Practical guide to the use of abiraterone in castration resistant prostate cancer

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Introduction: *While androgen deprivation therapy remains the primary treatment modality for patients with metastatic prostate cancer, treatment is uniformly marked by progression to castration resistant prostate cancer (CRPC). Abiraterone is the first new drug to enter clinical practice in a series of novel agents designed to potently target adrenal and tumor androgen production.*

Materials and methods: *Herein, we review the mechanism of action of abiraterone and the phase III data supporting its approval for patients with metastatic CRPC. We discuss practical treatment considerations, including the incidence and management of side effect and monitoring requirements, and conclude by discussing future directions in the use of abiraterone, including early data supporting an expanded role for abiraterone in castration sensitive disease.*

Results: *Accumulating data emphasize that 'androgen independent' or 'hormone refractory' tumors remain sensitive to hormonal activation and suggest that despite suppression of circulating testosterone (T), residual tumor androgens play a prominent role in mediating CRPC progression.*

Conclusions: *Accordingly, therapeutic strategies such abiraterone that more effectively target production of intratumoral androgens are necessary.*

Key Words: castration resistant prostate cancer, intratumoral androgen, CYP17A, abiraterone

Introduction

The efficacy of androgen deprivation therapy (ADT) is routinely based on achieving castrate levels of serum T, arbitrarily defined as T ≤ 20 or 50 ng/dL. However, tissue androgen measurements in men with either locally recurrent or metastatic castration resistant prostate cancer (CRPC) clearly demonstrate that prostate and tumor androgen concentrations remain well within the range capable activating the androgen receptor (AR).[1-4] Clinical and pre-clinical findings demonstrate that tumors remain sensitive to hormonal activation and suggest that despite suppression of circulating testosterone (T), residual tumor androgens play a prominent role in mediating CRPC progression.[5] Emerging data suggest residual intratumoral androgens are produced via the uptake and conversion of adrenal androgens, and potentially via de novo synthesis from cholesterol or progesterone precursors within the tumor.

The critical enzyme required for androgen synthesis from cholesterol is cytochrome P450 17 alpha-hydroxylase (CYP17A). Adrenal expression of this enzyme accounts for production of circulating adrenal androgens, including dehydroepiandrosterone (DHEA, which primarily circulates in its sulfated form, DHEA-S), and androstenedione (AED), and a number of studies have demonstrated expression of CYP17A in castration resistant prostate tumors. Given its central

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role in the production of either adrenal or tumor-derived extragonadal androgen synthesis, CYP17A has emerged as a primary target of novel therapeutics.

Mechanism of action

CYP17A is a single enzyme that catalyzes the sequential hydroxylase (required for cortisol synthesis) and lyase (required for adrenal androgen synthesis) steps that are required for conversion of C21 pregnenolone and progesterone precursors to the C19 adrenal androgens, DHEA and AED, Figure 1. Abiraterone acetate, an orally administered, rationally designed small molecule derived from the structure of pregnenolone, irreversibly inhibits both the hydroxylase and lyase activity of CYP17A with approximately 10-fold greater potency than ketoconazole.

Because adrenal inhibition of CYP17A results in blockade of glucocorticoid as well as adrenal androgen synthesis, abiraterone is co-administered with prednisone to ameliorate the secondary rise in adrenocorticotropic hormone (ACTH) that can lead to excess mineralocorticoid synthesis (discussed further below).[6]

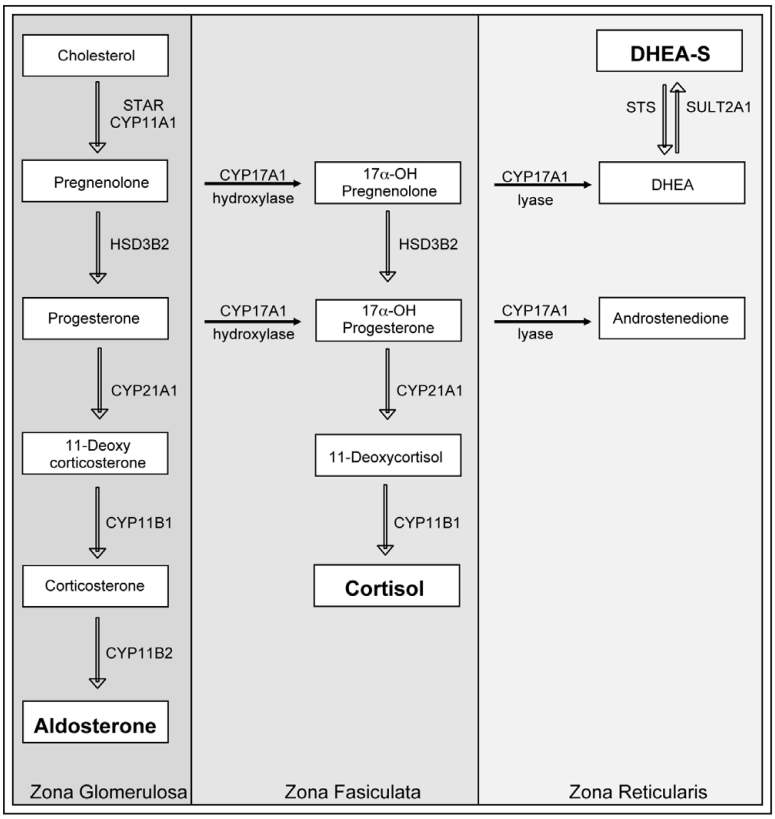

Figure 1. Steroid hormone pathways in the adrenal gland.

Efficacy data and FDA approved treatment indications

A number of phase I and II studies initially demonstrated that abiraterone suppresses serum androgen levels and achieves prostate-specific antigen (PSA) and clinical responses in chemotherapy naïve and docetaxel-treated CRPC patients. Phase III studies in chemotherapy naïve (COU-AA-302) and post-docetaxel treated men (COU-AA-301) have confirmed these findings, resulting in FDA approval of abiraterone for men with metastatic CRPC either before or after treatment with chemotherapy.

COU-AA-301

In the post chemotherapy setting, 1195 men with metastatic CRPC were randomized 2:1 to abiraterone/prednisone (n = 797) or placebo/prednisone (n = 398) with a primary endpoint of overall survival (OS). Median PSA was approximately 130 ng/dL, 90% of patients had an ECOG score of 0-1, median age was 70, and 28% were ≥ 75 years. Bone, lymph node and visceral metastases were present in approximately 90%, 40% and 10% of patients respectively, and 30% of patients had received more than one prior chemotherapy regimen. Treatment was continued until clinical or radiographic evidence of progression.

The first interim analysis demonstrated a 3.9 month OS benefit for men receiving abiraterone, prompting the independent data monitoring committee (IDMC) to recommend the study be unblinded and men on the placebo arm be offered abiraterone.[7] An updated analysis at a median survival of 20.2 months demonstrated a median OS of 15.8 months for abiraterone versus 11.2 months for prednisone (HR 0.74, $p < 0.0001$), extending the OS benefit to 4.6 months.

All secondary endpoints were statistically significant in favor of abiraterone, including median time to PSA progression (8.5 months versus 6.6 months), median radiologic progression-free survival (rPFS, 5.6 months versus 3.6 months), and proportion of patients with > 50% PSA response (29.5% versus 5.5%). The impact of abiraterone on OS was observed across all subgroups, including patients who had received one (15.4 months versus 11.5 months) or two prior chemotherapy regimens (14.0 months versus 10.3 months). Notably,

patients with a performance status (PS) of 2 had worse outcomes, with a median survival of 7.3 months versus 15.3 months for those with PS of 0-1 receiving abiraterone.[8]

In exploratory analyses abiraterone significantly increased the number of patients reporting an improvement in fatigue intensity (58.1% versus 40.3%, p = 0.0001),[9] and the number of patients reporting palliation of pain (45% versus 28.8%, p = 0.0005). Median time to first skeletal-related event was also significantly longer in abiraterone treated patients (25 months versus 20.3 months, p = 0.0001).[10] While visceral disease was associated with a poorer prognosis, the absolute benefit in OS from abiraterone was similar in those with and without visceral disease (from 8.3 months to 12.9 months in those with visceral disease, and from 12.3 months to 17.3 months in those without).[11]

COU-AA-302

In the pre-chemotherapy setting, 1088 men with asymptomatic or minimally symptomatic bone and lymph node (but not visceral) metastatic CRPC were randomized 1:1 to abiraterone/prednisone (n = 546) or placebo/prednisone (n = 542), with co-primary endpoints of rPFS and OS. The median PSA was approximately 40 ng/dL, about 30% of men were ≥ 75 years, and approximately 50% had bone-only metastatic disease.

At a median follow up of 22.2 months abiraterone doubled rPFS from 8.3 months to16.5 months (HR 0.53, p < 0.001), accompanied by a trend for increased OS from 27.3 months in the placebo arm to not-reached in the abiraterone group (HR 0.75, p = 0.01 which did not meet the prespecified p value of 0.001), again prompting the IDMC to recommend the study be unblinded and men on the placebo arm be offered abiraterone.[12] An updated analysis of OS at a median survival of 27.1 months again trended toward favoring abiraterone at 30.1 months in the placebo arm versus 35.3 months in the abiraterone arm (HR 0.79, p = 0.015).[13]

All secondary endpoints were statistically significant in favor of abiraterone, including median time to opiate use (not-reached versus 23.7 months), time to initiation of chemotherapy (25.2 months versus 16.8 months), time to performance status decline (12.3 months versus 10.9 months), time to PSA progression (11.1 months versus 5.6 months), and proportion of patients with > 50% PSA response (62% versus 24%).[12] While this study did not include patients with visceral disease or moderate to severe pain, exploratory analyses of these subpopulations in the post-chemotherapy setting (discussed above) suggest these patients are likely to benefit as well.

Also of note, although ketoconazole-treated patients were specifically excluded in the phase III studies, phase I/II data suggest abiraterone has activity in these patients. In a pre-chemotherapy phase I study PSA responses > 50% were observed in 64% of ketoconazole-naïve and 47% of ketoconazole pre-treated patients.[14] In a post-docetaxel study, PSA declines > 50% occurred in 45% of ketoconazole-naïve and 26% of ketoconazole-treated patients, with median TTP of 28 and 14 weeks, respectively.[15]

Incidence and management of side effects

Abiraterone is generally well tolerated, with 13% and 19% of abiraterone-treated patients in COU-AA-301 and COU-AA-302 (respectively) discontinuing therapy for adverse effects versus 18% and 23% of placebo-treated patients. The most common adverse events in both groups were fatigue, back pain, nausea, constipation, bone pain and arthralgia, all in the range of 25%-30%, summarized in Table 1. The incidence of urinary tract infection was statistically higher in abiraterone treated patients (12% versus 7% in placebo, p = 0.02). Here we discuss the incidence, management and monitoring of adverse events of special interest specifically associated with abiraterone therapy.

Impact of food

Phase I studies demonstrated 5-7 fold higher drug exposure when abiraterone is administered with a low fat meal (7% fat, 300 calories) as compared to the fasted state. To minimize the variability in absorption, abiraterone is administered as 1000 mg (four 250 mg tablets) daily on an empty stomach, defined as 1 hour before or 2 hours after a meal.

Mineralocorticoid and electrolyte effects

Adrenal inhibition of CYP17A results in blockade of glucocorticoid as well as adrenal androgen synthesis leading to a compensatory rise in ACTH that can lead to excess mineralocorticoid synthesis, Figure 1. Phase I and II trials demonstrated symptoms of mineralocorticoid excess occur in 50%-80% of patients treated with single-agent abiraterone.[6] Mineralocorticoid-related symptoms in the phase III studies were markedly attenuated by inclusion of prednisone 5 mg twice daily, and were generally of grade 1 or 2 in magnitude, including fluid retention (~33% versus 22%-24% in placebo), hypertension (~10% versus 8% in placebo), and hypokalemia (~18% versus 9% in placebo).[14,16,17]

Hypertension and hypokalemia should be corrected before and during therapy and patients should be

TABLE 1. **Adverse events (%) reported during treatment with abiraterone**

All grades	COU-001 (post-chemotherapy)		COU-002 (pre-chemotherapy)	
	abiraterone	placebo arms	abiraterone	placebo arms
Hematologic				
Anemia	25	28	23	26
General side effects				
Fatigue	47	44	39	34
Back pain	33	36	32	32
Arthralgia	30	24	28	24
Bone pain	27	30	20	19
Nausea	33	33	22	22
Vomiting	24	26		
Constipation	28	32	23	19
Diarrhea	20	15	22	18
Hot flash	10	9	22	18
Urinary tract infection	13	7	12	7
Mineralocorticoid effects				
Fluid retention	33	24	28	24
Hypertension	11	8	22	13
Hypokalemia	18	9	17	13
Hepatotoxicity (ALT/AST)	11	9	12	5
Cardiotoxicity				
All	16	12	19	16
Atrial fibrillation	2	1	4	5

monitored for hypertension, hypokalemia and fluid retention at least once a month. Spironolactone is avoided in patients who develop mineralocorticoid-related side effects due to its mixed AR agonist/antagonist activity. Instead, eplerenone, a second-generation mineralocorticoid receptor antagonist (MRA) in doses of 50 mg/day-200mg/day (in divided doses twice daily) can be used in combination with a salt-restricted diet.[18] Alternatively, potassium-sparing epithelial sodium channel antagonists such as amiloride and triamterene (in combination with hydrochlorthiazide if hypertension is significant) can be used in place of or added to eplerenone if necessary.[16,18] In rare instances, additional anti-hypertensive agents may be necessary in patients already receiving prednisone, eplerenone and diuretics.

Heptatotoxicity

Grade 3 or 4 hepatic transaminase abnormalities (5x upper limit of normal - ULN) occurred in approximately 4% of patients in the phase III studies, usually within the first 3 months of starting treatment, and more commonly in men whose baseline ALT or AST were elevated. Serum transaminases should be measured at baseline. Transaminases in patients with normal levels should be checked every 2 weeks for the first 3 months of therapy, and then monthly. No dose adjustment is necessary for mild hepatic impairment. For moderate hepatic impairment (Child-Pugh Class B) abiraterone should be started at 250 mg daily, and transaminases should be checked weekly for the first month, then every 2 weeks for the following 2 months, and then monthly.

If AST or ALT rise above 5 times the ULN, or bilirubin rises above 3 times the ULN, abiraterone should be held. It should be discontinued if the patient had moderate hepatic impairment at baseline, but in patients with normal hepatic function at baseline it can be restarted at 750 mg daily when LFT's decline to less than 2.5 times the ULN and total bilirubin is less than 1.5 times ULN. If hepatotoxicity recurs, a further dose reduction to 500 mg can be attempted (once levels have fallen below the thresholds given above), but recurrence of hepatotoxicity at the 500 mg dose requires discontinuation of the drug.

Cardiotoxicity

The overall incidence of adverse cardiac effects was not statistically increased by abiraterone in COU-001 (13% versus 11% in placebo), although the frequency of cardiac

failure was higher in the abiraterone group (2.1% versus 0.7% in placebo). The most frequently reported cardiac events were grade 1 and 2 tachycardia and grade 3 or lower atrial fibrillation. As patients with left ventricular ejection fraction < 50% were excluded from the phase III studies, pre-treatment assessment of cardiac status with electrocardiogram and echocardiography may warrant consideration in elderly patients with reduced cardiac function. A significant effect of abiraterone on the QT/QTc interval in patients with CRPC was not observed.[19]

Potential drug interactions

Abiraterone is a strong inhibitor of several microsomal drug metabolizing enzymes, including CYP1A2 and CYP2D6.[20] Abiraterone increased systemic exposure of dextromethorphan (metabolized by CYP2D6) approximately 2-3 fold, while the pharmacokinetics of theophylline (metabolized by CYP1A2) were unaffected. This suggests caution may be warranted when abiraterone is co-administered with known CYPD26 substrates (including beta blockers, serotonin reuptake inhibitors, anti-arrhythmics, neuroleptics, as well as codeine, tramadol, and of relevance to urologic patients, tolterodine).[21]

Practical treatment considerations

While the introduction of abiraterone has heralded a new era in the hormonal treatment of men with metastatic CRPC, there remain important questions regarding its optimal place in continuum of prostate cancer therapy. These include issues of sequencing of abiraterone with immunotherapy, chemotherapy and enzalutamide in men with metastatic CRPC, the efficacy of abiraterone in castration sensitive disease, the role of abiraterone as part of therapy in men with localized disease or biochemical relapse, whether co-administration of prednisone can be safely decreased to 5 mg/day, and whether sequential or combinatorial treatment strategies will yield the most durable responses.

In men with asymptomatic or minimally symptomatic metastatic CRPC, abiraterone is an attractive first line option given its ease of administration and relatively low toxicity profile. Similarly, the combination of abiraterone and sipuleucel T would likely be a well-tolerated regimen in this setting and is currently under clinical investigation.

The efficacy of abiraterone in men with symptomatic disease prior to chemotherapy has not been specifically demonstrated due to exclusion of these patients from the phase III trial; however, data from the post-chemotherapy trial suggest these patients are likely to benefit as well. The pace of disease may be the best guide to therapy in this setting. Patients with high Gleason scores, poor response to initial ADT, rapidly progressive disease, or poorly controlled symptoms may derive greater benefit from immediate chemotherapy, while a trial of abiraterone may be reasonable in patients with less extensive or more slowly progressing disease.[22] In this regard it should be noted that treatment with abiraterone in the phase III studies was continued until clinical or radiographic evidence of progression, thus it is reasonable to continue therapy in patients with PSA progression as long as there is evidence of ongoing clinical benefit.

While both abiraterone and enzalutamide are supported by phase III data demonstrating an OS benefit in the post-chemotherapy setting, the optimal approach to sequencing them is unknown. Retrospective evaluations of patients receiving abiraterone after enzalutamide or vice versa have shown modest response rates with median times to progression of 3-4 months.[23-25] Until biomarkers to stratify patients or clinical trial data to support combination or sequencing strategies are available, the sequencing of abiraterone and enzalutamide is likely to be dictated by insurance and regulatory approvals. From a practical perspective enzalutamide avoids the need for prednisone, although this may become less important if studies show abiraterone can be given with a lower 5 mg dose.

An emerging consideration is whether therapy with abiraterone (or enzalutamide) may influence the efficacy of subsequent chemotherapy.[22] Taxanes inhibit AR transcriptional activity by various mechanisms including induction of transcriptional corepressors and prevention of microtubule-mediated transit of AR to the nucleus, suggesting a mechanism by which development of resistance to hormonal AR pathway inhibitors may lead to cross-resistance with taxanes.[23,26,27] Notably, a small retrospective analysis of docetaxel after progression on the phase I/II studies of abiraterone showed > 50% PSA declines in only 26% of patients, compared to 45% in the TAX327 study.[28] At present these observations remain hypothesis-generating.

Conclusions and future directions

While clinical responses to abiraterone have been remarkable, not all patients respond and the majority ultimately progress with a rising PSA indicating reactivation of AR signaling. Emerging clinical and pre-clinical data similarly suggest resistance is associated with reactivation of AR signaling, including increased expression of CYP17A and induction of ligand-independent AR splice variants.[29,30] Interestingly, recent case reports describe instances of an 'abiraterone withdrawal syndrome,' in which (generally transient) PSA declines occur following discontinuation of

abiraterone, suggesting that mutations in the AR which can allow AR activation by exogenous corticosteroids may play a role.[31,32]

These observations provide a strong rationale for combining abiraterone with potent AR inhibitors such as enzalutamide rather than sequential strategies of single agents which may allow alternative pathways of AR activation to emerge. Moreover, early use of potent combined AR blockade may be particularly effective in hormone naïve tumors which have not yet had the opportunity to develop resistance. In this respect, neoadjuvant studies of multi-targeted AR blockade using LHRH agonists combined with bicalutamide, dutasteride and ketoconazole or LHRH agonists combined with abiraterone have demonstrated higher pathologic response rates than previously observed in historic studies of ADT prior to prostatectomy.[33,34]

Important clinical questions regarding the use of abiraterone in different disease settings and in combination with emerging novel agents remain to be answered. Numerous studies evaluating the sequencing and combination of abiraterone with immunotherapy, chemotherapy and other AR targeted agents in multiple disease settings are underway. Rapid accrual and completion of these studies will be imperative for determining rational treatment strategies with the highest likelihood of durable efficacy.

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Unlabeled/unapproved use of drugs or devices: Discussion of expanded indications in castration sensitive disease. □

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