Wydawnictwo UR 2024
ISSN 2544-1361 (online)
doi: 10.15584/ejcem.2024.2.18

http://www.ejcem.ur.edu.pl
European Journal of Clinical and Experimental Medicine
Eur J Clin Exp Med 2024; 22 (2): 262–269

ORIGINAL PAPER

Survival outcome and prognostic factors in patients with chemotherapy-naive metastatic castration-resistant prostate cancer treated with abiraterone acetate – real-world experience in Vietnam

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ABSTRACT

Introduction and aim. In real life, metastatic castration-resistant prostate cancer patients (mCRPC) had more complex clinical presentation than patients in the COU-AA-302 trial. This study primarily aimed to describe the overall survival of chemotherapy-naive mCRPC treated with abiraterone acetate plus prednisone (AAP). Other relevant outcomes and baseline characteristics of these patients were also evaluated.

Material and methods. This retrospective, observational study collected data from chemotherapy-naive mCRPC patients treated with AAP in Vietnam. Kaplan-Meier curves were used to estimate time to treatment failure (TTF), and overall survival (OS). The impact of baseline characteristics on OS was explored using univariate and multivariate Cox proportional hazard models.

Results. Data from 65 eligible patients were analyzed. The rate of PSA response was 73.8%, median PSA PFS was 10.5 months (95% CI: 7.4–13.6), median TTF was 15 months (95% CI: 11.1–18.9), and median OS was 24.9 months (95% CI: 18.9–30.9). Shorter OS was significantly associated with a higher Gleason score (≥8), shorter time from ADT start to mCRPC (<12 months), visceral metastases, and <50% PSA decline ($p<0.05$).

Conclusion. Abiraterone acetate plus prednisone is well tolerated and effective for chemotherapy-naive mCRPC patients in clinical practice. Moreover, Gleason score, visceral metastasis, time from ADT start to mCRPC, and PSA response are the independent indicators for predicting the OS of mCRPC patients in both univariate and multivariate analyses.

Keywords. abiraterone acetate, metastatic castration-resistant prostate cancer, overall survival, real-world evidence

Introduction

Prostate cancer (PCa) is one of the most common cancers in males, especially in developed countries. According to the estimates from GLOBOCAN 2020, PCa ranks second in terms of the number of new cases with 1,414,259, and fifth in terms of mortality with 375,304 cases.[1] In Vietnam, PCa ranks fifth in the incidence rate and seventh in mortality with 6,248 new cases and 2,628

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Received: 9.11.2023 / Revised: 2.01.2024 / Accepted: 2.02.2024 / Published: 30.06.2024

Do TA, Nguyen THT, Nguyen HX, Nguyen LD, Nguyen CV. Survival outcome and prognostic factors in patients with chemotherapy-naive metastatic castration-resistant prostate cancer treated with abiraterone acetate – real-world experience in Vietnam. *Eur J Clin Exp Med.* 2024;22(2):262–269. doi: 10.15584/ejcem.2024.2.18.

deaths reported in 2020.[1] In the United States, where PCa screening with PSA (prostate-specific antigen) and prostate biopsy is well-implemented, the rate of stage IV PCa is only 8%.[2,3] Therefore, for all stages combined, the 5-year relative survival rate for prostate cancer is 98%.[2,3] However, the rate of patients with stage IV prostate cancer in Vietnam is stated to be over 75%. This significantly compromises the overall prognosis of prostate cancer patients and amplifies the financial burden associated with treatment.

For nearly eight decades, androgen deprivation therapy (ADT) has served as the cornerstone of systemic treatment for men with metastatic prostate cancer. The antitumor effects of ADT improve quality of life by reducing bone pain and complication rates. However, following a median of 18–24 months of ADT, almost all patients progressed to mCRPC. A phase III pivotal study of chemotherapy-naïve mCRPC patients (COU-AA-302) demonstrated improvements in median radiographic progression-free survival (rPFS) from 8 to 16 months and the median overall survival (OS) from 30.3 to 34.7 months with AAP as compared with prednisone plus placebo.[4] However, in real life, mCRPC patients had more complex clinical presentation than those patients in the COU- AA-302 trial. The majority of mCRPC patients treated in clinical practice are elderly and have poor ECOG PS, and comorbidities such as cardiovascular disease, hypertension, and diabetes mellitus are thus common. Such patients along with those with visceral metastases may be under-represented in RCTs of mCRPC. Especially in Vietnam, mCRPC patients often have severe clinical symptoms and poor medical care conditions. Therefore, the outcome of mCRPC patients is often poor.

Aim

The main objective of this retrospective observational study was to add to the body of knowledge related to AAP by primarily describing the OS of chemotherapy-naïve mCRPC patients treated with AAP in routine clinical practice in Vietnam.

Material and methods

Study design and eligibility

This was a retrospective, observational cohort study conducted at Vietnam National Cancer Hospital from January 2014 to May 2023. The data collection period for each patient ranged from the initial date of prostate cancer diagnosis up to the date of data collection. The start of AAP treatment was considered as the baseline. Data from eligible patients treated with AAP were extracted from their medical records and entered into electronic case report forms. Patients were eligible if they had documented mCRPC and had received AAP for the treatment of mCRPC, were naive to chemotherapy, had an Eastern Cooperative Oncology Group (ECOG) performance status grade of 0 to 3, and hematological and chemical laboratory values that met predefined. Patients were excluded if they had received any chemotherapy or cytotoxic agent for the treatment of mCRPC or novel hormonal therapies before initiation of AAP, had short survival time (older people with many co-morbidities), and had second cancer.

All objects of the protocol in this study was approved by the Science and Ethical Committee of Hanoi Medical University, Vietnam as number: 6811/QD-DHYHN. Written informed consent was applied to all patients before enrolling them in the study. Patients could withdraw from the study at any time without any threats or disadvantages and for no stated reasons.

Data collection and outcomes of interest

Patient characteristics at the time of AAP treatment initiation were collected. These factors included age, comorbidities, Gleason score, the time from ADT start to abiraterone, initial diagnosis, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), the Brief Pain Inventory – Short Form (BPI – SF), location of metastases, prostate-specific antigen [PSA], hemoglobin.

The main endpoint of the study was overall survival (OS) with AAP. OS was defined as the time from the start of AAP treatment to treatment death for any reason. The secondary endpoint of the study was the time to treatment failure with AAP. Time to treatment failure (TTF) was defined as the time to treatment until 2 out of 3 progression factors were biochemical, imaging, and clinical progression and was considered equivalent to the duration of treatment.

Statistical analysis

All patients who met the eligibility criteria were included in the data set for analysis by SPSS 20.0 statistical software. The objective of the study was primarily descriptive, and most of the outcomes were analyzed using descriptive statistics (for categorical variables number and percentage of patients per response option, based on non-missing data; for continuous variables, the median and the inter-quartile range [IQR] are reported).

Time-to-event endpoints were analyzed using Kaplan-Meier survival plots. For all time-to-event endpoints, patients who had not experienced the event of interest at the time of data collection were censored. The impact of covariates on OS was explored using univariate and multivariate Cox proportional hazard models.

Results

From January 2014 to May 2023 in Vietnam National Cancer Hospital, a total of 65 patients were recruited in the study. At the time of data collection after three years

of treatment, 63 patients (96.9%) discontinued AAP, and 51 patients (78.5%) died. After treatment failure with AAP, 40 patients (61.5%) received second-line therapy with docetaxel, and 10 patients (15.4%) received third-line therapy with enzalutamide. The majority of patients (86.4%) were treated with an anti-osteoporotic drug (zoledronic acid or denosumab).

Table 1 shows the patients' baseline clinical and paraclinical features. The median age of patients at mCRPC diagnosis was 70 (IQR: 64–76), the rate of patients who had comorbidities was 43.1% which cardiovascular disease accounted for 35.4%, and Gleason scores ≥8 was 78.5%. The rate of patients de novo was 75.4%, and the median time from ADT to mCRPC was 16.0 months (IQR: 11–23). Patients had ECOG PS status ≥2 was 24.6%, and pain symptoms of BPS-SF >3 was 36.9%. The rates of bone, lymph node, and visceral metastasis were 87.7%, 38.5%, and 16.9%. The median PSA was 34.7 ng/ml (IQR: 13–106.8), and the median hemoglobin was 126 g/l (IQR: 116–132).

Table 1. Patient characteristics with mCRPC

	n (%)
Median age (IQR)	70 (64–76)
Comorbidities n (%)	28 (43.1)
Cardiovascular disorders	23 (35.4)
Metabolic disorders	6 (9.2)
Other disorders	4 (6.2)
Gleason score n (%)	
<8	14 (21.5)
≥8	51 (78.5)
Diagnosis n (%)	
Recurrent	16 (24.6)
De novo	49 (75.4)
Time from ADT start to abiraterone (months), median (IQR)	16 (11–23)
ECOG PS n (%)	
0	18 (27.7)
1	31 (47.7)
≥2	16 (24.6)
BPI – SF n (%)	
BPI-SF 0–3	41 (63.1)
BPI-SF >3	24 (36.9)
Location of metastases n (%)	
Bone	57 (87.7)
Non-regional lymph nodes	25 (38.5)
Viscera	11 (16.9)
Median PSA (IQR)	34.7 (13–106.8)
Median hemoglobin (IQR)	126 (116–132)

The median duration of treatment was 15 months (IQR: 8–19.8). The rate of PSA response was 73.8%, median PSA OS was 10.5 months (95% CI: 7.4–13.6), median TTF was 15 months (95% CI: 11.1–18.9) (Fig. 1A), and median OS was 24.9 months (95% CI: 18.9–30.9) (Fig. 1B). However, the median overall survival between subgroups was heterogeneous.

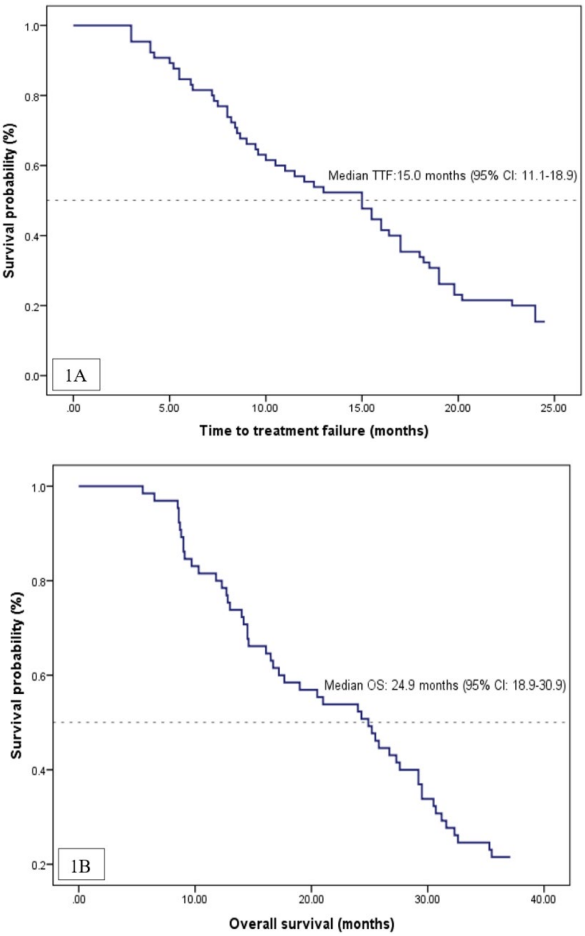

Fig 1. A: Time to treatment failure, B: overall survival during abiraterone treatment

The Kaplan-Meier analysis revealed significantly longer median OS for various factors: age <70 versus age ≥70 (30.7 vs 16.1 months) (Fig. 2A), ECOG PS 0-1 versus ECOG PS 2-3 (27.6 vs 11.8 months) (Fig. 2B), BPI-SF ≤3 versus BPI-SF >3 (29.5 vs 14.2 months) (Fig. 2C), Gleason score <8 versus Gleason score ≥8 (32.6 vs 19 months) (Fig. 2D), PSA ≤80 ng/ml (26.7 vs 12.8 months) (Fig. 2E), absence of visceral metastases versus presence of visceral metastases (27.6 vs 10.3 months) (Fig. 2F), "recurrent" status versus de novo status (29.2 vs 17.7 months) (Fig. 2G), time from ADT start to mCRPC ≥12 months versus time from ADT start to mCRPC <12 months (29.2 vs 12.7 months) (Fig. 2H), and PSA response with venous PSA response versus without PSA response (29.2 vs 9.1 months) (Fig. 2I).

In univariate analysis of the relationship between clinical characteristics at initiation and OS, higher age (≥70), higher ECOG PS (≥2), higher Gleason score (≥8), or higher BPI-SF (>3), or higher PSA (>80), or visceral metastases, de novo, or shorter time from ADT start to mCRPC (<12 months), and <50% PSA decline were all associated with shorter time to OS with AAP ($p<0.05$). However, in the multivariate analysis, only a high-

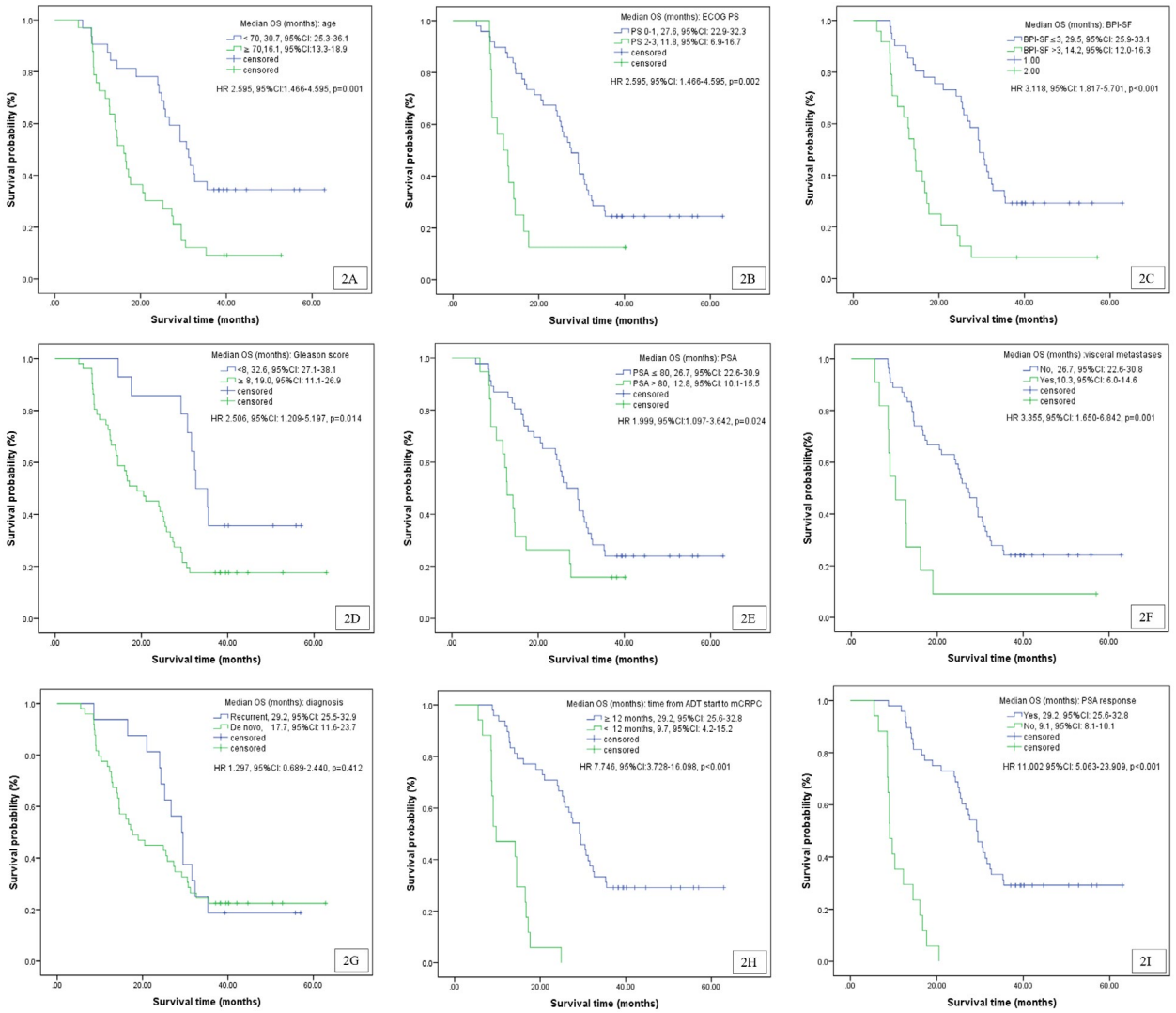

Fig. 2. Kaplan-Meier assessing the relationship between baseline characteristics and OS

er Gleason score (≥8), shorter time from ADT start to mCRPC (<12 months), visceral metastases, and <50% PSA decline were associated with shorter time to OS (Table 2).

During treatment with AAP, the most common symptoms were edema (23.1%), hypokalemia (15.4%), hypertension (10.7%), elevation of AST/ALT enzymes (7.7%), and hyperglycemia (7.7%). The majority of patients had mild to moderate adverse events, without patients had to discontinue the treatment due to adverse events of AAP.

Discussion

In the COU-AA-302 trial by Ryan et al. 1088 patients had asymptomatic or mildly symptomatic, ECOG PS 0-1, no visceral metastasis, no cardiovascular disease, and chemotherapy-naive prostate cancer.[4] The results showed that median overall survival was significantly longer in the abiraterone acetate group than in the placebo group (34.7 months vs. 30.3 months).[4] However, clinical practice shows that at the time of initial mCRPC diagnosis, patients have heterogeneous characteristics. Our sample has more complex characteristics than the COU-AA-302 trial. The median age was 70 (IQR: 64–76), cardiovascular disease was 35.4%, de novo was 75.4%, Gleason score ≥8 was 78.5%, and ECOG PS ≥2 was 24.6%. The rate of patients who had symptoms of pain BPS-SF >3 was 36.9% and visceral metastasis was 16.9%. The median PSA was 34.7 ng/ml (IQR: 13–106.8), and the median hemoglobin was 126.0 g/l (IQR: 116–132). In our study, PSA response was 73.8% higher than the COU-AA-302 trial (62%) but the median biochemical PFS was 10.5 months (95% CI: 7.4–13.6) lower than COU-AA-302 trial (11.1 months).

Prostate Cancer Clinical Trials Working Group 3 (PCWG3) evaluates the progression of bone metastases on bone scintigraphy according to the 2+2 rule.[5] However, in Vietnam, clinical practice conditions are often inadequate to assess bone metastases. In addition, the results of the COU-AA-302 trial by Rao et al. showed

that a substantial proportion (38%) of patients discontinued treatment for non-radiographic progression.[6] Therefore, in our study, we evaluated the time to treatment failure. The median time to treatment failure with AAP in our sample was 15 months (95% CI: 11.1–18.9), which was longer than the treatment duration of 13.8 months seen in the phase III COU-AA-302 trial by Ryan et al. and in other real-world studies by Pilon et al. and Boegemann et al. (6.8 and 10 months, respectively).[4,7,8]

Table 2. Univariate and multivariate analysis (Cox regression models) assessing the relationship between baseline characteristics and OS

		n (%)	Univariate HR (95% CI), p	Multivariate HR (95% CI), p
Age	<70	33 (50.2)		
	≥70	32 (49.8)	2.595 (1.466–4.595)	1.253 (0.629–2.494)
			p=0.001	p=0.512
PS	0–1	49 (75.4)		
	2–3	16 (24.6)	2.764 (1.465–5.216)	1.707 (0.775–3.736)
			p=0.002	p=0.715
Gleason	<8	14 (21.5)		
	≥8	51 (78.5)	2.506 (1.209–5.197)	3.136 (1.373–7.136)
			p=0.014	p=0.007
BPI–SF	≤3	41 (63.1)		
	>3	24 (36.9)	3.118 (1.817–5.701)	1.067 (0.522–2.184)
			p<0.001	p=0.858
PSA	≤80	46 (70.1)		
	>80	19 (29.9)	1.999 (1.097–3.642)	1.957 (0.906–4.227)
			p=0.024	p=0.88
Visceral metastases	No	54 (83.1)		
	Yes	11 (16.9)	3.355 (1.650–6.842)	2.735 (1.09–6.593)
			p=0.001	p=0.032
Diagnosis	Recurrent	16 (24.6)		
	De novo	49 (75.4)	1.297 (0.689–2.440)	0.439 (0.217–1.123)
			p=0.412	p=0.092
Time from ADT start to mCRPC	≥12 months	48 (73.8)		
	<12 months	17 (26.2)	7.746 (3.728–16.098)	3.883 (1.556–9.441)
			p<0.001	p=0.003
PSA response	Yes	48 (73.8)		
	No	17 (26.2)	11.002 (5.063–23.909)	6.425 (2.115–19.520)
			p<0.001	p=0.001

In the COU-AA-302 trial by Bjartell et al. 67% of patients after failure of AAP continued on second-line therapy, which was mainly docetaxel (48%) and third-line therapy was 36%.[9] The results showed that patients who received docetaxel second-line therapy improved prognosis compared with patients who received symptomatic treatment. In our study, after the failure of AAP, 40 patients (61.5%) received second-line therapy with docetaxel and 10 patients (15.4%) received third-line therapy with enzalutamide. The results showed that the median OS of 24.9 months (95% CI: 18.9–30.9) was similar to other real-world studies by Bjartell et al. and George et al. (27.1 months and 23.7 months, respectively) but shorter than the median OS of 34.7 months seen in the COU-AA-302 trial by Ryan et al.[4,9,10]

The results of the COU-AA 302 trial by Ryan et al. and real-world studies by Chen et al. and Valero et al. have indicated that the characteristics of patients at the time of initial mCRPC diagnosis, including age, Gleason score, ECOG performance status score, presence of visceral metastases, baseline PSA, hemoglobin, alkaline phosphatase, and PSA response, serve as significant prognostic factors for overall survival.[4,11,12] In our study, univariate analysis of the relationship between clinical characteristics at initiation and OS, higher age (≥70), or higher ECOG PS (≥2), or higher Gleason score (≥8), or higher BPI-SF (>3), or higher PSA (>80), or visceral metastases, de novo, or shorter time from ADT start to mCRPC (<12 months), and <50% PSA decline were all associated with shorter time to OS with AAP (p<0.05). However, in the multivariate analysis, only a higher Gleason score (≥8), shorter time from ADT start to mCRPC (<12 months), visceral metastases, and <50% PSA decline were associated with shorter time to OS.

The public health burden of prostate cancer treatment in elderly patients is anticipated to increase in the coming decades. Elderly patients often present with poor ECOG PS and numerous co-morbidities. Consequently, the effectiveness of treatment tends to be reduced compared to younger patients. However, many studies also showed that young patients often have more aggressive histological and molecular features than elderly patients. The study of Humphreys et al. involving 333 CRPC patients treated over 10 years, of age (>75) and (<55) at the time of initial prostate cancer diagnosis is associated with a statistically significant shorter OS.[13] In our study, the median OS of the subgroup of patients with age <70 was statistically significantly longer than the subgroup of patients with age ≥70 (30.7 months, 95%CI: 25.3–36.1 vs 16.1 months, 95%CI: 13.3–18.9; p=0.001).

Besides age, ECOG PS is an important factor in choosing therapy and has a great influence on treatment outcomes. Results from the COU-AA 302 trial by Ryan et al. showed that the subgroup of patients with PS 0 had statistically significantly higher OS than the subgroup of patients with PS 1.[4] In addition, the study of Chen et al. shows that patients with poor ECOG PS (PS 2-3) had statistically significantly lower OS than patients with good ECOG PS.[11] In our study, 24.6% of patients had poor ECOG PS (PS 2-3). The results indicated that the median overall survival of the subgroup with ECOG PS 0-1 was significantly longer than that of the subgroup with ECOG PS 2-3 (27.6 months, 95% CI: 22.9–32.3 vs. 11.8 months, 95% CI: 6.9–16.7; p=0.002).

The Gleason score is assessed based on the histopathology of prostate tumor biopsies, relying on the structural features of cancer cells and closely correlating with the patient's clinical characteristics. The Gleason sub-

type bears a strong relationship with the degree of clinical presentation, malignancy, time to progression, and survival of prostate cancer patients. In a study by Valero et al. involving 314 CRPC patients, the subgroup with a GS <8 exhibited significantly longer overall survival than the subgroup with a GS ≥8 (45 months vs. 34 months, p=0.009).[12] The results from our study demonstrated that the median overall survival of the subgroup with a Gleason score < 8 was notably longer than that of the subgroup with a Gleason score ≥ 8 (32.6 months, 95%CI: 27.1-38.1 vs. 19.0 months, 95%CI: 11.1–26.9; p=0.014).

Bone pain is one of the most common symptoms in mCRPC patients, greatly impacting their quality of life and treatment outcomes. Numerous studies consistently demonstrate that the extent of bone pain at the time of initial mCRPC diagnosis serves as a predictor of overall survival. In the study conducted by Fizazi et al. the subgroup of patients reporting no or mild bone pain exhibited significantly longer overall survival compared to the subgroup experiencing moderate to severe pain (p<0.001).[14] The results in our study showed that the median OS of the subgroup of patients with BPI-SF ≤3 was statistically significantly higher than the subgroup of patients with BPI-SF >3 (29.5 months, 95%CI: 25.9–33.1 vs 14.2 months, 95%CI: 12–16.3; p<0.001).

PSA is a valuable marker for screening, diagnosis, monitoring, and prognosis of prostate cancer. Patients with high PSA often have a worse prognosis than patients with low PSA. The study of Valero et al. showed that the subgroup of patients with PSA at the time of initial diagnosis mCRPC <50 ng/ml had statistically significantly longer OS than the subgroup of patients with PSA ≥50 (36 months vs. 24 months, p=0.008).[12] The results in our study showed that the median OS of the subgroup of patients with PSA ≤80 was statistically significantly higher than the subgroup of patients with PSA >80 (26.7 months, 95%CI: 22.6-30.9 vs 12.8 months, 95%CI: 10.1–15.5; p=0.024).

In our study, the rates of bone, lymph node, and visceral metastasis were 87.7%, 38.5%, and 16.9%. The results of many studies show that the site of metastasis prostate cancer is a prognosis factor for overall survival. The study of Mazzone et al. showed that patients with metastases involving only lymph nodes had superior survival compared to those with bone metastases only, or visceral metastases only and that harboring a combination of these sites at diagnosis was associated with poorer survival.[15] The results in our study showed that the median OS of the subgroup of patients without visceral metastases was statistically significantly longer than the subgroup of patients with visceral metastases (27.6 months, 95%CI: 22.6–30.8 vs 10.3 months, 95%CI: 6–14.6; p=0.001).

For nearly eight decades, androgen deprivation therapy (ADT) has served as the cornerstone of systemic treatment for men with metastatic prostate cancer. The antitumor effects of ADT improve quality of life by reducing bone pain and complication rates. Nevertheless, around 20% of patients respond poorly to ADT and this subgroup often also shows poor responses to second-line anti-androgens. The study of Wenzel et al. evaluated the impact of time to castration resistance (TTCR) in metastatic hormone-sensitive prostate cancer (mHSPC) patients on overall survival (OS).[16] The results of this study showed that the subgroup of patients with TTCR < 12 months had statistically significantly lower OS than the subgroup of patients with TTCR ≥ 12. The results of our study showed that the median OS of the subgroup of patients with time from ADT start to mCRPC <12 months was statistically significantly higher than the subgroup of patients with time from ADT start to mCRPC ≥12 months (29.2 months, 95%CI: 25.6–32.8 vs 9.7 months, 95%CI: 4.2–15.2; p<0.001).

In the United States, the majority of prostate cancer patients are diagnosed at an early stage; only 8% of patients are diagnosed at the metastatic stage.[2] The 5-year survival rate for patients is 98%.[3] However, at the metastatic stage, the 5-year survival rate is significantly reduced, to approximately 34%.[3] In the metastatic stage of the disease, patients who undergo radical treatment at the time of initial diagnosis have a better prognosis than de novo patients. The CHAARTED trial by Sweeney et al. and the GETUG-AFU 15 trials by Gravis et al. demonstrated that patients who underwent radical treatment at the time of initial diagnosis had significantly longer overall survival (OS) compared to de novo patients who relapsed.[17,18] In the study by Koura et al., 28.4% of patients who received radical treatment at the time of initial diagnosis showed significantly longer OS than de novo patients (HR 0.56, 95% CI: 0.33–0.93).[19] However, the results of our study showed that the median OS of the subgroup of patients with "recurrent" was not statistically significant compared to the subgroup of patients with de novo (29.2 months, 95%CI: 25.5–32.9 vs 17.7 months, 95%CI: 11.6–23.7; p=0.412).

PSA is widely used to monitor prostate cancer and its decline after chemotherapy and new-generation hormonal agents has been acknowledged as a valid surrogate for OS and PFS at 3 months. Retrospective studies have confirmed that patients with mCRPC who experience a PSA response exhibit a survival benefit compared to patients who do not achieve a PSA response. The study by Alvim et al. showed that median OS was significantly longer for patients with PSA response compared with patients without PSA response (29.3 vs. 9.7 months, p<0.001).[20] The results of our study showed that the median OS of the subgroup of patients with PSA response was statistically significantly higher than the subgroup of patients without PSA response (29.2

months, 95%CI: 25.6-32.8 vs 9.1 months, 95%CI: 8.1–10.1; p<0.001).

Abiraterone acetate inhibits CYP-17OH, leading to an increase in mineralocorticoid synthesis. As a result, it causes salt and water retention, hypokalemia, hypertension, edema, and an elevated risk of cardiovascular events. Additionally, AAP is metabolized by the liver and can lead to increased liver enzyme levels, a common occurrence within the first 3 months. In our study, the rate of patients experiencing adverse events due to AAP was lower than in the COU-AA-302 trial by Ryan et al.[4] The most frequent symptoms included edema (23.1%), hypokalemia (15.4%), hypertension (10.7%), elevation of AST/ALT enzymes (7.7%), and hyperglycemia (7.7%). The majority of patients experienced mild to moderate adverse events, and none had to discontinue the treatment due to AAP-related adverse events.

Study limitations

At present, some limitations still remained in the current study. In Vietnam, many mCRPC patients cannot be treated with AAP due to financial problems. Therefore, our study has a smaller sample size than other studies. In addition, this study was not designed to evaluate radiographic progression-free survival. Continued follow-up and analysis of more patients are planned to confirm the more therapy value of this regime in mCRPC patients.

Conclusion

The treatment with AAP is well tolerated and effective in mCRPC patients naïve to chemotherapy, even though in real life they are more vulnerable and have a high burden of disease such as visceral metastases and pain. Moreover, Gleason score, visceral metastasis, time from ADT start to mCRPC, and PSA response are the independent indicators for predicting the OS of mCRPC patients in both univariate and multivariate analyses.

Declarations

Funding

The authors received no financial support for this article's research, authorship, and/or publication.

Author contributions

Conceptualization, T.A.D. and L.D.N.; Methodology, T.A.D. and L.D.N.; Software, L.D.N.; Validation, T.A.D., H.T.T.N., H.X.N. and C.V.N.; Formal Analysis, C.V.N. and L.D.N.; Investigation, T.A.D. and L.D.N.; Resources, T.A.D., H.T.T.N., H.X.N. and L.D.N.; Data Curation, L.D.N.; Writing – Original Draft Preparation, C.V.N. and L.D.N.; Writing – Review & Editing, C.V.N. and L.D.N.; Visualization, C.V.N. and L.D.N.; Supervision, T.A.D., H.T.T.N., H.X.N. and C.V.N.; Project Administration, T.A.D. and L.D.N..

Conflicts of interest

The authors declare no potential conflicts of interest concerning this article's research, authorship, and/or publication.

Data availability

All data analysed during this paper are included in this article. Further enquiries can be directed to the corresponding author.

Ethics approval

All objects of the protocol's this study was approved by the Science and Ethical Committee of Hanoi Medical University, Vietnam as number: 6811/QD-DHYHN.

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