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ARTICLE

Clinical Research

Exposure–response analyses of abiraterone and its metabolites in real-world patients with metastatic castration-resistant prostate cancer

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Abstract

Background Abiraterone acetate is an oral 17α-hydroxylase/C17,20-lyase (CYP17) inhibitor approved for the treatment of metastatic castration-resistant prostate cancer (mCPRC) patients. Previously, a prospective observational trial demonstrated a relationship between abiraterone trough concentrations (C_{min}) in plasma and treatment efficacy. The aim of our study was to investigate the exposure–response relationship of abiraterone and its metabolites, and to study if the proposed target for abiraterone of 8.4 ng/mL is feasible in a "real-world" patient cohort.

Patients and methods mCRPC patients who had at least one abiraterone plasma concentration at steady-state were included in this study. Plasma abiraterone and its metabolites levels were analyzed using a validated liquid chromatography–mass spectrometry method. Using calculated C_{min} values of abiraterone and its active metabolite Δ(4)-abiraterone (D4A), univariate, and multivariable Cox regression analyses were performed.

Results Sixty-two patients were included in this retrospective analysis, of which 42% were underexposed (mean abiraterone $C_{min} \leq 8.4$ ng/mL). In multivariable analysis, $C_{min} \geq 8.4$ ng/mL was associated with longer prostate-specific antigen (PSA) independent progression-free survival (16.9 vs 6.1 months; $p = 0.033$), which resulted in a hazard ratio of 0.44 (95% confidence interval: 0.23–0.82, $p = 0.01$). D4A C_{min} did not show a relationship with treatment efficacy.

Conclusion Our study shows that mCRPC patients with an abiraterone $C_{min} \geq 8.4$ ng/mL have a better prognosis compared with patients with low C_{min}. Monitoring C_{min} of abiraterone can help to identify those patients at risk of suboptimal treatment for whom treatment optimization may be appropriate.

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Introduction

Abiraterone is an inhibitor of 17α-hydroxylase/C17,20-lyase (CYP17), an enzyme involved in the intra- and extragonadal biosynthesis of androgens, including testosterone. Initially, abiraterone acetate was approved for treatment of metastatic castration-resistant prostate cancer (mCRPC) as it improves overall survival (OS) and progression-free survival (PFS) in this patient population compared with placebo [1, 2].

Following oral ingestion, abiraterone acetate is rapidly deacetylated to form the active substance abiraterone. Further metabolism into its major inactive metabolites abiraterone sulfate and abiraterone N-oxide sulfate is facilitated by cytochrome P450 family 3A member 4 (CYP3A4) and sulfotransferase family 2A member 1 (SULT2A1) [3]. More recently, an active metabolite of abiraterone was discovered named Δ4-abiraterone (D4A), which is formed by the

enzyme 3β-hydroxysteroid-dehydrogenase [4, 5]. D4A blocks CYP17, several steroidogenic enzymes, and the androgen receptor [5, 6]. Conversely, D4A is further metabolized to 3-keto-5-α-abiraterone, which stimulates the androgen receptor [7, 8]. The net result of these pharmacologic actions on therapeutic outcome remains to be elucidated.

Abiraterone acetate is administered in a fixed dose of 1000 mg once daily (QD). Mean steady-state trough concentrations (C_{min}) at this approved dose are 11.1 ng/mL for abiraterone and 1.6 ng/mL for D4A [3, 9]. In a prospective observational trial, abiraterone C_{min} has been associated with treatment response in mCRPC patients. In this study, plasma trough concentrations of abiraterone were significantly higher in prostate-specific antigen (PSA) responders ($n = 38$) compared with nonresponders ($n = 23$) (12.0 vs 8.0 ng/mL, $p = 0.0015$) [10]. Furthermore, a threshold of 8.4 ng/mL has been identified, above which patients had a longer PFS compared with patients with C_{min} below this target (12.2 vs 7.4 months, $p = 0.044$) [10]. The same research group reported that higher D4A C_{min} is related to shorter OS, but not PFS ($n = 30$).

Abiraterone acetate has a large interpatient variability in C_{min} of 46% [10]. Part of this variability may be accounted for by the food-effect, causing a sevenfold increase in C_{max} with a low-fat meal and a 17-fold increase in C_{max} with a high-fat meal, compared with overnight fasting in healthy volunteers [11]. A prospective clinical trial has shown that abiraterone acetate 250 mg QD taken with a low-fat meal was noninferior to abiraterone acetate at a standard dose of 1000 mg QD in modified fasting state, in terms of PSA response and PFS ($n = 72$) [12]. Furthermore, Stover et al. show that some men may benefit from taking abiraterone acetate concomitant with food [13].

Previous studies clearly show an exposure–efficacy relationship between plasma trough concentrations of abiraterone and PFS. Yet, abiraterone acetate is still administered at fixed doses, which could lead to suboptimal treatment for some patients. Therapeutic drug monitoring (TDM), the clinical practice of measuring drug concentrations in biological fluids to individualize drug dosing, could be used to improve patient care. Based on the current data, TDM of abiraterone may be implemented with a C_{min} threshold of 8.4 ng/mL. This threshold was established in a restrictive clinical study and needs to be confirmed with real-life data from daily clinical practice. The aim of our study was to assess the exposure–efficacy relationship of abiraterone and its major metabolites for the purpose of TDM in a "real-world" patient cohort. We hypothesized that patients with abiraterone $C_{min} \geq 8.4$ ng/mL will have a longer PFS compared with patients with a $C_{min} < 8.4$ ng/mL. A retrospective study was conducted to test this hypothesis.

Methods

Patients and sampling

This was an observational study in the outpatient clinical of the Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital, Amsterdam. Abiraterone concentrations were monitored in all mCRPC patients using abiraterone acetate as part of routine clinical care. As authorized by the institute, data from clinical care were used retrospectively. Clinical characteristics were collected from medical records, including demographic data, medical history, abiraterone acetate dose, treatment duration, reason for discontinuation, concomitant medication, and PSA levels. Furthermore, testosterone and androstenedione concentrations were determined during treatment using a validated liquid chromatography–mass spectrometry (LC-MS/MS) assay [14].

Pharmacokinetics

Blood samples were drawn as part of routine clinical care every 3 months on average. The date and time of blood withdrawal, and date and time of drug intake were recorded. Patients with at least one available abiraterone plasma concentration at steady-state were included in this study. Steady-state was considered to be reached after 1 week of treatment, taken into account the 15-h half-life [3]. Abiraterone and its metabolites D4A, abiraterone sulfate, and abiraterone N-oxide sulfate were quantified using a validated LC-MS/MS method [15, 16]. Plasma samples were collected at random time points during a dosing interval at routine patient visits to the outpatient clinic, and therefore, C_{min} values were calculated from the measured concentrations. As abiraterone shows clear distribution pharmacokinetics, log-linear extrapolation was not feasible. Furthermore, the use of Bayesian estimates from a population pharmacokinetic model was considered, but this was complicated by high shrinkage. Therefore, we used the ratio of the observed concentration and median concentration as tool to calculate C_{min}. First, we simulated a full population concentration–time curve of abiraterone with the pharmacokinetic model published by Stuyckens et al. [17]. Second, measured concentrations were divided by the simulated concentrations of the population curve at the recorded time points. Third, the ratio between measured concentrations and simulated concentrations was multiplied by the simulated C_{min} of the population curve to obtain the final calculated C_{min}. Our data show that the shape of the D4A concentration–time curve is similar to that of abiraterone, and therefore, it is suggested that metabolite formation is rate-limiting in the clearance of D4A. As there is no pharmacokinetic model available for D4A, C_{min} was calculated

Table 1 Patient characteristics

	Total	Abiraterone C_{min}	
		>8.4 ng/mL	≤8.4 ng/mL
Number of patients (*n* (%))	62 (100)	36 (58)	26 (42)
Age (mean, range)	72 (60–87)	72 (60–87)	71 (61–83)
Weight (mean, range)	89 (57–175)	91 (57–175)	85 (68–117)
WHO performance status (*n* (%))			
0	22 (36)	12 (33)	10 (38)
1	36 (58)	22 (61)	14 (54)
2	4 (6)	2 (5)	2 (8)
Dose reduction (*n* (%))	4 (6)	2 (6)	2 (8)
Number of previous lines of therapy (*n* (%))			
0	33 (53)	23 (64)	10 (38)
1	13 (21)	7 (19)	6 (23)
2	10 (16)	3 (8)	7 (27)
3	4 (7)	2 (5)	2 (8)
4	2 (3)	1 (3)	1 (4)
Previous chemotherapy	26 (42)	9 (25)	17 (65)
Switch to dexamethasone during treatment (*n* (%))	33 (53)	25 (69)	8 (69)
Number of samples (*n*)	244	165	79
Samples per patient (mean (range))	4 (1–11)	5 (1–10)	3 (1–8)
Median (range) C_{min} (ng/mL):			
Abiraterone	9.3 (2.0–49.8)	14.9 (8.5–49.8)	6.3 (2.0–8.4)
D4A	1.0 (0.3–4.4)	14.9 1.3 (0.4–4.4)	0.7 (0.3–1.8)
Median testosterone levels (ng/mL)	<0.010[a]	<0.010[a]	<0.010[a]
Median androstenedione levels (ng/mL)	<0.010[a]	<0.010[a]	<0.010[a]

Demographic data and androgen levels are at values at baseline

D4A Δ(4)-abiraterone

[a]Data points below the lower limit of quantification of the bioanalytical method

in the same manner as the C_{min} of abiraterone. Measured concentrations of abiraterone sulfate and abiraterone N-oxide sulfate were divided into three groups based on the time of sampling after dosing (TAD), being 0–4, 4–10 and 10–24 h after drug intake. Samples taken before steady-state was reached or more than 24 h after the last dose were excluded from further analysis.

Outcome measures

Three clinical end points regarding treatment response were evaluated separately in this study; PSA response, PSA independent PFS, and time to PSA progression (TTPP). PSA response was defined as ≥50% decrease in PSA from baseline, both according to the Prostate Cancer Working Group 2 (PCWG2) criteria [18, 19]. PSA independent PFS was defined as the time from treatment start to the first event of progression, being either radiographic progression, symptomatic progression (start of radiotherapy, samarium treatment, increase of analgesic dose, or a WHO performance level increase of at least 2), onset of next treatment or death from any cause. Radiographic progression was evaluated according to modified Response Evaluation Criteria in Solid Tumors (version 1.1) [20]. TTPP was defined as the time from treatment start to a 25% or greater PSA increase from the nadir, with an absolute increase in PSA levels of at least 2 ng/mL [20], and had to be confirmed by a subsequent PSA value, also according to PCWG2 criteria. Toxicity was defined as discontinuation due to adverse events, dose reductions due to adverse events or temporary treatment interruption.

Statistics

For the purpose of exposure–response analyses, the mean of all available abiraterone and metabolite levels per patient was used as parameter for exposure. The association between abiraterone plasma concentrations and metabolite concentrations was determined using the Spearman correlation test. Mann–Whitney *U* tests were used for univariable

analysis of PSA response and plasma concentrations of abiraterone and its metabolites. Using the abiraterone C_{min} target of 8.4 ng/mL as a cutoff value, patients were divided into two groups (adequate vs low C_{min}) for PFS analyses. As no exposure target is known for D4A, D4A plasma concentrations were divided into quartiles for further analyses. PFS functions were estimated using the Kaplan–Meier method and predictive factors were assessed using the univariable model (log rank-test). A stepwise logistic regression was performed for the determination of a predictive score of PFS. Variables significantly associated with outcome in univariate analysis were used in the multivariate analysis. Ultimately, in multivariable analysis, PSA levels at baseline, WHO performance status, number of previous lines of treatment and whether patients switched from prednisone to dexamethason during treatment were included as covariates. The following variables were tested but not included in the final model: age, weight, testosterone levels, androstenedione levels, prior treatment with docetaxel, hemoglobin, alkaline phosphatase, kidney, and liver function. All statistical analyses were performed in R (version 3.6.0, package "survival"). A post hoc power analysis was conducted to evaluate the statistical power of this study.

Results

Evaluable patients

From June 2016 to June 2018, 62 patients on treatment with abiraterone acetate were included in this study. A full overview of patient characteristics is provided in Table 1. The median time of treatment was 13.6 months (range 1.1–73.0 months). At data cutoff on May 13, 2019, 12 patients were still on abiraterone treatment. No relevant CYP-inhibiting or inducing co-medication was used during this treatment period. The Spearman correlation test showed that abiraterone and metabolite concentrations were statistically correlated, meaning that plasma samples with high abiraterone levels also contained high metabolite concentrations. Testosterone and androstenedione levels were below the lower limit of quantification of 0.01 ng/mL in all patients.

Pharmacokinetics

In total, 244 plasma samples were included. The distribution of time of sampling after dosing is shown in Supplementary Fig. 1. Overall, a median (range) of 4 [1–11] samples were available per patient. In aggregate, the median ± SD abiraterone C_{min} concentration was 9.3 ± 10 ng/mL, and median ± SD metabolite plasma concentrations were 1.0 ± 0.9 ng/mL for D4A, $8.7 \pm 7.2 \times 10^3$ ng/mL for abiraterone sulfate and $7.8 \pm 3.9 \times 10^3$ ng/mL for abiraterone N-oxide sulfate. Interpatient variability (coefficient of variation; CV%) of mean plasma concentrations at a 1000 mg QD was 70% for abiraterone and 61% for D4A. Furthermore, mean intrapatient variability (CV%) at a 1000 mg QD was 53% for abiraterone and 45% for D4A.

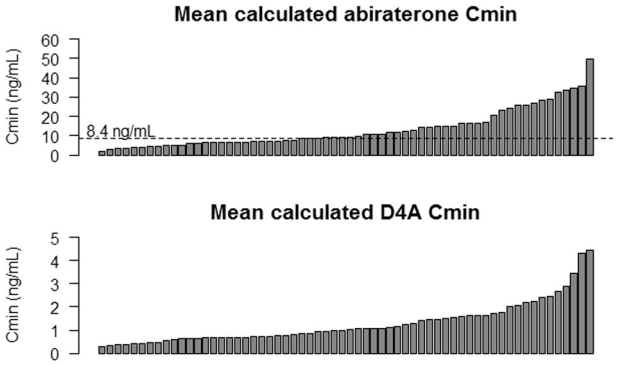

Fig. 1 Distribution of plasma concentrations of abiraterone and Δ(4)-abiraterone (D4A) in patients with metastatic castration-resistant prostate cancer (mCRPC), including the proposed target concentration for abiraterone of 8.4 ng/mL. Each bar represents one patient

An overview of the distribution of mean abiraterone and D4A C_{min} concentrations per patient is provided in Fig. 1. Twenty-six (42%) patients had an abiraterone C_{min} below the target of 8.4 ng/mL. Four patients received a dose reduction to 500 mg QD ($n = 2$) or 750 mg QD ($n = 2$) due to adverse events, including hepatotoxicity and fatigue. Two of these patients had an abiraterone C_{min} below the target of 8.4 ng/mL after dose reduction. Of all explored clinical parameters, none were found to be significantly predictive of abiraterone plasma concentrations, except for body weight at baseline. Linear regression indicated that patients with a higher body weight at baseline had a lower plasma concentration ($p = 0.014$).

Exposure–response analyses abiraterone

Among 62 included patients, 35 (56%) patients were considered PSA responders, vs 27 (44%) patients without a PSA response. Figure 2 shows the relationship between C_{min} of abiraterone PSA response. Mean plasma trough concentrations of abiraterone were 11.4 ng/mL in PSA responders compared with 7.2 ng/mL nonresponders ($p = 0.18$). The maximal change in PSA from baseline (%) after start of treatment is shown for each patient in Fig. 3. Plasma concentrations of the inactive metabolites abiraterone N-oxide sulfate and abiraterone sulfate are depicted in Supplementary Fig. 2. As no trough concentrations could be calculated for these metabolites, plasma levels are given in three groups based on the time after dosing. Median plasma concentrations were higher in PSA responders compared with nonresponders in all groups but one.

For PSA independent PFS, 62 patients were included with 50 events (81% of patients) of progression. The remaining patients were still on treatment with abiraterone acetate. Median PSA independent PFS was 16.9 months in patients with an abiraterone $C_{min} \geq 8.4$ ng/mL compared with 6.1 months in patients with a C_{min} below the target ($p = 0.077$, see Fig. 4). The multivariable analysis resulted in a hazard ratio (HR) of 0.44 (95% CI 0.23–0.82, $p = 0.01$).

For TTPP analysis, 62 patients were included with 53 events (85% of patients) of PSA progression. Three patients were still on treatment, one patient died prior to PSA progression, and five patients did not show PSA progression but discontinued treatment due to radiographic progression. These patients were censored for TTPP analysis. Median TTPP in patients with an abiraterone $C_{min} \geq 8.4$ ng/mL was 19.8 months compared with 3.7 months in patients with a C_{min} below the target ($p = 0.062$, see Fig. 4). In multivariable analysis, $C_{min} \geq 8.4$ ng/mL resulted in an HR of 0.52 (95% CI 0.29–0.97, $p = 0.038$).

A post hoc power analysis was conducted using the above described results. The power to detect a difference in PFS from 16.1 to 6.1 months (with an HR of 0.44) between patients with $C_{min} \geq 8.4$ ng/mL vs <8.4 ng/mL, when there are 36 subjects in the first group and 26 in the second, using a two-sided log rank-test with alpha = 0.05, was 80%.

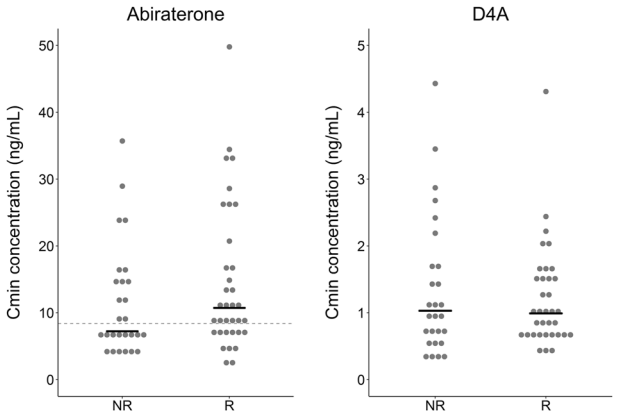

Fig. 2 Relationship between prostate-specific antigen response and the calculated trough concentration of abiraterone (left), Δ(4)-abiraterone (D4A) (right). Horizontal lines represent the median concentration for PSA responders (R, $n = 35$) and nonresponders (NR, $n = 27$) and the dotted lines represent the proposed target for abiraterone of 8.4 ng/mL. Mean plasma trough concentrations of abiraterone were 11.4 ng/mL in PSA responders compared with 7.2 ng/mL nonresponders ($p = 0.18$) and D4A plasma concentrations were 1.0 ng/mL in both PSA responders and nonresponders ($p = 0.88$)

Exposure–response analyses D4A

Figure 2 shows the relationship between C_{min} of D4A and PSA response. Plasma concentrations were 1.0 ng/mL in both PSA responders and nonresponders ($p = 0.88$).

Patients were divided into quartiles based on plasma concentrations of D4A, and PFS analyses were performed using these groups. There was no significant difference in the four quartiles regarding PSA independent PFS (7.7 vs 22 vs 13 vs 11 months, $p = 0.47$). Furthermore, there was no significant differences in the four quartiles regarding TTPP (8.2 vs 15 vs 5.1 vs 11 months, $p = 0.57$). Kaplan–Meier curves are shown in Supplementary Fig. 3. Both univariable and multivariable analysis did not support a relationship between D4A plasma concentrations and PFS.

Exposure-toxicity analysis

Of 62 included patients, four patients received a dose reduction and three patients temporarily discontinued

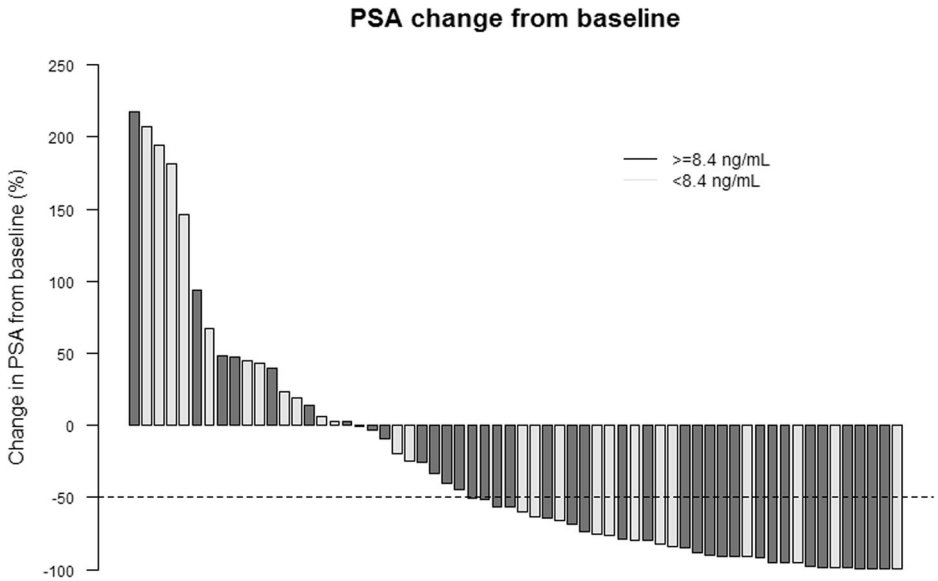

Fig. 3 Waterfall plot showing the PSA change from baseline (%) after start of abiraterone acetate treatment. Each bar represents one patient and the colors indicate if this patient had an abiraterone C_{min} above or below 8.4 ng/mL, The dotted line indicates a 50% PSA decrease from baseline, representing the cutoff for patients to be regarded PSA responders (>50%) or nonresponders

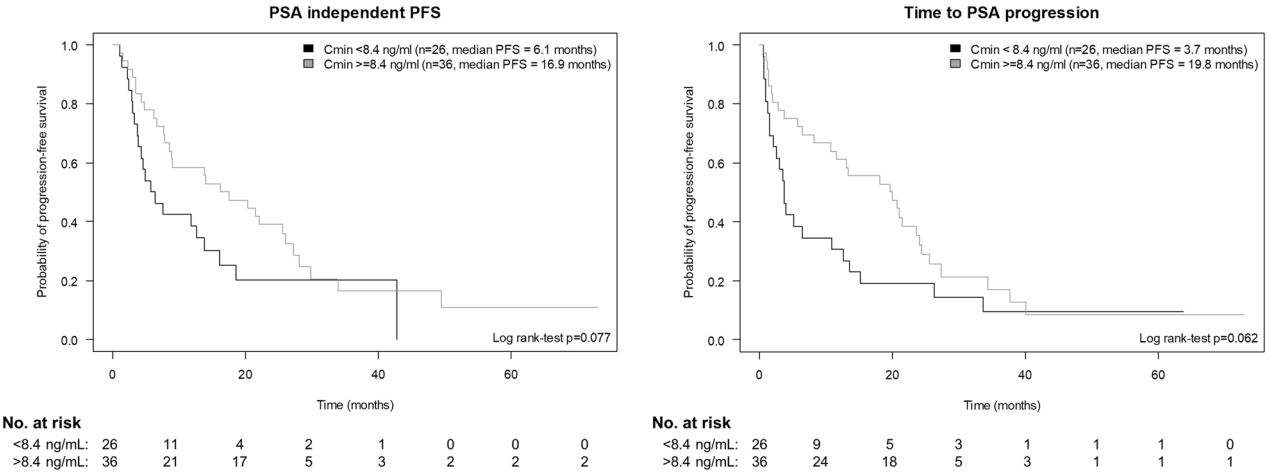

Fig. 4 Kaplan–Meier plots of PSA independent progression-free survival (PFS) in metastatic castration-resistant prostate cancer (mCRPC) patients with a mean abiraterone C_{min} above ($n = 36$, gray line) or below ($n = 26$, black line) the exposure target of 8.4 ng/mL. The left figure shows PSA independent PFS and the right figure shows time to PSA progression (TTPP)

treatment due to the presence of adverse events. Reasons for dose reduction or treatment interruption included fatigue, hepatotoxicity, and abdominal pain. Median abiraterone C_{min} was 9.0 ng/mL for patients experiencing clinically relevant adverse events, compared with 9.3 ng/mL in those who did not ($p = 1.0$). Moreover, median D4A C_{min} concentrations were 1.1 vs 1.0 for patients with and without adverse events, respectively ($p = 0.60$).

Discussion

In this study, plasma concentrations of abiraterone and its metabolites were monitored in a clinical setting. To our knowledge, this is the first study to evaluate the correlation between abiraterone C_{min} and response in a real-world patient cohort, including D4A and other metabolite data. Obtaining real-life data is relevant for clinical practice, as this better reflects daily practice than data derived from clinical trials [21]. Abiraterone acetate is administered at a fixed dose of 1000 mg QD. Our data show that patients with an abiraterone $C_{min} \geq 8.4$ ng/mL have a longer PFS compared with patients with a pharmacokinetic exposure below this threshold. Furthermore, this study shows that 42% of patients with mCRPC may be underdosed with this standard fixed dosing regimen and could benefit from an individualized dosing strategy, which is in line with the previously reported 35% of patients having a C_{min} below the target [10].

D4A was included in PFS analyses as it shows antiandrogen activity. However, it may be further converted to an androgen-stimulating metabolite and, therefore, the net contribution of D4A to the antitumor effect of abiraterone is ambiguous [7, 8]. Although a previous study has shown that a higher D4A C_{min} was associated with shorter OS (HR 1.54, 95% CI 1.06–2.22, $p = 0.022$) but not with PFS [9], our study did not reveal a relationship between D4A C_{min} and treatment response, PSA independent PFS or TTPP. Moreover, abiraterone and D4A concentrations are correlated, which indicates that abiraterone C_{min} may serve as a proxy for the total antitumor effect of abiraterone and its metabolites.

The exposure target for abiraterone of 8.4 ng/mL was based on a prospective observational study [10]. The CYP17 inhibitory concentrations 50% (IC50) value of abiraterone is 0.07 ng/mL. After correcting for plasma protein binding (99%), a minimum concentration of 7.0 ng/mL should be reached to inhibit 50% of CYP17 in plasma. The exposure target is close to this corrected IC50 value, which biologically substantiates the threshold. Moreover, the CYP17 IC50 of D4A is 0.035 ng/mL. Given a protein binding of 99%, a minimum concentration of 3.5 ng/mL should be achieved to inhibit 50% of the CYP17 enzyme [4, 5]. Only three patients reached this threshold, which could explain why no association was found between D4A plasma levels and response in this population.

Although we believe our study provides relevant information on exposure-response of abiraterone in real-life patients, our analysis does have some limitations. First, in this study not actual C_{min} but calculated (from measured) plasma concentrations were used. Although actual C_{min} may be more accurate than calculated C_{min}, the practical implementation of TDM is more feasible if samples can be drawn at random times during the dosing interval as it can be combined with routine visits to the outpatient clinic. Second, the extent of adherence to abiraterone acetate was not available due to the retrospective nature of this analysis. Although treating physicians provided instructions on drug

intake and usage, this may be a potential source of variability in abiraterone C_{min}.

Based on our study and previously published data, an exposure target for abiraterone of 8.4 ng/mL seems appropriate for TDM. Patients with a C_{min} below this target may be advised to take the drug concomitant with food, thereby avoiding expensive dose increments. A single-dose study of abiraterone in healthy volunteers has shown that the area under the plasma concentration–time curve (AUC) and C_{max} increase 10- and 17-fold after intake with a high-fat meal, respectively, and sevenfold and fivefold after intake with a low-fat meal compared with overnight fasting, respectively [11]. The same study showed a less pronounced effect in mCRPC patients when comparing a modified fasting state with food intake (similar exposure with low-fat meals and a twofold increase with high-fat meals) [11]. Furthermore, previous research has shown that some men may benefit from concomitant intake of abiraterone acetate with food in terms of PSA progression [13]. This may be attributed to the a lower percentage of patients with $C_{min} < 8.4$ ng/mL. Based on this information, concomitant intake of abiraterone with a low-fat meal may increase plasma levels up to fivefold, which would be sufficient for the majority of included patients with $C_{min} \leq 8.4$ ng/mL to reach plasma levels above the target. Treatment optimization by individualized dosing strategies could lead to better efficacy of abiraterone and higher treatment response. Furthermore, the lack of a relationship between exposure and toxicity suggests that increasing plasma levels will, in these ranges, not result in additional toxicity. Although more research is needed to confirm our findings and to furher study the 8.4 ng/mL threshold, we advise clinicians to consider integrating TDM of abiraterone into standard treatment of mCRPC patients. Currently, a study is performed in our Institute to investigate the feasibility of TDM with abiraterone using a food intervention [22] by which we hope to improve outcome for mCRPC patients treated with abiraterone acetate.

Conclusion

Our study shows that patients with an abiraterone trough level above 8.4 ng/mL have a longer PFS compared with patients with a pharmacokinetic exposure below this threshold. Exposure to the active metabolite D4A did not show a relationship with treatment efficacy and therefore may not add to the prognostic value of abiraterone plasma levels. Monitoring abiraterone C_{min} can identify those patients who are underdosed and we advise clinicians to consider integrating TDM of abiraterone into standard treatment of mCRPC patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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