Abiraterone Acetate in Castrate-Recurrent Prostate Cancer

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Prostate cancer is the most common cancer in men. It is estimated that 240,890 men will be diagnosed with prostate cancer and another 33,720 men will die from the disease in the United States in 2011 (Siegel, Ward, Brawley, & Jemal, 2011).

Testosterone is the primary hormonal driver of prostate cancer growth. Androgen deprivation using luteinizing hormone-releasing hormone (LHRH) agonists or antagonists suppresses LH secretion by the anterior pituitary, which inhibits production of testosterone from the testes (Sharifi, Gulley, & Dahut, 2005). Therefore, androgen deprivation therapy (ADT) by surgical or chemical castration with LHRH agonists or antagonists is the standard front-line treatment approach for patients with recurrent prostate-specific antigen (PSA) disease or metastatic prostate cancer (Mohler, 2011).

Inevitably, prostate cancer progresses into a castrate-recurrent state. Treatment options for patients with metastatic castrate-recurrent prostate cancer (mCRPC) include secondary hormonal manipulations with nonspecific adrenal androgen inhibitors, antiandrogens, estrogens, chemotherapy, and immunotherapy (Mohler, 2011). Docetaxel and sipuleucel-T (Provenge) are US Food and Drug Administration (FDA)-approved treatment options that have demonstrated improved overall survival (OS) as front-line systemic therapy for patients with mCRPC. Recently, cabazitaxel (Jevtana) and abiraterone acetate (AA; Zytiga) have demonstrated improved OS for patients with mCRPC who had failed to respond to prior docetaxel-based chemotherapy. This article will prepare the oncology advanced practitioner to manage patients with mCRPC who are initiating or receiving AA by focusing on the mechanism of action, clinical evidence, dosing, monitoring, and adverse events (AEs) associated with AA.

A growing amount of evidence indicates that the androgen receptor (AR) signaling pathway remains active in patients with CRPC (Attard, Cooper, & de Bono, 2009; Chen, Clegg, & Scher, 2009). Small amounts of testosterone produced by the adrenal glands are not inhibited by castration. Additionally, several other pathways may become upregulated in the CRPC state, including an upregulation of androgen biosynthesis enzymes that increases intratumoral androgen concentrations, overexpression of the AR, mutations of the AR leading to increased nonandrogen binding and activation, and ligand-independent activation of the AR.

Cytochrome P450 c17 (CYP17) is a critical enzyme in the production of cortisol and testosterone. Ketoconazole is a nonspecific, reversible inhibitor of CYP17 components, 17α-hydroxylase and 17,20-lyase, that is used as a second-line hormonal manipulation for patients with mCRPC (off-label indication; Hotte & Saad, 2010). However, ketoconazole is erratically absorbed and associated with increased liver enzymes, multiple drug interactions, and adrenal insufficiency, necessitating concomitant administration of a corticosteroid (Watkins, Atkinson, & Pagliaro, 2011). Recently FDA approved, AA is an irreversible CYP17 inhibitor with 10 to 30 times the potency of ketoconazole. In addition, AA has improved bioavailability, decreased toxicity profile, and fewer drug-drug interactions as compared with ketoconazole.

Pharmacology and Mechanism of Action

Abiraterone acetate is an orally bioavailable prodrug that is rapidly converted to abiraterone in vivo by deacetylation (Agarwal, Hutson, Vogelzang, & Sonpavde, 2010). Chemical structure alterations make AA a more specific, irreversible CYP17 inhibitor with increased potency and improved bioavailability as compared with ketoconazole. The drug is hepatically metabolized into two main inactive metabolites. The mean terminal half-life is 12 hours, and approximately 77% of the administered dose is excreted in the feces.

Abiraterone acetate inhibits the conversion of progesterone and pregnenolone to androstenedione and dehydroepiandrosterone (DHEA) in testicular, adrenal, and prostate tumor tissues (Figure 1). Androstenedione and DHEA are weak androgens that are eventually converted to the more potent androgens, testosterone and dihydrotestosterone. CYP17 inhibition also causes increased mineralocorticoid production, leading to symptoms of secondary mineralocorticoid excess, which account for many of the AEs observed with AA treatment. These symptoms include edema and hypertension. As a result, patients receiving AA in clinical trials were also treated with oral eplerenone (50–200 mg daily; selective aldosterone blocker) or a corticosteroid such as oral prednisone (5 mg twice daily).

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Clinical Trials

CHEMOTHERAPY-NAIVE PATIENTS

Two phase I clinical trials conducted in men with chemotherapy-naive mCRPC helped establish the safety and dosing of AA (Attard et al., 2008; Ryan et al., 2010). Prostate-specific antigen responses and partial response (PR) as determined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria were observed in both clinical trials. Dosing cohorts ranged from 250 to 2,000 mg per day. Abiraterone acetate was well tolerated, with hypertension, hypokalemia, and lower-limb edema seen as the most common AEs; these effects were controlled with eplerenone. Grade 3 or 4 toxicities were rare, and there were no dose-limiting toxicities. Although a clinical maximum-tolerated dose was not identified, oral AA 1,000 mg daily was selected as the target dose due to a plateau in clinical and pharmacodynamic effects at higher doses.

In the phase II expansion trial, by Attard and colleagues, of 42 chemotherapy-naive patients with mCRPC, 28 (67%) patients achieved a PSA response of more than 50% (Attard et al., 2009). Nine (37.5%) of 24 patients with measurable disease had a PR by RECIST criteria. The median time to PSA progression (TTPP) was 225 days (95% confidence interval [CI]: 162–287 days). Exploratory analysis of the phase I/II trials demonstrated that the addition of dexamethasone at disease progression reversed resistance in 33% of 39 patients, regardless of prior dexamethasone exposure.

The results of the phase II clinical trial by Ryan and colleagues in 33 chemotherapy- and ketoconazole-naive patients with progressive mCRPC demonstrated PSA declines of ≥ 50% in 26 (79%) patients (Ryan et al., 2011). Undetectable PSA levels (≤ 0.1 ng/mL) occurred in two patients. Median time on therapy and TTPP were 63 weeks and 16.3 months, respectively. All patients were receiving an LHRH agonist and were

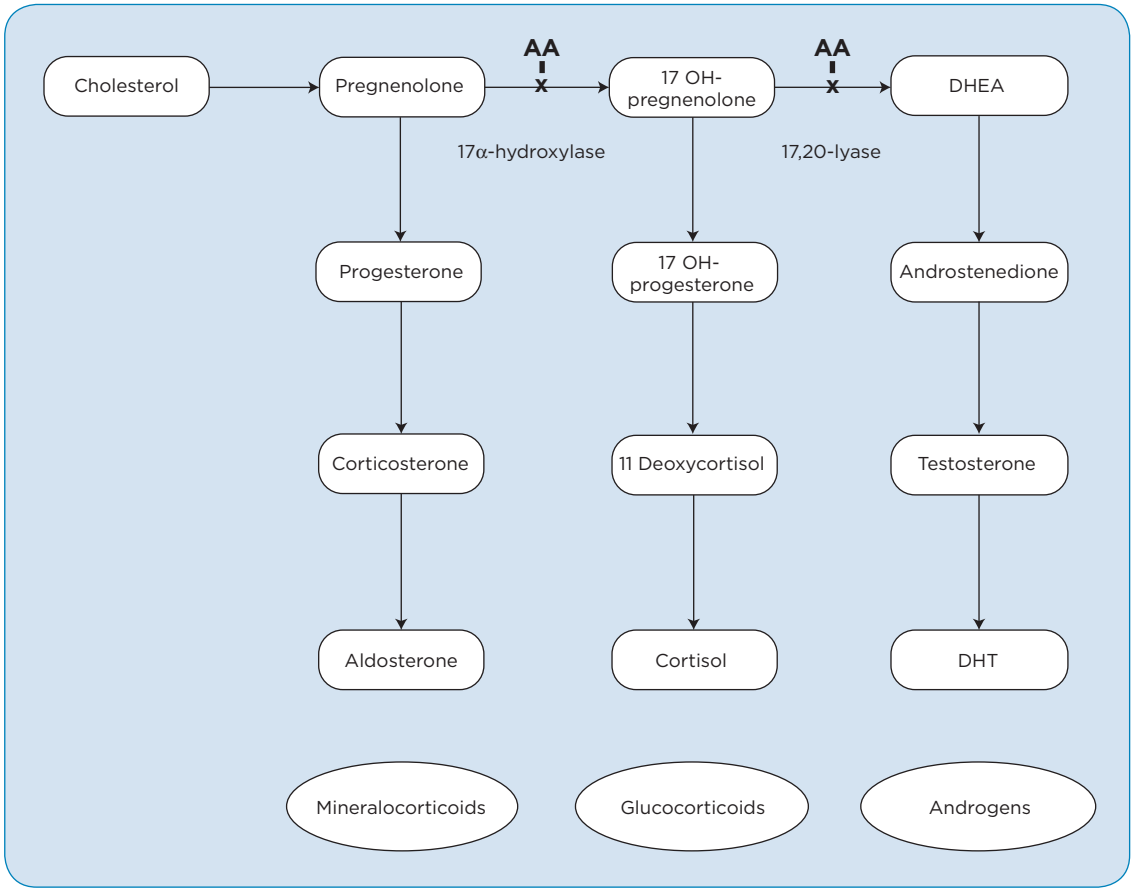

Figure 1. Steroid biosynthesis pathway and key steps. The enzyme CYP17 (17α-hydroxylase and 17,20-lyase) is inhibited by abiraterone acetate, which decreases levels of androgens and glucocorticoids while mineralocorticoid levels rise. AA = abiraterone acetate; DHEA = dehydroepiandrosterone; DHT = dihydrotestosterone.

treated with oral AA 1,000 mg once daily with oral prednisone 5 mg twice daily.

PREVIOUSLY TREATED PATIENTS

Two phase II studies have demonstrated the efficacy of AA in patients with progressive mCRPC who were previously treated with docetaxel-based chemotherapy. A phase II clinical trial by Reid and colleagues treated 47 patients with progressive mCRPC who had received prior docetaxel chemotherapy with oral AA 1,000 mg daily (Reid et al., 2010). The median baseline PSA was 403 ng/mL (range: 9.9–10,325 ng/mL). Eight of the 47 patients had received prior ketoconazole, and 18 patients were receiving concomitant corticosteroids. Prostate-specific antigen declines of more than 50% and 90% were demonstrated in 24 (51%) and 7 patients (15%), respectively. Furthermore, 6 (17%) of 35 patients who had measurable disease demonstrated PR by RECIST criteria, and 23 patients (66%) had stable disease. The median TTPP was 169 days (95% CI: 113–281 days).

A second phase II study of 58 men with mCRPC and treatment failure, with up to two cytotoxic regimens including docetaxel, was reported by Danila and colleagues (2010). Patients were treated with oral AA 1,000 mg once daily and oral prednisone 5 mg twice daily. A total of 27 men (47%) had received prior ketoconazole. Prostate-specific antigen responses were better in ketoconazole-naive patients, with declines of more than 50% and 90% demonstrated in 14 (45%) and 9 patients (29%), respectively, compared with 7 (26%) and 0 patients who had previously received ketoconazole. Partial responses by RECIST criteria were observed in 4 of 22 (18%) evaluable patients with measurable disease. The median TTPP was 169 days (95% CI: 82–200 days); ketoconazole-naive patients had longer

TTPP (198 and 99 days, respectively; p = NS). There was a lower incidence of fluid retention (< 10%), hypokalemia (< 5%), and hypertension (< 5%) with the up-front addition of prednisone compared with prior clinical trials. Fatigue and nausea were the most common AEs reported; no grade 4 AEs were noted.

The results of a landmark phase III trial of oral AA 1,000 mg daily compared with placebo (both groups received oral prednisone 5 mg twice daily) in 1,195 patients with progressive mCRPC previously treated with docetaxel were recently reported (de Bono et al., 2011). Patients were randomized 2:1 to AA or placebo. The primary endpoint of this trial was OS.

At the preplanned interim analysis, the independent data monitoring committee recommended unblinding the trial and allowing placebo patients to cross over to AA with prednisone therapy because the improvement of survival exceeded the predetermined boundary for stopping. Abiraterone acetate significantly prolonged OS compared with placebo (14.8 vs. 10.9 months; HR 0.65, 95% CI: 0.54–0.77), and this was consistent across all subgroups. Analysis of secondary endpoints, including PSA response (38% vs. 10.1%), TTPP (10.2 vs. 6.6 months), objective response rate by RECIST criteria (14% vs. 3%), and radiographic progression-free survival (5.6 vs. 3.6 months), all significantly (p < .001) favored AA over placebo. The final analysis of the phase III clinical trial was recently presented and demonstrated a greater improvement in OS with longer follow-up (AA 15.8 vs. placebo 11.2 months; HR = 0.74, p < .0001) (Scher et al., 2011).

Adverse Effects

In the large phase III clinical trial, common AEs that occurred with similar frequency in both treatment groups included fatigue, back pain, nausea, constipation, bone pain, and arthralgia (de Bono et al., 2011). Most of these events were grade 1 or 2. Urinary tract infections were more frequent in the AA group (12% vs. 7%; p = .02). Patients treated with AA had an increased incidence of AEs associated with secondary mineralocorticoid excess, including fluid retention and edema (31% vs. 22%; p = .04), hypokalemia (17% vs. 8 %; p < .001), and hypertension (10% vs. 8%; p = NS). A grade 4 elevation of aminotransferase level led to an early protocol amendment to monitor liver function tests more frequently during the first 12 weeks of treatment. However, liver-function test abnormalities occurred at a similar rate in AA and placebo groups (any grade, 10% vs. 8%; grade 3 or 4, 3.5% vs. 3%, respectively).

Cardiac events, including tachycardia and atrial fibrillation, occurred more frequently in patients receiving AA (13% vs. 11%; p = .14). Severe grade 3 or 4 toxicities were uncommon and no individual grade 4 event occurred in more than 2% of patients in either treatment group. The incidence of AEs leading to treatment discontinuation, dose modification, or interruption was similar in patients treated with AA or placebo.

Role in Therapy for Prostate Cancer

Abiraterone acetate with prednisone demonstrated a significant improvement in OS for patients with mCRPC who had progressed on prior docetaxel-based therapy; as such, AA was approved by the FDA for this indication. The outcomes with this novel therapy demonstrate that the AR in the castrate-recurrent state is still a very active pathway in prostate cancer pathogenesis. This challenges the conventional theory and distinction of advanced CRPC as hormone refractory, androgen independent, or castrate resistant. Currently, there are a number of androgen-axis–targeting therapies in clinical investigation.

The treatment landscape for men with mCRPC is vastly changing with other recent additions, including sipuleucel-T in patients with CRPC and cabazitaxel in patients with progressive mCRPC post-docetaxel therapy (Mohler, 2011). Currently, AA represents a convenient oral treatment option with minimal side effects as compared with cabazitaxel for mCRPC patients previously treated with docetaxel. Despite the significant outcomes in the recently reported phase III trial, the appropriate sequence of AA and cytotoxic chemotherapy has not been established.

As demonstrated in phase I and II trials, AA appears to have significant clinical effects in the chemonaive mCRPC setting as well. A phase III trial in the chemonaive mCRPC setting completed accrual of a planned 1,000 patients in 2009, with a primary endpoint of OS. If AA extends survival in this setting comparably to the phase III post-docetaxel trial, AA will likely be the preferential treatment in the chemonaive setting. A clinical trial of the combination of AA with ADT

and radiation therapy for locally advanced prostate cancer is ongoing. It is likely that AA, with its minimal AE profile, will be investigated further in sequencing and combination trials with cytotoxic, biologic, and other androgen-axis–targeted therapies.

Implications for the Advanced Practitioner

The novel androgen synthesis inhibitor AA is a convenient, well-tolerated, oral treatment option currently FDA approved in combination with prednisone for patients with progressive mCRPC who have received prior docetaxel-based chemotherapy. The use of AA in patients with mCRPC is expected to be substantial; therefore, it is imperative that the advanced practitioner in oncology be prepared to counsel patients, prescribe, monitor, and manage AEs associated with AA. The recommended dose of oral AA is 1,000 mg daily in combination with oral prednisone 5 mg twice daily (Centocor Ortho Biotech Inc., 2011).

Exposure to AA is increased approximately 10-fold when administered with a high-fat meal; therefore, AA should be taken on an empty stomach. Patients should be counseled not to eat at least 2 hours before taking AA and for at least 1 hour after. The starting dose of oral AA should be reduced to 250 mg daily for patients with baseline moderate hepatic insufficiency (Child-Pugh class B), and patients with severe hepatic impairment should not receive AA. No dosage adjustment is necessary for patients with renal impairment.

Adverse events associated with AA are usually mild (grade 1 or 2), with a low rate of drug discontinuation or dose reduction seen in the phase III clinical trial. Symptoms of secondary mineralocorticoid excess, including hypertension, hypokalemia, and fluid retention, were significantly more common in patients treated with AA in clinical trials and were largely abrogated with prednisone. The addition of eplerenone (50–200 mg oral daily) was beneficial in controlling these AEs in clinical trials. Spironolactone was not used due to its potential to bind and activate the AR (Luthy, Begin, & Labrie, 1988). The advanced practitioner should be sure to monitor blood pressure, serum potassium levels, and symptoms of fluid retention at least monthly.

Hepatotoxicity has been reported in patients treated with AA. Across all clinical trials, elevations of serum transaminases (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] increases of greater than 5× the upper limit of normal) were reported in 2.3% of patients, typically occurring within the first 3 months of treatment. Patients should have ALT, AST, and bilirubin levels measured prior to starting treatment with AA, every 2 weeks for the first 3 months of treatment, and monthly thereafter. If a patient develops hepatotoxicity during treatment, the clinician should withhold AA therapy until patient recovery. Retreatment may be initiated at a reduced dose of oral AA 750 mg daily with the first occurrence and 500 mg daily with the second occurrence, with discontinuation if there are subsequent reccurrences. Abiraterone acetate should be discontinued if patients develop severe hepatotoxicity.

The most common AEs resulting in drug discontinuation in the phase III clinical trial were increased serum transaminases, urosepsis, and cardiac failure (each in < 1% of patients). Patients should be counseled to monitor and reports signs and symptoms of urinary tract infections (fever, chills, hematuria, nocturia, polyuria, foul odor, etc.)

Abiraterone acetate is an inhibitor of CYP2D6; therefore, concomitant use of AA and medications metabolized via the CYP2D6 pathway with a narrow therapeutic index should be avoided. Abiraterone acetate is a substrate of CYP3A4. The effects of strong CYP3A4 inducers or inhibitors on AA pharmacokinetics have not been studied, thus patients should avoid concomitant use. Unless they have had previous orchiectomy, all patients should be maintained on an LHRH agonist or antagonist while receiving AA. Because treatment with AA may be associated with substantial cost,[1] patient assistance programs are available for qualified patients (see ZytigaOne; Janssen Biotech, 2011).

Summary

The treatment paradigm of mCRPC is changing swiftly with the FDA approval of sipuleucel-T, cabazitaxel, and most recently AA with prednisone. In a landmark phase III clinical trial, AA demonstrated extended OS compared with place-

[1]$6,000 (average wholesale price) per month's supply (Thomson Reuters, 2011).

bo in patients with progressive mCRPC previously treated with docetaxel chemotherapy (de Bono et al., 2011). Compared with cabazitaxel, abiraterone acetate is a convenient, well-tolerated treatment option in this setting. Ongoing clinical trials are evaluating AA in various stages of prostate cancer as well as in different combinations and sequences. It is likely that the use of AA or similar therapies will be substantial in prostate cancer. The advanced practitioner in oncology will need to be adept at appropriately prescribing, monitoring, and managing patients treated with AA.

DISCLOSURE

The authors have no conflicts of interest to disclose.

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