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ORIGINAL ARTICLE

Inter- and intra-patient variability in pharmacokinetics of abiraterone acetate in metastatic prostate cancer

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Abstract

Purpose This study examined the inter- and intra-patient variability in pharmacokinetics of AA and its metabolites abiraterone and Δ(4)-abiraterone (D4A), and potential contributing factors.

Methods AA administered daily for ≥4 weeks concurrently with androgen deprivation therapy (ADT) for mCRPC were included. Pharmacokinetic evaluation was performed at two consecutive visits at least 4 weeks apart. Plasma samples were collected 24 h after last dose of AA to obtain drug trough level (DTL) of two active metabolites, abiraterone and D4A.

Results 39 plasma samples were obtained from 22 patients, with 17 patients had repeat DTL measurement. Considerable inter-patient variability in DTL was seen, with initial DTL for abiraterone ranging between 1.5 and 25.4 ng/ml (CV 61%) and for D4A between 0.2 and 2.5 ng/ml (CV 61%). Intra-patient variability in DTL for abiraterone varied between 0.85 and 336% and for D4A between 1.14 and 199%. There was no increase in AA exposure with use of dexamethasone ($n=5$; DTL 13.9) compared with prednisone ($n=17$; DTL 11.0 $p=0.5$), dosing in fasted state ($n=13$, DTL 12.1) compared to dosing in fed state ($n=9$; DTL 11.1, $p=0.8$), or chemotherapy-exposed ($n=10$; DTL 8.9) compared to chemotherapy naïve ($n=12$; DTL 14.0, $p=0.1$).

Conclusions Our cohort demonstrated high inter- and intra-patient variability in both abiraterone and D4A with fixed dosing of AA, with no effect from choice of corticosteroids, prior use of chemotherapy, or dosing in fasting state. Monitoring DTL of AA may be necessary to minimise risk of patients being under-dosed and earlier development of resistance.

Keywords Abiraterone · D4A · Pharmacokinetics · Prostate cancer

Introduction

Prostate cancer remains the second leading cause of cancer death [1]. Despite androgen deprivation therapy remaining the cornerstone of treatment of metastatic prostate cancer, extragonadal production of androgen inevitably contributes to failure of therapy and progression to castration resistant prostate cancer (CRPC). The 17α-hydroxylase/C17,20-lyase (CYP17) enzyme has been shown to be an important enzyme in testis, adrenal gland, and intra-tumoural androgen synthesis [2]. Abiraterone acetate (AA) is the prodrug of abiraterone which is an orally administered steroidal irreversible selective inhibitor of CYP17, thereby targeting different pathways in androgen production [3]. AA in combination with prednisone demonstrated survival benefit in two landmark phase III clinical trials in men with metastatic CRPC following prior treatment with docetaxel chemotherapy and in those that were chemotherapy naïve [3–6]. AA also delayed time to chemotherapy,

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time to skeletal related events, improved cancer related pain, and halted decline in patient's performance status [4]. These benefits led to its approval in metastatic CRPC patients by multiple regulatory bodies worldwide and is most commonly prescribed treatment in this setting [7].

Therapeutic drug monitoring (TDM) is commonly implemented in the use of potent antibiotics and anti-rejection medications, which much like anti-neoplastic therapies have narrow therapeutic window. However, TDM has not gained widespread acceptance or implementation in chemotherapy or novel anti-cancer therapies, which can often have vastly differing efficacy and toxicity profile among patients. Like other novel targeted oral anti-cancer therapies, AA is recommended at a fixed-dose, with no variation to account for magnitude of benefit, drug–drug interaction, or inter-patient variation in pharmacokinetics. AA being administered orally is subject to variation in absorption through the gastrointestinal system and first-pass metabolism by the liver before entering the systemic circulation [8]. A multitude of factors can, therefore, lead to wide intra- and inter-patient variation in AA levels, with potential for excess toxicity or sub-therapeutic levels inducing resistance and limiting therapeutic efficacy. Food intake is a major factor that has been established to cause wide variation in bioavailability of AA, hence the current recommendation that it be taken on an empty stomach [9–11].

AA is essentially undetectable in the bloodstream, as it is rapidly hydrolysed by the liver to abiraterone, its active metabolite. Abiraterone is a potent and selective inhibitor of CYP17, with half-maximal inhibitory concentration (IC50) of 4 and 2.9 nmol/L for 17a-hydroxylase and C17,20-lyase, which compares with IC50 of 65 and 26 nmol/l, respectively, with non-selective CYP17 inhibitor ketoconazole. An abiraterone concentration of 8.4 ng/mL has been reported as a potential target to predict for PSA response [12]. AA is also converted to abiraterone sulphate and *N*-oxide abiraterone sulphate which are inactive metabolites and Δ4-abiraterone (D4A) [10]. The latter is present at substantially lower concentrations with conversion at around 5%, but is highly potent and enhances AA efficacy. However, relationship between exposure and response has not been established.

The objective of this study is to prospectively investigate variations in drug levels of abiraterone and D4A in Australian cancer patients receiving fixed-dose AA, explore potential factors contributing to this variation, and impact on outcomes.

Materials and methods

Study population

Eligible patients were at least 18 years with metastatic CRPC receiving treatment with AA for at least 4 weeks and able to comply with study procedures. All patients were required to have Eastern Cooperative Oncology Group performance status 0–2, life expectancy of at least 3 months, and adequate liver and renal function. Informed consent was obtained from all individual participants included in the study. The study was approved by the institution's ethics committee.

Study design and procedures

This study was a prospective, longitudinal, observational study conducted between February 2016 and December 2017 with patients recruited from two sites in Sydney, Australia. All patients were initiated on AA 1000 mg, but were allowed to be dose reduced for any toxicities prior to enrolment in the study.

At study entry, baseline demographic data including date of birth, concurrent medications, cancer details (diagnosis, Gleason score, sites of metastasis, and previous treatments received), date of abiraterone commencement, and dose, adverse events, and if presently responding or progressing on abiraterone as per, the Prostate Cancer Working Group criteria were recorded [13]. The second visit occurred at least 4 weeks later.

Blood collection for full blood count, biochemistry, and PSA was performed at each visit. The timing of the last dose of abiraterone and the timing of subsequent meal were recorded at each visit. Patients were recommended to take AA at least 1 h before or 2 h after a meal. Blood samples were taken approximately 24 h (4-h window was allowed) after the last dose of AA to obtain approximate drug trough levels. Two ten mL trough venous blood samples were collected in two EDTA tubes at each timepoint; the data presented here are from the sample analysed using the Macquarie University-based assay, while the second sample was used to verify this data using a validated assay from The Netherlands.

Pharmacokinetic evaluation

Once collected, the sample was processed on ice. Each sample was centrifuged at 1900 rpm for 15 min at 4 °C to separate the plasma. Separated plasma was collected in Eppendorf tubes and stored at − 80 °C until analysis.

For analysis, protein precipitation with acetonitrile was used to pre-treat the EDTA plasma samples. The samples were then analysed using a quantitative bioanalytical liquid chromatography–tandem mass spectrometric (LC–MS/MS) assay [14, 15]. Drug trough levels (DTL) of the two active metabolites abiraterone and D4A were measured.

Statistical analysis

The primary endpoint was to assess the inter-patient variation of DTL of AA and D4A. A secondary objective was to assess intra-patient variability, with DTL measured at two different timepoints for each patient. Patients were stratified into two cohorts according to their intra-patient DTL variation: excessive if ≥25% or acceptable if < 25%. PSA response was categorised as those who obtained a PSA decline of at least 50% [13].

SPSS was used for statistical analysis for association of inter-patient and intra-patient variation with variables including concurrent corticosteroid used, dosing in fasted vs. fed state, and prior treatment received.

Results

Between February 2016 and December 2017, 22 consecutive patients receiving AA for metastatic CRPC were recruited. Patient demographics and previous treatments are summarised in Table 1.

Two patients were receiving AA at reduced dose of 750 mg, with remaining 20 patients receiving standard recommended dose at 1000 mg per day. Initial plasma collection was performed after a median of 11.7 weeks (range 6–67 weeks) following commencement of AA. Seventeen (77%) patients had a second plasma sample obtained for DTL after a median of 6 weeks (4–21 weeks), with 39 plasma samples in total. Plasma samples were taken between 22 and 28 h after last dose of AA.

Inter-patient and intra-patient variability

Median DTL for abiraterone was 9.9 ng/ml in the initial sample, with wide inter-patient variation observed with DTL ranging between 1.5 and 25.4 ng/ml (CV 61%) (Fig. 1a). In the 17 subjects with a repeat sample, median DTL for abiraterone was 13.2 ng/ml, with again wide variation in DTL ranging between 3.4 and 28.6 ng/ml (CV 60.7%) (Table 2).

Median DTL for D4A was 0.8 ng/ml and showed a similar inter-patient variation, ranging between 0.2 and 2.5 ng/ml (CV 61%) in the first sampling, and a median DTL of 0.9 ng/ml, and ranging between 0.3 and 3.0 (CV 67%) in second sampling (Fig. 1a; Table 2).

Intra-patient abiraterone DTL varied between 0.85 and 336% (Fig. 1b). In the 17 patients with assessable repeat abiraterone levels, excessive intra-patient variation of ≥25% for abiraterone was observed in 11 (65%) patients, and acceptable intra-patient variation in 6 (35%). In the 15 patients with assessable repeat D4A levels obtained, intra-patient D4A varied between 1.14 and 199%, and 7 (47%) had excessive variation.

Table 1 Baseline patient characteristics

Characteristics	Patients
N	22
Median age	74 (55–95)
Gleason score	
6–7	10 (45%)
8–10	10 (45%)
Not available	2 (9%)
Median PSA at commencement of AA	77.5 (0.64–1500)
Sites of metastasis	
Lymph node	10 (45%)
Bone	19 (86%)
Lung	2 (9%)
Liver	2 (9%)
Prior therapy	
Anti-androgen therapy (excluding enzalutamide)	12 (55%)
Enzalutamide	8 (36%)
Docetaxel	10 (45%)
Cabazitaxel	4 (18%)
AA dose	
1000 mg	20 (91%)
750 mg	2 (9%)

Strong association was observed between abiraterone and D4A DTL (Pearson correlation −0.69, $p = 0.01$).

Corticosteroid use

All patients received concomitant corticosteroids with AA, with prednisone 10 mg in 17 (77%) and dexamethasone 0.5 mg in 5 (23%). Mean abiraterone DTL in those receiving prednisone was 11.0 ng/ml and in those receiving dexamethasone was 13.9 ng/ml ($p = 0.5$).

Effect of food timing

One patient took AA at midday, and all the remaining patients took AA in the morning. Dosing in fasted state was considered as AA being administered at least 1 h pre-meal and 2 h post-meal, and dosing in fed state considered if AA was administered less than 1 h pre-meal or 2 h post-meal. Thirteen patients dosed in the fasted state with mean abiraterone DTL of 12.1 ng/ml, and the 9 patients that administered AA in the fed state had DTL of 11.1 ng/ml ($p = 0.8$). All patients who took AA in the 'fed state' had the drug approximately 30 min before a meal.

Prior treatment

All patients had received prior treatment with ADT, and remained on ADT while on AA. Ten patients had received

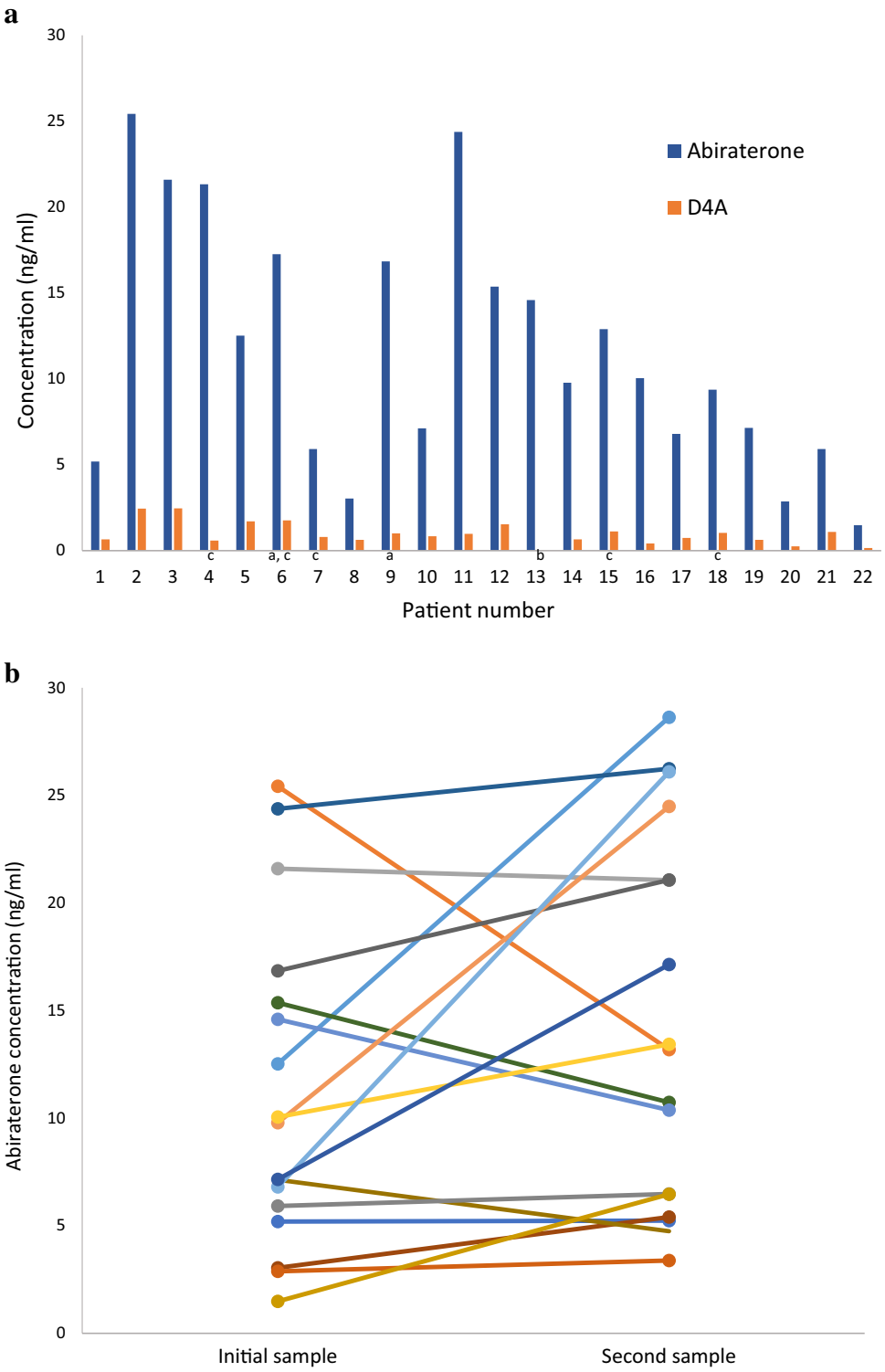

Fig. 1 **a** Inter-patient variability in abiraterone and D4A concentration in initial sample. [a]Patients 6 and 9 were on AA 750 mg. [b]Patient 13 D4A level below lower limit of quantification (LLOQ). [c]Patients 4, 6, 7, 15, and 18 only had initial sampling. Repeat sampling was not performed. **b** Intra-patient variation in abiraterone concentration at each sampling point. Only patients that had initial and repeat samples are included ($n = 17$). Matching colours dots at initial sample and repeat sample indicate same patient

prior chemotherapy and had mean abiraterone DTL of 8.9 ng/ml, while 12 patients were chemotherapy naïve with mean abiraterone DTL of 14.0 ng/ml ($p = 0.09$).

Safety

Adverse event profile of AA was consistent with prior trials and remained well tolerated, with no patients requiring dose reduction during the sampling interval. Two patients had

Table 2 Abiraterone and D4A concentrations

Parameter	Median value
Time from AA commencement to testing	11.7 (range 6–67) weeks
Trough sample after last AA administration	26.5 h
Initial sample ($n=22$)	
Median abiraterone concentration	9.9 ng/ml (CV 61%)
Median D4A concentration	0.8 ng/ml (CV 61%)
Second sample ($n=17$)	
Median abiraterone concentration	13.2 ng/ml (CV 61%)
Median D4A concentration	0.9 ng/ml (CV 67%)

dose reduction to 750 mg prior to inclusion into the trial. Six (27%) patients had grade 1 or 2 hypertension, 2 (9.1%) developed grade 1 hypokalaemia, and 7 (32%) had evidence of grade 1 peripheral oedema.

PSA response

The mean PSA reduction was 40.72% (range 0–99.9%), and 8 (47%) patients had a PSA response. Mean abiraterone DTL in those with a PSA response was 15.5 ng/ml, which was greater than mean abiraterone DTL of 9.6 ng/ml in those that did not obtain PSA response, but did not reach statistical significance ($p=0.1$). Mean D4A DTL in those that obtained PSA response was 1.1 ng/ml, compared with mean D4A DTL of 1.0 in those that did not obtain PSA response ($p=0.9$).

Survival outcomes

After a median follow-up of 12 months (range 2–36 months), the median time to PSA progression was 7.5 months, and median time on treatment was 11.6 months. The median OS of the cohort was 15.7 months. One patient continues to derive benefit and remains on AA. Subsequent therapy following discontinuation of AA is presented in Table 3. No association was identified between abiraterone levels and time to PSA progression (Pearson correlation 0.1, $p=0.7$) or OS outcome (Pearson correlation −0.1, $p=0.6$). Similarly, no association was identified between D4A level and time to PSA progression (Pearson correlation −0.1, $p=0.6$) and OS outcome (Pearson correlation −0.1, $p=0.5$).

Thirteen patients obtained target abiraterone DTL of at least 8.4 ng/ml compared with 9 patients that had lower levels. There were equivalent outcomes in those that obtained target therapeutic levels compared to lower levels, with regard to time to PSA progression (7.2 months vs. 8 months; $p=0.8$) and OS (12.8 months vs. 20 months; $p=0.1$).

Table 3 Treatment following discontinuation of AA

Therapy	
Best supportive care	13 (59%)
Docetaxel	4 (18%)
Cabazitaxel	2 (9%)
Cisplatin	1 (5%)
Lutetium	1 (5%)
Clinical trial	1 (5%)
Remain on AA	1 (5%)
Enzalutamide	0 (0%)

Discussion

AA is presently approved for men with metastatic CRPC at a fixed 1000 mg dosing regardless of derived therapeutic benefit or development of toxicities. This prospective longitudinal study of 22 patients demonstrates wide inter- and intra-patient variability in abiraterone and D4A drug levels in a 'real-world' setting, despite all patients remaining on stable doses. There was a strong association demonstrated between abiraterone and D4A concentrations. Median trough abiraterone concentration of 9.9 ng/ml is similar to what has been reported previously [12]. An important part of TDM is assessing for the clinically relevant metabolites. There was no excessive toxicity noted despite at least 15-fold variation in abiraterone and D4A levels. Similarly, a wide disparity was demonstrated in the early phase 1 trial, where there was a ninefold variation in abiraterone concentration in the 1000 mg cohort [2]. Such variation is increasingly being recognised in oral anti-cancer therapies using fixed-dose schedules which do not account for the considerable heterogeneity amongst patients in regard to absorption, comorbidities, concomitant medications, prior therapies received, and other physiological factors [16, 17]. In addition, pharmacogenomic factors have been recognised to play an important role in AA metabolism, where germline variation in HSD3B1(1245A>C) has demonstrated to alter concentration of various abiraterone metabolites and impact on its efficacy [18].

Wide inter-patient variability, a practical and reproducible drug assay, as well as a drug with either a small therapeutic window or a relationship between concentration and effect are important requirements for implementation of TDM [8]. AA is well-tolerated with 90% maintaining recommended standard 1000 mg dose. In the phase 1 trial, there were no dose limiting toxicities up to 2000 mg; hence, relationship between AA exposure and safety is of less clinical significance [2]. In addition, with the low side effect profile, the absence of toxicity cannot be reliably used to indicate under dosing. TDM has not been implemented as an endpoint or a target in landmark clinical trials; hence, an association between drug levels and survival outcomes has not been

demonstrated. Resistance to AA inevitably develops, and underdosing may result in less suppression of these escape pathways and earlier onset of resistance. We have not observed an association between abiraterone and D4A concentration and survival outcomes, though this study was not powered to assess for this. Optimal threshold had been suggested for a plasma target level of 8.4 ng/mL to predict for PSA response, with PSA response a good therapeutic target and surrogate marker to predict for survival benefit [12]. In our cohort, those that did obtain a PSA response did have a higher abiraterone concentration (mean 5.9 ng/mL difference), though was not statistically significant. However, the high intra-patient variability shown for AA limits the usefulness of TDM for this drug. Having a therapeutic level at one timepoint does not predict that the effective level will be maintained over time. Furthermore, increasing AA dose beyond 750 mg results in a plateau in levels and no significant difference in levels observed when dose is escalated up to 2000 mg [2]. Hence, increasing dose in those with below target levels of metabolites may not have the desired result. Further prospective exposure–efficacy analysis is necessary before adoption of TDM-guided dosing into clinical practice. TDM can still play a significant role in monitoring compliance and impact of medications that potentially interact with AA.

Despite AA being an irreversible inhibitor of CYP17, upon discontinuation, there is a rapid rise in testosterone and fall in luteinising hormone by day 5 postdose indicating its impact is reversible with likely replenishment of CYP17 enzyme and testosterone production [19, 20]. Hence, measuring peak plasma abiraterone concentration which occurs at 2 h may represent a better gauge for therapeutic variability and predictor for efficacy [20].

Although D4A concentration is low, it is an important metabolite with an increasing appreciation of its significance. D4A has a bi-functional role, as it is a more potent inhibitor of CYP17, 3β-hydroxysteroid dehydrogenase (3βHSD), and steroid-5α-reductase (SRD5A), which are key enzymes in androgen synthesis, as well as androgen receptor antagonistic activity comparable to enzalutamide [21]. Hence, D4A needs to be accounted for in TDM for a complete appreciation of AA pharmacokinetics and for more precise TDM-guided dosing. Strategies are being explored to increase D4A levels, such as with the addition of dutasteride. This approach appears to downregulate metabolites of D4A such as 5α-abi which have tumour-promoting androgen receptor agonistic activity while increasing D4A concentration providing a potential approach to intensify the benefit of AA therapy [22]. Combination AA with dutasteride should be further explored in prospective trials with incorporation of TDM of abiraterone and D4A levels.

Although AA was recommended to be taken in a fasting state as the previous reports demonstrated more consistent pharmacokinetics, 41% of this cohort still administered AA in the context of a recent meal. Despite numerous studies demonstrating variation in drug exposure with food, there was no clear difference in abiraterone levels in our analysis between those that administered AA on empty stomach and those in a fed state, although none of our patients took AA at the same time as food. In addition, timing of AA administration and last meal relied on patient's recall of the previous day rather than documentation in a diary. Patients appeared to administer AA at similar times at the two timepoints that were recorded. However, this may not necessarily reflect their long-term dosing pattern. In addition, not accounting for the fat content of the meal may partly explain the lack of difference in our small cohort. AA is better solublised when administered with high-fat meals and results in significantly higher drug exposure. However, low-fat meals resulted in minimal difference in concentration of abiraterone compared to when AA was administered in the fasted state [23]. More recent studies have demonstrated that the impact food has on AA exposure may not be as robust as previously reported, with a phase 2 trial demonstrating greater variation in the arm administering AA in the fasted state compared with those taken within 30 min of a meal [24]. Hence, recommending AA with specific meals may not be a warranted approach. Compliance with dietary restrictions can be difficult in patients with metastatic disease, where rates of sarcopenia are underreported and maintaining nutrition has its challenges [25]. In light of the conflicting data available and still current prescribing recommendation AA be administered in a fasted state, it is imperative further prospective trials be conducted with analysis of precise timing and nutritional content of meals to further understand the impact of food on the bioavailability of AA.

Prednisone remains the recommended choice of corticosteroid with AA. However, dexamethasone, with its longer half-life, represents a more potent corticosteroid. With cross-trial comparison, dexamethasone monotherapy had a PSA response rate of between 49 and 62%, compared with 9 and 33% observed with prednisolone monotherapy [26–32]. Switching from prednisone to dexamethasone at the time of progression in one trial resulted in almost 40% having further PSA reduction and induced radiological responses [26]. Corticosteroid itself has an anti-prostate cancer effect with downregulation of ACTH and subsequent suppression of adrenal production of androgen [33]. There was no observed trend favouring choice of corticosteroid in conjunction with AA in regard to DTL. However, this is a small cohort with large inter-patient variability in pharmacokinetics. The apparent increased potency of dexamethasone may in fact be a direct anti-tumour effect rather than an effect on AA or D4A levels.

Time to PSA progression on AA of 7.5 months appears inferior to landmark phase III clinical trials which ranged

between 10 and 11 months [3, 4]. This may be accounted for by an older and more heavily pre-treated cohort, with 36% having already failed enzalutamide with a low likelihood of response with subsequent AA therapy. Similar to the previous reports, prior use of chemotherapy has not been shown to impact abiraterone pharmacokinetics, though there was a trend to favouring higher abiraterone exposure in those that were chemotherapy naïve [16].

In conclusion, we found a high intra- and inter-patient variation for both D4A and abiraterone exposure in men with CRPC, with no clear clinical variables that explained the variation. Although we could not show a relationship between low trough levels and efficacy in our small cohort, it is possible that some patients on AA are experiencing sub-therapeutic exposure which may predispose to earlier development of resistance to AA in a fixed-dose schedule. TDM has the potential advantage of manipulating administration schedule, but high intra-patient variability may limit its usefulness and further investigation is warranted.

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Compliance with ethical standards

Conflict of interest HG reports personal fees from BMS, personal fees from MSD, personal fees from Roche, grants and personal fees from Pfizer, and personal fees from Astra Zeneca, outside the submitted work. The remaining authors declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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