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Changes in prostate-specific antigen kinetics during androgen-deprivation therapy as a predictor of response to abiraterone in chemonaïve patients with metastatic castration-resistant prostate cancer

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Purpose: Metastatic castration-resistant prostate cancer (mCRPC) has a poor prognosis. Abiraterone acetate (AA), enzalutamide, and chemotherapy are first-line treatments for patients with mCRPC. This study examined prognostic factors for AA response in the form of prostate-specific antigen (PSA) kinetics throughout androgen-deprivation therapy (ADT) in chemonaïve patients with mCRPC.

Materials and Methods: We retrospectively included data from 34 chemonaïve patients with mCRPC who had received AA at some point between January 2017 and December 2018. We separated patients into two study arms according to the decrease in PSA percentages after use of AA for 3 months. We correlated PSA kinetics parameters with response and compared the two study groups with respect to PSA kinetics.

Results: The patients' median age was 77 years. In the total group of patients, 64% had a response to AA, whereas 35% did not. The ratio of the PSA level at nadir to the level during ADT was significantly higher in the AA-sensitive group (19.78 vs. 1.03, p=0.019).

Conclusions: Patients who experienced a dramatic change in PSA level during ADT were more likely to be resistant to AA after progression to mCRPC. Chemotherapy rather than AA might be more suitable as a first-line treatment for these patients.

Keywords: Nonsteroidal anti-androgens; Prognosis; Prostate-specific antigen; Prostatic neoplasms

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INTRODUCTION

An estimated 15% of men will be diagnosed with prostate cancer at some point in their lives [1]. Androgen-deprivation therapy (ADT) has been used to treat patients with hormone-sensitive prostate cancer (HSPC) since 1941 [2]. With efficient ADT, androgen receptor (AR) activity can be suppressed to under castration levels. However, patients receiving ADT inevitably progress to castration-resistant prostate cancer (CRPC) [3]. CRPC has a poor prognosis with an overall survival rate of 13.2 and 24.2 months if distant metastases appear and do not appear, respectively [4]. Historically, chemotherapy with docetaxel was considered the first-line treatment for CRPC [5]. However, the efficacy of next-generation AR target therapy was proven to not be inferior to that of docetaxel. The most common androgen receptor-targeted agents (ARTAs) used in AR target therapy are abiraterone acetate (AA) and enzalutamide. Treatment with AA, which inhibits CYP17A activity [6] and blocks androgen synthesis, was demonstrated to be effective in patients with CRPC in the COU-AA-302 trial [7]. According to guidelines from the National Comprehensive Cancer Network, an American alliance of cancer centers [8], first-line treatment for patients with metastatic CPRC (mCRPC) includes the administration of chemotherapy and an ARTA.

Whether chemotherapy or ARTAs are most effective in treating CRPC is still a topic of debate. One study by the Mayo Clinic in 2020 suggested that a treatment sequence of chemotherapy followed by an ARTA may lead to a better survival rate [9]. However, because chemotherapy produces negative adverse effects, many practitioners are accustomed to first administering an ARTA for chemonaïve CRPC patients, especially for those who are in poor general condition and have poor bone marrow reserve [10]. In the COU-AA-302 trial, AA treatment was demonstrated to improve the overall survival rate of chemonaïve patients with mCRPC to 34.7 months [7]. However, reports have indicated that 22% of patients have a poor response to AA [11], and patients who respond poorly to an ARTA have poorer overall survival than do patients who respond well [12].

Data suggest that parameters and nomograms of prostate-specific antigen (PSA) kinetics may predict overall survival of patients with CRPC. Studies have concluded that half-time start of ADT to nadir [13], initial PSA level [14], time to PSA nadir [13,14], PSA level at nadir [13,14], duration of nadir, and PSA doubling time from nadir to diagnosis of CRPC [13] are prognostic factors. However, few markers exist that can aid in predicting whether patients with CRPC will have a good response to AA.

Given that PSA kinetics is the most commonly used parameter in predicting overall survival of CRPC patients, we hoped to determine whether PSA kinetics could also be used to predict patient response to AA. We hypothesized that whether a patient responded poorly to AA could be predicted by the change in their PSA kinetics at any point during primary ADT at the HSPC stage.

MATERIALS AND METHODS

1. Patient selection

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, Linkou, Taiwan (IRB no. 202100200B0). The informed consent was waived by the board due to retrospective design. The study population comprised consecutive patients treated with an ARTA for CRPC at our institution at some time between January 2017 and December 2018. The enrolled patients had histologically confirmed prostate adenocarcinoma. ADT was performed with either medical or surgical castration. Patients without distant lymph node metastases or distant solid organ metastases were ruled out from this study.

PSA was assessed from baseline to the end of our study at an interval of approximately 3 months. The eligibility criteria for CRPC accorded with the guidelines developed by the Prostate Cancer Trial Working Group 2. The criteria were an increase in the PSA level of 25% or more and an absolute increase of 2 ng/mL from nadir for two consecutive follow-ups [15], the presence or absence of PSA progression in new bone metastasis, and serum testosterone levels of less than 40 ng/dL. The endpoint of these trials was the proportion of patients achieving a decrease in PSA of ≥50% from baseline to 12 weeks after ARTA use. The enrolled patients had a traceable Gleason score, prostate cancer progression to CRPC status (either with or without having undergone radical prostatectomy), and AA as their chosen treatment for CRPC. Patients were excluded if they underwent chemotherapy for first-line treatment of CRPC, were deemed to have incomplete clinical data on review, or did not undergo AA treatment owing to adverse effects. In total, 34 patients with CRPC were included in the study.

We separated the patients into two groups, the AA-sensitive group and the AA-resistant group. Sensitivity to AA was defined as follows: after use of AA for 3 months, the PSA value declined >50% from the PSA value at the start of AA treatment. Resistance to AA was defined as follows: after use of AA for 3 months, the PSA value declined <50% or even increased from the PSA value at the start of AA treatment.

2. Treatment and retrieval of follow-up data

The participants' clinical parameters were retrospectively reviewed using the electronic medical record system of Chang Gung Memorial Hospital. The parameters that were retrieved were laboratory data (including hemoglobin, white blood cell count, platelet count, albumin, lactate dehydrogenase, and alkaline phosphatase) and dated PSA data that were recorded throughout the treatment period. Parameters on PSA kinetics were calculated with consideration of the following: PSA level at the beginning of ADT, amount of time to nadir, PSA level at nadir, length of time from beginning of ADT to progression, and PSA level at the time of AA introduction. Gleason scoring followed the revised criteria. Tumor node metastasis staging of tumors was conducted according to the standards of the American Joint Cancer Committee.

PSA kinetics were defined by the following:

1. PSA value on ADT (in ng/mL; the PSA value before initial ADT)
2. PSA value at nadir (in ng/mL; the minimum PSA value during ADT)
3. Decline ratio at ADT (in ‰; nadir PSA value/baseline PSA value×1,000)
4. Time to PSA nadir (in months; the length of time from baseline to PSA nadir)
5. Time to progression (in months; length of time from initial ADT to day of PSA progression according to the PCWG2 criteria)
6. Velocity at start of ADT (in ng/mL/y; decrease in PSA level/duration of examination at start of ADT)
7. PSA level on CRPC (in ng/mL; PSA value on the day of PSA progression according to the PCWG2 criteria)

These parameters are illustrated in Fig. 1.

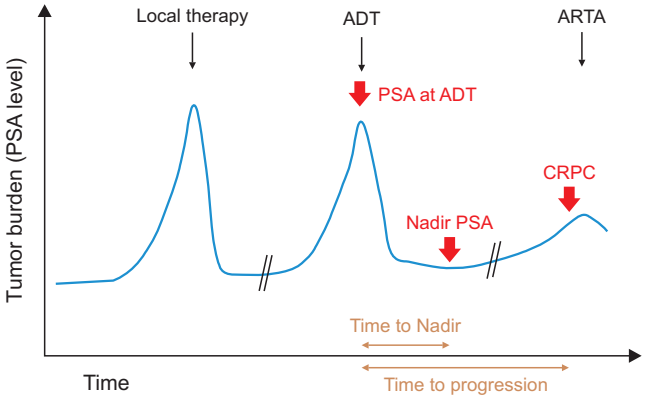

Fig. 1. Prostate-specific antigen (PSA) kinetics. ADT, androgen-deprivation therapy; ARTA, androgen receptor-targeted therapy; CRPC, castration-resistant prostate cancer.

3. Statistical analysis

Patient demographics, baseline characteristics, and PSA kinetics were descriptively summarized using the mean, standard deviation, and percentage. To test the difference between the AA response and AA resistance groups, a chi-square test, Mann–Whitney U-test, and t-test were used. Multivariate testing was done with Probit regression models. A p-value of <0.05 was considered significant. IBM SPSS

Table 1. Patients' general characteristics

Characteristic	Number or mean±standard deviation	Range
Total	34	-
HSPC to CRPC duration[a], mo	38.63±27.83	4.26–129.4
Age at the start of AA, y	77.05±9.41	56–97
Initial PSA, ng/mL	704.5±1,044	12–5,598
Alkaline phosphatase after ADT, U/L	191.45±406.28	47–1,976
Hemoglobin, g/dL	11.83±1.95	7.8–16.8
Platelet count, ×1,000/μL	202.86±50.5	119–317
White blood cell count, /μL	6,573.3±1,625.8	3,800–9,600
Neutrophil count, /μL	4,432.1±1,533.9	1,470–7,012
Lymphocyte count, /μL	1,503.4±583.67	419–2,774
Albumin, g/dL	3.73±0.58	2.59–4.52
Testosterone at diagnosis of CRPC, ng/mL	0.149±0.075	0.01–0.33
First ADT method		
Orchiectomy	6	17.7%
Leuprorelin	23	67.6%
Goserelin	4	11.8%
Degarelix	1	2.9%
ISUP grade		
1	2	-
2	0	-
3	4	-
4	7	-
5	21	-
Tumor staging		
T stage		
T2	4	-
T3	12	-
T4	15	-
N stage		
N0	9	-
N1	21	-
M stage		
M0	3	-
M1	29	-

HSPC, hormone-sensitive prostate cancer; CRPC, castration-resistant prostate cancer; AA, abiraterone acetate; PSA, prostate-specific antigen; ADT, androgen-deprivation therapy; ISUP, International Society of Urologic Pathologists; -, not significant.

[a]:Period of starting of ADT to diagnosis of CRPC status.

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Statistics, version 24.0 (IBM Corp., Armonk, NY, USA), was used for all analyses.

RESULTS

1. Clinical characteristics

A total of 34 patients with prostate adenocarcinoma were included in the study. The general clinical data for the patients are summarized in Table 1. The median age of the patients receiving AA treatment was 77 years (range, 56–97 years), and 6 patients (17.7%) achieved castration levels by undergoing bilateral orchiectomy. Others (n=28, 82.3%) achieved castration levels by medication (luteinizing hormone–releasing hormone agonist or antagonist). The length of time from diagnosis with HSPC to diagnosis of CRPC was approximately 3.2 years (38.63 months).

A comparison of the two arms of this study is presented in Table 2. No significant differences were noted with re-

Table 2. Characteristics between two groups (n=34)

Characteristic	AA sensitive	AA resistant	Univariate analysis	
			95% CI for Exp(B)	p-value
Initial PSA, ng/mL	621.54±614.4	870.6±1,628	-1,042, 544.6	0.527
Age at the start of AA, y	76.95±10.10	77.25±8.42	-7.28, 6.69	0.93
Extent of metastasis[a]	13.22±14.33	11.08±15.19	-8.55, 12.84	0.686
Blood laboratory test				
Hemoglobin, g/dL	11.69±1.755	12.09±2.35	-1.91, 1.12	0.598
Albumin, g/dL	3.806±0.533	3.637±0.672	-0.43, 0.77	0.561
Alkaline phosphatase before ADT, U/L	294.5±337.6	246.7±399.5	-348, 444	0.8
Alkaline phosphatase after ADT, U/L	265.9±522.6	83.88±39.37	-184, 548	0.313
Platelet count, ×1,000/μL	187.8±42.79	227.4±54.38	-76.8, -2.38	0.038*
ISUP grade				0.231
1	2	0	-	
2	0	0	-	
3	4	0	-	
4	5	2	-	
5	11	9	-	
LATITUDE definition of tumor volume				0.61
High volume	9	6	-	
Low volume	13	6	-	

Values are presented as median±standard deviation or number only.
AA, abiraterone acetate; CI, confidence interval; PSA, prostate-specific antigen; ADT, androgen-deprivation therapy; ISUP, International Society of Urologic Pathologists; -, not significant.
[a]:Number of bony metastasis spots based on bone scan study.
*Correlation is significant at the 0.05 level (2-tailed).

Table 3. PSA kinetics characteristics in patients with metastatic castration-resistant prostate cancer

Characteristic	AA sensitive	AA resistant	Univariate analysis		Multivariate analysis[a]	
			95% CI for Exp(B)	p-value	95% CI for Exp(B)	p-value
PSA kinetics following ADT	22	12	-	-	-	-
PSA value on ADT, ng/mL	516.54±628.32	1,222.34±1,778.87	-1,992, 581	0.25	-	-
Decline ratio at ADT, ‰	19.78±37.34	1.03±1.29	3.32, 34.11	0.019*	-2.068, -0.77	0.035*
PSA value at nadir, ng/mL	8.35±34.79	0.94±1.99	-16.5, 31.3	0.532	-0.014, 0.005	0.449
Time to PSA nadir, mo	12.41±7.55	16.78±10.26	-11.07, 2.34	0.194	-0.079, 0.085	0.943
Time to progression, mo	32.8±13.22	48.42±38.07	-4,348, 4,340	0.234	-0.955, 0.118	0.126
Velocity at start of ADT, ng/mL/y	-785.1±974.6	-1,114±1,966.3	-631, -1,291	0.491	-	-
PSA level on CRPC, ng/mL	146.43±439.84	30.06±55.42	-281.9, 749	0.363	-	-

Values are presented as number only or median±standard deviation.
PSA, prostate-specific antigen; AA, abiraterone acetate; CI, confidence interval; ADT, androgen-deprivation therapy; CRPC, castration-resistant prostate cancer.
[a]:Multivariate analysis was done with Probit regression models.
*Correlation is significant at the 0.05 level (2-tailed).

spect to laboratory data, such as albumin and alkaline phosphatase levels, between the AA-sensitive and AA-resistant groups. A hemogram revealed no significance. However, platelet counts in the AA-resistant group were higher than in the AA-sensitive group (227.4 vs. 187.8, p=0.038).

2. PSA kinetics parameters

The PSA kinetics of patients with mCRPC are presented in Table 3. Patients in the AA-resistant group had a significantly lower decline ratio than those in the AA-sensitive group (19.78 vs. 1.03, p=0.019). Multivariate analysis with PSA kinetics parameters showed also that the AA-resistant group had a significantly lower decline ratio. Other predictive factors remained nonsignificant in the multivariate analysis. As indicated in a tendency chart for both groups in Fig. 2, the ratio of ADT-induced decline was reflected in the decrease in PSA levels after the initial stages of ADT. The detailed statistical results of PSA kinetic difference between AA-resistant and AA-sensitive group was listed in Supplementary Table.

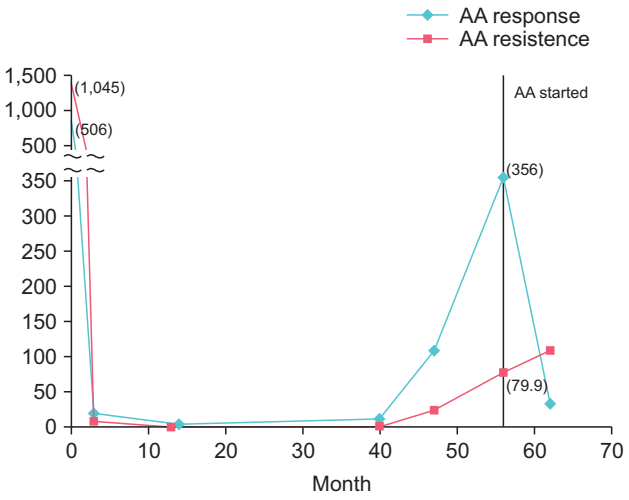

Fig. 2. Changes in prostate-specific antigen (PSA) in the two groups. AA, abiraterone acetate.

DISCUSSION

The optimal sequence of treatment of CRPC including chemotherapy and an ARTA is debatable. Generally, for individuals who are suitable candidates for both chemotherapy and treatment with an ARTA, docetaxel may serve as a first-line treatment [9]. However, not all patients can withstand the adverse effects of chemotherapy. In those patients, an ARTA is the preferred treatment. Many patients are chemonaïve and ARTA-naïve at the time of diagnosis of CRPC. In these patients, the choice of first-line agent and the treatment sequence that follows is imperative owing to cross-resistance between both different ARTAs [16] and docetaxel and ARTAs [17].

The PSA level has been used to determine overall survival rates in patients with CRPC. To evaluate overall survival and cancer-free survival rates of patients with CRPC, PSA kinetics and other laboratory parameters have been demonstrated to be good prognostic factors. A recent study showed that shorter time to nadir represented poor prognosis with earlier progression to CRPC if the nadir did not go under 0.64 ng/mL. However, complete response to ADT with a PSA nadir below 0.64 ng/mL still has the best prognosis regardless of length of time to nadir [18]. This indicates that if a patient's nadir does not decrease to undetectable levels, their response to ADT takes longer and a better prognosis can be observed. This observation led us to ask whether we could predict patient response to ARTA treatment by observing changes in PSA kinetics during ADT. However, the lack of data on risk factors before treatment hindered our evaluation of the efficiency of ARTA treatment.

Antonarakis et al. [19] suggested that levels of androgen receptor splice variant 7 (AR–V7) in circulating tumor cells are a potentially informative pretreatment prognostic marker. However, using circulating tumor cells is not cost-effective and is time consuming.

No previous studies have presented data supporting changes in PSA kinetics in patients with ADT status as a predictor of response to ARTA treatment in patients with CRPC. In this study, we concluded that the ratio of the decrease during ADT is associated with further response to treatment with an ARTA. During the HSPC phase, patients in the AA-resistant group had a higher PSA decline ratio after initial ADT than those in the AA-sensitive group. This signifies that the AA-resistant group had a more dramatic decline in PSA at the beginning of ADT. We also evaluated the LATITUDE study's high-risk classification; however, it was not significantly associated with response to an ARTA. These results indicate that high-risk patients may not respond strongly to further treatment with an ARTA when their condition has progressed to CRPC. To our knowledge, ours is the first study to identify the decrease in PSA ratio as a prognostic factor of ARTA responsiveness.

The mechanisms underlying resistance to ARTAs entail three explanations. First, prostate cancer is a high-heterogeneity tumor. Tumor cells might originate from a single cell. However, after oncogenic activity, the origin cell is transformed into a cancer cell [20]. AR-indifferent cells might lead to the suppression of AR-sensitive cell lines. The second factor that may explain the PSA decline ratio as a prognostic factor of ARTA responsiveness is AR-driven activity. AR-

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driven activity generally centers on AR genome alteration [21]. The alteration of AR genomes gives rise to the formation of AR variants, which commonly lack the C-terminal binding domain [21]. Furthermore, androgen receptor-splicing variants bypass AR signals and are, therefore, often continuously activated [21]. The well-known subtype AR-V7 is considered to be a predictor of prognosis in CRPC before ARTA use [22]. AR-V7 can be found in 75% of patients with CRPC [23]. Although the underlying mechanism is unknown, the proportion of AR-V7 increases after ADT in patients with HSPC [23].

The final factor is the presence of a non-AR-driven phenotype. A non-AR-driven phenotype involves prostate cancer transforming into another phenotype that is indifferent to ARTA treatment. This process is referred to as 'prostate lineage plasticity'. This state allows cells to transform from a luminal epithelial phenotype to other phenotypes [24]. Tumor cells in prostate cancer can take on a stem cell–like function either through a cancer stem cell (CSC) model or through an epithelial-mesenchymal transition (EMT) model. In a CSC model, tumor cells can dedifferentiate to stem cell-like cancer cells [25]. An EMT model is more important in prostate linear plasticity because it promotes tumorigenesis [26] and increases migratory properties [27]. Prostate adenocarcinoma can transdifferentiate to neuroendocrine prostate cancer (NEPC) tumor cells when a patient receives ADT by EMT [28].

According to our study, a high ratio of PSA decline indicated a large portion of prostate tissue death or latency. Local inflammation and oxidative stress triggered by prostate tissue death may induce hypoxia-inducible factor-1α and lead to NEPC transformation. These transformations lead to a phenotype of treatment-induced small-cell NEPC [28]. After patients receive ADT, the tumor consists of mixtures of adenocarcinoma and neuroendocrine cells. The NEPC phenotype has several characteristics: first, it has a greater prevalence of visceral and osteolytic metastases. Second, it produces lower PSA levels, leading to a slower progression of PSA levels. Third, it has resistance to AR pathway inhibitors, which are included in ADT and ARTA treatment [29]. Fourth, it has pathophysiology similar to that of a pure neuroendocrine tumor, including small-cell pathological features observed on biopsy and an increase of neuroendocrine serum markers (such as neuron-specific enolase or chromogranin A) [28].

The three aforementioned mechanisms of resistance to ARTAs may all occur in cases of CRPC, resulting in nonresponse to an ARTA. In addition, an EMT-causing NEPC phenotype may be the most important mechanism. The findings of a similar study support the argument that a dramatic change while undergoing ADT indicates a poor prognosis [30]. Ji et al. [30] found that a higher rate of PSA decline is associated with poorer outcomes in chemonaïve and ARTA-naïve CRPC patients. We can conclude from our findings that a dramatic change in PSA over the course of ADT entails a poorer prognosis. Our findings further imply that if the patient has a dramatic change in PSA over the course of ADT, the patient may be more likely to be indifferent not only to ADT but also to ARTA treatment.

The present study has several limitations. First, the investigation of overall survival was inappropriate owing to the small sample size and limited number of events. Although evidence exists that links (1) PSA kinetics to overall survival rates and (2) early sensitivity to ARTA to overall survival rates, our findings do not link established prognostic factors, such as time to nadir and level of nadir corresponding to response to ARTA treatment. This might be due to the insufficiently large sample sizes. However, studies must further investigate whether the risk factors for overall survival are the same as the risk factors for response to ARTA. Our study was further limited owing to an insufficiently large sample size. As a result, the multivariate analysis had only one significant factor. Additionally, in real-world practice, many factors may affect PSA kinetic profiles, such as patient conditions, prior therapies, and concomitant use of drugs. Finally, although many studies have reported a rapid decrease of PSA while the patient was undergoing ADT, this form of treatment might induce an NEPC phenotype, causing resistance to ARTA treatment. The present study cannot provide direct evidence that the large ratio of decline causes greater prostate plasticity. Further workup may be included in the prostate biopsy in both the resistant group and the responsive group to furnish evidence that NEPC was prevalent in the resistant group.

CONCLUSIONS

A high ratio of decline of PSA during ADT could be a clinical indicator of nonresponsiveness to AA in patients with CRPC. Closer monitoring of PSA values and a sequence of chemotherapy followed by treatment with an ARTA may improve prognosis in these patients.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Chung-Lin Lee and I-Hung Shao. Data acquisition: Chung-Lin Lee and Ying-Hsu Chang. Statistical analysis: Chung-Yi Liu and Ming-Li Hsieh. Data analysis and interpretation: Liang-Kang Huang and Yuan-Cheng Chu. Drafting of the manuscript: Hung-Cheng Kan and Po-Hung Lin. Critical revision of the manuscript: Chun-Te Wu and See-Tong Pang. Obtaining funding: I-Hung Shao. Administrative, technical, or material support: I-Hung Shao and Chun-Te Wu. Supervision: Cheng-Keng Chuang and Kai-Jie Yu. Approval of the final manuscript: I-Hung Shao and Chung-Lin Lee.

SUPPLEMENTARY MATERIAL

Supplementary material can be found via https://doi.org/10.4111/icu.20210450.

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