Abiraterone acetate: oral androgen biosynthesis inhibitor for treatment of castration-resistant prostate cancer

Yasser Rehman 1
Jonathan E Rosenberg 2

1Division of Hospital Medicine, UMass Memorial Healthcare, Worcester, MA, USA; 2Lank Center for Genitourinary Oncology, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Abstract: Prostate cancer is the second leading cause of cancer death in men in the US and Europe. The treatment of advanced-stage prostate cancer has been androgen deprivation. Medical castration leads to decreased production of testosterone and dihydrotestosterone by the testes, but adrenal glands and even prostate cancer tissue continue to produce androgens, which eventually leads to continued prostate cancer growth despite castrate level of androgens. This stage is known as castrate-resistant prostate cancer (CRPC), which continues to be a challenge to treat. Addition of androgen antagonists to hormonal deprivation has been successful in lowering the prostate-specific antigen levels further, but has not actually translated into life-prolonging options. The results of several contemporary studies have continued to demonstrate activation of the androgen receptor as being the key factor in the continued growth of prostate cancer. Blockade of androgen production by nongonadal sources has led to clinical benefit in this setting. One such agent is abiraterone acetate, which significantly reduces androgen production by blocking the enzyme, cytochrome P450 17 alpha-hydroxylase (CYP17). This has provided physicians with another treatment option for patients with CRPC. The landscape for prostate cancer treatment has changed with the approval of cabazitaxel, sipuleucel-T and abiraterone. Here we provide an overview of abiraterone acetate, its mechanism of action, and its potential place for therapy in CRPC.

Keywords: CRPC, abiraterone, CYP17, inhibitors, androgens, castration resistant prostate cancer

Introduction
Prostate cancer is widely known to be dependent on androgens. The testes secrete testosterone which accounts for 95% of androgens in the body while the remainder is produced in the adrenal glands.1,2 The majority of testosterone is primarily bound to albumin and sex hormone binding globulin, though some is transported as free testosterone in serum. Upon entering the testes, free testosterone is converted to dihydrotestosterone by the enzyme 5α-reductase. Dihydrotestosterone has a five-fold affinity for the androgen receptor compared with testosterone. Prostate cancer growth is dependent on levels of androgen in the body which help maintain the balance in favor of cell growth over apoptosis.3 Recently, the treatment of CRPC has changed dramatically with the approval of sipuleucel-T, cabazitaxel, denosumab, and abiraterone acetate by the US Food and Drug Administration.

Cabazitaxel is a semisynthetic taxane analog designed to overcome taxane resistance. Preclinical studies demonstrated cabazitaxel to overcome docetaxel-resistant cell lines. Phase I studies further demonstrated cabazitaxel to show efficacy not only
Androgen receptor and signaling

Androgen signaling is mediated through the androgen receptor, a ligand-dependent transcription factor located on the X chromosome. The receptor is composed of an amino terminal activating domain, a carboxy-terminal ligand binding domain, a hinge region, and a DNA binding domain. The inactive form of the androgen receptor resides within the cytoplasm and remains bound to heat shock proteins that prevent androgen receptor activation. The binding of androgens to the receptor leads to dissociation of the heat shock proteins and receptor phosphorylation which, in turn, leads to nuclear translocation, allowing for transcription of androgen-dependent genes.6

A number of different mechanisms appear responsible for castration resistance in prostate cancer. One of them is an androgen receptor mutation which is seen occasionally in advanced disease.7 Some androgen receptor mutations in CRPC make the androgen receptor lose its specificity to androgens and it becomes more responsive to estrogens, progesterone, and even antiandrogens.8 This can lead to prostate cancer growth despite castrate levels of testosterone. Occasionally, prostate cancer with resistance to flutamide will still respond to other antiandrogens like bicalutamide, suggesting that mutations in the androgen receptor are a direct result of selective pressure.9 Androgen receptor hyper-responsiveness can also result from androgen receptor gene amplification. Copy number gains of the androgen receptor allow continued prostate cancer growth despite low androgen levels. Androgen receptor gene amplifications are noted in 28% of recurrent therapy-resistant prostate cancer patients exposed to androgen ablation, but has not been observed in early tumor samples without exposure to androgen ablation.10 This suggests the possibility of clonal selection of cancer cells with the ability to grow despite very low levels of circulating androgens. Upregulation of nuclear transcription coactivators also allows androgen receptor-mediated gene transcription despite low levels of circulating androgens or presence of less potent androgens.11 In addition, prostate cancer cells have been shown to upregulate intratumoral steroidogenesis to maintain intratumor androgen at levels required for tumor growth.12 This mechanism leads to tumor growth despite castrate level androgens in the body. In addition, the fusion of androgen-activated TMPRSS2 with the ETS family of oncogenes ERG or ETV1 has been noted to occur frequently in prostate cancer. The precise role of TMPRSS2/ETS translocations in castration resistance is unclear at this time, although androgen-regulated ERG transcription is reactivated in the setting of androgen receptor reactivation in castration resistance, and may contribute to progression of CRPC.13

Cytochrome P17 enzyme

The CYP17 enzyme is a cytochrome P450 (CYP) enzyme. Located in the endoplasmic reticulum of the testis, ovaries, adrenals, and placenta, CYP17 drives the synthesis of glucocorticoids and sex hormones. The enzyme has both 17α hydroxylase and C17,20 lyase activity, and plays a critical role in the production of cortisol and androgen synthesis (Figure 1). Cytochrome b5 regulates the activity of CYP17,20 lyase. A high b5/CYP 17,20 lyase ratio usually occurs in the testes, which leads to production of androgens, while a low b5/c lyase ratio in adrenal glands will ensure cortisol production.14,15

Role in androgen production

Production of androgens or cortisol in the body begins by conversion of cholesterol into pregnenolone which can then be further converted to androgens or progesterone via 3β hydroxysteroid dehydrogenase. 17α hydroxylase then converts progesterone into 17α hydroxyprogesterone and pregnenolone into 17α hydroxypregnenolone. C17,20 lyase then converts 17α hydroxyprogesterone and 17α hydroxypregnenolone into androstenedione and dehydroepiandrosterone, respectively. Androstenedione
and dehydroepiandrosterone are eventually converted into testosterone by enzymatic pathways. The enzyme 5α reductase then converts testosterone into dihydrotestosterone. Abiraterone inhibits C17,20 lyase irreversibly.

Role in cortisol production
17α hydroxypregnenolone and 17α hydroxyprogesterone are also converted to cortisol precursors. Adrenocorticotropic hormone (ACTH) acts as a stimulus for converting cholesterol into pregnenolone, and is kept in check via a negative feedback loop by an increased cortisol level. By blocking the activity of 17α hydroxylase, cortisol production is diminished and the negative feedback effect on ACTH is removed. This leads to increased production of ACTH which, in turn, stimulates production of precursors above the 17α hydroxylase level. One of these precursors is corticosterone which is only a weak inhibitor of ACTH; high levels of corticosterone are required to inhibit the production of ACTH. The increased production of corticosterone leads to fluid retention, hypokalemia, and hypertension. These effects can be prevented by concomitant administration of low doses of prednisone, corticosterone, or dexamethasone.

CYP17 inhibition in prostate cancer
Inhibition of adrenal androgen steroid synthesis via CYP17 in men with prostate cancer has led to clinical antitumor responses. Use of ketoconazole and aminoglutethimide has been associated with prostate-specific antigen declines and measurable disease responses in some CRPC patients; these agents also have significant toxicity and are not associated with a survival benefit. However, these data suggested that a better inhibitor with less toxicity and more durable efficacy might lead to significant clinical benefit in CRPC. Abiraterone acetate was identified to be a potent and selective irreversible inhibitor of CYP17. Preclinical studies with abiraterone demonstrated reduction in androgen production downstream of CYP17 which resulted in decreased weight of the ventral prostate, testis, and seminal vesicles in mice. The first-in-human studies demonstrated a dose of 800 mg once daily to be effective in suppressing testosterone to below detectable levels in humans and also provided a preliminary insight into its safety profile.

Phase I studies
Based on the clinical data suggesting the importance of CYP17 in androgen synthesis and the activity of abiraterone in preclinical models, Phase I studies of this agent were initiated. One study evaluated 21 CRPC patients who received escalating doses of abiraterone from 250 mg to 2000 mg. Antitumor activity was noted at all levels. However, due to a plateau effect in pharmacokinetics noted at 1000 mg, this dose was selected for further drug development. Decreases in testosterone, estradiol, and androgenic steroids downstream of CYP17 blockade were noted in all patients, as well as an increase in ACTH and steroids upstream of the blockade. Declines in prostate-specific antigen of ≥30%, ≥50%, and ≥90% were observed in 14 (66%), 12 (57%), and six (29%) patients, respectively. A reduction in pain medication requirement and radiologic regression were noted in many patients. Adverse effects, mainly fluid retention, hypokalemia, and lower extremity edema, were easily reversed with eplerenone (a mineralocorticoid receptor antagonist). Interestingly, six patients in the study had an ERG rearrangement. Five of these patients responded well to treatment with abiraterone. ERG rearrangements can potentially be used in the future as a predictor of favorable outcome in response to abiraterone. This study also looked at the use of dexamethasone to test the hypothesis that potential resistance to abiraterone could be overcome with steroids by inhibiting ACTH and also to prevent upstream steroid production from stimulating a
Table 1 Summary of the Phase II and III study results

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Prior treatment</th>
<th>Agents used</th>
<th>Patients (n)</th>
<th>Corticosteroid</th>
<th>OR (%) (measurable disease only)</th>
<th>Decrease in CTC</th>
<th>OR (PR) (measurable disease only)</th>
<th>CTC of ≥ 5 to &lt; 5</th>
<th>PSA RR (≥50% decline)</th>
<th>PFS</th>
<th>OS</th>
<th>TTPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II Chemotherapy naïve</td>
<td>Abiraterone</td>
<td>Dexamethasone</td>
<td>42</td>
<td>yes</td>
<td>67%</td>
<td>6%</td>
<td>6%</td>
<td>38%</td>
<td>69%</td>
<td>PR</td>
<td>NR</td>
<td>225 days</td>
</tr>
<tr>
<td>Phase II Chemotherapy and CYP17 inhibitor naïve</td>
<td>Abiraterone</td>
<td>Prednisone</td>
<td>33</td>
<td>yes</td>
<td>79%</td>
<td>6%</td>
<td>7%</td>
<td>69%</td>
<td>NR</td>
<td>NR</td>
<td>169 days</td>
<td></td>
</tr>
<tr>
<td>Phase II Docetaxel-pretreated</td>
<td>Abiraterone</td>
<td>Ketoconazole use allowed</td>
<td>58</td>
<td>yes</td>
<td>38%</td>
<td>6%</td>
<td>6%</td>
<td>34%</td>
<td>patients had a CTC conversion from ≥5 to &lt;5</td>
<td>38%</td>
<td>18%</td>
<td>PR</td>
</tr>
<tr>
<td>Phase II Docetaxel-pretreated</td>
<td>Abiraterone</td>
<td>Prednisone</td>
<td>47</td>
<td>no</td>
<td>38%</td>
<td>6%</td>
<td>6%</td>
<td>27%</td>
<td>PR</td>
<td>NR</td>
<td>149 days</td>
<td></td>
</tr>
<tr>
<td>Phase III Docetaxel-pretreated</td>
<td>Abiraterone</td>
<td>Prednisone or Placebo</td>
<td>58</td>
<td>yes</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>5.6 months vs 3.6 months</td>
<td>14.8 months vs 10.9 months</td>
<td>10.2 vs 6.6 months</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: OR, objective response; CTC, circulating tumor cells; PFS, progression-free survival; OS, overall survival; TTPP, time to PSA progression; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors; PR, partial response; NA, not applicable; NR, not reported.

Until recently, patients previously treated with docetaxel had few proven treatment options. A Phase II trial tested the efficacy of abiraterone monotherapy in 47 CRPC patients previously treated with docetaxel. Prostate-specific antigen declines of ≥30%, ≥50%, and ≥90% were seen in 68%, 51%, and 15% of patients, respectively. This study demonstrated that abiraterone has potent antitumor activity in patients treated with docetaxel. The common side effects noted in this study were hypokalemia, hypertension, and fluid retention, which were able to be managed with eplerenone.

To overcome these side effects of secondary hyperaldosteronism associated with single-agent abiraterone, low-dose prednisone was added to abiraterone in another study of docetaxel-pretreated CRPC. Fifty-eight men were enrolled, of whom 27 had prior exposure to ketoconazole. Twenty-two patients (36%) experienced a ≥50% decline in prostate-specific antigen which also included 14 (45%) of 31 ketoconazole-naïve and seven (26%) of 27 ketoconazole-pretreated patients. While similar side effects were noted in this study compared with abiraterone mono-therapy, the addition of prednisone led to a reduction in the incidence of hyperaldosteronism. This study demonstrated the potential of abiraterone in combination therapy for CRPC, with the option of adding corticosteroids to manage hyperaldosteronism.
Another Phase II study assessed the efficacy of abiraterone in CRPC patients naïve to both chemotherapy and ketoconazole. Along with prostate-specific antigen, serial changes in bone scan lesions were used to assess the disease process. The study not only demonstrated the efficacy of abiraterone in CRPC, but also highlighted the discordance of bone scan intensity and disease progression. The study was designed to include 33 CRPC patients who received 1000 mg of abiraterone daily along with 5 mg of prednisone twice daily in 28-day cycles. Bone scan “flare” was defined as disease progression by a radiologist after 3 months of treatment in the context of a ≥50% decline in prostate-specific antigen, with scan improvement or stability after an additional 3 months. Median time on therapy was 63 weeks and time to prostate-specific antigen progression was 16.3 months. Twenty-two of the 23 patients (79%) showed a ≥50% decline in prostate-specific antigen levels. Overall, 26 of 33 patients (79%) showed a ≥50% decline in prostate-specific antigen. Twelve of 23 (52%) patients demonstrated a bone scan flare, of which 11 showed eventual improvement in bone scan over time. The side effects noted in the study were mainly grade 1-2. The results of the above-mentioned studies are summarized in Table 1 along with the Phase III study results.

Despite significant antitumor activity demonstrated by abiraterone, as evidenced by a declining prostate-specific antigen level, it was noted that the decline was short-lived, and the prostate-specific antigen ultimately increased. This could potentially be explained by the fact that although abiraterone blocks androgen synthesis at the CYP17 level, androgens upstream continue to accumulate and can potentially stimulate an altered androgen receptor. This was demonstrated by Zhao et al in their study of prostate cancer cells in a patient resistant to androgen ablation therapy. The androgen receptor contained a double mutation which had high affinity for cortisol/cortisone, leading to increased prostate-specific antigen production. These sorts of alterations lead to the possibility that increased hormone levels upstream of CYP17 blockade may cause prostate-specific antigen rises after an initial decline. However, more work needs to be done to explore this theory further.

Phase III studies

Based on the encouraging results of the above studies, a Phase III trial was initiated in April 2008 which randomized 1195 patients with docetaxel-refractory CRPC to either abiraterone or placebo in a 2:1 fashion; both arms received prednisone 5 mg twice daily. Based on the recommendations of an independent data monitoring committee, the study was unblinded on August 20, 2010. At this point, the abiraterone-treated patients had received a median of eight 28-day cycles, and the patients in the placebo arm had received a median four 28-day cycles. The study demonstrated a median overall survival in the abiraterone-treated arm of 14.8 months compared with 10.9 months in the placebo arm (hazards ratio 0.646, 95% confidence interval: 0.54–0.77; P < 0.0001). The abiraterone arm also yielded superior outcomes in time to prostate-specific antigen progression (10.2 months versus 6.6 months, P < 0.0001), radiographic progression-free survival (5.6 months versus 3.6 months P < 0.0001), and prostate-specific antigen declines ≥50% (confirmed, 29.1% versus 5.5%, P < 0.0001). Based on these data, abiraterone acetate was approved by the Food and Drug Administration on April 28, 2011. The recommended dose is 1000 mg daily along with prednisone 5 mg twice daily. The most common adverse effects seen on abiraterone therapy were joint discomfort, hypertension, and hypokalemia.

Ongoing studies

Currently, a Phase II study is looking at the addition of dutasteride to abiraterone in metastatic CRPC. This study will be looking at mechanisms of androgen receptor resistance to abiraterone, as well as the effects of a combination of abiraterone/dutasteride on levels of testosterone, dihydrotestosterone at baseline, and progression. It will also look at the effect of the combination on the toxicity profile and duration of prostate-specific antigen response. Another trial is underway looking at the addition of sunitinib or dasatinib to abiraterone acetate for the treatment of prostate cancer. Additional Phase III studies are investigating abiraterone in other contexts. One trial is currently looking at the comparison of abiraterone plus prednisone versus placebo and prednisone in asymptomatic or mildly symptomatic metastatic CRPC who have not received chemotherapy.

Conclusion

The recent Food and Drug Administration approvals of cabazitaxel, sipuleucel-T, and abiraterone acetate for the treatment of CRPC have provided clinicians with much needed additional treatment options for prostate cancer. The exact sequencing of these agents in CRPC treatment requires further evaluation. Both cabazitaxel and abiraterone have shown survival benefits in docetaxel-pretreated patients. The appropriate sequencing of abiraterone and cabazitaxel is not known at this time. Given the toxicity profiles of both agents, patients with significant docetaxel-associated toxicity might benefit from a break from.
cytotoxic chemotherapy and be guided towards abiraterone. Other patients with disease progression but excellent performance status and more modest chemotherapy-associated toxicity might be best served by further highly active chemotherapy. The recent approval of abiraterone and its proven efficacy in docetaxel-pretreated patients provides yet another treatment option for this patient population. Ongoing trials will evaluate whether abiraterone leads to a survival benefit in patients with chemotherapy-naive CRPC. The activity of abiraterone in prostate cancer suggests that it should also be explored as part of adjunctive hormonal therapy in localized prostate cancer to improve cure rates in high-risk patients. Localized prostate cancer trials are just beginning to be launched and will take many years to demonstrate benefits.

Disclosure
Dr Rosenberg has served as a consultant for Johnson and Johnson, Inc. Dr Rehman has no conflicts of interest to declare.

References