Article published online: 2020-12-14

A tertiary care audit of using abiraterone acetate in patients of metastatic castrate-resistant prostate cancer

Amit Joshi, Sameer Shrirangwar, Vanita Noronha, Nilesh Sable[1], Archi Agarwal[2], Palak Popat[1], Atanu Bhattacharjee[3], Kumar Prabhash

Abstract

Introduction: This is a retrospective analysis to assess the safety and efficacy of abiraterone acetate (AA) in metastatic castrate-resistant prostate cancer (mCRPC) patients treated at tertiary care institute. **Materials and Methods:** The clinical records of mCRPC patients treated with AA at our tertiary care institute between July 2013 and December 2015 were reviewed. The treatment efficacy, toxicities, and its determinants were analyzed. **Results:** A total of 59 mCRPC patients treated with AA were reviewed, of whom 37 were chemo-naive and 22 had received prior chemotherapy (postchemo). The median follow-up duration was 10.0/15.0 months for chemo-naïve/postchemotherapy patients. 43.2%/36.36% of chemo-naive/postchemo patients had visceral metastases. The median overall survival (OS) and progression-free survival (PFS) were 15/7.8 months and 10/5.3 months for chemo-naive/postchemo patients, respectively. Median time to best prostate-specific antigen response was 3.4 months. Abiraterone was relatively well tolerated with no grade 4 toxicity or treatment-related death. We found the presence of previous taxene use and baseline symptoms to be significantly determinant of OS with abiraterone. **Conclusion:** The present study reported the efficacy of abiraterone in both chemo-naïve and postchemo patients of mCRPC outside clinical trial setting. We found lower OS and PFS with abiraterone as compared to that reported in the clinical trial setting in both chemo-naïve and postchemo patients, and particularly in those patients with the visceral disease, and further clinical trial for abiraterone in this subgroup of patients is warranted.

Key words: Abiraterone, chemo-naive/postchemo, metastatic castrate-resistant prostate cancer, nontrial setting, visceral disease

Introduction

Androgen deprivation therapy (ADT) is the initial treatment of choice for men with metastatic prostate cancer for the past several years.[1] Although ADT is palliative, it can normalize serum levels of prostate-specific antigen (PSA) in over 90% of patients and can produce objective tumor responses in 80%–90%. This antitumor activity can improve quality of life by reducing bone pain as well as the rates of complications (e.g., pathologic fracture, spinal cord compression, and ureteral obstruction).[2,3] The duration of response to ADT for patients with metastatic disease is highly variable, and most patients eventually progressed to metastatic castrate resistant prostate cancer (mCRPC), although such patients may remain responsive to additional therapies directed against androgenic stimulation of the prostate cancer.

A unique molecular alteration in castration-resistant prostate cancer is the up-regulation of androgen biosynthesis enzymes, leading to an increase in intratumoral androgen concentrations.[4-6] Other alterations include overexpression of androgen receptors, and androgen receptor mutations leading to androgen-receptor binding by additional ligands that would not stimulate the wild-type receptor.[7,8] This has led to the development of drugs which act by inhibition of the enzymes responsible for androgen production, as well as those which inhibit the androgen receptor. Abiraterone acetate (AA), a prodrug of abiraterone, is a selective inhibitor of androgen biosynthesis that potently blocks cytochrome P450 c17, a critical enzyme in testosterone synthesis, thereby blocking androgen synthesis by the adrenal glands and testes and within the prostate tumor. Two randomized phase III trial COU-AA-301 and 302 have demonstrated the efficacy of AA in patients of castrate-resistant prostate cancer in both postdocetaxel and chemo-naïve patients. We report the clinical outcome of metastatic castration-resistant prostate cancer patients treated with AA in real-life clinical practice at our institute.

Materials and Methods

Study design and outcome measures

This is a retrospective analytical study for determining the outcomes of AA in mCRPC. The data regarding demographics, previous treatment, tumor details, toxicities, response, progression, and survival of patients receiving abiraterone was obtained from the electronic medical record. This study was approved by the institutional review board of the author's institution.

The definition of clinical, biochemical, and radiological progressive disease was according to the Prostate Cancer Clinical Trials Working Group-2 criteria.[9] PSA response was defined as ≥50% decline in PSA level from baseline on treatment. Overall survival (OS) and progression-free survival (PFS) were defined as the time from the first dose of AA to death, and to the first event of clinical, radiographic or PSA progression or death, in both chemotherapy naive and postdocetaxel group, respectively. The covariates of interest were explored for OS and PFS.

Study population

The present study included mCRPC patients both chemotherapy naïve and those who are progressed on one or multiple lines of therapy and started on AA between July 2013 and December 2015. Patients were treated with 1000 mg AA once daily in combination with 5 mg prednisone twice a day until disease progression, death or unacceptable toxicity. Clinical and biochemical follow-up with serum PSA, blood counts, liver, renal profile, and imaging when indicated were regularly undertaken during the treatment period.

Statistical analysis

R studio version 3.4.2 was used for analysis. Proportions and frequencies are mentioned for categorical variables while median with interquartile range is used for continuous variables. Patients

Access this article online
Quick Response Code:
Website: www.sajc.org
DOI: 10.4103/sajc.sajc_433_18

Departments of Medical Oncology, [1]Radiology and [2]Nuclear Medicine, Tata Memorial Hospital, [3]Centre for Cancer Epidemiology, TATA Memorial Centre, Mumbai, Maharastra, India
Correspondence to: Dr. Kumar Prabhash, E-mail: kprabhash1@gmail.com

How to cite this article: Joshi A, Shrirangwar S, Noronha V, Sable N, Agarwal A, Popat P, *et al*. A tertiary care audit of using abiraterone acetate in patients of metastatic castrate-resistant prostate cancer. South Asian J Cancer 2020;9:23-6.

who had not expired at last follow-up are censored during the estimation of OS by the Kaplan–Meier method. Factors affecting PFS and OS are identified by COX regression analysis.

Results

Characteristics of patients' cohort

A total of 59 patients were reviewed, of whom 37 were chemo-naïve and 22 were postchemotherapy. Table 1 summarizes the characteristics of the patient cohort. The median follow-up duration was 10 months (2.7, 29.6) and 15 months (3.6, 48.1) for chemo-naïve and postchemotherapy group, respectively. The mean age of the study cohort was 67 years. Comorbidities such as diabetes mellitus, hypertension, and ischemic heart disease were present in 17 (28.8%), 30 (50.8%), and 10 (16.9%) of patients, respectively. Median baseline PSA and Gleason score was 132.5 and 8, respectively. A total of 9 out of 59 patients were diagnosed with localized disease at the time of initial presentation and underwent definitive surgery[4] or radical radiotherapy.[5] These patients also received ADT when they developed metastatic disease. A total of 19 out of 59 (32.2%) patients opted for medical castration and rest of the patient underwent surgical orchidectomy for ADT. At the time of starting AA, visceral disease (lymph node and visceral organ metastases) was present in 16 (43.2%) chemo-naïve and 8 (36.36%) postchemo patients. About 85% of patients were symptomatic for disease, and 14 out of 59 patients received ketoconazole before initiation of AA.

Table 1: Patient's characteristics and treatment details

Parameters	Chemo-naive (*n*=37)	Postchemotherapy (*n*=22)
Age, median (range)	68 (49-84)	66 (55-75)
ECOG, *n* (%)		
0-1	26 (70.2)	19 (86.3)
2	8 (21.6)	3 (13.6)
3	1 (2.7)	0
4	2 (5.4)	0
Gleason score at baseline, *n* (%)		
<8	28 (75.6)	9 (40.9)
>8	8 (21.6)	13 (59.0)
Unknown	1 (2.7)	0
Median PSA	137	129
Symptomatic for disease at the time of starting abiraterone, *n* (%)	30 (81)	20 (90)
Disease location, *n* (%)		
Bone only	21 (56.7)	14 (63.6)
Viscera	16 (43.2)	8 (36.36)
Comorbidities, *n* (%)		
Diabetes mellitus	8 (21.6)	9 (40.9)
Hypertension	21 (56.7)	9 (40.9)
IHD	10 (16.9)	0
Previous cytotoxic regimen, *n* (%)		
1	0	19 (86.36)
2	0	3 (13.6)
ADT, n (%)		
Surgical	22 (59.4)	18 (81.8)
Medical	15 (40.5)	4 (18.1)
PSA response with abiraterone, *n* (%)	15 (39.4)	4 (18.1)
Reasons of discontinuation of abiraterone, *n* (%)		
Disease progression	36 (97.2)	19 (86.3)
Treatment-related complication	1 (2.7)	2 (9.0)
Patient's decision	0	1 (4.5)

PSA=Prostate specific antigen, ADT=Androgen deprivation therapy, ECOG=Eastern Cooperative Oncology Group, IHD=Ischemic heart disease

Clinical efficacy

Prostate-specific antigen response

The proportion of patients with best PSA response is 4 (18.1%) in postchemo groups and 15 (39.4%) in chemo-naïve group [Table 1]. Median time to best PSA response was 3.4 months, with 3/38 chemo-naïve, and 0/22 postchemo patients were still under treatment at the time of the last follow-up. Disease progression was the major reason of treatment discontinuation.

Overall survival and progression-free survival

The median OS and progression-free survival for the complete cohort were 11.9 (95% confidence interval [CI]: 10, 17) months and 6.7 (95% CI: 5.5, 9.9) months, respectively. The patients with visceral disease had numerically inferior OS (9.7 vs. 12.8 months) and inferior PFS (5.8 vs. 8.7 months) than those without visceral disease, which was not statistically significant (*P* value 0.088 and 0.25). The median OS and PFS was 15 months (95% CI: 11.4, 28.1) and 7.8 months (95% CI: 3.9–16.5) for chemo-naïve group and 10 months (95% CI: 7.4, 12.5) and 5.3 (95% CI: 4.3, 9.6) months for postchemo group, respectively [Table 2].

Adverse events

Table 3 shows the treatment-related toxicities in patients treated with AA. We found the following common adverse events (all grades). Nausea 12 (20.3%), hypertension 11 (18.6%), fatigue 11 (18.6%), liver function abnormality 10 (16.9%), vomiting 7 (11.8%), hypokalemia 6 (10.1%), fluid retention 5 (8.4%), thrombocytopenia 3 (5.0%), and cardiac toxicity 2 (3.3%). Two patients required dose modifications due to thrombocytopenia and transaminitis each. Only three patients stopped abiraterone due to toxicity; the reason for it was fluid retention and cardiac toxicity. There was no grade 4 toxicity or treatment-related death among them.

Univariate analysis

In univariate analysis, the presence of the previous taxene used or not was the significant determinant of both OS and PFS with Abiraterone [Table 4] with the $P = 0.004$ and 0.005, respectively. The presence of low Gleason score (hazard ratio [HR] 0.53, 95% CI: 0.33–0.85, $P = 0.0086$) was determinant of best PSA response. HR observed with other covariates such as initial PSA, performance status, stage at diagnosis, and baseline PSA are detailed in Table 4.

Discussion

In a Phase 3, multicenter, randomized, placebo-controlled study by de Bono *et al*.,[10] AA 1000 mg daily with prednisolone 5 mg BD has been shown to improves survival in patients with metastatic castration-resistant prostate cancer who have failed one or two prior chemotherapy regimens, one of which contained docetaxel. In addition, in a study done by Ryan *et al*.,[11] AA with prednisolone has been shown to improve survival in chemotherapy naïve patient also. Till date, no data is available for the use of AA in Indian patients. Hence, we have planned for retrospective analysis of patients receiving AA in mCRPC from July 2013 to December 2015 at our tertiary care institute.

In this study, we reported the efficacy and toxicity of abiraterone in patients of mCRPC from an unselected patient population in a nontrial

Table 2: Overall survival and progression-free survival

	Parameter	Number of patients	Event	Median	95% LCL	95% UCL
Overall study population	PFS	59	56	6.7	5.5	9.9
	OS	59	48	11.9	10	17
Visceral disease (*n*=24)	PFS	24	23	5.8	4.5	7.8
Without visceral disease (*n*=35)		35	33	8.7	5.3	12.8
Visceral disease (*n*=24)	OS	24	21	9.7	7.4	17.4
Without visceral disease (*n*=35)		35	27	12.8	11.3	30.1
Chemo-naïve (*n*=37)	PFS	37	34	7.8	3.9	16.5
Postchemotherapy (*n*=22)		22	22	5.3	4.3	9.6
Chemo-naïve (*n*=37)	OS	37	28	15	11.4	28.1
Postchemotherapy (*n*=22)		22	20	10	7.4	15.5

PFS=Progression-free survival, OS=Overall survival, LCL=Lower confidence limit, UCL=Upper confidence limit

Table 3: Adverse events during treatment

Toxicity	Grade I (%)	Grade II (%)	Grade III (%)	Grade IV (%)
Thrombocytopenia	2 (3.3)	0	1 (1.6)	0
Fatigue	3 (5.0)	6 (10.1)	2 (3.3)	0
Transaminitis	6 (10.1)	0	1 (1.69)	0
Hyperbilirubinemia	3 (5)	0	0	0
Hypokalemia	5 (8.4)	1 (1.69)	0	0
Nausea	12 (20.3)	0	0	0
Fluid retention	4 (6.77)	0	1 (1.69)	0
Cardiac disorder	0	0	2 (3.3)	0
Vomiting	6 (10.1)	0	1 (1.69)	0

Table 4: Univariate Cox proportional hazard analysis on overall survival and progression-free survival

Parameter	OS		PFS	
	HR	*P*	HR	*P*
Initial PSA	1.00	0.29	1.00	0.53
ECOG PS	1.22	0.29	1.20	0.38
Stage at diagnosis	0.91	0.83	1.12	0.74
Baseline PSA before starting of abiraterone	1.00	0.19	1.00	0.17
Gleason score	1.16	0.29	1.18	0.24
Previous taxene (yes or no)	2.42	0.004	2.24	0.005
Baseline symptoms	3.32	0.014	1.90	0.084
Site of metastasis (visceral or others)	1.65	0.088	1.377	0.25

PFS=Progression-free survival, OS=Overall survival, PSA=Prostate specific antigen, ECOG PS=Eastern Cooperative Oncology Group performance status, HR=Hazard ratio

setting. The inclusion of all abiraterone treated patients at our institute during a defined period serves to provide a representative picture of the efficacy of abiraterone in real-world setting.

In our study, unexpectedly, the median PFS and OS of chemo-naïve patients were remarkably much shorter than that reported in COU-AA-302 study.[11] In contradiction to above in post chemo group we found the tolerability and PFS with abiraterone similar to what reported in COU-AA-301 study, however OS was found to be inferior similar to chemo naive group.[10] The reasons for this difference may be explained by relatively high tumor burden (which is supported by a higher median baseline PSA level) in our patient cohort, unselected patient population in contrast to clinical trial, nonaffordability for further lines of therapy and small sample size. In addition, many of our patients received (14 out of 59) prior ketokonazole, (patient group that was excluded in both COU-AA-301 and COU-AA-302 study, due to the potential overlapping mechanism of action) which has been shown to be associated with inferior outcome with Abiraterone. In a study by Kim *et al*.[12] on sequential use of the androgen synthesis inhibitors ketoconazole and AA in castration-resistant prostate cancer demonstrated modest clinical efficacy with abiraterone inpatients previously treated with ketoconazole [Table 5]. Besides this, our study cohort included 85% of symptomatic patients when compared with COU-AA-302 study in which only asymptomatic or mildly symptomatic patients were included.

In our cohort, abiraterone effectively achieved a PSA response (≥50% PSA decline) in 15 (39.4%) chemotherapy-naive patients and 4 (18.1%) postdocetaxel patients. All biochemical responses were achieved within a median of 7 months of treatment. We found that achievement of the best PSA response after abiraterone is a favorable prognostic factor which is in consistency with prior studies.[10,11]

While the efficacy of abiraterone in with visceral metastases or symptomatic disease is not clear, our study suggests that patients with high tumor burden, visceral metastases may have inferior outcome with abiraterone in terms of PFS and OS. In contrast, as seen in the subgroup analysis in the TAX 327 study the presence of symptomatic or visceral metastasis did not confer inferior clinical outcome to docetaxel-based chemotherapy.[13] With the lack of randomized trial specifically addressing this issue, the practice of using abiraterone in this particular subgroup should be further evaluated.

Limitations of the present study include the usual shortcomings of retrospective study such as under-reporting of adverse events, incompleteness of data collection and selection bias. However, these limitations should not affect the ability to calculate the survival outcome of abiraterone.

Conclusion

The present study reported the efficacy abiraterone in both chemo-naïve and postchemo patients of mCRPC outside clinical trial setting. We found lower OS and PFS with abiraterone as compared to that reported in the clinical trial setting in both chemo-naïve and postchemo patients, and particularly in those patients with visceral disease, and further clinical trial for abiraterone in this subgroup of patients is warranted.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Hellerstedt BA, Pienta KJ. The current state of hormonal therapy for prostate cancer. CA Cancer J Clin 2002;52:154-79.
2. Loblaw DA, Virgo KS, Nam R, Somerfield MR, Ben-Josef E, Mendelson DS, *et al*. Initial hormonal management of androgen-sensitive metastatic,

Table 5: Clinical outcome in the present study and the abiraterone acetate pivotal trials

Survival outcome	Present study (Chemo-naïve)	COU-AA-302 study	Present study (postchemotherapy)	COU-AA-301 study
Median OS, months	15.06	34.7	10.06	15.8
Median PFS, months	7.86	16.5	5.36	5.6
PSA response, %	39.4	62	18.1	29

PFS=Progression-free survival, OS=Overall survival, PSA=Prostate specific antigen

recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology Practice Guideline. J Clin Oncol 2007;25:1596-605.
3. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, *et al.* EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol 2014;65:467-79.
4. Holzbeierlein J, Lal P, LaTulippe E, Smith A, Satagopan J, Zhang L, *et al.* Gene expression analysis of human prostate carcinoma during hormonal therapy identifies androgen-responsive genes and mechanisms of therapy resistance. Am J Pathol 2004;164:217-27.
5. Stanbrough M, Bubley GJ, Ross K, Golub TR, Rubin MA, Penning TM, *et al.* Increased expression of genes converting adrenal androgens to testosterone in androgen-independent prostate cancer. Cancer Res 2006;66:2815-25.
6. Montgomery RB, Mostaghel EA, Vessella R, Hess DL, Kalhorn TF, Higano CS, *et al.* Maintenance of intratumoral androgens in metastatic prostate cancer: A mechanism for castration-resistant tumor growth. Cancer Res 2008;68:4447-54.
7. Scher HI, Sawyers CL. Biology of progressive, castration-resistant prostate cancer: Directed therapies targeting the androgen-receptor signaling axis. J Clin Oncol 2005;23:8253-61.
8. Attard G, Cooper CS, de Bono JS. Steroid hormone receptors in prostate cancer: A hard habit to break? Cancer Cell 2009;16:458-62.
9. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, *et al.* Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008;26:1148-59.
10. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, *et al.* Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995-2005.
11. Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, *et al.* Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013;368:138-48.
12. Kim W, Zhang L, Wilton JH, Fetterly G, Mohler JL, Weinberg V, *et al.* Sequential use of the androgen synthesis inhibitors ketoconazole and abiraterone acetate in castration-resistant prostate cancer and the predictive value of circulating androgens. Clin Cancer Res 2014;20:6269-76.
13. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, *et al.* Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502-12.