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ORIGINAL ARTICLE

An exploratory analysis of the association between levels of hormones implied in steroid biosynthesis and activity of abiraterone in patients with metastatic castration-resistant prostate cancer

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ABSTRACT

BACKGROUND: Abiraterone acetate, approved for patients with metastatic castration-resistant prostate cancer (mCRPC), blocks androgen byosinthesis. We aimed to describe changes determined by abiraterone in hormones implied in steroid biosynthesis, exploring association between hormonal levels and drug activity.

METHODS: Patients with mCRPC, receiving standard abiraterone + prednisone after docetaxel failure, were studied. We determined serum levels of progesterone, 17OH-progesterone, cortisol, ACTH, DHEA-sulphate, androstenedione, testosterone, sex hormone-binding globulin, aldosterone, plasma renin activity, and cholesterol, baseline and every 12 weeks. For each hormone, association with treatment activity was tested 1) comparing baseline values in responders *vs.* non-responders; 2) comparing progression-free survival (PFS) of patients with baseline low *vs.* high values; 3) comparing values after 12 weeks in responders *vs.* non-responders.

RESULTS: Forty-nine patients were analyzed; 26 patients (53.1%) experienced PSA response. Baseline values of all hormones were not statistically different between responders and non-responders. For all hormones, PFS difference of patients with low *vs.* high baseline values was not statistically significant. Several hormones showed significant and sustained changes *vs.* baseline, but all significant changes were similar between responders and non-responders.

CONCLUSIONS: This analysis does not suggest a significant association between baseline hormonal values, or changes induced by abiraterone, and treatment activity.

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Key words: Abiraterone acetate - Biological markers - Prognosis - Prostatic neoplasms.

Prostate cancer is the second most frequent cancer in men, with 1.1 million new cases estimated to occur yearly.[1] The standard treatment of patients with advanced prostate cancer is androgen deprivation therapy, to reduce testosterone production by testes.[2]

However, despite initial response, after a variable interval the disease eventually progresses to castration-resistant prostate cancer (CRPC), usually by a rise in prostate-specific antigen (PSA).[3] Recently, clinical and preclinical studies have demonstrated that the andro-

gen receptor (AR) plays a critical role after disease progression, and continues to drive the proliferation of CRPC.[4] Several studies have shown that extragonadal androgen production, at adrenal and/or intratumor level, is one of the mechanisms allowing tumor progression despite castration level of serum testosterone.[5] This production is obtained by up-regulation of cytochrome P450–17α-hydroxylase/17,20-lyase (CYP17A1), a key enzyme in the production of androgens and estrogens, both in the adrenal glands and in tumor tissue.[6] Abiraterone acetate is the prodrug of abiraterone, that blocks CYP17, with 17α-hydroxylase/17,20-lyase inhibitory properties, and inhibits both testicular, adrenal and intratumor androgen production. Two randomized phase III trials have shown that abiraterone improves overall survival (OS) in patients with metastatic CRPC (mCRPC), both pretreated with chemotherapy and chemotherapy-naïve.[7, 8] Although this drug is a significant therapeutic advance, about one third of patients receiving abiraterone after docetaxel failure shows intrinsic, primary resistance.[9] Furthermore, virtually all patients, after a widely variable duration of response, develop acquired resistance. Nowadays, mechanisms of resistance have not been well defined yet. Recent studies have focused on the following mechanisms of resistance: systemic and intratumor androgens biosynthesis up-regulation,[10] alternative pathways of androgens production,[11] AR gene mutations,[12] amplification/over-expression and AR splice variants expression.[13, 14] Currently, there are no validated serum biomarkers that can predict mechanisms of resistance or the outcome of patients receiving abiraterone. Therefore, the absence of validated predictive factors for abiraterone, together with the recent availability of other effective treatments, such as cabazitaxel [15] or enzalutamide,[16] make treatment decisions about the best drug (or sequence) really challenging. In this study, we described changes of hormones involved in steroid hormones synthesis and evaluated adrenocorticotropic hormone (ACTH), sex hormone binding globulin (SHBG), plasma renin activity (PRA) and lipid profile, in patients with mCRPC receiving abiraterone. In addition, we conducted an exploratory analysis to evaluate the association between hormonal values (at baseline and during treatment) and drug activity, in terms of PSA response rate and progression-free survival (PFS). The aim of this exploratory study was to generate hypothesis about the use of serum biomarkers to predict abiraterone activity, before or early after treatment start. This information could be of great value toward treatment personalization and optimization of the use of abiraterone.

Materials and methods

Aim of the study

Main objective of this analysis was to describe the changes in serum hormonal values during treatment with abiraterone acetate plus prednisone, in metastatic CRPC patients progressing after first line chemotherapy. Secondary objective was an explorative analysis of the association between hormonal baseline values and treatment activity, and between changes in hormonal values and treatment activity. The following analytes were evaluated:

1) glucocorticoid hormone: cortisol;

2) progestagens: progesterone, 17hydroxyprogesterone;

3) sex hormones: testosterone, androstenedione, DHEA sulfate (DHEA-S);

4) hormones involved in mineralcorticoid pathway: PRA and aldosterone;

5) lipid profile: total cholesterol, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol;

6) ACTH and SHBG were evaluated.

Patients

The analysis was conducted on a series of patients with mCRPC, with disease progression following first-line chemotherapy with docetaxel, treated with abiraterone acetate within the Expanded Access Program and according to declaration of Helsinki. Patients were recruited between June 2010 and December 2010 at a single Institution (Medical

Oncology Division, "San Luigi Gonzaga" Hospital, Orbassano, Turin, Italy). Main inclusion criteria in the Expanded Access Program were: men aged 18 years and above with histologically confirmed prostate cancer; previous treatment with docetaxel; progressive disease defined as rising PSA according to Prostate Cancer Working Group (PCWG2) criteria or radiographic progression in soft tissue or bone with or without biochemical progression; ECOG performance status (PS) ≤2; level of testosterone <50 ng/dL; hemoglobin ≥9 g/dL; platelet count ≥100,000/mm^3; serum albumin ≥3.0 g/dL; normal liver and kidney function; serum potassium ≥3.5 mEq/L; able to swallow the study drug whole as a tablet; signed informed consent.

Exclusion criteria included: patients already treated with abiraterone acetate; concurrent serious disease or uncontrolled infection; uncontrolled hypertension; active or symptomatic viral hepatitis or chronic liver disease; history of gastrointestinal disorders that may interfere with drug absorption; history of pituitary or adrenal dysfunction; clinically significant heart disease; brain metastases; grade >2 treatment-related toxicity from prior therapy; previous treatment with azoles (fluconazole, itraconazole, ketoconazole) within 4 weeks before starting abiraterone acetate; administration of an investigational therapeutic within 30 days; psychiatric illness.

Treatment and procedures

Abiraterone acetate was administered orally, in 28-day cycles, at 1000 mg per day, with prednisone (5 mg twice a day), until disease progression or unacceptable toxicity. During treatment, clinical exam and blood test were performed every 2 weeks. Serum hormonal levels were evaluated before starting treatment, after 3 cycles (12 weeks), and every 3 cycles thereafter, until disease progression.

Measurement of analytes

The following hormones were measured by radioimmunoassay: ACTH (ACTH IRMA CT kit– RADIM); cortisol (Cortisol RIA CT kit – RADIM); aldosterone (ALDOSTERONE MAIA RIA kit –ADALTIS); 17hydroxyprogesterone (17 HYDROXYPROGESTERONE RIA CT kit–RADIM); PRA (RENCTK – DIASORIN); SHBG, DHEA-S and androstenedione were measured by chemiluminescent enzyme immunoassay (CLEIA) method with Immulite tool 2000 Siemens. Progesterone and testosterone were evaluated by Chemiluminescent Microparticle Immunoassay method (CMIA), with Architect Company Abbott Diagnostics.

Statistical analysis

All the statistical analyses described in this paper were not pre-planned, so there was no a priori calculation of sample size and statistical power.

For each analyte, samples obtained at each time-point during treatment (after 3 cycles, after 6 cycles, after 9 cycles, after 12 cycles) were compared to baseline values by Wilcoxon matched-pairs test.

For each analyte, association between hormones and treatment activity was tested in 3 different exploratory analyses:

1) comparing baseline hormonal values of responders (*i.e.* those patients with PSA reduction during abiraterone treatment ≥50%) *vs.* non-responders (*i.e.* those patients with PSA reduction during abiraterone treatment <50%). The distribution of baseline hormonal values was graphically represented by box plots, and statistical significance of the difference between the 2 groups was tested by non parametric Wilcoxon test;

2) comparing PFS of patients with baseline hormonal value ≤ median value *vs.* patients with baseline hormonal value higher than median value. The PFS was defined as the time from the beginning of treatment until progression or date of last follow-up for patients without progression at the time of analysis. PFS was evaluated using Kaplan-Meier methods and the two groups were compared by long-rank test. Hazard Radio (HR) of progression was calculated using Cox model, with catego-

ry of baseline hormonal value (high *vs.* low) as variable, not adjusted for other prognostic variables;

3) comparing values after 12 weeks of treatment with abiraterone, adjusted by baseline values, in responders *vs.* non-responders patients. In this analysis, only patients with data available about hormonal value at baseline and after 12 weeks were included. The distribution of values was graphically represented by box plots, and the statistical significance of the difference in values after 12 weeks between the 2 groups was tested in a linear model, using the baseline value as covariate.

Statistical analyses were performed using the S-Plus 6.1 Professional Edition for Windows and software SPSS (version 21). For all the analysis, statistical significance was set at P=0.05 and, given the exploratory aim, no correction for multiplicity was applied.

Results

Forty-nine consecutive patients were enrolled in this study. Demographic data are reported in Table I. Median age was 70 years (range, 56-85 years); ECOG PS was 0, 1 and 2 in 61%, 36% and 6% patients, respectively. Median serum PSA level at baseline was 116.95 ng/mL (range: 2.48-5580 ng/mL).

TABLE I.—*Main baseline characteristics of patients treated with abiraterone (N.=49).*

Age		
Median (range)	70 yrs	(56-85)
ECOG performance status		
0	30	(61%)
1	16	(33%)
2	3	(6%)
Gleason score (n.a. 4 patients)		
<=6	6	(13%)
7	16	(36%)
8	10	(22%)
9	13	(29%)
Baseline PSA		
Median (range)	116.95	(2.48-5580)
Sites of disease		
Bone	40	(82%)
Lymph-nodes	27	(55%)
Lung	5	(10%)
Local (prostate)	7	(14%)
Other	2	(4%)

Gleason score (GS) was evaluated according to NCCN classification: GS was 2-6, 7, 8-10 and unknown in 6 (13.3%), 16 (35.6%), 23 (51.1%) and 4 patients (8.1%), respectively. At the evaluation before starting treatment with abiraterone, 40 patients (82%) had bone lesions, 27 patients (55%) lymph nodes metastases, 5 patients (10%) lung metastases, 7 patients (14%) loco-regional recurrence and 2 patients (45%) secondary lesions in other sites.

Activity of treatment

Compliance to treatment was verified in all patients. In the whole series of 49 treated patients, PSA response rate was 53.1% and, with 43 events recorded, median PFS was 10.2 months. In detail, 95.9%, 71.4% and 39.5% of patients were without progression after 3, 6 and 12 months, respectively. Median follow-up, according to Schemper method (reverse Kaplan Meier) was 23.8 months, with 6 censored patients. Decreasing of number of patients was due to PSA progression and not to lost at follow-up.

Hormonal levels

Baseline values for all analytes are reported in Table II. Changes in glucocorticoid hormone and progestagens are described in Table II and in Figure 1 (panels 1A-1D). A progressive, statistically significant decrease of cortisol was observed. Median cortisol value was 13.6 mcg/dL at baseline, 3.60 after three months (P=0.001) and 1.50 mcg/dL after twelve months (P=0.008). Progesterone was statistically increased after three and nine months: median value was 0.10 ng/mL at baseline, 1.40 ng/mL (P=0.001) after three months and 1.70 ng/mL (P=0.001) after nine months. 17hydroxyprogesterone was not significantly changed during treatment. A statistically significant increase in ACTH was observed after three months of treatment. Median ACTH value was 27 pg/mL at baseline and 29.3 pg/mL after three months (P=0.047). Changes in sex hormones are described in Table II and Figure 1 (panels 1E-1H). A statistically significant

TABLE II.—*Hormonal levels at baseline and during treatment with abiraterone.**

Hormone	Baseline		After 3 cycles			After 6 cycles			After 9 cycles			After 12 cycles		
	N. pts	median	N. pts	median	P	N. pts	median	P	N. pts	median	P	N. pts	median	P
Progesterone	43	0.10 (0.005-5.5)	39	1.40 (0.10-9.30)	<0.001	25	1.20 (0.10-13.0)	<0.001	20	1.70 (0.10-15.0)	0.001	8	1.65 (0.10-14.20)	0.07
17-OH-progesterone	48	0.60 (0.05-1.90)	47	0.60 (0.05-1.70)	0.62	33	0.50 (0.05-1.60)	0.53	21	0.40 (0.05-1.20)	0.025	9	0.40 (0.05-1.30)	0.48
Cortisol	49	13.6 (0.09-27.2)	48	3.60 (0.09-14.30)	<0.001	34	3.06 (0.50-22.1)	<0.001	23	2.89 (0.50-17.5)	<0.001	9	1.50 (0.50-5.26)	0.008
ACTH	49	27 (3.1-96.8)	49	29.3 (4.0-193.0)	0.047	35	30.5 (4.0-201.0)	0.26	23	36.0 (4.0-255.0)	0.076	10	33.7 (4.0-243.0)	0.57
DHEA sulphate	47	22.6 (7.5-125)	47	7.5 (7.5-15.0)	<0.001	32	7.5 (7.5-7.5)	<0.001	21	7.5 (7.5-7.5)	0.003	10	7.5 (7.5-7.5)	0.07
Andro-stenedione	49	0.57 (0.15-1.70)	49	0.15 (0.15-0.15)	<0.001	34	0.15 (0.15-0.15)	<0.001	23	0.15 (0.10-0.15)	<0.001	10	0.15 (0.15-0.15)	0.018
Testosterone	49	0.14 (0.07-0.51)	48	0.23 (0.07-1.35)	<0.001	35	0.29 (0.07-1.10)	0.003	23	0.25 (0.02-1.49)	0.007	10	0.19 (0.03-0.48)	0.86
SHBG	49	48.50 (17-152)	49	40.9 (21.4-89.4)	0.001	35	46.2 (18.2-93.8)	0.042	22	39.7 (25.8-76.8)	0.004	10	45.1 (16.0-65.6)	0.086
Aldosterone	49	178 (53-571)	49	246 (39-1205)	0.009	35	261 (72-640)	0.033	23	355 (3.6-1239)	0.016	10	302 (114-594)	0.39
Renin (PRA)	49	1.00 (0.2-22.4)	49	1.00 (0.10-60.5)	0.58	35	1.50 (0.20-16.8)	0.92	23	1.30 (0.20-15.0)	0.97	10	2.95 (0.50-9.6)	0.72
Cholesterol (total)	48	204.5 (113-316)	48	214.5 (103-301)	0.89	34	210.5 (141-315)	0.84	22	224.5 (99-296)	0.81	10	230.5 (106-295)	0.33
HDL cholesterol	48	46.5 (28-93)	48	53.0 (30-88)	0.002	34	48.0 (26-85)	0.50	22	43.5 (27-80)	0.53	10	58.0 (26-86)	0.31
LDL cholesterol	41	139 (57.1-245)	41	139 (45.2-206)	0.035	30	140.5 (15-229)	0.019	16	144.0 (57.6-190.6)	0.35	9	140.0 (118.0-219.2)	0.51

*Only patients with available baseline values are included in this analysis.

decrease of DHEA-S was observed: median DHEA-S value was 22.6 mcg/dL at baseline, 7.5 mcg/dL after three months (P=0.001). A significant decrease in androstenedione value was observed: median androstenedione value was 0.57 ng/mL at baseline *vs.* 0.15 ng/mL after three months (P<0.001). Testosterone, that was already suppressed at baseline as expected, remained suppressed according to the cut-off <50 ng/dL, SHBG value decreased significantly during treatment: median SHBG value was 48.5 nmol/L at baseline, 40.9 nmol/L after 3 months (P=0.001) and 39.7 nmol/L after 9 months (P=0.004). Changes in mineralcorticoid hormones are reported in Table II and Figure 1 (panels 1I-1J). A significant increase in aldosterone values was observed: median aldosterone was 178 pg/mL at baseline, 246 pg/mL after three months (P=0.009), and values increased significantly even after six and nine months. The PRA activity was not significantly changed. The levels of total cholesterol, HDL cholesterol and LDL cholesterol did not change significantly during treatment Table II.

Association between hormones and treatment activity

Comparison of baseline values between responders and non-responders is reported in Figure 2. For all the analytes, baseline values were not statistically different between responders and non-responders.

Comparison of PFS between patients with low basal values and patients with high baseline values, for each analyte, is reported in Figure 3. For all analytes, difference in PFS between patients with low baseline values *vs.* patients with high baseline values was not statistically significant. Comparison of hormonal values after 12 weeks between responders and non-responders, adjusted by baseline value,

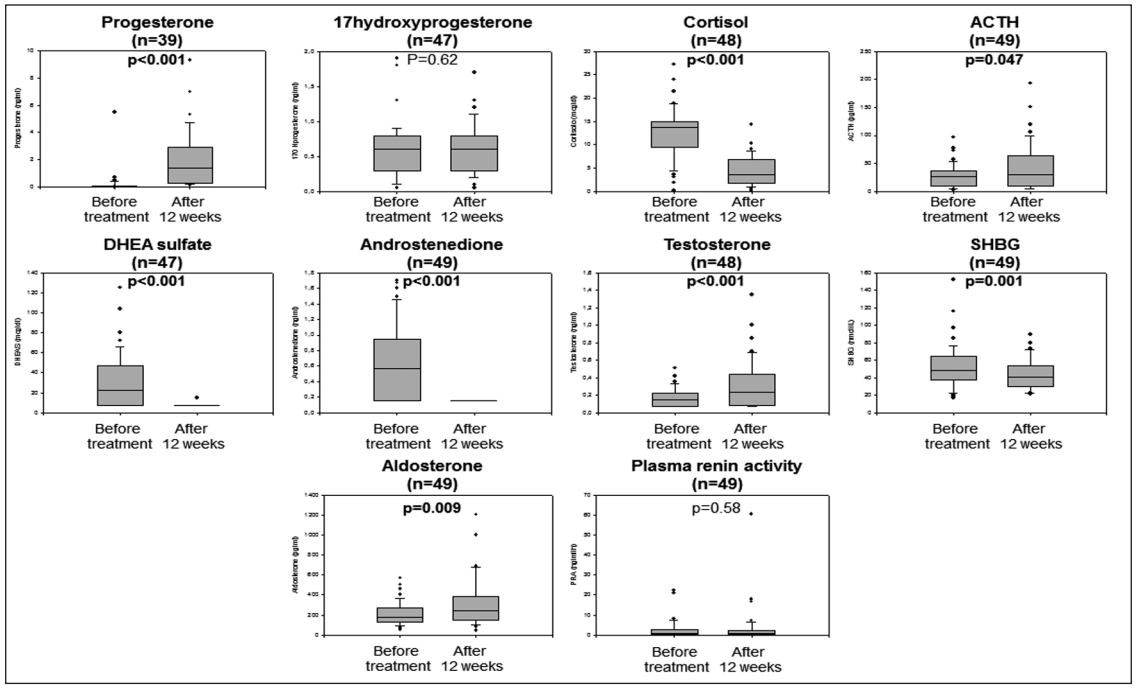

Figure 1.—Changes in hormonal values during treatment with abiraterone. For each analyte, 2 box plots are depicted: baseline values (on the left) and values obtained after 12 weeks of treatment (on the right). Line in the box: median value; box hinges: 25-75th percentile; ends of the segments:10-90th percentile; dots: outliers.

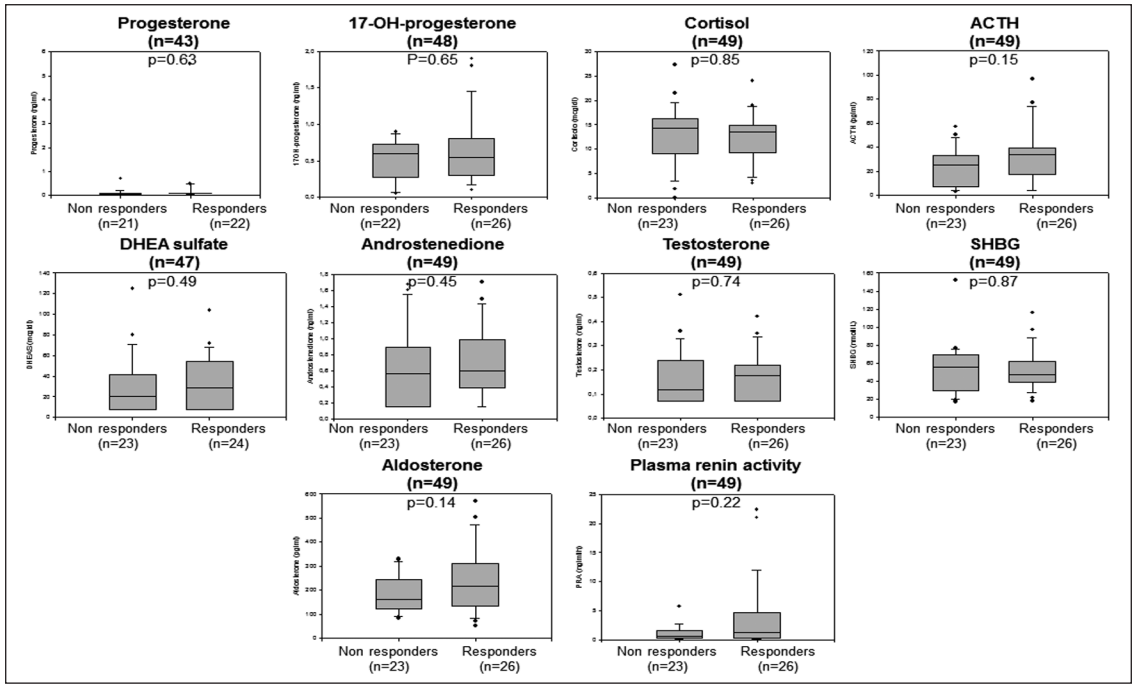

Figure 2.—Comparison of baseline hormonal values between responders (*i.e.* those patients with PSA reduction during abiraterone treatment ≥50%) and non-responders (*i.e.* those patients with PSA reduction during abiraterone treatment <50%). For each analyte, 2 box plots are depicted: non-responders (on the left) and responders (on the right). Line in the box: median value; box hinges: 25-75th percentile; ends of the segments: 10-90th percentile; dots: outliers.

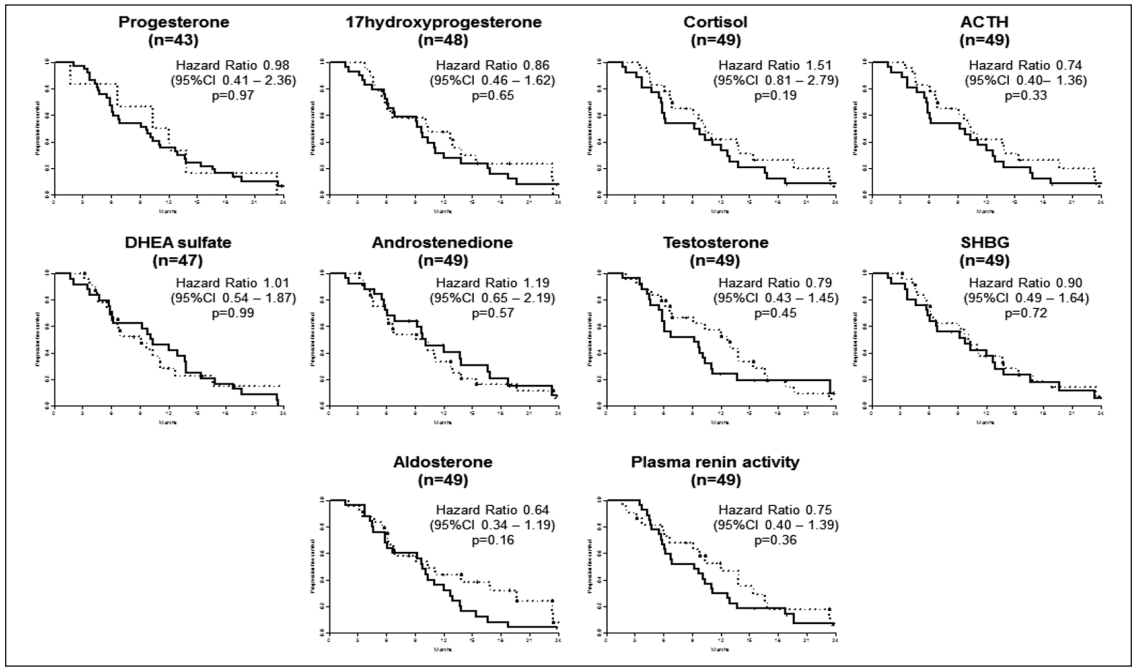

Figure 3.—Comparison of progression-free survival between patients with low basal values (continuous line) and patients with high baseline values (dotted line), for each analyte.

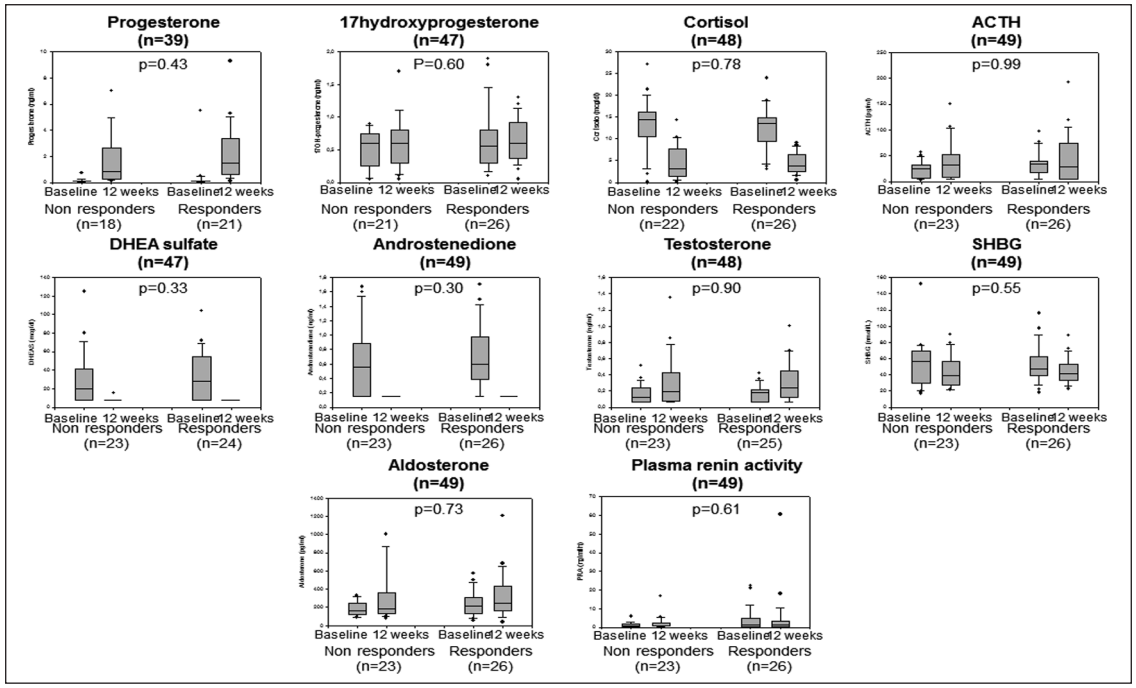

Figure 4.—Comparison of hormonal values after 12 weeks between responders and non- responders, adjusted by baseline value. For each analyte, 4 box plots are depicted from left to right: baseline values in non-responders, values after 12 weeks in non-responders, baseline values in responders, values after 12 weeks in responders. Line in the box: median value; box hinges: 25-75th percentile; ends of the segments: 10-90th percentile; dots: outliers.

for each analyte, is reported in Figure 4. Also the comparison of patients with early failure *vs.* long-responders patients did not show any significant difference in baseline hormonal values (data not shown).

For all analytes, the difference in the value after 12 weeks of treatment between responders and non-responders was not statistically significant. When a significant change compared to baseline was described, this change was similar between responders and non-responders.

Discussion

In this study, our aim was to describe the changes of hormonal levels during treatment with abiraterone in mCRPC patients progressing after docetaxel therapy, and to explore a correlation between baseline hormonal values, hormonal changes during treatment and activity of abiraterone. Compared to baseline values, we found statistically significant changes in several hormones: among others, a significant increase in the level of progesterone and aldosterone and a significant decrease in the level of cortisol, DHEA-S and androstenedione. For all hormones, baseline values were not statistically different between responders and non-responders, and difference in PFS between patients with low baseline values and patients with high baseline values was not statistically significant. Several hormones showed significant and sustained changes compared to baseline, but all significant changes were similar between responders and non-responders. As demonstrated in randomized trials, abiraterone treatment significantly prolongs OS, modifying the natural history of mCRPC.[7] Nowadays, we do not have validate biomarkers which could be predictors of response to abiraterone and help clinicians to personalize therapy. A better understanding of resistance mechanisms to this new drug is crucial in order to identify these biomarkers. Androgens synthesis in prostatic cancer cells is an important androgen source under the pressure of androgen deprivation therapy.[10] Preclinical models show that, during abiraterone, various genes involved in androgen biosynthesis pathway are upregulated. Studies in animal models have also shown that tumour relapse on abiraterone was associated with further up-regulation of intratumor CYP17A1 and other key genes involved in intratumor androgen synthesis. Resistance to abiraterone can be due to activation of alternative pathways of androgens synthesis.[11] The potent inhibition of CYP17A1 induced by abiraterone causes androgens accumulation upstream the enzymatic block, as pregnenolone and progesterone. Progesterone can be converted to 5 α-dihydrotestosterone (DHT) by "backdoor pathway".[11] This pathway consists in eight enzymatic steps that induce DHT synthesis *via* 3α-androstanediol production. Moreover, abiraterone does not completely ablate DHEA-S, which can be transported and metabolized in tumoral cells to DEA, a steroid downstream of CYP17A1, bypassing the enzymatic block caused by abiraterone. To our knowledge, this is the first study that evaluated baseline and variations in adrenal hormones during treatment with abiraterone, in order to explore their impact in terms of prognosis and potential mechanisms of resistance. In a retrospective analysis of trial COU-AA-301, evaluating the baseline serum androgen (testosterone, androstenedione and DHEA-S) and their association with OS in patients with mCRPC, baseline serum testosterone levels were prognostic of survival, independent of treatment arm.[17] Authors suggested that testosterone levels may affect the study outcomes and represent a more aggressive disease.[17] As expected, according to potent CYP17A1 block induced by abiraterone, we showed an important inhibition of testosterone precursors synthesis and an increase of steroids concentrations upstream the enzymatic block, as progesterone. Our data also demonstrated a significant reduction of cortisol levels that was not associated with an increase of ACTH. These results confirm that, despite the dramatic serum cortisol reduction induced by abiraterone, concomitant prednisone is efficacious in preventing ACTH elevation. Moreover, we investigated relationship between treatment response and hormonal values at baseline and during abiraterone treatment, in order to

identify a predictive biomarker. Although this analysis was not pre-planned and characterized by a small statistical power, our attempt to explore the association between values of hormones implied in steroid biosynthesis pathway and activity of abiraterone did not produce statistically significant results. Our data cannot confirm the hypothesis that changes of adrenal hormonal levels, induced by CYP17A1 block, is one of the most important resistance mechanisms to abiraterone treatment, because changes in hormonal values were similar between responding and non-responding patients. However, these negative results could be due to the small number of patients enrolled, but also to the complexity of resistance mechanisms. On this point, Ryan *et al.* investigated the ability of abiraterone to reduce serum androgens under the lower limit of quantification from baseline to week 12 and the relationship between changes in androgen levels and PSA response rate in patients with mCRPC, enrolled in clinical trial COU-AA-301.[18] Abiraterone treatment significantly reduced the mean serum androgens from baseline to week 12. The reduction of androgens did not predict uniformly PSA decline, supporting the hypothesis that progression of mCRPC is also driven by ligand-independent mechanisms.[18] Preclinical data showed that AR under the pressure of androgen deprivation is susceptible to somatic changes and aberrant transcription which let it responsive to glucocorticoids and progesterone.[19] The increased progesterone levels during abiraterone treatment can activate the mutated form of AR, causing resistance to abiraterone. Furthermore, mCRPC has an increased expression of progesterone receptor (PR),[20] and the binding of progesterone can activate transcription of androgen-dependent genes. On the basis of this preclinical evidence, a phase 1-2 study conducted in patients with CRPC progressed after abiraterone, enzalutamide or two lines of chemotherapy showed that PR inhibition by onapristone, a PR antagonist, is feasible and safe.[21] Preclinical data also demonstrated that abiraterone treatment is associated with a 3-fold increased expression of both full-length AR and truncated AR splice variant (ARV).[13, 14] ARV lacks the ligand-binding domain and is able to activate itself in the absence of ligand. These ARVs may be one major potential mechanism of resistance to new AR-targeting drugs. ARV7 and ARV567 are the most clinically prevalent splice variants in metastatic CRPC.[22] Recently Antonarakis *et al.* reported that the detection of ARVs in circulating tumour cells of patients with mCRPC treated by enzalutamide or abiraterone could predict resistance to these agents.[14] ARV-7 positive patients, treated with abiraterone, had a dramatically lower PSA response rate (0% *vs.* 68%, P=0,004) and worse outcomes compared to ARV-7 negative counterpart. Patients ARV7-positive, treated with enzalutamide, had lower PSA response rates (0% *vs.* 53%, P=0.004) and worse outcomes than ARV7-negative patients. These data supported the hypothesis that both intrinsic and acquired resistance to these agents may be associated with ARV7. We acknowledge that a robust study of the predictive role of baseline hormonal values, or their early changes during treatment, should be conducted within a randomized controlled trial. However, in the absence of optimal data, our aim was to perform an exploratory analysis, in order to generate hypotheses to be subsequently validated. Unfortunately, none of the hormones tested appear to be strongly related to abiraterone activity, neither in terms of baseline values nor in terms of early changes during treatment.

Conclusions

In conclusion, this analysis, conducted in patients with mCRPC, treated with abiraterone in the post-docetaxel setting, failed to identify a predictive biomarker in terms of baseline value of hormones implied in steroid biosynthesis pathway, or in terms of early modification during treatment. In order to allow better treatment choices, and optimization of the use of abiraterone, it would be important to conduct further studies to identify predictive markers, and to better understand mechanisms of drug resistance. Furthermore, it would be important to evaluate predictive biomarkers also in chemotherapy-naïve patients.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global Cancer Statistics. Ca Cancer J Clin 2015;65:87-108.
2. Pagliarulo V, Bracarda S, Eisenberger MA, Mottet N, Schröder FH, Sternberg CN, *et al.* Contemporary role of androgen deprivation therapy for prostate cancer. Eur Urol 2012;61:11-25.
3. Hellerstedt BA, Penta KJ. The current status of hormonal therapy for prostate cancer. Cancer J Clin 2002;52:154-79.
4. Ramsay AK, Leung HY. Signalling pathways in prostate carcinogenesis: potentials for molecular-targeted therapy. Clin Sci 2009;117:209-28.
5. Bluemn EG, Nelson PS. The androgen/androgen receptor axis in prostate cancer. Curr Opin Oncol 2012;24:251-7.
6. Zobniw CM, Causebrook A, Fong MK. Clinical use of abiraterone in the treatment of metastatic castration resistant prostate cancer. Res Rep Urol 2014;6:97-105.
7. 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.
8. 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.
9. Chi K, Hotte SJ, Joshua AM, North S, Wyatt AW, Collins LL, *et al.* Treatment of mCRPC in the AR axis-targeted therapy resistant state. Ann Oncol 2015;26:2044-56.
10. Mostaghel EA, Marck BT, Plymate SR, Vessella RL, Balk S, Matsumoto AM, *et al.* Resistance to CYP17A1 inhibition with abiraterone in castration-resistant prostate cancer: induction of steroidogenesis and androgen receptor splice variants. Clin Cancer Res 2011;17:5913-25.
11. Fiandalo MV, Wilton J, Mohler JL. Roles for the back-door pathway of androgen metabolism in prostate cancer response to castration and drug treatment. Int J Biol Sci 2014;10:596-60.
12. 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. Cance Res 2006;66:2815-25.
13. Dehm SM, Schmidt LJ, Heemers HV, Vessella RL, Tindall DJ. Splicing of a novel androgen receptor exon generates a constitutively active androgen receptor that mediates prostate cancer therapy resistance. Cancer Res 2008;68:5469-77.
14. Antonarakis ES, Lu C, Wang H, Luber B, Nakazawa M, Roeser JC, *et al.* AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med 2014;371:1028-38.
15. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, *et al.* Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment:a randomised open-label trial. Lancet 2010;376:1147-54.
16. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, *et al.* Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187- 97.
17. Ryan CJ, Molina A, Li J, Kheoh T, Small EJ, Haqq CM, *et al.* Serum androgens as prognostic biomarkers in castration-resistant prostate cancer: results from an analysis of a randomized phase III trial. J Clin Oncol 2013;31:2791-8.
18. Ryan CJ, Peng W, Kheoh T, Welkowsky E, Haqq CM, Chandler DW, *et al.* Androgen dynamics and serum PSA in patients treated with abiraterone acetate. Prostate Cancer Prostatic Dis 2014;17;192-8.
19. Isikbay M, Otto K, Kregel S, Kach J, Cai Y, Vander Griend DJ, *et al.* Glucocorticoid receptor activity contributes to resistance to androgen-targeted therapy in prostate cancer. Horm Cancer 2014;5:72-89.
20. Bonkhoff H, Fixemer T, Hunsicker I, Remberger K. Progesterone receptor expression in human prostate cancer: correlation with tumor progression. Prostate 2001;48:285-91.
21. Jayaram A, Nowakowska K, Mateo J, Nava Rodrigues D, Riisnaes R, Zukiwski A, *et al.* Phase 1-2 study of progesterone receptor (PR) inhibition with extended-release (ER) onapristone (ONA) in patients (pts) with castration-resistant prostate cancer (CRPC):PK, safety and PR testing results from the dose escalation cohort. J Clin Oncol 2015;33(Suppl;abstract 5051).
22. Sun S, Sprenger CC, Vessella RL, Haugk K, Soriano K, Mostaghel EA, *et al.* Castration resistance in human prostate cancer is conferred by a frequently occurring androgen receptor splice variant. J Clin Invest 2010;120:2715-30.

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