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Original Article

Efficacy of abiraterone combined with prednisone in castration-resistant prostate cancer and its impact on miR-221/222 expression

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Abstract: Objective: To assess the therapeutic efficacy of abiraterone combined with prednisone in patients with castration-resistant prostate cancer (CRPC) and investigate its effects on miR-221/222 expression. Methods: A retrospective cohort of 43 CRPC patients from Henan Provincial People's Hospital, People's Hospital of Zhengzhou University was divided into two groups: the treated group (n=22, treated with abiraterone and prednisone) and the control group (n=21, treated with prednisone acetate alone). Expression of miR-221/222 was quantified in CRPC cell lines using quantitative fluorescence polymerase chain reaction. Results: The treated group demonstrated significantly higher rates of bone pain relief and prostate-specific antigen (PSA) response compared to the control group (P=0.032, P=0.022, respectively). Post-treatment, the treated group also showed increased Karnofsky Performance Status scores and reduced plasma testosterone levels relative to controls (P=0.021, P=0.016). There was no significant difference in the incidence of adverse reactions between the treated group (31.82%) and the control group (28.57%) (P=0.125). Conclusions: Abiraterone combined with prednisone effectively relieves bone pain and improves PSA response rates in CRPC patients, suggesting benefits in enhancing quality of life and reducing testosterone levels without increasing adverse reactions. This therapy appears to have a safety profile comparable to that of conventional treatments.

Keywords: Abiraterone, prednisone, CRPC, miR-221/222

Introduction

MicroRNAs miR-221 and miR-222 have been identified as significant targets in castration-resistant prostate cancer (CRPC) [1, 2]. These miRNAs also play critical roles in the targeted diagnosis of various cancers such as breast cancer, glioblastoma, and chronic lymphocytic leukemia. However, the specific role of miR-221 in prostate cancer (PCa) remains controversial [3]. Studies indicate a significant positive correlation between the activity of miR-221/222 in CRPC and cancer cell survival, with decreased miRNA expression correlating with improved therapeutic effects [1]. This study investigates the treatment of CRPC with abiraterone and prednisone, noting a reduction in miR-221/222 activity associated with therapeutic efficacy, suggesting their potential as diagnostic markers in CRPC management [2-4].

Androgen deprivation therapy (ADT), endorsed by the Chinese Urology Association, remains the standard for treating advanced PCa, involving hormone drugs such as prednisone or surgical castration [4]. However, clinical evidence shows that many patients with advanced PCa progress, typically relapsing within 1-2 years of treatment initiation [5]. Abiraterone, a CYP17 inhibitor, suppresses androgen synthesis in the testes, adrenal glands, and prostate cancer cells, making it a critical agent in treating CRPC [6]. Prednisone, a glucocorticoid, is known for its anti-inflammatory and anti-allergic effects, reducing capillary wall permeability and cell membrane activity, thus alleviating inflammatory exudation. It also suppresses the formation and release of histamine and other inflammatory mediators, providing significant anti-inflammatory, antitoxic, and anti-shock benefits [7].

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This study evaluates the combined effect of abiraterone and prednisone on CRPC, particularly focusing on changes in miR-221/222 expression, analyzed using fluorescence quantitative polymerase chain reaction (PCR) in CRPC cell lines.

Methods

Study design and patient screening

Using the hospital information system, clinical data from 56 patients with CRPC admitted to Henan Provincial People's Hospital, People's Hospital of Zhengzhou University from July 2022 to October 2023 were collected. Patients were selected based on established diagnostic criteria for CRPC [5, 8, 9] with serum testosterone levels maintained at <1.65±0.03 nmol/L. Eligibility required a maximum interval of three treatment cycles and intermittent elevation of prostate-specific antigen (PSA) levels.

Inclusion criteria: (1) patients with a clear pathologic diagnosis of CRPC; (2) patients with complete baseline clinical data; (3) patients with availability of comprehensive; (4) no androgen deprivation therapy received within 1 month prior to inclusion; (5) patients receiving treatment at the above hospital (i.e., the control group receiving prednisone acetate tablets, and the treated group receiving abiraterone combined with prednisone).

Exclusion criteria: (1) concurrent psychiatric disorders; (2) allergy to hormone therapy; (3) radiographic evidence of bone metastasis or other site metastases; (4) concurrent adrenal or pituitary insufficiency; (5) concurrent other malignancies.

After rigorous screening, 43 patients were enrolled and divided into two groups based on treatment type: 22 in the treated group and 21 in the control group. The treated group was treated with abiraterone (ZYTIGA, Xi'an Janssen, 1000 mg/qd) and prednisone (5 mg/bid), and the control group received prednisone acetate tablets (5 mg/bid). Treatment lasted for 10 weeks, in 5-week cycles.

This study protocol was approved by the ethics committee of Henan Provincial People's Hospital, People's Hospital of Zhengzhou University. The flow of the study is illustrated in **Figure 1**.

Data extraction

Utilizing the hospital's information system, we recorded general clinical data, including age, ethnicity, Eastern Cooperative Oncology Group performance status, Gleason score, and presence of lymph node metastasis. Additionally, we measured bone pain relief, PSA treatment efficacy, mean/treatment values of miR-221, Karnofsky Performance Status (KPS) scores pre- and post-treatment, testosterone levels pre- and post-treatment, and the incidence of adverse reactions during the treatment period. These variables were compared between the two treatment groups.

Outcome measurements

Primary outcomes: (1) Therapeutic efficacy: We assessed the rate of bone pain relief and changes in PSA levels post-treatment, calculated as (pre-treatment PSA - post-treatment PSA)/pre-treatment PSA. (2) Incidence of adverse reactions: Adverse reactions, including hypertension, arrhythmia, diarrhea, and erectile dysfunction, were recorded for both groups during the treatment and compared.

Secondary outcomes: (1) MiRNA expression analysis: miR-221 and miR-222 expression levels were quantitatively analyzed using primers manufactured by Beijing Chemical Industry (sequence details in **Table 1**). For the reverse transcription reaction, 1 μg of total RNA was mixed with the miR-221 stem-loop RT primer and incubated at 17°C for 35 minutes, followed by 45°C for 40 minutes, then stored at -22°C. The reaction used 17 μg of total RNA for real-time quantitative PCR, with the RT product subsequently extracted for analysis. Quantitative sampling of PCR samples included three negative controls. Using Applied Biosystems fluorescence quantitative PCR equipment, the threshold value, determined by the fluorescence signal, represented the expression levels of miR-221/222 [10-12]. The expression of miR-221/222 in CRPC tissues and changes post-treatment with abiraterone and prednisone were analyzed to determine the expression levels [13-16]. (2) Evaluation of physical condition: The physical condition of patients in both groups was assessed using the KPS scale before and after treatment. The KPS scale ranges up to 100, with higher scores indicating better physical condition. Scores below 60 sug-

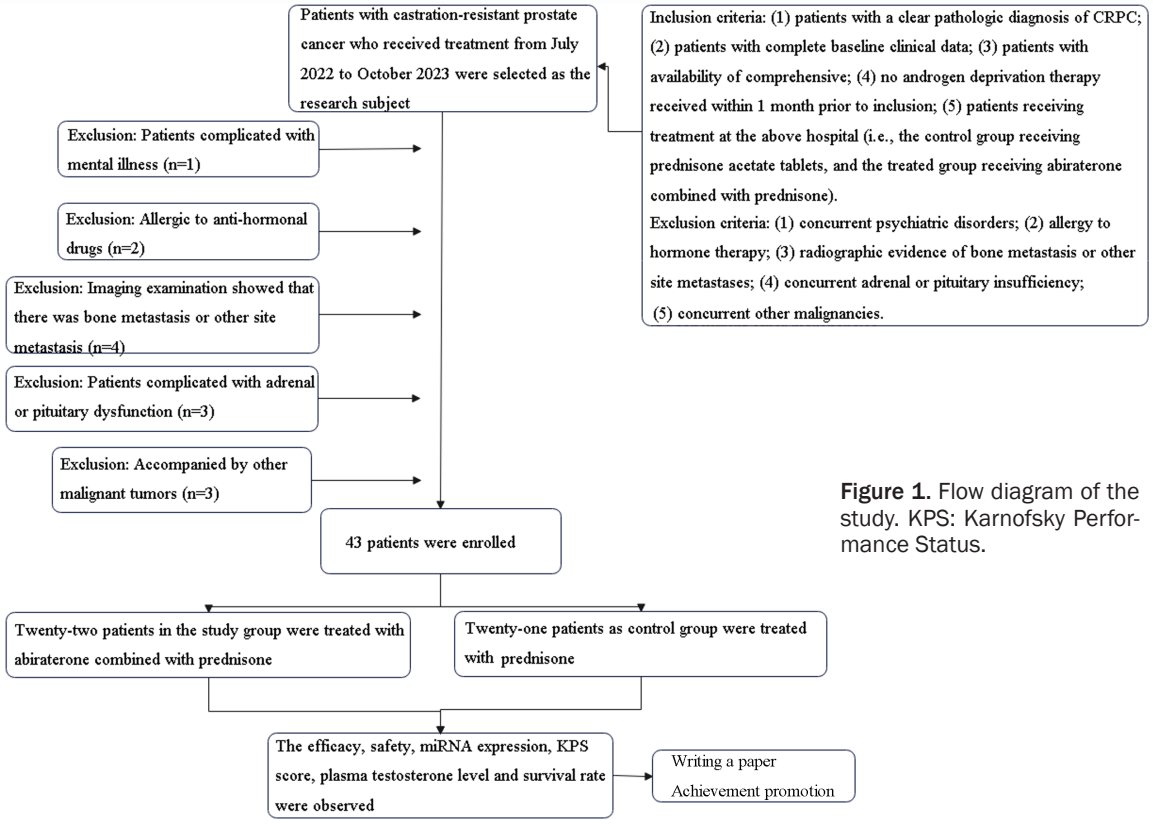

Figure 1. Flow diagram of the study. KPS: Karnofsky Performance Status.

Table 1. List of RT and PCR primer sequences

Genetic	Primer standards	Serial number	Product standards
miR-221	Stem ring RT primers	CBGTVCCGTACCGCTCAGGT-	56 bp
	Forward RT	-ATCCGCCGTACGGACGTACA	
	Reverse RT	GTTCCGGGTAGACATTTGTACG	
miR-221	Stem ring RT primers	GTACCTACRGTCATGGRACCG	66 bp
	Forward RT	-ATTCGGACGGATAGGCGACCCA	
	Reverse RT	TAGCAGTAACGTTATAGTACCGC	
U6	Stem ring RT primers	CCCGCCCGCCCACCCTAGCAACC	111 bp
	Forward RT	AACGACCACCGACGRRGTACGGG	
	Reverse RT	-AACGGTACGGGCTGGACGAGGAG	

RT: reverse transcription; PCR: polymerase chain reaction.

gest that antitumor treatment may not be feasible. (3) Detection of plasma testosterone levels: Blood samples were collected from both patient groups before and after treatment. Testosterone levels were measured using an automatic biochemical analyzer and results were compared between the groups. (4) Survival analysis: The survival rates of the two groups were compared with follow-up to June 2024.

Statistical analysis

Graphical representations were produced using Mx-prism8, and statistical analyses were conducted using SPSS 22.0. Measurement data, assumed to follow a normal distribution, were expressed as mean ± standard deviation (mean ± SD). Independent sample t-tests were used to compare differences between groups, and paired sample t-tests for within-group compari-

Table 2. Comparison of clinical data between the two groups

Clinical data		Treated group (n=22)	Control group (n=21)	t/χ^2	*P*
Average age (years)		72.53±5.26	71.98±4.98	0.352	0.727
PSA (ng/ml)		208.53±70.51	210.56±68.98	0.095	0.924
Ethnic	Han ethnic group	15	14	0.011	0.916
	Others	7	7		
ECOG score	0	12	13	0.251	0.882
	1	6	5		
	2	4	3		
Gleason score	≤7 points	6	5	0.068	0.795
	>7 points	16	16		
Lymph node metastasis	Yes	3	3	0.004	0.951
	No	19	18		

PSA: prostate-specific antigen; ECOG: Eastern Cooperative Oncology Group.

Table 3. PSA response rate and bone pain relief in both groups (n%)

Grouping	Bone pain relief	PSA (response rate)
Treated group (n=22)	65.43%	75.55%
Control group (n=21)	45.34%	54.67%
χ^2	5.86	5.66
P	0.032	0.022

PSA: prostate-specific antigen.

sons. Counting data were expressed as percentages and analyzed using chi-square tests. A *P*-value <0.05 was considered statistically significant.

Results

Comparison of baseline data

There were no significant differences in baseline data between the two groups, confirming their comparability (P=0.727, P=0.924, P=0.916, P=0.882, P=0.795, P=0.951) (**Table 2**).

Comparison of treatment efficacy

The treated group demonstrated a significantly higher rate of bone pain relief and PSA response compared to the control group (P=0.032, P=0.022) (**Table 3**; **Figure 2**).

Comparison of miR-221/222 expression

Figure 3A demonstrates that miR-221 expression in PCa was relatively consistent. During treatment, the baseline expression level of miR-221 in CRPC patients was 0.003, with average values of 0.075 pre-treatment and 0.011 post-treatment [17-20]. **Figure 3B** reveals a significant reduction in miR-221/222 expression correlated with improved treatment outcomes in the treated group [21, 22].

In the control group, the expression levels of miR-221/222 remained stable during treatment, with baseline at 0.003, and mean levels changing from 0.085 pre-treatment to 0.058 post-treatment, as shown in **Figure 4**. This minor decrease (less than 15%) indicates a limited response to therapy, highlighting the potential of miR-221/222 expression as a direct marker of therapeutic effectiveness [23, 24].

The median values derived from t-tests for miR-221 and miR-222 are presented in **Figure 5**.

Comparison of KPS scores

Initially, no significant difference was observed in KPS scores between the two groups (P=0.126). Post-treatment, both groups showed improvements in KPS scores, with the treated group exhibiting significantly higher scores compared to the control group (P=0.021) (**Figure 6**).

Comparison of plasma testosterone levels

Before treatment, there were no significant differences in plasma testosterone levels between the groups (P=0.206). Following treatment, both groups experienced significant reductions in testosterone levels, with the treated group showing a greater decrease compared to the control group (P=0.016) (**Figure 7**).

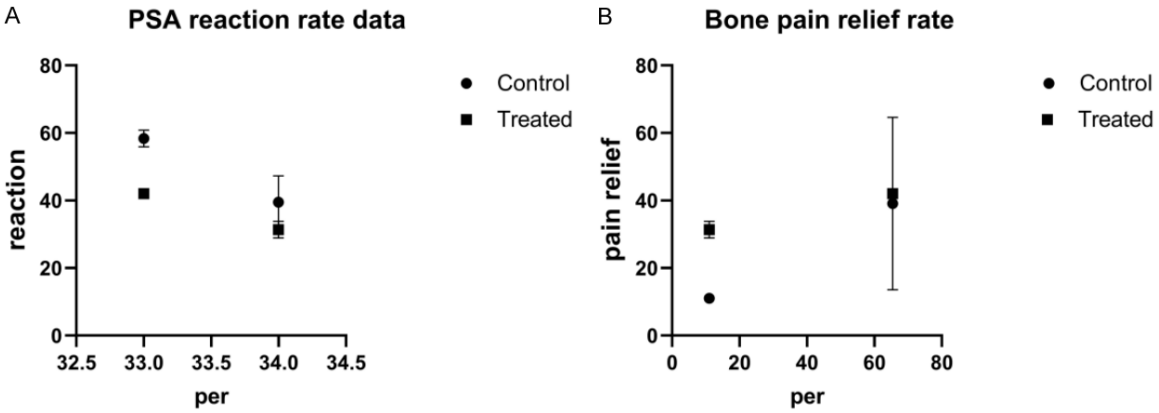

Figure 2. PSA response rate and bone pain relief. The PSA was significantly lower in the treated group than in the control group (A). In the treatment of castration-resistant prostate cancer, the combination of abiraterone and prednisone in the treated group demonstrated superior efficacy compared to prednisone acetate tablets alone in the control group. Specifically, the rate of bone pain relief decreased from 65% to 17% in the treated group, while in the control group, it only slightly decreased from 35% to 33% (B). PSA: prostate-specific antigen.

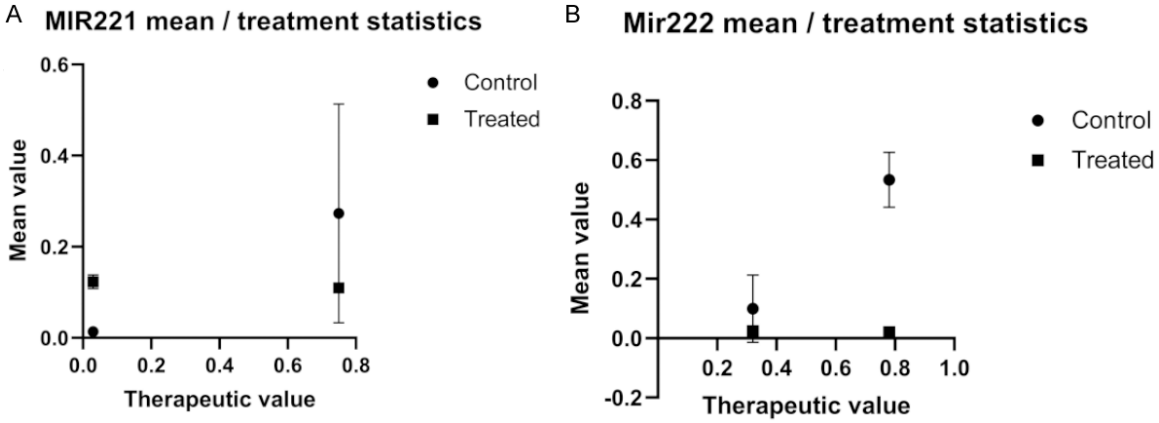

Figure 3. Mean values of miR-221 and miR-222 during treatment in both groups. The mean therapeutic value of miR-221 decreased from 0.774 before treatment to 0.145 after treatment (A). Similarly, the mean therapeutic value of miR-222 decreased from 0.719 before treatment to 0.145 after treatment (B).

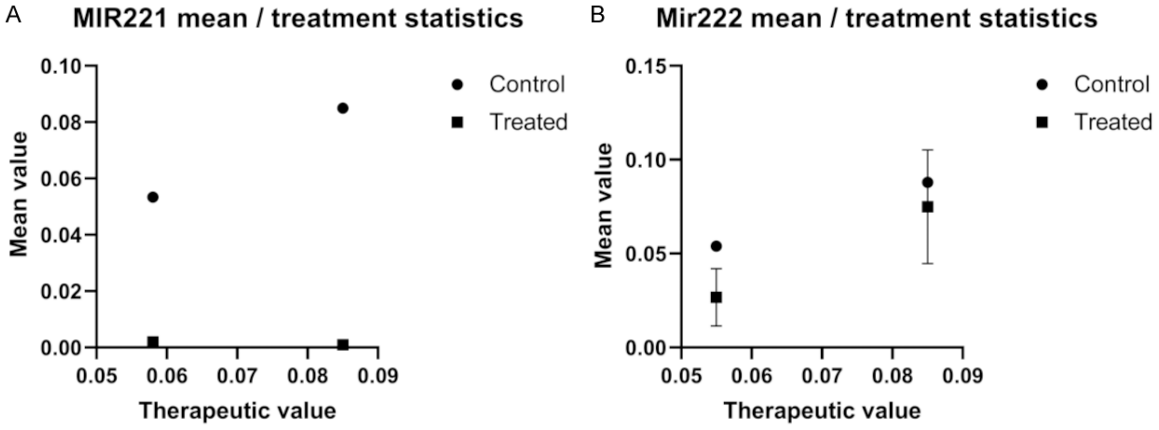

Figure 4. Mean values of miR-221 and miR-222 during treatment in both groups. The mean values of miR-221 before and after treatment were 0.433 and 0.331, respectively, with no significant difference observed (A). Similarly, the mean values of miR-222 before and after treatment were 0.513 and 0.231, respectively, with no significant difference observed (B).

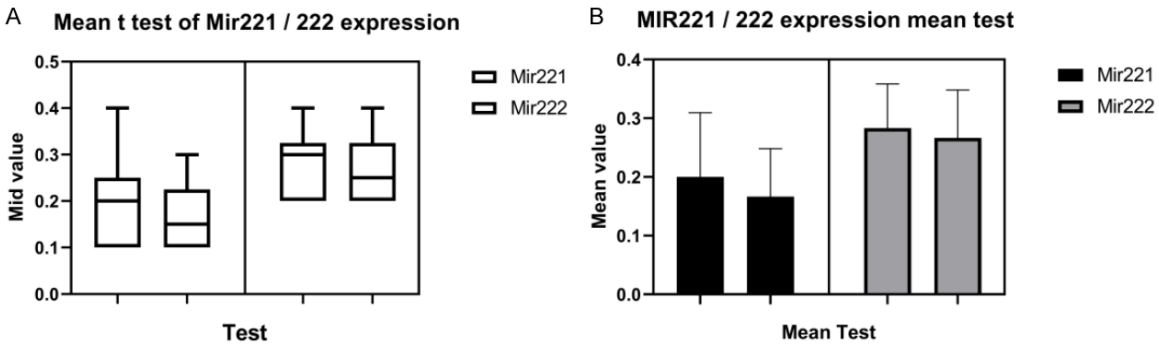

Figure 5. Median and mean t-test results of miR-221/222 expression. miR-221 expression levels ranged from 0.411 to 0.311, while miR-222 expression levels ranged from 0.423 to 0.225 (A). The mean test results for miR-221/222 expression were consistent with the previous findings, and no negative value was observed (B).

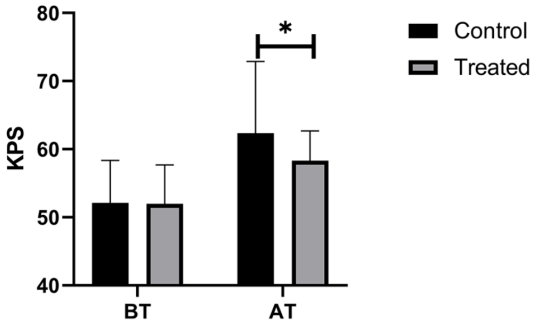

Figure 6. Comparison of KPS scores before and after treatment between the two groups. Before treatment, there was no statistically significant difference in KPS scores between the two groups (P=0.126). After treatment, the treated group exhibited higher KPS scores than the control group (P=0.021). * indicates statistically significant difference between groups. KPS: Karnofsky Performance Status; BT: before treatment; AT: after treatment.

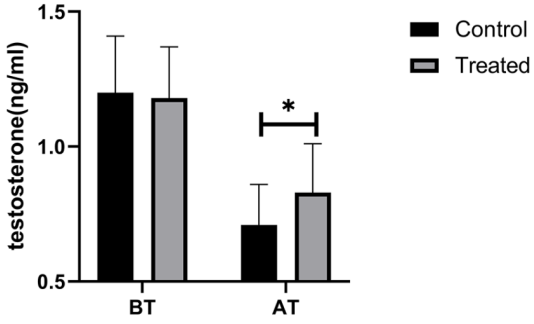

Figure 7. Comparison of plasma testosterone levels before and after treatment between the two groups. The plasma testosterone levels showed no statistically significant difference between the two groups before treatment (P=0.206). After treatment, the plasma testosterone levels in the treated group were lower than those in the control group (P=0.016). * indicates statistically significant difference between groups. BT: before treatment; AT: after treatment.

Comparison of treatment safety profile

During treatment, the treated group reported 1 case of hypertension, 1 case of arrhythmia, 2 cases of diarrhea, and 3 cases of erectile dysfunction, totaling an adverse reaction incidence of 31.82%. This rate did not significantly differ from the control group, which had an incidence of 28.57% (6/21) (P=0.125) (**Figure 8**).

Comparison of survival rate

As of June 2024, the control group reported 2 deaths, corresponding to a survival rate of 90.48% (19/21), while the treated group had 3 deaths, with a survival rate of 86.36% (19/22). The difference in survival rates between the groups was not statistically significant (P= 0.674) (**Figure 9**).

Discussion

In this study, patients in the treated group received abiraterone and prednisone, while those in the control group were treated with prednisone acetate tablets. The treatment duration was 10 weeks, structured in 5-week cycles. The expression levels of miRNAs were measured using quantitative fluorescence PCR in CRPC cell lines. miRNAs have been well-documented across multiple studies to play a role in the pathogenesis of various malignancies, modulating protein expression and regulating tumor cell proliferation, differentiation, and invasion. The change in miRNA levels correlates with the degree of cancer control and related factors.

MiR-221/222, members of the miRNA family, are involved in the biological processes of

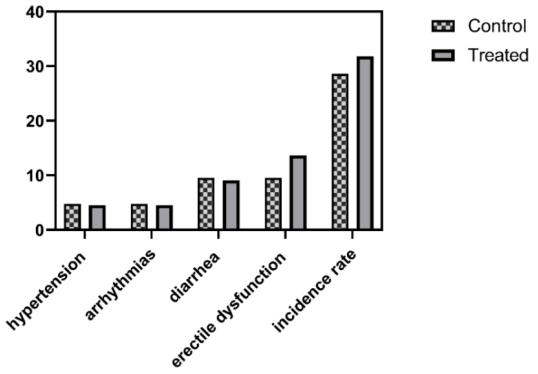

Figure 8. Comparison of treatment safety profile between the two groups. The overall incidence of adverse reactions was 31.82% in the treated group, exhibiting no statistically significant difference compared 28.57% in the control group (P=0.125).

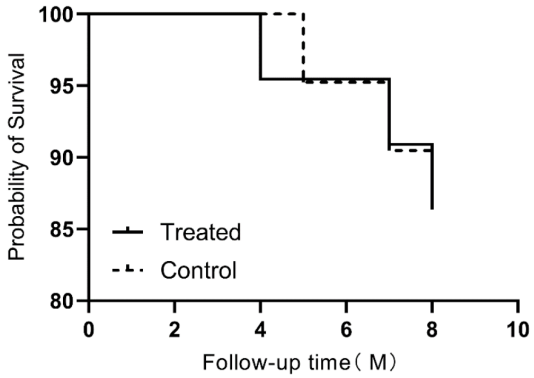

Figure 9. Comparison of survival rate between the two groups. The difference in survival rate between the two groups was not statistically significant (P=0.674) at follow-up until June 2024.

malignant tumors, including ovarian, breast, and PCa, showing active expression in these cancers [16, 17]. During treatment, the normal expression value of miR-221/222 in the treated group was consistently at 0.003, with mean values changing from 0.075 before treatment to 0.011 post-treatment. Similarly, in the control group, the baseline expression was 0.003, with mean values decreasing from 0.085 before treatment to 0.058 afterwards. This sensitivity of miR-221/222 expression to treatment interventions reveals a strong positive correlation with the survival of cancer cells in CRPC, indicating that miR-221/222 can serve as a diagnostic marker to gauge treatment efficacy [18, 19, 25].

The findings confirm that abiraterone combined with prednisone is more effective than treatment with prednisone acetate alone in managing CRPC, providing a more precise therapeutic target [1, 26]. This study highlights the potential of miR-221/222 as significant biomarkers in the assessment and treatment of castration-resistant prostate cancer.

This study confirmed that miR-221/222 levels in both cancerous and adjacent normal prostate tissues significantly decreased after treatment with abiraterone and prednisone, demonstrating a correlation between reduced miRNA expression and improved treatment outcomes. This finding aligns with other research [27], which revealed a correlation between miR-221/222 levels and the differentiation degree of PCa tissues. In animal models, treatment with abiraterone acetate and prednisone notably enhanced biological activity, with significant alterations in miR-221/222 target protein levels observed. These findings suggest that combined therapy may influence PCa progression by modulating miR-221/222 [27].

Additionally, the study established a link between miR-221/222 levels in PCa tissues and the degree of tissue differentiation and distant metastasis, proposing miR-221/222 as potential diagnostic markers in CRPC. The expression changes in the treated group suggest a relationship with the suppression of cancer cell progression, providing a targeted genetic indicator for assessing cancer deterioration and progression.

Further corroborating these results, research on other malignancies, including breast cancer, thyroid cancer, chronic lymphocytic leukemia, and bile duct cancer, indicated that combined interventions produced similar changes in miRNA expression, though these studies did not explore the underlying mechanisms [28]. Another study [29] reported significant bone pain relief in PCa patients post-treatment, with improvement rates comparable to those found in our study, suggesting a high efficacy of the treatment regimen.

This research also compared the KPS scores and testosterone levels before and after treatment in both groups. Patients in the treated group showed higher KPS scores and lower testosterone levels post-treatment compared to the control group, indicating that the combination of abiraterone and prednisone not only enhances therapeutic efficacy but also im-

proves quality of life. These changes reflect a clinical improvement consistent with the outcomes observed in the study group.

The primary limitation of this study is the small sample size and the relatively homogenous source of participants, which may affect the generalizability of the findings. Conducting a large-scale, multi-center randomized study in the future would likely enhance the reliability and accuracy of the results.

In conclusion, abiraterone combined with prednisone is effective in alleviating bone pain and enhancing the PSA response rate, thereby improving the quality of life and lowering testosterone levels in patients with PCa. The treatment has a safety profile comparable to traditional therapies and holds considerable potential for broader application in clinical practice.

Disclosure of conflict of interest

None.

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