Abiraterone Acetate in Patients with Advanced Castrate Resistant Prostate Cancer: Initial Real Life Experience in 2 Cancer Units

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Abstract: *Introduction*: Abiraterone Acetate (AA) improves outcome of patients with castrate resistant prostate cancer (CRPC) and is currently recommended for chemo-naïve patients and after progression on chemotherapy. We reviewed our initial experience with the use of AA in these patients.

Patients and Methods: Forty six consecutive CRPC patients were treated with AA 1000 mg/day and prednisolone 5 mg twice daily in 2 cancer centres in England and Saudi Arabia. Treatment was continued until disease progression or unacceptable toxicity. Patients achieving prostate specific antigen decline (PSA) ≥ 50% were considered as marker responders.

Results: Median age was 76 (52-91) years. 28 and 18 patients received AA in pre-chemotherapy and post-chemotherapy setting respectively. PSA marker response was achieved in 56.1% (23/41) assessable patients. Objective radiological response rate was seen in 31.6% (6/19) and stable disease in 15.8% (3/19) assessable patients. After a median follow up of 20 months, median time to PSA progression was 12 months (95% CI: 9.5-14.5) and median overall survival was not reached (mean = 21 months, 95% CI: 18-24.5). Toxicity was assessed in 18 patients. All grades adverse events of special interest were hypokalaemia (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, marker progression free survival and OS that are comparable to those reported in clinical trials. Monitoring of blood pressure and serum potassium is recommended.

Keywords: Abiraterone Acetate, Castrate resistant, Prostate cancer, Hormonal therapy.

INTRODUCTION

Growth of prostate cancer is androgen-driven through the activation of the androgen receptors (AR). Surgical or medical castration can achieve significant reduction of testicular sources of androgens resulting in tumour regression and Prostate Specific Antigen (PSA) reduction [1]. Eventually, the tumour escapes from the control of this castration level and thus labelled castrate resistant prostate cancer (CRPC) which has a poor prognosis and remains a significant therapeutic challenge. There is evidence that CRPC frequently continues to be hormone driven by using adrenal intracrine androgens [2,3]. Thus further inhibition of androgen biosynthesis in CRPC by targeting CYP17 enzyme represents a rational therapeutic approach. Certainly, ketoconazole, a weak CYP17 inhibitor has long been recognized to have a modest anti-tumour activity in this setting [4,5].

Abiraterone acetate (AA), a potent, selective and irreversible CYP17 inhibitor was designed and investigated through a complete preclinical and clinical development program. This has led in April 2011 to the United States Food and Drug Administration (US-FDA) approval of AA for the treatment of patients with metastatic CRPC (mCRPC) following docetaxel. In December 2012, the approval was extended to include patients before docetaxel. Due to its efficacy and cost effectiveness, many other licensing and rationing bodies including the United Kingdom National Institute of Clinical Excellence recommended the use of AA.

There is lack of reports from large international post marketing trials. Thus, reports describing the use of AA in daily clinical setting are expected to expand the knowledge of relevant health care professionals. Here, we report the combined initial experience with the use of AA in patients with CRPC in routine clinic practice at 2 cancer units in England and Saudi Arabia.

PATIENTS AND METHODS

Patients were identified from 2 cancer units, namely Colchester General Hospital (CGH) in England and

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ISSN: 1927-7210 / E-ISSN: 1927-7229/16

King Faisal Specialist Hospital-Jeddah (KFSH-J) in Saudi Arabia. All (n=46) consecutive patients (CGH=28 and KFSH-J=18) treated by AA at both units from August 2012 until November 2014 were included. Data was collected retrospectively by the investigators from paper and electronic records. The starting dose of AA was 1000 mg/day combined with prednisolone 5 mg twice daily. Patients achieving PSA decline (PSA) ≥ 50% were considered as marker responders. PSA progression was defined as 25% increase over the nadir PSA. Data on adverse events of special interest namely, hypokalaemia and hypertension was collected.

Statistical Package for the Social Sciences (SPSS 11.5) software was used for data analysis. Time related progression and survival events were analysed using Kaplan-Meier analysis.

RESULTS

Median age was 76 (52-91) years. 28 (70%), 16 (35%) and 2 (4%) had only bone metastases, mixed bone & visceral/nodal metastases and locally extensive disease respectively. 28 (61%) and 18 (39%) patients received AA in pre-chemotherapy and post-chemotherapy setting respectively.

PSA marker response was achieved in 23 (56.1%) of 41 assessable patients (pre-chemotherapy 52% and post-chemotherapy 62.5%, Chi-square P=0.54). Objective radiological response rate was seen in 6 (31.6%) and stable disease in 3 (15.8%) out of 19 assessable patients.

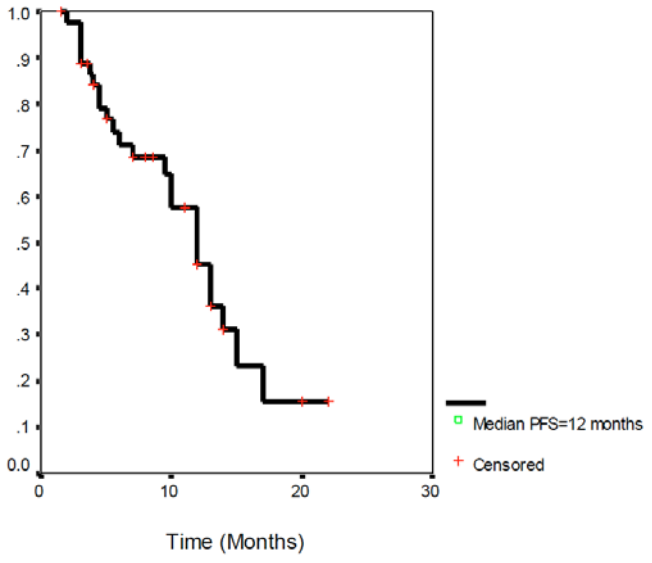

Figure 1: Kaplan-Meier curve for time to PSA progression of all 46 patients.

At time of analysis, 24 (52%) experienced marker and/or radiological progression and 11 (24%) patients died. After a median follow up of 20 months, median time to PSA progression (TTPP) for all patients was 12 months (95% CI: 9.5-14.5) (Figure **1**) and was 12 months for both pre and post-chemotherapy groups.

Median overall survival (OS) was not reached (mean = 21 months, 95% CI: 18-24.5) (Figure **2**) and was not reached for both pre and post-chemotherapy groups (mean; 16.8 and 20.8 respectively).

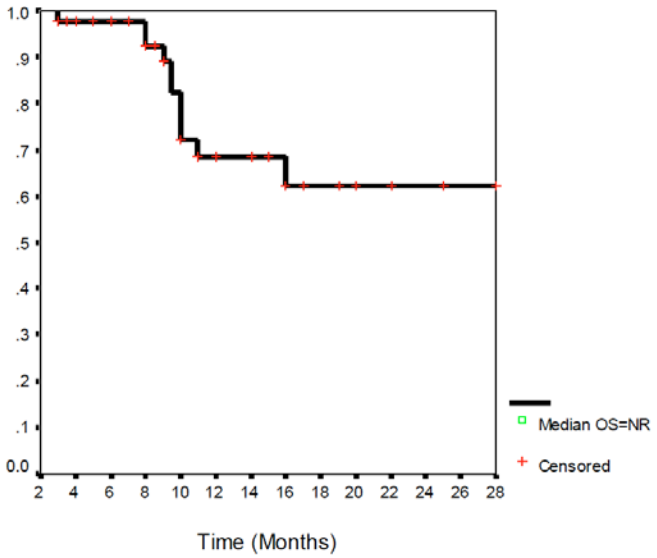

Figure 2: Kaplan-Meier curve for overall survival of all 46 patients.

Data on adverse events of special interest namely, hypokalaemia and hypertension was available only for the 18 patients' cohort from KFSH-J. All grades adverse events of special interest were hypokalaemia (22%) and hypertension (11%). No patient interrupted treatment due to AA toxicity.

DISCUSSION

AA (with low dose prednisone) was first approved for the treatment of patients with mCRPC after progression on docetaxel chemotherapy after the positive results of the COU-AA-301 landmark trial. This was a randomized double-blind, placebo-controlled study which randomized patients to either AA plus prednisone (n=797) or placebo plus prednisone (n=398). The primary endpoint was OS. At median follow-up of 20.2 months, median OS for the AA group was longer than in the placebo group (15·8 vs. 11·2 months; HR 0·74, 95% CI 0·64–0·86; P<0·0001). Median TTPP was 8·5 months in the AA group vs. 6·6 months in the placebo group (HR 0·63, 95% CI

0·52−0·78; P<0·0001). More patients in the AA achieved PSA response (29·5% vs 5·5%; P<0·0001) [6].

Within about a year and a half of the first approval, the US-FDA extended the indication to include patients before docetaxel treatment based on the results of the randomized phase III COU-AA-302 landmark trial. The study was un-blinded after a planned interim analysis after 43% of the expected deaths had occurred and results were published in January 2013. The co-primary end points were radiographic progression free survival (PFS) and OS. Median follow-up period was 22.2 months. The median radiographic PFS was 16.5 months with AA and 8.3 months with prednisone alone (HR 0.53; 95% CI 0.45-0.62; P<0.001). At the time of this first publication, OS improved with AA (median not reached vs. 27.2 months HR 0.75; 95% CI 0.61-0.93; P=0.01) but did not cross the efficacy boundary [7].

The final OS analysis was published in February 2015 after a median follow up of 49.2 months.

At this analysis, median OS was significantly longer in the AA group than in the placebo group (34.7 vs. 30.3 months; HR 0.81; 95% CI 0.70-0.93; P=0.0033). This 4.4 months improvement in median OS was shown in spite of 238 (44%) patients initially receiving prednisone alone subsequently received AA plus prednisone as crossover per protocol (93 patients) or as subsequent therapy (145 patients) [8].

Docetaxel has been the standard of care for patients with CRPC since 2004 [9]. However, eventually all patients develop the disease progression and PSA rises within 7-8 months. In addition, many patients will not be fit enough to receive docetaxel chemotherapy.

For these reasons and based on the above results, AA is as an effective treatment for CRPC whether patients received prior docetaxel or not [6–8]. Both patients groups were included in our cohort. Table **1** illustrates our results and those of the 2 landmark trials [6,7]. We chose the early analysis of COU-AA-302 for comparison as the median follow up was 22.2 months which is close to that of our cohort (20 months). The outcome results compare well to those of the AA arms of the 2 landmark trials reflecting the inclusion of both pre and post-docetaxel patients in our cohort.

It is expected that patients recruited to both phase III trials may have had more favorable feature than patients in our cohort as follow: (a) In COU-AA-301 trial, 90% and 10% of patients had Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0-1 and 2 respectively and all patients in COU-AA-302 trial had ECOG PS of 0-1. We were unable to accurately verify PS of our patients but it is highly likely that many patients in real life practice will have worse PS than those in phase IIII trials. (b) Our patients were older (Table **1**). (c) COU-AA-301 (pre-docetaxel trial) trial included only patients who had no or mild symptoms and also excluded patients with visceral disease. However, these restrictions were not applied to our patients. For example, 7 (25%) of pre-docetaxel patients in our cohort had visceral

Table 1: Comparison of Our Results with Results from Abiraterone Arms of Landmark Trials

	COU-AA-301 Ref [5]	**Our series**	**COU-AA-302 Ref [6]**
Number of patients	797	46	546
Setting	Post-docetaxel	Pre-docetaxel: 28 Post-docetaxel: 18	Pre-docetaxel
Median age (range)	69 (42−95) years	76 (52-91) years	71 (44-95) years
Median follow up (months)	20.2	20	22.2
PSA response	29.5%	56.1%	62%
Radiological response	14.8%	31.6%	36%
Median time to PSA progression (months)	8.5	12	11.1
Median OS (months)	15.8	NR	NR
Hypokalaemia	23%	22%	19%
Hypertension	12%	11%	26%

PSA: Prostate Specific Antigen; OS: Overall Survival; NR: Not Reached.

metastases. This indicates that despite these possible differences, results of AA therapy obtained in phase III trials can be repeated in day to day clinical practice.

Apart from AA, the recent years have seen the development of another effective hormone targeted therapy. Enzalutamide, a potent multi-targeted androgen signaling pathway inhibitor is effective in chemo-naive patients and in those who received docetaxel [10,11].

The currently available evidence indicates that docetaxel, AA and enzalutamide are effective first line treatments for patients with CRPC. However, the optimum sequence is yet to be defined. Choice of treatment can be guided by a) concomitant medical conditions, b) potential side effects of each therapy, c) ECOG-PS of the patient, d) practicality and convenience of treatment administration, e) patient's choice and f) drug availability.

There is rising evidence that adding docetaxel to androgen deprivation therapy (ADT) early in patients with advanced/metastatic castrate sensitive prostate cancer improves OS compared to ADT alone [12,13]. In this case, AR targeting agents such as AA and enzalutamide will likely be the first treatment of choice for patients with mCRPC if they have received docetaxel (with ADT) at earlier castrate sensitive stage.

There is early evidence for cross-resistance between the taxanes (docetaxel and cabazitaxel) and AR targeting agents [14]. Limited data suggests that sequential administration of AA and Enzalutamide in either order has limited activity after docetaxel therapy [15]. Our results do not allow interpretation of AR targeting agents sequencing effect because all patients did not receive enzalutamide prior to AA. However, reassuringly it seems that prior docetaxel therapy did not compromise the effect of AA as PSA response was achieved in 62.5% of post-docetaxel and 52% of pre-docetaxel patients.

Other effective therapeutic interventions available for patients with CRPC include Radium-223 and sipuleucel-T [16,17]. Detailed discussion of these treatments is beyond the scope of this report. Unfolding molecular mechanisms of prostate cancer carcinogenesis, invasion, angiogenesis and drug resistance will likely pave the path to novel therapeutic strategies and thus improving patient's outcome [18].

Our patients tolerated treatment very well. No patient interrupted treatment due to AA toxicity. The design of prospective clinical studies allows excellent capture and documentation of toxicity data. However, this is not necessarily the case during daily routine clinical practice. For this reason we focused on objective treatment specific side effects of AA. Regular assessment of blood pressure and serum electrolytes was conducted for all patients at both units. However, this data is available for analysis in only 18 patients from KFSH-J due to the presence of electronic records system at this unit. Table **1** shows that frequency of hypertension and hypokalemia were in line with reports from other landmark trials.

CONCLUSION

Within the limitations of a relatively small retrospective study, our results demonstrate the favourable safety and efficacy of AA treatment for patients with CRPC. The findings also support the applicability of the COU-AA-301 and COU-AA-301 results to daily clinical practice.

ACKNOWLEDGEMENTS

The authors conducted all this work themselves.

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Received on 22-10-2015 Accepted on 15-01-2016 Published on 05-04-2016

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