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RESEARCH ARTICLE

Assessment of initial real life experience with Abiraterone Acetate in patients with castrate resistant prostate cancer: A retrospective study in Saudi Arabian patients

Rasha Haggag[1]*, Jamal Zekri [2], Kamel Farag[3]

1. Department of Medical Oncology, Faculty of Medicine, Zagazig University, Sharkia, Egypt
2. King Faisal Specialist Hospital and College of Medicine, ALFAISAL University, Jeddah, Saudi Arabia
3. Oncology Center, Faculty of Medicine Mansoura University, Mansoura, Egypt

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Corresponding Author

Rasha Haggag

Abstract

Background: Abiraterone Acetate (AA) improves outcome of patients and is currently an adopted standard of care in chemo-naïve patients and after progression on chemotherapy. We audited our initial experience with the use of AA in these patients.

Patients and methods: Eighteen consecutive CRPC patients were treated with AA 1000 mg/day and prednisolone 5 mg twice daily. Patients achieving prostate specific antigen decline (PSA) ≥ 50% were considered as marker responders.

Results: A total of 10 patients (55.6%) achieved PSA response. The median time to PSA progression was 9 months (95% CI: 4.1-13.8). Objective radiological response was achieved in 6 (33%) patients (2 CR & 4 PR). Three patients (16.7%) achieved SD. After a median follow up of 13 months, the median overall survival was not reached and the mean was 20 (3-23) months. Selected grade III/IV adverse events of special interest were hypokalemia (22%) and hypertension (11%).

Conclusion: In daily clinical practice, AA is an effective treatment for patients with CRPC. It produces meaningful marker and objective responses, PFS and OS that are comparable to those reported in clinical trials. Monitoring of blood pressure and serum potassium is recommended.

INTRODUCTION

Prostate cancer is the most commonly diagnosed solid organ malignancy in the United States and remains the second leading cause of cancer deaths among American men [1].

In Saudi Arabia, prostate cancer is the 6 th most common cancer among men of all ages and the most common cancer among men over the age of 75. It accounts for 6.1% of all newly diagnosed cases among males in year 2010 with an age-standardized incidence rate of 5.5/100,000 among the male population. Stage at the time of diagnosis is localized in 43.9% of cases with the remainder being locally advanced, metastatic or unknown [2]. Until 2010, the only systemic regimen known to extend survival in men with metastatic castration-resistant prostate cancer (mCRPC) was docetaxel-based chemotherapy [3]. Since April 2010, five new agents have been approved in the United States based on an extension of survival including sipuleucel-T, cabazitaxel, abiraterone acetate (AA), enzalutamide, and radium-223 [4].

Abiraterone acetate, a selective androgen biosynthesis inhibitor, potently blocks persistent androgen synthesis from adrenal and intratumoral (autocrine/paracrine) sources, and inhibits an important driver of mCRPC progression [5-6]. It has shown clinical benefits in patients with mCRPC, with a minimal risk. [7-8]. Abiraterone inhibits CYP17, a

dual function enzyme that is necessary for testosterone synthesis. Abiraterone in combination with prednisolone has shown to prolong overall survival in both, chemotherapy-naïve and postchemotherapy patients. [7, 9, 10].
Little is known regarding AA efficacy and safety in our region. The present study was designed to provide more clinical data about this in Saudi Arabian patients with CRPC.

Materials and methods:

Patients

We identified consecutive patients with CRPC who had received abiraterone. Patients were not excluded on the basis of any factors.

Men with CRPC who initiated abiraterone at King Faisal Specialist Hospital from June 2012 to October 2013 were included in this retrospective study.

A total of 18 patients with CRPC treated with abiraterone were included. Patient demographics, prior treatments, clinico-pathological characteristics and outcomes on abiraterone (PSA response and survival parameters) were documented from medical records of each patient. Research ethics board of our centre approval was obtained in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Treatment

All patients received AA 1000 mg/day and prednisolone 5 mg twice daily. AA treatment was interrupted when radiological and clinical or biochemical progression was confirmed.

Outcome Measures

We aimed to assess the confirmed PSA response to abiretarone, which was defined as a PSA decline 50% from baseline maintained for 3 weeks.

Overall survival, time to PSA and radiological PFS and on abiretarone was analysed. PFS was defined as time from commencement of abiretarone to PSA and/or radiological progression as per Prostate Cancer Working Group 2 (PCWG2) criteria [11].

Statistical analysis

Statistical analysis is carried out using SPSS 21.0 soft-ware (SPSS, Inc. Headquarters, Chicago, IL, USA). In first place a descriptive analysis of the variables is performed. Afterwards, univariate analysis with chi-square test was performed for qualitative variables. The survival rates were analyzed using Kaplan Meier functions and the log rank statistic.

Results

Patients' characteristics:

Overall, 18 patients were enrolled from June 2012 to October 2013. The median was age 73 (55 - 84) years when starting treatment with AA. The median PSA levels at the time of enrolment was 56(0.1-1087) ng/mL,
A total of 17 patients (94.4% %) had metastasis to bone, 11patients (61.1%) had nodal involvement, 6 patients (33.3%) had visceral involvement combined bone and lymph node metastasis and 50% (8/18 patients) had a Gleason score of ≥ 8. All patients were supplemented with calcium-vitamin D, zoledronic acid in (61.1%) and denosumab in (33.3%) of patients.

All patients had received at least 2 hormonal treatment lines before AA treatment; 22.2 % of them (4/18 patients) received third-line hormonal treatment with ketoconazole. 22.2 % of patients received chemotherapy before AA treatment (5.6% of whom received 2 treatment lines with docetaxel and mitoxantrone). Series characteristics are resumed in table 1.

Figure 1. Kaplan–Meier curve of overall survival (Overall series).

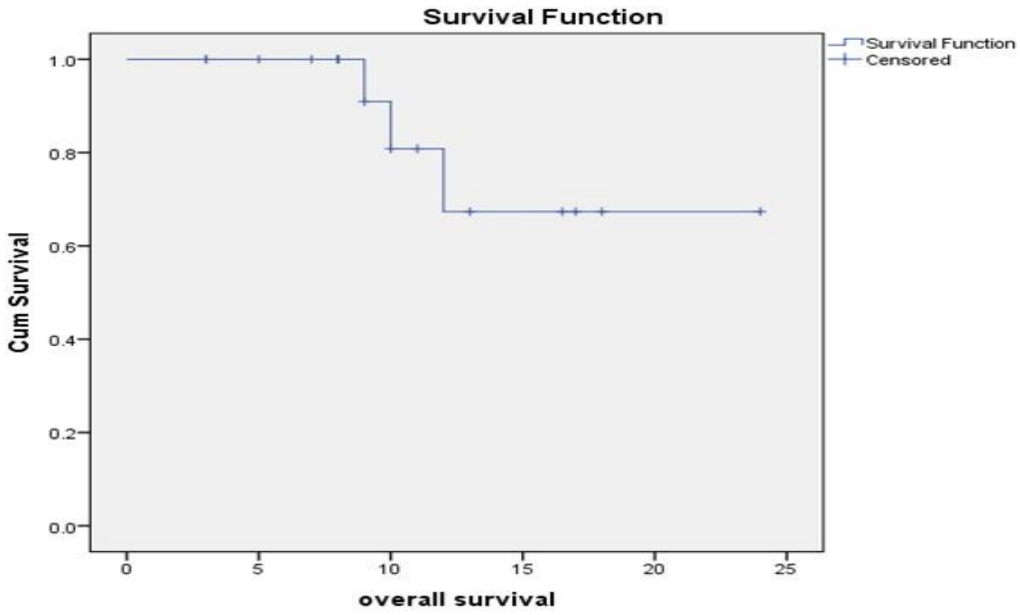

Figure 2. Kaplan–Meier curve of time to marker progression

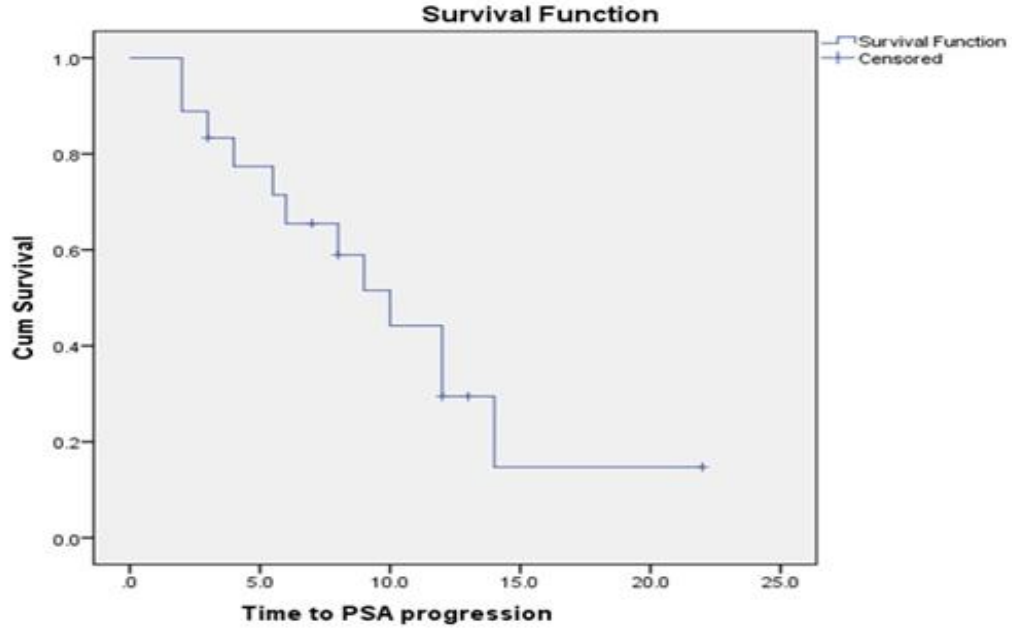

Figure 3. Kaplan–Meier curve of time to radiological progression

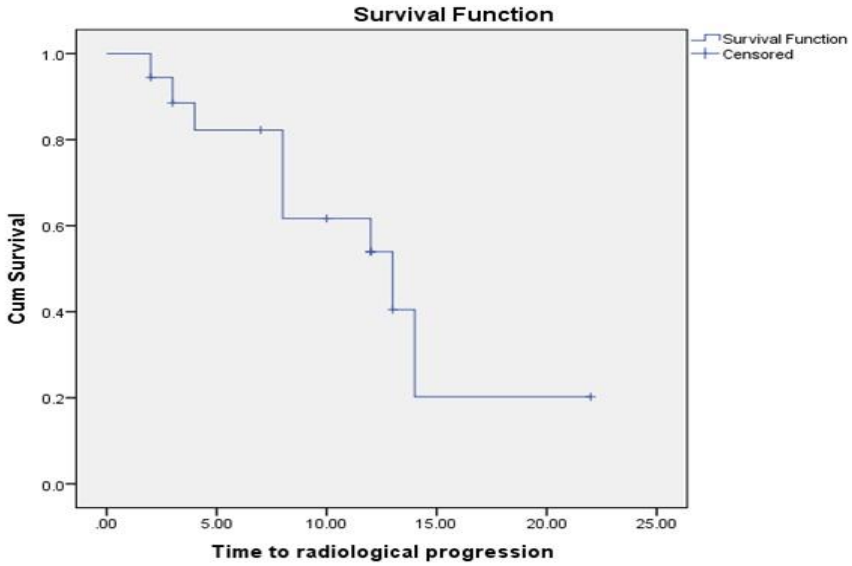

Figure 4: Univariate analysis of clinical and radiological free- survival progression in terms of biochemical response (PSA decline >50% from baseline) at 3 months of treatment

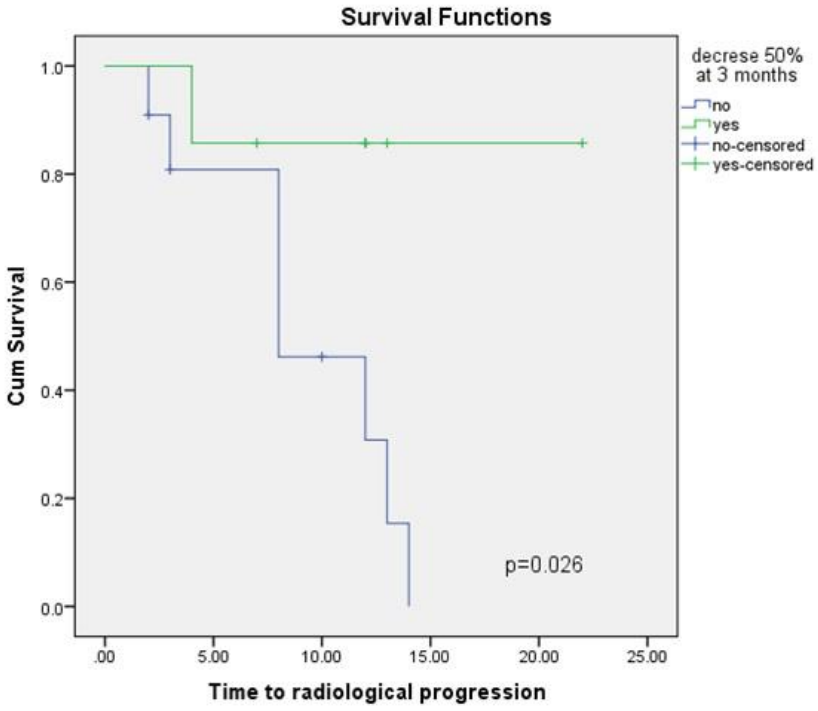

Table 1: Distribution of the different clinical variables in the overall series.

Characteristics	Overall series
Age, years	
Median (range)	**73 (55-84)**
Gleason score	
5-7	**2 (11.2%)**
8-10	**9(50 %)**
Unknown	**7(38.8 %)**
Baseline PSA, ng/ml	
Median	**56**
Range	**(0.1-1087)**
Metastatic disease, n (%)	
Bone	**17 (94.4%)**
Lymph node	**11(61.1%)**
Visceral	**6 (33.3%)**
Both bone and node	**6 (33.3%)**
Duration of treatment (months)	
Mean ± standard deviation	**9.7 ± 5.7**
Median (range)	**9 (2-22)**
PSA reduction > 50%	**55.6% (10/18 patients)**
Prior hormonal therapies	**18 (100%)**
Previous Ketoconazole	**4 (22.2%)**
Prior lines of chemotherapy	
1	**3 (16.7%)**
> 1	**1(5.6%)**

Table 2. Radiographic overall response.

Response	N. (%)
CR	**2 (11.1%)**
PR	**4(22.2%)**
SD	**3(16.7%)**
PD	**9(50%)**
Total	**18(100%)**

Efficacy:

Overall, 10 patients (55.6%) achieved PSA response. The median time to PSA progression was 9 months (95% CI: 4.1-13.8). Six (33%) out of 18 patients evaluable for radiographic response per modified RECIST achieved objective radiological response (2 CR & 4 PR) , while 3 patients (16.6%) achieved SD (Table 2).

After a median follow-up time of 13 months (95% CI 6.8–9.2), there were 3 (17%) deaths, and the 1-year OS was 67%. Median overall survival was not reached and the mean was 20 (3-23) months (95% CI 15.4-23.8; Fig. 1).

A total of 12 patients (66.7%) experienced PSA progression. The median time to PSA progression was 10 months (95% CI 6.6–13.4; Fig. 2). The estimated median time of clinical-radiological progression was 13 months (CI 95%: 5.9-20; Fig. 3).

Median time to PSA progression showed no significant statistical differences between patients with and without radiological progression (9 months [CI: 5.3-12.6] vs. 12 months [CI: 5.9-20.3], respectively, $p = 0.3$).

At 3 months of treatment, differences statistically significant are identified regarding median time to radiological progression free survival among patients with and without marker response (13 months [CI: 5.9-20] vs. 8 months [CI: 2.1-13.8], respectively, $p < 0.026$; Fig. 4).
In post-chemotherapy patients, median time to radiological progression free survival was 4 months vs. 13 months in chemo-naïve patients ($p < 0.87$). As well as, median time to PSA progression free survival for post-chemotherapy vs. Chemo-naïve patients was 5 and 10 months, respectively ($p = 0.78$).

Safety:

Due to retrospective design of the study, not all the adverse effects were observed. Selected grade 3/4 adverse events of special interest were hypokalemia (22%) and hypertension (11%). Discontinuation or doses reduction were not required in any patient.

Discussion:

In this retrospective study, we evaluated the effects and tolerability of abiraterone in 18 CRPC Saudi Arabian patients after failure of androgen deprivation therapy or chemotherapy.
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The median age was 73 years, The median PSA levels at the time of enrolment was 56(0.1-1087) ng/mL, visceral metastasis were in 33.3% of our patients which is comparable to the non-clinical trial experience with abiraterone done by Clayton et al. [12] who undertook a multicentre retrospective analysis of Canadian mCRPC patients treated with abiraterone. They included 187 patients who initiated abiraterone. The median age was 73 years. Seventy three (39%) patients had metastatic disease at diagnosis. The median prostate-specific antigen (PSA) at abiraterone start was 132 ng/mL.
The current study showed that AA effectively achieved a PSA response rate (RR) (≥50% decrease) in 55.6% of the patients. The higher PSA response rate is consistent with higher response rates reported in the chemo-naïve subgroup is in COU-AA-302 (62%) [13] While it was higher than in post-chemotherapy (29.5%) reported in COU-AA-301 (29%) [8] and 39% reported by Clayton et al [12].

In the AA-302[13] mean time for radiological progression in patients without previous chemotherapy treatment was16.5 months, higher than the results reported in our series: 13 months (87.8% of patients were treated in pre-chemotherapy).
In post-chemotherapy group, median radiological free-survival progression was 5 months, which is comparable to that published in the COU AA-301[8] (5.6 months) and slightly lower than 6.4months reported by Beardo-Villar et al [14].
In our study, after median follow-up time for survival was 13 months (95% CI 6.8–9.2), there were 3 (17%) deaths, and the 1-year OS was 67%. Median overall survival was not reached, which is the same of COU-AA-302 [13] , in which the median OS was not yet reached in the abiraterone arm and inconsistent with COU-AA-301[8] in which, at a median follow-up of 12.8 months, OS was 14.8 months in the abiraterone.
In our series AA has been well tolerated with grade 3/4 hypokalemia of (22%) and hypertension of (11%) which were consistent with that reported in other clinical studies [8, 12, and 13].
Our study has several limitations: These include its retrospective design, short series enrolment and short follow up period. However, the lack of clinical trials pre-selection of patients, can bring us closer to the expected efficacy of this drug in clinical practice.

Conclusions:

In our series of patients with CRPC, AA is an effective and tolerable treatment. It produces meaningful marker and objective responses, PFS and OS that are comparable to those reported in clinical trials. Better results with chemo-naive patients suggest that AA may be a logical first choice after failure of androgen deprivation therapy.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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