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ORIGINAL ARTICLE

Prostate Cancer

Prior switching to a second-line nonsteroidal antiandrogen does not impact the therapeutic efficacy of abiraterone acetate in patients with metastatic castration-resistant prostate cancer: a real-world retrospective study

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Even in the era of novel targeted agents, switching to a second-line nonsteroidal antiandrogen (NSAA) is still widely used in treating metastatic castration-resistant prostate cancer (mCRPC), especially in undeveloped countries. However, whether prior treatment with a second-line NSAA would impact the efficacy of abiraterone acetate (Abi) remains uncertain. In the current study, 87 mCRPC patients treated with Abi were analyzed. Among them, 21 were treated with a second-line NSAA (from bicalutamide to flutamide) before receiving abiraterone, while the remaining 66 received Abi directly. Therapeutic efficacy of Abi was compared between those with and without prior second-line NSAA using Kaplan–Meier curves, log-rank test, and Cox regression models. The therapeutic efficacy of Abi was similar between those with or without the prior switching treatment of flutamide, in terms of either prostate-specific antigen progression-free survival (PSA-PFS, 5.5 *vs* 5.6 months, $P = 0.967$), radiographic progression-free survival (rPFS, 12.8 *vs* 13.4 months, $P = 0.508$), overall survival (OS, not reached *vs* 30.6 months, $P = 0.606$), or PSA-response rate (71.4% [15/21] *vs* 60.6% [40/66], $P = 0.370$). This is the first time that the impact of prior switching of treatment to a second-line NSAA on the efficacy of Abi in mCRPC patients has been addressed. Our data support that, use of prior sequential bicalutamide and flutamide does not seem to preclude response to abiraterone, although larger cohort studies and, ideally, a randomized controlled trial are needed. These findings will facilitate doctors' decision-making in the treatment of mCRPC patients, especially for those with previous experience of switching NSAA second-line treatments in the clinic.

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Keywords: abiraterone; antiandrogen; castration-resistant prostate cancer; flutamide

INTRODUCTION

Metastatic castration-resistant prostate cancer (mCRPC) is the end stage of prostate cancer (PCa), with an irreversibly poor prognosis.[1] Despite the emergence of novel agents in the past decade, the median survival time was only 2.2–4.4 months longer in patients using these novel treatments than those in the control group, according to data from phase III clinical trials.[2–4] Due to mild/moderate therapeutic efficacy, high health care costs, and even particular novel agent-related toxicities,[5–7] some patients with mCRPC, especially those being cared for in undeveloped countries, cannot afford to or are unwilling to receive standard first-line therapies, including abiraterone acetate (Abi), enzalutamide, and docetaxel-based chemotherapy.

In real-world practice, although prospective evidence is still lacking, switching to a second-line nonsteroidal antiandrogen (NSAA) after the occurrence of CRPC as one of the earliest treatment strategies for mCRPC is still widely used, especially in Asian countries.[8–11] One important reason for adopting this strategy is that compared with novel therapies, a second-line NSAA is much more economical and has some degree of efficacy as well.

However, it may be of concern whether the therapeutic efficacy of Abi would be affected by prior use of a second-line NSAA in mCRPC patients. Indeed, a majority of patients with mCRPC would not benefit from switching NSAA treatments. Both second-line antiandrogens (including NSAAs, estrogen, progesterone, and ketoconazole) and novel second-generation antiandrogens (including Abi and enzalutamide) have similar mechanisms targeting the androgen receptor signaling. It has been hypothesized that for those who did not achieve a satisfactory response after switching to

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an alternative NSAA, the efficacy of sequential treatment with Abi or enzalutamide could be compromised by potential drug cross-resistance. Several studies have demonstrated that prior ketoconazole therapy could reduce the efficacy of sequential Abi therapy in patients with mCRPC.[12,13] A similar risk may also potentially exist whereby switching treatment to a second-line NSAA was applied before Abi. Unfortunately, until now, no study has focused on the influence of prior switching of treatment before Abi in patients with mCRPC.

Therefore, the aim of this retrospective study was to compare the therapeutic efficacy of Abi in mCRPC patients previously switched or not to a second-line NSAA, and determine if this prior second-line NSAA therapy would impact the efficacy of Abi in the real world.

PATIENTS AND METHODS

Patient population

A total of 87 patients with mCRPC at West China Hospital (Chengdu, China) from 2015 to 2017 were retrospectively analyzed in this study. Among them, five harbored visceral metastases. Informed consent was obtained from all patients before treatment. Data collection and analysis were authorized by the Ethics Committee of the West China Hospital, Sichuan University. At the time of initial diagnosis, all cases immediately received maximal androgen blockade (MAB), which consisted of surgical or medical castration combined with bicalutamide (BCL; 50 mg per day; AstraZeneca, Macclesfield, UK). After the median treatment with MAB of 12.5 months, mCRPC occurred in all of them. Twenty-one patients switched treatment from one NSAA to another (switching from BCL to flutamide [FLU; 750 mg per day; Schering-Plough Corporation, Kenilworth, NJ, USA]) before being treated with Abi. The reason for switching treatment before giving Abi included: (1) Abi was not conveniently available in some underdeveloped areas of China; (2) some patients needed time to raise money to pay for Abi, and during this period, chose switching treatment to delay disease progression; (3) switching treatment was observed to have some effect in some CRPC patients; and (4) some patients would not use the expensive treatment without exhausting all less expensive alternatives. The remaining 66 men received the standard dosage of Abi directly (1000 mg per day; Janssen Biotech Inc., Horsham, PA, USA) plus prednisone (10 mg per day; Harbin pharmaceutical group, Harbin, China). Abi treatment was administered until radiographic progression disease, clinical progression of disease occurred, or both. Median follow-up time was 32.0 months. At the time of the cutoff day (June 1, 2017), 61 and 40 cases of PSA- and radiographic-progression on Abi had occurred, respectively. However, only 15 patients had the opportunity to receive sequential therapy, such as docetaxel-based chemotherapy. Because enzalutamide is yet to be approved in China, no patient received enzalutamide following treatment with Abi.

Baseline clinicopathologic characteristics of all patients at the time of mCRPC diagnosis were collected, including age, Gleason score (GS), prostate-specific antigen (PSA) doubling time (PSADT), the Eastern Co-operative Oncology Group (ECOG) score, CRPC-free survival (CFS), pain score, and serum PSA, hemoglobin (HGB), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and testosterone level. The pain score was evaluated using a visual analog scale of 1–10. mCRPC was defined according to the 2017 European Association of Urology (EAU) guidelines.[14] CFS was defined as the time from initial diagnosis of PCa to the occurrence of mCRPC. PSADT was calculated according to the Memorial Sloan Kettering Cancer Center (MSKCC) online nomogram by using the first three or more PSA measurements after diagnosis of mCRPC.[15]

End points

Because of the relatively short follow-up time, and the multivariable interference of overall survival (OS), PSA progression-free survival (PSA-PFS) and radiographic progression-free survival (rPFS), according to the Prostate Cancer Working Group 3 (PCWG3) criteria,[16] were chosen as the primary end points in this study. PSA progression was defined as an increase in PSA levels of 25% or more above the nadir (and by ≥2 ng ml^{-1}), with confirmation of this elevation 4 or more weeks later. Radiographic progression was defined as at least two new lesions on the first posttreatment scan, with at least two additional lesions on the next scan.

Secondary end points included PSA response and OS. PSA response was defined as ≥50% decline in PSA levels from baseline, maintained for ≥4 weeks. OS was defined as the period between the initiation of Abi treatment to death from any cause.

Statistical analyses

Continuous variables were presented as median and interquartile range (IQR), whereas categorical variables were reported as number and percentage. The Mann–Whitney *U* test and the Chi-square test were used to compare the baseline characteristics between patients with and without second-line FLU. Kaplan–Meier curves were used to evaluate PSA-PFS, rPFS, and OS. Differences between survival curves were compared using the log-rank test. Waterfall plots were used to describe the PSA response rate.

The predictive ability of each parameter in predicting the treatment efficacy of Abi was assessed as follows: first, a univariate Cox proportional hazards model was used to assess each parameter's power in predicting the treatment efficacy of Abi. Then, parameters with a value of $P < 0.05$ were further analyzed in a multivariate Cox regression model using a backward selection procedure ($P > 0.10$ as the removal criterion, using a likelihood ratio test removal criterion).

All analyses were performed using SPSS (version 21.0; IBM, SPSS Inc., Chicago, IL, USA). All tests were two-sided. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

The clinicopathologic characteristics of all patients are summarized in **Table 1**. The median age for the whole cohort was 73 years. The median CFS was 12.5 (95% confidential interval [CI]: 7.0–27.0) months. Twenty-nine (33.3%) were dead before the cutoff follow-up day. Sixty-six (75.9%) patients received Abi as first-line standard therapy at the time of diagnosis of mCRPC, while 21 (24.1%) patients were first switched to a second-line NAAS (FLU) before initiation of Abi treatment, mainly for economic and psychologic reasons or physicians' discretion. The baseline characteristics at the time of the initial diagnosis of PCa or at the time of diagnosis of mCRPC were balanced between patients treated with or without prior second-line FLU.

Therapeutic efficacy of switching treatment to second-line FLU and the sequential Abi

Among the 21 men switching to second-line FLU treatment before Abi, the median duration of FLU treatment was 6.0 (IQR: 3.0–10.8) months. Two patients switched to Abi treatment before the occurrence of PSA-progression because of intolerance to FLU, while the remaining 19 patients received Abi after PSA-progression on second-line FLU therapy. During FLU treatment, PSA levels decreased in 9/21 (42.9%) patients, while only 7/21 (33.3%) obtained PSA response. The median PSA-PFS was 4.8 (95% CI: 2.6–6.8) months for patients receiving prior second-line FLU.

Table 1: Baseline characteristics of all patients treated with abiraterone acetate at the time of castration-resistant prostate cancer

Characteristics	*All patients (n=87)*	*With second-line FLU (n=21)*	*Without second-line FLU (n=66)*	*P*
Age (year), median (IQR)	73.0 (68.0–80.0)	74.0 (67.0–80.5)	73.0 (68.0–79.5)	
≥70, *n* (%)	61 (70.1)	15 (71.4)	46 (69.7)	0.880
<70, *n* (%)	26 (29.9)	6 (28.6)	20 (30.3)	
Gleason score				
<8, *n* (%)	17 (19.5)	4 (19.1)	13 (19.7)	0.948
8–10, *n* (%)	70 (80.5)	17 (81.0)	53 (80.3)	
PSADT at CRPC (day), median (IQR)	44.1 (28.5–68.4)	42.0 (33.0–66.6)	44.9 (26.9–68.9)	
≥30, *n* (%)	60 (69.0)	17 (81.0)	43 (65.2)	0.173
<30, *n* (%)	27 (31.0)	4 (19.1)	23 (34.9)	
ECOG score at CRPC				
≥2, *n* (%)	12 (13.8)	4 (19.1)	8 (12.1)	0.423
<2, *n* (%)	75 (86.2)	17 (81.0)	58 (87.9)	
CFS (month), median (IQR)	12.5 (7.0–27.0)	11.1 (6.0–17.3)	13.5 (7.1–28.5)	
≥12, *n* (%)	47 (54.0)	10 (47.6)	37 (56.1)	0.499
<12, *n* (%)	40 (46.0)	11 (52.4)	29 (43.9)	
Pain score at CRPC				
>3, *n* (%)	24 (27.6)	5 (23.8)	19 (28.8)	0.657
≤3, *n* (%)	63 (72.4)	16 (76.2)	47 (71.2)	
PSA at CRPC (ng ml^{-1}), median (IQR)	61.3 (24.9–190.4)	99.7 (22.5–401.5)	54.8 (24.9–174.1)	
≥50, *n* (%)	47 (54.0)	12 (57.1)	35 (53.0)	0.742
<50, *n* (%)	40 (46.0)	9 (42.9)	31 (47.0)	
HGB at CRPC (g l^{-1}), median (IQR)	124.0 (110.0–130.0)	116.5 (106.0–125.0)	125.5 (112.5–132.3)	
≥120, *n* (%)	52 (59.8)	9 (42.9)	43 (65.2)	0.070
<120, *n* (%)	35 (40.2)	12 (57.1)	23 (34.9)	
ALP at CRPC (IU l^{-1}), median (IQR)	118.5 (79.8–218.9)	94.0 (65.0–210.5)	120.0 (86.0–254.3)	
≥160, *n* (%)	24 (27.6)	5 (23.8)	19 (28.8)	0.657
<160, *n* (%)	63 (72.4)	16 (76.2)	47 (71.2)	
LDH at CRPC (IU l^{-1}), median (IQR)	212.0 (188.0–290.0)	248.0 (187.0–332.5)	208.0 (187.0–261.3)	
≥250, *n* (%)	25 (28.7)	8 (38.1)	17 (25.8)	0.277
<250, *n* (%)	62 (71.3)	13 (61.9)	49 (74.2)	
Testosterone at CRPC (ng ml^{-1}), median (IQR)	0.03 (0.02–0.11)	0.02 (0.02–0.08)	0.03 (0.02–0.12)	
≥0.1, *n* (%)	37 (42.5)	6 (28.6)	31 (47.0)	0.137
<0.1, *n* (%)	50 (57.5)	15 (71.4)	35 (53.0)	

IQR: interquartile range; FLU: flutamide; PSADT: prostate-specific antigen doubling time; ECOG: Eastern Cooperative Oncology Group; CRPC: castration-resistant prostate cancer; CFS: CRPC-free survival; PSA: prostate-specific antigen; HGB: hemoglobin; ALP: alkaline phosphatase; LDH: lactate dehydrogenase

At the end of follow-up, PSA-progression and radiographic-progression of Abi treatment occurred in 61 (70.1%) and 40 (46.0%) patients, respectively. Twenty-nine (33.3%) patients died. The median PSA-PFS, rPFS, and OS for all men treated with Abi were 5.6 (95% CI: 4.7–9.4) months, 13.4 (95% CI: 10.8–16.0) months, and 30.6 (95% CI: 14.7–30.6) months, respectively (**Figure 1**). Decreased PSA levels were observed in 67 (77.0%) patients, whereas PSA response was achieved in 55 (63.2%) patients (**Figure 2a**).

The impact of switching treatment to second-line FLU prior to Abi on the therapeutic efficacy of Abi

Kaplan–Meier curves (**Figure 3**) and waterfall plots (**Figure 2b**) showed that switching to second-line FLU prior to Abi compared with no switching prior to Abi had no impact on either PSA-PFS (5.5 *vs* 5.6 months, $P = 0.967$), rPFS (12.8 *vs* 13.4 months, $P = 0.508$), OS (not reached *vs* 30.6 months, $P = 0.606$), or PSA response (71.4% [15/21] *vs* 60.6% [40/66], $P = 0.370$).

The stacked bar chart also showed that the therapeutic effect of Abi was not affected by switching treatment to second-line FLU prior to Abi treatment (**Figure 4**).

Univariate and multivariate analyses of the efficacy of Abi

The influence of each parameter on the efficacy of Abi was analyzed using univariate and multivariate Cox proportional models. Univariate analyses indicated that factors including ECOG score, CRPC-free survival, pain score, and ALP at the time of mCRPC were statistically associated with the therapeutic effect of Abi in terms of PSA-PFS, rPFS, and OS, while PSADT and LDH, at the time of mCRPC, were only predictors of PSA-PFS. Parameters that achieved a *P* value below 0.05 in univariate analysis were further assessed in multivariate analysis using a backward selection procedure ($P > 0.10$ as a removal criterion). The results indicated that ECOG score and ALP at the time of mCRPC were independent prognosticators for PSA-PFS, rPFS, and OS, while CRPC-free survival was the only independent prognosticator for rPFS and OS (**Table 2**).

DISCUSSION

To the best of our knowledge, this is the first study to investigate the impact of prior switching of treatment to an alternative second-line NSAA on the therapeutic efficacy of sequential Abi treatment in patients with mCRPC. In the current study, we found that prior switching of treatment to second-line FLU before administering

sequential Abi treatment seemed to have no effect on the sequential Abi treatment, in terms of either PSA-PFS, rPFS, OS, or PSA response.

Many studies have proven that even in mCRPC, the androgen signal remains crucial for tumor progression.[17,18] Recently, a new generation of androgen receptor (AR)-targeting agents, for example, Abi and enzalutamide, have shown promising effects in prolonging the survival of mCRPC patients.[3,4] Yet, these new therapies are expensive and not affordable for many patients, especially for those without medical insurance. In this context, the strategy of switching from one NSAA to another is still being adopted in real clinical practice.

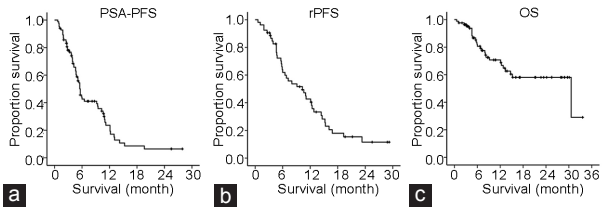

Figure 1: The overall treatment efficacy of Abi. (**a**) The Kaplan–Meier curve shows the PSA-PFS from the initiation of Abi to progression. (**b**) The Kaplan–Meier curve shows the radiographic progression-free survival from the initiation of Abi to progression. (**c**) The Kaplan–Meier curve shows the OS from the initiation of Abi to death. Abi: abiraterone acetate; OS: overall survival; PSA: prostate-specific antigen; PFS: progression-free survival; rPFS: radiographic progression-free survival.

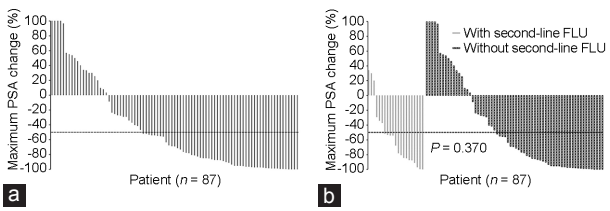

Figure 2: The Waterfall plot showing the PSA-response to Abi treatment. Each bar in the waterfall plot represents one patient. (**a**) PSA-response to Abi in all patients. (**b**) PSA response to Abi in patients with or without the switching of treatment to second-line FLU. PSA response was defined as ≥50% decline in PSA levels from baseline, maintained for ≥4 weeks. PSA: prostate specific antigen; FLU: flutamide; Abi: abiraterone acetate.

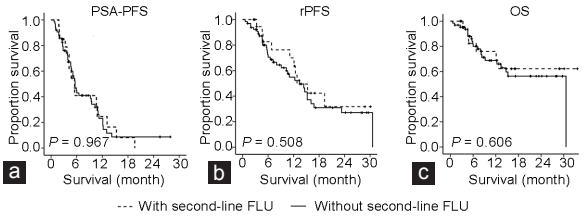

Figure 3: The therapeutic efficacy of Abi in patients with or without the prior switching of treatment to second-line FLU. (**a**) The Kaplan–Meier curve shows the PSA-PFS from the initiation of Abi to progression. (**b**) The Kaplan–Meier curve shows the rPFS from the initiation of Abi to progression. (**c**) The Kaplan–Meier curve shows the OS from the initiation of Abi to death. PSA: prostate-specific antigen; PFS: progression-free survival; rPFS: radiographic progression-free survival; Abi: abiraterone acetate; FLU: flutamide; OS: overall survival.

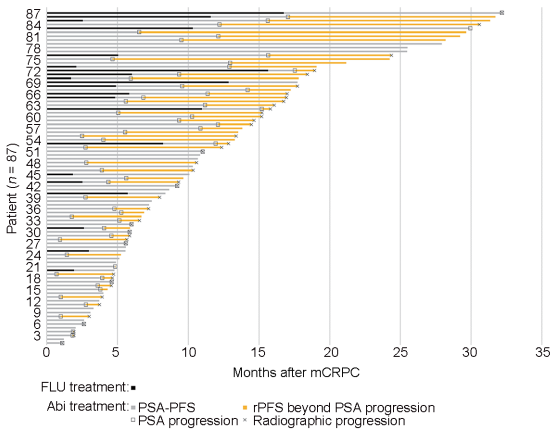

Figure 4: Stacked bar chart shows the treatment schemes and disease status for all patients. Each bar in the plot represents one patient. P: patient; Abi: abiraterone acetate; FLU: flutamide; PSA: prostate-specifc antigen; PFS: progression-free survival; rPFS: radiographic progression-free survival.

Table 2: Univariate and multivariate analyses for the treatment efficacy of abiraterone

Analyses	*PSA-PFS*		*rPFS*		*OS*	
	HR (95% CI)	*P*	*HR (95% CI)*	*P*	*HR (95% CI)*	*P*
Univariate analysis						
Gleason score 8–10 versus <8	1.60 (0.83–3.06)	0.159	1.18 (0.57–2.46)	0.651	0.91 (0.38–2.19)	0.837
With switching ADT versus without	1.01 (0.56–1.82)	0.968	0.79 (0.39–1.60)	0.510	0.79 (0.32–1.96)	0.608
PSADT ≥30 days versus <30 days	0.56 (0.32–0.99)	0.046	0.96 (0.50–1.85)	0.914	0.72 (0.32–1.63)	0.435
ECOG score ≥2 versus <2	3.15 (1.64–6.02)	0.001	2.80 (1.42–5.53)	0.003	2.73 (1.18–6.30)	0.018
CFS ≥12 months versus <12 months	0.58 (0.34–0.98)	0.043	0.47 (0.25–0.86)	0.015	0.37 (0.17–0.81)	0.014
Pain score >3 versus ≤3	2.70 (1.51–4.85)	0.001	2.69 (1.42–5.09)	0.002	2.65 (1.21–5.78)	0.015
PSA at CRPC ≥50 ng ml^{-1} versus <50 ng ml^{-1}	1.46 (0.87–2.44)	0.148	1.36 (0.74–2.51)	0.320	1.76 (0.80–3.84)	0.158
HGB at CRPC ≥120 g l^{-1} versus <120 g l^{-1}	0.88 (0.51–1.50)	0.634	0.85 (0.44–1.64)	0.628	1.01 (0.46–2.22)	0.988
ALP at CRPC ≥160 IU l^{-1} versus <160 IU l^{-1}	2.37 (1.30–4.31)	0.005	3.13 (1.60–6.13)	0.001	2.65 (1.21–5.80)	0.015
LDH at CRPC ≥250 IU l^{-1} versus <250 IU l^{-1}	1.90 (1.06–3.39)	0.031	1.77 (0.94–3.33)	0.079	1.92 (0.87–4.24)	0.107
Testosterone at CRPC ≥0.1 ng ml^{-1} versus <0.1 ng ml^{-1}	1.14 (0.67–1.94)	0.626	0.84 (0.45–1.58)	0.594	0.93 (0.43–2.01)	0.854
Multivariate analysis						
ECOG score ≥2 versus <2	2.70 (1.40–5.22)	0.003	2.42 (1.20–4.91)	0.014	2.72 (1.15–6.40)	0.022
ALP at CRPC ≥160 IU l^{-1} versus <160 IU l^{-1}	2.13 (1.16–3.90)	0.014	0.52 (0.27–1.00)	0.051	1.99 (0.89–4.46)	0.094
CFS ≥12 months versus <12 months			2.16 (1.04–4.49)	0.038	0.38 (0.17–0.86)	0.020

PSA: prostate-specific antigen; PSA-PFS: PSA-progression-free survival; rPFS: radiographic progression-free survival; OS: overall survival; ADT: androgen deprivation therapy; PSADT: prostate-specific antigen doubling time; ECOG: Eastern Cooperative Oncology Group; CRPC: castration-resistant prostate cancer; CFS: CRPC-free survival; HR: hazard ratio; HGB: hemoglobin; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; CI: confidence interval

Several studies have evaluated the efficacy of switching NSAA treatment.[8–11] Early in 1998, Joyce *et al*.[8] first reported on 14 patients who underwent BCL treatment following the failure of the initial FLU therapy. In their study, PSA levels decreased in 6/14 (42.9%) patients. Later, many centers shared their experiences with switching treatment.[9–11] The PSA response rate in these studies ranged from 30.0% to 50.0%, which was in accordance with our findings. These studies, therefore, indicated that BCL and FLU are not completely cross-resistant. Lacking long-term efficacy and the prospective evidence, switching NSAA treatment is not routinely recommended as standard therapy in patients with mCRPC. However, it continues to be used in clinical practice for several reasons. The mechanism underlying the therapeutic response from an alternative second-line NSAA has been described by many scientists. Most noteworthy is the *AR* mutation hypothesis, which assumes that long-term antiandrogen treatment may alter the ligand of AR, turning a certain antiandrogen into a partial agonist.[19] For example, two mutations, W741C and T877A, were reported to be related to the resistance of BCL.[20] Because this alteration is structurally specific to one antiandrogen, a molecularly different antiandrogen could retain the inhibitory activity to a mutated *AR*.[19,21]

Importantly, besides the fact that FLU could reactivate the mutated AR caused by BCL, it might also have the capacity to suppress the adrenal antiandrogen.[22–24] In 1990, Ayub and his colleagues[22] reported that FLU had an inhibitory effect on human adrenal microsomal 17 α-hydroxylase-17,20-lyase (CYP17). Similarly, Narimoto *et al*.[24] found that compared with BCL, FLU could suppress the synthesis of dehydroepiandrosterone, androstenedione, and androstenediol in an adrenal cancer cell line. Similar results were also reported in another Japanese paper.[23] FLU's potency of inhibiting CYP17 naturally is reminiscent of another CYP17 inhibitor, ketoconazole,[25] which was widely used in treating mCRPC before the era of novel AR-targeted drugs. Owing to the similar mechanism, prior treatment with ketoconazole in mCRPC patients was observed to hinder the therapeutic efficacy of sequential Abi.[12,13] Nevertheless, the OS difference was not significant between patients with and without ketoconazole treatment.[26] This finding raises the issue of whether the prior switching of treatment to second-line FLU will hinder sequential Abi therapy or if drug–drug interactions exist between Abi and FLU.

In the present study, the use of FLU as a second-line NSAA before treatment with Abi was observed to have no adverse effect on the therapeutic efficacy of the sequential Abi treatment in mCRPC patients. Survival analyses indicated that regarding Abi treatment, patients first treated with second-line FLU had almost the same PSA-PFS, rPFS, OS, and PSA response rate as those directly receiving Abi after being diagnosed with mCRPC. However, recently, the STAMPEDE and LATITUDE trials showed that starting Abi earlier increased OS;[27,28] therefore, it is possible that postponing the start of Abi might worsen the outcome of patients, which should not be ignored in clinical practice.

We note that compared with the therapeutic efficacy of Abi in a phase III clinical trial,[29] the PSA response rate was comparable in this study (63.2% *vs* 62.0%, respectively), whereas PSA-PFS and rPFS were relatively shorter in the current study (PSA-PFS: 5.6 months *vs* 11.1 months; rPFS: 13.4 months *vs* 16.5 months). Further comparison revealed that patients in this study had more advanced diseases than those in the COU-AA-302 trial, with a larger proportion of men having a GS of 8–10 (80.3% *vs* 54.0%), a pain score >3 (28.8% *vs* 2.0%), and a higher median level of baseline PSA (54.8 ng ml^{-1} *vs* 42.0 ng ml^{-1}) and ALP (120.0 IU l^{-1} *vs* 93.0 IU l^{-1}). These differences provide a reasonable explanation for the different therapeutic efficacies observed between these two studies.

This study had several limitations. First, this was a retrospective single-center study with characteristics related to its study type. Second, because all patients in this cohort were initially treated with BCL, the second-line NSAA could only be switched from BCL to FLU. Therefore, further work is needed to illuminate the impact of other therapy switching after the failure of the first-line antiandrogen on the sequential treatment with Abi.

CONCLUSIONS

By comparing the therapeutic efficacy of Abi between mCRPC patients with or without the prior switching of treatment to second-line FLU after the failure of BCL, this study primarily addressed the impact of prior switching of treatment to another NSAA on the therapeutic outcome of the sequential treatment with Abi. Data from our cohort revealed that, use of prior sequential BCL and FLU does not seem to preclude response to Abi, although larger cohort studies and ideally, a randomized controlled trial is needed. Our work will facilitate doctors' decision-making in the treatment of mCRPC patients, especially for those with previous experience of switching NSAA second-line treatments in the clinic.

AUTHOR CONTRIBUTIONS

Data collection was carried out by JGZ, JDL, XT, JRC, and KPS. Data analyses were conducted by JGZ, JDL, PFS, and XMZ. The article was written by JGZ, JDL, HZ, and MS. The manuscript was revised by HZ and MS. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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