Original Research Article

Effect of abiraterone combined with prednisone on serum CgA and NSE in metastatic castration-resistant prostate cancer without previous chemotherapy

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Abstract

Purpose: To investigate the influence of a combination of abiraterone and prednisone on serum chromogranin A (CgA) and neuron-specific enolase (NSE) in patients with metastatic castration-resistant prostate cancer (mCRPC) without previous chemotherapy, so as to provide reference data for drug therapy of prostate cancer.

Methods: A total of 103 mCRPC patients without chemotherapy from January 2013 to March 2017 were included in this retrospective study. Seventy-one (71) patients received prednisone combined with abiraterone (study group), while 32 patients accepted prednisone (control group). The CgA, NSE and prostate-specific antigen (PSA) in the two groups were monitored, while PSA progression-free survival (PSA-PFS), radiographic PFS (rPFS), and overall survival (OS) were determined during follow-up.

Results: PSA-PFS, rPFS and OS in the study group were significantly higher than those in the control group (p < 0.05). The increased proportion of CgA or NSE in the study group was significantly lower than that in the control group at 6 months of treatment (p < 0.05). The occurrences of NED before treatment and 6 months after treatment were both independent predictors of PSA and radiographic progression in the study group (p < 0.05).

Conclusion: The combination of prednisone and abiraterone is helpful for prognosis in mCRPC patients that are not on chemotherapy. The occurrence of NED predicts mostly poor prognosis of mCRPC patients on a combination of abiraterone and prednisone.

Keywords: Abiraterone, Metastatic castration-resistant prostate cancer, Neuroendocrine, Chromogranin A, Neuron-specific enolase

INTRODUCTION

Prostate cancer is the most frequently-diagnosed malignancy in males. Most patients with prostate cancer are at the advanced stage at the point of definite diagnosis. Castration method is a standardized suppressive treatment in patients with aggressive prostate cancer; it decreases tumor burden, lowers PSA level, and inhibits the secretion of testosterone [1]. However, research has shown that castration has poor prognosis in mid- and long-term outcomes: almost all the

patients would deteriorate into metastatic castration-resistant prostate cancer (mCRPC) [2]. The tumor is still sensitive to androgen after becoming mCRPC. Thus, a new generation of endocrine drugs such as abiraterone is used to inhibit androgen receptor axis, which helps control mCRPC [3].

Neuroendocrine differentiation (NED) is one of the important mechanisms involved in prostate cancer deterioration to mCRPC. Chromogranin A (CgA) and neurone-specific enolase (NSE) are important markers of NED [4]. Prostate cancer with NED has an extremely high malignancy which may be one of the important reasons why it is does not respond to abiraterone treatment in patients [5]. Neuroendocrine differentiation (NED) is related to endocrine therapy, but it is still unclear whether abiraterone promotes NED or not. This study retrospectively analyzed changes in CgA and NSE in patients with mCRPC during treatment with combination of abiraterone and prednisone, and investigated whether abiraterone promoted the occurrence of NED. In addition, the relationship between NED and prognosis of patients was studied.

METHODS

General patient information

A retrospective analysis was carried out on 103 patients with mCRPC who had not received chemotherapy from January 2013 to March 2017. Seventy-one (71) patients were treated with prednisone combined with abiraterone (study group), while 32 patients were treated with prednisone (control group).

This research has been approved by the Ethical Committee of Department of Urology, Jinhua Central Hospital, Jin Hua city, 321000, Zhejiang Province, China (approval no. HP201301005), and performed according to Declaration of Helsinki promulgated in 1964 as amended in 1996 [6].

Inclusion and exclusion criteria

Inclusion criteria

The included patients were: (1) Patients diagnosed with prostate cancer, and confirmed metastatic lesions by bone scan and CT/MRI; (2) patients who received medication or castration treatment, with serum testosterone < 50 ng/dL (also patients without castration who received treatment with analog of luteinizing hormone-releasing hormone for at least 4 weeks and continued with the treatment during the period of study); (3) patients who were not treated with androgen deprivation and ketoconazole 4 weeks before the study; (4) patients with ECOG score ≤ 2; and (5) patients who signed informed consent.

Exclusion criteria

(1) mCRPC patients on cytotoxic chemotherapy or biological therapy; (2) patients with severe liver damage, hypopituitarism or hypoadrenalism, and (3) patients with poor compliance during prior endocrine, therapy was excluded.

Surgical procedures

The patients in the study group were given oral abiraterone acetate (Xian-Janssen Pharmaceutical Ltd, approval no. J20150112) at a dose of 1000 mg once a day, and oral prednisone acetate (Beijing Kangtini Pharmaceutical Co. Ltd, approval no. H20058375), 5 mg twice a day. In the control group, the patients received only prednisone treatment at the same dose used in the study group. One course of treatment was 4 weeks of continuous drug use. Routine blood tests, liver and kidney function tests, levels of blood glucose, blood lipids, PSA and electrolytes were carried out/determined at every treatment course. If indices were abnormal, targeted interventions were given in time. Bone scanning, CT and MRI were done every 2 courses within the first 6 courses. These parameters were re-examined every 3 cycles after 6 courses. The above indicators at any time were re-examined when the patients' conditions changed abnormally, and the frequency of examination was appropriately adjusted.

Study indices

Enzyme-linked immunosorbent assay (ELISA) was used to determine the level of serum CgA (normal range < 100 ng/mL). Electro chemiluminescence immunoassay (ECLIA) was used to determine the level of serum NSE (normal range, < 18 ng/mL). Neuroendocrine differentiation (NED) was diagnosed with serum CgA or NSE levels (≥ normal range). Failure of abiraterone acetate treatment was defined as PSA and/or radiographic progression in mCRPC patients. The proportion of patients with elevated CgA and NSE was calculated. The progression free survival (PFS), radiographic PFS (rPFS) and overall survival (OS) of PSA were recorded. The Recommendations of the Prostate Cancer Clinical Trials Working Group was used as reference in the definitions of PSA-PFS, rPFS and OS [7]. The deadline for follow-up was June 2018.

Statistical analysis

Measurement data are expressed as mean ± SD. They were analyzed using *t*- test. Counting data are expressed as percentage, and analyzed using chi-square test was used to analyze the data. Ordered categorical data are expressed as percentages, and analyzed with Mann-Whitney U test. Values of PSA-PFS, rPFS and OS were compared by Kaplan-Meier method. The influence of abiraterone on serum CgA and NSE were analyzed by multiple-stepwise logistic regression analysis. The influence of NED on PSA-PFS and rPFS were analyzed by multivariate Cox regression analysis. All data analyses were carried out with SPSS 25.0 software. Differences were assumed statistically significant at $p < 0.05$.

RESULTS

Baseline data

There showed no statistically significant differences between the two groups with respect to age, PSA, Eastern Cooperative Oncology Group (ECOG), Gleason score, and bone metastases, lymph node metastasis and visceral metastasis ($p > 0.05$). The results are shown in Table 1.

Changes in serum CgA and NSE in patients

As shown in Table 2, before treatment, the CgA and NSE between the two groups were no statistically significant differences ($p > 0.05$). At 6 courses after treatment, the levels of CgA and NSE in the study group were significantly lower than those in the control group ($p < 0.05$). The proportion of elevated cases in the study group were significantly higher than that in the control group ($p < 0.05$). The elevated cases of CgA and NSE in the study group and control group were 51 cases and 30 cases, respectively ($\chi^2 = 6.309$, $p = 0.012$).

PSA-PFS, rPFS and OS

In the follow-up, there were 44 cases of PSA progression in the study group (61.97 %), and the median time of PSA-PFS was 14.4 months, while in the control group, there were 32 cases of PSA progression (100.00%),

Table 1: Surgical effectiveness {*n* (%), (mean ± SD)}

Group (*n*)	Age (years)	PSA (ng/mL)	ECOG score (points)			Gleason score (points)	
			0	1	2	≤7	>7
Study (71)	64.70±4.75	71.85±28.42	37 (52.11)	19 (26.76)	15 (21.13)	28 (39.44)	43 (60.56)
Control (32)	65.81±5.13	74.62±31.28	15 (46.88)	9 (28.13)	8 (25.00)	13 (40.63)	19 (59.38)
t/*Z*/χ^2	1.071	0.444	0.529			0.013	
P-value	0.287	0.658	0.597			0.909	

Group (*n*)	Bone metastases				Lymph node metastasis		Visceral metastasis
	0	1~3	4~10	>10	N_0	N_1	
Study (71)	1 (1.41)	23 (32.39)	17 (23.94)	30 (42.25)	42 (59.15)	29 (40.85)	1 (1.41) [#]
Control (32)	0 (0.00)	8 (25.00)	5 (15.63)	19 (59.38)	21 (65.63)	11 (34.38)	0 (0.00)
Z/χ^2		1.468			0.389		- [*]
P-value		0.142			0.533		1.000

[*] Fisher's exact test; [#] one case of pulmonary metastasis in the study group

Table 2: Changes in serum CgA and NSE (mean ± SD, ng/mL)

Group (*n*)	CgA			NSE		
	Before treatment	After 6 courses	Proportion of elevated cases	Before treatment	After 6 courses	Proportion of elevated cases
Study (71)	117.35±21.33	127.24±20.38	37 (52.11)	12.85±1.75	14.66±1.82	35 (49.30)
Control (32)	113.68±21.78	139.36±19.58	24 (75.00)	13.37±1.82	16.19±2.04	26 (81.25)
t/χ^2	0.803	2.827	4.785	1.378	3.802	9.327
P-value	0.424	0.006	0.029	0.171	0.000	0.002

and the median time of PSA-PFS was 3.0 months: the two groups differed significantly (log rank χ^2 = 60.358, p < 0.001). There were 39 cases of radiographic progression in the study group (54.93%), and the median rPFS time was 15.6 months, while in the control group, there were 32 cases of radiographic progression (100.00%), and the median rPFS time was 5.5 months (log rank χ^2 = 29.714, p < 0.001). In the study group, 24 patients died (33.80 %), which had not been followed up until effective median survival time, while 18 patients died in control group (56.25 %), and the median survival time was 13 months. The differences in comparison between the study and control groups were statistically significant (log rank χ^2 = 15.815, p < 0.001). These results are shown in Figures 1, Figure 2, and Figure 3.

Effect of abiraterone on elevation of serum CgA or NSE in patients

Multiple-stepwise logistic regression analysis was performed. The results showed that the degree of baseline bone metastasis lesions, baseline regional lymph node metastasis, and duration of endocrine therapy were independent risk factors for elevation of serum CgA and NSE (p < 0.05; Table 3).

Effects of NED on PSA and radiographic progression in patients

Single-factor analysis: There were 31 cases of patients with baseline NED in study group; 25 cases of PSA progression, and 25 cases of radiographic progression; the median times of PSA-PFS and rPFS were 11.7 months and 12.4 months, respectively. There were 40 cases of patients without NED, 19 had PSA progression, 14 cases had radiographic progression, and the median times of PSA-PFS and rPFS were 18.0 months and 19.4 months, respectively. The differences in comparison of PSA-PFS and rPFS in patients with and without baseline NED were statistically significant (log rank χ^2 = 57.612, 72.315, p < 0.001).

There were 58 patients with NED in the study group after 6-cycle treatment, 41 cases had PSA progression, 39 cases had radiographic

progression, and the median times of PSA-PFS and rPFS were 12.2 months and 13.0 months, respectively.
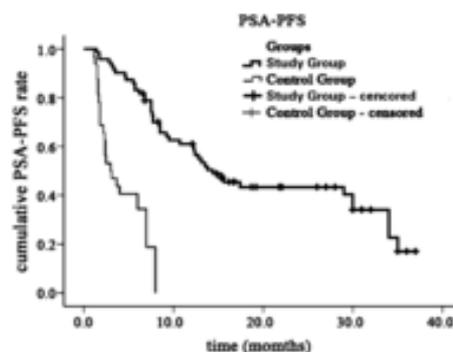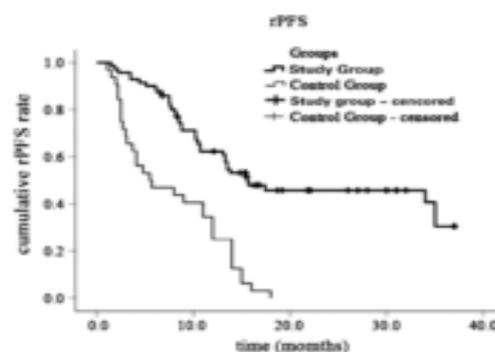

Figure 1: PSA-PFS between the two groups

Figure 2: Comparison of rPFS between the two groups
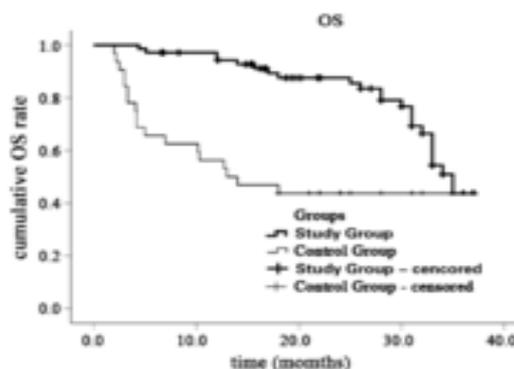
Figure 3: Comparison of OS between the two groups

Table 3: Analysis for independent factors that influence serum CgA and NSE in patients

Factor	β	Standard error	Wald	P-value	OR	95 % CI
Baseline bone metastasis lesions	0.266	0.120	4.901	0.026	1.305	1.031 - 1.652
Baseline regional lymph node metastasis	2.026	0.424	22.870	0.000	7.581	3.305 - 17.389
Duration of endocrine therapy	0.195	0.058	11.377	0.001	1.215	1.085 - 1.361

There were 13 cases of patients without NED after 6-cycle treatment, and 3 of them had PSA progression, but none of them had radiographic progression. The follow-up time was not median time of PFS and rPFS. The differences in comparison of PSA-PFS and rPFS in patients with and without NED were statistically significant (log rank χ^2 = 92.031, 103.315, $p < 0.001$).

(2) ***Multivariate analysis:*** Multivariate cox regression analysis was carried out. The occurrence of NED at baseline and first 6 cycles (yes = 1, no = 0) was regarded as independent variable; age, baseline PSA level, duration of endocrine therapy, baseline ECOG score, Gleason score, baseline bone metastases lesions, baseline regional lymph node metastasis, and the condition of previous radiotherapy and radical operation were regarded as concomitant variables, while progression of PSA and radiographic progression were regarded as dependent variables.

Due to the short-time follow-up and many censored data which might lead to the lack of practical significance of cox regression analysis, OS was not included in the analysis of influencing factors. The results of the multivariate cox regression analysis (Tables 4 and 5) revealed that baseline NED, NED after 6-cycles treatment and quantities of baseline bone metastases lesions were independent risk factors of PSA progression and radiographic progression ($p < 0.05$).

DISCUSSION

Abiraterone is a new generation of endocrine drugs for mCRPC. This study showed that it can significantly prolong OS and PFS of patients. This indicates it produces better survival benefits, which is consistent with some previous reports [8-10]. During endocrine therapy, patients may appear NED, which lead to tumor drug resistance and further affect therapeutic effects. Previous studies regarded CgA and NSE as markers of NED, and showed 43 – 85 % of patients with castration-resistant prostate cancer had NED [11,12]. It is believed that NED cells are transformed by prostate cancer cells.

Through castration treatment, the transformation of prostate cancer cells into NED cells may be a self-reaction of cancer cell resistant to drugs [13]. Thus, long-term endocrine therapy may promote the progression of NED. The current study also showed that the duration of endocrine therapy before the investigation was related to the elevation of CgA and NSE after 6-cycle treatment. This also indicates that endocrine therapy may promote the progression of NED, and the longer the duration was, the more obvious the occurrence of NED. Studying the influence of abiraterone on the progression of NED can help predict prognosis, so that treatment scheme can be adjusted for the benefit of the patients.

This study has shown that although the proportion of patients whose CgA and NSE were elevated in study group was significantly higher than that of the control group, abiraterone was not an independent risk factor for increased levels of CgA and NSE. This contradiction indicates that the effect of abiraterone on the progression of NED may be affected by heterogeneity of factors. It might be caused by the heterogeneous mechanisms involved in the formation of mCRPC, which include mutation of androgen receptor gene, paracrine and autocrine effects of androgens, and amplification of androgen receptor [14-16].

Table 4: Analysis for independent factors that influence of PSA progression in study group

Factor	β	Standard error	Wald	P-value	HR	95%CI
Baseline NED	0.759	0.370	4.215	0.040	2.137	1.035 - 4.412
NED after 6-cycle treatment	1.674	0.804	4.335	0.037	5.331	1.103 - 5.766
Baseline bone metastasis lesions	0.161	0.074	4.791	0.029	1.175	1.017 - 1.358

Table 5: Analysis for independent factors that influence radiographic progression in study group

Factor	β	Standard error	Wald	P-value	HR	95 % CI
Baseline NED	0.812	0.400	4.117	0.042	2.253	1.028 - 4.938
NED after 6-cycle treatment	1.630	0.790	4.257	0.039	5.104	1.085 - 24.010
Baseline bone metastasis lesions	0.103	0.042	6.042	0.014	1.108	1.021 - 1.202

Moreover, heterogeneity of mCRPC may affect the reaction of serum CgA and NSE towards abiraterone, thereby leading to different changes in NED markers during the therapy. This study showed that along with the duration of endocrine therapy, baseline bone metastasis lesions, and baseline regional lymph node metastasis may also affect changes in CgA and NSE during the therapy. There was similarity in the reactions of serum CgA and NSE to abiraterone, probably because the tumor metastasis status patients was similar to the mechanism of formation of their mCRPC. For patients with NED, the effectiveness of abiraterone was poor, which is consistent with other reports [17-19]. This also indicates that continuous monitoring of NED markers is very important for predicating prognosis during abiraterone administration.

Studies have shown that the CgA levels of patients taking abiraterone is 3 times higher than normal, with significant reduction in survival time [20]. It has also been reported that CgA and NSE are both predictive factors for prognosis of abiraterone therapy [21]. These reports are in favour of the results of the present study. NED can stimulate cancer cells to secrete various hormones and regulatory factors which affect the multiplication of surrounding cells through internal secretions, paracrine, and autocrine, thereby increasing difficulty in controlling cancer.

Limitation

This research is a retrospective analysis for a small sample case-control study. There should be some statistical biases and defects because of non-randomized controlled design. Therefore, large sample study of randomized controlled design should be performed to verify the results of this study.

CONCLUSION

The results obtained in this study indicate that in patients who are not on chemotherapy, administration of combination of abiraterone and prednisone enhances prognosis. The effect of abiraterone on serum CgA and NSE is heterogeneous, which implies that it may not affect the development of NED in mCRPC patients. In mCRPC patients receiving this therapy, the occurrence of NED before treatment or after 6 months predicts poor prognosis.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All authors read and approved the manuscript for publication. Weiwei Zhang conceived and designed the study, Ke Yang, Tieqiu Li, Zhiyong Gao, Weiwei Zhang collected and analyzed the data. Ke Yang wrote the manuscript.

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