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Safety of long-term exposure to abiraterone acetate in patients with castration-resistant prostate cancer and concomitant cardiovascular risk factors

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Abstract

Background: We aimed to evaluate the long-term safety profile of abiraterone in patients with metastatic castration-resistant prostate cancer (mCRPC) with controlled cardiovascular comorbidities or risk factors.

Methods: We retrospectively analysed the clinical charts of consecutive mCRPC patients with cardiac disorders/risk factors who had been treated with abiraterone 1000 mg once daily plus prednisone 5 mg twice daily for a median duration of 16 months at an oncology referral centre between April 2011 and July 2015. Patients underwent an electrocardiogram (ECG) and echocardiographic assessments, including measurement of left ventricular ejection fraction (LVEF) at baseline and at the end of treatment. Blood pressure (BP) was measured daily at home. During follow up (median 24 months), all adverse events were recorded. Cardiac events (CEs) were defined, according to Common Terminology Criteria for Adverse Events version 4.0, as the appearance of a symptomatic CE that required medical intervention.

Results: A total of 51 patients (median age 71 years) were evaluated. Pre-existing cardiovascular conditions included hypertension (41%), cardiac ischaemia (12%), stroke (9%), dyslipidaemia (18%) and type 2 diabetes mellitus (12%). No CEs were recorded and no changes in LVEF were observed. The most frequently reported adverse events were Grade 1–2 fluid retention (18%), hypertension (16%) and asthenia (16%). No patients permanently discontinued abiraterone due to cardiac events.

Conclusions: Long-term abiraterone treatment was well tolerated in mCRPC patients with controlled cardiovascular comorbidities/risk factors, with no apparent worsening of cardiovascular conditions from baseline over an extended observation period.

Keywords: abiraterone acetate, cardiovascular risk factors, castration-resistant prostatic cancer, prostate cancer, retrospective study, safety

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Introduction

Long-term safety has become a central issue in the selection of prostate cancer treatments, for several reasons. Prostate cancer mostly affects older men, with a median age at diagnosis of 68 years [Mottet *et al*. 2015]. The percentage of the population aged ⩾65 years is rapidly growing, and it is estimated that by year 2040 it will represent 14% of the overall population worldwide, compared with 7% recorded in 2008 [Kinsella and Wan, 2009]. The proportion of men with 5-year survival after prostate cancer diagnosis has also increased considerably in the last two decades, with data from Italian registries documenting an increase from 79.1% between 1995 and 1999 to 89.7% between 2005 and 2009 [Allemani *et al*. 2015], and further improvement of survival is expected after the recent introduction of a number of new treatment options, especially in the metastatic disease setting [Sternberg *et al*.

2014b]. The ageing of the population and the improved life expectancy are generating an increasingly larger subgroup of men with advanced age who require prostate cancer therapy for longer periods of time. Although it is generally agreed that older age (whatever cut-off point one decides to use to define 'elderly') does not reduce the chance of benefit from systemic therapy [Mottet *et al.* 2015; Suzman and Eisenberger, 2014], selecting an appropriate and well tolerated treatment in this patient population can be challenging. As age increases, so does the likelihood of frailty, comedication and comorbidities, making this age group particularly vulnerable to the potential toxicity of anticancer drugs [Falci *et al.* 2009; Sajid *et al.* 2011]. Patients with metastatic prostate cancer show a high prevalence of cardiovascular comorbidities [Gandaglia *et al.* 2015], and cardiovascular disease is known to be the most common cause of nonprostate cancer-related death [Groome *et al.* 2011]. It is necessary, therefore, for a careful assessment of the impact that drugs used in this context might have on the cardiovascular risk of treatment candidates.

While the correlation between androgen deprivation therapy and cardiovascular toxicity remains a controversial topic [Alibhai, 2011; Bourke *et al.* 2013; Iacovelli *et al.* 2015], much attention has been focused in recent years on the new hormonal agents, abiraterone acetate and enzalutamide, that have changed treatment paradigms in patients with metastatic castration-resistant prostate cancer (mCRPC). Abiraterone inhibits testosterone production by inhibiting CYP-17, an enzyme expressed in gonadal, adrenal and prostatic tumour tissues. Its mechanism of action leads to a rebound increase in adrenocorticotropic hormone (ACTH) levels, resulting in mineralocorticoid excess (a process which is mitigated by coadministration of corticosteroids) [Attard *et al.* 2012]. Mainly for this reason, there are concerns that abiraterone therapy might increase the risk of cardiovascular adverse events, especially in predisposed subjects. In fact, data on the cardiovascular safety of abiraterone obtained during clinical development have been largely reassuring [Hoy, 2013]. In pivotal phase III trials, abiraterone plus prednisone significantly increased survival in mCRPC patients, both chemotherapy-naïve and post-docetaxel, while demonstrating a favourable tolerability profile, although fluid retention, hypokalaemia, hypertension and cardiac events (CE) were reported in a higher percentage of abiraterone-treated patients compared with placebo [Fizazi *et al.* 2012; Ryan *et al.* 2015]. A recent meta-analysis found an increased risk of cardiovascular toxicity associated with the use of new hormonal agents *versus* placebo [relative risk (RR) 1.32, 95% CI 1.08–1.60; $p = 0.006$], although the absolute difference in the incidence of CEs was small [Iacovelli *et al.* 2015]. However, patients taking part in clinical trials are generally selected to exclude cardiovascular comorbidities and thus are not necessarily representative of the population encountered in real-world practice. To the best of the authors' knowledge, no prospective studies have been conducted on the safety of abiraterone in patients with cardiovascular comorbidities.

In a previously published study, we retrospectively assessed the safety of abiraterone in a real-world cohort of consecutive patients with mCRPC and concomitant cardiovascular diseases or risk factors treated at our institution over a 21-month follow-up period [Procopio *et al.* 2015]. In this paper, we report conclusive safety data in this patient population after an extended observation period up to 4 years.

Patients and methods

The charts of patients with histologically-confirmed mCRPC who had been treated with abiraterone at our institution between April 2011 and July 2015 and had $\geqslant 1$ concomitant controlled cardiovascular diseases or cardiovascular risk factors were reviewed. Cardiovascular comorbidities and risk factors for consideration in our study were defined according to the indications of the European Society of Cardiology (ESC) and included hypertension [defined as a repeated elevation in blood pressure (BP) exceeding 140 over 90 mmHg], cardiac ischaemia, rhythm disorders, valvular disorders, stroke, thrombosis, peripheral vascular disease, diabetes, hypercholesterolaemia, smoking and obesity. ESC risk charts were used to assess the cardiovascular risk of the observed population.

Full details of the study methods have been published previously [Procopio *et al.* 2015]. Briefly, patients were $\geqslant 18$ years old, had received $\geqslant 1$ docetaxel-based regimen, their Eastern Cooperative Oncology group (ECOG) performance status (PS) was $\leqslant 2$ and their life expectancy was $\geqslant 3$ months. Patients with brain metastases or concomitant illnesses other than

controlled cardiovascular diseases, including serious respiratory diseases, unstable angina, uncontrolled hypertension (defined as ⩾160 mmHg systolic BP or ⩾90 mmHg diastolic BP unresponsive to medical treatment), unstable diabetes mellitus, serious infections or autoimmune disorders, were excluded.

At baseline, patients were screened for the presence of cardiac risk factors as part of the clinical assessment, and a cardiologist performed an electrocardiogram (ECG) and an echocardiographic examination, which included measurement of the left ventricular ejection fraction (LVEF). ECG and echocardiographic evaluation were repeated at the end of the treatment period. BP was measured at baseline and patients were instructed to take daily measurements at home and keep a record of the values obtained. CEs were defined, according to Common Terminology Criteria for Adverse Events version 4.0, as the appearance of a symptomatic CE (hypertension grade ⩾2, heart failure, myocardial infarction, angina, rhythm disorders) that required medical intervention.

Patients received oral treatment with abiraterone 1000 mg once daily plus prednisone 5 mg twice daily until disease progression, symptomatic deterioration or onset of unacceptable toxicity. In case of grade 3–4 toxicities considered to be treatment related, abiraterone was reduced to a daily dose of 500 mg or temporarily discontinued. If no recovery to grade 0–1 toxicity was achieved within 2 weeks, treatment was permanently discontinued. Efficacy assessments, based on evaluation of biochemical and objective response, were made at 3-monthly intervals. Biochemical response was defined as partial response [(PR) ⩾50% prostate-specific antigen (PSA) reduction from baseline], complete response [(CR) PSA normalization], progressive disease [(PD) ⩾50% PSA increase from baseline] or stable disease [(SD), any other PSA variation]. Radiological objective response was assessed by computed tomography or bone scan according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 criteria [Eisenhauer *et al.* 2009] and Prostate Cancer Clinical Trials Working Group (PCWG2) criteria [Scher *et al.* 2008].

The study protocol was approved by the Institutional Review Board and all patients included in the study provided written informed consent.

Data regarding safety and efficacy were independently extracted from standardized forms. Descriptive statistics were used to analyse all clinical and instrumental variables (mean, standard deviation, minimum–maximum values for continuous variables, and absolute and relative frequencies for categorical variables).

Results

A total of 51 patients with mCRPC and cardiovascular comorbidities or risk factors who were treated with abiraterone between April 2011 and July 2015 were included in our analysis. The patients' baseline characteristics are summarized in Table 1. Median age was 71 years, mean PSA was 154 ng/ml and most patients had metastatic bone disease (74%). Prior to abiraterone, patients had received ⩾2 lines of hormonal therapy and ⩾1 docetaxel-based chemotherapy regimen. Cardiovascular comorbidities or risk factors are summarized in Table 2. The most frequent pre-existing cardiovascular diseases were hypertension (41%), cardiac ischaemia (12%) and stroke (9%). Among patients with cardiovascular risk factors, 39% were overweight, 31% were heavy smokers (>20 cigarettes/day), 30% had hyperglycaemia, 18% had dyslipidaemia and 12% had type 2 diabetes mellitus. Cardiovascular comorbidities and risk factors had been present for ⩾1 year. Overall, the risk to develop fatal cardiovascular diseases was ⩽4%, as calculated from ESC score risk charts for 82.3% of patients. During the study, cardiovascular comorbidities and risk factors were controlled by using appropriate medical treatment, including antihypertensive therapies (e.g. ACE inhibitors, angiotensin II receptor antagonists, β-blockers, calcium antagonists or diuretics), statins, metformin and insulin. Most patients (71%) who were treated for cardiovascular conditions received a monotherapy.

During the observation period, no CEs were recorded and no changes in LVEF were observed in the final echocardiographic evaluation. All recorded adverse events are reported in Table 3. The most common adverse events were grade 1–2 fluid retention (18%), hypertension (16%) and asthenia (16%). The only grade 3–4 adverse events were asthenia, skin disorders (2 patients each) and nausea (1 patient). The reason for abiraterone discontinuation was disease progression. No patients permanently discontinued abiraterone due to adverse events. A dose

Table 1. Demographic and clinical characteristics of the study cohort ($n = 51$) at baseline.

Characteristic	Median (range)
Age (years)	71 (51–85)
Gleason score	4 + 4 (1 + 2–5 + 5)
PSA (ng/ml)	154 (6.4–2634)
ECOG performance status	1 (0–2)
Metastatic sites, n (%)	
Bone only	19 (37)
Other (lung + liver + nodes)	13 (26)
Bone + other	19 (37)
Previous lines of therapy, n (%)	
Hormonal therapy	
1	30 (59)
>1	21 (41)
Chemotherapy	
1	26 (51)
>1	25 (49)

ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.

Table 2. Pre-existing cardiovascular comorbidities and risk factors in the study population.

	n (%)
Hypertension	21 (41)
Controlled	20 (39)
Uncontrolled	1 (2)
Cardiac ischaemia	6 (12)
Rhythm disorders	3 (6)
Vascular disorders	3 (6)
Stroke	5 (9)
Thrombosis	4 (7)
Peripheral vascular disease	2 (4)
Hyperglycaemia	15 (30)
Type 2 diabetes mellitus	6 (12)
Hypercholesterolaemia	9 (18)
Smoker status	
Never smoker	16 (31)
Smoker	25 (49)
>20 cigarettes/day	16 (31)
⩽20 cigarettes/day	9 (18)
Former smoker	10 (20)
>20 cigarettes/day	5 (10)
⩽20 cigarettes/day	5 (10)
BMI	
Normal BMI	31 (61)
Overweight	20 (39)
Obesity class I (BMI ⩾ 30 but <35 kg/m^2)	10 (20)
Obesity class II (BMI ⩾ 35 but <40 kg/m^2)	6 (12)
Obesity class III (BMI ⩾ 40 kg/m^2)	4 (8)

BMI, Body mass index.

reduction to 500 mg/day was needed in 5 (9.8%) patients.

At the end of the follow-up period (July 2015), 12 (23%) patients were alive and 3 (6%) were still receiving abiraterone. Median follow up for alive patients was 33 months (range 12–48 months) and median duration of abiraterone exposure was 16 months (range 9–21 months). For all deceased patients, the cause of death was prostate cancer.

As for the efficacy analysis, the median duration of overall survival was 19 months. PSA assessment showed CR in 5 (9%) patients, PR in 19 (37.4%), SD in 9 (17%) and PD in 18 (35%). Of the 25 patients (49%) evaluable for radiological response, 5 (20%) had PR, 10 (40%) had SD and 10 (40%) had PD.

Discussion

A favourable tolerability profile is crucial for an anticancer drug, such as abiraterone, which is used very often in elderly patients, including those who are considered unsuitable for chemotherapy because of their increased vulnerability to the adverse event spectrum of cytotoxic regimens [Sajid *et al.* 2011; Falci *et al.* 2009]. In our study, long-term exposure (median 16 months) to abiraterone in mCRPC docetaxel-pretreated patients with low-risk, controlled cardiovascular comorbidities or risk factors resulted to be safe and well tolerated. Over a median observation period of 36 months, no cardiovascular deaths or emergent symptomatic CEs were reported and no clinically significant changes in echocardiographic parameters (including LVEF) were observed. In particular, there was no apparent trend towards increased toxicity with the lengthening of the period of drug exposure from 12–24 months [Procopio *et al.* 2015]. As expected from the known effect of abiraterone on mineralocorticoid excess, fluid retention and hypertension were the most frequently reported adverse events (16–18%). Most adverse events were mild (grade 1–2) and only in a few patients were asthenia, skin rash and nausea associated with grade 3–4 severity (2–3%). No patients

Table 3. Adverse events associated with abiraterone treatment.

Adverse event	Patients, *n* (%)	
	Grade 1–2	Grade 3–4
Fluid retention	9 (18)	0
Hypertension	8 (16)	0
Asthenia	8 (16)	2 (3)
Abdominal pain	2 (4)	0
Pruritus and cutaneous rash	1 (2)	2 (3)
Nausea	1 (2)	1 (2)
Anaemia	1 (2)	0
Diarrhoea	1 (2)	0

required permanent drug withdrawal due to adverse events.

Specific information on the cardiovascular safety of abiraterone is scarce. In an exploratory phase Ib study aimed at assessing the effect of abiraterone plus prednisone on QT/QT_c intervals in mCRPC patients by using pharmacokinetic and time-matched ECGs, no clinically significant changes in the QT/QT_c interval were observed, suggesting that abiraterone does not substantially affect ventricular repolarization and has, therefore, a low potential for inducing arrhythmias (especially torsade de pointes) [Tolcher *et al.* 2012]. Safety data extracted from both controlled clinical trials and retrospective studies show a good tolerability profile of abiraterone regarding cardiac events, also in elderly patients receiving this drug after multiple lines of previous therapies. In the COU-AA-301 study in mCRPC patients post-docetaxel, mineralocorticoid-related events were slightly more frequent in the abiraterone arm compared with placebo (fluid retention 33% *versus* 24%, hypertension 11% *versus* 8%, hypokalaemia 18% *versus* 9%, respectively) [Fizazi *et al.* 2012]. The overall incidence of cardiac events was not significantly increased by abiraterone (16% *versus* 12%), although cardiac failure was reported more frequently in abiraterone recipients (2.1% *versus* 0.7% in placebo), and tachycardia and atrial fibrillation were the most commonly reported cardiac adverse events [Fizazi *et al.* 2012; Mostaghel and Lin, 2014]. A *post-hoc* subgroup analysis of the COU-AA-301 trial focused on the patients aged ⩾75 years found that the incidence of hypertension and hypokalaemia was unaffected by age, while a slightly higher percentage of elderly patients in the abiraterone arm, compared with placebo, experienced atrial fibrillation (5% *versus* 1%) and tachycardia (5% *versus* 2%), a difference that was not observed in the younger (<75 years) patients group [Mulders *et al.* 2014]. When the results of the COU-AA-301 trial about the clinical benefits of abiraterone were first reported, a number of protocols were established worldwide with the aim to grant preapproval access to abiraterone in post-docetaxel mCRPC patients for whom no alternative treatment was available. Retrospective analyses of the efficacy and safety of abiraterone in the unselected patient populations who were treated in the context of these protocols document a favourable cardiovascular tolerability profile. In a multicentre early-access protocol trial which involved >2300 patients from 23 countries, grade 3 hypertension was reported in 4% of patients, grade 3 and grade 4 cardiac events were reported in 2% and <1%, respectively, and grade 3 and grade 4 fluid retention in 1% and <1%, after a median follow up of 5.7 months (there were no available data about grade 1–2 adverse events) [Sternberg *et al.* 2014a]. Among the 265 patients who took part in the Italian Named Patient Programme, of whom many presented cardiovascular comorbidities or risk factors, the incidence of all-grades cardiovascular toxicities, over a median 12-month follow-up period, was 7.9% for oedema, 2.6% for hypertension and 3.8% for cardiac events. No grade 3–4 cardiac events were reported, and grade 4 hypertension was recorded in only 1 patient (0.4%) [Caffo *et al.* 2015]. Interestingly, when data from patients aged ⩾80 years who took part in this compassionate use programme were analysed separately, no substantial differences from the younger group were found regarding the incidence of adverse events [Maines *et al.* 2015]. In the Belgian compassionate use program, the records from 368 patients showed a higher rate of grade ⩾3 hyperkalaemia and hypertension (7.3% and 3.5%, respectively) compared with the COU-AA-301 study data (4.4% and 1.3%, respectively) [van Praet *et al.* 2016]. Grade ⩾3 cardiac events, however, were reported less frequently in the Belgian retrospective study *versus* the phase III trial (0.8% *versus* 5.2%), probably partly due to the protocol-required intensive monitoring that was adopted in the clinical trial.

Despite the largely favourable data that have emerged so far on the cardiovascular tolerability of abiraterone, caution is needed. A recently

published meta-analysis on the incidence and relative risk of cardiovascular toxicity associated with the use of new hormonal agents, enzalutamide, abiraterone and orteronel (the latter's development now having been discontinued) in mCRPC patients, found an overall significant increase in the risk of cardiac toxicity and hypertension *versus* placebo, with notable differences between drugs [Iacovelli *et al.* 2015]. CYP-17 inhibitors were associated with an increased risk of cardiac events, while enzalutamide was linked with an increased risk of hypertension.

The findings of our study in a specific group of real-world-practice mCRPC patients with cardiovascular comorbidities or risk factors, who are generally excluded from participation in controlled clinical trials, provide some useful information on the safety of abiraterone. Notably, there were no treatment-emergent cardiac events being recorded during exposure to abiraterone, nor did we observe, over an extended follow-up period, the development of signs or symptoms of cardiotoxicity in predisposed patients. This is an important aspect, especially when considering that abiraterone is now generally introduced in much earlier phases of prostate cancer, before chemotherapy, and patients may thus be facing a long period of treatment with this drug, often lasting a few years. Of course, our study has many limitations, mostly its retrospective nature, the limited number of patients who were followed, and the lack of a control group. In particular, it would have been interesting to compare data from our cohort with those of a matched group of patients who did not have concomitant cardiovascular comorbidities or risk factors. Such detailed analysis, however, was precluded by the limited number of age-matched mCRPC patients without pre-existing cardiovascular risk factors who were treated in our centre in the timeframe considered. We are also aware that the frequency of examinations may affect results related to cardiovascular endpoints, as highlighted by van Praet and colleagues [van Praet *et al.* 2016]. In our study, as in daily clinical practice, cardiac examinations were not routinely performed in the absence of symptoms, and this may have caused bias toward a lower rate of cardiac events compared with phase III clinical trials. However, it is still unclear how to best monitor cardiovascular function in patients with risk factors undergoing abiraterone treatment (i.e. imaging techniques, measurement of cardiac biomarkers such as troponins or B-type natriuretic peptide) or, indeed, whether an intensive monitoring is justified in clinical practice. Clearly, more research on the subject would be useful. At present, based on indications from guidelines and expert opinion, pretreatment assessment of cardiovascular function with ECG and echocardiography deserves consideration in elderly patients with reduced cardiac function; during treatment, monitoring for hypertension, hypokalaemia and fluid retention is recommended at least on a monthly basis, and symptom-directed monitoring for cardiac disease should be adequate in patients with pre-existing cardiovascular disease [NCCN Guidelines, 2016; Mostaghel and Lin, 2014].

Conclusion

Long-term abiraterone treatment was well tolerated in mCRPC patients with nonserious, controlled cardiovascular comorbidities or risk factors who had previously received docetaxel-based chemotherapy. No treatment-emergent cardiac events were recorded and there was no apparent worsening of cardiovascular conditions from baseline over an extended observation period, suggesting that, provided that cardiac illnesses are adequately stabilized with appropriate therapies before starting abiraterone and adequately monitored thereafter, patients with mCRPC who are considered suitable candidates for hormonal agents should not be excluded from abiraterone treatment based on the presence of comorbid cardiovascular disorders.

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Conflict of interest statement

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