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Is Low-Dose Abiraterone for Prostate Cancer An Attractive Strategy for Limited Resource Settings?

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Abstract

Abiraterone acetate in combination with prednisone is approved for locally advanced as well as metastatic (hormone-sensitive and castrate-resistant) prostate cancer, with overall or disease-free survival gains in suitable patients. Long-term use poses a significant financial strain on the self-paying patients as well as the national health insurance schemes. Abiraterone is known to be a drug with a high "food effect" with increased bioavailability following high fat diet. Some retrospective series and phase 1 and 2 clinical studies have explored the use of low-dose abiraterone (at 25% of standard dose) with high fat meal with similar bioavailability and biochemical response to the standard drug dose. We review and report the available literature for this approach and discuss the financial and scientific implications of the same.

Keywords

- prostate cancer
- abiraterone acetate
- low dose abiraterone
- pharmacokinetics
- PSA response

Introduction

Metastatic castration-resistant prostate cancer (mCRPC) poses a significant therapeutic challenge and is an area of active research. The past decade has witnessed availability and use of several approved agents (docetaxel or cabazitaxel-based chemotherapy, androgen receptor targeting agents such as abiraterone and enzalutamide, vaccines such as sipuleucel-T, bone targeted agents such as radium-223 and denosumab) for mCRPC. Patients with high disease burden or visceral metastases have survival limited to 1 to 2 years but well-preserved patients with no visceral metastases may have median overall survival (OS) of approximately 3 years.[1] One of the therapeutic agents, abiraterone acetate (AA) selectively and irreversibly blocks 17α hydroxylase and 17,20 lyase, both of which play a crucial role in androgen and glucocorticoid synthesis, leading to a rebound increase in mineralocorticoid levels. AA along with prednisone has been approved by Central Drugs Standard Control organization (Directorate General of Health Services, India) and United States Food and Drug Administration (USFDA) for use in both chemotherapy naïve and resistant patients in mCRPC along with standard androgen deprivation therapy (ADT) due to its survival benefit.[2,3] Currently, its role has extended, allowing its use to manage metastatic castration sensitive prostate cancer (mCSPC) and high-risk disease in combination with standard initial ADT. The recommended dosage is AA (1,000 mg) once daily to be taken on an empty stomach, i.e., no food consumed for at least 2 hours before or 1 hour after oral intake (modified fasting state).[4] The common associated side effects are fatigue, nausea and vomiting, hypertension, mild elevation of hepatic transaminases, hot flashes, arthralgia, myalgia, and hypokalemia.

Early clinical studies have shown that the drug absorption is significantly altered when administered with food. It is

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recommended that AA not be taken with food to keep the drug toxicity low and avoid erratic dosing effects due to its highly lipophilic nature. "Food effect" for AA is probably the largest among the commercially available drugs.[5,6] According to drug label information, the blood level of AA rises five to sevenfold when administered with low fat meal (7% fat, 300 calories) and 10 to 17 times with high fat meal (57% fat, 825 calories).[7] Hence, a few trials have explored the low dose AA regimen with food considering the potential economic gain and possible lower toxicity profile for the patient, while removing the need for fasting. In this short literature review, we discuss the evidence that may favor an alternate approach of giving low dose AA as opposed to the standard regimen.

Methods

A PubMed search using MeSH terms "abiraterone acetate" and "prostate neoplasms" within English language yielded 499 entries. The abstracts of all of these were hand-sorted to identify pharmacologic and clinical studies exploring alternate dose regimes or drug formulations of AA. Cross-references of the identified studies were further screened for additional studies exploring the same subject, and abstracts of the selected references were also screened for possible inclusion. Since the usage of abiraterone is relatively recent and the data on alternate regimes of the drug are sparse, the preclinical and clinical data are synthesized in the form of a narrative review.

Pharmacokinetics

Extensive in vitro studies have analyzed the metabolism and elimination of abiraterone in human liver microsomes and cryopreserved hepatocyte cell lineage.[4] After administration, ester hydrolysis converts AA to its active metabolite, abiraterone. Further metabolism by hydroxylation and sulfation and finally conjugation by UDP-glucuronyl transferase gives rise to its chief circulating form, abiraterone sulfate.

It has been seen that following oral administration of 1,000 mg AA, the plasma abiraterone concentration rises rapidly to reach the maximum concentration in approximately 2 hours. The mean half-life for elimination is 16 hours. Hence, approximately 90% of the drug is eliminated via feces and urine 96 hours after the oral intake. A study on healthy volunteers showed that those taking AA with high fat meals attained a plasma concentration 4.6 times higher than those taking it with low-fat meals.[8] This led to the observation that food intake might alter the absorption of AA in patients of prostate cancer.

Phase 1 studies (COU-AA-008, COU-AA-009, COU-AA-014) that explored AA pharmacokinetics in healthy males after a single dose defined a fasting state as overnight 10 hours fasting with no food intake for at least 4 hours after AA as well.[7,8] Based on data from these three phase 1 studies, a phase 1b study and two phase 3 studies comprising patients of mCRPC (both chemotherapy naïve and docetaxel pre-treated), Stuyckens et al evaluated a clinical model to determine the covariates affecting the pharmacokinetics of AA.[9] They found that plasma concentration of AA was 3.8 and 7.6 times higher when consumed 30 minutes after a low fat (298.7 cal) and a high fat (826.3 cal) meal, respectively, as compared with fasting state. The metabolism of AA was similar in both chemotherapy naïve as well as docetaxel pre-treated patients. However, when taken in the modified fasting state as per recommendation, the bioavailability increased to 1.14 times that of fasting state. The modified fasting state was defined when AA was taken at least 2 hours after a meal or an hour before a meal, and this modified fasting schedule was used for subsequent clinical studies.[9] However, in this study, the authors did not consider dose reduction of AA from 1,000 mg to achieve similar plasma concentration when combined with food.

Another study explored the pharmacokinetic profile of AA in modified fasting state versus low fat (7.3% fat) and high fat meals (56.5% fat) in both healthy subjects as well as mCRPC patients.[10] This was indeed a dose-escalation study with respect to the fat content of the meal, to determine the dose-limiting toxicities of AA. In healthy subjects, abiraterone area under curve (AUC) was approximately five times higher after a low-fat meal and 10 times higher after high-fat meal as compared with overnight fasting state. However, in mCRPC patients, the AUC of AA was almost similar in modified fasting state and when consumed with low fat meal but two times higher with high fat meals. The median time to reach maximum concentration also varied between these groups (2 hours for fasting, 2.5 hours with low-fat meal, and 4 hours with high-fat meal). No subjects or patients experienced any grade 3 or higher treatment-emergent adverse effects, and the adverse effects did not vary with the timing of drug in relation to food intake. The difference in AUC of fed states in healthy subjects and mCRPC patients was attributed to small patient numbers, possibly different gastric emptying times between young healthy volunteers and older mCRPC patients, and the impact of concomitant drugs affecting AA or steroid metabolism in patients.

Another phase I dose-escalation trial assessed the safety and effects on prostate-specific antigen (PSA) and androgen levels in chemotherapy naïve progressive CRPC in fasted and fed cohorts with AA doses of 250 mg, 500 mg, 750 mg, and 1,000 mg.[11] No dose-limiting adverse events were noted. Grade 3 hypertension (12%) and hypokalemia (6% grade 3, 3% grade 4) were the most frequently observed serious toxicities that responded well to medical management. Substantial decline in serum levels of androgen and rise in mineralocorticoids were observed with all doses. The plasma levels of abiraterone were higher across all doses in fed state compared with fasting indicating its enhanced absorption with food intake.

The Dutch Pharmacology Oncology Group undertook a therapeutic drug monitoring (TDM) program to analyze the minimum plasma concentration of AA.[12] They observed that clinical efficacy was not attained in nearly 40% patients if the plasma drug concentration fell below 8.4 ng/mL. If the minimum concentration (C_{min}) of AA taken in modified fasting state dipped below 8.4 ng/mL, a pharmacokinetic intervention was done, i.e., patients were instructed to consume AA with light meal or snack, but not with high

fat meal, and this led to 87.5% patients eventually having an adequate exposure ($C_{min} \geq 8.4$ ng/mL); the exposure in others could not be determined due to progression-related treatment discontinuation. They proposed TDM to be an effective strategy to optimize drug exposure with concomitant food intake and thereby, improve biochemical control.

An Indian study highlighted that food enhanced pharmacokinetics when they compared the standard dose of AA (1,000 mg in modified fasting state) and low dose 250 mg AA with low fat meal (7% fat) in mCRPC patients.[13] There was no significant difference between the maximum plasma concentration achieved or the mean AUC although the trough concentration was significantly lower in the low dose arm.

Thus, across all the pharmacokinetic studies, it has been unanimously seen that bioavailability and serum concentration of AA increase in the presence of food but not at the cost of increased toxicity. Hence, low dose regimen may be explored as a cost-effective approach, provided the biochemical control and disease-free survival are neither compromised, nor is there higher toxicity.

Clinical Efficacy

The randomized study by de Bono et al established the OS gain (14.8 months vs. 10.9 months, $p = 0.001$) with standard dose AA (1,000 mg daily) over placebo in mCRPC in docetaxel-pretreated patients.[14]

Attempts to reduce dose to 750 mg daily in elderly patients ($\geq$85 years) with several comorbidities and performance status $\leq$2 without altering the food intake pattern have yielded comparable OS of 14.3 months with no unexpected increase in toxicity in small studies.[15]

A retrospective study on mCRPC patients at Princess Margaret Hospital described experience with low dose AA (250 or 500 mg) with similar PSA response rate, biochemical PFS, and OS for standard and low dose AA patients.[16]

A phase II trial by Szmulewitz et al enrolled patients with progressive CRPC and compared standard dose schedule (AA 1,000 mg in modified fasting state) and low dose schedule (AA 250 mg with low fat meal).[17,18] A greater decline in serum PSA levels was observed in the low dose arm, thus establishing its non-inferiority. At 12 weeks, the observed PSA response rate was 58% in the low dose and 50% in the standard dose arm, median PFS being 8.6 months in both groups. Despite the similar decline in androgen levels in both groups, abiraterone concentrations (both maximum and trough) were higher in the standard dose arm. Interestingly, the frequency of grade 3 or higher adverse events was more in low dose arm (32.4 vs. 17.6%), although not clinically significant. This study has been criticized for possible drug non-compliance within the AA arm as the median PFS in this study compares with the prednisone arm of COU-AA-302 trial (8.3 months) while that in the AA (1,000 mg) arm of COU-AA-302 trial was 16.5 months.[19] Of note, the biochemical PFS was not a study end point in COU-AA-302 trial, the aforementioned PFS values being radiographic PFS, and the PSA response at 12 weeks was 62% in the study arm (vs. 24% in prednisone arm), closer to the low dose abiraterone arm of Szmulewitz's study.[17,19] Unfortunately, since Szmulewitz's study did not require patients to follow-up after PSA progression, and did not collect data on radiographic PFS or OS, its direct applicability in the setting of CRPC will not be validated even on future follow-up.

Other Approaches to Improve Bioavailability

Apart from dietary modifications, various drug manufacturers have devised strategies to reduce particle size, alternate compounds such as abiraterone hydrochloride monohydrate salts with improved solubility, nano-amorphous AA with better permeability, and combination of reduced size and inclusion of excipients such as surfactants (SoluMatrix fine particle technology: Yonsa). These formulations overcome the food effect of AA, and lower doses (250 mg of nano-amorphous AA or 500 mg of Yonsa) are bioequivalent to conventional AA doses, with similar PSA response and testosterone reduction in phase 1 and 2 studies.[5,20–22]The fine particle abiraterone formulation has been suggested as an alternative by National Comprehensive Cancer Network (NCCN) guidelines version 1.2022.[23] It has been suggested by some investigators that reliable assays for TDM or adrenal androgen pharmacodynamics may ensure better titration and compliance of drug dosage.[24]

Cost Benefit Analysis

The economic gain attained by using low dose AA with low fat meal evokes great interest. In the United States, the approximate retail cost of AA is approximately USD 10,000 per month. For metastatic CRPC, the median radiographic progression free survival is 16.5 months, and assuming the same as median duration of therapy for these patients, the average cost per patient (for AA 1,000 mg/d) would be USD 165,000 ($10{,}000 \times 16.5$).[17,19] If low dose abiraterone can be used instead, the cost would be a quarter (USD 41,250) of this, and the average lifetime financial gain per patient would be more than USD 120,000 ($165{,}000 \times 0.75 = 123{,}750$ USD). In mCSPC, AA use increases the median radiographic PFS to 33 months as per LATITUDE trial data.[25] The cost per patient taking AA 1,000 mg/d for this duration would be USD 330,000 ($10{,}000 \times 33$); with low dose AA, the per capita cost would just be a quarter of this (USD 82,500) and the per capita savings with low dose abiraterone could go up to USD 250,000 ($330{,}000 \times 0.75 = 247{,}500$). Utilization of low dose abiraterone would result in annual savings of approximately USD 700 millions of Medicare cost.[26] In the Indian context, where the cheapest generic drug costs nearly USD 110 a month, the average saving per patient would be approximately USD 1360 [$(110 \times 16.5) \times 0.75 = 1{,}361.75$] for mCRPC and USD 2700 for mCSPC [$(110 \times 33) \times 0.75 = 2{,}722.50$). To put this in perspective, the per capita gross national income in India is approximately USD 1900 for the year 2020-21, and the national insurance scheme for the underprivileged (Ayushman Bharat Pradhan Mantri Jan Aarogya Yojna) offers a total assistance of up to USD 700 per capita.[27,28] With the use of AA for certain locally advanced cases as per STAMPEDE, the applicability of this equation would happen across

a larger population, and if low dose abiraterone is indeed proven useful, it would translate into a much higher national saving.[29]

Several analyses have surmised that abiraterone is not a cost-effective strategy with incremental cost effectiveness ratio (ICER) higher than accepted standards; consequently, the drug has been denied inclusion into the reimbursement schemes for several countries including Sweden and Brazil.[30] University of Hong Kong has also published a cost effectiveness analysis comparing AA with docetaxel-based approaches for mCSPC, based on two outcomes—quality-adjusted life years (QALY) and ICER. They determined that AA improved QALY over docetaxel but would be more cost effective than docetaxel only if its cost were reduced by at least 63%; low dose AA could potentially bridge this gap.[31]

Perspectives of Practitioners

A survey of 118 Indian medical oncologists revealed that despite lack of strong evidence, nearly 62% were using low dose abiraterone either routinely (6.8%) or in resource limited setting (55.1%), 29% were willing to switch to this practice, and only a little under 10% were reluctant in using it.[32] Nearly 60% were aware of Szmulewitz's phase 2 trial in 2018 and almost 75% were already aware that NCCN guidelines (version 2.2019) had included low dose abiraterone as an option. The latest NCCN guidelines (version 2.2022) continue to recommend this despite the lack of a phase 3 trial, and also state that lower financial toxicity of low dose abiraterone may ensure better compliance.[23] As per interventional pharmacoeconomics principle, wherein studies are designed with intervention and a biomarker like serum PSA, dehydroepiandrosterone, or cortisol are studied, there is a strong case to consider low dose abiraterone as a phase 3 study will not be done by companies.[33]

Challenges with Low Dose Abiraterone

Patients from different backgrounds and ethnicities may not find the high or low fat content of meal palatable for long periods, and compliance may be an issue. Also, certain comorbid conditions may place further restrictions on the dietary constituents and patterns. A fasting or modified fasting state is easier to adhere to and understand compared with a fixed fat concentration. Patients with cachexia or anorexia would be unable to consume the prescribed high fat. Evidenced by pharmacokinetic studies showing variability in bioavailability with low and high fat content, there may be potential under- or overdosing with erratic adherence leading to inconsistent benefit although safety appears to be unaltered. Lack of availability of 250 mg formulation in certain regions such as Europe limits usage even for compassionate use, leading to high financial toxicity.[34] ►**Table 1** lists the available strengths of innovator and generic AA in several countries along with retail price.

To overcome the constraint of availability, Szmulewitz et al have recommended alternate day use of 500 mg formulation in resource-constrained settings based on small data on AA use for other indications, or single-arm clinical trials exploring this approach with measurement of androgen levels.[35]

Table 1 Available data on the strengths of abiraterone acetate, cost of 30-day therapy, and any national schemes that cover the cost

S No	Country	Abiraterone acetate strengths available	Approximate cost of 30 days of therapy (USD)	Any national schemes	Source
1	USA	250 mg 500 mg	10,000 (240–840 for generics)	Discounted through insurance cover and pharmacies (50–97% covered)	www.drugs.com/price-guide/abiraterone https://www.goodrx.com/zytiga
2	Canada	250 mg 500 mg	3470 (380 for generic)	Discounted through national health scheme (80–100% covered)	www.canadadrugstore.com/zytiga-abiraterone www.canadianpharmacyking.com/drug/zytiga
3	United Kingdom	500 mg	3900	Discounted through National Health Service, NHS (80–90% covered)	http://bnf.nice.org.uk/medicinalforms/abiraterone-acetate.html
4	Australia	250 mg 500 mg	2460	Discounted through Pharmaceutical Benefits Scheme, PBS (>99% covered, 30 USD)	https://www.pbs.gov.au/medicine/item/11206T
5	India	250 mg 500 mg (generics)	2000 (110–400 for generics)	Discounted through patients assistance programmes of	https://www.1mg.com/drugs/

(*Continued*)

Table 1 (*Continued*)

S No	Country	Abiraterone acetate strengths available	Approximate cost of 30 days of therapy (USD)	Any national schemes	Source
				individual companies by 20–30%	
6	China	250 mg	4000 (↓30% for generics)	Discounted through government and health insurance (70% covered)	https://www.xian-janssen.com.cn/en/
7	Japan	250 mg	3800	Discounted through national health insurance (70% covered)	https://www.evaluate.com/vantage/articles/analysis/big-japan-drug-costs-surge-diabetes-and-cancer-win-healthy-premiums
8	Bahrain	250 mg	2800		https://www.nhra.bh/Departments/PPR
9	South Africa	250 mg	2400		https://canceralliance.co.za/important-new-report-on-patent-barriers-to-cancer-treatment-in-sa-released/
10	Egypt	250 mg 500 mg	3000		http://egyptiandrugstore.com/
11	Kenya	250 mg 500 mg	2000	Discounted ↓50% through National Hospital Insurance Fund	https://khusoko.com/2019/02/11/nhif-janssen-partner-to-enhance-access-to-prostate-cancer-drugs/
12	Trinidad & Tobago	500 mg 250 mg (some generics only)	5000 (generic available at approx. 15–20% price)	Individual pharmacies offer at 50–60% discount	https://caricom.org/
13	Brazil	500 mg 250 mg	3000 (2000 for generics)		https://br.kairosweb.com/precio/
14	Denmark	500 mg	3350		https://www.medicinpriser.dk/default.aspx
15	Sweden	250 mg 500 mg	2900		https://www.tlv.se/
16	Germany	500 mg 250 mg (some generics only)	6150	Pharmacies and insurance covers reduce cost by ↓30%	https://www.rote-liste.de/suche/stoff/125012/Abirateron
17	Spain	500 mg	4000		https://www.ema.europa.eu
In Europe, 250 mg is available only as generics in some countries. Generic drugs cost ↓75% of the original molecule					

Abbreviations: NHS, National Health Service; PBS, Pharmaceutical Benefits Scheme.

Conclusion

The available evidence from pharmacokinetic studies and a phase 2 clinical study shows encouraging trends of using low dose abiraterone with non-inferior biochemical response in short term, making it an attractive option especially for patients and national health schemes due to better economic viability. However, this proposition possibly does not seem lucrative for the drug manufacturing and marketing firms evidenced by lack of any ongoing or planned phase 3 studies exploring this possibility further. The onus of establishing any utility of low dose abiraterone lies with the independent investigators and academic institutions through initiation of investigator-initiated studies. If any phase 3 data are not generated, we would not have any justification to offer low dose abiraterone in the clinic except for compassionate use in patients who are otherwise not able to afford any therapy when not supported by national insurance. Unless we know that reducing the dose would not compromise on the survival gains achieved over ADT alone or prednisone, we would not be serving our patients well despite the cost reduction. Possibly the newer formulations of abiraterone such as nano-amorphous or fine particle agents would be tested further and emerge as alternatives with a viable cost.

Authors' Contribution

T.D. contributed toward Concept, design, definition of intellectual content, literature search, data acquisition, data analysis, statistical analysis, manuscript preparation, and manuscript review. S.G. worked toward concept, design, definition of intellectual content, literature search, clinical studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review. K.P. defined intellectual content and did data acquisition and manuscript review. R.M. contributed toward concept, design, literature search, data acquisition, data analysis, manuscript editing, and manuscript review.

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Conflict of Interest

None declared.

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