Association of Biomarkers with Serious Cardiac Adverse Events during Abiraterone Acetate Treatment in Castration Resistant Prostate Cancer

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Abstract

BACKGROUND: Abiraterone acetate is an effective drug for castration-resistant prostate cancer, but cardiac serious adverse events (SAEs) may occur. We studied their association with N-terminal pro–brain natriuretic peptide (NT-proBNP) and troponin T (TnT) during abiraterone therapy. *PATIENTS AND METHODS*: In a single institution, 17 patients were treated with abiraterone acetate 1 g daily with concomitant prednisone and then switched to dexametasone plus canrenone. Blood samples for PSA, NT-proBNP, and TnT were obtained at baseline and after 1, 3, and 6 months. *RESULTS*: Five patients (29.4%) experienced G3 to 4 cardiac SAEs after a median of 13 weeks (range, 9-32), including pulmonary edema, heart failure, acute coronary syndrome, sinus bradycardia with syncope, and pulmonary edema. At baseline, 4 weeks, and 3 months, median NT-proBNP and TnT levels were higher in patients with subsequent cardiac SAEs ($P=$ .03 and $P=$ .04 for NT-proBNP and TnT at 3 months, respectively). After switching to dexametasone and introducing canrenone, no additional cardiac SAEs were noted. Overall response rate was 67%. *CONCLUSIONS*: Our study suggests a higher than expected risk of cardiac SAEs during abiraterone treatment which may well be due to the small sample size and the unrestricted entry criteria. However, baseline and frequent NT-proBNP and TnT monitoring predicted a higher risk for cardiac SAE. Larger studies should confirm our findings.

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Introduction

Abiraterone acetate, an inhibitor of the enzyme 17α hydroxylase/C17,20-lyase which regulates the androgen biosynthesis pathway, has been approved to treat metastatic castration-resistant prostate cancer (mCRPC) after docetaxel failure because of a 4.6-month median overall survival advantage over placebo in the study COU-AA-301 [1,2]. Patients were randomly assigned (2:1) to receive either abiraterone acetate orally at a dose of 1000 mg once daily plus

prednisone or prednisolone 10 mg daily (*n*= 797) or placebo plus prednisone or prednisolone 10 mg daily (*n*= 398). Mineralocorticoid-related adverse events due to the ACTH rise following 17α hydroxylase/C17,20-lyase blockade were more frequent in the abiraterone arm and were mainly of G1 to 2. Specifically, fluid retention and hypokalemia were significantly more frequent on abiraterone than placebo (33% vs 24% and 18% vs 9%, respectively), although they were mitigated by the concomitant administration of prednisone. However, these effects may lead to serious cardiac events, which were slightly higher on abiraterone (5% vs 1%) [1].

More recently, abiraterone acetate in combination with prednisone has been approved by the Food and Drug Administration and European Medicines Agency for the treatment of patients with mCRPC after failure of androgen deprivation therapy [3]. The median overall survival was 35.3 months for patients treated with abiraterone acetate and 30.1 months for patients treated with placebo (hazard ratio 0.79, 95% confidence interval [CI], 0.66-0.96). Safety data were evaluated in 1333 patients with mCRPC who received abiraterone acetate plus prednisone and in 934 patients who received placebo plus prednisone in a combined analysis of trial COU-AA-301 and -302 [4]. Grade 3 to 4 cardiac failure occurred more commonly in patients treated with abiraterone acetate compared with those receiving placebo (1.6% vs 0.2%). Adrenal insufficiency occurred in 0.5% of patients taking abiraterone acetate and in 0.2% of those receiving placebo.

To minimize risk of cardiac serious adverse events (SAEs), several attempts have been proposed, including addition of oral potassium supplementation or selective mineralocorticoid receptor antagonists such as canrenoate or eplerenone [5,6], which, in contrast to spironolactone [7], seem to be devoid of androgen receptor activity. Moreover, in a pilot study, addition of dexametasone to abiraterone acetate significantly suppressed ACTH and endogenous steroids, including 3-5α-17-hydroxypregnanolone, thus reverting fluid retention toxicity and preventing backdoor androgen biosynthesis [6]. However, identification of early predictive markers of cardiac events would be an important step forward to exclude patients at increased risk for cardiac toxicity during abiraterone acetate treatment.

Here we report our preliminary results of the association between N-terminal pro–brain natriuretic peptide (NT-proBNP) and troponin T (TnT) and serious cardiac adverse events during abiraterone acetate treatment in a small series of mCRPC patients. Both biomarkers have previously been associated with an increased risk of subsequent cardiac events in different medical disorders, including cancer [8–12].

Patients and Methods

Treatment Plan and Study Procedures

Seventeen patients with mCRPC were screened and treated with abiraterone acetate according to a Named Patient Program sponsored by Janssen and approved by the Hospital Review Board. A written informed consent was obtained from each subject. We collected an additional informed consent for the cardiac biomarker study.

Abiraterone acetate was administered at the recommended oral dose of 1 g daily (four 250-mg tablets once daily at 11 A.M.) until disease progression. All patients received concomitant prednisone, two 5-mg tablets daily after breakfast. After April 1, 2012, prednisone was switched in all patients to dexametasone 0.5 mg 1 tablet once

daily after breakfast, and canrenone was added at the dose of 50 mg on alternate days after dinner because of its favorable effects on left ventricular function [13,14]. The switch was due to the occurrence of five cardiac SAEs and the report of an inadequate ACTH suppression by prednisone, with consequent increased mineralocorticoid activity and residual androgen activity [6].

Blood samples for hematology and biochemistry, including PSA, TnT, and NT-proBNP, were obtained at baseline and after 1, 3, and 6 months of treatment. Disease response was assessed every 3 months using fusion (18)F-fluoride positron emission tomography (PET)–computed tomography (CT) and/or ceCT scan, depending on the site of metastases. Baseline cardiological examination, including electrocardiography and echocardiography, was initially performed only in patients with New York Heart Association (NYHA) class >1 but were then performed systematically every 3 months in all patients on treatment after April 1, 2012. Toxicity was evaluated using the National Cancer Institute–Common Terminology Criteria for Adverse Events Version 4 [14]. Tumor response by ceCT scan was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) [15] and European Organization for Research and Treatment of Cancer (EORTC) criteria for (18)F-fluoride PET–CT [16].

Serum NT-proBNP and TnT high-sensitivity assays were performed using electrochemiluminescence immunoassay for Modular platform E170 (Roche Diagnostics GmbH, D-68298 Mannheim).

Statistical Methods

The primary end point variable of this ancillary study was the level of PSA in all patients enrolled. We calculated a sample size of 15 patients to detect, with greater than 80% power, a 50% decline in mean PSA levels from baseline to 12 weeks of treatment, according to modified Prostate Cancer Working Group (PCWG2), as described in study COU-AA-302 [3]. The sample size was calculated using a paired *t* test with a 5% two-sided significance level and assuming a standard deviation of the difference of PSA between 12 weeks and baseline equal to 40 ng/ml using data from patients with similar characteristics who were treated in our institution. Summary descriptive statistics included number (percentage) or rate of subjects for categorical data, mean ± standard deviation (SD), or median and interquartile range (IQR) for continuous data. χ^2 or Fisher exact tests were used to compare categorical characteristics. Due to the small sample, nonparametric test statistics were employed. Waterfall plot was used to show how individual subjects' PSA responded to the study drug, and box plots were used to compare NT-proBNP and TnT levels in patients who experienced cardiac SAEs versus those who did not and to show PSA change (difference 0-12 weeks) according to NT-proBNP median value at baseline. Two-sample Wilcoxon rank-sum (Mann-Whitney) test was used to test these differences. A nonparametric test for trend across ordered groups was used to compare PSA concentrations over time [17]. Median progression-free survival and overall survival were calculated using Kaplan-Meier estimates of the cumulative probability of progression and death, defined as the time from enrollment to the onset of first progression disease and death, respectively. Follow-up times of patients dying before diagnosis of progression were censored at the time of death. Two-tailed *P* value of .05 was adopted to define nominal statistical significance. Analyses were conducted using STATA (version 13; StataCorp., College Station, TX).

Table 1. Descriptive Characteristics of Cardiac SAEs (*n*= 5)

Patient ID	1	2	3	4	5
Age	73	65	73	57	78
Prior history of cardiovascular disease (grade)	Acute coronary syndrome (2)	Atrioventricular block first degree complete (1)	Acute coronary syndrome (3)	Acute coronary syndrome (3)	Atrial fibrillation (1)
Prior ketoconazole not within 4 weeks (Y/N)	N	Y	N	Y	N
Type of SAE (grade)	Pulmonary edema (4), acute coronary syndrome (3), atrial fibrillation (1)	Syncope (4), sinus bradycardia (4)	Ileal perforation (4), heart failure (3), atrial fibrillation (3)	Acute coronary syndrome (3), pulmonary edema (4)	Atrial fibrillation (4), acute coronary syndrome (3)
Time from abiraterone acetate initiation to SAE (weeks)	32	20	12	8	12
Intervention	Medical	Pacemaker	Medical	Medical	Pacemaker
Potassium just before/after SAE	3.8/3.89	4.5/4.4	3.6/3.8	4.2/4.15	4.3/2.6
Resolution (Y/N)	Y	Y	Y	Y	Y
Cause of death	Prostate cancer	Sudden death	Prostate cancer	Prostate cancer	Prostate cancer

Results

Drug Activity

The main patient characteristics are shown in Supplemental Table 1. Briefly, median age was 67 years, 15 of 17 patients had performance status = 0, and the median time from initial diagnosis to abiraterone treatment was 6 years (IQR, 4-7). All patients had liver function test results that were normal or within 1.5 upper limit of normal for bilirubin and 2.5 upper limit of normal for transaminases, as per protocol. A total of eight patients had a prior cardiac disease history. Patients had received a median of 3 (IQR, 3-4) cancer therapeutic regimens before abiraterone acetate, including docetaxel in 14 patients and ketoconazole not within 4 weeks in 7 patients. All patients were started with the full dose of 1000 mg daily without dose reductions. Most patients (14/17, 82%) were on cardiac medications.

Best tumor response with abiraterone is reported in Supplemental Table 2. On ceCT, the overall response rate according to RECIST was 67% (95% CI, 30%-93%). On 18-fluoride PET, the overall response rate by EORTC criteria was 70% (95% CI, 35%-93%). Median progression-free survival was 407 days (IQR, 90-496), and median overall survival was 457 days (IQR, 140-814; data not shown).

The best PSA response at week 12 in 14 evaluable patients is shown in Supplemental Figure 1. According to the waterfall plot, 57% of the patients experienced some decrease of circulating PSA, with 43% showing a 30% or greater decrease and a third showing a 75% or greater decrease.

Cardiac SAEs

The main noncardiac adverse events were grade 1 to 2 and included fatigue, back pain, nausea, constipation, bone pain, arthralgia, and liver function test alterations in fewer than 5%. In contrast, a high number of patients (5/17, 29%) experienced G3 to 4 cardiac SAEs, including arrythmia, acute coronary syndrome, and heart failure. The main characteristics of subjects with cardiac SAEs are summarized in Table 1. All patients had a prior history of cardiovascular disease, and one patient had a NYHA class = 2, with left ventricular ejection fraction (LVEF) < 50%. In all 17 patients, normal potassium levels were recorded before (median, 4.2 mEq/l; IQR, 4.0-4.7 mEq/l) and during treatment (median, 4.2 [3.7-4.3] and 4.2 [3.8-4.3] mEq/l at 3 and 6 months, respectively). Also, serum potassium levels were above the normal level in all patients except for patient no. 5 (Table 1). Cardiac SAEs occurred after a median of 13 weeks (range, 9-32) from treatment initiation and resolved in all cases with medical or instrumental intervention (Table 1). All patients stopped abiraterone treatment after the cardiac SAE.

The relationships between circulating NT-proBNP and TnT and subsequent cardiac SAE are shown in Table 2 and Figure 1. Patients who subsequently developed a cardiac SAE had higher NT-proBNP and TnT at baseline, although the difference did not reach statistical significance (*P*= .3 and .07, respectively; Table 2). The biomarker changes after 1 month between patients who experienced a cardiac SAE and patients who did not were borderline significantly different for NT-proBNP (*P*= .09) but not for TnT (*P*= .6). Moreover, after 3 months of abiraterone treatment, both biomarkers were significantly higher in patients cardiac SAE compared with those without cardiac SAEs (*P*= .03 and *P*= .04 for NT-proBNP and TnT, respectively). Finally, patients with NT-proBNP above the median value of 250 pg/ml exhibited a 36.3-ng/ml median increase in PSA at 3 months, whereas those with NT-proBNP levels below 250 pg/ml had a 25.4-ng/ml median decrease in PSA at 3 months (*P*= .025, Figure 2). This association did not change (*P*= .032) when the patient who stopped treatment after 9 weeks for a cardiac SAE was excluded from analysis.

Table 2. Time Course of NT-proBNP and TnT Overall and in Patients with or without Subsequent Cardiac SAE

		All Patients (*n*= 17)		Cardiac SAE (*n*= 5)		No Cardiac SAE (*n*= 12)		
	Time	*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	*P*
NT-proBNP (pg/ml)	Baseline	17	250 (178-588)	5	1052 (226-1159)	12	245 (161-380)	.3
	Month 1	13	130 (98-419)	4	725 (139-2227)	9	116 (98-333)	.3
	Month 3	14	227 (121-738)	5	1164 (738-1320)	9	175 (107-234)	.03
	Month 6	7	98 (71-261)	1	207 (–)	6	94 (71-261)	.6
TnT (pg/ml)	Baseline	17	12.9 (11.2-19.1)	5	21.3 (18.3-22.5)	12	12.4 (9.8-17.1)	.07
	Month 1	14	13 (9.5-18.1)	4	23.7 (11.3-43.3)	10	12.4 (9.5-15.0)	.4
	Month 3	14	14.7 (11.6-22.8)	5	22.8 (17.2-78.5)	9	13.3 (11.0-14.9)	.04
	Month 6	7	11.4 (10.0-13.5)	1	24.9 (–)	6	10.8 (10.0-13.3)	.1

* *P* for the difference between cardiac SAE versus no cardiac SAE (Mann-Whitney test).
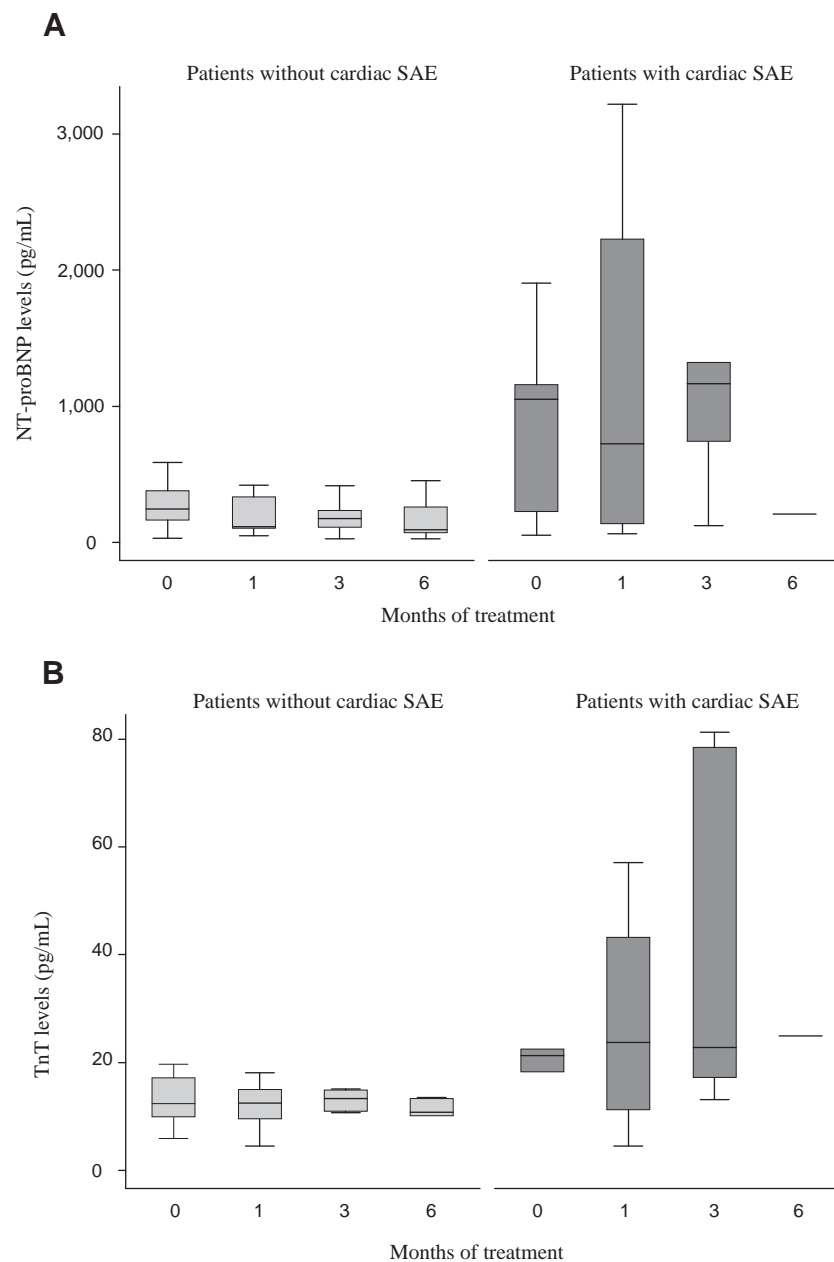
Figure 1. Box plots of the changes of NT-proBNP (A) and TnT (B) during abiraterone acetate treatment according to the subsequent occurrence of a cardiac SAEs.

Discussion

In our pragmatic study in unselected patients, abiraterone acetate was confirmed to be an active treatment in mCRPC, leading to a response rate of 70% and a median progression-free survival of 407 days (IQR, 90-496), which is far longer than the 168 days of study 301 in docetaxel-pretreated patients [1,2] and approaches the 495 days of study 302 in chemotherapy-untreated patients [3]. However, patients with previous cardiac disease (5 out of 8) experienced a G3 to G4 cardiac SAE when treated with abiraterone acetate. Although based on a very small sample, this proportion is higher than the 3% incidence of G3 cardiac disorders reported in the phase III trials with abiraterone acetate in patients with mCRPC [2–4]. In a large open-label, early-access protocol trial in over 2300 patients [17], the incidence of grade 3 and 4 cardiac events was 2%. Noticeably, patients with significant heart disease or uncontrolled hypertension

were excluded from the registration or early-access trials. In our study, 8 patients had a prior history of heart disease and 82% were on cardiac medications, although none except 1 patient had clinical manifestations of cardiac dysfunction (NYHA = 2) at enrollment. Also, seven patients were previously treated with ketoconazole, at variance with the registration trials, and might therefore be at increased risk for fluid retention and hypokalemia-associated cardiac toxicity. Thus, our unrestricted population may be at higher risk for cardiac SAE compared with the registration trials. Importantly, no subject in our study had hypokalemia immediately before or at the time of the cardiac SAEs, except for one patient with moderate hypokalemia (2.6 mEq/l) concomitant with the atrial fibrillation event.

Following the occurrence of five cardiac SAEs, we switched to an alternative corticosteroid regimen and a potassium-sparing drug to minimize the cardiac risks of a mineralocorticoid excess, including
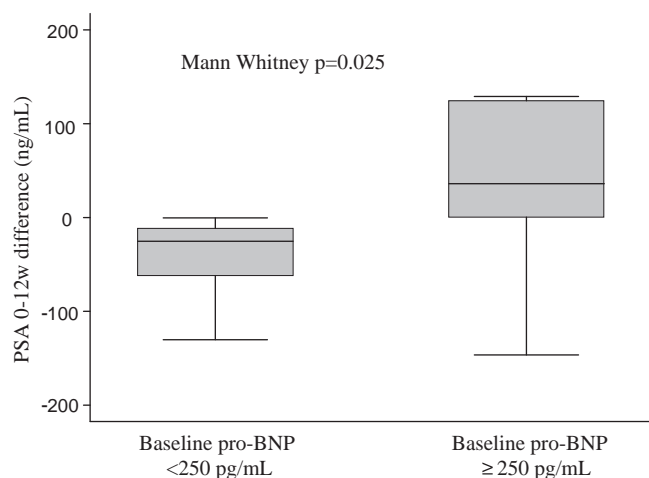
Figure 2. Box plots of the changes of PSA (difference 0-12 weeks) according to NT-proBNP median level at baseline.

hypokalemia and heart failure. Because prednisone may not be the optimal corticosteroid drug in this context due to its intrinsic mineralocorticoid activity [7], we switched to dexametasone, which has been reported to restore normokalemia in patients with hyperaldosteronism [18,19]. Moreover, addition of dexametasone to abiraterone acetate significantly suppressed ACTH and endogenous steroids, including 3-5α-17-hydroxypregnanolone, thus reverting toxicity and preventing backdoor androgen biosynthesis [6]. Although spironolactone is a well-known potassium-sparing drug, a few reports have shown binding and activation of the androgen receptor *in vitro,* thereby promoting tumor growth [7]. Thus, we choose canrenone, an analog of aldosterone, which competitively binds to the mineralocorticoid receptors in the distal renal tubules and collector ducts and favors sodium and water elimination while limiting potassium excretion. Canrenone has not been associated with tumor growth [20], is an inexpensive drug, and induced a significant improvement of LVEF in a randomized trial [13,14,21]. After switching to dexametasone and introducing canrenone, no additional cardiac SAEs were noted. Although this is clearly an underpowered comparison, our hypothesis deserves to be tested in a larger study.

Although the generalizability of our findings is clearly hampered by the low number of subjects, our study may provide interesting information regarding the significant relationship between the 3-month increase in circulating NT-proBNP and TnT and the subsequent development of cardiac SAEs. Moreover, patients with higher NT-proBNP levels at baseline had no PSA response to abiraterone acetate, suggesting a possible association between initial cardiac dysfunction and response to drug, a finding which has no clear explanation and should be confirmed in future studies.

These preliminary findings suggest that monitoring both cardiac biomarkers might be useful in identifying patients at increased risk of cardiac SAE. A recent observational study conducted in Italy showed the cardiac safety of abiraterone acetate [22]. Our different findings may be explained by subtle differences in the patient population in terms of higher cardiovascular risk and prior use of ketoconazole, which was used in two out of five patients who had a cardiac SAE. However, the registration trials indicate that cardiac SAEs were more frequent on abiraterone acetate than placebo [1–4,17], and EMA has identified prior hypertension, hypokalemia, fluid retention, edema, and cardiac disorders as risk factors for the risk management plan [21].

In conclusion, we observed a higher incidence of cardiac SAE in our pilot study compared with the registration trials. The small sample size and the lack of a control group prevent us to draw definitive conclusions about the causal relationship between abiraterone treatment and cardiac SAEs. However, the correlation with the cardiac biomarker increase is suggestive of an association. Our observation underlines the importance of monitoring cardiac conditions of patients at baseline and during abiraterone therapy. In addition to a thorough medical history and evaluation of LVEF, NT-proBNP and TnT may be useful biomarkers to identify patients at high risk of subsequent cardiac SAEs, particularly if a significant increase of these biomarkers is demonstrated early during treatment. Because abiraterone acetate is an effective agent which can significantly prolong overall survival in mCRPC, exclusion of patients at risk for a cardiac SAEs can further improve its risk/benefit ratio.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.tranon.2016.08.001.

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