Antitumor Activity with CYP17 Blockade Indicates That Castration-Resistant Prostate Cancer Frequently Remains Hormone Driven

Gerhardt Attard, Alison H.M. Reid, David Olmos, and Johann S. de Bono

Section of Medicine, The Institute of Cancer Research, Sutton, Surrey, United Kingdom

Abstract

Abiraterone acetate is a potent, selective, and orally bioavailable small molecule inhibitor of CYP17, an enzyme that catalyzes two key serial reactions (17 alpha hydroxylase and 17,20 lyase) in androgen and estrogen biosynthesis. Clinical trials have confirmed that specific inhibition of CYP17 is safe and results in clinically important antitumor activity in up to 70% of castrate patients with advanced prostate cancer resistant to currently available endocrine therapies. These clinical data indicate that castration-resistant prostate cancer frequently remains hormone dependent and has confirmed that this disease should no longer be described as “hormone resistant or refractory”. Biomarker studies, including the analysis of ETS gene fusion status, on patients treated with abiraterone acetate may allow enrichment of patients with a sensitive phenotype in future studies of therapeutics targeting CYP17. [Cancer Res 2009;69(12):4937–40]

Introduction

Prostate cancer that is resistant to all currently available endocrine therapies may remain driven by ligand-dependent or ligand-independent activation of androgen receptor (AR) signaling. AR, and other nuclear steroid receptors including ERs, have been implicated in impacting the expression of the ETS oncogenes that could be critical to prostate carcinogenesis. Although chemical or surgical castration, which can reduce serum testosterone levels to <50 ng/dL, has remained the most effective treatment for this disease for more than 60 years, recent studies indicate that prostate cancers may generate intracrine androgenic steroids or become “hypersensitive” to low steroid levels through AR gene mutations or amplification supporting continued tumor growth (1, 2).

Androgenic steroids are the most potent known AR agonists (Fig. 1A), and high intratumoral levels of these hormones can be maintained in the castrate state either by the intratumoral conversion of serum adrenal androstenedione to testosterone (secondary to overexpression of aldo-keto reductase family 1, member C3) (ref. 3) or by the de novo intratumoral synthesis of androgens from substrates such as cholesterol or progesterone (4). Steroid hormone synthesis is dependent on CYP17, a key enzyme in the generation of both androgens and estrogens (Fig. 1A). Inhibition of CYP17 can be induced by the nonspecific, weak, inhibitor of several CYP enzymes, ketoconazole (2). However, owing to low specificity for CYP17, the doses required for CYP17 blockade are several-fold higher than utilized for antifungal treatment, are hepatotoxic, and result in up to 30% of patients stopping treatment due to toxicity (2). Moreover, resistance to ketoconazole can develop secondary to loss of CYP17 inhibition (2). Similarly, currently available antiandrogens, such as bicalutamide, that are used prior to ketoconazole are weak and reversible antagonists of the AR and in up to 30% of cases become AR agonists (2). Clinical benefits induced by other hormonal manipulations, for example with the estrogenic compound diethylstilbestrol (DES) or steroids, are also short-lived (5). In fact, this disease state was until recently referred to as “hormone-refractory” or “androgen-independent,” which however, is more a reflection of the ineffective pharmacological properties of currently available therapies than an accurate representation of the disease biology. Novel drugs targeting AR signaling such as the potent and specific inhibitor of CYP17, abiraterone acetate, and novel antiandrogens such as MDV-3100 have confirmed the presence of a hormone-dependent castration-resistant prostate cancer (CRPC) phenotype.

Inhibition of CYP17 with Abiraterone Acetate

Chemists at our institution utilized testicular extracts and radiolabeled CYP17 steroid substrates, with the detection of CYP17 steroid products by high-performance liquid chromatography, to screen for small molecule chemical inhibitors of this enzyme (6). These studies led to the identification of a potent, selective, and irreversible inhibitor of CYP17, abiraterone. Preclinical studies indicated that this agent substantially decreased androgenic steroids downstream of CYP17 resulting in decreased ventral prostate, testicular, and seminal vesicle weights (7). The acetate form of this compound was recommended for oral dosing owing to improved bioavailability. On the basis of studies of the rare syndrome of congenital CYP17 deficiency, patients treated with abiraterone acetate were predicted to develop a syndrome of mineralocorticoid excess but not adrenocortical insufficiency (8).

The recently published 21-patient phase I study of once-daily continuous abiraterone acetate confirmed that specific inhibition of CYP17 was safe. Because abiraterone suppressed both 17-alpha-hydroxylase and C-17,20-lyase CYP17 activity (Fig. 1A), its continuous administration resulted in an increase in adrenocorticotropic hormone (ACTH) levels that increased C-17 steroids upstream of CYP17 including corticosterone and deoxycorticosterone. These steroids maintained glucocorticoid activity but also caused a syndrome of mineralocorticoid excess, characterized by hypokalemia, fluid retention, and hypertension. This was reversible either with the mineralocorticoid antagonist eplerenone (spironolactone was contraindicated as it can activate AR, see ref. 9) or with daily low dose steroids that suppress ACTH. Importantly, abiraterone suppressed downstream C-21 androgenic steroids to below the lower limit of detection of conventional assays, although cross-reaction of abiraterone with the dehydroepiandrosterone (DHEA) assay resulted in a false reading of incompletely suppressed DHEA (10). Downstream metabolites of these steroids, including testosterone and estradiol were suppressed to undetectable levels.
Because previous studies had shown that concomitant castration prevents a compensatory luteinizing hormone (LH) surge that can overcome testicular CYP17 inhibition by abiraterone, these patients treated on abiraterone acetate were maintained on luteinizing hormone-releasing hormone (LHRH) analogs on which they had previously had progressive prostate cancer (11).

Continuous administration of abiraterone acetate resulted in prostate-specific antigen (PSA) declines, radiological tumor regression, falls in circulating tumor cell (CTC) count, normalization of lactate dehydrogenase, and symptom improvement in up to 70% of CRPC patients who had previously received multiple hormonal treatments (median: three lines) and investigational therapies (10). Five doses from 250 mg to 2,000 mg daily were investigated, treating three patients in each dose cohort. Although the study was not designed to compare the antitumor activity of different doses, clinical responses were reported at every dose level and no dose-limiting toxicities were observed. One thousand milligrams was recommended for phase II evaluation on the basis of a plateau in the increase of upstream steroids at doses above 750 mg daily. Treatment with 1,000 mg of abiraterone acetate of a further 33 chemotherapy-naive patients at our institution and a similar number of chemotherapy-naive patients at the University of California, San Francisco (CA), have confirmed the antitumor activity reported in this first study. Similarly, three separate multicenter studies have reported similar evidence of antitumor activity in 40% to 60% of patients with end-stage CRPC who had previously progressed on docetaxel and often, multiple prior hormone therapies, second line chemotherapy, and various experimental agents. These studies have been presented at scientific meetings but are currently not yet published.

These results have led to the commencement in 2008 of a 1,180-patient multicenter, double-blinded phase III study of abiraterone acetate plus prednisolone/prednisone versus placebo plus prednisone/prednisolone in a 2:1 randomization. The primary endpoint of this study is overall survival and will incorporate the prospective evaluation of whether CTC counts post-treatment can serve as a robust intermediate endpoint for overall survival in order to accelerate new drug approval for CRPC. Evaluation of abiraterone acetate in chemotherapy-naive patients in the metastatic, adjuvant, and neoadjuvant settings is also warranted due to the high level of activity observed and the low incidence of side effects. Importantly, in the adjuvant and neoadjuvant settings, treatment with abiraterone acetate could improve cure rates.

Figure 1. A, Abiraterone acetate inhibits CYP17-dependent synthesis of DHEA resulting in suppression of circulating adrenal androgens, testosterone, and estrogens and of de novo tumor androgen synthesis. Reduced levels of AR ligands result in reduced transcription of AR-regulated genes, including PSA and ERG, and tumor regression. B, 30% of patients do not have any response to abiraterone acetate and virtually all patients will ultimately progress on treatment. Proposed mechanisms of resistance include either activation of a promiscuous AR by alternative ligands, such as deoxycorticosterone or ligand-independent AR activation due to cross-talk with activated receptor tyrosine kinases, or activation of cell signaling pathways (e.g., the PI3K/AKT pathway in association with PTEN loss), or following AR amplification or mutations. Also, transcription of genes such as TMPRSS2 could be activated by other steroid receptors, for example the estrogen receptor (ERα) or progesterone receptor (PR).
Biomarkers to Identify Hormone-Dependent Castration-Resistant Prostate Cancer

Fusion of an ETS gene with a hormone-dependent promoter gene occurs in up to 70% of therapy-naive prostate cancers (12). If the majority of cancers lacking an ETS gene fusion were dependent on a mechanism that is not hormone driven, then the presence of an ETS gene fusion could identify cancers that are hormone dependent. The most robust method for identifying ETS gene rearrangements in formalin-fixed paraffin-embedded or fresh-frozen tissue or in CTC is by fluorescence in situ hybridization investigating rearrangements at the ERG, ETV1, ETV4, or ETV5 gene loci (13). Fusion of TMPRSS2 with ERG accounts for the majority of ETS gene fusions. Evaluation of ERG gene status in 77 patients treated on abiraterone acetate phase I/II clinical trials reported that 12/15 patients who had a ≥90% PSA decline had an ERG gene rearrangement (14). These data suggest that cancers with a TMPRSS2-ERG fusion represent a subpopulation enriched for hormone-dependent CRPC but do not account for all clinical responses to abiraterone acetate. Moreover, as yet unexplained mechanisms of primary resistance exist that can result in failure of patients with a hormone-dependent fusion positive cancer to respond to abiraterone acetate (12/77 patients with a TMPRSS2-ERG fusion did not have a ≥50% PSA decline after commencing abiraterone acetate). Pretreatment serum androstenedione has been reported to be significantly associated with a clinical response to ketoconazole (15), and preliminary data have suggested that there is a similar trend for adrenal androgens in the upper quartile to associate with response to abiraterone acetate. However, these translational studies have utilized changes in PSA as a predictor of clinical benefit. As PSA is an androgen-regulated gene, these associations with PSA declines may not translate into associations with an improvement in overall survival: this will require further evaluation in larger, future studies.

Mechanisms of Resistance to Abiraterone Acetate

AR signaling is maintained in a proportion of patients after the development of resistance to abiraterone acetate, as evidenced by responses to subsequent hormone treatments. Nonandrogenic ligands can activate an amplified AR or a promiscuous AR that has undergone structural change following single base-pair mutations (Fig. 1B). Single-agent abiraterone acetate results in high levels of upstream steroids, such as deoxycorticosterone, that can activate the AR in the LNCaP cell line (16). Suppression of upstream steroids by addition of dexamethasone resulted in re-induction of sensitivity to abiraterone acetate, including in patients who had previously progressed on the same dose and schedule dexamethasone. These data suggest that activation of the AR by nonandrogenic ligands may occur in some patients and could result in resistance to single-agent abiraterone acetate (10). Future studies will combine abiraterone acetate with steroids in order to prevent this.

Ligandless activation of AR signaling may occur secondary to AR mutation or amplification that results in constitutive activation (Fig. 1B). More recently, AR variants have also been described in CRPC patients that lack the ligand-binding domain. These constitutively active variants can induce canonical androgen-responsive gene expression in the absence of androgens (17). Also, cross-talk with related signaling pathways, such as the Epidermal Growth Factor Receptor (EGFR) family or the phosphoinositide-3 kinase pathways, could reactivate downstream targets of AR signaling (Fig. 1B) (refs. 18, 19). Drugs targeting these pathways would only prove effective when ligand-activation of AR signaling is completely abrogated, potentially explaining the absence of clinical responses in CRPC with agents targeting the EGFR family. Moreover, the 5’-end of ETS gene fusions can be activated by other steroid receptors, such as the estrogen receptor (20) activation of which could also become important in CRPC when AR signaling is completely abrogated. Furthermore, abiraterone suppresses estrogen synthesis and this may contribute to its antitumor activity (Fig. 1A).

Future Directions

These data suggest that complete suppression of ligand synthesis could become the standard of care for CRPC patients. This may be achieved by combining a CYP17 inhibitor with castration. Furthermore, the promising results reported with abiraterone acetate in CRPC have introduced the possibility of CYP17 proving active in other hormone-driven cancers and abiraterone is now undergoing evaluation in metastatic breast cancer. The current phase III clinical study of abiraterone acetate in docetaxel-treated patients will be followed by clinical studies in chemotherapy-naive patients and in hormone-therapy naive disease. This strategy will not, however, reverse constitutive activation of the AR or AR-independent activation of ETS gene fusions or other downstream targets. We envision the future use of combinations of agents targeting multiple such signaling pathways, selected for individual patients on the basis of prior molecular characterization of their tumors which could utilize the molecular characterization of CTC. Changes in CTC counts are also currently being evaluated as a possible intermediate endpoint to accelerate prostate cancer drug development because changes in PSA and currently available radiological imaging are not considered acceptable endpoints for regulatory approval. Also, a major challenge for all these studies is the selection of biomarkers that predict clinical benefit.

Disclosure of Potential Conflicts of Interest

Competing Interests Statement: Abiraterone acetate was discovered at The Institute of Cancer Research, which therefore has a commercial interest in the development of this agent. The authors are part of the Section of Medicine that is supported by a Cancer Research UK program grant and an Experimental Cancer Medical Centre grant from Cancer Research UK and the Department of Health (Ref: C51/A7401). GA and AHR were also supported by the Royal Marsden Hospital Research Fund. GA is also supported by the Prostate Cancer Foundation, Santa Monica, CA. The authors also receive funding from the Prostate Cancer Research Foundation, London, the Prostate Cancer Charity, London and the Medical Research Council, UK (Ref: G0603308). The authors acknowledge NHS funding to the National Institute for Health Research (NIHR) Biomedical Research Centre, GA, AHR, and JSDB have served as unpaid consultants for Cougar Biotechnology, which owns the rights of development of abiraterone acetate.

Acknowledgments

Received 11/28/08; revised 2/19/09; accepted 2/22/09; published OnlineFirst 6/9/09.

References

Antitumor Activity with CYP17 Blockade Indicates That Castration-Resistant Prostate Cancer Frequently Remains Hormone Driven

Gerhardt Attard, Alison H.M. Reid, David Olmos, et al.


Updated version  Access the most recent version of this article at: doi:10.1158/0008-5472.CAN-08-4531

Cited articles  This article cites 19 articles, 9 of which you can access for free at: http://cancerres.aacrjournals.org/content/69/12/4937.full.html#ref-list-1

Citing articles  This article has been cited by 22 HighWire-hosted articles. Access the articles at: /content/69/12/4937.full.html#related-urls

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.