

Abiraterone acetate in the treatment of metastatic castration-resistant prostate cancer: review of clinical data

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Abiraterone acetate (AA), after metabolization to abiraterone, is an oral inhibitor of the cytochrome P450C17 (CYP17) complex. It inhibits the production of androgens by interfering with the enzymes C17 α hydroxylase and C17-C20 lyase. It was tested in patients with metastatic castration-resistant prostate cancer and showed promising results in Phase I and II studies with prostate specific antigen and radiological responses. In a randomized Phase III trial, AA in combination with prednisone increased median overall survival compared with prednisone alone in progressive docetaxel-pretreated patients with metastatic castration-resistant prostate cancer. Side effects of AA were mild with urinary tract infections, edema and hypokalemia when used in combination with prednisone. There was an influence on pharmacokinetic parameters in patients with renal and moderate hepatic failure without severe clinical complications and no dose adjustments are necessary. AA is a potent inhibitor of CYP2D6 and CYP1A2, and can interact with the metabolism of other drugs as shown in 'in vitro' studies.

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• renal failure • side effects

Abiraterone acetate (AA), after conversion *in vivo* to abiraterone, is a selective, irreversible inhibitor of CYP P450 17 α (17 α -hydroxylase/C17–20 lyase; CYP17). This enzyme complex is important for the conversion of cholesterol into cortisol and the subsequent biosynthesis of androgens such as testosterone. As a consequence, the production of testosterone is blocked in all tissues by AA while the production of other steroid hormones (e.g., cortisol) is decreased (Figure 1). Owing to the negative feedback mechanism by steroids, there is an increased production of adrenocorticotropic hormone in the pituitary gland. This results in an increase of upstream hormones that can lead to arterial hypertension, hypokalemia and fluid retention [1]. The feedback mechanism can be inhibited by the concomitant administration of low dose glucocorticosteroids.

Castration-resistant prostate cancer (CRPC) is defined as prostate cancer that progresses under complete androgen deprivation by hormonal or surgical castration, in combination with an antiandrogen and after secondary antiandrogen withdrawal.

In order to be diagnosed with CRPC, patients should have been on antiandrogen withdrawal for at least 4 weeks and their testosterone level should be <50 ng/dl or <1.7 nmol/l; there should be a prostate specific antigen (PSA) progression despite secondary hormonal manipulations defined as three consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir with a PSA level >2 ng/ml, or progression of osseous lesions defined as the appearance of two or more lesions on bone scan, or soft tissue lesions using the Response Evaluation Criteria in Solid Tumours

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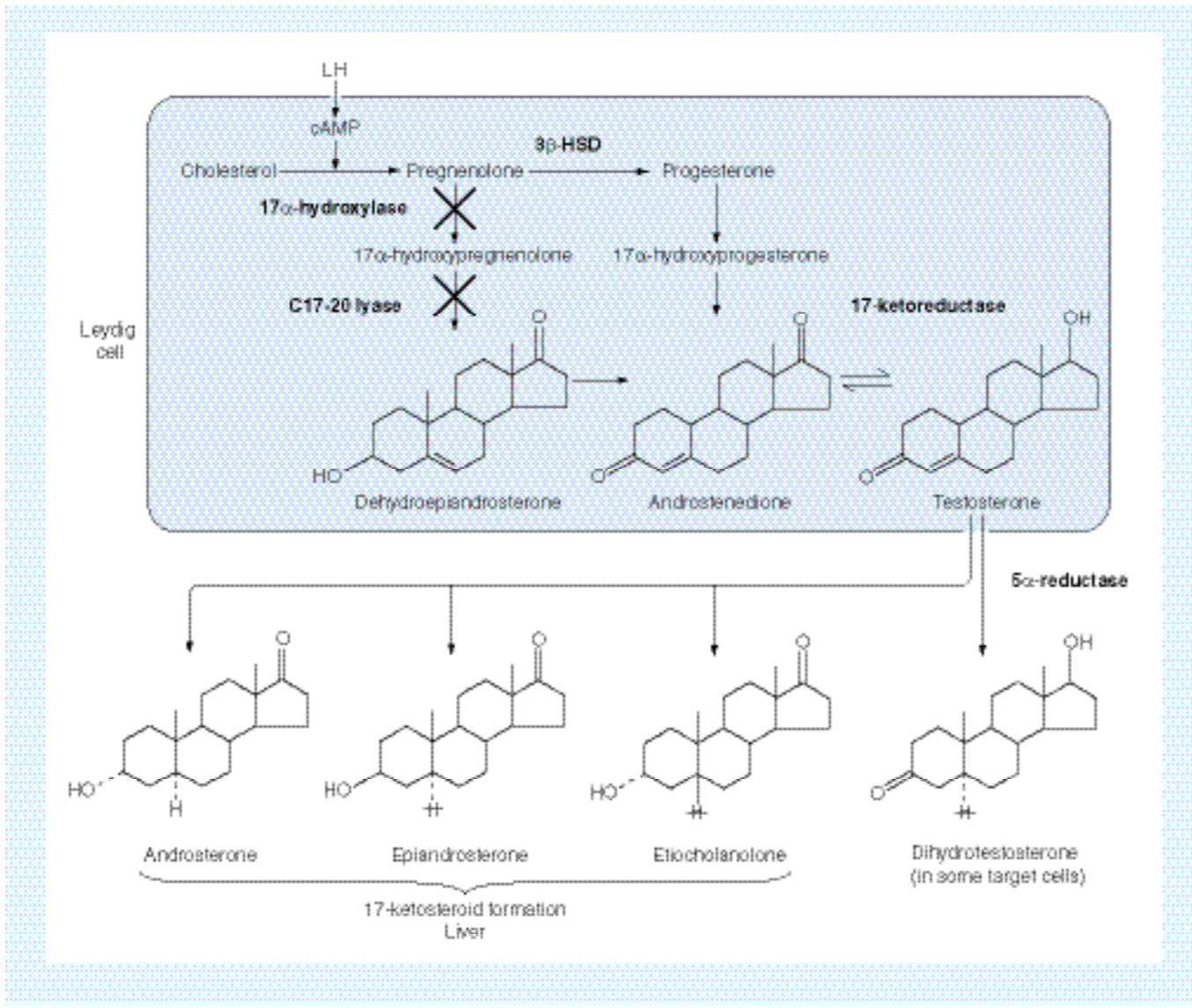


Figure 1. Mechanism of action of abiraterone acetate.

LH: Luteinizing hormone; 3β-HSD: 3-β-hydroxysteroid dehydrogenase.

(RECIST) criteria [2].

Since 2004, first-line treatment of CRPC was by docetaxel and prednisone, resulting in a survival benefit, while there was no standard second-line treatment. More recently, several trials have been performed in the second-line treatment of CRPC after docetaxel and effective chemotherapeutic (e.g., cabazitaxel-prednisone), immunotherapeutic (sipuleucel-T) and hormonal (e.g., AA) treatments with improvement in overall survival were approved as second-line treatment in this patient population. This review focuses on the development of AA.

Phase I results

A Phase I dose escalation study with single agent AA

was performed in 21 patients with progressive CRPC without previous chemotherapy or radionuclide therapy. They were treated in five dose levels starting from 250 mg AA per day to 2000 mg AA/day in three-patient cohorts. There were no treatment-related grade 3 or 4 toxicities and a plateau of endocrine effects was reported at doses greater than 750 mg/day. Based on these data, a daily oral dose of 1000 mg of AA was selected for Phase II studies.

In nine patients treated at a dose of 1000 mg/day, two developed hypertension and five hypokalemia. These side effects were controlled with eplerenone, a selective mineralocorticoid receptor antagonist. One patient with a history of migraines developed grade 2 migraineous headaches after 8 weeks of treatment,

which necessitated interruption of AA. Other side effects were fatigue (1/9) and hot flushes (1/9) and one patient with pre-existing asthma experienced exacerbation of dyspnea.

A PSA response, defined as a 50% decline in PSA confirmed after 1 month, was observed in 57% of patients and in eight patients with evaluable disease according to RECIST, 62% showed a partial response [1].

A second Phase I trial was performed in 33 men with chemotherapy-naive progressive CRPC. In total, 19 of these patients (58%) had previously received ketoconazole for CRPC. Fasted or fed cohorts received AA in doses of 250, 500, 750 or 1000 mg/day. In this study, no dose-limiting toxicities were observed; grade 3 hypertension (12%) and grade 3–4 hypokalemia (9%) were the most frequent serious toxicities and responded to medical management. At a dose of 1000 mg of AA (n = 12) grade 3 toxicities were arthralgia (one patient); hypokalemia (one patient); and hypertension (two patients).

Confirmed PSA responses at week 12 were seen in 55% of patients; 47% in patients with prior ketoconazole treatment (n = 19) and 64% in patients without prior ketoconazole therapy (n = 14). Based on safety, endocrinologic and pharmacokinetic parameters, a dose of 1000 mg/day of AA was recommended for further study [3].

Phase II results

An extension of the first Phase I study was performed and 42 patients with progressive chemotherapy-naive CRPC were treated with 1000 mg AA/day in the Phase II part. A two-stage design was used to reject an obsolete treatment defined as <10% of patients showing a PSA response of 50% or more after 12 weeks. The first stage ended after the evaluation of 20 patients, with continued accrual to the second stage if more than one patient had a PSA response. A PSA response, the primary end point of the study, was observed in 67% and the median time to PSA progression (TTPP) for all Phase II patients was 225 days (95% CI: 162–287 days). Independent radiologic evaluation showed a partial response in 37.5% of 24 Phase II patients with measurable disease.

A syndrome of secondary mineralocorticoid excess characterized by hypokalemia (88% of 42 patients), hypertension (40%), and fluid overload (31%) was observed. These side effect could be controlled by treatment with eplerenone 50–200 mg/day, except in three patients who required glucocorticosteroid replacement for symptomatic fluid overload. Hot flushes and asymptomatic grade 3 transaminase elevation developed in 9.5 and 5% of patients, respectively

[4].

A second Phase II trial looked at the combination of AA and prednisone. Prednisone was added to reduce the symptoms associated with secondary hyperaldosteronism such as hypertension, hypokalemia and fluid retention. A total of 58 men with progressive metastatic CRPC (mCRPC) and pretreated with docetaxel, received 1000 mg/day of AA in combination with prednisone (2 × 5 mg/day). Twenty-seven (47%) patients had received prior ketoconazole. A ≥50% decline in PSA was observed in 36% of patients (45% in 31 ketoconazole-naive; 26% of 27 ketoconazole-pretreated patients) with a TTPP of 169 days (95% CI: 82–200 days). The partial response rate in 22 patients with RECIST-evaluable target lesions was 18%. Improved Eastern Cooperative Oncology Group (ECOG) performance status was seen in 28% of patients.

This combination was well tolerated and grade 3 fatigue was observed in 2% of patients. The association with prednisone prevented the occurrence of significant hypertension or hypokalemia [5].

In these Phase II studies, PSA responses and radiological responses were seen that were higher than reported in historical series. The radiological responses especially showed the possibility of a successful molecule. In addition, the side effect profile was tolerable and when corticosteroids were given in combination with AA, the mineralocorticoid syndrome could be prevented. This was the rationale to combine AA with prednisone in the Phase III design. However, the syndrome could also be treated with eplerenone. Since toxicities of prednisone may occur when treatment with prednisone is long, the opportunity to evaluate AA without prednisone has been missed.

Phase III results

Based on the Phase II results, a randomized Phase III study was initiated comparing AA in combination with prednisone to placebo plus prednisone as second-line treatment in patients with progressive mCRPC, pretreated with docetaxel. Patients had histologically or cytologically confirmed prostate cancer, disease progression defined as two consecutive increases in PSA or radiographic evidence of disease progression in soft tissue or bone, with or without disease progression on the basis of the PSA value, and ongoing androgen deprivation, with a serum testosterone level of 50 ng/dl or less. They had an ECOG performance status score <2, and hematologic and chemical laboratory values within predefined measures. Exclusion criteria were serious comorbidities, active or symptomatic viral hepatitis or chronic liver disease, uncontrolled

hypertension, a history of pituitary or adrenal dysfunction, clinically significant heart disease, or previous therapy with ketoconazole.

Patients were randomized in a 2:1 ratio to receive either AA 1000 mg/day plus prednisone 5 mg twice-daily or placebo plus prednisone 5 mg twice-daily in 28-day cycles. Treatment could continue until both radiographic and PSA progression occurred in combination with signs of clinical progression such as pain progression or skeletal-related events or if the treating physician decided to initiate a new systemic anticancer treatment. Other factors for ending study participation were dosing non-compliance, sustained side effects, administration of prohibited medications and patient consent withdrawal.

The primary end point of the study was overall survival, while secondary end points were PSA response rate, TTPP and radiographic evidence of progression-free survival.

In total, 1195 patients were randomized (AA plus prednisone 797; placebo plus prednisone 398 patients). The median follow-up was 12.8 months. At the pre-planned interim analysis, there was a 35.4% reduction in the risk of death in the AA group (hazard ratio [HR]: 0.65; 95% CI: 0.54–0.77; $p < 0.001$); the median overall survival was 14.8 months in the AA group and 10.9 months in the placebo group. This led to the unblinding of the study and patients in the placebo group were offered AA [6]. An updated analysis after a median follow-up of 20.2 months confirmed the survival benefit remained [7] with a HR of 0.74 (95% CI: 0.64–0.86; $p < 0.0001$) and a median overall survival of 15.8 months (95% CI: 14.8–17.0) for the AA treatment group compared with 11.2 months (95% CI: 10.4–13.1) for the placebo group.

All the secondary end points from the interim analysis were better in the AA group with improvement in PSA response rate (29 vs 6%; $p < 0.001$), TTPP (10.2 vs 6.6 months), objective response rate (14 vs 3%; $p < 0.001$) and median progression-free survival on the basis of radiographic evidence (5.6 vs 3.6 months). When subgroup analyses of the updated analysis were performed, the median overall survival was significantly improved in all subgroups except in patients receiving two lines of chemotherapy, an ECOG performance status of 2, visceral disease at entry, and no increase in baseline alkaline phosphatase above the median level [7].

AA also had a beneficial effect on pain and skeletal-related events. During the study, pain was assessed at baseline and at each treatment cycle until discontinuation using the Brief Pain Intensity-SF questionnaire. Palliation/progression of pain intensity and pain interference was consistently in favor of AA resulting

in a significantly improved pain outcome with fewer patients progressing in palliation/progression of pain intensity and pain interference at 6 (22 vs 28%; 20 vs 31%), 12 (30 vs 38%; 28 vs 32%) and 18 months (35 vs 46%; 30 vs 35%). Also, time to skeletal-related events (pathologic fracture, spinal cord compression or palliative radiation/bone surgery) was longer in the AA arm compared with placebo (301 vs 150 days; $p = 0.0006$) [8].

Treatment with the combination of AA plus prednisone was well tolerated. Non-hematological side effects observed in at least 10% of patients were fatigue (44%), fluid retention and edema (31%), back pain (30%), nausea (30%), arthralgia (27%), constipation (26%), bone pain (25%), vomiting (21%), diarrhea (18%), hypokalemia (17%), pain in arm or leg (17%), asthenia (13%), dyspnea (13%), cardiac disorder (13%), abdominal pain (12%), urinary tract infection (12%), liver-function test abnormalities (10%) and hypertension (10%), while anemia was the only hematological toxicity seen in more than 10% of patients (23%). Grade 3 and 4 toxicities were rarely observed and those reported in at least 5% of patients in the AA plus prednisone arm were fatigue (8%), anemia (7%), back (6%) and bone pain (5%).

Side effects more frequently observed in the AA group were urinary tract infections (12 vs 7%; $p = 0.02$), fluid retention and edema (31 vs 22%; $p = 0.04$), hypertension (10 vs 8%) and hypokalemia (17 vs 8%; $p < 0.001$) [6].

The study showed a clear benefit of patients treated with AA in combination with prednisone in terms of median overall survival. Treatment could continue if there was an increase in PSA only since a combined end point was used to discontinue treatment. This prevented the early discontinuation of a possible beneficial treatment and a PSA rise only should not be used in future trials as a stopping end point.

Although there was the possibility of a crossover after the first positive results, the median overall survival benefit remained in the patient treated initially with AA. This may indicate that an early start of AA is indicated in patients with characteristics similar to the inclusion criteria. Since at the moment there are more treatment options for this patient population such as cabazitaxel chemotherapy, the selection which treatment should be used first is challenging. The moderate toxicity of AA may be an advantage in the mainly elderly patient population with mCRPC.

Special groups

To be included in the Phase I, II and III studies, patients had to have an adequate renal function (<1.5 of the upper normal limit [UNL] or creatinine

clearance > 60 ml/min) and liver function (serum bilirubin <1.5 UNL; aspartate aminotransferase or alanine transaminase <2.5 UNL, or aspartate aminotransferase or alanine transaminase <5 UNL in case of liver metastases).

In a Phase I study that involved 33 patients with progressive CRPC, pharmacokinetic analyses showed that in patients treated with the 1000 mg/day schedule, AA was rapidly converted to abiraterone. Maximum drug concentrations (C_{max}) were achieved within 1.5–4 h; the mean C_{max} varied between $510 + 366.5$ and $2194 + 1096.9$ nM/l in patients who fasted and who did eat, respectively, showing an influence of food on absorption of AA. The terminal half-life ranged between $12.5 + 1.2$ and $14.4 + 7.7$ h [3].

Information regarding patients with renal insufficiency, liver function impairment and concomitant medication interfering with the P450 CYP2D6 and 1A2 have been published recently.

Renal insufficiency

In patients with end stage renal failure on dialysis and treated with a dose of 1000 mg/day AA, the systemic exposure to abiraterone was 35–45% lower than in patients with a normal renal function while other pharmacokinetic parameters were similar in both groups (Table 1). However, the tolerability of AA was similar between both groups [9].

Hepatic impairment

In patients with mild and moderate hepatic impairment, based on the Child-Pugh (CP) classification, pharmacokinetic studies at the 1000 mg/day AA dose showed an increase in C_{max} , AUC and median half-life

in patients with moderate hepatic impairment (CP: 7–9), while only the half-life increased in patients with mild hepatic impairment (CP: 5–6) compared with normal patients (Table 1). The tolerability among groups was similar [10].

Drug–drug interaction

Since AA is a potent inhibitor of CYP2D6 and CYP1A2 *in vitro*, it may potentially interfere with drugs that are metabolized by these systems.

CYP2D6 is responsible for the metabolism of drugs such as antiarrhythmics, adrenoceptor antagonists, and antidepressants. The CYP2D6 gene is highly polymorphic and its activity ranges widely from ultrarapid, extensive, intermediate and poor (PM) metabolizer phenotypes. Ultrarapid metabolizer phenotypes and PM are most at risk for treatment failure or dose-dependent drug toxicity, respectively. Of the Caucasian populations of Europe and North America, 5–10% are of the PM phenotype and are unable to metabolize the anti-hypersensitive drug debrisoquine and numerous other drugs [11]. Substrates for CYP2D6 are given in Box 1.

The influence of AA on CYP2D6 was evaluated by the metabolism of dextromethorphan HBr. There was a 100% higher exposure to dextromethorphan with the combination of AA, prednisone and dextromethorphan than with dextromethorphan alone based on the mean values for C_{max} and AUC_{0-24} . Although there were interference with the metabolism of dextromethorphan, no excessive toxicities were reported [12].

CYP1A2 is part of the CYP450 group of heme-thiolate mono-oxygenases and is involved in a

PK parameter	Patients (n)	Median T_{max} (range; h)	$C_{max} \pm SD$ (ng/ml)	$AUC_{0-last} \pm SD$ (ng \times h/ml)	$T_{1/2} \pm SD$ (h)	Ref.
Mild hepatic impairment	8	2.0 (0.5–3.0)	71.9 ± 40.2	355 ± 191	17.7 ± 7.91	[10]
Moderate hepatic impairment	8	1.5 (1.0–2.0)	297 ± 258	1530 ± 1350	18.6 ± 5.04	[10]
Normal hepatic function	8	1.75 (1.0–3.0)	85.7 ± 46.6	321 ± 166	13.1 ± 4.19	[10]
Impaired renal function	8	3	38.8	228	16.0 ± 2.0	[9]
Normal renal function	8	1.5	73	363	19.0 ± 4.1	[9]
Normal renal and hepatic function; fasted	6	1.8	510 ± 366.5 nM/l		14.4 ± 7.7	[3]
Normal renal and hepatic function; fed	6	4	2194 ± 1096.9 nM/l		12.5 ± 1.2	[3]

AUC_{0-last} : Area under the curve from the time of dosing to the last measurable concentration; C_{max} : Maximum drug concentration; PK: Pharmacokinetic; $T_{1/2}$: Terminal half-life; T_{max} : Time of maximum observed concentration.

Box 1. Drugs metabolized by the CYP17 system.**Drugs metabolized by CYP2D6**

Analgesics (e.g., codeine, phenacetin, oxycodone, tramadol)
Antidepressants: selective serotonin reuptake inhibitors (e.g., fluoxetine, paroxetine)
Antidepressants: serotonin–norepinephrine reuptake inhibitor (e.g., duloxetine, venlafaxine)
Antidepressants: tetracyclic (e.g., mianserin)
Antidepressants: tricyclic (e.g., amitriptyline, imipramine)
Antidepressants: reversible inhibitor of monoamine oxidase A (e.g., minaprine)
Antiemetics (e.g., metoclopramide, ondansetron, promethazine, tropisetron)
Antipsychotics (e.g., chlorpromazine, haloperidol)
Anti-tussive drugs (e.g., dextromethorphan)
Cardiovascular medication (e.g., debrisoquine, metoprolol, propranolol, perhexiline)

Drugs metabolized by CYP1A2

Analgesics (e.g., naproxen, paracetamol, phenacetin)
Anticoagulants (e.g., warfarin)
Antidepressants: tricyclic antidepressants (e.g., amitriptyline, clomipramine, imipramine)
Antidepressants: selective serotonin reuptake inhibitors (e.g., fluvoxamine)
Antiemetics (e.g., ondansetron)
(Anti)hormones (e.g., estradiol, tamoxifen)
Antipsychotics (e.g., clozapine, haloperidol, olanzapine)
Caffeine
Cardiovascular medication (e.g., verapamil)
Tyrosine kinase inhibitors (e.g., erlotinib)
Local anesthetics (e.g., ropivacaine)
Respiratory drugs (e.g., theophylline)

nicotinamide adenine dinucleotide phosphate-dependent electron transport pathway in liver microsomes. It oxidizes a variety of compounds, including steroids, fatty acids and xenobiotics. It is involved in the metabolism of caffeine, aflatoxin B1, acetaminophen, phenacetin, and heterocyclic amines and participates in the bioactivation of carcinogenic aromatic and heterocyclic amines. The *CYP1A2*1F* allele is quite common (40–50%) owing to a substitution of a base in the non-coding region of the *CYP1A2* gene and has the effect of decreasing the enzyme inducibility. Individuals who are homozygous for the *CYP1A2*1F* allele are 'slow' caffeine metabolizers, which may lead to an increase in the risk of non-fatal myocardial infarction with high caffeine consumption [13]. Substrates for CYP1A2 are given in **Box 1**.

The influence of AA on CYP1A2 was evaluated by

the metabolism of theophylline, a substrate of the enzyme system. There was no interference with the metabolism of theophylline [12].

These findings show that AA can interfere with the metabolism of certain drugs and drug–drug interaction should be taken into account when using drugs metabolized by these enzyme systems.

Conclusion

AA has a specific activity blocking the conversion of cholesterol to testosterone by interfering with the CYP17 system. In combination with prednisone, AA has shown activity in patients with mCRPC who have received docetaxel-based chemotherapy with an improvement in median overall survival compared with prednisone alone. Side effects were mild and treatment was supported well. It was shown that AA can be safely used in patients with renal insufficiency, while in patients with severe liver disease its use should be further studied. There are also possible drug–drug interactions and the combination with drugs metabolized by the same enzyme systems should be used with caution. The drug has been registered in the USA, Europe and other regions for the treatment of patients with mCRPC who have received chemotherapy containing docetaxel and a study in chemotherapy-naïve patients has been completed.

AA is an important addition to the treatment of patients with prostate cancer.

Future perspective

At the moment, AA is registered for the treatment of patients with mCRPC who have received chemotherapy containing docetaxel. The COU-AA-302 (NCT00887198) was studying patients with mCRPC not pretreated with docetaxel. The study was unblinded by the Independent Data Monitoring Committee in March 2012 after review of the efficacy and safety outcomes of the pre-specified COU-AA-302 interim analysis. The Independent Data Monitoring Committee concluded that the overall survival, radiographic progression-free survival and secondary end point outcomes all pointed to a highly significant advantage in favor of the AA arm. The interim analysis also confirmed the tolerability and acceptable safety profile of AA. After publication of these results, AA may have a place immediately after the development of castration resistance instead of chemotherapy due to its beneficial toxicity profile compared with chemotherapy. Other hormonal treatments are being tested in patients with CRPC and may compete with AA in the treatment of this indication. Nevertheless, chemotherapy will have a place in the treatment of mCRPC after hormonal manipulations. If chemotherapy alone

Executive summary**Introduction**

Abiraterone acetate (AA) is an oral inhibitor of the CYP 17 enzyme complex, blocking the production of testosterone and other androgens. Prostate cancer is a hormone-sensitive cancer and AA was tested in patients with metastatic castration-resistant prostate cancer.

Phase I results

In Phase I studies, single agent AA was tested in patients with castration-resistant prostate cancer before and after docetaxel-based treatment. The recommended dose for Phase II testing was 1000 mg/day. Main toxicities were hypertension and hypokalemia. Prostate specific and radiological responses were observed in the Phase I studies.

Phase II results

In Phase II studies, AA showed responses in patients with castration-resistant prostate cancer without and with docetaxel pretreatment. The prostate-specific antigen response rate was between 36–67% and the radiological partial response rate between 18–37.5%. The association with prednisone prevented the occurrence of significant hypertension or hypokalemia.

Phase III results

In a randomized Phase III study in 1195 patients with mCRPC and pretreated with docetaxel, AA in combination with prednisone increased overall survival from 10.9–14.8 months with a reduction of the risk of death of 35% (Hazard Ratio: 0.646).

Special groups

There was an influence on pharmacokinetics in patients with end-stage renal failure and moderate impaired hepatic function. AA might influence the pharmacokinetics of drugs metabolized with the CYP2D6 and CYP1A2 systems.

Conclusion

AA is an important addition to the treatment of patients with mCRPC who have received chemotherapy containing docetaxel.

or in combination with these newer molecules provides the best results remains to be determined.

Breast cancer is also a hormone-sensitive cancer in many cases and AA is currently being tested in women with hormone-sensitive breast cancer. A Phase II study is comparing AA plus oral prednisone and AA plus oral prednisone plus oral exemestane with oral exemestane alone in postmenopausal women with estrogen receptor-positive metastatic breast cancer, who relapsed after treatment with letrozole or anastrozole [101].

Financial & competing interests disclosure

D Schrijvers has participated in the Cougar-AA-301 and Cougar-AA-302 studies and served on the speakers board and the advisory board for Janssen Pharmaceuticals. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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