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ABIRATERONE ACETATE

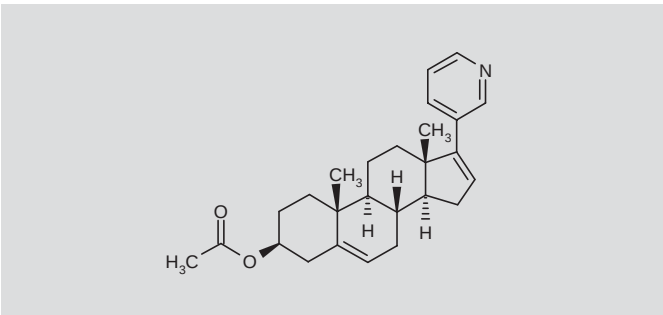
CYP17 inhibitor
Oncolytic

Prop INNM; USAN

CB-7630

Acetic acid 17-(3-pyridyl)androsta-5,16-dien-3β-yl ester

InChI=1S/C26H33NO2/c1-17(28)29-20-10-12-25(2)19(15-20)6-7-21-23-9-8-22(18-5-4-14-27-16-18)26(23,3)13-11-24(21)25/h4-6,8,14,16,20-21,23-24H,7,9-13,15H2,1-3H3/t20-,21-,23-,24-,25-,26+/m0/s1



$C_{26}H_{33}NO_2$
Mol wt: 391.5457
CAS: 154229-18-2
EN: 217053
CB-7630

ABSTRACT

Androgen deprivation therapy has been the standard of care in advanced prostate cancer for over 50 years. Although castration is initially effective, most patients eventually develop progressive disease despite low levels of testosterone. The term castration-resistant prostate cancer (CRPC), however, is a misnomer, as the disease is still dependent on continued activation of the androgen receptor (AR). New secondary hormonal therapies seek to prolong suppression of the AR and thus delay the development of truly hormone-''refractory'' prostate cancer. Extra-gonadal androgens, and specifically adrenal androgens, represent a means for continued AR-mediated growth in CRPC and have thus become a therapeutic target. Abiraterone acetate (CB-7630) is an orally administered, specific inhibitor of CYP17A1, a rate-limiting enzyme in androgen biosynthesis. Preliminary data from phase I and II trials suggest that prostate-specific antigen declines occur in a large proportion of patients and that the toxicity profile is acceptable. Two large phase III clinical trials are currently open to accrual, and if abiraterone acetate is proven to be efficacious, it will result in widespread use of a drug specifically developed to suppress adrenal androgens.

SYNTHESIS**

Abiraterone acetate has been synthesized by two related routes. a) Reaction of dehydroepiandrosterone acetate (Ia) with trifluoromethanesulfonic anhydride and triethylamine in dichloromethane gives the enol triflate (II), which is finally coupled with diethyl(3-pyridyl)borane (III) by means of $PdCl_2(PPh_3)_4$ in tetrahydrofuran (1-4). Scheme 1.

b) In an improved procedure, dehydroepiandrosterone (Ib) is converted to the corresponding hydrazone (IV) by treatment with hydrazine hydrate and a catalytic amount of hydrazine sulfate in EtOH. Subsequent reaction of hydrazone (IV) with iodine and 1,1,3,3-tetramethylguanidine (TMG) in THF/Et_2O gives the vinyl iodide (V), which undergoes palladium–catalyzed cross coupling with diethyl(3-pyridyl)borane (III) to yield abiraterone (VI). Finally, alcohol (VI) is acetylated using acetic anhydride in pyridine (5, 6). Scheme 1.

BACKGROUND

Prostate cancer is a common disease in the US; in 2009 there was an estimated 192,280 men diagnosed with the disease and an estimated 27,360 deaths (7). Although the majority of patients diagnosed with prostate cancer are likely to be cured with definitive primary treatment such as surgery or radiation, prostate cancer remains the second leading cause of male cancer-related death in the western world (8).

Localized prostate cancer can be definitively treated by surgical resection or radiation therapy. However, invasive or even micrometastatic disease presents a clinical challenge, as these tumors respond poorly to and are virtually never cured with standard cytotoxic regimens. Prostate cancer, however, has a unique characteristic in that it is exquisitely dependent on androgens for development, growth and survival (9). Androgen ablation triggers cell cycle arrest of prostate cancer and thus remains the primary treatment for all patients with

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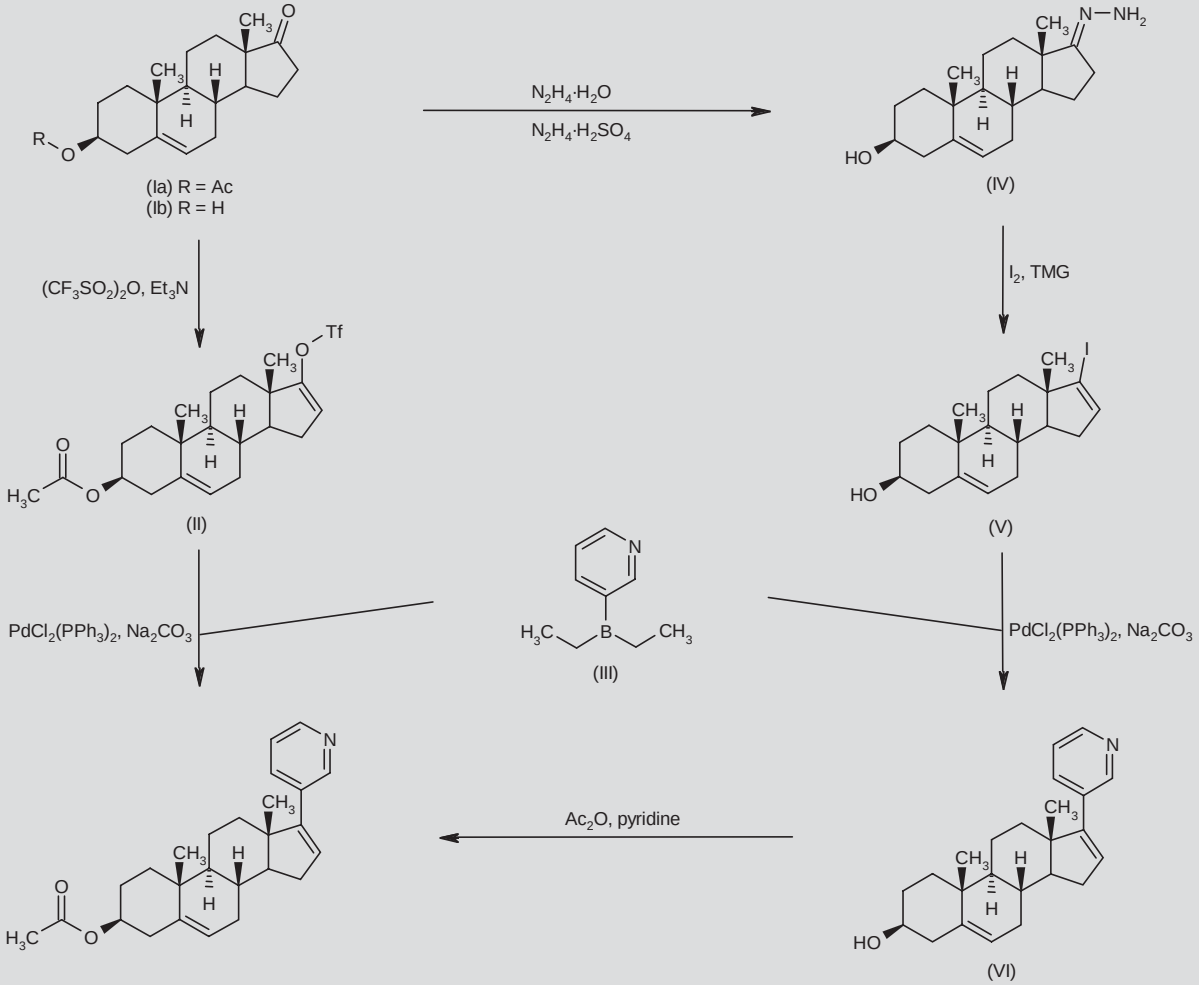
**Synthesis prepared by J. Bolós, R. Castañer. Thomson Reuters, Provenza 388, 08025 Barcelona, Spain.

Scheme 1. Synthesis of Abiraterone acetate



metastatic disease (10). Unfortunately, however, disease progression typically occurs within a median of 2 to 3 years. In these cases, it is thought that androgen signaling has been inappropriately restored or that progressive disease occurs through the outgrowth of a tumor compartment that is sensitive to low levels of circulating androgens. Given the dependence of prostate cancer cells on the androgen signaling axis, a concerted effort has been undertaken to determine the mechanism(s) by which androgens induce prostate cancer cell proliferation and survival (11). Through the years, androgens and the androgen receptor have been researched as targets for development of drugs such as abiraterone acetate.

Androgens

Androgens exert their biological effects through activation of the androgen receptor (AR), a member of the nuclear receptor superfamily that acts as a ligand-dependent transcription factor. Testosterone and dihydrotestosterone (DHT) are the two major androgens in men, with testosterone present mainly in the circulation, and DHT being the primary androgen in prostatic tissues. The Leydig cells of the testis produce 90 to 95% of circulating testosterone, with 5 to 10% of circulating testosterone synthesized in the adrenal glands (12). In contrast, DHT primarily arises from conversion of testosterone to DHT at the tissue level by the two isoforms of 5α-reductase, S5A1 and S5A2. Approximately 25% of circulating DHT is produced in the testes, with the remaining 75% produced in the prostate and skin (13).

Prior to ligand (i.e. DHT) binding, the AR is held inactive through association with heat shock proteins (Hsps) and thus is unable to bind to DNA. Ligand binding releases the inhibitory Hsps, and the receptor translocates to the nucleus, where it binds DNA on androgen-responsive elements (AREs) within the regulatory regions of target genes (14). Furthermore, recruitment of co-activators (histone acetylases) and chromatin remodeling complexes facilitates transcriptional initiation, and AR-dependent gene expression ensues

(15). Thus, stimulation of the AR induces a gene expression cascade that promotes cell cycle progression. It is hypothesized that during tumorigenesis, the proliferative function of the AR becomes autonomous and promotes prostate cancer survival (2).

Given that activation of the AR stimulates mitogenesis and is ligand dependent, inhibition of AR activity is the major therapeutic goal for management of metastatic disease (9). First-line treatment ablates AR function through ligand depletion, either by bilateral orchiectomy or by the use of gonadotrophin-releasing hormone agonists, either as monotherapy or in conjunction with direct AR antagonists (i.e. bicalutamide), which is termed combined androgen blockade (CAB) (16). AR antagonists compete for DHT binding and selectively trigger the recruitment of transcriptional co-repressors to AREs (thus repressing AR target gene expression) (17). At the cellular level, androgen ablation induces cell death or cell cycle arrest, both of which are fundamental to tumor regression (10). Effective AR inhibition is observed by a loss of detectable serum prostate-specific antigen (PSA; a major androgen-regulated gene product). However, this remission is transient, and tumor recurrence is almost invariably observed (9, 11). Tumor persistence or recurrence following androgen deprivation is typically preceded by a rise in PSA (termed 'castration resistance' in the contemporary literature); an observation that supports the hypothesis that tumor progression is associated with inappropriately restored or sustained AR function (despite sustained androgen ablation and/or the use of AR antagonists) (11). Persistent activation or re-activation is thought to arise through multiple mechanisms, including: AR amplification; hypersensitivity to a low-ligand environment; AR mutation; excessive production of AR co-activators; ligand-independent AR activation; alternative sources of androgen; enhanced local production of androgens; and upregulation of anti-apoptotic genes in prostate cancer cells (18).

Non-gonadal sources of androgens

Non-gonadal sources of androgens (adrenal and intracrine de novo synthesis) have recently become widely considered to be a potential source of androgens responsible for tumor progression (19). New data suggest that, while medical or surgical castration results in low serum testosterone levels, this may not reflect the true intracellular concentration of androgens in tumor cells. Prostate cancer cells have the ability to convert adrenal androgens to DHT intracellularly and synthesize androgens de novo from cholesterol, thereby providing higher intracellular androgen levels despite the low serum levels of testosterone. Data indicate that, at 'castrate' serum testosterone levels, prostatic androgen concentrations remain at approximately 10 to 25% of the levels found in untreated patients, well within the range capable of mediating continued AR signaling and gene expression (20, 21). Mohler et al studied recurrent prostate cancer specimens from 22 men (whose prostate cancer recurred locally during androgen-deprivation therapy (ADT)) and benign prostate specimens from 48 men who had received no prior treatment (22). Findings demonstrated that the AR was present and activated (as suggested by the presence of the androgen-regulated gene product, PSA) in both the recurrent prostate cancer tissue and the benign prostate cancer tissue. In addition, tissue levels of testosterone, DHT, dehydroepiandrosterone (DHEA) and androstenedione (AED) were detectable, albeit lower in the recurrent prostate cancer than in the benign prostate tissue. The authors concluded that testosterone and DHT occur in recurrent prostate cancer tissue at levels sufficient to activate the AR (22).

Hormone ablation therapy reduced serum testosterone from > 200 ng/mL to a mean of 15 ng/mL while serum levels of adrenal androgens such as DHEA and AED were unaffected (23). The follicular zone and reticular zone cells in the adrenal cortex synthesize three major inactive pro-hormones of androgen via cytochrome P450 enzymes, DHEA, AED and DHEA sulfate (DHEAS). DHEA and DHEAS can be reversibly interchanged, and subsequently DHEA is converted to testosterone by a two-step reduction reaction (24). Nishiyama et al investigated the change of androgen concentration in both serum and prostatic tissue of 30 prostate cancer patients before and after 6-month ADT in the neoadjuvant setting (25). After ADT, the DHT level in serum correlated with both adrenal androgen and testosterone levels in serum. These findings suggested that serum testosterone after ADT came mostly from adrenal androgens converted in the prostatic cells. It also indirectly revealed that the DHT in cancer tissue after ADT was derived from the conversion of adrenal androgens in peripheral tissues and the prostate (25). Subsequently, Page et al demonstrated that, despite a 94% decrease in serum testosterone concentrations, intraprostatic testosterone and DHT levels remained at 20 to 30% of control values. Furthermore, a strong relationship between serum DHEA and prostatic tissue androgen after medical castration was found (26). Findings from Labrie and colleagues further suggested that approximately 50% of andogen in prostatic tissue originates from adrenal DHEA (27). Lastly, intra-prostatic adrenal androgens have been detected at significant levels in patients treated to suppress testosterone. Although levels of DHEA, DHEAS and AED were decreased by approximately 50% in tumor tissue from castrated patients with recurrent prostate cancer, they far exceeded the values of testosterone and DHT in the recurrent tumor tissue (28). This discrepancy in values (between intra-prostatic adrenal androgens and intra-prostatic testosterone/DHT in castrate patients with recurrent prostate cancer) potentially implies that some, but not all, of the adrenal androgens are converted into testosterone/DHT within the prostate (25).

Aside from the uptake of adrenal androgens, an unresolved question is whether intratumoral androgens are synthesized de novo from progesterone, cholesterol or earlier precursors. Soft tissue metastases in patients with anorchid serum testosterone contain levels of testosterone that are up to three times higher than those in prostate tumors in eugonadal men (29). Transcript levels of enzymes involved in androgen synthesis were upregulated in the tumors (8- to 30-fold), suggesting that tumoral synthesis of androgens from cholesterol might occur (30, 31). Furthermore, androgen-independent prostate cancer cell lines synthesize testosterone from radiolabeled cholesterol in vitro, and human prostate cancer xenografts are capable of synthesizing DHT from acetate and cholesterol, again confirming that tumoral androgen synthesis is possible (32, 33). Locke et al used LNCaP xenograft models to demonstrate that tumor explants isolated from castration-resistant prostate cancer (CRPC) not only exhibited de novo conversion of [^{14}C]-acetic acid to DHT, but also exhibited uptake of [^{3}H]-progesterone and subsequent detection of six other steroids upstream of DHT (34). These data suggest that the tumor progression in certain patients with CRPC can occur through intracrine mechanisms, not the classic endocrine mechanisms responsible for growth of the untreated tumor. However, the

processes responsible for sustaining intratumoral androgen levels in the setting of systemic testosterone suppression are still unknown.

Inhibition of CYP17

The human cytochrome P450 17 (*CYP17*) gene is located on chromosome 10(q24.3) and encodes for an enzyme that localizes to the endoplasmic reticulum of Leydig cells in the testis, theca interna region of the ovaries, and zona fasciculata and reticularis in the adrenal glands (35). It is a key enzyme in the generation of androgens and estrogens in the adrenal glands and tumor tissue, and facilitates the catalysis of two independently regulated steroid reactions (via the two components of CYP17, 17α-hydroxylase and C17,20-lyase). The 17α-hydroxylase activity converts pregnenolone to 17α-hydroxypregnenolone and progesterone to 17α-hydroxyprogesterone, whereas C17,20-lyase converts 17α-hydroxypregnenolone to DHEA and 17α-hydroxyprogesterone to AED (see Fig. 1) (36). Given the key role of CYP17 in androgen production, inhibition of this enzyme suppresses androgen production in all endocrine organs, including the testis, adrenal glands and postulated tumoral sites of androgen production (37, 38).

One rationale for CYP17 inhibition in prostate cancer stemmed from the realization that congenital CYP17 deficiencies (i.e. congenital adrenal hyperplasia) led to impaired production of cortisol, androgens and estrogens, with preserved synthesis of corticosterone, a weaker glucocorticoid. Hence, patients have impaired sexual development without classic adrenal insufficiency (39). A relative paucity of glucocorticoid levels leads to a secondary rise in adrenocorticotrophic hormone (ACTH), which is responsible for mineralocorticoid excess, characterized by fluid overload, hypertension and hypokalaemia. Treatment of this syndrome with glucocorticoids typically leads to ACTH suppression and normalization of mineralocorticoid, serum potassium levels and blood pressure (19).

Ketoconazole, an antifungal with weak and non-specific CYP17 inhibitory properties, has been utilized extensively in patients with CRPC. Efficacy data from phase II trials demonstrated that the response rate by PSA working group criteria (PSAWG) ranged from 40 to 62%, with a median duration of response up to 7 months (40, 41). A randomized study conducted by the Cancer and Leukemia Group B evaluated anti-androgen withdrawal alone versus anti-androgen withdrawal plus ketoconazole and demonstrated a 50% or greater decline in PSA in 11 versus 27% of participants, respectively. Despite this, no difference in overall survival was observed (although the lack of effect may have been attributable to the fact that 82% of patients initially undergoing only anti-androgen withdrawal eventually 'crossed over' to receive ketoconazole). Importantly, an observation arose from this study that, at the time of resistance to ketoconazole, androgen levels rose by a significant margin above nadir values, suggesting either the development of tachyphylaxis to the inhibitory effects of ketoconazole or, less likely, a growing contribution to serum androgen levels from intracrine hormone production (42). A follow-up study demonstrated that those patients with lower levels of baseline adrenal androgens were less likely to respond to ketoconazole administration - supporting the hypothesis that adrenal androgens are partially responsible for driving tumor progression in CRPC (43).

The limitations of ketoconazole and the desire to optimize androgen deprivation motivated research into the development of more potent

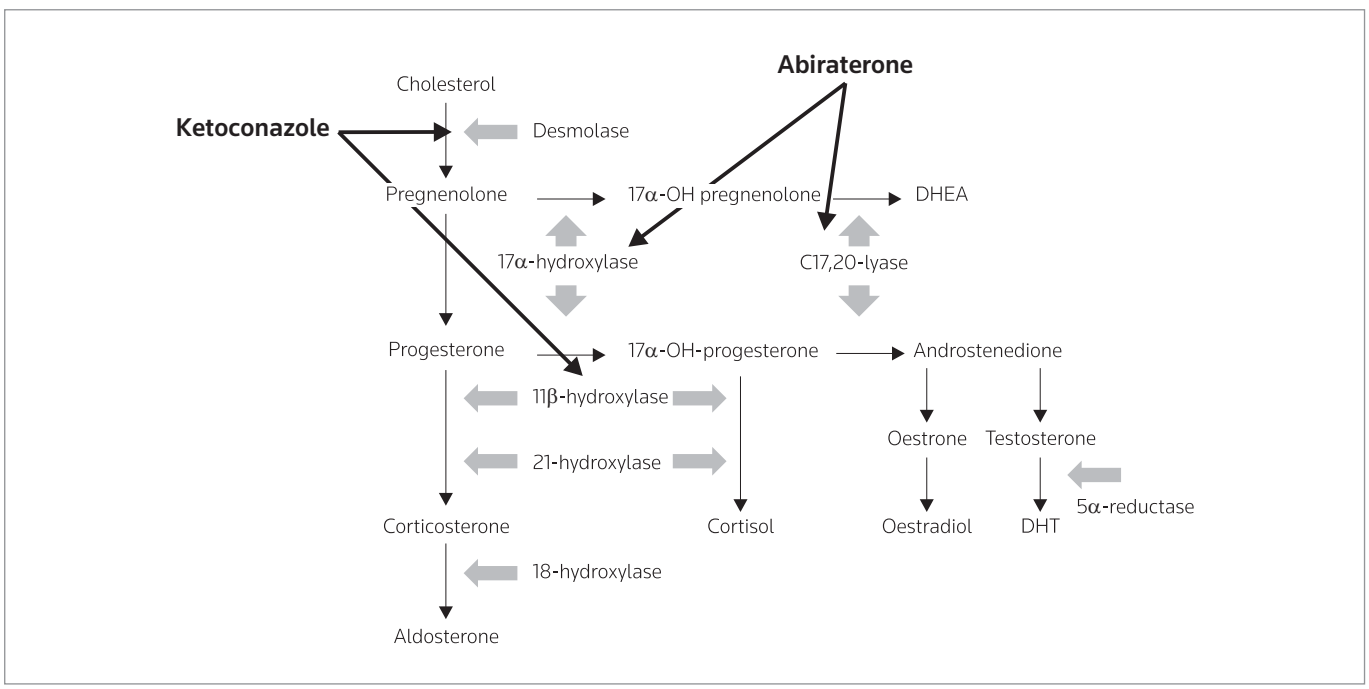


Figure 1. Adrenal androgen biosynthesis pathway indicating the enzymes inhibited by ketoconazole and abiraterone. Adrenal androgen biosynthesis pathway indicating the enzymes inhibited by ketoconazole and abiraterone.

and selective CYP17 inhibitors. A series of potent inhibitory 17-(3-pyridyl)-steroids were developed at the Institute of Cancer Research in the UK, of which the most extensively studied was the pregnenolone-derived compound abiraterone (CB-7598) (1, 44, 45).

PRECLINICAL PHARMACOLOGY

The key design features of abiraterone include the 3-pyridyl substituent and the 16,17-double bond, which together account for more potent and irreversible inhibition of CYP17 (1, 44, 45). Abiraterone is a highly potent and selective inhibitor, with a Ki_{app} value of < 1 nM (1). When administered to WHT mice as its acetate prodrug (CB-7630; administered on a daily basis for two weeks at a dose of 0.5 mmol/kg), circulating testosterone was suppressed to undetectable levels and the weights of androgen-sensitive organs were markedly decreased. Plasma testosterone was reduced to 0.1 nM or less, despite a 3- to 4-fold increase in the plasma level of luteinizing hormone (LH). Adrenal weights were unchanged following treatment with abiraterone acetate (and were markedly increased following ketoconazole), indicating no inhibition of corticosterone production (35, 44).

Unlike ketoconazole, abiraterone is a potent, selective and irreversible inhibitor of CYP17 (ketoconazole is nonspecific and less potent; Fig. 1). In a preclinical comparison of both drugs, IC_{50} values obtained for abiraterone were 2.9 and 4 nM for the lyase and hydroxylase assays, respectively, while IC_{50} values for ketoconazole were 26 and 65 nM, respectively, suggesting that abiraterone was approximately 10-fold more potent than ketoconazole (1).

PHARMACOKINETICS AND METABOLISM

Abiraterone acetate demonstrated rapid deacetylation following intraperitoneal administration in a rodent model. Levels of abiraterone drug reached 41 mM at 6 h, with persistence of relatively high levels of compound (approximately 0.3 mM) for 24 h. These findings led researchers to believe that sustained target inhibition could be achieved with this drug (46).

Phase I pharmacokinetic (PK) studies suggested good bioavailability; the mean elimination half-life of abiraterone in these studies was 27.6 h, thus supporting the use of once-daily dosing (46). However, there was up to 10-fold inter-patient variability in the area under the curve (AUC) for a given dose, making analysis of dose-dependent PK relationships difficult. There was no evidence of drug absorption saturation at doses of up to 800 mg/day (46).

SAFETY

Abiaterone acetate was well tolerated in phase I trials when administered to men with prostate cancer for up to 12 days continuously with no clinical manifestations of adrenocortical insufficiency. Mild headaches, hot flushes and transient mood changes were observed, however, there were no clinically significant toxicities (46).

Dose escalation to 2000 mg was achieved in a phase I dose-escalation study, with no treatment-related grade 3/4 toxicities or dose-limiting toxicities. The toxicities observed in this study were predominantly due to secondary mineralocorticoid excess (i.e., hypertension, hypokalemia and lower extremity edema). These symptoms were controlled with the mineralocorticoid receptor antagonist eplerenone; spironolactone was deliberately avoided since this has been previously reported to activate AR signaling. As predicted from the syndrome of congenital CYP17 deficiency, no patient developed clinical adrenocortical insufficiency in the trial (35, 45). Based on the development of mineralocorticoid-induced hypertension and hypokalemia in patients treated with abiraterone acetate monotherapy, the conclusion of phase I investigators was that in subsequent studies, abiraterone acetate would be administered in combination with prednisone 10 mg daily (35, 45).

In a phase II study, 33 chemotherapy-naïve CRPC patients were administered abiraterone acetate plus prednisone (1000 mg daily and 5 mg twice daily, respectively). The majority of adverse events reported were grade 1 or 2, with the exception of one grade 3 treatment-related hypertension (47, 48).

CLINICAL STUDIES

First-in-human studies entailed a series of three dose escalations carried out in men with histologically confirmed prostate cancer in both castrated and noncastrated males (there were no healthy volunteers in these studies, i.e. all participants had prostate cancer) (46).

All three of these pilot studies demonstrated suppression of testosterone synthesis. However, when given to noncastrated men, an LH surge occurred that overcame gonadal testosterone synthesis inhibition by abiraterone acetate (at doses of 500 mg/day and greater). In contrast, the data from single dosing in castrated males suggested that the compensatory LH surge was inhibited when used in conjunction with an LHRH agonist and there was sustained suppression of testosterone. This data implied that abiraterone would be effective when coupled with continuing use of LHRH agonists in patients who have failed medical castration alone (46, 49). A notable limitation in these early studies was the lack of investigation into antitumor effects.

Two parallel phase I dose escalation studies were initiated in 2006 to evaluate abiraterone acetate as a novel secondary hormonal therapeutic in patients with CRPC (one conducted at the Royal Marsden Hospital in London and the other at the University of California-San Francisco and the Dana Farber Cancer Institute in the United States through the Department of Defense Prostate Cancer Clinical Trials Consortium) (45). In the UK study, abiraterone acetate was administered once daily to 21 patients in three-patient cohorts escalating through the preplanned doses of 250, 500, 750, 1000 and 2000 mg. This phase I study revealed an overall 30% or greater decline in PSA in 66% of the CRPC patients. Circulating testosterone levels in all patients were in the castration range at baseline and rapidly became undetectable at all doses. There was no rise in testosterone, AED, DHEA or DHEAS levels while on treatment, or at PSA or radiological progression (indicating durable and irreversible CYP17 inhibition). In addition, there was symptomatic improvement (with 8 out of 11 patients reducing or discontinuing analgesics), reduction in serum alkaline phosphatase, normalization of elevated lactate dehydrogenase levels (five out of seven patients), and partial responses by Response Evaluation Criteria In Solid Tumors (RECIST; five out of eight patients with measurable disease at baseline had confirmed

partial responses by RECIST). Tumor responses to abiraterone acetate were observed in castrated patients who had failed several prior lines of AR-targeting therapy (there was a median of three prior hormonal therapies) (45). This was the first study to show that selective and continuous CYP17 inhibition is safe and associated with durable suppression of serum androgens.

In the second phase I dose-escalation (with a phase II dose expansion) study conducted at the University of California, San Francisco and the Dana Farber Cancer Institute, an evaluation of the impact of prior ketoconazole treatment on the response to abiraterone acetate was reported. Of the 27 patients enrolled, 14 (52%) experienced a > 50% decline in PSA on abiraterone acetate. Eighteen patients (67%) had received prior ketoconazole and 9 had not. Five of 9 (56%) patients who did not receive prior ketoconazole responded to abiraterone acetate, whereas 9 of 18 ketoconazole-treated patients (50%) experienced a > 50% or greater decline in PSA while on abiraterone acetate. Two of three patients who previously discontinued ketoconazole due to toxicity experienced a PSA decline on abiraterone acetate and 7 of 15 patients (47%) who had experienced disease progression on ketoconazole experienced a PSA decline on abiraterone acetate. These data suggested that patients with prior ketoconazole exposure do not appear to have an increased risk of toxicity on abiraterone, and also that a high proportion of these patients respond to this therapy (50).

Phase II evaluations of abiraterone acetate in CRPC patients have subsequently been performed in patients both with and without prior docetaxel chemotherapy. In a cohort of 56 evaluable patients who had received docetaxel, including 24 patients with known prior ketoconazole exposure, approximately 45% of patients treated with abiraterone acetate achieved a decline in PSA of 50% or greater. Median time to PSA progression was 169 days (95% CI 82-200) (35, 51, 52). In a second phase II study of abiraterone acetate in docetaxel-pretreated CRPC patients, Reid et al reported that of the 47 patients, 24 (51%) had a 50% or greater decline in PSA (observed at any point in the study) (53). Of the 35 patients evaluable by RECIST, six (17%) had a partial response and 23 (66%) had stable disease. Median duration on treatment was 167 days (95% CI 130-201), 17 patients received > six cycles and eight patients received 12 or more cycles (53).

Treatment with abiraterone acetate in the pre-chemotherapy (as opposed to the post-docetaxel) setting suggests an even higher rate of response. In another phase II study, 33 chemotherapy-naïve CRPC patients were administered abiraterone acetate plus prednisone (1000 mg daily and 5 mg twice daily, respectively) (47, 48). In the 27 evaluable patients, there was an 89% (24/27 patients) response rate (defined as any PSA decline). A 50% or greater PSA decline was observed in 85% (23/27) of the patients and at 12 weeks this decline was maintained in 78% (21/27) of patients. Median time to PSA progression had not been reached at the time of publication. This regimen was well-tolerated and demonstrated noteworthy antitumor activity (47, 48). Attard et al from the Royal Marsden also completed their phase II study (which was part of the phase I/II study reported above). The phase II expansion of the phase I/II trial tested 1000 mg of abiraterone acetate and involved 42 patients. A decline in PSA of 50% or greater was observed in 28 (67%) out of 42 patients, and declines of 90% or greater were observed in eight (19%) patients. Independent radiological evaluation reported partial responses in nine (37.5%) out of 24 patients with measurable disease. Decreases in circulating tumor cell counts were also documented. The median time to PSA progression during abiraterone acetate treatment for all phase II patients was 225 days (95% CI 162-287 days). One interesting analysis (performed on all 54 phase I/II patients receiving 1000 mg/day) was that high pretreatment levels of DHEA, DHEAS, AED and estradiol were associated with increased probability of a 50% or greater PSA decline following abiraterone acetate treatment (Ryan et al previously demonstrated that higher AED levels predicted likelihood of response to ketoconazole) (43, 54).

The encouraging antitumor activity observed in the abiraterone acetate phase II trials in both docetaxel-naïve and post-docetaxel patients suggests that abiraterone acetate may be useful across a wide range of clinical situations in CRPC. These preliminary data also suggest that patients previously exposed to (and even progressed on) ketoconazole continue to experience antitumor activity with abiraterone acetate, although this observation requires prospective validation (35). Two placebo-controlled randomized phase III studies of abiraterone acetate are underway with the aim of securing approval by the US Food and Drug Administration. One study is being conducted in patients with prior docetaxel exposure and the other in patients without docetaxel exposure. In the post-docetaxel study, estimated enrollment is 1158 patients (152 locations); the primary endpoint is overall survival with the secondary endpoint being proportion of patients achieving a PSA decline of 50% or greater according to PSAWG criteria (ClinicalTrials.gov identifier NCT00887198). In the pre-docetaxel study, 1000 patients (48 locations) with asymptomatic or mildly symptomatic metastatic CRPC will be enrolled. The primary endpoints will be overall and progression-free survival (ClinicalTrials.gov identifier NCT00638690).

CONCLUSION

Although ADT continues to be the mainstay of treatment in locally advanced and metastatic prostate cancer, the development of CRPC heralds the onset of a lethal form of the disease. It is caused, in part, by adaptive changes in AR, continued downstream signaling by non-androgen ligands and alternative sources of androgen (46).

Inhibitors of CYP17 are effective therapeutics, as they not only affect testicular androgen formation but also adrenal biosynthesis (55). Given its greater selectivity for CYP17 than ketoconazole, abiraterone acetate has a better toxicity profile and has demonstrated clinical efficacy in the studies carried out so far. Further elucidation of both safety and the efficacy of abiraterone acetate is awaited from the publication of the phase II and III trial data.

DISCLOSURE

The authors state no conflicts of interest.

SOURCE

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