Abiraterone acetate in castration-resistant prostate cancer

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The palliative goal of the treatment of metastatic prostate cancer is to prolong survival and decrease cancer-related complications. Androgen ablation therapy is widely accepted as the initial treatment of choice; when the disease becomes resistant to castration-resistant prostate cancer (CRPC), docetaxel-based chemotherapy aids in prolonging overall survival and controlling disease-related symptoms. Until a few years ago, no drug had showed efficacy in docetaxel-resistant patients. Recently, cabazitaxel, a taxane family compound, has been shown to help prolong survival in patients previously treated with docetaxel, even if a high grade of myelotoxicity has been reported. Moreover, a better understanding of the biology of CRPC has demonstrated that prostate cancer proliferation is largely mediated through the androgen receptor, which could be reactivated by androgens produced by the adrenal glands. Abiraterone acetate is an orally active acetate salt of the steroidal compound abiraterone with antiandrogen activity. Abiraterone inhibits the enzymatic activity of steroid 17α-monooxygenase, a member of the cytochrome P450 family that catalyzes the 17α-hydroxylation of steroid intermediates involved in testosterone synthesis from the adrenal glands. This review focuses on abiraterone acetate, the first compound that, through the inhibition of adrenal gland production of testosterone, increases the overall survival in CRPC patients. The role of possible predictive biomarkers and future perspectives are also discussed. ***Anti-Cancer Drugs*** **23:247–254 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

With the exception of skin cancer, prostate cancer is the most commonly diagnosed cancer among men in the USA and the second most common cause of cancer death among men. In 2010, an estimated 217 730 new cases of prostate cancer will be diagnosed in the USA and approximately 32 050 men are expected to die from this disease [1].

Treatment of clinically localized disease consists of surgery, radiation therapy (external beam or brachytherapy), androgen suppression, or a 'wait-and-see' approach in selected cases.

In the advanced setting, the goal of treatment is to prolong survival and to decrease the cancer-related complications such as bone pathological fractures, urethral obstruction, cord compression, and development of skeletal and visceral metastases.

In patients with metastatic prostate cancer, the standard treatment choice is androgen ablation therapy, achieving a response rate ranging from 80 to 90%. Unfortunately, all patients progress and become refractory to castration after 15–20 months of treatment [2].

In 2004, the TAX327 and SWOG99-16 trials reported a significant increase in overall survival (OS) in castration-resistant prostate cancer (CRPC) patients receiving first-line chemotherapy with docetaxel compared with mitoxantrone [3,4]. Until then, mitoxantrone plus prednisone or hydrocortisone was considered the standard of care because of its demonstrated efficacy in palliation of bone pain even if an improvement in OS was never reported [5,6].

In the TAX327, two schedules of docetaxel (weekly and every 3 weeks) were compared with mitoxantrone and both types of chemotherapy were administered with prednisone. The results showed a significant increase in terms of OS for the docetaxel given every 3 weeks compared with mitoxantrone (19.3 vs. 16.3 months, $P < 0.005$) [3].

The SWOG99-16 trial comparing docetaxel and estramustine versus mitoxantrone and prednisone confirmed that docetaxel-based chemotherapy may significantly improve survival in patients with prostate cancer (17.5 vs. 15.6 months, $P = 0.02$) [4]. Altogether, these results established first-line docetaxel as the standard of care for metastatic CRPC.

However, as the tumor cells became resistant to docetaxel-based therapy, no further treatment was available. Recent results from three independent clinical trials have demonstrated that the use of cabazitaxel could improve survival in patients with CRPC following docetaxel therapy.

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Cabazitaxel was able to extend a patient's OS further than mitoxantrone, resulting in a relative risk reduction death of 30% [15.1 vs. 12.7 months, hazard ratio (HR) 0.70, 95% confidence interval (CI) 0.59–0.83, $P < 0.0001$] and a significant increase in the median progression-free survival (PFS) (2.8 vs. 1.4 months, $P < 0.0001$) [7]. The remarkable efficacy of cabazitaxel led the US Food and Drug Administration (FDA) to approve its use in second-line treatment after the failure of docetaxel. Nevertheless, due to the high risk of dose-limiting neutropenia, treatment with cabazitaxel is not suitable for all CRPC patients.

In-vitro studies have demonstrated that in prostate cancer, cell proliferation and survival largely depend on the androgen receptor (AR), even during castration; furthermore, these could be stimulated by testosterone produced by the same prostate cancer cells in a paracrine manner or in the extragonadal sites as the adrenal gland [8–10].

Five to ten percent of circulating androgens are synthesized in the zona reticularis of the adrenal glands, specifically, testosterone, dihydrotestosterone (a metabolite of testosterone a higher affinity for ARs), androstenedione, which is metabolically converted into testosterone and other androgens, and dehydroepiandrostenedione (DHEA), the primary precursor of natural estrogens.

In-vitro and in-vivo studies have shown that adrenal androgens such as DHEA and androstenedione, which are converted into dihydrotestosterone in prostate cancer tissue [11,12], may be responsible for prostate cancer cell stimulation despite the use of antiandrogen therapy [13]. In fact, castrate prostate tumor tissue under androgen depletion therapy is characterized by the presence of amplified ARs that may enhance tumor growth [14].

Abiraterone acetate is an orally active acetate salt of the steroidal compound abiraterone with antiandrogen activity. Abiraterone inhibits the enzymatic activity of steroid 17α-monooxygenase (17α-hydrolase/C17, 20-lyase complex), a member of the cytochrome P450 family that catalyzes the 17α-hydroxylation of steroid intermediates involved in testosterone synthesis (Fig. 1). The administration of this agent may suppress testosterone production by both testes and adrenal glands to castrate-range levels.

This review focuses on abiraterone acetate, the first inhibitor of adrenal gland testosterone to effectively increase OS in CRPC patients.

Clinical studies

Preclinical and phase I studies

Preclinical data revealed that 17-(3-pyridyl) androsta-5, 16-dien-3β-ol (formally abiraterone or CB7598), is a potent steroidal inhibitor of the key enzyme for androgen biosynthesis, the cytochrome P450 17α-monooxygenase. In animal models, this agent and its 3β-O-acetate form (CB7630) caused a more significant reduction in the weight of the ventral prostate, seminal vesicles, kidneys, and testes compared with flutamide, surgical castration, and ketoconazole. Moreover, abiraterone cannot inhibit the synthesis of corticosterone as ketoconazole [15].

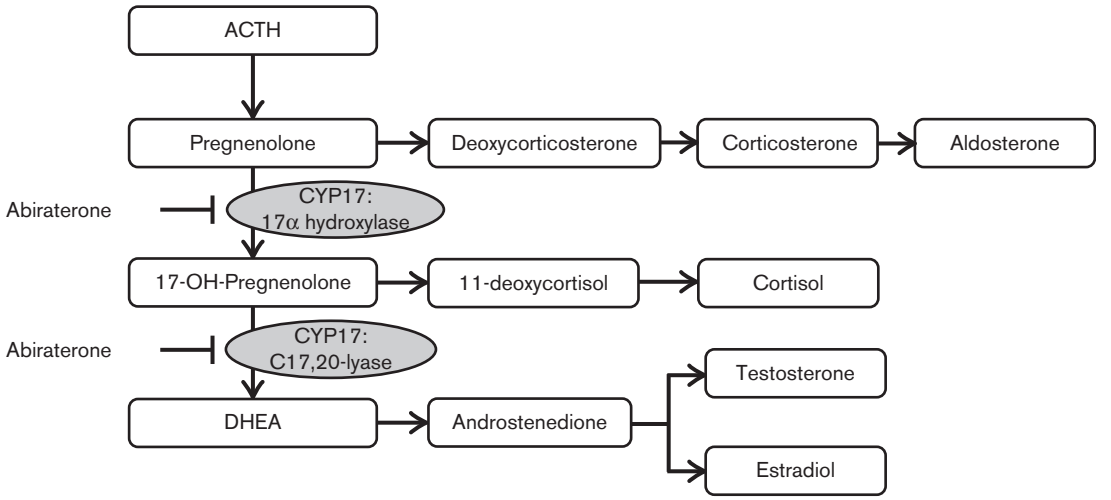
A single-dose study was performed in patients with castrate levels of testosterone (≤ 2 nmol/l) following orchidectomy or gonadotropin-releasing hormone agonist therapy, in order to determine the dose of abiraterone acetate that may induce suppression of testosterone synthesis to undetectable levels (< 0.14 nmol/l) [16]. The study showed that a dose of 500 mg of abiraterone acetate was sufficient to cause suppression of testosterone synthesis to castrate levels with a variable duration of suppression; these effects were influenced by previous patient compliance to the gonadotropin-releasing hormone agonist therapy. In addition, a suppression of the testosterone–androstenedione axis was observed in castrated patients during the course of the treatment without any effect on the 17α-OH-progesterone production due to an offsetting effect. Although the 17α-hydroxylase and C17, 20-lyase activities constitute a single enzyme (17α-hydrolase/C17, 20-lyase complex), the offsetting effect of abiraterone on 17α-hydroxylase activity clearly did not influence the inhibition of C17, 20-lyase.

All pharmacokinetic parameters showed a considerable variability between patients, with a mean T_{max} of 2.70 h (± SD 2.71) and a mean elimination half-life of 27.6 h (± SD 20.17). A range of up to 10-fold in area under curve (AUC) was seen for a given dose with a nonlinear association between AUC and dose. This variability can be attributed to a different absorption that may be influenced by gastric pH, the presence of residual food in the stomach, and body fat percentage or alternatively may represent the effect of concomitant medications on enzyme function.

Two phase I studies have shown the safety and the activity of abiraterone acetate in patients with CRPC regardless of previous treatments with ketoconazole [17,18]. Overall, 54 patients were enrolled in these two dose-escalation studies. In the first, Attard and his colleagues investigated a once-daily oral dose of abiraterone ranging from 250 to 1000 mg in patients previously treated with ketoconazole, whereas ketoconazole-naïve patients received doses of up to 2000 mg in the second study.

The most common treatment-related adverse events were fatigue, hypertension, headache, nausea, and diarrhea, which were predominantly grade 1 or 2. The most frequent treatment-related grade 3 or 4 toxicities were hypertension, hypokalemia, constipation, diarrhea, muscular weakness, and arthralgia. These were mainly observed in patients without prior exposure to ketoconazole, where the toxicity related to secondary mineralocorticoid excess was controlled by eplerenone (50–200 mg/day), which is a

Fig. 1



Adrenal gland steroidogenesis and the main targets of abiraterone acetate. DHEA, dehydroepiandrostenedione.

specific mineralocorticoid receptor antagonist with low activity in the control of hypertension.

Moreover, the administration of a corticosteroid normalized mineralocorticoid levels and regulated blood pressure. Dexamethasone was less effective than hydrocortisone or prednisone probably due to the low mineralocorticoid activity of dexamethasone.

Further biochemical studies were performed to determine the testosterone and DHEA-sulfate regression after abiraterone intake; these showed a decrease in serum levels to undetectable or almost undetectable values (testosterone < 1 ng/dl) within 8 days of administration of all doses. Treatment was also associated with about 40-fold increased levels of adrenocorticotropic hormone and steroid precursor upstream the CYP17, such as deoxycorticosterone and corticosterone.

The pharmacokinetic analysis showed that abiraterone acetate was rapidly converted into abiraterone, and confirmed the variability in metabolism among patients and the influence of food. In fact, the absorption was significantly extended after food intake, so that drug exposure was significantly increased (by 4.4-fold) by high-fat content food, compared with fasting administration.

Maximum drug concentrations (C_{max}) were achieved between 1.5 and 4 h; less than proportional increases in both C_{max} and AUC $0-\infty$ were reported across dose levels in fed and fasted patients but were less pronounced among fed patients. The terminal half-life ranged from 5 to 14 h (Table 1).

Neither study reported any cross-resistance between ketoconazole and abiraterone acetate, and they recommended a dose of 1000 mg daily for phase II trials. The pharmacodynamic and pharmacokinetic data also support the once-daily administration. At this dose level, the most expected toxicities were hypertension and fatigue, but the use of corticosteroid allowed better control of blood pressure.

Table 1 Summary of abiraterone acetate characteristics

Properties of abiraterone acetate (CB7630)	
Indication	
Castration-resistant prostate cancer after one or two lines of chemotherapy, of which one was docetaxel based	–
Mechanism of action	–
Inhibitor of CYP-17	Abiraterone inhibits the enzymatic activity of steroid 17α-monooxygenase (17α-hydrolase/C17, 20-lyase complex), a member of the cytochrome P450 family that catalyzes the 17α-hydroxylation of steroid intermediates involved in testosterone synthesis in the adrenal gland.
Dosage and administration	–
Route	Oral
Dose	1000 mg (four 250-mg tablets) with prednisone 5 mg BID
Frequency	Daily
Pharmacokinetic profile [18]	–
Geometric mean maximum plasma concentration (C_{max})	510 nmol/l/l
Geometric mean area under the plasma concentration-time curve	3478 nmol/l/l × h
Median time to reach C_{max}	1.5–4 h
Mean elimination half-life	14.4 h
Effect of food	Increase the absorption
Most frequent treatment adverse events: Fluid retention (30.5%); hypokalemia (17.1%; G3/4 3.8%); and grade 3/4 hypertension (1.3%)	–

BID, twice a day; CRPC, castration-resistant prostate cancer.

Phase II trials.

Three phase II studies have been conducted in CRPC patients either previously treated with docetaxel or not (Table 2).

In docetaxel-naïve patients, abiraterone was administered once daily, continuously, on an empty stomach in 28-day cycles. The primary endpoint was the prostatic-specific antigen (PSA) value decrease of at least 50% at any time after 12 weeks of treatment confirmed by a second measure of PSA value at a 4-week interval. The secondary endpoints were the rate of PSA decrease (≥ 30 and $\geq 90\%$), the median time to PSA progression (TTPP), the radiologic response, and the changes in the circulating tumor cell (CTC) count. The patient population showed disease progression after luteinizing hormone-releasing hormone (LHRH) analogs or after dual blockade with LHRH analogs and antiandrogen therapy.

Abiraterone showed clinical activity with a decrease in the PSA value of at least 50 in 67% of the patients; a PSA decrease of at least 30 and at least 90% was reported in 71 and 19% of the patients, respectively. Among the secondary endpoints, the median TTPP on abiraterone acetate was 225 days (253 days for patients with PSA decrease $\geq 50\%$ and 393 days for patients with PSA decrease $\geq 90\%$); a partial response defined by the Response Evaluation Criteria in Solid Tumors (RECIST) was reported in 37.5% of patients. Moreover, 59% of the patients experienced a CTC count decline from at least five to less than five cells per 7.5 ml. The addition of dexamethasone at disease progression reversed resistance in 33% of the patients [19].

The activity of abiraterone acetate was studied in two clinical trials in which 105 metastatic CRPC patients previously treated with docetaxel were enrolled. Patients with metastatic prostate cancer who had experienced treatment failure with different percentages of androgen deprivation therapy (antiandrogens, estrogens, and ketoconazole) and docetaxel-based chemotherapy were included in both studies [20,21].

In both trials, the primary objective was to determine the rate of patients with a PSA decrease of at least 50% and the secondary endpoints were as follows: PSA decrease of at least 30 and at least 90%; TTPP; rate of RECIST responses; changes in Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; safety and tolerability; and pretherapy and post-therapy CTCs counts (Table 2).

The difference between trials was the coadministration of prednisone 5 mg twice daily, in addition to abiraterone acetate 1000 mg once daily, continuously on an empty stomach.

The first trial (without prednisone) reported a PSA decrease of at least 50% from baseline in 51% of the patients. Moreover, decreases of at least 30 or at least 90% were reported in 68 and 15% of the patients, respectively; the median TTPP was 169 days and 27% of the patients with measurable disease had a partial response defined by the RECIST criteria. A decrease in the CTC count (≤ 5 cells/7.5 ml) was also observed in 41% of the patients; among them, 63% showed a decrease of at least 50% [21].

The second trial (with prednisone) reported a PSA decrease of at least 50% in 36% of patients and at least 30 or at least 90% in 47 and 16%, respectively; the median TTPP was 169 days and partial responses were observed in 18% of patients with soft tissue measurable lesions. A decline in the CTC count (≤ 5 cells/7.5 ml) was found in 34% of the patients [20].

These trials showed that the treatment with abiraterone is well tolerated and toxicity may be influenced by the concomitant administration of steroids. Abiraterone acetate alone showed hypokalemia, hypertension, and fluid retention in 55, 17, and 15% of the patients, respectively, in contrast to the combined modality, which showed hypokalemia and fluid retention in 5 and 7%, respectively, with no significant hypertension ($< 5\%$). Other reported toxicities in each study were not influenced by concomitant administration of steroids and were fatigue in 31% (G3 = 6%) and 36% (G3 = 2%); nausea 14% in both studies (G3 = 4%); anorexia in 21% (G3 = 2%); headache and aspartate aminotransferase increased in 10% of patients [20,21].

Table 2 Summary of abiraterone acetate activity in phase II–III trials

Phase	Study	PSA decrease $\geq 30\%$	PSA decrease $\geq 50\%$	PSA decrease $\geq 90\%$	Median TTPP (days)	Partial responses (RECIST)	CTCs count decline to <5 cells/7.5 ml	OS (months)
II	Attard *et al.* [19]	71%	67%	19%	225	37.5%	59%	–
II	Danila *et al.* [20]	47%	36%	16%	169	18%	34%	–
II	Reid *et al.* [21]	68%	51%	15%	169	27%	41%	–
III[a]	de Bono *et al.* [22]	–	29 vs. 6% ($P<0.001$)	–	10.2 vs. 6.6 months (PFS)	14 vs. 3% ($P<0.001$)	–	14.8 vs. 10.9 HR: 0.65 (0.54–0.77; $P<0.001$)

CTCs, circulating tumors cell count; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PSA, prostatic-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors; TTPP, time to prostatic-specific antigen progression.

[a]Abiraterone 1000 mg/daily + prednisone 5 mg twice a day (BID) was compared with placebo + prednisone 5 mg BID.

Phase III trial

The results of the phase III trial have been recently published [22]. This study enrolled 1195 patients from 13 countries affected by metastatic CRPC previously treated with one or two chemotherapeutic agents including docetaxel and under medical or surgical castration with a serum level of testosterone less than 50 ng/dl. Patients who received more than two lines of chemotherapy or a previous treatment with ketoconazole were not included in the study.

Patients were stratified according to the baseline ECOG PS score (0 or 1 vs. 2), the pain level evaluated by the Brief Pain Inventory–Short Form, the number of previous chemotherapy regimens (one vs. two), and the type of evidence of disease progression (PSA progression only vs. radiographic evidence of progression).

Before abiraterone treatment, 67% of the patients had radiological evidence of disease progression, with a median age of 69 years in both groups; the main sites of disease were bone and nodes in about 90 and 43% of the patients, respectively. The majority of patients (90 and 89%) had ECOG PS of 0 or 1 and had received one previous chemotherapy regimen both in the abiraterone and in the placebo group (70 and 69%).

Patients were randomized 2 : 1 to receive abiraterone acetate 1000 mg once daily or placebo, each with prednisone 5 mg twice daily continuously. The primary endpoint of the study was OS and the secondary endpoints were TTPP, radiographic PFS, and PSA response.

The 797 patients who received abiraterone acetate plus prednisone had a median survival of 14.8 months compared with 10.9 months of the 398 patients who received placebo (HR 0.646. 95% CI 0.54–0.77; $P < 0.0001$). Moreover, significant differences emerged between the placebo and the treatment groups for all the secondary endpoints, including TTPP (10.2 vs. 6.6 months, $P < 0.0001$), radiographic PFS (5.6 vs. 3.6 months, $P < 0.0001$), PSA response rate (29.1 vs. 5.5%, $P < 0.001$), and the objective response rate (based on RECIST) among patients with measurable disease (14 vs. 3%, $P < 0.001$). The PSA response coincided with an objective response rate in 14% of the patients (Table 2).

The effects of abiraterone were significant in all subgroups independent of baseline visceral extension, number of previous treatments, baseline PSA value, pain, and biochemical values for lactic dehydrogenase (LDH) and alkaline phosphatase; the impact on OS was less significant only in ECOG = two patients (HR: 0.81; 95% CI 0.53–1.24).

The most common adverse events in both groups were fatigue (30 vs. 33%), nausea (30 and 32%), constipation (26 and 31%), and bone pain (25 and 28%). Patients treated with abiraterone reported an increased incidence of urinary tract infection (12 vs. 7%; $P = 0.02$), generally grade 1–2.

Mineralocorticoid-related adverse events were more common in patients treated with abiraterone than placebo. The most common toxicity related to CYP17 blockade was more frequent in the abiraterone group. Fluid retention, hypokalemia, and grade 3/4 hypertension were reported in 31, 17, and 1.3%, respectively, of patients treated with abiraterone compared with the 22, 8, and 0.3% of patients receiving placebo. Grade 3–4 hypokalemia was the most common toxicity in patients treated with abiraterone (3.8 vs. 0.8%), with only three patients experiencing grade 4 hypokalemia. Cardiac disorders such as tachycardia and atrial fibrillation were more frequently observed in the abiraterone-treated than the placebo-treated (13 vs. 11%, $P = 0.14$) patients.

Altogether, these data confirm the efficacy and the good tolerability profile of this molecule, which may potentially be used as the standard treatment for second-line or third-line therapy after first-line chemotherapy with docetaxel in CRPC patients.

Predictive biomarkers

Standard biochemical prognostic markers in metastatic CRPC include PSA, LDH, alkaline phosphatase, and hemoglobin. In the above-mentioned phase III trial, their predictive role was confirmed as reporting a median survival in the treatment arm of 18.8, 10.4, and 11.6 months for PSA, LDH, and alkaline phosphatase above the normal value, respectively, compared with 16.2 months for PSA under the normal value, whereas the median time to death had not been reached for the LDH and alkaline phosphatase [22].

Attard *et al.* [19] reported that the biochemical values of DHEA, DHEA-sulfate, and estradiol at baseline and androstenedione during therapy were associated with increased probability of PSA response and TTPP.

The role and characteristics of CTCs were assessed in patients treated with abiraterone acetate. Although many techniques are available to isolate CTCs or to analyze their genetic profile during the course of treatment, to date, the CellSearch system (Veridex, LLC, Raritan, New Jersey, USA) is the only technique approved by the FDA in metastatic prostate cancer patients.

The main study showed that metastatic CRPC patients who had a CTC count of more than five cells per 7.5 ml of blood had worse prognosis compared with patients who had less than or equal to 5 CTC/7.5 ml (11.5 vs. 21.7 months, respectively, $P < 0.0001$). Moreover, this study showed that the CTC count is a dynamic prognostic factor; in fact, patients who change the risk class from low to high had a worsening of prognosis at any time during disease independent of the number of previous cytotoxic chemotherapy lines [23].

In trials testing abiraterone, between 40 and 70% of patients had more than 5 CTCs/7.5 ml at baseline; after treatment, CTCs declined to less than 5 CTCs/7.5 ml in 30–59% of the patients [19–21].

Nevertheless, the predictive role of CTCs under abiraterone treatment was not demonstrated, due to the small number of patients enrolled. It is important to note that the maximum change in the CTC count was not found to be related to the maximum PSA change [21]; moreover, an early increase in the CTC count was found to be more significantly associated with a risk of death compared with PSA change [24].

Despite the increasing number of studies performed with CellSearch in prostate cancer, the most promising approach seems to be the molecular characterization of CTCs. To this end, several targets such as HER2, AR, or information about tumor chromosomal ploidy have been found in CTCs [25]; the extent of AR mutations concomitant to castration resistance has also been investigated [26].

The TMPRSS2-estrogen-regulated gene (ERG) rearrangement was found to be related to more aggressive prostate cancer with increasing tumor stage at diagnosis and involvement of pelvic lymph nodes [27,28].

Although fusion of the ERG oncogene with TMPRSS2 occurs in 30–70% of therapy-naive prostate cancers [29], its role in castration-resistant tumors remains contentious.

Attard *et al.* [30] reported the expression of TMPRSS2-ERG gene rearrangement in CTCs of patients treated with abiraterone acetate, with a significant association between its expression in CTCs and therapy-naive tumors or CRPCs biopsies. These data confirm that ERG gene rearrangement was unchanged during the development of castration resistance and it represents an early event in prostate carcinogenesis that may contribute to a more aggressive disease.

Furthermore, the proved homogeneity of ERG rearrangement in all phases of prostate cancer compared with the heterogeneity of AR mutations offers a new, more fashionable target for future RNA interference-based therapy [31].

Future perspectives

The role of abiraterone in overcoming resistance to medical castration before the use of chemotherapy in advanced prostate cancer is currently under investigation.

A second large phase III trial is ongoing involving comparison of abiraterone acetate 1000 mg and prednisone with placebo and prednisone in CRPC patients who have not yet received docetaxel (NCT00887198). The criteria for enrollment of patients include CRPC, previous antiandrogen therapy, ECOG PS of 0 or 1 and, medical or surgical castration with a testosterone level less than 50 ng/dl. The presence of visceral metastasis, prior ketoconazole, or pain-requiring opiate analgesics are the exclusion criteria. A total of 1000 patients have been enrolled with a 1 : 1 randomization.

Evaluation of the safety and role of abiraterone and prednisone with an LHRH agonist as a neoadjuvant and concurrent therapy with external beam radiation in patients with intermediate-risk or high-risk localized prostate cancer is ongoing in a phase II trial. The study aims to investigate whether pharmacologic suppression of the prostatic androgen axis by inhibition of adrenal androgen production with abiraterone may be more efficient in decreasing tissue androgen levels than the GnRH agonist. Moreover, the inhibition of androgen-regulated gene expression and the rate of apoptotic cell deaths are assessed by comparing abiraterone and LHRH with bicalutamide and LHRH (NCT01023061).

The effect on androgen deprivation by LHRH and abiraterone combination is currently under investigation in patients with intermediate-risk or high-risk prostate cancer suitable for prostatectomy in a nonrandomized (NCT00924469) and in a randomized (NCT01088529) phase II trial, comparing the combined therapy with the LHRH alone.

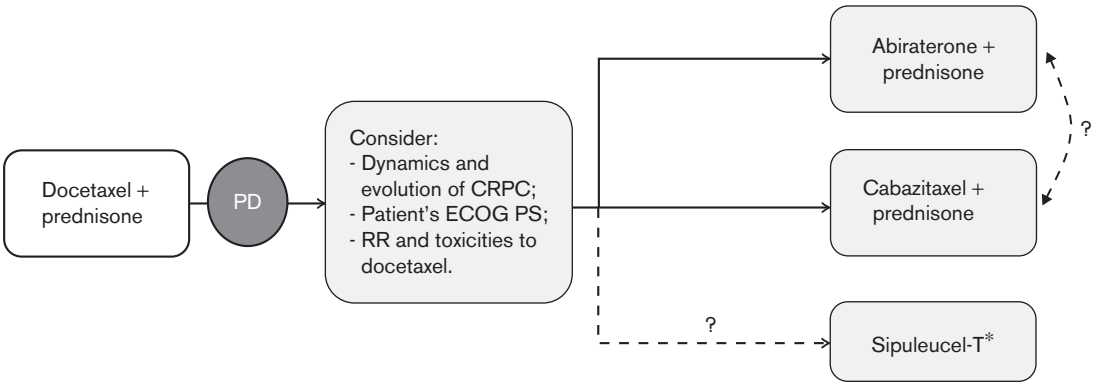
Considering the feasibility and safety of combination with LHRH agonists, future combinations with new-generation antiandrogen molecules (MDV3100, TAK-700, etc.) may be feasible as well as the possible combination with chemotherapy [32,33].

Conclusion

Although other adrenal inhibitors such as ketoconazole and aminoglutethimide have been used in the past few years after androgen deprivation therapy, they have only showed transient clinical benefits without any improvement in the OS, and the side-effect profile has limited their wide use in CRPC patients [34]. Abiraterone acetate is a potent and specific adrenal inhibitor of the CYP17 pathway. This molecule, which has recently been approved by the FDA, is expected to alter the therapeutic landscape of prostate cancer as already supported by different studies.

In the same setting, cabazitaxel, a semisynthetic derivative of the natural taxoid with antineoplastic activity, has been shown to lead to an improvement in OS from 12.7 to 15.1 months (HR: 0.70; 95% CI: 0.59–0.83; $P < 0.0001$) compared with mitoxantrone [7]. Moreover, the IMmunotherapy Prostate AdenoCarcinoma Treatment study showed for the first time that the autologous vaccine sipuleucel-T yielded an improvement in OS compared with placebo in CRPC patients (25.8 vs. 21.7 months; HR: 0.77; 95% CI: 0.61–0.98; $P = 0.04$). Although the study mainly enrolled patients who had not received docetaxel (84.5%), a survival benefit

Fig. 2



Complexity of treatment algorithm with currently approved drugs in metastatic CRPC after docetaxel progression and new emerging questions about their sequential use. *Sipuleucel-T has only been approved for patients who had not received previous docetaxel, even if 15% of the study population had docetaxel before sipuleucel-T. CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progression disease; RR, response rate.

for previously treated patients has been reported as well [35].

These trials have been contributing toward considerable advancement of postdocetaxel CRPC treatment, increasing therapeutic opportunities and improving both patient survival and quality of life. At the same time, they are increasing the complexity of the treatment algorithm: if recent European Association of Urology guidelines suggest the use of cabazitaxel in rapidly evolving disease, the evidence of a similar response rate between abiraterone and cabazitaxel (14 vs. 14.4%, respectively) is changing this criterion [36]. Moreover, abiraterone has also shown activity in ECOG = two patients, a group not sufficiently represented in the prostate trials.

Considering the emerging questions about sequential strategies with new agents and the absence of predictive biomarkers, the choice of second-line treatment should be guided by the patient's clinical performance status, toxicity reported in previous docetaxel therapy, compliance to therapy, and the evolution of prostate cancer.

Although predictive biomarkers are not available, at the moment, to select patients for cabazitaxel, abiraterone, or sipuleucel-T, several parameters such as clinical performance status, toxicity reported in previous docetaxel therapy, the dynamics of prostate cancer evolution (presence of visceral metastasis and growth rate), and patients' compliance may be useful to guide the choice of second-line treatment, but questions about sequential strategies with new agents are emerging (Fig. 2).

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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