Original Article

Oncological outcomes of metastatic castration resistant prostate cancer (mCRPC) treated with different therapies sequences after completion of docetaxel: a retrospective study in Songklanagarind Hospital

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Abstract

Objective: Many treatment options of metastatic castration-resistant prostate cancer (mCRPC) after docetaxel chemotherapy have proved efficacious in clinical trials but, to date, knowledge regarding oncological outcomes is limited.

Materials and Methods: We assessed the oncological outcome of 4 drugs (abiraterone acetate, cabazetaxel, enzalutamide and ketoconazole) in a normal clinical setting in a university-based hospital. Our cohort consisted of 69 patients with post-docetaxel mCRPC. The primary endpoint was overall survival (OS). The secondary endpoint was predicted factor associated overall survival with all second-line mCRPC treatment outcomes according to the Cox proportional hazards regression model.

Results: This cohort consisted of 69 patients with progressive mCRPC after docetaxel chemotherapy. Median overall survival following treatment with abiraterone acetate and ketoconazole was 25.92 and 9.59 months respectively ($p < 0.05$). Overall survival rates at 1-year following abiraterone acetate, cabazetaxel, enzalutamide and ketoconazole therapy were 76.3%, 83.3%, 100% and 41.9%, respectively. Multivariable analysis found that abiraterone acetate, cabazitaxel and enzalutamide significantly improved survival in comparison to ketoconazole ($p < 0.001$).

Conclusion: Analysis of overall survival following second-line treatment of mCRPC post docetaxel in our study statistically significantly confirmed that abiraterone acetate, cabazitaxel and enzalutamide improve overall survival in comparison to ketoconazole. The study also found that enzalutamide treatment resulted in better outcomes in comparison to the other drugs.

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Introduction

Approximately 8630 new cases of prostate cancer were diagnosed in Thailand in 2020, representing about 9.2% of all new cancer diagnoses in Thai men[1] and age-standardized (World) incidence and mortality rate are 14.5 and 6.9 per 100,000 respectively. Prostate cancer with a high risk of advancement usually progresses quickly. Despite accounting for less than 15% of diagnoses, high-risk prostate cancer patients have a cancer-specific death rate of 15% after ten years and are more likely to acquire advanced prostate cancer. The development of drugs to target these pathways or therapeutic interventions for disease prevention has been sparked by a better knowledge of the mechanisms that lead to the establishment of advanced metastatic disease .[2] If prostate cancer progresses to metastatic castration- resistant prostate cancer (mCRPC) a positive clinical outcome is uncertain despite the discovery of novel therapeutic agents.[3,4] However, many drugs have been approved in Thailand for alternative treatment of mCRPC which are associated with survival improvement. These include the androgen receptor (AR)-targeted agents: abiraterone acetate, enzalutamide, cabazitaxel and ketoconazole.[5] The lack of evidence from prospective studies regarding second-line mCRPC post docetaxel treatment and its association with the best possible patient outcomes, also remains limited.[6]

Most patients with mCRPC have received docetaxel as part of their long-term treatment regimen as it is a standard treatment for patients with symptomatic metastases. In patients with mCRPC who have progressed after docetaxel, there is no strong evidence or direct comparison between a second-line option of chemotherapy (cabazitaxel), second-line AR-targeted therapy (abiraterone acetate or enzalutamide) or ketoconazole. Understanding the treatment outcome of each drug will be useful in informing health professionals and hence be beneficial for patients.[7,8]

The objective of this study was to evaluate the clinical outcomes of mCRPC post-docetaxel treatment in a real-world setting in a university-based hospital. We have retrospectively evaluated and analyzed the outcomes of second-line treatments post-docetaxel and their association with overall survival. Currently, little is known about these treatment outcomes in Thailand.

Materials and Methods

Study design

This study was retrospective in design. Overall survival was defined as a period from the start of the second-line therapy to either the end of data availability, the data cut-off date or death, depending on which event came first. The study protocol was approved by the Ethical Committee of Prince of Songkhla University (Study Code: REC.63-068-10-4).

Eligibility criteria

Inclusion criteria were a confirmed diagnosis of prostate cancer, an age of 18 years or over at the time of the diagnosis of prostate cancer, had received docetaxel as a first-line therapy and had received an mCRPC treatment of interest (abiraterone acetate, cabazitaxel, enzalutamide or ketoconazole).

Endpoints of the study

The primary endpoint was overall survival (OS), which was defined as the time from the start of the second-line therapy to death from any cause.

Study population

Medical records from the electronic database of post-docetaxel mCRPC patients who were treated in Songklanagarind Hospital from April, 2015 to March, 2019 were reviewed. All mCRPC patients who had had 6 cycles of docetaxel and then had been treated with second-line treatment were included. We defined high volume as ≥ 4 lesions of bone metastasis or visceral metastasis. Patients were excluded if the diagnosis was accidental or staging was incomplete or had there had been a switch to other treatment. Demographic data including patient age at diagnosis, initial prostate specific antigen, diagnosis date, Gleason score, volume of metastasis, nadir of the prostate specific antigen, PSA at the start of the second line treatment, the date treatment was started and the end point of the study were recorded.

Statistical analysis

The median OS was assessed using the Kaplan-Meier method. The primary statistical method of comparison for the time-to-event endpoints was log-rank test stratified by potential factors. The Cox proportional hazards model

was used to estimate the hazard ratio (HR) and its associated CI. Disease factors including the initial Prostate specific antigen, ECOG status, volume of disease, Gleason score, PSA at the start of the second-line treatment were recorded and their correlations with the overall survival were calculated by univariable regression analyses. Statistical significance for each correlation were estimated with a 95% confidence interval and a $p < 0.05$. Multivariable analysis for overall survival was performed to evaluate potential prognostic factors take as those registering as $p < 0.05$ from the univariable analysis (ECOG status, volume of disease, Gleason score, PSA at the second-line start of treatment). These were analyzed using Cox proportional hazards regression.

Descriptive statistics were used to summarize patient demographic and clinical characteristics at the start of second-line therapy. Demographic data was tabulated as mean (SD), and median (IQR). Comparisons between cohorts were carried out using Chi-squared tests for categorical variables and Wilcoxon rank-sum tests for continuous variables.

The data was amassed using a spreadsheet template in Microsoft Excel and all statistical analysis was performed using R program version 3.6.1.

Results

Out of all mCRPC patients treated with docetaxel in Songklanagarind Hospital, a total of 69 patients were treated with second-line therapy and all were included in the study. The proportions of patients undergoing each form of treatment, linked to survival status after treatment are shown in Figure 1.

Demographic data

A total of 69 cases of metastatic castration resistant prostate cancer (mCRPC) patients were treated with second-line treatment, post-docetaxel, at Songklanagarind Hospital between 2015 and 2019. Patient characteristics are presented in Table 1. The initiation of post-docetaxel therapy, and the characteristics of patients in each group were generally similar. The mean age of the patients was 71.9 years old (± 9.7), Gleason score in the high risk category (GS ≥ 8) had an incidence of 40 out of 69 patients (58%), and the volume of metastases was high in 55 out of 69 patients (79.7%). The median PSA at the date of the start second-line treatment was 130 ng/ml (IQR 53-330).

Median overall survival and 1-year overall survival

Out of 69 patients with progressive mCRPC after 6-cycles of docetaxel the median OS was 16.6 months [95% CI; 13.1-NA] as shown in Figure 2.

The median overall survival of each treatment arm showed that the OS of patients treated with abiraterone acetate was 25.92 months, and those with ketoconazole was 9.59 months. The difference in median OS for patients receiving abiraterone acetate in comparison to ketoconazole was statistically significant (25.92 vs. 9.59 months; $p < 0.05$). However, cabazitaxel and enzalutamide did not have median overall survival due to less event occurred to calculated, but appeared higher than ketoconazole. The 1-year OS for abiraterone acetate, cabazitaxel, enzalutamide

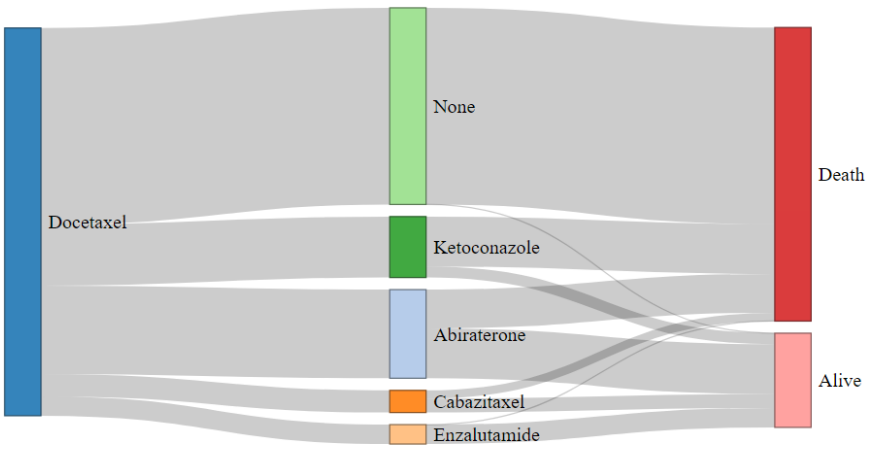

Figure 1. Sankey diagram: proportion of second-line treatment of mCRPC patients associated to survival status.

Table 1. Characteristics of mCRPC patients receiving second-line treatment in post-docetaxel setting.

Characteristics	Second-line therapy received					
	Abiraterone (n=32)	Cabazitaxel (n=8)	Enzalutamide (n=7)	Ketoconazole (n=22)	Total	P-value
Total	32	8	7	22	69	
Age (years)						0.488
Mean (SD)	73.3 (10.2)	67.8 (6.6)	69.9 (7.5)	71.9 (10.3)	71.9 (9.7)	
PSA at diagnosis (ng/mL)						0.783
Median (IQR)	300 (175,766.2)	681.5 (244,1061.8)	347 (227.5,601)	275 (142.8,750)	300 (172,780)	
ECOG						1
0-1	31 (96.9)	8 (100)	7 (100)	22 (100)	68 (98.6)	
2	1 (3.1)	0 (0)	0 (0)	0 (0)	1 (1.4)	
Gleason score						0.557
≤ 7	15 (46.9)	2 (25)	4 (57.1)	8 (36.4)	29 (42)	
≥ 8-10	17 (53.1)	6 (75)	3 (42.9)	14 (63.6)	40 (58)	
Volume of metastasis						0.6
High	24 (75)	6 (75)	7 (100)	18 (81.8)	55 (79.7)	
Low	8 (25)	2 (25)	0 (0)	4 (18.2)	14 (20.3)	
PSA at start of second line treatment						0.057
Median (IQR)	69 (35.8,225.5)	130 (80,319.5)	120 (98,143.5)	294 (69,1051.2)	130 (54,330)	
Anemia						0.018
No	16 (50)	4 (50)	4 (57.1)	3 (13.6)	27 (39.1)	
Yes	16 (50)	4 (50)	3 (42.9)	19 (86.4)	42 (60.9)	

PSA = prostate specific antigen, ECOG = Eastern Cooperative Oncology Group scale.

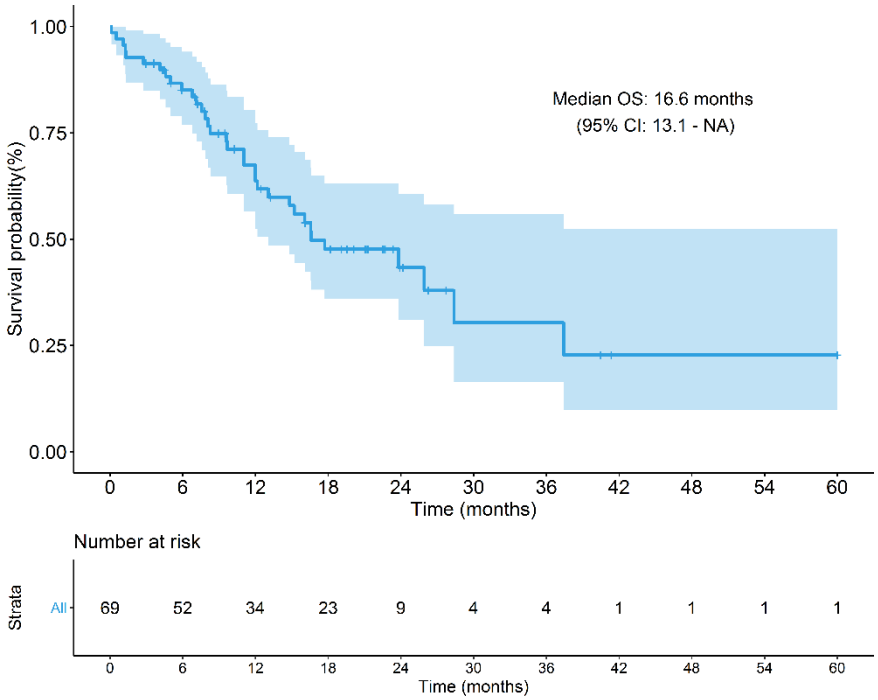

Figure 2. Kaplan Meier overall survival curve of all mCRPC patients treated with second-line treatment.

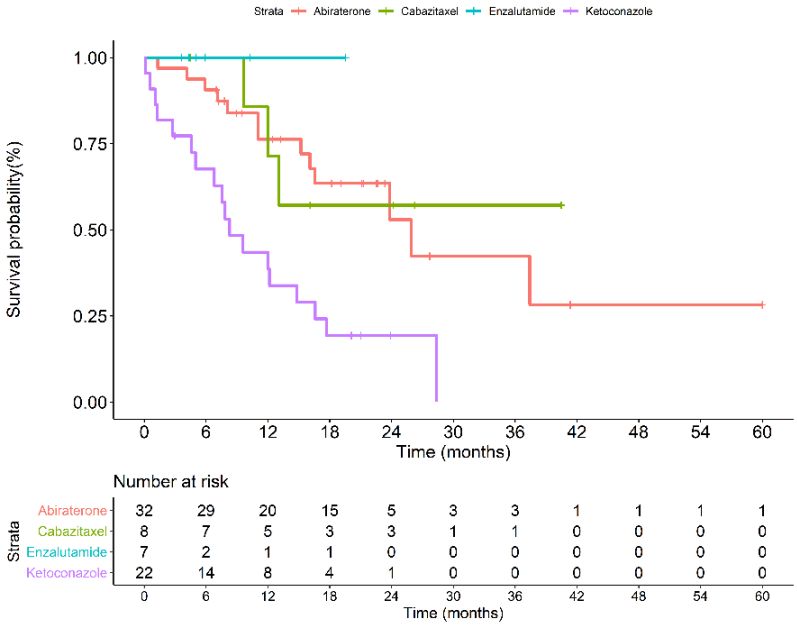

Figure 3. Kaplan Meier's survival curve demonstrating overall survival of post-docetaxel mCRPC patients treated with abiraterone acetate, cabazitaxel, enzalutamide and ketoconazole.

Table 2. Univariable and multivariable analysis of each affected factors associated to overall survival.

Factor	Univariable analysis		Multivariable analysis	
	Crude HR (95%CI)	P-value	HR (95%CI)	P-value
Ketoconazole		0.034*		0.001*
Abiraterone	0.3 (0.14, 0.62)		0.32 (0.15, 0.66)	
Cabazitaxel	0.25 (0.07, 0.87)		0.22 (0.06, 0.77)	
Enzalutamide	0 (0, Inf)		0 (0, Inf)	
Age group > 75 vs ≤ 75	1.39 (0.71, 2.74)	0.849		
ECOG 2 vs 0-1	1.66 (0.23, 12.3)	0.491		
GS 8-10 vs ≤ 7	2.06 (0.98, 4.31	0.034*	2.1 (0.99, 4.47)	0.046*
Volume metastasis low vs high	1.32 (0.62, 2.83)	0.832		
Median PSA at started second-line treatment > 130 vs ≤ 130 ng/ml	1.69 (0.83, 3.44)	0.377		
Anemia: Yes vs No	2.8 (1.3, 6.05)	0.199		

*Statistical significance < 0.05

and ketoconazole were 76.3%, 83.3%, 100% and 41.9% respectively, as shown in Figure 3.

The univariable analysis by drug as a second line treatment of mCRPC indicated that abiraterone acetate, cabazitaxel, and enzalutamide have statistically significant better survival outcomes in comparison to ketoconazole (p = 0.034). The analysis also shows that a high Gleason score has significantly higher risk of mortality than a lower Gleason score (p = 0.034). However, there was no statistically significant association between age, ECOG, volume of metastasis, median PSA level at the date of the start of second line treatment at a cutoff of 130 ng/ml and anemia before treatment and overall survival.

The multivariable Cox regression showed significantly better overall survival following abiraterone acetate, cabazitaxel and enzalutamide therapy in comparison to ketoconazole (hazard ratio: 0.29, 0.19 and 0, respectively; 95% Confidence Interval [CI] 0.13–0.61, p = 0.001) as shown in Table 3.

Discussion

Findings from this retrospective study provide an insight into the efficacy of post-docetaxel treatment in mCRPC patients. It also describes the characteristics of patients who received either abiraterone acetate, cabazitaxel, enzalutamide or ketoconazole as second-line treatments in a real-world setting. Our study assessed the OS following a novel phase of treatment in a post-docetaxel setting in Songklanagarind Hospital. Therapies used included AR-targeted therapy (abiraterone acetate and enzalutamide), cabazitaxel, and ketoconazole. The majority of patients received abiraterone acetate post-docetaxel for many reasons, including the clinical condition of patients, reimbursement and the drug registry period.

In the post-docetaxel setting, recent studies have suggested that there may be a survival benefit when the patient receives abiraterone acetate, cabazitaxel and enzalutamide.[9-11] In our study we found that abiraterone acetate, cabazitaxel and enzalutamide improved overall survival in comparison to ketoconazole. Interestingly, we did find that the subgroup of patients with a worse disease prognosis at the initiation of second-line therapy benefitted from receiving second-line abiraterone acetate, cabazitaxel, or enzalutamide when compared with ketoconazole.

Interestingly, we did not find any differences in terms of OS in patients in head-to-head comparison between cabazitaxel versus AR-targeted (abiraterone acetate or enzalutamide) therapies. This may have been due to some results not reaching the median OS of the entire cohort and the small numbers of the 4 treatment populations, but it seems likely that enzalutamide had the greatest potential benefit to survival as all cases were still alive after the 18 month follow up. This is a limitation of this investigation and longer term studies need to be carried out to confirm these findings. Several studies reported that enzalutamide therapy results in a better PSA response rate and PFS in treating mCRPC patients. A meta-analysis, showed that OS was 8.3 months higher in the pre-docetaxel setting, and 2.2 months in the post-docetaxel setting, in enzalutamide-treated mCRPC patients in comparison to the abiraterone acetate group. However, these differences did not reach statistical significance.

In another network meta-analysis, the findings suggested that enzalutamide was the most effective agent in improving OS (HR = 0.71) and abiraterone acetate was less effective in comparison to enzalutamide (HR = 0.78).[12] However, based on a pooled data analysis, differences between the pre- and post-chemotherapy settings were neglected. A pooled data analysis of major phase III clinical trials including PREVAIL, AFFIRM COU-AA-301 and COU-AA-302, yielded similar but contradictory findings between the different regimens in mCRPC have been observed in literature indicating that sensitivity to one compound is impaired by another with a similar or overlapping mechanism of action.[12]

Therefore, a more confident clinical application of our results requires further randomized control studies with larger sample sizes. A second limitation is that patient numbers differ between groups, limiting the power of the statistical analysis. Prospective randomized trials are warranted to validate these results. Future research should also consider other approved therapies, as well as adverse events or the impact on health-related quality of life.

Conclusion

Our findings confirm that in this study all the second line treatments of mCRPC tested prolong overall survival in a post-docetaxel setting. Abiraterone acetate, cabazitaxel and enzalutamide therapy were statistically significantly associated with better overall survival in comparison to ketoconazole. Enzalutamide showed the most benefit with regard to prolonging survival.

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Conflict of Interest

The authors declare no conflict of interest.

References

1. Thailand. Source: Globocan 2020. The Global Cancer Observatory (Internet). 2021 (cited 2021 March 15). Available from: https://gco.iarc.fr/today/data/factsheets/populations/764-thailand-fact-sheets.pdf.

2. Kiatbamrungpunt C, Nualyong C, Srinualnad S, Leewansangtong S, Taweemonkongsap T, Chaiyaprasithi B, et al. Long term outcomes between adjuvant radiotherapy and combined radiotherapy with hormonal treatment after radical prostatectomy in high risk prostate cancer. Insight Urol 2021;42:7-12.
3. Bejrananda T, Pripatnanont C, Tanthanuch M, Karnjanawanichkul W. Oncological Outcome of Docetaxel-Based Chemotherapy for Men with Metastatic Castration-Resistant Prostate Cancer. J Med Assoc Thai 2016;99:1315-21.
4. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol 2014;65:467-79.
5. Karantanos T, Evans CP, Tombal B, Thompson TC, Montironi R, Isaacs WB. Understanding the mechanisms of androgen deprivation resistance in prostate cancer at the molecular level. Eur Urol 2015;67:470-9.
6. Lorente D, Mateo J, Perez-Lopez R, S de Bono J, Attard G. Sequencing of agents in castration-resistant prostate cancer. Lancet Oncol 2015;16: 279-92.
7. Kyriakopoulos CE, Chen YH, Carducci MA, Liu G, Jarrard DF, Hahn NM, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial. J Clin Oncol 2018;36:1080-7.
8. McNamara M, Sweeney C, Antonarakis ES, Armstrong AJ. The evolving landscape of metastatic hormone-sensitive prostate cancer: a critical review of the evidence for adding docetaxel or abiraterone to androgen deprivation. Prostate Cancer Prostatic Dis 2018;21:306-18.
9. Rathkopf DE, Smith MR, de Bono JS, Logothetis CJ, Shore ND, de Souza P, et al. Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). Eur Urol 2014;66:815-25.
10. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels J, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomized open-label trial. Lancet 2010;376:1147-54.
11. Chang LW, Hung SC, Wang SS, Li JR, Yang CK, Chen CS, et al. Abiraterone Acetate and Enzalutamide: Similar Efficacy in Treating Post Docetaxel Metastatic Castration-resistant Prostate Cancer: Single Center Experience. Anticancer Res 2019;39:3901-8.
12. Chung DY, Kang DH, Kim JW, Kim DK, Lee JY, Hong CH, et al. Comparison of Oncologic Outcomes Between Two Alternative Sequences with Abiraterone Acetate and Enzalutamide in Patients with Metastatic Castration-Resistant Prostate Cancer: A Systematic Review and Meta-Analysis. Cancers (Basel) 2019;12:8.