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Abiraterone Acetate and Enzalutamide: Similar Efficacy in Treating Post Docetaxel Metastatic Castration-resistant Prostate Cancer: Single Center Experience

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Abstract. *Background/Aim: Abiraterone (AA) and enzalutamide (ENZ) were introduced in Taiwan since 2012 for the treatment of patients with post-docetaxel metastatic castration-resistant prostate cancer (mCRPC). This study aims to retrospectively compare the efficacy of the two regimens. Materials and Methods: The study cohort consisted of 77 mCRPC patients previously treated with docetaxel and subsequently with AA (n=63, the AA group) or ENZ (n=13, the ENZ group), all treated in our hospital. Clinical parameters of the two groups were compared to determine differences between pre-treatment variables and treatment outcomes. Results: Sixty-four patients received AA and 13 received ENZ, with a median 18.2 vs. 14.5 months follow-up (p=0.434). Prostate-specific antigen (PSA) response >50% was 31 (48.4%) in AA and 9 (69.2%) in ENZ (p=0.171), while PSA response >90% was 16 (25%) in AA and 5 (38.5%) in ENZ (p=0.32). The median progression-free survival (PFS) was 7.3 (95%CI=4.796-9.804) months in AA and 9.5 months (95%CI=5.743-13.257) in ENZ (p of log rank=0.766). The median overall survival (OS) from second-line hormone treatment was 30.2 months in AA group and 16.2 months in ENZ group (p of log rank=0.734). Neither the uni- nor the multi-variate COX-regression analysis distinguished any advantage of the two-drug regimen in terms of PFS or OS. Metastasis volume (HR=3.032, 95%CI=1.281-7.178, p=0.012) and nadir PSA (HR=1.000, 95%CI=1.000-1.001, p=0.010) were shown as independent risk factors for the survival of AA/ENZ-treated patients. Conclusion: AA and ENZ had a similar efficacy in treating post-docetaxel mCRPC patients. Metastatic volume and nadir PSA were independent risk factors of these patients in predicting their disease-specific survival and overall survival.*

Human ethical statement: certification of approval with IRB: CE13240A-2

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Key Words: Abiraterone acetate, enzalutamide, metastatic castration-resistant prostate cancer, prostate-specific antigen (PSA) progression.

Metastatic prostate cancer accounts for nearly 30% of newly diagnosed prostate cancers in Taiwan (1). Currently the standard protocol for treatment is a sequence involving androgen deprivation therapy (ADT), chemotherapy, and medication with androgen receptor signaling inhibitors (2). Abiraterone acetate (AA), a selective inhibitor of cytochrome CYP17 that blocks androgen synthesis in the adrenal gland, testis and prostate tumor (3), has demonstrated therapeutic efficacy in treating chemo-naïve or post-chemotherapy metastatic castration-resistant prostate cancer (mCRPC) (4, 5). Enzalutamide (ENZ), an androgen-receptor inhibitor that blocks the translocation of androgen-receptor to cell nucleus and its binding with DNA (6), has also proven efficacy in both setting of mCRPC with AFFIR and PREVAIL trial (7, 8).

Docetaxel, AA, and ENZ are often used to treat mCRPC at different courses of the disease, and all have tolerable side effects along with convenient outpatient therapy (4, 5, 7, 8). Determining the best treatment sequence is a challenge for clinicians. However, no large-scale clinical trial has yet been

done to directly compare treatment efficacies of AA and ENZ. In the post-chemotherapy setting, COU-AA-301 trial reported 10.2 months of progression-free survival (PFS) and 14.8 months of overall survival (OS), with a response rate of 38.0% (4). In contrast, the AFFIRM trial showed a PFS of 8.3 months and OS of 18.4 months, with a 54% response rate (8). One retrospective study suggested that in treating chemo-naïve mCRPC, AA has a more favorable outcome for PFS but not OS, when compared with ENZ (9). Conflicting results were, however, reported in another meta-analysis study, which suggested that in treating chemo-naïve mCRPC, ENZ, rather than AA, yields a better PFS, while finding no difference between the two drugs in the post-chemo setting (10). Cross resistance may exist in mCRPC patients. For example, ENZ shows antitumor effects after AA fails, while AA has less antitumor effects after ENZ fails (11-13). Both AA and ENZ, with similar action target for mCRPC (*i.e.*, the androgen-signaling pathway), have demonstrated clinical benefits, treatment efficacy and adverse effect tolerability in chemo-naïve, as well as in post-chemotherapy settings. Only the additional use of prednisolone, if applicable, would be another factor to consider in the choice between AA and ENZ for the treatment (14).

Herein, we conducted a retrospective study and clinical investigation to determine the treatment efficacy of AA and ENZ in post-docetaxel mCRPC patients and validated several clinical factors correlated with PFS and OS before treatment.

Patients and Methods

Patients. From April 2012 to January 2018 we studied a total of 77 mCRPC patients under treatment at Taichung Veteran General Hospital. They all had prior treatment-failure with docetaxel. Other patients who had been treated with carbazitaxel or other chemotherapy were excluded. Of these 77 patients, 64 subsequently received AA (the AA group) and 13 received ENZ (the ENZ group). Treatment regimens were (a) AA: 1,000 mg plus prednisolone 5 or 10 mg once daily or (b) ENZ: 160 mg, in combination with persisted ADT. Written informed consents were obtained from each patient before study. Our protocol was approved by the Institute Review Board of Taichung Veterans General Hospital, number CE13240A-2.

Clinical-pathological evaluation. The development of mCRPC was characterized based on imaging studies, and the metastasis of disease was confirmed by computer tomography (CT) or bone scan, as well as the following indications: a continuous rise of serum prostate-specific antigen (PSA) levels, the progression of pre-existing disease, and/or the appearance of new metastases under castration levels of testosterone (<50 ng/dl). Metastatic volume was categorized and defined by the presence of visceral metastases, or ≥4 bone lesions with ≥1 locations outside the vertebral bodies and pelvis. The end-point evaluation was PSA progression, as defined according to the criteria outlined in the Prostate Cancer Working Group second publication (PCWG2): *i.e.*, first PSA increase that is ≥25% and ≥2 ng/ml above the nadir, and which is confirmed by a second value ≥3 weeks later (15) and OS, defined as all cause deaths.

Statistical analysis. The Mann-Whitney *U*-test and Fisher's exact *t*-test were used for comparing continuous variables, and χ^2 test was used for categorical variables. Kaplan-Meier survival curve with log-rank test was used to evaluate the OS and for inter-group comparisons. All statistical tests were done using IBM SPSS version 22 for Windows (SPSS, Chicago, IL, USA), and *p*-values <0.05 were considered significant differences.

Results

Median age for each group was 67.5 years old (IQR=61.25-73.75) for AA, and 71.0 years old (IQR=60.50-78.50) for ENZ (p=0.718). The median initial PSA were 112.50 ng/ml (IQR 39.73-450.75) for AA, and 284.00 ng/ml (83.49-723.85) for ENZ (p=0.395). Both groups had similar hormone-sensitive periods (AA *vs*. ENZ: 20.00 *vs*. 18.00 months, p=0.718) and docetaxel cycles (AA *vs*. ENZ: 75 mg: 5 *vs*. 6 months, p=0.835; 50 mg: 7 *vs*. 12.5 months, p=0.056).

The group median PSA levels (before AA/ENZ) were 19.52 ng/ml (IQR=16.25-124.38) for AA, and 8.42 (IQR=1.17-24.81) for ENZ (p=0.242). High volume metastases were similar in the two groups (54.70% for AA, and 61.50% for ENZ, p=0.65). After medication, PSA levels declined to 36.95% in the AA group and 77.79% in the ENZ group (p=0.103). Although PSA response rate appeared better in the ENZ group, the inter-group difference was not statistically significant (AA *vs*. ENZ: PSA response >50%: 48.40% *vs*. 69.20%, p=0.171); PSA response >90%: 25% *vs*. 38.5%, p=0.320) (Table I, Figure 1).

Among all patients, 57 in the AA group suffered from PSA progression compared to 9 in the ENZ group (Figure 2A). The median time to PSA progression was 7.3 months for AA, and 9.5 months for ENZ. Figure 2B shows temporal changes of their overall survivals. Among all patients, 29 in the AA group and 6 in the ENZ group expired (with the median duration to OS at 30.2 months for AA, and 16.2 months for ENZ).

Cox regression and multivariate adjusted harzard ratio (HR) model was further used to evaluated the risk of PFS and OS. After multivariate adjustment, hormone sensitive period (HR=0.989, 95%CI=0.978-1.000, p=0.046), high volume metastasis (HR=2.431, 95%CI 0.372-4.308, p=0.002), and nadir PSA after drug (HR=1.000, 95%CI=1.000-1.001, p=0.020) were independent risk factors of PSA progression after second line hormone therapy (Table II). Furthermore, high volume metastasis (HR=3.032, 95%CI=1.281-7.178, p=0.012) and nadir PSA after the medication (HR=1.000, 95%CI=1.000-1.001, p=0.010) were independent risk factors of overall survival after second line hormone therapy (Table III).

Adverse events of medication are summarized in Table IV. Two patients in the AA group were withdrawn before the end of study due to Grade 3/4 liver function impairment, and two in the ENZ group had withdrawn due to Grade 3/4 fatigue. No seizure was observed in any of the patients.

Table I. B*asic characteristics of patients who received abiraterone acetate and enzalutamide*.

		Abiraterone (n=64)		Enzalutamide (n=13)		
		Median or n	(IQR) or %	Median or n	IQR or %	*p*-Value
Age		67.5	(61.25-73.75)	71,00	(60.50-78.50)	0.718
Performance status (ECOG)	1	(0-1)	1	(0-1)	0.988	
Hypertension		31	48.4	6	46.2	0.881
Diabetes		11	17.2	3	23.1	0.616
Coronary artery disease		8	12.5	1	7.7	0.623
Radical prostatectomy		10	15.6	1	7.7	0.456
Radiation therapy		16	25,00	2	15.4	0.455
Initial PSA		112.5	(39.73-450.75)	284	(83.49-723.85)	0.395
Gleason score		9	(7-9)	9	(8-9.5)	0.438
Hormone therapy period		20	(10-38.5)	18	(10.50-34.50)	0.718
Metastasis	Viseral	13	20.3	3	23.1	0.823
	Lung	7	10.9	2	15.4	0.649
	Liver	2	3.1	1	7.7	0.438
	Bone	64	100	13	100	
	High volume	35	54.7	8	61.5	0.650
	Low volume	29	45.3	5	38.5	
Taxotere	Age	72.5	(64.25-79.00)	72,00	(62.50-80.50)	0.849
	Hb	12,00	(10.30-12.60)	12.85	(11.75-13.48)	0.063
	Albumin	4.1	(3.80-4.30)	4.1	(4.0-4.1)	0.563
	Alk-P	118,00	(86.25-273.00)	156,00	(135.50-374.00)	0.224
	LDH	216,00	(190.00-253.00)	228,00	(205.00-296.50)	0.448
	PSA before drug	27.48	(9.34-119.75)	17.14	(8.27-82.05)	0.422
	Best PSA	9.98	(3.58-54.27)	7.7	(2.85-18.57)	0.523
	PSA decline (%)	–57.26	(–86.68- –8.85)	–26,00	(–89.13-5.39)	0.967
	PSA response	46	71.9	10	76.9	0.709
	PSA response >50%	33	51.6	6	46.2	0.722
	PSA response >90%	13	20.3	3	23.1	0.823
	Taxotere 75mg	53	82.8	9	69.2	0.260
	Cycle	5	(3-9)	6	(2.75-8.25)	0.835
	Taxotere 50mg	11	17.2	4	30.8	0.260
	cycle	7	(3.3-9.3)	12.5	(8.5-20.25)	0.056
2nd line hormone therapy	Age	74,00	(65.00-80.00)	74,00	(64.00-82.00)	0.935
	Hb	11.1	(10.08-12.20)	12,00	(9.95-12.70)	0.301
	Albumin	3.7	(3.38-4.20)	3.6	(3.5-3.6)	0.953
	ALK-P	129,00	(79-209.5)	120,00	(94.00-221.00)	0.612
	LDH	257,00	(191.50-319.50)	228,00	(172.00-293.00)	0.823
	PSA before Drug	45.3	(16.25-124.38)	24.38	(8.85-90.42)	0.242
	Best PSA	19.52	(3.18-92.85)	8.42	(1.17-24.81)	0.133
	PSA decline (%)	–36.95	(–90.29-78.69)	–77.79	(–93.44 - –15.96)	0.103
	PSA response	35	54.7	10	76.9	0.138
	PSA response >50%	31	48.4	9	69.2	0.171
	PSA response >90%	16	25,00	5	38.5	0.320
	Drug Duration	7.5	(3.25-18.00)	7	(4.50-9.50)	0.668
Subsequent therapy						
Abiraterone	Number			1		
	Response			0	0,00	
	Best decline (%)			98.72		
	Duration			6		
Enzalutamide	Number	11				
	Response	7	63.6			
	PSA decline (%)	–12.81	81.71			
	Best decline (%)	–99.72				
	Duration	8	6.573			
Docetaxel rechallenge	Number					
	Dosage 75 mg	3		1		
	Dosage 50 mg	0		1		
	Response	1	33.33	2	100,00	
	Best decline (%)	–22.37		–25.33		
Median follow-up time from mCRPC		31.45	(31.6-51.9)	24.9	(20.10-37.35)	0.231
Median follow-up time from 2nd line hormone therapy		18.2	(6.43-26.85)	14.5	(7.85-17.80)	0.434

Continuous variable analysis using the Mann–Whitney *U*-test and Fisher's exact test *t*-test. Categorical variables analysis using the Pearson Chi-Square test. *$p<0.05$. PSA, Prostate-specific antigen; Hb, hemoglobin; Alk-P, alkaline phosphatase; LDH, lactic dehydrogenase; mCRPC, metastastic castration-resistant prostate cancer.

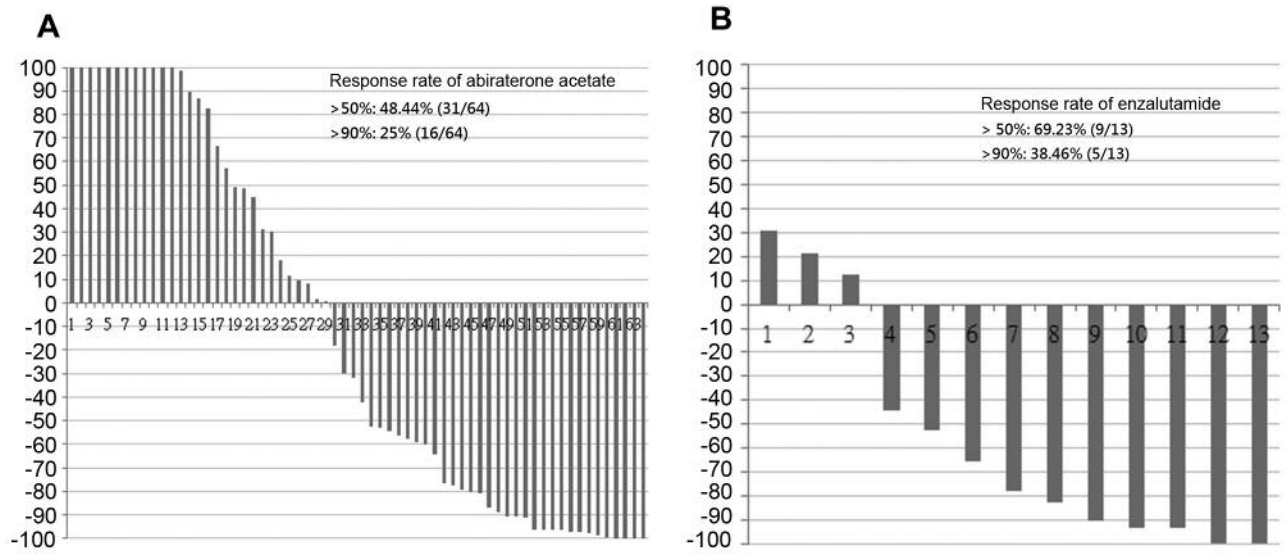

Figure 1. *Response rate of abiraterone acetate (AA) and enzalutamide (ENZ) in mCRPC patients after docetaxel. Bar charts show PSA response rate for each patient in the AA group (A) and the ENZ group (B). PSA response rate >50% was 48.44% and 69.23%, while PSA response >90% was 25% and 38.46 %, in patients receiving AA or ENZ, respectively.*

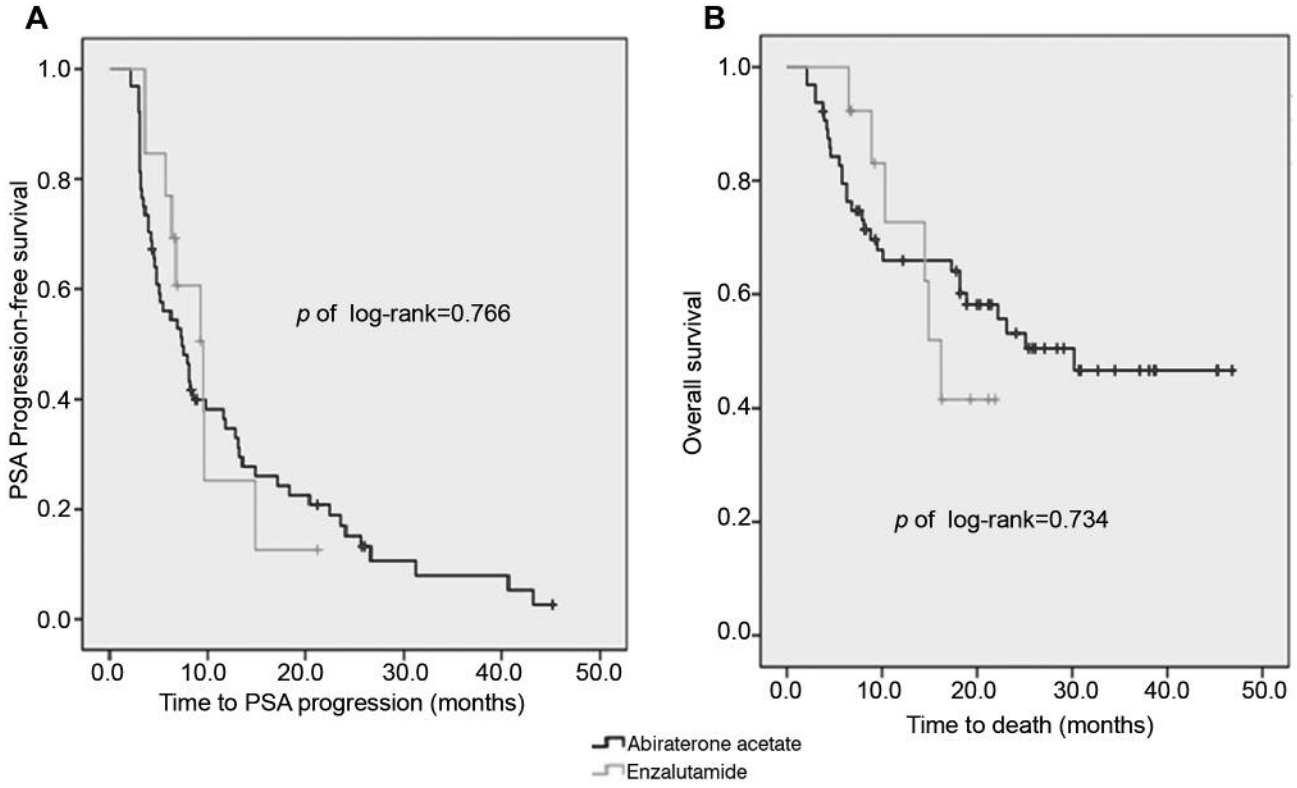

Figure 2. *Prostate-specific antigen (PSA) progression-free survival (PFS) and overall survival (OS) in mCRPC patients treated with abiraterone acetate (AA) or enzalutamide (ENZ) after docetaxel. Median PFS was 7.3 months in the AA group and 9.5 months in the ENZ group (p of log rank=0.766) (A). Median OS was 30.2 months in the AA group and 16.2 months in the ENZ group (p of log rank=0.734) (B).*

Table II. *Univariate and multivariate Cox proportional hazard regression analysis for prediction of disease progression.*

	Univariate analysis		Multivariate analysis	
Covariate	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Performance status	1.329 (0.921-1.917)	0.128		
Age	1.004 (0.973-1.036)	0.813		
Hypertension	1.098 (0.666-1.810)	0.715		
Diabetes	0.839 (0.447-1.575)	0.584		
Coronary artery disease	1.298 (0.613-2.748)	0.495		
Radical prostatectomy	1.513 (0.763-3.000)	0.236		
Radiation therapy	1.204 (0.683-2.122)	0.52		
Initial PSA	1.000 (1.000-1.000)	0.816		
Gleason score	1.158 (0.930-1.443)	0.19		
Hormone sensitive period	0.986 (0.975-0.997)	0.011*	0.989 (0.978-1.000)	0.046*
Metastatic volume				
Low	Reference		Reference	
High	2.793 (1.610-4.845)	0.000*	2.431 (1.372-4.308)	0.002*
Taxotere cycle	0.958 (0.915-1.002)	0.063		
Hb before drug	0.920 (0.792-1.069)	0.275		
Albumin before drug	0.437 (0.093-2.058)	0.295		
Alk-P before drug	1.001 (0.999-1.003)	0.464		
LDH before drug	1.001 (1.000-1.003)	0.133		
PSA before drug	1.001 (1.000-1.001)	0.018*	1.000 (0.999-1.001)	0.897
Nadir PSA after drug	1.000 (1.000-1.001)	0.000*	1.000 (1.000-1.001)	0.020*
2nd line hormone therapy				
Abiraterone	Reference			
Enzalutamide	0.898 (0.439-1.838)	0.769		

Cox regression with multivariate adjustment. *$p<0.05$. HR, Hazard ratio; CI, confidence interval; PSA, prostatic-specific antigen; Hb, hemoglobin; Alk-P, alkaline phosphatase; LDH, lactic dehydrogenase.

Discussion

This study, through data analysis based on retrospective chart reviews in a single medical center, revealed no difference between the efficacy of AA and ENZ in treating mCRPC patients after the docetaxel failure. ENZ, compared with AA, appeared to be slightly better in preserving the PSA response rate and PSA decline, but the differences were not statistically significant in terms of PFS and OS.

Several studies reported that ENZ provides a better PSA response rate and PFS in treating mCRPC patients. Fang *et al*. in a trial-level meta-analysis, showed that OS was increased by 8.3 months in the pre-docetaxel setting, and by 2.2 months in post-docetaxel setting, in ENZ-treated mCRPC patients, compared to the respective AA-groups; however, differences did not reach statistical significance (10). In another network meta-analysis, Kang *et al*. also suggested that ENZ was the most effective agent in improving OS (HR=0.71), and AA seemed to be less effective compared to ENZ (HR=0.78). Such report was however, based on pooled data analysis, and differences between the pre- and post-chemotherapy settings were neglected (16). A pooled data analysis of major phase III clinical trials COU-AA-301, COU-AA-302, PREVAIL and AFFIRM yielded similar but less significant results; particularly it suggested that ENZ may be superior to AA only with respect to radiographic PFS, but not to OS, in both pre- and post- docetaxel settings (17). Consequently, pairwise meta-analysis of randomized controlled trials revealed that the use of novel AR pathway-targeted agents reduced the risk of death as well as the risk of disease progression in 21% and 52% of mCRPC patients, respectively (18).

Cross-resistance between the different regimens in mCRPC has been observed in literature indicating that sensitivity to one compound is impaired by another with a similar or overlapping mechanism of action (19). Moughan *et al*. using a retrospective study, compared the sequences 'AA-to-ENZ' and 'ENZ-to-AA' in mCRPC patients, and found that the former sequence had better PFS (HR=0.37, $p<0.001$) (20). More specifically, response of ENZ after AA failure was higher compared to that of AA after ENZ failure (37% *vs*. 13%) (20). Another study by Terada *et al*., investigated AA-to-ENZ *versus* ENZ-to-AA in Asian CRPC patients and revealed an advantage favoring ENZ in the second-line setting (HR=0.67, $p=0.009$) compared t o AA (21). Similar results were shown in a randomized phase II cross-over study in mCRPC patients, in which first-line ENZ was associated with a better response rate compared to AA, while no difference in time to PSA progression was found (12).

Table III. *Univariate and multivariate Cox proportional hazard regression analysis for prediction of overall survival.*

	Univariate		Multivariate	
Covariate	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Performance status	2.123 (1.262-3.572)	0.005*	1.703 (0.977-2.970)	0.061
Age	1.009 (0.967-1.054)	0.666		
Hypertension	0.914 (0.460-1.816)	0.797		
Diabetes	0.564 (0.198-1.609)	0.284		
Coronary artery disease	1.478 (0.568-3.849)	0.423		
Radical prostatectomy	1.861 (0.801-4.323)	0.149		
Radiation therapy	1.368 (0.633-2.957)	0.425		
Initial PSA	0.999 (0.998-1.000)	0.072		
Gleason score	1.068 (0.787-1.451)	0.672		
Hormone sensitive period	0.989 (0.974-1.004)	0.161		
Metastatic volume				
Low	Reference		Reference	
High	3.776 (1.627-8.764)	0.002*	3.032 (1.281-7.178)	0.012*
Taxotere cycle	0.967 (0.903-1.036)	0.338		
Hb before drug	0.836 (0.679-1.028)	0.089		
Alk-P before drug	0.998 (0.994-1.003)	0.417		
LDH before drug	1.002 (1.000-1.005)	0.059		
PSA before drug	1.000 (1.000-1.001)	0.382		
Nadir PSA after drug	1.000 (1.000-1.001)	0.002*	1.000 (1.000-1.001)	0.010*
2nd line Hormone therapy				
Abiraterone	Reference			
Enzalutamide	1.168 (0.477-2.860)	0.735		

Cox regression with multivariate adjustion. *$p<0.05$. HR, Hazard ratio; CI, confidence interval; PSA, prostatic specific antigen; Hb, hemoglobin; Alk-P, alkaline phosphatase; LDH, lactic dehydrogenase.

Table IV. *Adverse events of abiraterone and enzalutamide.*

	Abiraterone acetate (n=64)		Enzalutamide (n=13)	
Adverse events	Grade 1/2 (n)	Grade 3/4 (n)	Grade 1/2 (n)	Grade 3/4 (n)
Anemia	1	1	2	0
Fatigue	2	0	4	2
Nausea	1	0	2	0
Constipation	1	0	1	0
Diarrhea	1	0	1	0
Hypertension	4	0	0	0
Peripheral Edema	2	0	0	0
Hot flush	0	0	1	0
Electrolyte Imbalance	4	0	0	0
Elevated ALT	1	2	0	0
Seizure	0	0	0	0
Vertigo	1	0	0	0
Stasis Dermatitis	2	0	0	0

ALT, Alanine aminotransferase.

One possible explanation on the observed efficacy of ENZ after AA failure is the increased expression levels of AR after AA treatment, as demonstrated in the model of mouse-bearing human prostate cancer tumor cells, since ENZ is known to be effective in CRPC with increased AR expression (22, 23). In terms of the mechanisms underlying drug actions, AA is known to specifically inhibit two enzymes (17α-hydroxylase and C17,20-lyase) that are necessary for testosterone synthesis from cholesterol precursors in the testis, adrenal gland, and prostatic cancer tissues. The result is a reduction in the circulating

testosterone level (24). In contrast, ENZ selectively inhibits AR activities by interfering nuclear translocation and impeding DNA binding to androgen response elements and co-activator recruitment as well. ENZ may therefore have selective actions exceeding AA on the androgen receptor signaling pathways (6).

In contrast to COU-AA-301 and AFFIRM trials, our results revealed similar PFS in AA and ENZ second-line treatment in mCRPC patients. On the other hand, OS was longer in the AA group (14.8 months *vs*. 30.2 months) in compared with COU-AA-301(4, 8). However, this may be due to the relative small number of patients in the ENZ group; an extreme value may cause the survival prediction to shift right.

Regarding treatment efficacy of second-line hormonal therapy, several factors are known as predictors, including the AR splice variant-7 mRNA, which is likely involved in the mechanism of drug-resistance (25). Although we did not examine this factor, other clinical factors appeared useful in predicting disease prognosis. Specifically, high volume metastasis predicted poor prognosis in terms of PSA progression and OS. This finding is consistent with what was known in the CHAARTED trial; high volume metastatic disease was associated with better chemotherapy response rate, compared to low volume metastatic disease in hormonal sensitive prostate cancer patients (26). Moreover, we showed that nadir PSA after novel androgen target agents is another predicting factor of the prognosis. Miyake *et al*. suggested that patients with docetaxel-naïve mCRPC as well as those who require longer time to reach PSA nadir under AA treatment show better control of the disease (27).

One important limitation of our study is its retrospective design and sample size. Therefore, clinical application of our results would require further randomized control studies with larger sample sizes. A second limitation is that patient numbers are rather different between the two groups, and therefore the power of statistics is weakened. The reason of this bias is that AA was approved for use in Taiwan earlier than ENZ for such treatments; hence, more patients were under AA treatment. Finally, due to the relatively short follow-up periods in the ENZ group, inter-group comparison was difficult.

Conclusion

Both regimens AA and ENZ had similar treatment efficacy in post-docetaxel mCRPC patients. Metastatic tumor volume and nadir PSA were independent risk factors in predicting the prognosis of progression in terms of free survival and overall survival.

Authors' Contributions

LW Chang drafted this manuscript. SC Hung and KY Chiu designed this study and collected clinical data. LW Chang and SC Hung encountered statistical analysis and figure drafting. LW Chang, SC Hung, SS Wang, JR Li, CK Yang, CS Chen, HC Ho, CL Cheng, YC Ou and KY Chiu contribute to all patients' clinical care and follow up. All authors read and approved the final manuscript.

Conflicts of Interest

The contributing Authors have no conflicts of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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