high sensitivity, and high specificity, and it is used for the prediction of a variety of tumors [10]. Previous studies have demonstrated high level of ctDNA detection, with 75 % of mCRPC cases having ctDNA fraction > 2% [11]. The present study added carrelizumab to the conventional docetaxel-prednisone treatment regimen for mCRPC patients in order to determine its clinical effect, ctDNA changes, and clinical prognosis of patients with different ctDNA fractions.

METHODS

General patient information

This prospective randomized controlled trial (RCT) was conducted among 100 mCRPC patients treated in the Oncology Department of Harbin Medical University Cancer Hospital between January 2018 and January 2019. They were assigned (1:1) to study and control groups by random number table method. The patients were allocated into high fraction group and low fraction group after determination of their ctDNA fraction levels. This protocol was reviewed and approved by the ethics committee of Harbin Medical University Cancer Hospital (approval no. LC2017-12(1134), and followed internal guidelines for human studies.

Inclusion and exclusion criteria

Inclusion criteria

Participants were assessed as eligible per the follows: adult patients aged ≥ 18 years, with prostate adenocarcinoma confirmed via histology or cytology, and who were diagnosed in line with the diagnostic criteria for CRPC [12]; those with evidence of metastatic disease in imaging examination, such as evidence of soft tissue metastasis in computed tomography/magnetic resonance imaging (CT/MRI) and/or bone lesion confirmed through bone scan; patients with willingness to provide core tumor tissue or biopsy tissue or blood for genetic testing; Eastern Cooperative Oncology Group (ECOG) status of 0 or 1; patients with expected survival period ≥ 12 weeks, and those voluntarily participate with signed informed consent form provided.

Exclusion criteria

Patients in the following categories were excluded from the study: those who had other primary malignant tumors; patients with congenital immunodeficiency or at active period of autoimmune disease; patients with a history of (non-infectious) pneumonia requiring steroid treatment, or who had pneumonia at the time of the study; those with brain metastases; patients who were allergic to carrelizumab and/or any of its excipients; those who had received anti-PD-1 and/or anti-PD-L1 treatment, and those who, in the judgment of the investigator, had other conditions which might affect the results of the study or cause the study to be terminated midway.

Treatments

Control group

Control group was treated with docetaxel (Zhejiang Hisun Pharmaceutical Co. Ltd, license no. H20093092) in combination with prednisone. Docetaxel was given at a dose of 75 mg/m^2 via intravenous drip for 1 - 1.5 h on the first day, while 5 mg prednisone was given orally, 2 times/day, for 21 consecutive days (one cycle). Dexamethasone (Xi'an Lijun Pharmaceutical Co. Ltd, license no. 20140725) at a dose of 16 mg/day was given orally 1 day before, on the same day, and 1 day after administration of

docetaxel, for the prevention of allergic reactions and fluid retention.

Study group

Patients in the study group were given carrelizumab (Suzhou Shengdia Biomedicine Co. Ltd., NMPA approval number = S20190027), in addition to the treatment given to the control group. The drug was given via intravenous drip, 200 mg at a time, once every 2 weeks, until the disease regressed or intolerable toxicity appeared.

Evaluation of indices

Clinical efficacy

Based on PSA levels, clinical efficacy of treatment was divided into complete remission (CR, serum PSA < 4 ng/d); partial remission (PR, more than 50 % decrease in serum PSA); stable disease (SD, less than 50 % decrease in serum PSA), and progressive disease (PD, increased serum PSA). Objective response rate (ORR) was computed as in Eq 1.

$$(ORR(\%) = \frac{\text{(illegible)}}{\text{Total number of cases}} \times 100 \ldots\ldots\ldots (1)$$

Serum PSA and TTE levels

Before chemotherapy and after 3 cycles of chemotherapy, 5 mL of fasting venous blood was collected from each patient, and radioimmunoassay was used to measure serum PSA level, while chemiluminescence method was used to determine serum TTE level.

Quality of life

The Karnofsky performance scale (KPS) was used to evaluate the quality of life of patients [13]. The KPS has a full score of 100 points, with higher score suggesting better health, and more tolerable towards side effects of treatment.

Voiding function test

A urinary flow rate meter (urinary flow rate chart recorder) was used to trace the peak value of continuous urinary flow rate curve during urination so as to determine the maximum flow rate (MFR) of urine. Immediately after urination, catheter or B-mode ultrasound was used to determine post-void residual urine (PVR).

Assay of ctDNA

Fasting venous blood was collected from each patient before chemotherapy, and after 3 cycles of chemotherapy. Whole-exome sequencing and targeted sequencing technology were used to determine the peripheral blood levels of ctDNA in patients and the proportion of ctDNA. The proportion of patients with ctDNA fraction > 2 % was calculated. Then, the patients were divided into high-ctDNA fraction group and low ctDNA-fraction group, based on the median of the initial ctDNA fraction, and the clinical prognosis of the two groups was compared.

Statistical analysis

Measurement data are expressed as mean ± standard deviation (SD), and two independent sample *t*-test was used for comparison between the two groups, while paired sample *t*-test was employed for comparison at different time points within a group. Counting data are presented as numbers and percentages [n (%)], and were processed via chi-square test. Survival is expressed as mean and 95 % CI, and were analyzed using K-M curve and Log-rank test. All data were tested with two-sided test. The SPSS 22.0 software was used for data analysis, while GraphPad Prism 8.0 was used to plot graphics. Statistically significant difference was set at $\alpha = 0.05$.

RESULTS

General patient profile

There were no significant differences in general data between the two groups, with respect to age, serum hemoglobin levels, serum LDH activity, and metastasis status ($p > 0.05$; Table 1).

Clinical efficacy

As shown in Table 2, the control group had 4 cases of CR, 31 cases of PR, 10 cases of SD, and 5 cases of PD, with an ORR of 70 % (35/50). In contrast, the study group had 6 cases of CR, 39 cases of PR, 3 cases of SD, and 2 cases of PD, with an ORR of 90 % (45/50). Thus, higher ORR was observed in the study group vs. control group ($\chi^2 = 6.250$, $p = 0.012$).

KPS scores

Prior to treatment, KPS scores were similar in the two groups, with 48.88 ± 14.85 points in the control group and 50.12 ± 15.49 points in the study group ($p > 0.05$). However, after treatment, KPS scores in both groups were markedly increased, with higher values in the study group (69.82 ± 20.14 vs. 60.28 ± 18.08; $p < 0.05$, Figure 1).

Table 1: Comparison of general data between the two groups

Variable		Control group (n=50)	Study group (n=50)	t/χ2	*P*-value
Age		60.25±11.54	62.07±9.13	0.845	0.384
Hemoglobin (g/L)		44.02±14.58	45.98±13.25	0.704	0.483
LDH (U/L)		365.4±68.4	376.8±57.5	0.902	0.369
Bone metastases				0.832	0.362
	Yes	39	35		
	No	11	15		
Lung metastases				0.444	0.505
	Yes	6	4		
	No	44	46		
Liver metastases				1.099	0.295
	Yes	3	6		
	No	47	44		
Gleason score				0.208	0.648
	≤ 7	12	14		
	8~10	38	36		

Table 2: Clinical efficacy in the two groups

Group	CR	PR	SD	PD	ORR
Control (n=50)	4	31	10	5	35
Study (n=50)	6	39	3	2	45
χ^2					6.250
P-value					0.012

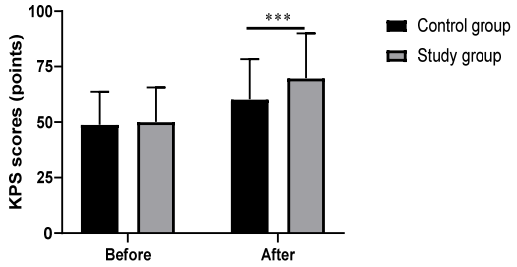

Figure 1: Comparison of KPS scores between the two groups. ****P* < 0.001

Serum PSA and testosterone levels

Significant differences were witnessed in the levels of PSA and TTE before and after treatment, and also between the two groups (p < 0.05). Before treatment, the levels of PSA and testosterone (TTE) in the control group were 58.26 ± 12.44 and 1.25 ± 0.26 ng/mL, respectively, while the corresponding levels in the study group were 50.12 ± 15.49 and 1.18 ± 0.34 ng/mL, respectively (p > 0.05). After the treatment, PSA and TTE levels in the control group were 18.21 ± 5.29 and 0.74 ± 0.18 ng/mL, respectively, while those of the study group were 10.22 ± 4.21 ng/mL and 0.55 ± 0.24 ng/mL, respectively (p < 0.05). See Figure 2.

MFR and PVR

Results in Figure 3 show that before treatment, no significant differences were noticed in MFR and PVR between the two groups. The values of MFR and PVR in the control group were 8.28 ± 2.03 mL/s and 32.15 ± 5.98 mL, respectively, while those of the study group were 8.11 ± 1.84 mL/s and 33.95 ± 4.23 mL, respectively (p > 0.05). In both groups, post-treatment levels of MFR were significantly higher in relative to pre-treatment levels, with a higher value in the study group. In contrast, post-treatment levels of PVR were decreased in both groups, with a lower value in the study group. After the treatment, the MFR and PVR of the control group were 12.28 ± 2.84 mL/s and 24.28 ± 4.41 mL, respectively, while the corresponding values in the study group were 15.05 ± 2.19 mL/s and 21.82 ± 2.68 mL, respectively (p < 0.01).

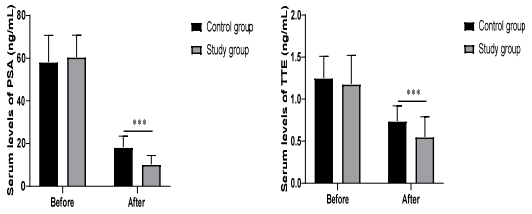

Figure 2: Serum levels of PSA and TTE in the two groups. ****P* < 0.001

Prognosis

Table 3 shows that the progression-free survival of the control group was 8.22 months (95 % CI: upper and lower limits were 6.592 and 9.848 months, respectively) and the overall survival was 14.640 months (95 % CI: upper and lower limits were 12.600 and 16.680 months, respectively). The progression-free survival of the study group was 11.040 months [95 % CI: upper and lower limits were 9.062 and 13.018 months, respectively),

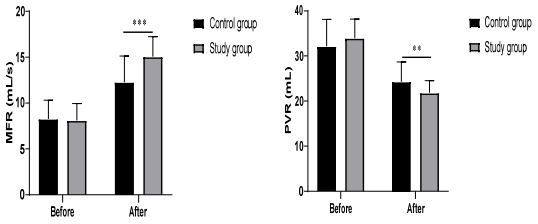

Figure 3: MFR and PVR values in the two groups. ***P* < 0.01; ****p* < 0.001

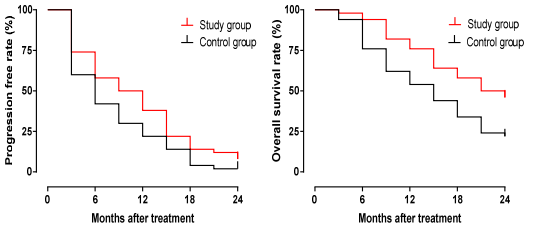

Figure 4: K-M analysis of prognosis in the two groups

and the overall survival was 18.660 months [95% CI: upper and lower limits were 16.840 and 20.480 months, respectively). The study group had more desirable outcome in terms of progression-free survival and overall survival than the control group ($p < 0.05$). The survival curves of the two groups of patients are shown in Figure 4.

CtDNA test results

Before treatment, 70 patients had ctDNA fraction > 2 %, while 30 patients had ctDNA fraction < 2 %. However, after treatment, there was a sharp reduction in the proportion of patients with ctDNA fraction > 2 % (49 patients had ctDNA fraction > 2%, while 51 patients had ctDNA fraction < 2 %) ($p < 0.05$). There was no significant difference in the distribution of ctDNA fraction before and after treatment in the control group ($p > 0.05$). In contrast, the proportion of patients with ctDNA fraction < 2% in the study group was significantly increased after treatment ($p < 0.05$, Table 4).

Prognosis of patients with different baseline levels of ctDNA

After admission, all patients were divided into high ctDNA fraction group (ctDNA fractions of 19 - 100 %) and low ctDNA fraction group (ctDNA fractions of 0 - 18%) based on the median baseline ctDNA fraction, with 50 cases in each group. It was found that the progression-free survival and overall survival of patients with low ctDNA fractions were significantly superior to those of patients with high ctDNA fractions ($p < 0.05$; Table 5, Figure 5).

Table 3: Comparison of prognosis between the two groups (n = 50)

Group	Progression-free survival (months)			Overall survival (months)		
	Mean	*95% CI*		*Mean*	*95% CI*	
		Upper limit	*Lower limit*		*Upper limit*	*Lower limit*
Control	8.220	6.592	9.848	14.640	12.600	16.680
Study	11.040	9.062	13.018	18.660	16.840	20.480
χ^2 (Log-rank test)	4.333			8.102		
P-value	0.037			0.004		

Table 4: Comparison of the ctDNA fraction change

Variable	Total (n=100)		Control group (n=50)		Study group (n=50)	
	Before	*After*	*Before*	*After*	*Before*	*After*
<2%	30	49	14	22	16	27
>2%	70	51	36	28	34	23
χ2	7.553		2.778		4.937	
P-value	0.006		0.096		0.026	

Table 5: Comparison of prognosis between high ctDNA fraction and low ctDNA fraction

Variable	Progression-free			Overall survival		
	Mean	*95% CI*		*Mean*	*95% CI*	
		Upper limit	*Lower limit*		*Upper limit*	*Lower limit*
Low ctDNA fraction (n=50)	11.280	9.237	13.33	19.62	17.956	21.284
High ctDNA fraction (n=50)	7.980	6.453	9.507	13.680	11.693	15.667
χ2 (Log-rank test)		7.231			14.64	
P-value		0.007			<0.001	

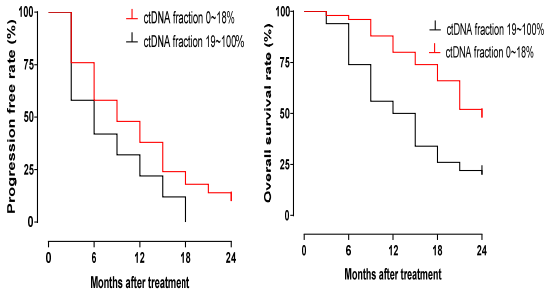

Figure 5: K-M analysis of prognosis of high and low ctDNA fraction groups

DISCUSSION

The incidence of prostate cancer witnesses a rising trend year by year, with development of mCRPC at an advanced stage in most cases, and poor prognosis of patients. Prostate cancer immunotherapy is the fourth treatment alternative after surgery, radiotherapy, and chemotherapy, with inhibitors of programmed cell death-1 (PD-1)/programmed cell death-ligand-1 (PD-L1) being the most promising therapeutic drugs [15]. Carrelizumab is a PD-1 inhibitor independently developed by Chinese scientists. It exerts an anti-tumor effect by targeting PD-1 and blocking the interaction between PD-L1 and programmed death ligand 2 (PD-2), thereby restoring immune function [16]. In this study, mCRPC patients were treated with carrelizumab in addition to a regimen of docetaxel and prednisone. The treatment produced promising results. To be specific, the addition of carrelizumab significantly increased patient's ORR, lowered serum PSA and TTE levels, and improved urination function and long-term prognosis of patients.

Previous studies on patients with metastatic prostate cancer revealed that the number of PD-L1/2 in DCs was related to chemotherapeutic drug resistance. This indicates that the upregulation of PD-L1 may be an immune escape method for drug-resistant prostate cancer. It has been suggested that mCRPC patients with PD-1-related T lymphocyte activity > 5 % are the best population for immunotherapy. In addition, with the binding strength of carrelizumab to PD-1 receptor being dose-dependent, its degrees of binding to the receptor on circulating T lymphocytes at doses of 200 and 400 mg were 85 and 88 %, respectively, and the duration of action exceeded 28 days, indicating a long-lasting anti-tumor effect [17].

Carrelizumab has been rarely studied in prostate cancer, but its application in solid tumors has been widely confirmed. A study which enrolled 86 patients suffered relapsed or refractory non-Hodgkin's lymphoma after second-line treatment demonstrated an anti-tumor effect of carrelizumab, with ORR, CR and PR values of 76, 28 and 48 %, respectively after 13 months of follow-up [18]. Moreover, carrelizumab produced promising therapeutic effects against esophageal squamous cell carcinoma and gastric cancer etc. [19].

It is known that ctDNA is cell-free DNA shed by tumor cells into the circulatory system. It can be used to identify epigenetic changes in the primary tumor, with the advantages of fast sampling, sufficient sample size, and repeatable detection. Thus, ctDNAs are very useful in research on malignant tumors. The present study compared changes in ctDNA fractions before and after treatment with carrelizumab, and analyzed the clinical prognosis of patients with high and low ctDNA fractions, based on differences from baseline ctDNA levels. The results showed that after carrelizumab treatment, the proportion of patients with a ctDNA fraction > 2 % decreased significantly, with a better clinical prognosis in the low-ctDNA fraction group.

A study has revealed that ctDNA epigenetic changes are consistent with tumor biopsy, and that somatic mutations in metastatic lesions are also present in ctDNA, with the consistency of some key driver genes exceeding 90 % [20]. The abundance of ctDNA is a prognostic indicator independent of clinical characteristics. Thus, it shows great potential for use as a stratified biomarker [21]. A study has shown that the abundance of ctDNA is an independent predictor of the therapeutic effect of PD-1 inhibitors in non-small cell lung cancer [22]. This is similar to the results obtained in this study [22].

CONCLUSION

The combined use of carrelizumab and docetaxel-prednisone regimen in mCRPC patients substantially improves clinical efficacy, quality of life, and long-term prognosis, and reduces ctDNA abundance. These results provide a novel lead for the treatment of mCRPC patients. In addition, the level of ctDNA shows a great potential as an independent predictor of the prognosis of mCRPC patients.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Henan Zhou and Yanning Chen wrote the main manuscript text. Xiaonan Zhang and Yuanyuan Sang prepared the Figures and Tables. All authors reviewed and approved the manuscript.

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