Cancer Biology & Therapy 13:11, 1001-1008; September 2012; © 2012 Landes Bioscience

Medical strategies for treatment of castration resistant prostate cancer (CRPC) docetaxel resistant

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Keywords: CRPC, second-line therapy, antiangiogenic therapy, chemotherapy, hormone therapy, abiraterone acetate, cabazitaxel, MDV3100, TAK 700, sipuleucel-T

Abbreviations: CRPC, castration-resistant prostate cancer; FDA, Food and Drug Administration; OS, overall survival; HR, hazard ratio; ADT, androgen deprivation therapy; ASCO, American Society of Clinical Oncology; ESMO, European Society of Medical Oncology; PSA, prostate-specific antigen; PR, partial response; PFS, progression-free survival; CI, confidence interval; TPP, time to pain progression; PSA RR, PSA response rate; PRR, pain response rate; TRR, objective tumor response rate; TTPP, time to PSA progression; TTP, time to tumor progression; AR, androgen-receptor; RECIST, Response Evaluation Criteria In Solid Tumors; rPFS, radiographic progression-free survival; LHRHa, luteinizing hormone-releasing hormone agonist; CTC, circulating tumor cells; BID, bis in die; QD, quaque die; VEGF, vascular endothelial growth factor; PDGF, platelet derived growth factor; TGF, transforming growth factor; MVD, microvessel density; ECOG, Eastern Cooperative Oncology Group

The current landscape of treatment of castration-resistant prostate cancer (CRPC) has recently changed. Cabazitaxel, a new taxane with potential antineoplastic activity, has been approved by Food and Drug Administration (FDA) after docetaxel failure. In a phase III trial, cabazitaxel showed increased overall survival (OS) compared with mitoxantrone (15.1 vs. 12.7 mo, HR 0.70, 95% CI 0.59–0.83, p < 0.0001). Furthermore, chemotherapy is not the only strategy available: several studies have shown as CRPC remains dependent on androgen receptor function for growth. Abiraterone acetate, an irreversible inhibitor of CYP17, has also been approved by the FDA after docetaxel failure. In a phase III trial comparing abiraterone acetate to placebo, abiraterone showed improvement in OS (14.8 vs. 10.4 mo, HR 0.65, 95% CI 0.54–0.77; p < 0.0001).

This review will discuss current options and the ongoing trials for second-line treatment of CRPC including chemotherapy, hormonal therapies, antiangiogenetic and immune strategies.

Introduction

In Europe, prostate cancer is the most common cancer among men with 382,000 new cases and 89,000 deaths annually.[1] Androgen deprivation therapy (ADT) is the cornerstone for recurrent or metastatic prostate cancer, but almost all patients will develop progressive castration-resistant disease in 12–18 months.[2]

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Submitted: 03/19/12; Accepted: 06/20/12
http://dx.doi.org/10.4161/cbt.21188

Mitoxantrone, estramustine and docetaxel are currently approved for first-line treatment of CRPC. Until 2004, mitoxantrone was the only therapy available because it showed improvement in quality of life, pain control and palliation of symptoms in two randomized trials, although not any benefit in OS over prednisone alone was reported.[3,4]

In 2004, two landmark phase III studies have established that docetaxel plus prednisone is the standard first-line therapy in CRPC. In TAX327 trial, docetaxel every three weeks demonstrated a survival benefit over mitoxantrone and weekly docetaxel (18.9 vs. 16.5 vs. 17.4 mo, respectively).[5] An update analysis at three years confirmed an increased OS for docetaxel compared with mitoxantrone (19.2 vs. 16.3 mo, p = 0.004).[6]

The Southwest Oncology Group 99-16 study, comparing docetaxel plus estramustine to mitoxantrone plus prednisone, confirmed the increased OS for docetaxel arm (17.5 vs. 15.6 mo, p = 0.02).[7] Furthermore, the addition of estramustine to docetaxel and prednisone did not provide any clinical advantage and more digestive and cardiovascular toxicities were reported.[8]

According to these data, docetaxel plus prednisone is considered the gold standard first-line chemotherapy for CRPC. Unfortunately, median OS for patients affected by metastatic prostate cancer is less than 20 months.

Recently, the FDA approved cabazitaxel and abiraterone acetate as second-line therapies after docetaxel failure. Furthermore, other agents have been tested in this setting and interesting results have recently been published. In this article, we review the current options and the ongoing trials for second-line treatment of CRPC.

Methods

We performed a review of publications identified through searches of Medline/PubMed from 2000 to the present, with particular focus on phase II/III trials. Abstracts from annual oncology meeting [e.g., American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO)] were taken into account. The ongoing phase II/III trials were searched from www.clinicaltrials.gov. Studies evaluating radiotherapy and systemic isotope therapy were not considered.

Chemotherapy

Satraplatin. Satraplatin is an oral platinum compound that forms platinum-DNA adducts and cross links but is not susceptible to some cisplatin resistance mechanisms. Phase I trials have tested satraplatin in different types of tumors and have explored several different dosing schedules, from daily dose for 5 days to a single dose every 3 weeks. Because of myelosuppression, the recommended dose and schedule is 100 and 120 mg/mq, for previously treated and untreated patients, for 5 days repeated every 4–5 weeks.[9]

A phase II trial evaluated safety and antitumor activity of satraplatin in 39 patients affected by CRPC.[10] Satraplatin was administered at 120 mg/mq for 5 days every 4 weeks. Twenty-six percent of patients had prostate-specific antigen (PSA) decline > 50% and 10% of patients with measurable disease had partial response (PR). Most frequent grade 3–4 toxicities were hematologic (54% thrombocytopenia, 52% neutropenia, 24% anemia) and gastrointestinal (28% diarrhea, 16% vomiting and 13% nausea).

The important side effects reported in the phase II led to two phase III studies based on different dose and schedule. The first one was prematurely closed to further accrual by the sponsoring company.[11] In this trial, satraplatin at dose of 100 mg/mq for 5 d every 5 weeks plus prednisone was compared with prednisone alone as first-line chemotherapy in CRPC. The ad hoc analysis of 50 enrolled patients showed improvement in progression free survival (PFS; 5.2 vs. 2.5 mo; HR 0.50, 95% CI 0.28–0.92, p = 0.02) and OS (14.9 vs. 11.9 mo) for satraplatin arm but the advantage in OS was not statistically significant due to the small sample size. These data led to the SPARC trial where satraplatin was compared with placebo on 950 patients affected by CRPC progressing after one prior chemotherapy. They were randomly assigned (2:1) to receive satraplatin 80 mg/mq for 5 days every 35 days or placebo, both plus prednisone 10 mg daily.[12] Crossover between treatment arms was not allowed. Primary endpoints of the study were OS and PFS, secondary endpoint was time to pain progression (TPP), exploratory endpoints were PSA response rate (PSA RR), pain response rate (PRR) and objective tumor response rate (TRR). PFS was 11.1 vs. 9.7 weeks, p < 0.001, HR 0.67 (95% CI 0.57–0.77, p < 0.001) and median TPP was 66.1 vs. 22.3 weeks, p < 0.001, both higher in satraplatin arm. PSA RR (25.4% vs. 12.2%, p < 0.001), PRR (24.2% vs. 13.8%, p = 0.005) and TRR (8 vs. 0.7%, p = 0.002) were all in favor of satraplatin. Median OS was 61.3 weeks for satraplatin and 61.4 weeks for placebo (HR 0.98, 95% CI 0.84–1.15, p = 0.80). A quality-of-life assessment was not part of the trial, but satraplatin showed a positive effect on pain control.

Treatment was well tolerated: hematologic and gastrointestinal toxicities were more frequent adverse events in satraplatin group, but in contrast to other platinum analogs, no significant worsening of renal function or neuropathy occurred with satraplatin.

Because of the lack of survival benefit, the sponsor decided to not pursue on the drug's development in prostate cancer.

Cabazitaxel. Cabazitaxel is a novel tubulin-binding taxane that showed antitumor activity in models resistant to docetaxel and paclitaxel. Cabazitaxel binds to and stabilizes tubulin and unlike other taxane compounds, this agent has decreased propensity for P-glycoprotein-mediated drug resistance. Cabazitaxel side effect profile is similar to that reported for other taxanes, with neuropathy and neutropenia being the most commonly reported toxicities.

A phase I trial evaluated cabazitaxel in 25 patients affected by advanced solid tumors refractory to conventional therapies.[13] Patients were treated with a 3-weekly schedule at four dose levels (from 10 to 25 mg/mq). Neutropenia was the principal dose-limiting toxicity and the recommended dose for further studies was 20 mg/mq. PR was documented in two patients, both affected by metastatic prostate cancer and in one case after docetaxel failure.

The lack of effective second-line therapies for CRPC and the encouraging results of the phase I trial conducted directly to a phase III study.

The TROPIC is a randomized, multicenter, open-label, phase III trial undertaken in 26 countries comparing cabazitaxel with mitoxantrone as second-line therapy in CRPC.[14] In this trial 755 men affected by metastatic prostate cancer after progression with taxane-based chemotherapy were enrolled. Although the recommended dose was 20 mg/mq in the phase I study, 25 mg/mq of cabazitaxel was used in the phase III trial based on a previous phase II study conducted in younger women with metastatic breast cancer.[15]

Patients were randomly assigned to treatment groups: 378 received cabazitaxel 25 mg/mq every 3 weeks and 377 received mitoxantrone 12 mg/mq every 3 weeks, both plus prednisone 10 mg daily. Premedication consisting of corticosteroids, histamine H2-antagonist and antihistamine was administered 30 min before cabazitaxel. The primary endpoint of the study was OS, the secondary endpoints were PFS, PSA RR, time to PSA progression (TTPP), TRR, PRR, TPP, time to tumor progression (TTP) and safety. After a median follow-up of 12.8 mo, cabazitaxel showed an improvement in OS (15.1 vs. 12.7 mo) with a 30% reduction in relative risk of death (HR 0.70, 95% CI 0.59–0.83, p < 0.0001). PFS (2.8 vs. 1.4 mo, p < 0.0001), PSA RR (39.2 vs. 17.8%, p = 0.0002), TRR (14.4 vs. 4.4%, p = 0.0005), TTP (8.8 vs. 5.4 mo, p < 0.0001) and TTPP (6.4 vs. 3.1 mo, p = 0.001) were all in favor of cabazitaxel arm. PRR (9.2 vs. 7.7%, p = 0.63) and TPP were similar in the two groups.

Grade 3–4 related adverse events were: anemia, neutropenia (82% for cabazitaxel vs. 58% for mitoxantrone, febrile 8% vs. 1% respectively) and diarrhea (23% vs. < 1%). Death within 30 days from the last infusion was reported in 5% of patients treated with cabazitaxel and 2% treated with mitoxantrone,

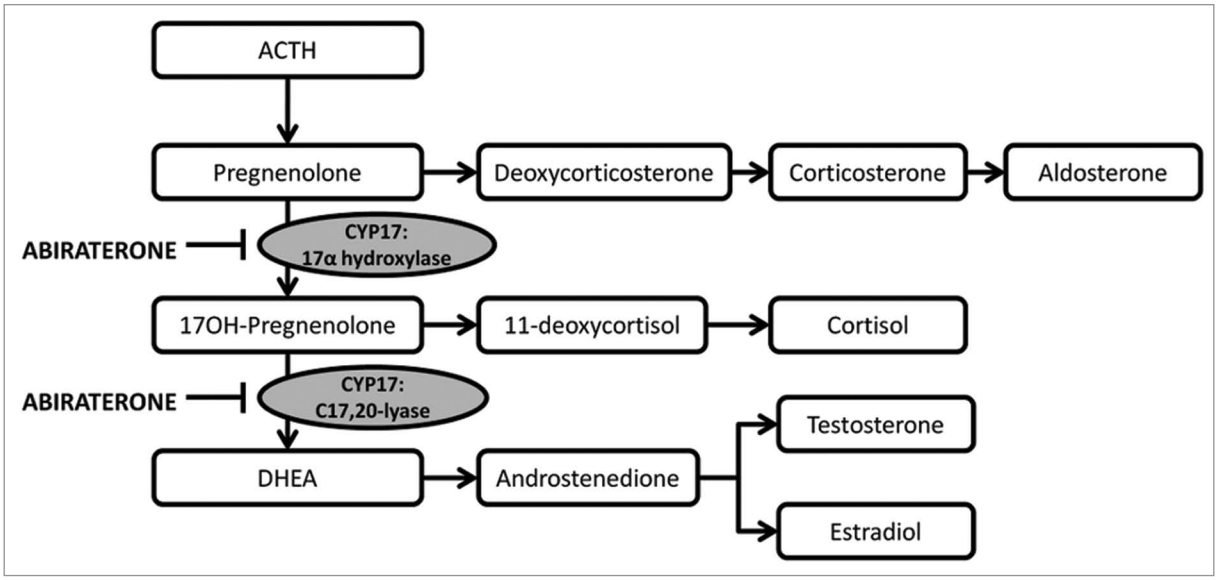

Figure 1. Mechanism of action of Abiraterone acetate.[52]

respectively. The most frequent cause of death in the cabazitaxel group was neutropenia and its clinical consequences. The higher risk of death within 1 month from the last drug dose and high rates of neutropenia and diarrhea suggest that cabazitaxel treatment requires careful monitoring. Prophylactic use of granulocyte colony-stimulating growth factors and dose modifications can be considered correct strategies to manage side effects. To assess whether a lower dose of cabazitaxel has a better safety profile with the same efficacy, a phase III trial has been designed. The PROSELICA trial (NCT01308580) compares cabazitaxel at 25 mg/mq vs. cabazitaxel at 20 mg/mq, both every 3 weeks in combination with prednisone. The primary endpoint of the study is OS and the secondary endpoint is PFS.

Considering the improvement in OS and the manageable toxicity profile, cabazitaxel has been approved by the FDA as second-line treatment for CRPC.

Hormonal Strategies

After an initial response to ADT, about 90% of patients with metastatic prostate cancer register an increase of serum PSA concentrations, with or without radiological progression of disease, and develop site-related symptoms which indicate the androgen-receptor (AR) reactivation after a time variable of length from months to several years.[16] These events characterize a different phase of disease, referred as CRPC, with the development of a clone of cells insensible to the ADT.[17]

Over the past decade, several studies have shown that CRPC remains dependent on AR function for growth. The molecular basis for AR reactivation remains unclear, but some possible mechanisms include increased AR expression, AR mutations that enhance activation by weak androgens and AR antagonists, increased expression of transcriptional coactivator proteins and activation of signal transduction pathways that can enhance AR responses to low levels of androgens. Moreover AR may be activated by other endogenous steroids as those produced by adrenal gland.[18,19]

Several molecules with antiandrogen activity are currently under investigation in CRPC patients who have received or not docetaxel: abiraterone acetate, MDV3100 and TAK-700.

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

Preclinical data revealed as 17-(3-pyridyl)androsta-5,16-dien-3 β-ol (CB7598) is a potent steroidal inhibitors of cytochrome P450(17) α, a key enzyme for androgen biosynthesis.[20]

Two phase I studies demonstrated safety and activity of abiraterone acetate in patients with CRPC.[21,22] A total of 54 patients were enrolled and received once daily orally escalating dose of abiraterone: from 250 to 1,000 mg in patients previously treated with ketoconazole and from 250 to 2,000 mg in ketoconazole-naïve patients. The most common adverse events were fatigue, hypertension, headache, nausea and diarrhea, which were predominantly grade 1–2. The most frequent treatment-related grade 3–4 toxicities were hypertension, hypokalemia, constipation, diarrhea, muscular weakness and arthralgia.

The pharmacokinetics analysis showed as abiraterone acetate was rapidly converted to abiraterone, confirming the intrapatient variability of metabolism and the influence of food. Particularly, the absorption was significantly extended after food intake and drug exposure was significantly increased (by 4.4-fold) by high-fat content food, compared with fasting administration. These studies did not show any cross-resistance between ketoconazole and abiraterone acetate and the recommended dose for

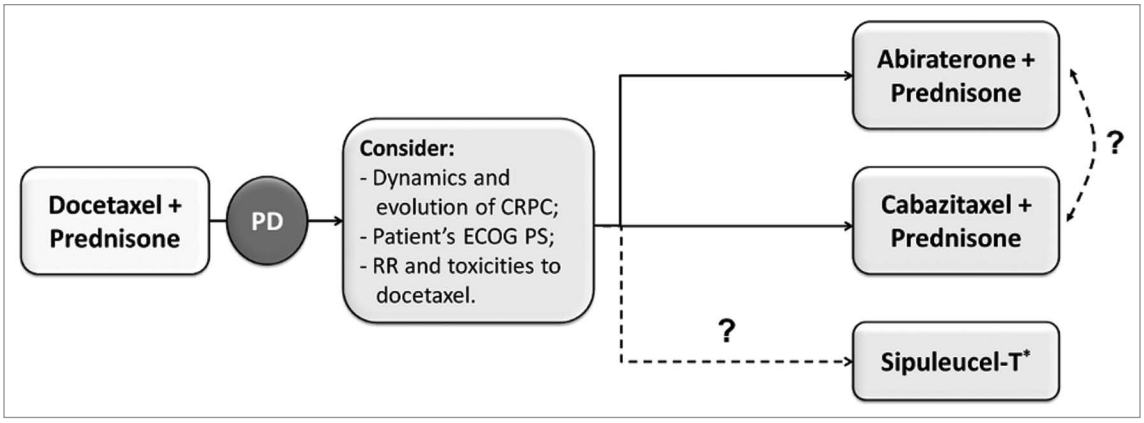

Figure 2. Possible algorithm for treatment of docetaxel progressed CRPC.[52] PD, progression of disease; CRPC, castration resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group. Performance status; RR, response rate. *Unlike other drugs approved for CRPC patients progressing during or after docetaxel-based chemotherapy, Sipuleucel-T has been approved for patients with metastatic, asymptomatic or minimally symptomatic, hormone-refractory prostate cancer.

subsequent phase II trials was 1,000 mg daily, supporting the once daily administration based on the pharmacodinamics and pharmacokinetics data.

Three phase II studies have been conducted in CRPC patients. In a first study conducted in patients who did not receive first-line docetaxel chemotherapy, abiraterone acetate showed a significant clinical activity, with a ≥ 50% PSA reduction in 67% of patients and PR according to Response Evaluation Criteria In Solid Tumors (RECIST) in 37.5% of patients. Furthermore, the addition of dexamethasone at disease progression reversed resistance in 33% of patients.[23]

The other two studies tested the activity of abiraterone acetate in 105 patients with docetaxel-treated CRPC.[24,25] The first trial reported a ≥ 50% PSA decline from baseline in 51% of patients. Moreover, ≥ 30% or ≥ 90% PSA decline was reported in 68% and 15% of patients respectively; 27% of patients with measurable disease had PR defined by RECIST criteria.[24]

The second trial, evaluating the activity of abiraterone acetate plus prednisone, reported a ≥ 50% PSA decline in 36% of patients and a ≥ 30% or ≥ 90% PSA decline in 47% and 16% of patients, respectively; PR was observed in 18% of patients with soft tissue measurable lesions. Both studies showed a period of 169 days TTPP.[25]

The aforementioned trials demonstrated that treatment with abiraterone is well tolerated and toxicities could be influenced by the concomitant administration of steroids. Abiraterone acetate alone caused hypokalemia, hypertension and fluid retention in 55, 17 and 15% of patients, respectively; on the contrary, the combined modality caused hypokalemia and fluid retention in 5 and 7% of patients, respectively. Other reported toxicities in both studies such as fatigue, nausea, anorexia, headache and AST increase were not influenced by concomitant administration of steroids.

Recently the results from a pre-specified interim analysis of the phase III study have been published.[26] The COU-AA-301 is a multinational, randomized, double blind, placebo-controlled trial conducted in 13 countries. The trial enrolled 1,195 patients whose metastatic CRPC had previously been treated with one or two chemotherapeutic agents, included docetaxel. Patients were randomized 2:1 to receive abiraterone acetate 1,000 mg once daily or placebo, each with prednisone 5 mg twice daily continuously. OS was the primary endpoint of the study and the secondary were TTPP, PSA RR, radiographic progression-free survival (rPFS) and TRR.

The 797 patients in the abiraterone acetate arm reported a median OS of 14.8 months compared with 10.4 months of the 398 patients who received placebo (HR 0.65, 95% CI 0.54–0.77, $p < 0.0001$). Moreover, significant differences emerged between placebo and treatment groups for all secondary endpoints, including TTPP (10.2 vs. 6.6 mo, $p < 0.0001$), rPFS (5.6 vs. 3.6 mo, $p < 0.0001$), PSA RR (29% vs. 6%, $p < 0.0001$) and TRR (14 vs. 3%, $p < 0.001$).[26] The most severe abiraterone-related adverse events were fluid retention (31 vs. 22% in placebo arm), hypokalemia (17 vs. 8%) and cardiac disorders (13 vs. 11%). Patients receiving placebo were permitted to cross over to the abiraterone arm. On the basis of these results, abiraterone acetate has been approved by the FDA for CRPC after docetaxel failure on April 2011.

Given its efficacy and manageable toxicities, ongoing trials explore the effects of abiraterone in different setting. A second large phase III trial is ongoing involving comparison of abiraterone acetate 1,000 mg with placebo, both with prednisone, in CRPC patients who have not yet received docetaxel (NCT00887198). A phase II trial is evaluating the role of abiraterone and prednisone with an LHRHa agonist as neoadjuvant and concurrent therapy with external beam radiation in patients with intermediate-risk or high-risk localized prostate cancer (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 LHRHa alone.

Considering the feasibility and safety of combination with LHRH agonists, future combinations with new-generation

Table 1. Clinical trials in CRPC after docetaxel progression

Class of drug	Molecule	Phase study	Patients	Comparator	PSA-RR (%)	ORR (%)	PFS (months)	OS (months)	HR
Chemotherapy	Satraplatin + prednisone[a]	III	950 (2:1)	Placebo + prednisone	25.4 vs 12.4 p < 0.001	8.0 vs. 0.7 p = 0.002	11.1 vs 9.7 weeks p = 0.001	66.1 vs. 62.9 weeks p = 0.8	0.91 (95% CI, 0.72–1.14)
	Cabazitaxel + prednisone	III	755 (1:1)	Mitoxantrone + prednisone	39.2 vs. 17.8 p = 0.0002	14.4 vs. 4.4 p = 0.0005	2.8 vs. 1.4 p = 0.0001	15.1 vs. 12.17 p < 0·0001	0.70 (95% CI, 0.59–0.83)
Immunotherapy	Sipuleucel[b]	III	512 (2:1)	Placebo	2.6 vs. 1.3	N.A.	3.7 vs. 3.6 p = 0.63	25.8 vs. 21.7 p = 0.02	0.76 (95% CI, 0.61–0.95)
Hormonal	Abiraterone + prednisone	III	1195 (2:1)	Placebo + prednisone	29.0 vs. 6.0 p < 0.001	14.0 vs. 3.0 p < 0.001	5.6 vs. 3.6 p < 0.001	14.8 vs. 10.9 p < 0.001	0.67, (95% CI, 0.58–0.78)
	MDV3100 ± prednisone	III	1199 (2:1)	Placebo ± prednisone	54.0 vs. 1.5 P < 0.0001	28.9 vs. 3.8 p < 0.0001	8.3 vs. 2.9 p < 0.0001	18.4 vs. 13.6 p < 0.0001	0.63 (95% CI, 0.53-0.75)

Abbreviations: CRPC, castration resistant prostate cancer; PSA-RR, PSA response rate (≥ 50%); ORR, overall response rate; PFS, progression free survival; OS, overall survival; HR, hazard ratio (for OS); CI, confidence interval. [a]Only 51% of patients have received docetaxel; [b]only 14.4% of patients have received docetaxel.

antiandrogen molecules (MDV3100, TAK-700, etc.) may be feasible as well as the possible combination with chemotherapy.[27,28]

MDV3100. MDV3100 is an orally bioavailable, organic, non-steroidal small molecule targeting the androgen receptor with potential antineoplastic activity. MDV3100 inhibits the activity of prostate cancer cell ARs, which may result in prostate cancer cell proliferation reduction and, correspondingly, in PSA levels decline. This compound has been demonstrated to bind ARs in castration resistant xenograft prostate cancer cells with five to 8-fold greater affinity than bicalutamide, did not show agonist activity and antagonized the induction of PSA and other genes regulated by ARs, impairing DNA binding.[29]

A multicenter phase I–II trial enrolled patients with histologically proven prostate cancer and progressive castration-resistant disease, defined by the combination of castrate levels of testosterone (< 1.7 nmol/L), and a rising PSA with or without detectable metastases.[30]

A total of 140 patients were enrolled, with a median age of 68 years and radiological evidence of metastasis in the majority of patients. Both chemotherapy-naïve and previously treated patients were enrolled.

MDV3100 was associated with tumor regression and stable disease in 22 and 49% of patients with soft tissue disease, while stable disease was shown in 56% of patients with bone metastases. Median TTPP was 27 weeks and median TTP was 47 weeks. PSA decline ≥ 50% was observed in 62% of chemotherapy-naïve patients and in 51% of post-chemotherapy patients.

The most common adverse events were fatigue, nausea, constipation, diarrhea and anorexia. Considering that only 1% of patients treated at 240 mg or below discontinued treatment for an adverse event, it was chosen as maximum tolerated dose.

The AFFIRM trial is a randomized, double-blind, multinational phase III trial comparing MDV3100 (160 mg orally per day) vs. placebo in 1,199 patients with CRPC previously treated with at least one docetaxel-based chemotherapy.[31] Corticosteroids were not required but allowed. The primary endpoint of the study was OS, and secondary endpoints included PSA RR, Soft tissues objective response rate, circulating tumor cells (CTC) count conversion rate, rPFS, TTPP and time to first skeletal-related event. Recently, a planned interim analysis revealed that estimated median OS is 18.4 months for men in the MDV3100 arm compared with 13.6 months for men treated with placebo, with a reduction of the risk of death by 37% (p < 0.0001, HR 0.631). PSA RR (54 vs. 1.5%, p < 0.0001), TTPP (8.3 vs. 3.0 mo, p < 0.0001), soft tissue response rate (28.9 vs. 3.8%, p < 0.0001), rPFS (8.3 vs. 2.9 mo, p < 0.0001) were all in favor of MDV3100. MDV3100 was also well tolerated and the most frequent adverse events were fatigue (33.6 vs. 29.1% in the placebo arm), cardiac disorders (6.1 vs. 7.5%), liver function tests abnormalities (1 vs. 1.5%) and seizure (0.6% vs. 0%)

As a result, the trial's Independent Data Monitoring Committee recommended that AFFIRM trial be stopped early and that men who were receiving placebo be offered MDV3100.[31]

Further ongoing trials evaluate MDV3100 in different setting. An ongoing trial will determine the effect of MDV3100 on the androgen-signaling pathway in order to identify potential predictors of response or resistance to therapy in patients affected by prostate cancer with bone metastasis, already treated with ADT (NCT01091103). MDV3100 is compared with placebo in patients with metastatic CRPC who have failed ADT but not yet received chemotherapy (PREVAIL trial, NCT01212991). Furthermore, a phase II trial is testing the efficacy and safety of MDV3100 in patients with prostate cancer for whom ADT is indicated (except when indicated in a neoadjuvant/adjuvant therapy), with non-castrate level of testosterone (≥ 8 nmol/L) and PSA ≥ 2 ng/mL (NCT01302041). Another phase II trial evaluates MDV3100 vs. bicalutamide in men with metastatic prostate cancer who have failed medical or surgical castration (NCT01288911).

TAK-700. TAK-700 is an orally bioavailable non-steroidal androgen synthesis inhibitor of steroid 17alpha-monooxygenase (17,20 lyase) with potential antiandrogen activity. TAK-700

binds to and inhibits the steroid 17alpha-monooxygenase in both the testes and adrenal glands, thereby inhibiting androgen production.

TAK-700 has shown impressive activity in a phase I/II study.[32,33] In the first portion of the study,[32] 26 patients affected by metastatic CRPC received TAK-700 at five doses levels (from 100 to 600 mg BID, plus prednisone 10 mg daily). All patients receiving at least 300 mg BID had a PSA decrease. The most common adverse events were fatigue, nausea, constipation, anorexia and vomiting.

The second portion of the study[33] is a open-label, multicenter, phase II trial evaluating four additional dose cohorts (300 mg BID, 400 and 600 mg BID plus prednisone 10 mg daily, 600 mg QD). Patients enrolled have not received prior chemotherapy, have baseline testosterone < 50 ng/dL and PSA ≥ 5 ng/ml. TAK-700 appears well tolerated and active in all groups. PSA decline ≥ 50% at 12 weeks was observed in 63, 50, 41 and 60% of patients in the 300 mg BID, 400 and 600 mg BID plus prednisone and 600 mg QD groups. At 12 weeks, median dehydroepiandrosterone sulfate, testosterone levels and CTC numbers decreased from baseline in all groups.

An ongoing phase III trial (NCT01193257) evaluates TAK-700 vs. placebo, both with prednisone, in patients with CRPC who have progressed following taxanes-based therapy.

Antiangiogenic and Immune Strategies

Antiangiogenic therapies. Tumor angiogenesis is a well-known, crucial target in many solid tumors such as colon, lung, breast and renal cancer. Antiangiogenic therapy represents as well a fashionable approach in advanced prostate cancer treatment. Main markers of angiogenesis such as vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), and transforming growth factor (TGF) are highly expressed in prostate carcinoma compared with nonmalignant prostate cells.[34] Moreover, angiogenesis (measured as microvessel density, MVD) seems to be correlated with tumor stage, grade and clinical course in prostate cancer.[35,36]

Some antiangiogenic strategies have been studied and are currently under investigation in patients with CRPC. Tyrosine kinases inhibitors including sorafenib, sunitinib and cediranib or monoclonal antibodies against circulating VEGF have been tested in phase II-III trials.

Sorafenib is a synthetic compound targeting RAF kinase, a critical component of the RAF/MEK/ERK signaling pathway that controls cell division and proliferation. In addition, sorafenib inhibits vascular endothelial growth factor receptor 2/platelet derived growth factor receptor β (VEGFR-2/PDGFR-β) signaling cascade, thereby blocking tumor angiogenesis. In prostate cancer cell lines, sorafenib inhibits ERK phosphorylation and induces apoptosis.[37]

Three phase II[38-40] tested sorafenib at the dose of 400 mg orally twice daily in CRPC patients, but only one included patients that have received a previous line of chemotherapy.[38] In this trial the primary endpoint was disease progression, defined as either the appearance of new lesions or unidimensional or bidimensional tumor measurements increasing > 50% or increase of PSA. Results showed reduction of bone lesions despite PSA raising, reporting manageable side effects. In the study's conclusions, it is hypothesized an activity only in patients presenting primarily with metastatic bone lesions whereas PSA seems to be a poor marker of disease progression.

Sunitinib is a tyrosine kinase inhibitor with potential antineoplastic activity in prostate cancer. It acts blocking the tyrosine kinase activity of VEGFR2, PDGFR-b and c-kit, thereby inhibiting angiogenesis and cell proliferation. Sunitinib is currently considered the best therapeutic approach for patient with advanced renal cell carcinoma and for the treatment of gastrointestinal stromal tumors after disease progression or intolerance to imatinib mesylate.

Preclinical evidence of sunitinib activity in prostate cancer cells[41,42] leaded to a phase II trial in patients with CRPC after a docetaxel-based chemotherapy.

The primary end-point of the study was reached, with a PFS at 12 weeks of 75.8% and a median PFS of 19.4 weeks. Twelve percent of patients had a ≥ 50% PSA decline and 21% had a ≥ 30% PSA decline compared with baseline; decrease of measurable disease and of pain score were also reported. A favorable safety profile characterized by fatigue, anemia, nausea, anorexia and neutropenia as the most common toxic effects was also demonstrated.[43] Despite these encouraging results, the subsequent phase III trial was prematurely closed due to lack of any advantage compared with placebo.

Bevacizumab, a recombinant humanized monoclonal antibody directed against VEGF, was also tested in CRPC patients. Particularly, at the 2010 ASCO Annual Meeting was reported that bevacizumab plus docetaxel/prednisone prolongs PFS as first-line therapy but is unable to prolong OS compared with docetaxel/prednisone in a phase III trial.[44]

Moreover, a combined therapy with docetaxel and bevacizumab was administered to a group of highly pretreated patients with CRPC in a non randomized phase II trial.[45] The combination showed a favorable safety profile with grade 4 toxicity limited to neutropenia and thrombocytopenia and a ≥ 50% PSA decline in 55% of patients. Objective responses were observed in 37.5% of patients with measurable disease.

In conclusion, angiogenesis remains an attractive target in prostate cancer although clinical trials did not show any encouraging result. Current data are extremely confused due to heterogeneity of studied populations and of endpoints used. Probably, deeper insights in prostate cancer biology and a better understanding of the optimal timing of the angiogenic switch may improve the clinical activity of these therapeutic strategies in CRPC patients.

Immune strategies. The IMPACT study showed first as therapy with the autologous vaccine sipuleucel-T yielded an improvement in OS compared with placebo in CRPC patients.

Sipuleucel-T is an active cellular immunotherapy, a type of therapeutic cancer vaccine, consisting of autologous peripheral-blood mononuclear cells, including antigen-presenting cells, that have been activated ex vivo with a recombinant fusion protein (PA2024). PA2024 consists of a prostate antigen, prostatic acid

phosphatase, that is fused to granulocyte-macrophage colony-stimulating factor, an immune cell activator.

Although the IMPACT study was designated to assess Sipuleucel-T in first-line setting, the trial enrolled patients who had received docetaxel (15%). The results confirmed an improvement in OS (25.8 vs. 21.7 mo, HR 0.78, 95% CI 0.61–0-98, p = 0.03) for the whole group.[46]

Conclusions

All these data show the traditional approach to CRPC progressed after docetaxel in first-line therapy is changing. Cabazitaxel, abiraterone acetate, Sipuleucel-T and MDV3100 have demonstrated improvement in OS in second-line setting (**Table 1**).

Although new drugs are available, many questions should be resolved as the best sequence after docetaxel failure or the selection of appropriate predictive factors of response to second-line therapies.

Further clinical trials are needed to better understand which patients will most benefit from a second-line cytotoxic chemotherapy rather than hormonal approaches. Probably patient's conditions, response and toxicities reported with previous therapies and the history of disease may be the most useful parameters in clinical practice before that new guidelines will be published. In asymptomatic patients, timing of treatment is not clear and it should be tailored individually (**Fig. 2**).[47] Symptomatic patients need a rapid response rate to improve pain and disease related symptoms. For them, both cabazitaxel and abiraterone should be considered an appropriate treatment, reporting the same TRR (14.4% for cabazitaxel and 14% for abiraterone). Patients with an ECOG performance status of 2 represent only a small part (about 10%) of the study population of the main phase III trials. For them, best supportive care is still a feasible option. Recent data have demonstrated that a previous duration of prostate cancer sensitivity to ADT ≥ 16 months is a predictive factor for efficacy of subsequent endocrine manipulations in patients with CRPC.[48]

Furthermore, new biomarkers predictive of efficacy have to be evaluated. Until now, PSA has been the most studied biomarker of disease evolution for prostate cancer, but some data suggest that it is not a surrogate of survival in all phases of disease.[49] Recently, there is a strong interest for CTC and it has been demonstrated that pre-treatment CTC count is an independent predictor of OS in CRPC.[50] The role of CTC count in second-line setting is still under investigation, but it appears promising.[51]

Further trials have to be designed to better understand how to use the new agents in sequence or in combination for treating CRPC. Results of the ongoing trials evaluating hormonal treatments after ADT failure (NCT00887198 for abiraterone and PREVAIL trial for MDV3100) are awaited to better define the role of docetaxel in CRPC.

Nowadays we have more opportunities than in the past, so next challenge should be to find out the best sequential therapy after docetaxel failure and a possible third-line for selected patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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