CLINICAL INVESTIGATION

Abiraterone acetate for metastatic castration-resistant prostate cancer post-docetaxel

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Abiraterone acetate (AA) 1000-mg daily, a selective irreversible androgen biosynthesis inhibitor of cytochrome P450 c17 (CYP17) enzyme, is used in combination with prednisone 10-mg daily to treat docetaxel-treated patients with metastatic castration-resistant prostate cancer (mCRPC). Several studies have demonstrated the safety and efficacy of this compound in men with mCRPC. Interim results from a randomized Phase III study in CRPC patients previously treated with docetaxel demonstrated an improvement in overall survival (OS) for the AA–prednisone group versus the placebo–prednisone group (14.8 vs 10.9 months; hazard ratio [HR] = 0.646, p < 0.001). An updated survival analysis showed an improvement in median OS in the treatment group (15.8 vs 11.2 months, HR = 0.740, p < 0.0001). The objective is to critically analyse the emerging role of AA as novel, orally administered androgen synthesis inhibitor and its place for treatment of mCRPC patients following failure of docetaxel chemotherapy. This manuscript reviews the pharmacology, clinical evidence data and use of AA in post-docetaxel patients with mCRPC.

Keywords: abiraterone acetate • castration-resistant prostate cancer • CYP17 inhibitors • prostate cancer

Prostate cancer (PCa) is the most common non-skin cancer and the second leading cause of cancer mortality in men in most western countries. Androgen deprivation therapy is widely accepted as initial treatment for patients with advanced PCa. Although most patients respond well to this therapy, in most cases the tumor eventually progresses despite continued therapy, known as castration-resistant prostate cancer (CRPC) [1]. Docetaxel-based chemotherapy represents the standard first-line treatment in CRPC patients, with a median survival advantage of 2–3 months [2]. A large number of agents are currently under investigation for CRPC. Recently, four new agents with different mechanisms of action have been approved by the US FDA for treatment of CRPC: sipuleucel-T, cabazitaxel, denosumab and abiraterone acetate (AA [ZYTIGA®; Janssen-Cilag International NV, Beerse, Belgium]). A better understanding of the biology of CRPC has demonstrated two important mechanisms:

- The androgen receptor (AR) is overexpressed in many of the CRPC tumor cells
- PCa cells are capable of producing steroids, activating the AR [1,3].

These observations clearly demonstrate that the AR is still the key therapeutic target. In April 2011, AA in combination with prednisone was approved by the FDA for the treatment of mCRPC patients previously treated with docetaxel [4], followed by approval in the European Union in September of the same year.

Background

▪ Indications

AA is indicated with prednisone or prednisolone for the treatment of metastatic castration-resistant prostate cancer in adult men whose disease has progressed

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on or after a docetaxel-based chemotherapy regimen [101].

▪ Pharmacology

Mechanism of action

Androgen deprivation therapy decreases androgen production in the testes but does not affect androgen production by the adrenals or in the tumor. AA is converted *in vivo* to abiraterone, a potent and selective irreversible androgen biosynthesis inhibitor of cytochrome P450 c17 (CYP17) enzyme blocking 17 alpha-hydroxylation and C17,20-lyase activity (Figure 1). This results in blocking the androgen synthesis by the adrenal glands and testes and within the prostate tumor [5–8]. Although ketoconazole also inhibits CYP17, it is less selective and AA has an inhibitory effect on CYP17 that is 10–30 times greater [5,8].

Pharmacokinetic properties

Intake of AA with food has the potential to result in increased and highly variable drug exposures and results in up to a tenfold AUC and up to a 17-fold (C_{max}) increase in mean systemic exposure of abiraterone, depending on the fat content of the meal. Therefore, AA should be taken on an empty stomach. Following oral administration of AA in the fasting state, the time to reach maximum plasma abiraterone concentration is approximately 2 h. In the circulation, abiraterone is highly bound (to an extent of >99%) to the human plasma proteins, alpha-1-acid glycoprotein and albumin. The mean half-life of abiraterone in plasma is approximately 15 h based on data from healthy subjects. Drug excretion is largely through feces, with approximately 5% appearing in the urine [101].

Clinical evidence

▪ Phase I studies

AA was found to be safe and effective in lowering serum androgen levels in two Phase I studies [9,10] conducted in both ketoconazole-exposed and ketoconazole-naive patients. Doses of AA from 250 to 2000 mg were used. A maximum tolerated dose was not reached. Due to a plateau effect in pharmacokinetics noted at 1000 mg, this dose was chosen for the Phase II studies. The adverse events (AEs) – mainly hypokalemia, hypertension and fluid retention – were easily managed with the mineralocorticoid receptor antagonist eplerenone [11].

Phase II and III studies are summarized in Table 1.

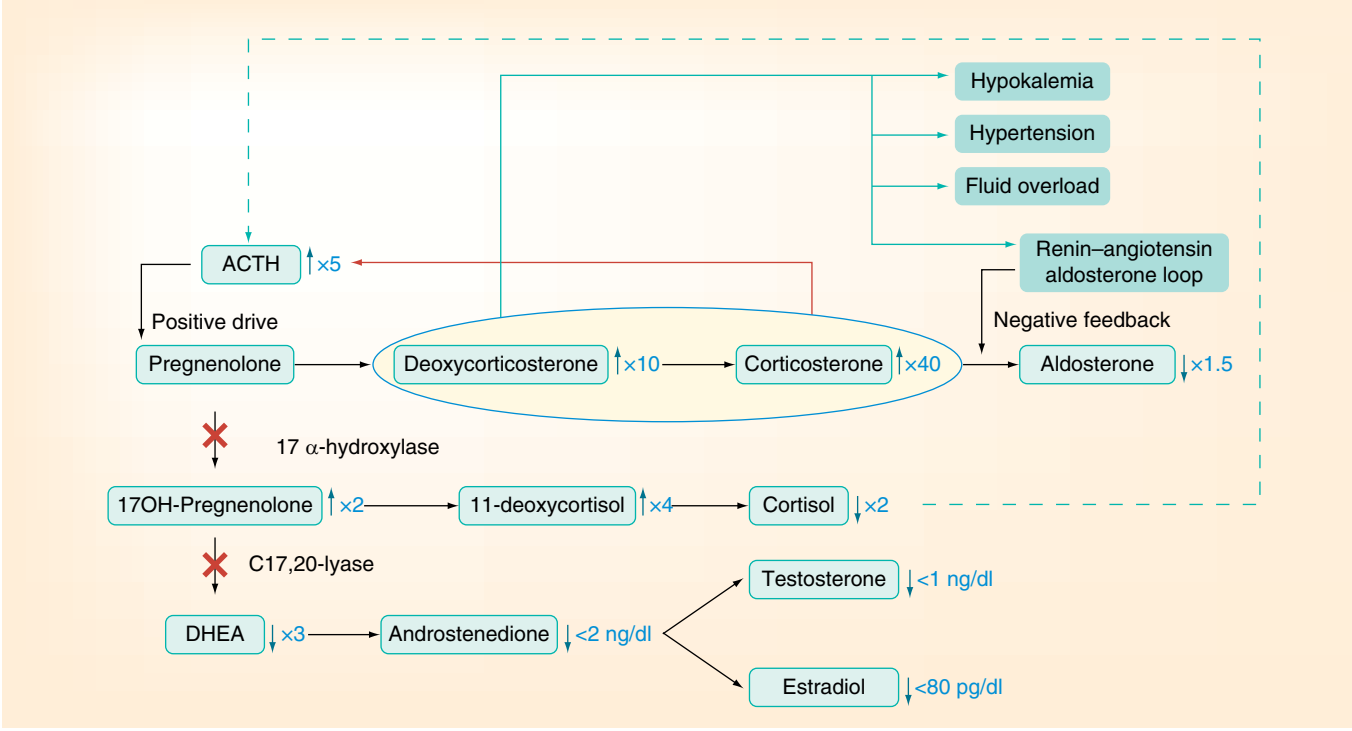

Figure 1. Effect of abiraterone on the steroid synthesis pathway. Abiraterone inhibits 17α-hydroxylase, which results in a reduction in serum cortisol and a consequent increase in ACTH that drives the steroid biosynthesis pathway: levels of deoxycorticosterone and corticosterone increase. Abiraterone also inhibits C17,20-lyase, which results in a reduction of DHEA, androstenedione and testosterone. The presented mechanism of action of abiraterone is without adding prednisone.
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Table 1. Summary of Phase II and III study results of abiraterone acetate.

Study	Prior treatment	Agents used	No.	Outcome	Expected toxicity (%)	Ref.
Phase II						
Attard *et al.* (2009)	Chemotherapy naive	AA dexamethasone	42	PSA decline ≥50% = 67% OR = 38% TTPP = 225 days	Hypokalemia: 88 Hypertension: 40 Fluid retention: 31	[12]
Reid *et al.* (2010)	Docetaxel-pretreated Prior ketoconazole allowed (naive 17%)	AA	47	PSA decline ≥50% = 51% OR = 27% TTPP = 169 days	Hypokalemia: 55 Hypertension: 17 Fluid retention: 15	[13]
Danila *et al.* (2010)	Docetaxel-pretreated Prior ketoconazole allowed (naive 52%)	AA and prednisone	58	PSA decline ≥50% = 36% OR = 18% TTPP = 169 days	Hypokalemia: 5 Hypertension: 4 Fluid retention: 9	[14]
Ryan *et al.* (2011)	Chemotherapy- and ketoconazole-naive	AA and prednisone	33	PSA decline ≥50% = 79% OR = 69% TTPP = 16.3 months	Hypokalemia: 21 Hypertension: 18 Fluid retention: 24	[15]
Phase III						
de Bono *et al.* (2011)	Docetaxel-pretreated No prior ketoconazole allowed	AA and prednisone vs placebo and prednisone	1195	PSA decline ≥50% = 29 vs 6% OR = 14 vs 3% TTPP = 10.2 vs 6.6 months OS = 14.8 vs 10.9 months PFS = 5.6 vs 3.6 months	Hypokalemia: 17 vs 8 Hypertension: 10 vs 8 Fluid retention: 31 vs 22	[4]

AA: Abiraterone acetate; OR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PSA: Prostate-specific antigen; TTPP: Time to PSA progression.

Phase II studies

Attard *et al.* carried out an open-label, single-arm Phase II extension [12] to their original Phase I study [9] to examine the efficacy of AA monotherapy at a daily dose of 1000 mg in 42 chemotherapy-naive CRPC patients in 28-day cycles. Patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. Dexamethasone 0.5 mg was added if a patient's disease progressed. In the Phase I study, dexamethasone addition suppressed high levels of ACTH and steroids upstream of CYP17 and reversed resistance to AA [9]. The study met its primary end point, demonstrating a decline in prostate-specific antigen (PSA) of ≥50% in 28 (67%) patients after 12 weeks of treatment. PSA declines of ≥30% and ≥90% were observed in 30 (71%) and eight (19%) patients, respectively. In total, 24 patients had measurable disease on computed tomography scan according to the Response Evaluation Criteria in Solid tumors (RECIST) and nine (37.5%) patients had tumor regression that constituted a partial response. The median follow-up time was 505 days with a median time to PSA progression (TTPP) on AA alone of 225 days. Of the 30 patients who were assessable for magnitude of PSA decline, 10 had a ≥50% decline in PSA after initiation of dexamethasone. Hypokalemia, hypertension and fluid retention were easily managed with eplerenone except for three patients who received glucocorticoid replacement for symptomatic fluid overload [12].

Reid *et al.* carried out an open-label, single-arm Phase II study in which they tested the efficacy of AA monotherapy at a daily dose of 1000 mg in 47 docetaxel-treated CRPC patients in 28-day cycles [13]. Eight out of 47 patients received prior ketoconazole. The median duration of therapy was 24 weeks and 12 (25.5%) patients remained on the study at least 48 weeks. The primary end point was to determine the proportion of patients who experienced a ≥50% decline in PSA, and this was observed in 24 (51%) patients. PSA declines of ≥30% and ≥90% were achieved in 32 (68%) and seven (15%) patients, respectively. Partial response per RECIST criteria was observed in 27% of patients. The ECOG PS improved by one point in 11 patients, and remained stable in 35 patients. The median TTPP was 169 days. Eleven (41%) of 27 patients had a decline in circulating tumor cells (CTCs) from ≥5 to <5 and 18 (67%) had a ≥30% decline in CTCs after starting treatment. The expected AEs were easily managed with eplerenone or a low-dose glucocorticoid [13].

To overcome the treatment-related AEs of AA, Danila *et al.* added prednisone 5-mg twice daily in an open-label, single-arm Phase II study that enrolled 58 mCRPC patients previously treated with docetaxel [14]. A total of 27 of the 58 patients (48%) had also previously failed to respond to ketoconazole. The study met its primary end point, demonstrating a PSA decline ≥50% at 12 weeks post-therapy in 22 (36%) patients, including 14 (45%) of

31 ketoconazole-naive and seven (26%) out of 27 ketoconazole-treated patients. The median TTPP was 99 and 198 days, respectively. The overall median TTPP was 169 days. Soft tissue lesions showed a partial response in four (18%) of 22 patients according to RECIST criteria. An improvement in the ECOG PS was seen in 16 (28%) patients. CTC counts improved in ten out of 29 (34%) patients with unfavourable CTC count at baseline (≥ 5 cells/7.5 ml blood). AEs (primarily grade 1 or 2) were similar as in previous studies but the incidence was significantly reduced by adding low-dose prednisone [14].

Ryan *et al.* reported the first Phase II study with AA and prednisone that treated chemotherapy- and ketoconazole-naive CRPC patients [15]. In total, 33 CRPC patients received AA 1000-mg daily with 5-mg prednisone twice daily in 28-day cycles. The study met its primary end point, demonstrating a PSA decline ≥50% at 12 weeks in 22 (67%) patients. Overall, 26 (79%) patients showed a PSA decline ≥50%. Median duration of therapy was 63 weeks. Median TTPP was 16.3 months. Of 13 patients with measurable disease, nine (69%) had a partial response, and three (23%) had stable disease. Bone scans and tumor imaging studies were repeated every three cycles. The study underlined the discordance between bone scan intensity and disease progression. Bone scan 'flare' was defined as apparent disease progression as seen in the bone scan after 3 months of treatment (based on the radiologist's interpretation), in seeming contradiction to the observed PSA decline ≥50%, with improvement or stability of metastases in a follow-up scan taken 3 months later. Of the 23 patients with a positive baseline scan and a PSA decline ≥50% at 3 months, 12 patients showed disease progression on their bone scan at 3 months. Of these 12 patients only one showed progression on the scan at 6 months. Of the 11 (48%) patients with bone scan flare, seven and four patients showed stable and improved scans at 6 months, respectively. This phenomenon could lead to premature discontinuation of potentially effective therapy and it emphasizes the need for caution in using bone scans as the basis for determining disease progression [15]. The Prostate Cancer Working Group 2 defined disease progression per bone scan as two or more new lesions in the first follow-up scan 12 or more weeks after the start of therapy that are confirmed on a second scan at least 6 weeks later [16]. The types of AEs were consistent with those in previous studies and were most often grade 1 or 2 [15].

▪ Phase III studies

In April 2011 the FDA and in September 2011 the European Medicines Agency approved the use of AA for the treatment of chemotherapy-treated CRPC patients, on the basis of the results of the COU-AA-301 Phase III study [4]. The study randomly assigned, in a 2:1 ratio, 1195 docetaxel-treated patients to receive 1000 mg AA along with 5-mg prednisone twice daily (797 patients) versus placebo and the same dose of prednisone (398 patients). The median treatment duration was 8 and 4 months, respectively. The median follow-up in the overall study population was 12.8 months. The study met its primary end point, demonstrating an improved OS with AA and prednisone compared with placebo and prednisone (14.8 vs 10.9 months; HR = 0.646; p < 0.001) [4]. An updated survival analysis showed an improvement in median OS in the treatment group (15.8 vs 11.2 months; HR = 0.740) [17,101]. Secondary end points favoured the treatment group; PSA decline ≥50% in 29% vs 6% (p < 0.001), TTPP (10.2 vs 6.6 months; p < 0.001) and progression-free survival on the basis of radiographic evidence (5.6 vs 3.6 months; p < 0.001), indicating that advanced CRPC remains hormone driven. Hypokalemia, hypertension and fluid retention were more frequently reported in the treatment group than in the placebo group (Table 1). Cardiac events (primarily grade 1 or 2; 13 vs 11%, p = 0.14), tachycardia (grade 1 or 2; 3 vs 2%, p = 0.22), atrial fibrillation (grade 3 or lower; 2 vs 1%, p = 0.29) were slightly more common in the treatment group than in the placebo group. Fatal cardiac events were similar in both groups (1.1 vs 1.3%). The risk for grade 1 or 2 urinary tract infections was slightly greater in the treatment group (12 vs 7%; p = 0.02). The most common AEs occurred at a similar frequency in the two groups: fatigue, back pain, nausea, constipation, bone pain and athralgia. Abnormalities in the results of liver function tests were equivalent in both groups [4].

Dosing & administration

The recommended dose of AA is 1000 mg (four 250-mg tablets) administered orally once daily at least 1 h before and 2 h after a meal, in combination with 10-mg daily oral prednisone. For patients with hepatotoxicity see recommendations in the section titled 'Use in specific populations' [101].

Safety & tolerability

▪ Adverse events

AA may cause hypertension, hypokalemia and fluid retention (edema) due to mineralocorticoid excess resulting from blockade of CYP17. In the COU-AA-301 Phase III study, these AEs occurred in significantly more AA–prednisone- than in placebo–prednisone-treated patients. AEs were most often grade 1 or 2. The percentages of grades 3 and 4 hypokalemia in this study were 3 versus 1% and <1 versus 0% in AA-prednisone versus placebo-prednisone-treated patients, respectively. The

Table 2. Adverse reactions identified in clinical studies.

Disorders	Adverse reactions
Infections and infestations	Very common: urinary tract infection
Endocrine disorders	Uncommon: adrenal insufficiency
Metabolism and nutrition disorders	Very common: hypokalemia Common: hypertriglyceridemia
Cardiac disorders	Common: cardiac failure†, angina pectoris, arrhythmia, atrial fibrillation, tachycardia
Vascular disorders	Very common: hypertension
Hepatobiliary disorders	Common: alanine aminotransferase increased
General disorders and administration site conditions	Very common: edema peripheral

†Cardiac failure also includes congestive heart failure, left ventricular dysfunction and ejection fraction decreased.
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness [101].

percentages of grade 3 hypertension were 1 versus <1% in AA–prednisone versus placebo–prednisone-treated patients, respectively. No grade 4 hypertension occurred [4]. These AEs were well managed with a corticosteroid that suppresses ACTH drive. There was a low rate of drug discontinuation or dose reduction. The incidence of AEs resulting in drug discontinuation was similar in both groups (19 and 23%, respectively, p = 0.09) [4].

AEs observed during clinical studies are listed by frequency category in Table 2. Frequency categories are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000). Table 3 presents the grade 3 and 4 AEs according to Common Terminology Criteria for Adverse Events (version 3.0) that occurred in AA-prednisone-treated patients [101].

▪ Special warnings & precautions for use

AA should be used with caution and monitored in patients with a history of cardiovascular disease and conditions that increase blood pressure, hypokalemia (e.g., those on cardiac glycosides) or fluid retention (e.g., those with heart failure), severe or unstable angina pectoris, recent myocardial infarction or ventricular arrhythmia, and those with severe renal impairment. The safety of AA in patients with left ventricular ejection fraction <50% or New York Heart Association class III or IV heart failure has not been established. AA should be used with caution and monitored for signs of hepatotoxicity and adrenocortical insufficiency. The use of AA in combination with a glucocorticoid could increase the effect of decreased bone density seen with mCRPC. Lower response rates to AA might be expected in patients previously treated with ketoconazole for PCa. Patients with the Lapp lactase deficiency or glucose–galactose malabsorption should not take AA as the drug contains lactose. The use of AA should be taken into consideration by patients on a controlled sodium diet as the drug contains more than 1-mmol (27.2 mg) sodium per dose of 1000 mg [101].

▪ Drug interactions

Due to its specificity, AA is not expected to cause any major problems with drug interactions. Concomitant use of strong CYP3A4 inhibitors (e.g., itraconazole, ritonavir, indinavir, nelfinavir and voriconazole) or inducers (e.g., phenytoin, carbamazepine and phenobarbital) or CYP2D6 substrates that have a narrow therapeutic index (e.g., thioridazine) should be avoided or considered with caution [101].

▪ Use in specific populations

Patients with renal impairment

No dosage adjustment is required for patients with renal impairment. However, there is no clinical experience and caution is advised in patients with PCa and severe renal impairment [101].

Table 3. Grade 3 and 4 adverse events according to the Common Terminology Criteria for Adverse Events (version 3.0) in patients treated with abiraterone acetate.

Adverse event	Grade 3 (%)	Grade 4 (%)
Hypokalemia	3	<1
Urinary tract infection	2	<1
Peripheral edema	1	<1
Alanine aminotransferase increased	1	0
Hypertension	1	0
Cardiac failure	1	<1
Atrial fibrillation	1	0
Hypertriglyceridemia	<1	0
Angina pectoris	<1	0

Terminology Criteria for Adverse Events taken from [101].

Patients with hepatic impairment

AA should be avoided in patients with preexisting moderate or severe hepatic impairment [101].

Patients with hepatotoxicity

Before starting treatment serum transaminase levels should be measured, every 2 weeks for the first 3 months of treatment, and monthly thereafter. For patients who develop hepatotoxicity (alanine aminotransferase five-times the upper limit of normal), treatment should be interrupted. Retreatment may be started at return of liver function tests to the patient's baseline at a lower dose of 500-mg once daily. If patients develop severe hepatotoxicity (alanine aminotransferase 20-times the upper limit of normal), treatment should be discontinued and patients should not be retreated [101].

Duration of therapy

The median treatment duration in the COU-AA-301 Phase III study was 8 months for the AA prednisone group compared with 4 months for the placebo–prednisone group [4]. It is mportant that the drugs are given sufficient time to work and are not discontinued prematurely. Early changes in PSA or imaging after initiation of therapy can be misleading. A minimum of 12 weeks of treatment is generally advised [18]. The Phase II study by Ryan *et al.* indicates that at least some men will have a short-term bone scan flare as a consequence of starting treatment with AA [15]. The clinical significance of the bone scan flare with AA and the impact on patient management and interpretation of the results are still to be fully evaluated.

Selection of therapy for CRPC

In defining the most appropriate treatment for individual patients with CRPC, one should consider the life expectancy, the functional status and the ability of a patient to tolerate the potential side effects of the drugs [19]. Docetaxel chemotherapy improves symptoms and prolongs survival among men with CRPC. However, not all patients respond to docetaxel and such patients are exposed to significant toxicity without direct benefit [2,20]. Patients may be rechallenged with docetaxel after response to first-line docetaxel [21]. However, the results of this approach are not well studied. Alternative options include cabazitaxel (Sanofi-Aventis, Paris, France) and sipuleucel-T (Dendreon, Seattle, WA, USA). Both treatments have been associated with an improved OS in docetaxel-resistant CRPC. Nevertheless, cabazitaxel is associated with serious toxicity and sipuleucel-T is not yet available on the European market. AA with prednisone is a good alternative for retreatment with docetaxel or other chemotherapy as it prolongs survival and has a good safety profile [4]. Moreover, a subanalysis of the COU-AA-301 Phase III study revealed that treatment of docetaxel-treated mCRPC patients with AA and prednisone offered pain relief and delay of pain recurrence while preventing skeletal-related events [22]. In addition, AA plus prednisone delayed fatigue progression and yielded better patient-reported fatigue outcomes compared with placebo plus prednisone. It also improved fatigue more rapidly than placebo plus prednisone [23], as well as improving functional status and delaying the time to functional decline [24]. These recent findings have an impact on the quality of life for mCRPC patients. There are insufficient data to determine which agent, AA or cabazitaxel, should be used in which population. There are several small studies suggesting a correlation between baseline parameters (such as Gleason score) and response to AA, but lack of similar studies on cabazitaxel or direct comparative studies between the two agents prohibit any definite conclusions. On the basis of a few small and/or retrospective studies it is sometimes suggested that there is cross resistance of AA with taxanes, or that patients with a high Gleason score or low androgen levels at baseline have a worse response on AA. The scientific data are insufficient to support these suggestions and patients with high Gleason score have a poor prognosis anyway. Suggestions on this subject are purely speculative. The use of biomarkers for prediction of clinical benefit in mCRPC has the potential to improve patient selection strategies. These biomarkers continue to be refined and should provide more specific end points and guidance in the future management of men with CRPC [18].

Conclusion & future perspective

The study that led to FDA and EMA approval showed that AA plus prednisone, as compared with placebo and prednisone, prolonged survival in docetaxel-treated mCRPC patients by approximately 4 months (4.6 months in an updated analysis) with a low frequency of treatment-related AEs. Subanalyses showed that AA with prednisone improved functional status from baseline and improved pain outcomes and fatigue more rapidly than did prednisone alone while preventing skeletal-related events.

Currently, two treatments, AA and cabazitaxel, are approved for mCRPC patients previously treated with docetaxel. At the latest American Society of Clinical Oncology Genitourinary Oncology meeting, the results of a Phase III trial (AFFIRM) have been presented, demonstrating a 4.8-month OS benefit for MDV3100 compared with placebo in post-docetaxel CRPC patients [25]. A broad range of agents are currently tested for efficacy in mCRPC. Clinical practice is likely to change over the next 5 years with novel treatments likely to

Executive summary

- A large number of agents are currently under investigation for castration-resistant prostate cancer.
- In April 2011, the US FDA approved the use of abiraterone acetate (AA) in combination with prednisone for the treatment of metastatic castration-resistant prostate cancer (mCRPC) patients previously treated with docetaxel.
- AA is converted into abiraterone, a potent and selective irreversible inhibitor of CYP17 which results in the suppression of androgen production in all endocrine organs.
- Several studies have demonstrated the safety and efficacy of AA in post-docetaxel mCRPC patients.
- The recommended dose of AA is 1000 mg (four 250-mg tablets) administered orally once daily at least 1 h before and 2 h after a meal, in combination with twice-daily oral prednisone.
- AA plus prednisone prolonged survival in docetaxel-treated mCRPC patients with 4.6 months in an updated analysis with a low frequency of treatment-related adverse events.
- A minimum of 12 weeks of treatment is generally advised.
- AA with prednisone improved functional status from baseline and improved pain outcomes and fatigue more rapidly than did prednisone alone while preventing skeletal-related events.
- Further evaluation of AA in earlier settings and in combination therapies is planned.

have a positive impact in the treatment of mCRPC. The double-blind protocol of the COU-AA-302 Phase III study of AA has recently been unblinded. This Phase III study of AA in chemotherapy-naive patients with mCRPC is an off-label use study and is not discussed in this manuscript. Because of the positive results it seems likely that the current indication will be expanded to asymptomatic or mildly symptomatic chemotherapy-naive mCRCP patients [26]. Further evaluation of AA in earlier settings and in combination therapies is planned. The best combination and sequence of the drugs for the treatment of mCRCP should be evaluated in clinical trials.

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