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Original Research

Concomitant intake of abiraterone acetate and food to increase pharmacokinetic exposure: real life data from a therapeutic drug monitoring programme

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Abstract ***Aim:*** Abiraterone acetate is approved for the treatment of metastatic prostate cancer. At the currently used fixed dose of 1000 mg once daily in modified fasting state, 40% of patients do not reach the efficacy threshold of a minimum plasma concentration (C_{min}) ≥ 8.4 ng/mL and are thereby at risk of decreased treatment efficacy. This study aims to evaluate whether pharmacokinetically (PK) guided abiraterone acetate dosing with a food intervention is feasible and results in an increased percentage of patients with concentrations above the target.

Methods: Patients starting regular treatment with abiraterone acetate in modified fasting state were included. Pharmacokinetic analysis was performed 4, 8 and 12 weeks after start of treatment and every 12 weeks thereafter. In case of C_{min} < 8.4 ng/mL and acceptable toxicity, a PK-guided intervention was recommended. The first step was concomitant intake of abiraterone acetate with a light meal or a snack.

Results: In total, 32 evaluable patients were included, of which 20 patients (63%) had a C_{min} < 8.4 ng/mL at a certain time point during treatment. These patients were recommended to take abiraterone acetate concomitantly with food, after which C_{min} increased from 6.9 ng/mL to

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27 ng/mL ($p < 0.001$) without additional toxicities. This intervention led to adequate exposure in 28 patients (87.5%).
Conclusion: Therapeutic drug monitoring of abiraterone was applied in clinical practice and proved to be feasible. Concomitant intake with food resulted in a significant increase in C_{min} and offers a cost-neutral opportunity to optimise exposure in patients with low C_{min}.

1. Introduction

Abiraterone acetate is an antihormonal prodrug, which is rapidly converted to its active form abiraterone after oral ingestion. Abiraterone inhibits 17α-hydroxylase/C17,20-lyase (CYP17) and thereby blocks the androgen biosynthesis. Initially, abiraterone acetate was approved for the treatment of metastatic castration-resistant prostate cancer, but recently, it has also been approved for the treatment of metastatic hormone-sensitive prostate cancer [1].

Exposure-response analyses have shown that plasma concentrations of abiraterone are related to efficacy [2–4]. Carton *et al.* demonstrated that progression-free survival (PFS) was significantly longer in patients with a minimum plasma concentration (C_{min}) above 8.4 ng/mL compared with those below (12.2 versus 7.4 months, $p = 0.044$) [3]. We have confirmed this exposure-efficacy threshold in a real-life patient cohort [4].

Abiraterone acetate is currently administered using a one-size-fits-all approach, in which all patients receive a dose of 1000 mg once daily (QD) without food. This dosing strategy results in high interindividual variability in exposure to abiraterone, with a coefficient of variation (CV%) of 46–70% for C_{min} [3,4]. At the currently used fixed dose, 35–42% of patients do not reach the efficacy threshold of $C_{min} \geq 8.4$ ng/mL and are thus underdosed [3,4]. This provides a strong rationale for therapeutic drug monitoring (TDM) to intervene and to increase the number of patients having an adequate abiraterone exposure.

As food intake impacts the absorption of abiraterone, concomitant intake of abiraterone acetate and food could be applied in case of low exposure. According to the drug label [5], abiraterone acetate should be administered in a modified fasting state, which means no food 2 h before and 1 h after intake of the drug. However, concomitant intake with food has been shown to result in a clinically relevant increase in exposure in a previous food-effect study [6].

The aim of this study was to evaluate whether TDM of abiraterone with a food intervention is feasible in clinical practice and results in an increased percentage of patients with efficacious exposure to abiraterone without additional toxicities.

2. Methods

2.1. Patients

Patients starting regular treatment with abiraterone acetate at the registered dose of 1000 mg QD in a modified fasting state were included in an ongoing prospective study on TDM of oral anticancer drugs (www.trialregister.nl; NL6695) [7].

2.2. Objectives

The primary objective of this study was to halve the percentage of patients with an exposure below the target of 8.4 ng/mL after 12 weeks compared to historical data. The study of Carton *et al.* was taken as a reference, in which 35% of patients had a mean $C_{min} < 8.4$ ng/mL[3]. Secondary objectives were to evaluate the feasibility, tolerability and efficacy of TDM of abiraterone with a food intervention in clinical practice and to achieve a physician adherence > 90% (i.e. whether TDM recommendations were followed by the treating physician). Feasibility was defined as the percentage of successful pharmacokinetically (PK) guided interventions (i.e. target attainment without additional toxicities). Tolerability was evaluated by the incidence of clinically relevant toxicities, defined as toxicities leading to dose reduction, treatment interruption or discontinuation, as evaluated by the treating physician. Preliminary efficacy was assessed by comparing PFS and prostate-specific antigen (PSA) responses between patients who needed a PK-guided intervention and those who did not (i.e. all $C_{min} \geq 8.4$ ng/mL). PFS was defined as the time from start of treatment to progression, as assessed by the treating physician based on either PSA increase, radiological progression or clinical progression. PSA response was defined as ≥ 50% decrease in PSA from baseline, according to the Prostate Cancer Working Group 2 criteria [8,9].

2.3. PK samples

PK samples were collected 4, 8 and 12 weeks after start of treatment and every 12 weeks thereafter. Fig. 1 provides an overview of the study design. Abiraterone

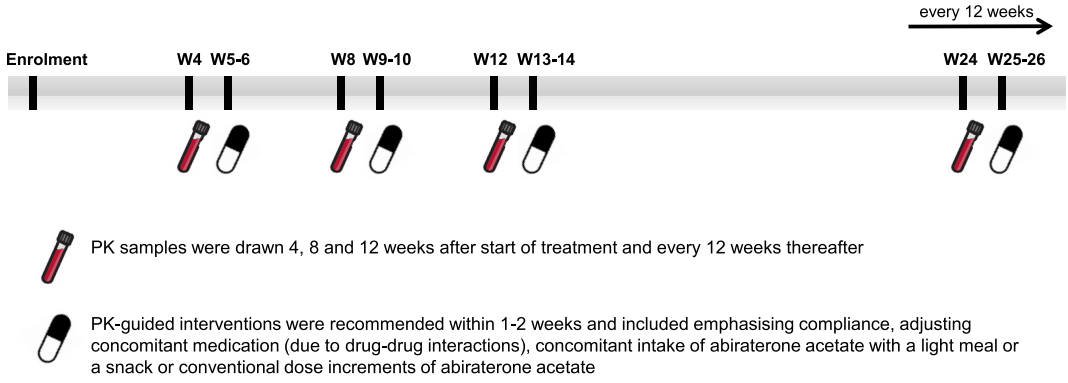

Fig. 1. Schematic overview of study design. PK = pharmacokinetic(ally), W = week.

concentrations were measured using a validated liquid chromatography-tandem mass spectrometry assay [10]. C_{min} was estimated using the following formula:

$$C_{min} = C_{measured} * 0.5^{\frac{dosinginterval - TAD}{t_{1/2}}}$$

in which $C_{measured}$ is the measured plasma concentration, dosing interval is the time between two consecutive administrations of the drug (i.e. 24 h), TAD is the time after dose (i.e. time between last intake of the drug and collection of the PK sample) and $t_{1/2}$ is the elimination half-life of the drug (i.e. 12 h [11]).

2.4. PK-guided interventions

In case of $C_{min} < 8.4$ ng/mL and acceptable toxicity, a PK-guided intervention was recommended. After compliance and drug-drug interactions were checked, the first step was concomitant intake of abiraterone acetate with a light meal or a snack. No specified meals were used. Patients were instructed to take abiraterone acetate for example with some bread, yoghurt or fruit, but not with food high in fat. If exposure remained below the target, dose increments of abiraterone acetate were recommended (to 1250 and 1500 mg, respectively). Dose reductions were solely based on toxicities, not on exposure.

2.5. Statistical analyses

Patients were evaluable for the primary end-point if they completed the first three PK measurements. The effect of concomitant intake of abiraterone acetate and food was evaluated by a Wilcoxon-signed rank rest and a Mann-Whitney U test. Preliminary efficacy was evaluated using univariable and multivariable Cox regression and logistic regression analyses. Other data were analysed using descriptive statistics. Statistical analyses were performed using R version 3.3.2 [12].

2.6. Ethical regulations

This study was assessed by the accredited Medical Ethics Committee of the Netherlands Cancer Institute, Amsterdam, The Netherlands, in May 2017, and it was reviewed not to fall under the Dutch Medical Research Involving Human Subjects Act, because TDM is performed as standard care, and no additional procedures were required for participants. The study was authorised by the institutional review board. Patients provided written informed consent. The study protocol followed the principles of the Declaration of Helsinki.

3. Results

3.1. Patient characteristics

In total, 32 evaluable patients were enrolled in the study between June 2017 and December 2018 (Fig. 2). Baseline characteristics of these patients are provided in Table 1. Twenty-nine patients completed the first three PK measurements and were eligible for evaluation of the

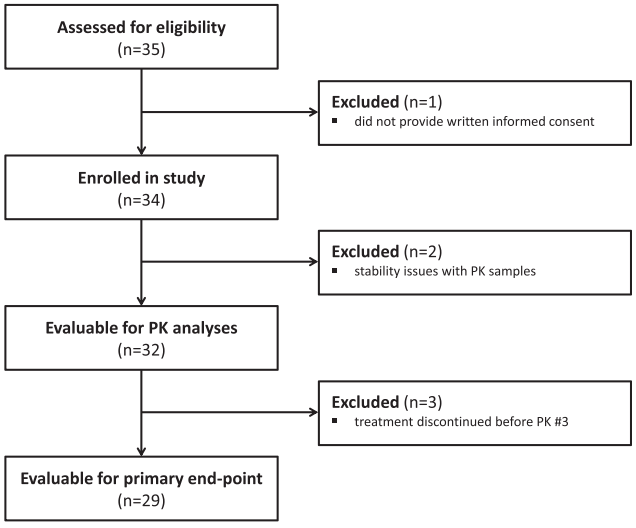

Fig. 2. Patient flow chart. PK = pharmacokinetic.

Table 1
Baseline characteristics.

Characteristic	Patients with ≥1 measurement of abiraterone C_{min} < 8.4 ng/mL (n = 20)	Patients with all measurements of abiraterone C_{min} ≥ 8.4 ng/mL (n = 12)	All evaluable patients (n = 32)
Age (years)	73 [52–87]	73 [63–83]	73 [52–87]
WHO performance status			
0	3 (15%)	5 (42%)	8 (25%)
1	11 (55%)	6 (50%)	17 (53%)
2	5 (25%)	1 (8%)	6 (19%)
3	1 (5%)	0	1 (3%)
Treatment setting			
Castration-resistant	19 (95%)	12 (100%)	31 (97%)
Hormone-sensitive	1 (5%)	0	1 (3%)
Previous lines of systemic treatment[a]			
0	11 (55%)	9 (75%)	20 (63%)
1	4 (20%)	2 (17%)	6 (19%)
≥ 2	5 (25%)	1 (8%)	6 (19%)
Previous systemic treatment[a]			
Docetaxel	9 (45%)	2 (17%)	11 (34%)
Enzalutamide	3 (15%)	1 (8%)	4 (13%)
Radium-223	3 (15%)	1 (8%)	4 (13%)
Cabazitaxel	4 (20%)	0	4 (13%)
Gleason score			
≤ 7	10 (50%)	7 (58%)	17 (53%)
8–10	9 (45%)	5 (42%)	14 (44%)
Missing	1 (5%)	0	1 (3%)
Baseline PSA (ng/mL)	83 [6–1036]	32 [6–282]	48 [6–1036]

Data are expressed as no. (%) or median [range], as appropriate.
C_{min} = minimum plasma concentration, PSA = prostate specific antigen.
[a] In castration-resistant setting.

primary end-point. Twenty patients (63%) had C_{min} < 8.4 ng/mL at a certain time point during treatment. In general, these patients tended to have received more prior lines of treatment, had a worse World Health Organisation (WHO) performance status and had a higher baseline PSA compared with patients with all C_{min} ≥ 8.4 ng/mL. At the time of data cut-off (30 August 2019), 13 patients (41%) were still on treatment with a median duration of 11.4 months (range: 2.8–26.3 months).

3.2. Pharmacokinetically guided dosing

In total, 194 samples have been collected, with a median number of samples per patient of 6 (range: 1–13). First, the results with regard to the primary outcome will be described (i.e. to halve the percentage of patients with a low exposure after 12 weeks). An overview of the median C_{min} and the percentage of patients with C_{min} below the efficacy threshold at each time point can be found in Table 2. After 4 weeks of abiraterone acetate treatment at 1000 mg QD in modified fasting state, median abiraterone C_{min} was 12.5 ng/mL (range: 1.0–100 ng/mL), and 8 patients (25%) had a C_{min} < 8.4 ng/mL. After 12 weeks, median abiraterone C_{min} increased to 17 ng/mL (range: 6.7–126 ng/mL) after a

Table 2
Abiraterone C_{min} and percentage of patients with low pharmacokinetic exposure after 4, 8 and 12 weeks.

Parameter	Result
Abiraterone C_{min}	**in ng/mL [range]**
PK sample #1 (week 4)	13 [1.0–100]
PK sample #2 (week 8)	17 [5.8–114]
PK sample #3 (week 12)	17 [6.7–126]
Patients with C_{min} below the target of 8.4 ng/mL	**n (%)**
PK sample #1 (week 4)	8 (25%)
PK sample #2 (week 8)	6 (19%)
PK sample #3 (week 12)	3 (10%)
Any time point during treatment	20 (63%)

Data are expressed as median [range] or number (%), as appropriate.
PK#1: 32 patients; PK#2: 31 patients; PK#3: 29 patients.
C_{min} = minimum plasma concentration, PK = pharmacokinetic.

food intervention was implemented in patients with a low exposure, with 10% of patients not reaching the target.

To evaluate the secondary objectives, all PK-guided interventions were taken into account, so also the interventions that were performed after 12 weeks. Fig. 3 provides an overview of the PK-guided interventions and its results. The 20 patients (63%) with C_{min} < 8.4 ng/mL at a certain time point during treatment were recommended to take abiraterone acetate concomitantly with a light meal or a snack. In one patient, this PK-guided intervention could not be performed, because treatment was discontinued because of progression. The interventions resulted in adequate exposure (i.e. C_{min} ≥ 8.4 ng/mL) in 16 patients (84%). In two patients, the effect could not be evaluated, as treatment was discontinued because of progression before the next PK measurement. In one patient, C_{min} remained below the target initially, and further dose escalation was not deemed feasible because of prior liver toxicity. Eventually, the target was reached with the initial recommended intake of food. Physician adherence to the recommendations was 100%. In total, 28 patients (87.5%) eventually had an adequate exposure. Only one patient (3%) had a median C_{min} < 8.4 ng/mL.

Fig. 4 shows boxplots of abiraterone C_{min} in patients with adequate and low exposure, before and after concomitant intake with food. In the group of patients with adequate exposure (i.e. all C_{min} ≥ 8.4 ng/mL), in which no PK-guided intervention was needed, median abiraterone C_{min} was 23 ng/mL (range: 15–70 ng/mL). In the group with low exposure (i.e. C_{min} < 8.4 ng/mL), median abiraterone C_{min} before the PK-guided intervention was 6.9 ng/mL (range: 1.0–8.2 ng/mL). Concomitant intake of abiraterone acetate and food resulted in an increase in C_{min} to 27 ng/mL (range: 4.3–94 ng/mL, $p < 0.001$), which was comparable to the patients with all C_{min} above the target.

For the patients who had a C_{min} < 8.4 ng/mL at a later time point during treatment, median C_{min} in previous PK samples was 14 ng/mL (range: 9.0–77 ng/mL), with a median intraindividual variability (CV%) of 23%.

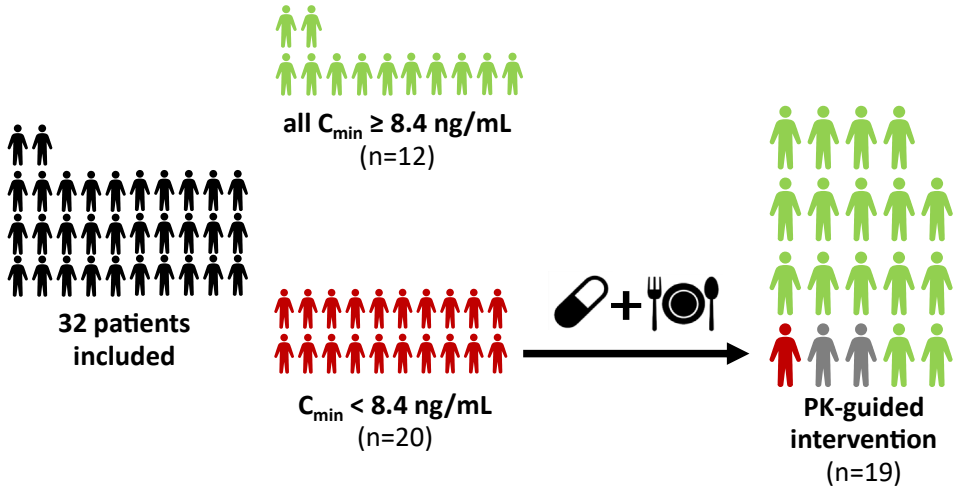

Fig. 3. Schematic overview of study results. The group of patients with C_{min} < 8.4 ng/mL (n = 20) had one or more PK-samples with a calculated C_{min} < 8.4 ng/mL at a certain time point during their treatment. In one patient, a PK-guided intervention could not be performed, because treatment was discontinued because of progressive disease. In two patients, the effect of the PK-guided intervention could not be evaluated, because treatment was discontinued because of progressive disease before the next PK measurement. In one patient, the PK-guided intervention did not result in C_{min} ≥ 8.4 μg/L, further dose escalation was not deemed feasible because of prior liver toxicity. C_{min} = minimum plasma concentration, PK = pharmacokinetically.

In the Supplementary data, individual graphs of the patients who received a food intervention are shown, depicting all measured abiraterone concentrations before and after concomitant intake with a light meal or a snack.

3.3. Toxicity

Three patients needed a dose reduction to 500 mg QD because of toxicity (elevated liver enzymes (n = 2) and fatigue (n = 1)). None of these patients had received a PK-guided intervention when toxicity emerged. Median C_{min} at presentation was 33 ng/mL (range: 11–48 ng/mL). After dose reduction, exposure remained adequate in two patients. In one patient, C_{min} dropped below the target, after which the dose was carefully increased to 1000 mg QD concomitant with food, and the target was reached eventually.

In the patients who did receive a PK-guided intervention, this did not lead to additional toxicities.

3.4. Efficacy

Median PFS was 9.3 months (95%CI: 6.8–NA) in patients with one or more C_{min} < 8.4 ng/mL compared with not reached yet (95% confidence interval [CI]: 15.8–NA) in patients with all C_{min} ≥ 8.4 ng/mL (hazard ratio: 2.59, 95% CI: 0.84–7.97, p = 0.097). However, in multivariable Cox regression, C_{min} < 8.4 ng/mL resulted in a hazard ratio of 1.14 (95%CI 0.34–3.85, p = 0.834), when WHO performance status and number of prior lines of treatment were taken into account. In five patients, the last C_{min} before progression was <8.4 ng/mL (three of them received successful PK-guided interventions before).

In the initially low C_{min} cohort, 10 patients had a PSA response (50%), whereas in the group with all C_{min} ≥ 8.4 ng/mL, 11 patients (92%) had a PSA response. Multivariable logistic regression resulted in an odds ratio of 0.15 for C_{min} < 8.4 ng/mL (p = 0.154).

4. Discussion

In this prospective study, we evaluated the feasibility of PK-guided abiraterone acetate dosing. At the authorised dose of 1000 mg QD in modified fasting state, 63% of patients had a C_{min} < 8.4 ng/mL at a certain time point during treatment. Concomitant intake with a light meal or a snack in these patients resulted in a 3.8-fold increase in C_{min} without additional toxicities (Figs. 3 and 4; Table 2). Hence, TDM of abiraterone is feasible, and concomitant intake with food offers a strategy to optimise exposure in patients with a low C_{min}. For the small proportion of patients in whom the target is not attained with this food intervention, a dose increase can be recommended, although this has not been the case in this study.

In our study, 63% of patients had a low exposure at a certain time point during treatment, which is notably higher than the 35–42% reported in literature [3,4]. However, these values refer to the mean or median value of multiple abiraterone C_{min} measurements, whereas in our study, it represents every patient with a single measurement below the target. In our cohort, only one patient (3%) had a median C_{min} below 8.4 ng/mL because of the successful PK-guided interventions. It is remarkable that especially patients with more prior lines

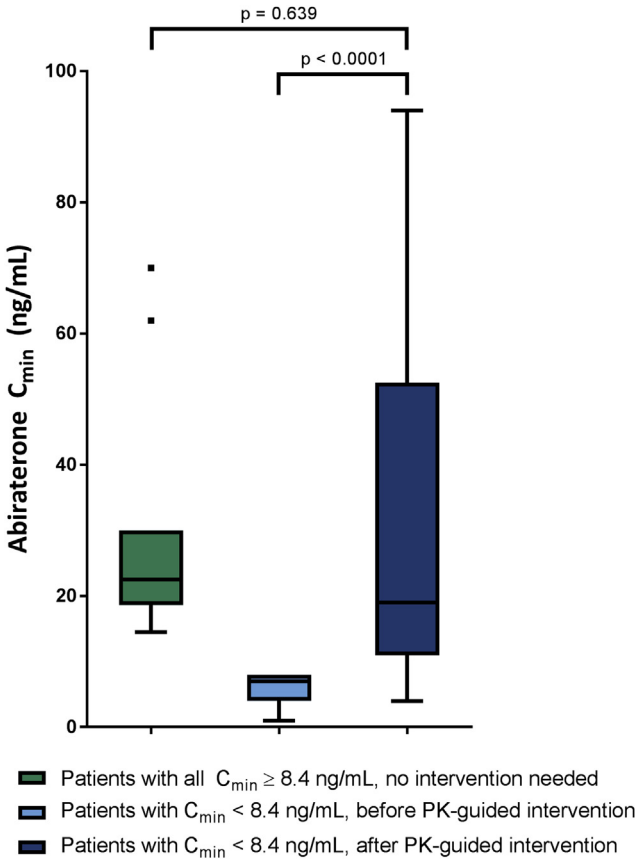

Fig. 4. Box plots of abiraterone C_{min} in patients with adequate and low pharmacokinetic exposure, before and after concomitant intake with food. C_{min} = minimum plasma concentration, PK = pharmacokinetically.

of treatment appear to be at risk of low exposure, which was also seen in our previous exposure-response analysis for abiraterone [4]. It would be of interest to further investigate the mechanism behind the lower exposure in this subgroup (e.g. higher clearance because of enzyme induction or decreased absorption).

Concomitant intake with food not only resulted in an increased exposure but also led to a considerably higher interindividual variability (Fig. 4). As a result, some patients attained very high C_{min} levels. This may be attributed to the fact that meals were not specified and that the composition could thus differ between patients and time points. However, no additional toxicities were experienced by these patients, which is in line with previous literature where no exposure-toxicity relationship was found either [1,3,4]. Therefore, the increased interindividual variability in exposure is considered acceptable, as long as C_{min} levels are above 8.4 ng/mL.

Since abiraterone also shows a high intraindividual variability, many patients had a C_{min} below 8.4 ng/mL at a later time point during treatment. From that moment, patients were recommended to take abiraterone acetate concomitant with food, whereas it was uncertain if this would have been necessary all the time. However, owing to the absence of an exposure-toxicity relationship, long-term implementation of this PK-guided intervention does not appear to be harmful.

The magnitude of the food effect in our study is not in line with the previous study by Chi *et al.* [6] While they found a similar exposure (i.e. area under the concentration-time curve [AUC]) for a low-fat meal compared with modified fasting state, our study shows a 3.8-fold increase in C_{min} after concomitant intake with a light meal or a snack. A possible explanation for this could be that many patients (65%) took abiraterone acetate early in the morning, which was probably after an overnight fast. In that case, the results would be more consistent with the study of Chi *et al.*, who reported a five-fold increase in AUC for a low-fat meal compared with overnight fasting in healthy volunteers [6].

Compared with conventional dose increments, concomitant intake with food offers a cost-neutral strategy to increase pharmacokinetic exposure, although a longer treatment duration could result in higher total treatment costs. Additional costs for a 250 mg or 500 mg dose increase would be €862 or €1782, respectively, per patient per month in the Netherlands. Furthermore, concomitant intake with food is more patient-friendly because patients do not have to take into account the modified fasting conditions.

This prospective study provides real-life data on a TDM programme. Advantages of this study design include the fact that data are representative for the abiraterone population in clinical practice and that our findings can easily be implemented in routine care. On the other hand, this is simultaneously a limitation of our study because compliance could not be guaranteed (i.e. no drug accountability has been performed, and no patient diaries were used).

Although this study demonstrated that an adequate exposure could be attained in the majority of patients by the support of TDM, the ultimate goal is to improve treatment efficacy. Preliminary data on efficacy in this small group of patients indicate that patients who needed a PK-guided intervention still have a shorter PFS than patients with all adequate C_{min}. However, patients with a low C_{min} had a less favourable prognosis at baseline, as they received more prior lines of treatment, had a worse WHO performance status and a higher baseline PSA. We have statistically shown that the adverse results in this cohort are influenced by the adverse patient characteristics in the initially low C_{min} cohort. To evaluate whether TDM actually improves treatment outcomes, a larger cohort of patients will be needed. Therefore, patient inclusion in this study will continue to investigate the effect on treatment efficacy as well.

The significant food effect of abiraterone raises two other interesting concepts. The first is a cost-saving approach: treating patients at a lower dose with food, as has been evaluated by Szmulewitz *et al.* [13] Ideally, this

would be investigated using a two-step procedure. To start, it should be proven that adding food to efficiently raise C_{min} is associated with better treatment outcomes for the standard dose of abiraterone. Then, the same should be proven for lower doses of abiraterone. The other concept is a more pragmatic approach: to recommend concomitant intake with food to all patients, regardless of pharmacokinetic exposure.

In conclusion, we demonstrated that TDM of abiraterone is feasible in clinical practice. Furthermore, concomitant intake of abiraterone acetate and food resulted in a significant increase in C_{min} and thereby offers a safe and cost-neutral opportunity to optimise exposure in patients with a low C_{min}. Therefore, we recommend to implement TDM of abiraterone for all patients in routine care.

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Conflict of interest statement

A.M.B. received research grants for the institute from Sanofi, Bayer and Astellas (outside the submitted work). J.H.B. received research grants for the institute from Astex, PharmaMar and Roche (outside the submitted work) and is a part-time employee, stock holder and patent holder of Modra Pharmaceuticals (a spin-out company developing oral taxane formulations, not related to this study). The other authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.02.012.

References

[1] Committee for medicinal products for human use (CHMP) European medicines agency. Abiraterone European Public Assessment Report; 2011. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_- _Product_Information/human/002321/WC500112858.pdf.

[2] Steven X, Charles X, Kim JR, Matthew S, Saad F, Griffin TW, et al. Modeling the relationship between exposure to abiraterone and prostate-specific antigen dynamics in patients with metastatic castration-resistant prostate cancer. Clin Pharmacokinet 2017;56:55–63. https://doi.org/10.1007/s40262-016-0425-0.

[3] Carton E, Noe G, Huillard O, Golmard L, Giroux J, Cessot A, et al. Relation between plasma trough concentration of abiraterone and prostate-specific antigen response in metastatic castration-resistant prostate cancer patients. Eur J Canc 2017;72:54–61. https://doi.org/10.1016/j.ejca.2016.11.027.

[4] van Nuland M, Groenland S, Bergman A, Steeghs N, Rosing H, Venekamp N, et al. Exposure-response analyses of abiraterone and its metabolites in real-world patients with metastatic castration-resistant prostate cancer. Prostate Cancer Prostatic Dis 14 Oct 2019. https://doi.org/10.1038/s41391-019-0179-5.

[5] Summary of product characteristics of abiraterone acetate. Available from: https://www.ema.europa.eu/en/documents/product-information/zytiga-epar-productinformation_ en.pdf.

[6] Chi KN, Spratlin J, Kollmannsberger C, North S, Pankras C, Gonzalez M, et al. Food effects on abiraterone pharmacokinetics in healthy subjects and patients with metastatic castration-resistant prostate cancer. J Clin Pharmacol 2015;55:1406–14. https://doi.org/10.1002/jcph.564.

[7] Groenland SL, van Eerden RAG, Verheijen RB, Koolen SLW, Moes DJAR, Desar IME, et al. Therapeutic drug monitoring of oral anticancer drugs: the DPOG-TDM protocol for a prospective study. Ther Drug Monit 2019;41:561–7. https://doi.org/10.1097/ftd.0000000000000654.

[8] Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the prostate cancer clinical trials working group. J Clin Oncol 2008;26:1148–59. https://doi.org/10.1200/JCO.2007.12.4487.

[9] Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the prostate cancer clinical trials working group 3. J Clin Oncol 2016;34:1402–18. https://doi.org/10.1200/JCO.2015.64.2702.

[10] Nuland M Van, Venekamp N, Vries N De, Jong KAM De, Rosing H, Beijnen JH. Development and validation of an UPLC-MS/MS method for the therapeutic drug monitoring of oral antihormonal drugs in oncology. J Chromatogr B 2019;1106–1107:26–34. https://doi.org/10.1016/j.jchromb.2019.01.001.

[11] Food and Drug Administration. Center for drug evaluation and research. Abiraterone clinical pharmacology and biopharmaceutics review. 2010. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202379Orig1s000ClinPhar mR.pdf.

[12] R Core Development Team. A language and environment for statistical computing. Vienna: R Found Statistical Computing; 2016.

[13] Szmulewitz RZ, Peer C, Ibraheem A, Martinez E, Kozloff MF, Carthon B, et al. Prospective international randomized phase II study of low-dose abiraterone with food versus standard dose abiraterone in castration-resistant prostate cancer. J Clin Oncol 2018;36:1389–95. https://doi.org/10.1200/JCO.2017.76.4381.