Corticosteroid switching can reverse abiraterone resistance in some patients with metastatic castration-resistant prostate cancer (mCRPC). Here, we investigated the potential biomarkers for predicting the efficacy of corticosteroid switching during treatment with abiraterone acetate (AA). We retrospectively analyzed 101 mCRPC patients receiving corticosteroid switching from West China Hospital and Sun Yat-Sen University Cancer Center between January 2016 and December 2018. All cases received AA plus prednisone as first-line therapy during mCRPC. Primary end points were biochemical progression-free survival (bPFS) and overall survival (OS). The risk groups were defined based on multivariate analysis. A total of 42 (41.6%) and 25 (24.8%) patients achieved 30% and 50% decline in prostate-specific antigen (PSA), respectively, after corticosteroid switching. The median bPFS and median OS on AA plus dexamethasone were 4.9 (95% confidence interval [CI]: 3.7–6.0) months and 18.8 (95% CI: 16.2–30.2) months, respectively. Aldo-keto reductase family 1 member C3 (AKR1C3) expression (hazard ratio [HR]: 2.15, 95% CI: 1.22–3.80, P = 0.008) and baseline serum alkaline phosphatase (ALP; HR: 4.95, 95% CI: 2.40–10.19, P < 0.001) were independent predictors of efficacy before corticosteroid switching in the multivariate analysis of bPFS. Only baseline serum ALP >160 IU l⁻¹ (HR: 3.41, 95% CI: 1.57–7.38, P = 0.002) together with PSA level at switch ≥50 ng ml⁻¹ (HR: 2.59, 95% CI: 1.22–5.47, P = 0.013) independently predicted poorer OS. Based on the predictive factors in multivariate analysis, we developed two risk stratification tools to select candidates for corticosteroid switching. Detection of serum ALP level, PSA level, and tissue AKR1C3 expression in mCRPC patients could help make clinical decisions for corticosteroid switching.

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Keywords: abiraterone acetate; alkaline phosphatase; corticosteroid switching; dexamethasone; metastatic castration-resistant prostate cancer

INTRODUCTION

Abiraterone acetate (AA), a potent CYP17A1 inhibitor, is one of the earliest and most widely used standard treatments for patients with metastatic castration-resistant prostate cancer (mCRPC). Clinically, AA is recommended to be used with prednisone (AA+P) to ameliorate the secondary increase in adrenocorticotropic hormone that may induce mineralocorticoid excess. Glucocorticoids also have a role in inhibiting the synthesis of adrenal androgens. Although AA improves the prognosis of mCRPC patients, development of drug resistance is inevitable. Chemotherapy or alternative androgen-signaling targeting agents are recommended to mCRPC patients after AA resistance. However, recent studies have indicated that a strategy of corticosteroid switching from AA+P to AA plus dexamethasone (AA+D) could reverse the AA resistance in mCRPC.

To date, the exact mechanism underlying the effectiveness of switching from AA+P to AA+D remains largely unknown, although several hypotheses have been proposed. The activation of glucocorticoid receptors can confer resistance to AA by bypassing androgen receptor (AR) blockade. Because of the lower equivalent dose of D compared with P, glucocorticoid receptor activation is reduced after switching from AA+P to AA+D, which eventually reverses AA resistance. Besides, when used as monotherapy, D shows superior antitumor activity compared to P. Attard et al. reported that AA+D (1000 mg once a day [qd]) + 0.5 mg qd) appeared to have greater antitumor activity but more adverse metabolic effects than AA+P (1000 mg qd + 5 mg twice a day [bid]). The difference in pharmacodynamics between P and D could be another mechanism. The half-life of D is longer than that of P; therefore, D is more effective in suppressing adrenocorticotropic hormone synthesis.
hormone and shows more powerful antitumor activity.12,13 Lorente et al. speculated that D could reverse AA resistance by decreasing the AR point mutations induced by P. However, none of these hypotheses has been fully validated yet, and further basic studies are needed to uncover the rationale for switching from AA+P to AA+D.

Despite the exact mechanism remaining unknown, several studies have shown the feasibility and promising efficacy of corticosteroid switching in mCRPC patients after development of AA resistance.4-8 According to these studies, 9.1%–48.2% of patients could achieve a 50% decline in prostate-specific antigen (PSA) after corticosteroid switching, while progression-free survival (PFS) ranged from 2.7 months to 11.8 months. The distinct responses suggested that not all patients who failed treatment with AA+P benefited from corticosteroid switching. Romero-Laorden et al.9 reported that AR copy numbers and mutation status in plasma circulating tumor DNA could successfully distinguish the candidates for corticosteroid switching. However, widespread clinical use of circulating tumor DNA testing is limited by the high cost of liquid biopsy and requirement for high specimen quality. Thus, the identification of easily accessible biomarkers for corticosteroid switching remains an unmet need in clinical practice.

Therefore, the aims of the current study were to evaluate the efficacy of corticosteroid switching and to investigate the potential factors for predicting the efficacy of switching AA+P to AA+D in patients with mCRPC.

**PATIENTS AND METHODS**

**Patients**

This study totally included 101 patients with mCRPC between January 2016 and December 2018 from two medical centers (54 from West China Hospital, Chengdu, China, and 47 from Sun Yat-Sen University Cancer Center, Guangzhou, China). The Medical Ethics Committee of West China Hospital of Sichuan University has approved this study protocol (No. 2017-16). Every relevant detail has been explained to the patient himself, and written consent forms were obtained from each patient. Consent for publication was obtained from the patients involved in this study. The study was performed in accordance with the Declaration of Helsinki. In our study, 79 of 101 (78.2%) patients received androgen deprivation therapy plus antiandrogen treatment (bicalutamide or flutamide), and eight (7.9%) received androgen deprivation therapy only at the metastatic hormone-sensitive prostate cancer stage, and all 101 patients received AA+P (1000 mg qd + 5 mg bid) as the first-line therapy during the mCRPC stage. After biochemical progression, which was defined as a ≥25% increase in PSA level above the nadir (and by ≥2 ng ml−1), with confirmation ≥3 weeks later according to the Prostate Cancer Working Group 3 (PCWG3),14 all cases underwent corticosteroid switching from AA+P to AA+D (1000 mg qd + 0.5 mg qd). AA+D continued until the occurrence of biochemical progression with symptomatic or radiographic progression. Twenty-three of 101 (22.8%) patients underwent imaging examination, and ten (43.5%) of them had radiographic progression. Thirty-one of 101 (30.7%) patients received second-line therapy including chemotherapy and novel androgen-directed agents (enzalutamide) after resistance to AA+D therapy.

The baseline characteristics of all cases were collected at the time of corticosteroid switching, including age, Eastern Cooperative Oncology Group score, International Society of Urological Pathology grading, CRPC-free survival (CFS, defined as duration from initial diagnosis of prostate cancer to development of mCRPC), time to PSA progression on AA+P, metastatic sites, and serum levels of PSA, alkaline phosphatase (ALP), lactic dehydrogenase, and hemoglobin. All patients in this study were monitored as recommended by the PCWG3.15 They received PSA test every 4 weeks, bone scans and/or computed tomography every 12 weeks (every 8 weeks for the first 24 weeks).

All patients in this study received prostate repeat biopsy at the time of mCRPC. Expression of aldo-keto reductase family 1 member C3 (AKR1C3) was tested in each patient by immunohistochemical (IHC) staining of the repeat biopsy samples. IHC staining was performed using AKR1C3 monoclonal antibodies (1:800 dilution; A6229, Sigma, St. Louis, MO, USA). Prostate samples with >20% positive AKR1C3 immunostaining in tumor cells were considered positive. All pathological results were reviewed independently by two experienced urological pathologists (NC and YJZ).

**End points**

The efficacy of corticosteroid switching was evaluated from two aspects: PSA decline and disease-related survival data. We set two cut-off point values for PSA decline: ≥30% decline in PSA level after corticosteroid switching (PAS30) and ≥50% decline in PSA level after corticosteroid switching (PAS50). Biochemical PFS (bPFS) and overall survival (OS) were used for further analyses. bPFS was the time interval from switching treatment to biochemical progression, which was defined as a ≥25% increase in PSA level above the nadir (and by ≥2 ng ml−1), with confirmation ≥3 weeks later according to the PCWG3.13 OS was the duration from AA+D treatment to death from any cause.

**Statistics**

Univariate Cox regression models were performed to assess the predictive value of each factor in forecasting bPFS and OS. Factors with P < 0.05 were further tested in multivariate analyses. Survival curves of bPFS and OS were generated by the Kaplan–Meier U test method and compared by log-rank test. Based on multivariate Cox analysis, the different risk groups were defined. A univariate Cox model was realized according to the different risk groups, and log-rank tests were performed between every two risk groups. All tests in this study were two-sided. P < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 25.0 (SPSS Science, Chicago, IL, USA).

**RESULTS**

**Baseline characteristics**

The baseline characteristics of the 101 mCRPC patients are presented in Table 1. The median CFS was 12.1 months for the whole cohort, and the median time to progression on AA+P was 6.2 months. Positive AKR1C3 expression was confirmed in 38 of 101 (37.6%) patients in the repeat biopsy specimens at the time of mCRPC. The IHC profile of AKR1C3 is exhibited in Figure 1.

The median follow-up time was 15.9 months for the total cohort. At the end of follow-up, PSA30 and PSA50 were achieved in 42 (41.6%) and 25 (24.8%) of 101 patients, respectively, with corticosteroid switching from AA+P to AA+D. PSA progression after corticosteroid switching and death occurred in 78 (77.2%) and 41 (40.6%) of 101 patients, respectively. The median bPFS and median OS after corticosteroid switching were 4.9 (95% confidence interval [CI]: 3.7–6.0) months and 18.8 (95% CI: 16.2–30.2) months, respectively.

**Prognostic analysis of survival outcomes of corticosteroid switching**

The univariate and multivariate analyses of the predictive factors for switching from AA+P to AA+D are shown in Table 2. In univariate analyses for bPFS (Table 2), four prognostic indicators...
Table 1: Baseline characteristics of all patients at the time of corticosteroid switching

| Clinicopathologic variable | All patients (n=101) |
|----------------------------|---------------------|
| Age (year), median (IQR)   | 73.0 (68.0–78.3)    |
| >70, n (%)                 | 58 (57.4)           |
| ≤70, n (%)                 | 43 (42.6)           |
| ISUP grading, n (%)        |                     |
| 5                          | 60 (59.4)           |
| ≤4                         | 30 (29.7)           |
| Unknown                    | 11 (10.9)           |
| ECOG score, n (%)          |                     |
| ≥1                         | 34 (33.7)           |
| <1                         | 67 (66.3)           |
| Prior treatment in HSPC stage, n (%) |         |
| ADT alone                  | 79 (78.2)           |
| MAB                        | 8 (7.9)             |
| Unknown                    | 14 (13.9)           |
| CRPC-free survival (month), median (IQR) | 12.1 (7.7–27.4) |
| >12, n (%)                 | 52 (51.5)           |
| ≤12, n (%)                 | 49 (48.5)           |
| TTP on AA+P (month), median (IQR) | 6.2 (3.1–9.2) |
| >6, n (%)                  | 53 (52.5)           |
| ≤6, n (%)                  | 48 (47.5)           |
| Metastatic sites, n (%)    |                     |
| Bone metastasis only       | 74 (73.3)           |
| Visceral metastasis        | 27 (26.7)           |
| PSA level at switch (ng ml⁻¹), median (IQR) | 24.1 (8.3–72.5) |
| ≥20, n (%)                 | 54 (53.5)           |
| <20, n (%)                 | 47 (46.5)           |
| Baseline ALP (IU l⁻¹), median (IQR) | 104.00 (74.2–155.0) |
| >160, n (%)                | 18 (17.8)           |
| ≤160, n (%)                | 57 (56.4)           |
| Unknown, n (%)             | 26 (25.7)           |
| Baseline LDH (IU l⁻¹), median (IQR) | 204.9 (185.0–238.0) |
| >220, n (%)                | 29 (28.7)           |
| ≤220, n (%)                | 45 (44.6)           |
| Unknown, n (%)             | 27 (26.7)           |
| Baseline HGB (g l⁻¹), median (IQR) | 120.0 (113.0–129.8) |
| >120, n (%)                | 40 (39.6)           |
| ≤120, n (%)                | 43 (42.6)           |
| Unknown, n (%)             | 18 (17.8)           |

IQR: interquartile range; ISUP grading: the International Society of Urological Pathology grading system; ECOG: Eastern Cooperative Oncology Group; HSPC: hormone-sensitive prostate cancer; ADT: androgen deprivation therapy; MAB: maximum androgen blockage; ARPC: androgen receptor prostate cancer; TTP on AA+P: time to the biochemical progression on the acetate abiraterone plus prednisone; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; HGB: hemoglobin

were identified, including CFS >12 months (P = 0.046), baseline ALP >160 IU l⁻¹ (P < 0.001), positive AKR1C3 expression (P = 0.006), and the occurrence of PSA50 during AA+D (P = 0.001). In multivariate analysis, three independent factors still predicted bPFS of corticosteroid switching: baseline ALP >160 IU l⁻¹ (P < 0.001), positive AKR1C3 expression (P = 0.008), and occurrence of PSA50 during AA+D (P = 0.002).

In univariate analyses of OS (Table 2), two prognostic indicators were identified, including PSA level at switching ≥50 ng ml⁻¹ (P = 0.006) and baseline ALP >160 IU l⁻¹ (P = 0.005). Both of them (PSA level at switch ≥50 ng ml⁻¹, P = 0.013; baseline ALP >160 IU l⁻¹, P = 0.002) could independently predict OS in multivariate analyses.

As shown in Supplementary Figure 1a, ALP >160 IU l⁻¹ was significantly associated with lower PSA30 rate (2/18 [11.1%] vs 28/57 [49.1%], P = 0.004) but not PSA50 rate (2/18 [11.1%] vs 15/57 [26.3%], P = 0.179) in corticosteroid switching. Abnormal ALP was accompanied by significantly shorter median bPFS (P < 0.001) and OS (P = 0.003), as shown in Figure 2a and 2b. The PSA30 rate (10/27 [37.0%] vs 32/74 [43.2%], P = 0.577) and PSA50 rate (4/27 [14.8%] vs 21/74 [28.4%], P = 0.164) were only numerically lower in cases with AKR1C3 expression compared with those without AKR1C3 expression (Supplementary Figure 1b). Positive AKR1C3 expression was associated with significantly shorter median bPFS (P = 0.005; Figure 2c), but only with shorter median OS (P = 0.11; Figure 2d). Although PSA level at switching ≥50 ng ml⁻¹ was negatively related to PSA30 rate (13/35 [37.1%] vs 29/66 [43.9%], P = 0.510; Supplementary Figure 1c), PSA50 rate (8/35 [22.9%] vs 17/66 [25.8%], P = 0.748; Supplementary Figure 1c), and bPFS (P = 0.437; Figure 2e), it predicted poor OS for corticosteroid switching (P = 0.005; Figure 2f).

Prognostic risk stratification of corticosteroid switching

Based on the independent predictors’ significance in multivariate analysis of bPFS, we defined four risk groups: low risk, without unfavorable prognostic predictors (baseline ALP >160 IU l⁻¹ or positive AKR1C3 expression); intermediate risk A, with only one unfavorable prognostic predictor (positive AKR1C3 expression); intermediate risk B, with only one unfavorable prognostic predictor (baseline ALP >160 IU l⁻¹); and high risk, with both unfavorable prognostic predictors (baseline ALP >160 IU l⁻¹ and positive AKR1C3 expression). The Cox model analysis of the four risk groups is summarized in Table 3, and the bPFS curves of the four risk groups are shown in Figure 3a. Most of them were able to reach significant differences (low risk vs intermediate risk A, log-rank P = 0.001; low risk vs intermediate risk B, log-rank P < 0.001; low risk vs high risk,
Predictors of efficacy of corticosteroid switching

YC Ni et al

Table 2: Univariate and multivariate analyses of each factor's value in predicting biochemical progression-free survival and overall survival of the corticosteroid-switching treatment

| Characteristic                  | Univariate analysis of bPFS | Multivariate analysis of bPFS | Univariate analysis of OS | Multivariate analysis of OS |
|--------------------------------|-----------------------------|------------------------------|---------------------------|-----------------------------|
|                                | HR (95% CI)                 | P                            | HR (95% CI)               | P                            |
| Age (year)                     |                             |                              |                           |                              |
| >70 versus ≤70                 | 0.77 (0.49–1.21)            | 0.251                        | 1.09 (0.59–2.03)          | 0.777                        |
| ISUP grading                   |                             |                              |                           |                              |
| 5 versus ≤4                    | 1.12 (0.86–1.46)            | 0.409                        | 0.94 (0.68–1.32)          | 0.735                        |
| ECOG score                     |                             |                              |                           |                              |
| ≥1 versus <1                   | 1.19 (0.75–1.89)            | 0.452                        | 1.42 (0.77–2.62)          | 0.264                        |
| Metastatic sites               |                             |                              |                           |                              |
| Bone only versus visceral      | 0.80 (0.50–1.30)            | 0.377                        | 0.77 (0.39–1.52)          | 0.454                        |
| Prior treatment in HSPC stage  |                             |                              |                           |                              |
| ADT alone versus MAB           | 1.81 (0.66–4.99)            | 0.249                        | 0.89 (0.27–2.93)          | 0.853                        |
| PSA level at switch (ng ml⁻¹)  |                             |                              |                           |                              |
| ≥50 versus <50                 | 1.20 (0.75–1.93)            | 0.439                        | 2.36 (1.28–4.36)          | 0.006                        |
| CRPC-free survival (month)     |                             |                              |                           |                              |
| >12 versus ≤12                 | 0.63 (0.40–0.99)            | 0.046                        | 0.71 (0.40–1.28)          | 0.262                        |
| TTP on AA+P (month)            |                             |                              |                           |                              |
| >6 versus ≤6                   | 0.68 (0.43–1.07)            | 0.094                        | 1.24 (0.67–2.29)          | 0.494                        |
| Baseline ALP (IU l⁻¹)          |                             |                              |                           |                              |
| >160 versus ≤160               | 5.66 (2.91–11.01)           | <0.001                       | 4.95 (2.40–10.19)         | <0.001                       |
| Baseline LDH (IU l⁻¹)          |                             |                              |                           |                              |
| >220 versus ≤220               | 1.35 (0.79–2.30)            | 0.275                        | 1.31 (0.63–2.73)          | 0.472                        |
| Baseline HGB (g l⁻¹)           |                             |                              |                           |                              |
| >120 versus ≤120               | 0.61 (0.37–1.02)            | 0.057                        | 0.65 (0.32–1.34)          | 0.242                        |
| AKR1C3 (IHC)                   |                             |                              |                           |                              |
| Positive versus negative       | 1.99 (1.21–3.27)            | 0.006                        | 2.15 (1.22–3.80)          | 0.008                        |
| PSA decrease during AA + D     |                             |                              |                           |                              |
| ≥50% versus ≤50%               | 0.39 (0.22–0.69)            | 0.001                        | 0.33 (0.16–0.67)          | 0.002                        |

HR: hazard ratio; CI: confidence interval; bPFS: biochemical progression-free survival; OS: overall survival

Table 3: Results of univariate Cox analysis in the prognostic risk stratification of biochemical progression-free survival and overall survival

| Risk group                  | n (%)   | HR    | 95% CI     | P       |
|-----------------------------|---------|-------|------------|---------|
| bPFS                        |         |       |            |         |
| Total                       | 75 (100.0) | <0.001 |           |         |
| Low                         | 41 (54.7) | 1     | 1.48–5.91  | 0.002   |
| Intermediate A              | 16 (21.3) | 2.96  | 3.23–17.73 | <0.001  |
| Intermediate B              | 11 (14.7) | 7.57  | 3.90–25.11 | <0.001  |
| High                        | 7 (9.3)  | 9.90  | 3.14–28.42 | <0.001  |
| OS                          |         |       |            |         |
| Total                       | 75 (100.0) | <0.001 |           |         |
| Low                         | 36 (48.0) | 1     |            |         |
| Intermediate                | 32 (42.7) | 2.21  | 0.94–5.23  | 0.070   |
| High                        | 7 (9.3)  | 4.44  | 3.14–28.42 | <0.001  |

HR: hazard ratio; CI: confidence interval; bPFS: biochemical progression-free survival; OS: overall survival

DISCUSSION

AA+P to AA+D switching was first reported in a retrospective study early in 2014. Four years later, a phase II study validated the feasibility and clinical efficacy of this alternative therapeutic strategy in mCRPC patients. According to the voting results of the 2017 Advanced Prostate Cancer Consensus Conference, 37% and 35% of clinicians agreed corticosteroid switching in the majority and minority of selected patients, respectively. Despite various agents have been developed for mCRPC patients, the best therapeutic strategy for sequential therapy is still uncertain. Corticosteroid switching is a cost-effective treatment strategy and is particularly relevant for patients who cannot afford other effective sequential therapies, such as chemotherapy or other AR-signaling targeting agents. This is especially true in China where mCRPC patients have fewer second-line agents to choose from compared with those in developed countries. Even in the USA, only a small proportion of patients receive effective second-line treatment.
Predictors of efficacy of corticosteroid switching

YC Ni et al

Five studies have reported the efficacy of switching from AA+P to AA+D treatment. Although they all reported the positive clinical value of corticosteroid switching, the therapeutic effect was not completely consistent (Supplementary Table 1). The PSA50 response rate after switching treatment ranged from 9.1% to 48.2%, and the median bPFS ranged from 2.7 months to 11.8 months. In our cohort, the PSA50 response was achieved in 25/101 (24.8%) patients and the median bPFS reached 4.9 months, which was in the middle of previous research results. According to a study of heavily pretreated mCRPC patients, compared with other studies, switching treatment had limited clinical efficacy with PSA50 response rate of about 11% and median bPFS of about 2.7 months. These results implied that the effectiveness of corticosteroid switching might be compromised as treatment process accumulates, which emphasizes the importance of distinguishing optimal candidates for this treatment in clinical practice.

In this study, we found three potential predictors of the efficacy of corticosteroid switching: baseline ALP, AKR1C3 expression, and PSA level at switching. ALP is a biomarker that is commonly used to measure the metastatic burden for mCRPC patients, and the test is inexpensive and easily available in routine practice. Many studies have confirmed that high baseline serum ALP is associated with worse response to therapy and poorer survival outcomes in prostate cancer patients. In our study, abnormal ALP (>160 IU l\(^{-1}\)) also had power to predict poor bPFS and OS in multivariate analysis. We also found that AKR1C3 expression in repeat biopsy specimens could distinguish optimal patients before switching treatment. However, it seemed that patients with two risk factors had similar bPFS to those with one risk factor (baseline serum ALP >160 IU l\(^{-1}\)) in the risk stratification, which indicated that baseline ALP level might be a better predictor of bPFS than AKR1C3 expression. We concluded that corticosteroid switching was an effective and inexpensive strategy for those who failed AA+P.

Figure 2: Kaplan–Meier curves of bPFS and OS for patients. (a) bPFS and (b) OS for patients stratified by baseline ALP (>160 IU l\(^{-1}\) vs ≤160 IU l\(^{-1}\)); (c) bPFS and (d) OS for patients stratified by AKR1C3 expression (positive vs negative); (e) bPFS and (f) OS for patients stratified by PSA level at switching (≥50 ng ml\(^{-1}\) vs <50 ng ml\(^{-1}\)). ALP: alkaline phosphatase; AKR1C3: aldo-keto reductase family 1 member C3; PSA: prostate-specific antigen; bPFS: biochemical progression-free survival; OS: overall survival.

Figure 3: Kaplan–Meier curves of (a) bPFS and (b) OS based on risk factors. bPFS: biochemical progression-free survival; OS: overall survival.
treatment but had a better disease status (baseline ALP ≤160 IU l⁻¹) or negative AKR1C3 expression.

The mechanism regarding the role of AKR1C3 in predicting the efficacy of corticosteroid switching remains unclear. A previous study reported that, in switching treatment, patients with AR gain status had shorter PFS compared with those with AR normal status. Besides, no patient with AR gain status achieved PSA response after switching treatment, while all AR normal cases presented a >30% decline.⁴ These findings together with the hypothesis that D can suppress the mutated AR caused by P revealed that AR-signaling pathway is involved in switching treatment. AKR1C3 plays a crucial role in regulating the AR pathway; therefore, we speculated that the predictive effect of AKR1C3 on the effect of switching treatment might partially correlate with AR signaling.¹⁵–²¹ AKR1C3 can influence the AR pathway in several ways: promoting intratumoral androgen synthesis; increasing AR and AR-V7 expression through enhancing protein stability via activation of the ubiquitin-mediated proteasome pathway; and acting as a coactivator of AR to facilitate its transcriptional regulation ability.¹⁵,²⁰,²² We previously found that AKR1C3 is a pathological marker with prognostic value for first-line AA+P treatment of mCRPC.²³ Based on these findings, we hypothesize that patients with positive AKR1C3 expression have strong activation of the AR pathway, which cannot be compromised by switching treatment from P to D.

Another hypothesis underlying the ability of AKR1C3 to predict the efficacy of corticosteroid switching might be that AKR1C3 potentially interacts with corticosteroids, which may affect the efficacy of corticosteroid switching. In our study, AKR1C3 had predictive ability for bPFS but not OS. However, HIC expression of AKR1C3 was a qualitative and binary factor, which may restrict its predictive accuracy. Perhaps, measuring AKR1C3 expression quantitatively by RNA sequencing or exosomes would be helpful to enhance its predictive power, which is worthy of further investigation. Given the individualized metabolic ability among different individuals, perhaps, the distinct pharmacokinetics of the steroids could be a potential mechanism underlying corticosteroid switching. Further prospective investigation is needed to verify this hypothesis.

This study had several limitations. First, this was a retrospective study with inherent limitations such as selection bias. Second, the sample size of the total cohort was small. Third, despite all patients receiving AA+P before switching treatment, sequential treatment after progression on AA+D could have influenced the OS analysis. Fourth, although AKR1C3 expression, ALP, and PSA levels were identified as promising markers to predict the efficacy of switching from AA+P to AA+D, the mechanism behind it is still unknown and needs further study.

In conclusion, we showed that switching from AA+P to AA+D is a feasible and effective therapeutic strategy for mCRPC patients after development of AA resistance. At the time of switching, AKR1C3 expression in prostate repeat biopsy specimens and baseline serum ALP and PSA level could predict the efficacy of switching treatment. Patients with positive AKR1C3 expression, abnormal baseline serum ALP (>160 IU l⁻¹), and higher serum PSA at switch (≥50 mg l⁻¹) might be associated with poor survival outcome of switching treatment. Thus, these patients might not be good candidates for corticosteroid switching. Our results will facilitate clinicians in selecting the optimal candidates for switching from AA+P to AA+D.

AUTHOR CONTRIBUTIONS
YCN and JGZ analyzed the data, and wrote and revised the manuscript. YHL, HZ, YCN, and JGZ planned and conducted the study. YCN, JGZ, MNZ, YIJ, ZYY, NC, JRC, PFS, GXS, XMZ, YHL, and HZ collected and interpreted the data. HZ and YHL supervised the project, participated in its coordination, and revised the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS
All authors declare no competing interests.

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Predictors of efficacy of corticosteroid switching
YC Ni et al

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Supplementary Table 1: Literature review about the existing studies concerning the clinic significance of the corticosteroid-switching treatment in metastatic castration-resistant prostate cancer patients

| Study              | Year | Country       | Patients (n) | Main conclusion                                                                                                                                 |
|--------------------|------|---------------|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Zanardi et al.     | 2019 | Italy         | 11           | Corticosteroid switching from prednisone to dexamethasone is effective but should be limited to asymptomatic patients, with a limited tumor burden, presenting a PSA progression and/or limited radiological progression based on the present data |
| Romero-Laorden et al. | 2018 | Spain         | 26           | Corticosteroid switching from prednisone to dexamethasone can lead to PSA and radiological responses in clinically stable patients progressing on abiraterone plus prednisone; AR amplifications, AR mutations, and ERG rearrangements are identified as potential predictive biomarkers |
| Roviello et al.    | 2018 | Italy         | 36           | Corticosteroid switching could be an option for selected CPRC patients who responded well to prior abiraterone acetate treatment, but not suitable for all heavily pretreated CRPC; corticosteroid-switching treatment was well tolerated |
| Fenioux et al.     | 2018 | France        | 48           | Corticosteroid switching from prednisone to dexamethasone is safe and nonexpensive; patients with previous longer hormone sensitivity duration, lower PSA level, and shorter time to PSA progression on abiraterone acetate plus prednisone are associated with longer bPFS |
| Lorente et al.     | 2014 | UK and Switzerland | 30         | Corticosteroid switching can delay the development of resistance and induce radiological responses in selected patients progressing on abiraterone acetate plus prednisone |

CRPC: castration-resistant prostate cancer; PSA: prostate-specific antigen; bPFS: biochemical progression-free survival; AR: androgen receptor; ERG: erythroblast transformation-specific (ETS) transcription factor

Supplementary Figure 1: PSA response rate for patients of different baseline factors in the corticosteroid-switching treatment. Patients were stratified by (a) baseline ALP (>160 vs ≤160 IU l⁻¹), (b) AKR1C3 expression (positive vs negative), (c) PSA level at switching (≥50 vs <50 ng ml⁻¹). ALP: alkaline phosphatase; AKR1C3: aldo-keto reductase family 1 member C3; PSA: prostate-specific antigen.