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Outcome of Patients with Metastatic Castration-resistant Prostate Cancer After PSA Progression with Abiraterone Acetate

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Abstract. *Background/Aim: The main purpose of this study was to evaluate the outcome of patients with prostate-specific antigen (PSA) progression after abiraterone acetate (AA) treatment for metastatic castration-resistant prostate cancer (mCRPC). Patients and Methods: Between 2012 and 2017, 83 patients with clinically-confirmed mCRPC previously treated with docetaxel with/without cabazitaxel followed by AA were included in this retrospective study. All patients received 1,000 mg AA with 5 or 10 mg prednisolone. Among them, 59 were eligible for this study based on PSA progression during the clinical course. Patients were divided into two groups, AA responders and AA non-responders according to previous PSA response to AA treatment. Overall survival and treatment response to subsequent therapy were analyzed. Results: The median overall survival of the 59 patients after AA-treated PSA progression was 12 (95% confidence interval(CI)=7.6-16.4) months and was longer in the AA-responding group compared to the non-responding group (25 vs. 8 months, p<0.001). The survival time after PSA progression on AA was longer in the AA-responsive group despite not being statistically different (13 vs. 7 months, p=0.126). Patients with AA treatment who received subsequent therapies after PSA progression had better overall survival than those without (18 vs. 4 months, p=0.003). In addition, there was a trend for better chemotherapy response in AA non-responders than AA responders, 62.5% (5/8) vs. 12.5% (1/8) respectively. Conclusion: In our small retrospective patient experience, effective sequential treatments for patients with mCRPC provided overall survival benefit. Previous treatment response can act as a clinical predictor for subsequent treatment.*

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Prostate cancer formation and progression relate to the activation of androgen receptor (AR). Intercepting androgen-related signaling has been the therapeutic strategy and AR-targeted agents have been the mainstay treatment for metastatic prostate cancer for decades (1). Androgen blockade, as well as surgical or medical castration, are not curative and disease may, therefore, progress into advanced or metastatic disease at a later stage. Disease may also progress to an AR-resistant stage at which hormonal therapy is no longer effective, so called castration-resistant prostate cancer (CRPC) or metastatic castration-resistant prostate cancer (mCRPC). To compensate for hormonal therapy, docetaxel, first introduced in 2003, is applied as non-hormonal systemic treatment to prolong the survival of patients with mCRPC (2). Abiraterone acetate (AA) is a potent and selective inhibitor of cytochrome *P450*, family 17, subfamily A, polypeptide 1 (CYP17A1), which is a critical enzyme in androgen biosynthesis. Administration of AA may block androgen production in adrenal glands, testes and even the prostate tumor, thus leading to the decline of testosterone both in circulation and in intra-prostatic tissues. That a therapeutic effect of AA in mCRPC has been achieved is based on PSA response, symptom improvement and tumor

shrinkage (3-5). Additionally, randomized placebo-controlled phase III clinical trial of AA with prednisolone demonstrated the overall survival benefit in patients with mCRPC previously treated with docetaxel, with 15.8 months compared to 11.2 month in the placebo-treated arm (6, 7). Treatment efficacy was also examined in Asian patient groups in a phase II study, demonstrating a median overall survival of 11.8 months and a response rate of 43%, thus implying that the combination of AA and prednisolone is a favorable second-line treatment (8).

At our institution, AA has been administered post-chemotherapy to patients with mCRPC since 2012. We reported that the duration of first-line androgen deprivation therapy (ADT) is positively associated with AA treatment efficacy in terms of progression-free and overall survival (9).

Despite the survival benefit of AA treatment observed, the progression of disease in subsequent months is inevitable. Continued application of AA, re-challenge with docetaxel, or a switch to enzalutamide or radioisotope therapy may be options for patients with mCRPC unresponsive to second-line AA therapy (10). There is neither a standard treatment nor appropriate diagnostic markers to accurately determine subsequent therapy for such cases. To clarify what happens to patients with mCRPC which had progressed after AA treatment and further investigate favorable therapeutic strategies after AA is invalidated, we conducted a clinical investigation of the responses and outcomes of patients with mCRPC who had PSA progression after AA treatment.

Patients and Methods

From April 2012 to March 2017, a total of 83 patients with mCRPC who had been treated with docetaxel followed by AA treatment were retrospectively reviewed from our institute. Written informed consent was obtained from all the included patients before treatment, according to the certification of the Institute Review Board of Taichung Veterans General Hospital, number CE13240A-2. All these patients received 1000 mg AA plus 5 or 10 mg prednisolone once daily combined with continued ADT.

Fifty-nine patients who had PSA progression after AA were retrospectively reviewed for this study and were grouped into AA-responsive (n=26) and -non-responsive groups (n=33). PSA response was characterized as a decrease in PSA of at least 50% from baseline. All the patients were under a castration level of <50 ng/dl testosterone during the clinical course; the clinical discrimination of patients is described in Figure 1.

The development of CRPC was characterized based on a continuous rise of serum PSA, the progression of pre-existing disease, or the appearance of new metastasis under castration levels of testosterone (<50 ng/dl). According to the criteria of the Prostate Cancer Working Group's second publication (PCWG2), progressive disease (PD) was based on PSA progression with an increase of ≥25% and ≥2 ng/ml above the nadir since the start of therapy, which had to be confirmed 3 or more weeks later (11). Imaging studies were not routinely used, but were based on clinical condition such as symptomatic metastasis. According to the Response Criteria for Solid Tumors (RECIST), soft-tissue PD was defined as the target lesion in soft-tissue sites (*i.e.*, liver or lung) or lymph nodes enlarged ≥2 cm in diameter (12). If there were two or more new lesions on a bone scan, this was defined as bone PD (11). When bone scan results suggested a flare reaction or trauma, other imaging modalities, such as computed tomography, was used for confirmation. Patients who developed PSA progression after AA treatment were to receive re-challenge of chemotherapy with docetaxel, cabazitaxel, or another second-line therapy of enzalutamide depending on clinical symptoms, such as a good performance status and affordability. Docetaxel was administered intravenously at 75 mg/m^2 once every 3 weeks or 50 mg/m^2 once every 2 weeks up to 14 cycles if tolerated.

The study end-point was overall survival, defined as the time from AA treatment to any cause of death.

The Mann–Whitney *U*-test and Fisher's exact *t*-test were used for continuous variables, while the chi-squared test was used for categorical variables. Kaplan–Meier survival curve with log-rank test was used for evaluating the overall survival between the two groups. All statistical tests were carried out using IBM SPSS version 22 for Windows (IBM Corp., Armonk, NY, USA), with a *p*-value of less than 0.05 considered statistically significant.

Results

The basic characteristics of all the 59 patients with mCRPC before AA treatment are shown in Table I. The median age of diagnosis was 65 years, and the median first line duration of ADT was 20 months. Docetaxel was given with a median of six cycles as first-line therapy after the development of mCRPC. Nineteen of these patients (19/59, 32.2%) received cabazitaxel after failed docetaxel treatment.

Table II demonstrates the characteristics of patients who developed PSA progression after AA treatment. For the whole patient group, the median follow-up time was 11 months (interquartile range (IQR)=7-20 months), and 38 patients had died by the cutoff time. The median AA treatment duration was 7 months in the responsive group compared to 2 months in the non-responsive group ($p<0.001$). Except for PSA progression, a total of 42 patients (42/59, 71.3%) also had radiologically proven disease progression. Among them, 22 patients had soft-tissue PD, 38 had bone PD, and 18 patients were diagnosed with both types of progression. After PSA progression developed, eight patients of each group received re-challenge chemotherapy with docetaxel or cabazitaxel. There was a better response rate to chemotherapy re-challenge in the AA-non-responsive group (responsive *vs.* non-responsive groups, 12.5% *vs.* 62.5%, $p=0.039$). A total of 13 patients received enzalutamide after AA failed, and five of them (38.5%) achieved a decrease in PSA of 50%, with a higher response rate in the AA-responsive group (40.0% *vs.* 33.3%, $p=0.835$).

The median duration of survival after AA treatment failed was 12 months (95% confidence interval (CI)=7.6-16.4 months) (Figure 2). The median overall survival starting from administration of AA was 25 months (95% CI=21.67-28.33 months) in the responsive group and 8 months (95%

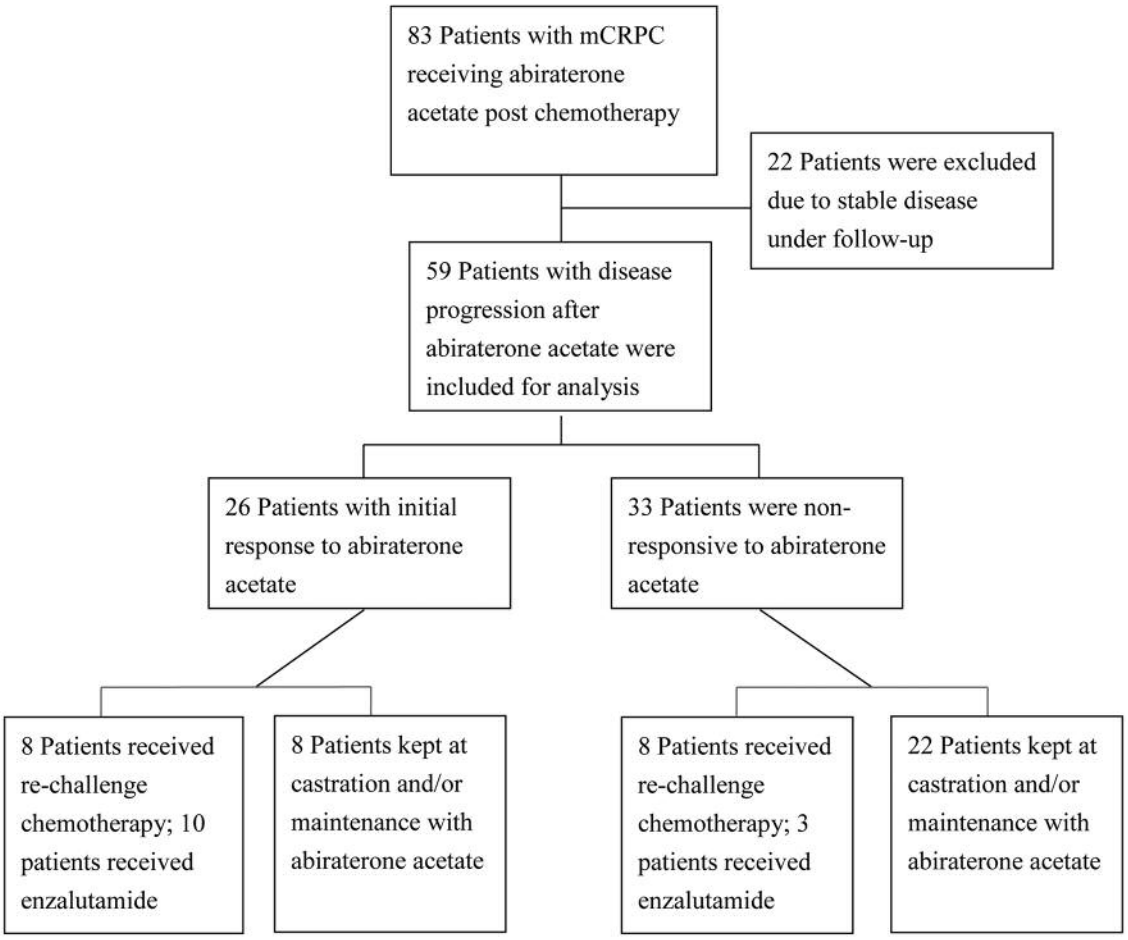

Figure 1. *The distribution of patients according to clinical behavior. Fifty-nine out of 83 patients with PSA progression after abiraterone acetate therapy were eligible for this study.*

CI=3.73-12.27 months) in the non-responsive group (log-rank $p<0.001$) (Figure 3A). The median duration of survival starting from AA treatment failure was 13 months in the responsive group and 7 months in non-responsive group, without statistically significant difference (log-rank $p=0.126$) (Figure 3B).

Patients received subsequent therapy (re-challenge of chemotherapy or treatment of enzalutamide) after AA treatment failure appeared to have a superior survival duration in comparison with those treated with best supportive care, with a median overall survival of 18 months *vs*. 4 months, sequential therapy *vs*. not sequential therapy (log-rank $p=0.003$) (Figure 4). Furthermore, in both univariate and multivariate Cox regression analyses, sequential therapy was positive correlated with superior overall survival in patients with PSA progression after AA ($p=0.005$ and $p=0.01$, respectively; Table III).

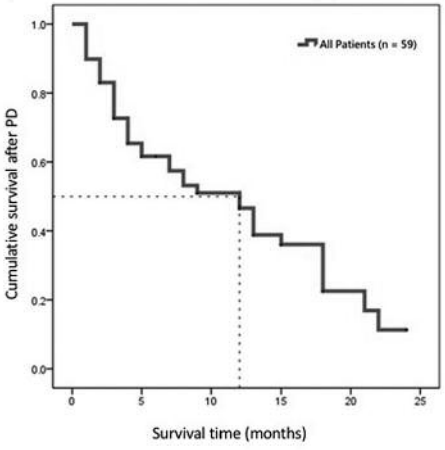

Figure 2. *Survival curve of all patients after PSA progression after abiraterone acetate. The median survival was 12 months (interquartile range=3-18 months).*

Table I. *Basic characteristics of all patients before abiraterone acetate use.*

		Total (n=59) Value
Hormone-sensitive stage	Median age at diagnosis (IQR), years	65 (60-74)
	Median primary PSA (IQR), ng/ml	113.24 (38.99-381.00)
	RRP, n (%)	13 (22.0%)
	RT, n (%)	14 (23.7%)
	Median Gleason score (IQR)	9 (7-9)
	Median duration of first-line line ADT (IQR), months	20.0 (10.0-35.5)
CRPC stage (docetaxel and cabazitaxel)	Median PSA (IQR), ng/ml	35.88 (11.25-120.75)
	Median no. of docetaxel cycles (n=59) (IQR)	6 (3-10)
	Median no. of cabazitaxel cycles (n=19) (IQR)	4 (3-5)
	Median duration of chemotherapy period (IQR), months	12.0 (6.0-22.0)

IQR: Interquartile range; PSA: prostatic-specific antigen; RRP: radical retropubic prostatectomy; RT: radiation therapy; ADT: androgen-deprivation therapy; CRPC: castration-resistance prostate cancer.

Table II. *Characteristics of patients after prostatic-specific antigen (PSA) progression under abiraterone acetate (AA) therapy.*

Characteristic	Total (n=59)	Group		*p*-Value
		Response (n=26)	Non-response (n=33)	
Median age at AA start (IQR), years	71 (64-78)	69 (62.5-78.0)	72 (66.5-79.5)	0.477
Median PSA pre-AA (IQR), ng/ml	75.26 (21.13-306.00)	56.25 (17.08-144.75)	90.44 (26.95-510.50)	0.228
Median best PSA on AA (IQR), ng/ml	51.12 (15.41-447)	18.55 (4.77-50.03)	287.00 (24.78-718.50)	**<0.001**
Median duration of AA use (IQR), months	3.0 (2.0-6.0)	7.0 (4.0-13.5)	2.0 (2.0-3.0)	**<0.001**
Median PSA (IQR) at PSA progression, ng/ml	96.56 (40.07-687.00)	60.33 (32.60-195.25)	211.00 (58.89-985.00)	**0.023**
Median ALP (IQR) at PSA progression, U/I	181.00 (121.00-405.00)	146.00 (124.50-283.00)	272.00 (100.75-484.50)	0.161
Median LDH (IQR) at PSA progression, U/I	256.00 (202.00-344.50)	249.00 (205.75-315.00)	290.50 (200.50-563.75)	0.403
Radiographic PD (bone and soft tissue), n (%)	42.00 (71.2%)	17.00 (65.4%)	25.00 (75.8%)	0.184
Response to chemotherapy rechallenge (n=16), n (%)	6.00 (37.5%)	1/8 (12.5%)	5/8 (62.5%)	**0.039**
Response to enzalutamide (n=13), n (%)	5 (38.5%)	4/10 (40.0%)	1/3 (33.3%)	0.835
Survival, n (%)	21 (35.6%)	12 (46.2%)	9 (27.3%)	0.133
Median follow-up time (IQR), months	11.0 (7-20)	19.5 (9.0-25.5)	7.0 (5.0-15.0)	**<0.001**

IQR: Interquartile range; PD: progressive disease; ALP: alkaline phosphatase; LDH: lactic dehydrogenase. Radiographic PD defined as two new bone lesions or soft tissue metastasis ≥20% increase in size using RECIST criteria (12). Continuous variable analysis used Mann–Whitney *U*-test and Fisher's exact tes*t t*-test, categorical variables analysis used Pearson Chi-square test, with significance acceptable at $p<0.05$ (shown in bold).

Discussion

This study demonstrates real-world data of clinical course for patients with mCRPC and PSA progression after chemotherapy and AA treatment. Additionally, subsequent therapy provides a superior survival benefit after AA treatment failure.

Our previous study evaluated the effect of AA on the clinical outcome of patients with mCRPC who received AA treatment after docetaxel and provided evidence that clinical parameters, such as first-line ADT duration or pre-AA PSA level, may correspond to progression-free survival and serve as simple predictors for the outcome of AA treatment (9). Therefore, we expanded and continued to collect and record the post-chemotherapeutic clinical responses of patients with mCRPC to AA treatment. In this study, all eligible patients treated with AA had a median survival of 12 months after PSA progression developed. Among these patients, the AA-responsive group had better overall survival than the non-responsive group (median of 25 *vs*. 8 months, $p<0.001$).

In a final analysis of the COU-AA-301 study, Fizazi *et al*. revealed that AA significantly prolonged overall survival in patients with mCRPC whose disease progressed after docetaxel treatment and that the survival benefit in the AA-treated group compared to the placebo group was consistent

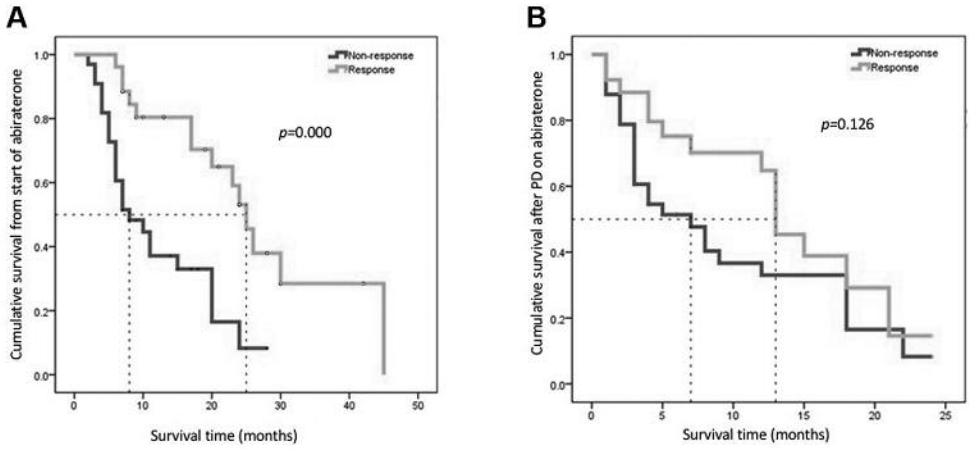

Figure 3. *Kaplan–Meier survival curve for evaluation of overall survival according to response to abiraterone acetate (AA) of patients with metastatic castration-resistant prostate cancer. A: Overall survival according to AA use. The median survival of 25 months for the AA-responding group was significantly better than the 8 months for the AA non-responsive group (log-rank p<0.001). B: Overall survival after progression of disease on AA. The median survival of the responding group was 13 months, while the median survival of the non-responding group was 7 months (log-rank p=0.126).*

across most protocol-specified subgroups. Their finding suggests that mCRPC remains androgen-driven and that the survival benefit of AA is independent of previous docetaxel therapy (7).

AA is a selective inhibitor of an enzyme (CYP17A1) critical for androgen production. Enzalutamide, an inhibitor of AR, is another second-line therapy for mCRPC that acts on multiple steps of the AR signaling pathway. In this study, the effect of AA on overall survival for AA-responsive patients was significantly better than for non-responsive patients. Additionally, there was a 40% (4/10) response in AA-responsive patients who received enzalutamide treatment as subsequent therapy after PSA progression. Moreover, our previous study provided evidence that ADT-duration is related to AA efficacy (9). The observations from our series of clinical studies implied that in the AA-responsive population, androgen-related signaling plays a critical role in driving the tumorigenesis and progression of prostate cancer, even in the late stage of advanced prostate cancer. In addition to our speculation, a pooled analysis of 10 case series for the treatment of enzalutamide after docetaxel and AA in mCRPC also suggests a greater benefit of enzalutamide in patients who responded to AA (13). However, Davies *et al*. studied a series of 34 patients receiving enzalutamide after docetaxel and AA and suggested that the response to previous AA is not predictive of subsequent response to enzalutamide (14).

A *post-hoc* analysis of the COU-AA-302 trial (chemotherapy-naive men with mCRPC) investigated clinical responses to docetaxel as the first subsequent therapy among patients who developed PD following AA treatment. It found

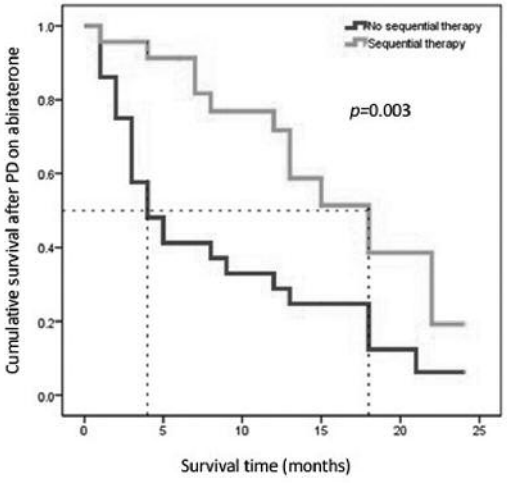

Figure 4. *Overall survival among patients who received sequential therapy after PSA progression on abiraterone acetate and those who did not. In patients who received sequential therapy, the median survival was 18 months, while it was only 4 months for those who did not (log-rank p=0.003).*

that chemotherapy-naive patients with mCRPC whose disease progressed with AA treatment may still benefit from subsequent docetaxel therapy (15), which supports the need for further assessment of treatment patterns following AA for mCRPC, particularly among older patients. In our study, the median age of patients starting to receive AA was 71 years (IQR=64-78 years) with a median Gleason score=9 (IQR 7-9). Sequential therapy (re-challenge of chemotherapy or

Table III. *Univariate and multivariate analysis for predictors of all-cause death after prostatic-specific antigen (PSA) progression under abiraterone acetate (AA) therapy by Cox regression, with significance acceptable at p<0.05.*

	Comparison	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Age at AA start	Per yearly increment	1.024 (0.989-1.061)	0.177		
Initial PSA	Per ng/mI increment	1.000 (0.999-1.000)	0.561		
RRP	Yes *vs*. no	0.674 (0.292-1.536)	0.348		
Gleason score	Per point increment	1.260 (0.846-1.875)	0.256		
Hormone-sensitive period	Per monthly increment	0.994 (0.978-1.011)	0.487		
Chemotherapy period	Per monthly increment	0.977 (0.947-1.007)	0.135		
AA Period	Per monthly increment	0.946 (0.886-1.011)	0.101		
AA Response	Response *vs*. non response	0.613 (0.316-1.187)	0.147		
Age at PSA progression	Per yearly increment	1.020 (0.986-1.056)	0.243		
PSA at PSA progression	Per ng/mI increment	1.000 (1.000-1.001)	**<0.001**	1.000 (1.000-1.001)	0.092
Alk-P at PSA progression	Per U/I increment	1.001 (1.000-1.002)	**0.002**	1.001 (0.999-1.002)	0.234
LDH at PSA progression	Per U/I increment	1.001 (1.000-1.001)	**0.013**	1.000 (0.999-1.001)	0.862
Soft tissue PD	Yes *vs*. no	2.717 (1.400-5.273)	**0.003**	2.109 (0.833-5.335)	0.115
Bone metastasis PD	Yes *vs*. no	3.314 (1.447-7.588)	**0.005**	7.159 (1.830-28.011)	**0.005**
Subsequent therapy	Yes *vs*. no	0.364 (0.179-0.742)	**0.005**	0.270 (0.099-0.736)	**0.010**

HR, Hazard ratio; CI, confidence interval; RRP: radical retropubic prostatectomy; PD: progressive disease; ALP: alkaline phosphatase; LDH: lactic dehydrogenase. Significance acceptable at $p<0.05$ (shown in bold).

administration of enzalutamide) showed a positive correlation to a superior overall survival in post-chemotherapeutic mCRPC patients with PD after AA (multivariate analysis, HR=0.270, 95% CI=0.099-0.736, $p=0.010$). In addition, a better response rate for chemotherapy re-challenge in the AA non-responsive group was obtained in our study (responsive *vs*. non-responsive groups, 12.5% *vs*. 62.5%, $p=0.039$). The analyzed results from our patients might echo those of previous studies, in which docetaxel had an impactful antitumor activity as the first subsequent therapy for patients with mCRPC who experienced PSA progression on AA (15), with a modest activity for enzalutamide and docetaxel in progressive mCRPC after AA (16).

The usage of AA for patients with mCRPC has changed the therapeutic situation for prostate cancer. Although AA increases the survival opportunities of patients with mCRPC, this agent is unfortunately not curative. Ultimately, drug resistance often develops. The phenomenon of cross-resistance among AA, enzalutamide and taxanes has been investigated in recent years (17, 18). Androgen receptor splice variants, namely ARv567 and ARv7, may contribute to resistance to these drugs. Van Soest *et al*. found an impaired efficacy of docetaxel, cabazitaxel and enzalutamide in an abiraterone-resistant cell line, suggesting cross-resistance between taxanes and hormonal agents such as abiraterone and enzalutamide (19). The preclinical evidence for cross-resistance between taxanes and AR-targeting agents may not be consistent with our finding that there was still a response rate of 37.5% to chemotherapy re-challenge in the AA non-responsive group. The efficacy of chemotherapy re-challenge in patients, especially those who are non-responsive to AA, may require further exploration.

Zhang *et al*. reported clinical cross-resistance in men with mCRPC who had disease progression during AA treatment. The cross-resistance appeared more frequently with enzalutamide and less in docetaxel-treated groups (16). This finding suggests that patients whose disease is initially resistant to AA and who have a PSA response during subsequent docetaxel treatment may have a different (non–AR-related) mechanism of resistance to AA or enzalutamide. Thus, this coincides with the result of our study that the response rate to docetaxel was significantly higher in the AA non-responsive group.

The treatment strategy for mCRPC has been discussed in several studies (20-22), but the optimal sequencing of these innovative therapies remains unclear. The re-challenge of docetaxel at occurrence of PD after AA showed that in order to maintain antitumor activity in mCRPC in selective patients, a valid treatment option for patients with favorable response to first-line docetaxel may be required (23).

Although the nature of our study and the small number of patients did not allow for definitive conclusions, our study provides evidence for the clinical benefit of subsequent chemotherapy re-challenge in docetaxel/cabazitaxel pre-treated patients mCRPC with disease progression after AA treatment.

In summary, for docetaxel/cabazitaxel-pre-treated patients with mCRPC who suffer from PSA progression after AA, subsequent therapy with chemotherapy re-challenge or enzalutamide application may contribute to a better survival benefit. Our findings may also provide the basis for

management of sequential therapy in the terminal stage of prostate cancer.

In addition to a retrospective setting, other limitations of this study were a small sample size and the treatment protocol, while the follow-up schedule, PSA check-up schedule and other variables were not well controlled. The performance of subsequent treatment may also have been biased due to preference or burden considerations.

Conclusion

In our small retrospective patient experience, effectively sequential treatments for patients with mCRPC provided an overall survival benefit. Previous treatment response can act as a clinical predictor for subsequent treatment.

Human Ethical Statement

Certification of approval with IRB: CE13240A-2.

Conflicts of Interest

None of the contributing Authors have any conflict of interest, including specific financial interests or relationships and affiliations, relevant to the subject matter or materials discussed in the manuscript.

Conflict of Interests

The Authors declare that they have no competing interests in regard to this study.

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