Real-world safety profile of abiraterone acetate in patients with castration-resistant prostate cancer and cardiovascular comorbidities: a retrospective, single center study

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Abstract

Background Abiraterone acetate became a referral treatment for metastatic castration-resistant prostate cancer (mCRPC) in a post-docetaxel setting despite a remarkable percentage of cardiovascular adverse events (AEs). As a consequence, the evaluation of cardiovascular safety in patients at risk should be mandatory. We aimed to assess the cardiovascular safety of abiraterone acetate in a real-world series of mCRPC patients treated at our institution.

Materials and Methods We retrospectively included mCRPC patients with at least 1 active cardiovascular comorbidity or risk factor according to the European Society of Cardiology (ESC) guidelines and who started treatment with abiraterone acetate from April 2011 to July 2012. Cardiac assessment with electrocardiogram and echocardiogram was performed at baseline and at treatment discontinuation. AEs were defined according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Statistical analyses were performed by descriptive statistics as appropriate.

Results We included 51 patients of whom 18% had an ESC score risk for a major cardiovascular event ≥4%. At a median follow-up of 36 months, no cardiac AEs (rhythm abnormalities or left ventricular function decrease) were observed. The most frequent grade 1-2 AE reported was fluid retention (18%) followed by hypertension and asthenia (16%). The most frequent grade 3-4 AEs were asthenia and pruritus/rash. No patients discontinued abiraterone because of toxicity.

Conclusions Abiraterone acetate showed a favorable safety profile in mCRPC patients with cardiovascular comorbidities or risk factors in a post-docetaxel setting, but further studies are needed to confirm our findings and to explore other settings of disease.

Key words: mCRPC, abiraterone, cardiovascular safety

Introduction

In metastatic castration-resistant prostate cancer (mCRPC), abiraterone acetate has been shown to prolong patient survival [1,2] and became a referral treatment both in a pre- and post-docetaxel setting. However, sequential strategy and agents used should be tailored to patient characteristics. Of note, a large proportion of metastatic prostate cancer (mPC) patients is represented by elderly patients usually typified by the presence of frailty and cardiovascular comorbidities [3], that could affect prognosis independently from the outcomes of prostate cancer [4]. As a consequence, the evaluation of cardiovascular risk for each treatment option should be mandatory.

Due to its action of lowering testosterone by inhibition of CYP-17, abiraterone acetate could lead to a mineralocorticoid excess mediated by a rebound upregulation of ACTH levels, raising the global cardiovascular risk [5]. Despite the favorable tolerability profile of abiraterone in mCRPC patients, a remarkable percentage of adverse events (AEs) potentially worsening cardiovascular risk have been reported in pivotal phase III studies (i.e. fluid retention, hypokalemia, hypertension and cardiac

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events) [6, 7], and these evidences were corroborated by the results of a metanalysis assessing the cardiovascular risk linked with new hormonal agents [8].

Here we aim retrospectively to assess the cardiovascular safety of abiraterone acetate in a real-world series of mCRPC patients treated at the Fondazione IRCCS Istituto Nazionale dei Tumori of Milan.

Materials and methods

Patient population

We retrospectively included mCRPC patients with at least 1 active cardiovascular comorbidity or risk factor according to the European Society of Cardiology (ESC) guidelines [9] and who started a treatment with abiraterone acetate 1000 mg once daily plus prednisone 5 mg twice daily at the Fondazione IRCCS Istituto Nazionale dei Tumori of Milan from April 2011 to July 2012. The presence of the following cardiovascular comorbidities or risk factors was considered for patient inclusion: hypertension, ischemic heart disease, rhythm disorder, valvular disorder, stroke and peripheral vascular disease, diabetes and hyperglycemia, hypercholesterolemia, nutritional status (assessed using body mass index) and smoking history. All patients should have received at least one docetaxel-based treatment and have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2. Other key criteria for patient inclusion were: age ≥18 years old and absence of brain metastases or concomitant illnesses other than controlled cardiovascular diseases. Data regarding clinicopathological characteristics were retrieved from medical charts.

Cardiovascular and safety assessment

Cardiovascular risk was assessed using the ESC score risk chart [9]. As per clinical practice, baseline cardiovascular assessment was performed and included electrocardiogram (ECG), echocardiogram (ECHO), left-ventricular ejection fraction (LVEF) and blood pressure. ECG, ECHO and LVEF were repeated at the end of treatment. Blood pressure was assessed daily. Data regarding cardiovascular history and cardiac AEs, defined according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [10], were retrieved from medical charts.

Statistical analysis

Safety data were analyzed by descriptive statistics as appropriate (mean, standard deviation, minimum and maximum values for continuous variables; absolute and relative frequencies for categorical variables).

Results

Patient characteristics

A total of 51 patients who started a treatment with abiraterone acetate at our institution from April 2011 to July 2012 and presented cardiovascular comorbidities or risk factors were included. Clinical and pathologic characteristics are summarized in Table 1. Median age was 71 years (range 51-85), and 41% of patients received more than 1 previous line of hormonal therapy, while 49% received more than 1 line of docetaxel-based chemotherapy.

Cardiovascular comorbidities and risk factors

Overall, 9 out of 51 patients (18%) had an ESC score risk for major cardiovascular event ≥4%. Cardiovascular comorbidities and risk factors for the entire study population are shown in Table 2. The most frequent cardiovascular comorbidity was hypertension (80%) followed by ischemic heart disease (12%) and stroke history (9%). The most prevalent risk factor was smoking (current or former, 69%) followed by overweight (39%) and hyperglycemia (30%). All patients received medications for cardiovascular comorbidities or risk factors, and 15 (29%) received a polytherapy.

Table 1. Patient demographical and clinical characteristics at baseline.

Characteristic	Study population (n=51)
Age, median (range)	71 (51-85)
Gleason score, median (range)	4+4 (1+2-5+5)
ECOG PS, n (%)	
0	25 (49)
1	15 (29)
2	11 (22)
Sites of metastasis, n (%)	
Bone only	19 (37)
Visceral only	13 (26)
Visceral and bone	19 (37)
Previous hormonal therapies, n (%)	
1	30 (59)
>1	21 (41)
Previous chemotherapies, n (%)	
1	26 (51)
>1	25 (49)

ECOG PS: Eastern Cooperative Oncology Group performance status.

Table 2. Cardiovascular comorbidities and risk factors.

Cardiovascular comorbidities, n (%)	
Hypertension	
Controlled	21 (41)
Uncontrolled	20 (39)
Ischemic heart disease	6 (12)
Rhythm disorders	3 (6)
Vascular disorders	3 (6)
Stroke	5 (9)
Thrombosis	4 (7)
Peripheral vascular disease	2 (4)
Cardiovascular risk factors, n (%)	
Metabolic disorders	
Hyperglycemia	15 (30)
Type 2 diabetes mellitus	6 (12)
Hypercholesterolemia	9 (18)
Nutritional status	
Overweight	20 (39)
Obesity class I	10 (20)
Obesity class II	6 (12)
Obesity class III	4 (8)
Former smoker status	
>20 cigarettes/day	5 (10)
≤20 cigarettes/day	5 (10)
Current smoker status	
>20 cigarettes/day	16 (31)
≤20 cigarettes/day	9 (18)

Safety of abiraterone acetate

The median follow-up for safety observation was 36 months (range 12-48) while the median duration of abiraterone treatment was 16 months (range 9-21). No cardiac AEs (ECG abnormalities or LVEF decrease) were observed during the study period (Table 3). The most frequent grade 1-2 AE reported was fluid retention (18%) followed by hypertension and asthenia (16%). Most frequent grade 3-4 AEs were asthenia and pruritus/rash. While a dose reduction was needed in 5 out of 51 patients (9.8%), no abiraterone discontinuation was due to toxicity. At the end of follow-up, 3 out of 51 patients (6%) were still receiving abiraterone while 12 (23%) were alive.

Discussion

In prostate cancer, selecting a safe and appropriate antitumor treatment in patients with cardiovascular comorbidities may be a hard challenge. The introduction of abiraterone acetate unquestionably improved clinical outcomes and treatment manageability in mCRPC [6], but numerous doubts arose regarding its cardiovascular safety profile, due to the mechanism of action and characteristic toxicity [11]. Here we have shown that, in a retrospective series of 51 mCRPC patients with cardiovascular comorbidities or risk factors, long-term exposure to abiraterone acetate in a post-docetaxel setting did not result in a clinically relevant incident of cardiac or cardiovascular AEs. In particular, in line with previous reports [12], no ECG abnormalities were observed, and no decrease in left ventricular function occurred during abiraterone treatment. Notably, long-term follow-up did not show any cardiovascular impairment, even in patients with clinically- impacting cardiovascular comorbidities (i.e., ischemic heart disease or rhythm disorders).

It has been reported that androgen synthesis inhibitors used as second-line agents in mCRPC after docetaxel cause a significant increase in risk for mineralocorticoid-related AEs due to elevated mineralocorticoid secretion [11-13]. Linked to this effect, the AEs most frequently reported in our study were fluid retention and hypertension. Notably, hypertension had an incidence comparable to that previously reported in the same setting (11%) in the phase III study COU-AA-301 [6] while fluid retention had a lower incidence (18% in our series *vs* 33% in the COU-AA-301 study).

It is clear that balancing the risks and effectiveness of androgen deprivation therapy remains an open question in mCRPC [14-16]. In alignment with data from several reports showing a very low incidence of grade 3-4 cardio-

Table 3. Adverse events (AEs) during abiraterone acetate treatment.

Adverse events	Grade 1-2 n (%)	Grade 3-4 n (%)
Mineralocorticoid-related AEs		
Fluid retention	9 (18)	–
Hypertension	8 (16)	–
Other AEs		
Asthenia	8 (16)	2 (3)
Abdominal pain	2 (4)	–
Pruritus/rash	1 (2)	2 (3)
Nausea	1 (2)	1 (2)
Anemia	1 (2)	–
Diarrhea	1 (2)	–
Cardiac AEs		
ECG abnormalities	–	–
LVEF decrease	–	–

Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
ECG: electrocardiogram; LVEF: left-ventricular ejection fraction.

vascular AEs [17-20], we did not report any grade 3-4 AEs following abiraterone treatment in our series, confirming a favorable safety profile for this frail population.

Clearly, the retrospective nature of the study, the small number of patients included and the lack of a control group limits the power of our observations. Thus, large multicentric, prospective trials are needed to corroborate our findings. Moreover, two large studies, the LATITUDE trial and the STAMPEDE trial, recently supported the use of abiraterone acetate as a treatment option for metastatic castration-naive prostate cancer (mCNPC) but showed an incidence of mineralocorticoid-related AEs even higher than that reported in mCRPC [21, 22]. Certainly, the assessment of the safety profile of abiraterone acetate in the presence of cardiovascular comorbidities or risks is essential in this setting.

In conclusion, abiraterone acetate seems to be safe in mCRPC patients with cardiovascular comorbidities or risk factors in the post-docetaxel setting. Further studies are needed to confirm our findings and to explore the manageability of abiraterone acetate administration in patients with mCRPC in the pre-docetaxel setting and in mCNPC.

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Conflicts of Interest

The Authors declare there are no conflicts of interest in relation to this article.

References

1. de Bono JS, Logothetis CJ, Molina A et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364(21):1995-2005.
2. Ryan CJ, Smith MR, de Bono JS et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013;368(2):138-48.
3. Gandaglia G, Sun M, Popa I et al. Cardiovascular mortality in patients with metastatic prostate cancer exposed to androgen deprivation therapy: a population-based study. Clin Genitourin Cancer 2015;13(3):e123-e130.
4. Groome PA, Rohland SL, Siemens DR et al. Assessing the impact of comorbid illnesses on death within 10 years in prostate cancer treatment candidates. Cancer 2011;117(17):3943-52.
5. Attard G, Reid AH, Auchus RJ et al. Clinical and biochemical consequences of CYP17A1 inhibition with abiraterone given with and without exogenous glucocorticoids in castrate men with advanced prostate cancer. J Clin Endocrinol Metab 2012;97(2):507-16.
6. Fizazi K, Scher HI, Molina A et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2012;13(10):983-92.
7. Ryan CJ, Smith MR, Fizazi K et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2015;16(2):152-60.
8. Iacovelli R, Verri E, Cossu Rocca M et al. The incidence and relative risk of cardiovascular toxicity in patients treated with new hormonal agents for castration-resistant prostate cancer. Eur J Cancer 2015;51(14):1970-77.
9. Perk J, De Backer G, Gohlke H et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J 2012;33(13):1635-701.
10. National Institutes of Health/National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. 2009.
11. Perletti G, Monti E, Marras E et al. Efficacy and safety of second-line agents for treatment of metastatic castration-resistant prostate cancer progressing after docetaxel. A systematic review and meta-analysis. Arch Ital Urol Androl 2015;87(2):121-9.
12. Mulders PF, Molina A, Marberger M et al. Efficacy and safety of abiraterone acetate in an elderly patient subgroup (aged 75 and older) with metastatic castration-resistant prostate cancer after docetaxel-based chemotherapy. Eur Urol 2014;65(5):875-83.
13. O'Donnell A, Judson I, Dowsett M et al. Hormonal impact of the 17alpha hydroxylase/C(17,20)-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer. Br J Cancer 2004;90(12):2317-25.
14. Alibhai SM. Cardiovascular toxicity of androgen deprivation therapy: a new door opens. J Clin Oncol 2011;29(26):3500-2.
15. Bourke L, Kirkbride P, Hooper R et al. Endocrine therapy in prostate cancer: time for reappraisal of risks, benefits and cost-effectiveness? Br J Cancer 2013;108(1):9-13.
16. Prati V, Ruatta F, Gernone A et al. Prospective evaluation of the cardiovascular safety profile of abiraterone acetate (AA) in mCRPC patients (pts) [Abstract]. J Clin Oncol 2016;34(no. 15_suppl):e16534.
17. Tolcher AW, Chi KN, Shore ND et al. Effect of abiraterone acetate plus prednisone on the QT interval in patients with metastatic castration-resistant prostate cancer. Cancer Chemother Pharmacol 2012;70(2):305-13.
18. Sternberg CN, Castellano D, Daugaard G et al. Abiraterone acetate for patients with metastatic castration-

resistant prostate cancer progressing after chemotherapy: final analysis of a multicentre, open-label, early-access protocol trial. Lancet Oncol 2014;15(11):1263-8.
19. Caffo O, De Giorgi U, Fratino L et al. Safety and clinical outcomes of patients treated with abiraterone acetate after docetaxel: results of the Italian Named Patient Programme. BJU Int 2015;115(5):764-71.
20. Maines F, Caffo O, De Giorgi U et al. Safety and clinical outcomes of abiraterone acetate after docetaxel in octogenarians with metastatic castration-resistant prostate cancer: results of the Italian Compassionate Use Named Patient Programme. Clin Genitourin Cancer 2016;14(1):48-55.
21. James ND, de Bono JS, Spears MR et al. Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 2017;377(4):338-51.
22. Fizazi K, Tran N, Fein L et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017;377(4):352-60.