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REVIEW

New treatment options for patients with metastatic prostate cancer

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ABSTRACT

Prostate cancer is one of the most common cancers in men. When metastasised (40% of patients), classic anti-androgen therapy is the first-line treatment. Usually, this treatment becomes ineffective when castration-resistant prostate cancer (CRPC) develops. Thus far, docetaxel was the only chemotherapeutic option that has shown to be able to extend overall survival and improve quality of life in these patients. Recently, cabazitaxel and abiraterone have shown significant survival benefits for patients progressive on or after docetaxel treatment, as did enzalutamide and radium-223. In North America, immune therapy (sipuleucel-T) became available for a subgroup of CRPC patients. These new treatment options will change the treatment paradigm of patients with metastatic castration-resistant prostate cancer. A multidisciplinary approach by both medical oncologists and urologists seems mandatory.

KEYWORDS

Abiraterone, cabazitaxel, CRPC, enzalutamide, prostate cancer

INTRODUCTION

Recently a wide variety of novel treatment options for patients with advanced prostate cancer became available. In this article we want to introduce new drugs that have shown survival advantages in patients with metastatic prostate cancer.

New treatment options are welcome, since one in 11 men will develop prostate cancer during life. Of these patients, 18% have metastatic disease at the time of diagnosis and 40% will develop metastatic disease (2011, cijfersoverkanker.nl).[1,2] Until recently, the treatment options for these patients were sparse.[3]

Before 2011, metastatic prostate cancer was treated with classic androgen ablation therapy. The goal of this therapy was to achieve castrate levels of testosterone (<15 ng/dl), thereby depriving prostate cells of their most important stimulant for growth, function and proliferation *(figure 1)*. The testes are the largest source of most androgens, and adrenal biosynthesis provides an additional 5-10% of circulating androgens levels. Castrate levels of testosterone can be achieved surgically by bilateral orchidectomy, or medically with gonadotropin-releasing hormone (GnRH) agonists or antagonists. Classic anti-androgens inhibit the action of circulating androgens by competitive binding of the androgen receptor of prostate cancer cells.

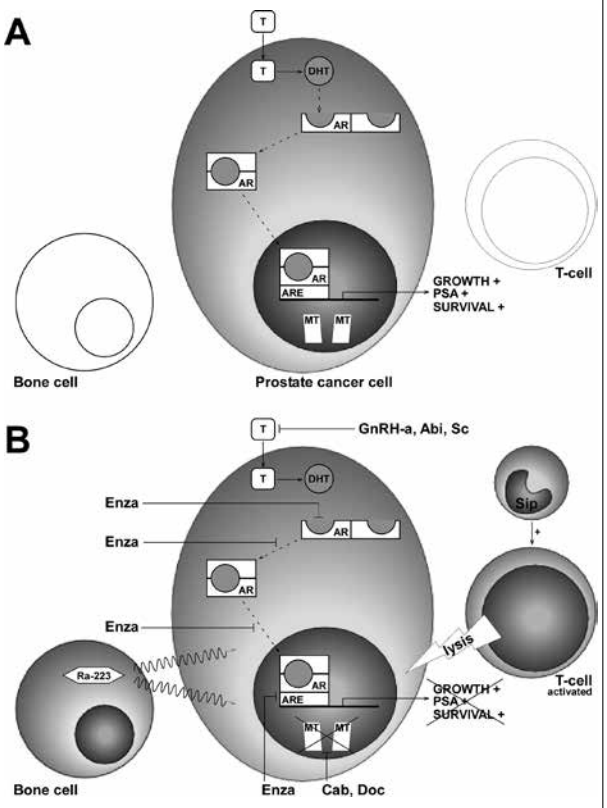
After a median of 2-3 years of therapy, metastatic prostate cancer usually becomes refractory to conventional androgen ablation therapy.[3,4] Prostate-specific antigen (PSA) levels increase again, despite castrate levels of androgens. This phase is called biochemical progressive disease. Clinical manifestations due to bone, lymph node and visceral metastases and local pelvic symptoms usually develop thereafter.

Recent insights, however, show that progression in this stage of the disease is still androgen-dependent due to changes of structure and function of the androgen receptor.[5] There appears to be a gradual shift during prostate cancer progression from dependence of androgens from endocrine sources to dependence of androgens from paracrine, autocrine and intracrine sources.[6] This stage of the disease, where prostate cancer grows despite castrate levels of androgens, is now called castration-resistant prostate cancer (CRPC).[7] The insights into the persistent crucial role of the androgen receptor route led to the

development of new androgen receptor route pathway inhibitors (*figure 1*).

Until 2011, second-line endocrine therapy in patients with progressive metastatic disease consisted of anti-androgen withdrawal or switch, possibly combined with prednisone. Although these treatments have a positive effect on symptoms, none of them extends overall survival.[8] In this phase, chemotherapy may also play a role. In 2004, treatment consisting of docetaxel demonstrated both improved quality of life and overall survival rates when compared with standard treatment consisting of mitoxantrone plus prednisone.[9] Therefore, over the last decade docetaxel plus prednisone became the new standard treatment for metastatic castration-resistant disease. For patients with refractory disease, only palliative systemic or local therapy remains.[10]

Figure 1. *Mechanisms of action of new drugs used in metastasised prostate cancer*



A) Testosterone (T) is the most important external growth stimulus for prostate (cancer) cells. It is internalised by prostate (cancer) cells and converted intracellularly to dihydrotestosterone (DHT). Both T and DHT are ligands of the intracellular androgen receptor (AR). Ligand binding induces a conformational change of the AR after which it transfers to the nucleus. In the nucleus, AR binds to androgen-responsive elements (ARE) in the DNA, thereby inducing gene expression leading to growth and survival of the prostate (cancer) cell. Prostate specific antigen (PSA) is also induced by the AR. Serum level rise is a sign of an active AR route. MT = microtubuli.

B) Blocking the androgen receptor (AR) route is an effective way of depriving the prostate (cancer) cell growth and survival stimuli. GnRH agonist/antagonists (GnRH-a), abiraterone (Abi) and surgical castration (Sc) all lower circulating testosterone levels around prostate (cancer) cells, thereby depleting AR of its ligand. The AR remains inactive. Enzalutamide (Enza) binds the AR ligand site, inhibiting nuclear translocation of the AR, DNA binding, and coactivator recruitment. Cabazitaxel (Cab), like docetaxel (Doc), is a microtubuli (MT) stabilisator. This results into blocking of cell division, thereby inducing cell death. Sipuleucel-T (Sip) induces native T cells to kill prostate cancer cells in an antigen-dependent manner. Radium-223 (Ra-223) targets new bone growth in and around bone metastases. It induces double-strand DNA breaks through alpha radiation over a short distance, thereby inducing cell death.

RECENT DEVELOPMENTS: NEW TREATMENT OPTIONS FOR METASTATIC CRPC

In the past two years several new treatment strategies have been developed for patients with metastatic CRCP (mCRPC). Several of these strategies have shown survival advantages in large phase III trials in patients who are refractory after docetaxel treatment. These strategies consist of cytotoxic, anti-androgen, immune, and radiopharmaceutical therapies (*table 1*). All studies were done in patients with a World Health Organisation (WHO) performance status (PS) of mostly 0-1.

NEW CYTOTOXIC THERAPY: CABAZITAXEL

Cabazitaxel, (Jevtana®) like docetaxel, is a microtubuli stabilisator. It is a second-generation taxane which has shown antitumor activity in cell lines resistant to docetaxel. The TROPIC study (Treatment of Hormone Refractory Metastatic Prostate Cancer Previously Treated with a Docetaxel-Containing Regimen) included 755 mCRPC patients with progressive disease after treatment with docetaxel.[11] The median age was 67 years (18% were >70 years), and patients had a beneficial WHO performance status (92% PS 0-1, others: 2). They were treated with tri-weekly cabazitaxel plus prednisone or mitoxantrone plus prednisone.

The median overall survival in the cabazitaxel-treated group was 15.1 months *vs* 12.7 months in the mitoxantrone group (HR 0.70; 95% CI 0.59-0.83; p<0.0001). Median time to tumour progression was longer and pain palliation was equal in both groups. The most common clinically significant grade 3 or higher adverse events were neutropenia (cabazitaxel 82% of patients *vs* mitoxantrone 58% of patients) and diarrhoea (cabazitaxel 6% *vs* mitoxantrone <1% of patients). Eight percent of patients in the cabazitaxel group and 1% in the mitoxantrone group had febrile neutropenia. Eighteen patients (5%) died in the cabazitaxel group and nine patients (2%) in

Table 1. *Phase III trials of drugs showing improved overall survival in mCRPC patients*

Trial	Tested drug	Tested patients	Number of patients	Survival in months (HR)
TROPIC[11]	Cabazitaxel (iv)/prednisone vs mitoxantrone/prednisone	Post-docetaxel	755	15.1 vs 12.7 (0.70)
COU-AA-301[12]	Abiraterone (oral)/prednisone vs placebo/prednisone	Post-docetaxel	1195	14.8 vs 10.9 (0.65)
COU-AA-302[13]	Abiraterone/prednisone vs placebo/prednisone	mCRPC	1088	NR vs 27.2
AFFIRM[15]	Enzalutamide (oral) vs placebo	Post-docetaxel	1199	18.4 vs 13.6 (0.70)
IMPACT[16]	Sipuleucel-T (i.v.) vs controls	mCRPC	512	25.8 vs 21.7 (0.78)
ALSYMPCA[17]	Radium-223 (i.v.)/BSC vs placebo/BSC	Post-docetaxel or unsuitable for docetaxel	921	14.9 vs 11.3 (0.63)

BSC = best supportive care; HR =hazard ratio; mCRPC = metastatic castration-resistant prostate cancer.

the control group because of treatment-related side effects. Eighteen percent of the cabazitaxel group patients *vs* 8% in the mitoxantrone group discontinued study treatment because of side effects. Cabazitaxel is available in Europe for patients with a good PS (0-1) since its approval by the European Medicines Agency (EMA) in March 2011.

NEW ANTI-ANDROGEN THERAPY: ABIRATERONE ACETATE AND ENZALUTAMIDE

Abiraterone acetate

Abiraterone acetate (Zytiga®), an oral prodrug of abiraterone, is a first-in-class selective cytochrome P-450c17 (CYP17) complex inhibitor, thereby making it an androgen synthesis inhibitor. Androgen synthesis in the adrenal glands, testes and prostate cancer cells and their microenvironment is effectively inhibited, thereby further lowering the serum testosterone levels.[6] Inhibition of CYP17 also leads to increased production of mineralocorticosteroids in the adrenal glands, leading to important but treatable side effects. Two trials investigating treatment using abiraterone have been published: one trial in the post-docetaxel setting[12] and another trial in the pre-docetaxel setting.[13]

Abiraterone post-docetaxel

The COU-AA-301 study included 1195 patients with progressive mCRPC with castrate levels of testosterone who had been previously treated with docetaxel.[12] Median age of the patients was 69 years (28% >75 years, PS 0-2). Patients were randomised 2:1 to receive either once a day abiraterone 1000 mg plus prednisone 10 mg or placebo plus prednisone 10 mg, until disease progression. The study was stopped at the first pre-planned interim analysis because of the significant reduction in death in the group of patients treated with abiraterone. The median follow-up was 12.8 months; the median overall survival in the abiraterone group was 14.8 months *vs* 10.9 months in the placebo group (HR 0.65; 95% CI 0.54-0.77; p<0.001). Progression-free survival (5.6 *vs* 3.6 months) and other secondary endpoints (disease progression measured by PSA, radiological response, pain response, time to bone complications) improved significantly in the group of patients treated with abiraterone. Mineralocorticoid side effects (oedema, hypokalaemia and hypertension) were noticed more often in the treatment group (55 *vs* 42% of patients; p<0.001), but were usually mild.

Recently, overall survival analysis data were published after a median follow-up of 20.2 months: the median overall survival was 15.8 *vs* 11.2 months in favour of the abiraterone-treated group (HR 0.74; p<0.0001).[14] At that moment, 16 *vs* 5% of the patients were still alive, suggesting no durable benefit of abiraterone on survival. Disease progression is only deferred. Abiraterone in combination with prednisone after docetaxel treatment is approved by EMA since September 2011.

Abiraterone pre-docetaxel

COU-AA-302 is a randomised controlled trial that compared placebo with abiraterone plus prednisone in asymptomatic or mildly symptomatic, and thus chemo-naive, mCRPC patients (n=1088; median age of patients 70.5 years; 32% ≥75 years; PS 0-1).[13] Very recently, this study was stopped at the second planned interim analysis because one of the co-primary endpoints was reached. Radiographic progression-free survival was 16.5 months in the abiraterone group and 8.3 months in the prednisone-alone group (HR 0.53; 95% CI 0.45-0.62; p<0.001). As for the second co-primary endpoint: there was a strong trend towards improved survival in patients on abiraterone plus prednisone versus prednisone alone (median follow-up 22.2 months: overall survival not reached in abiraterone group *vs* 27.2 months in placebo group). Secondary endpoints (palliative care) showed important improvement: median time to PS decline, cancer-related opiate use and start of cytotoxic chemotherapy were all significantly delayed in the abiraterone group. Based on these results, the EMA approved abiraterone plus prednisone for chemo-naive

asymptomatic or mildly symptomatic chemo-naive mCRPC patients in December 2012.

Enzalutamide

Enzalutamide (XTandi®) is an androgen-receptor-signalling inhibitor (ARSI) that binds the AR ligand site and thereby inhibits nuclear translocation of the AR, DNA binding, and coactivator recruitment. It has no known agonistic effects.[6,15] The AFFIRM trial (A Study Evaluating the Efficacy and Safety of the Investigational Drug MDV3100) enrolled 1199 patients 2:1 to enzalutamide 160 mg daily or placebo.[15] Patients median age was 69 years (25% ≥75 years) and they had a PS of 0-2 (8% PS 2) (supp data). They all had objective progressive disease on or after treatment with docetaxel. At the pre-specified interim analysis the study was stopped because of the reduction in death in the enzalutamide group. The median follow-up was 14.4 months, the median overall survival in the enzalutamide group was 18.4 months *vs* 13.6 months in [the] placebo group (HR 0.63; 95% CI 0.53-0.75; p<0.001). Superiority for enzalutamide was shown for all secondary endpoints, including PSA level response rate, soft tissue response rate, radiographic progression-free survival and time to first skeletal-related event. Although the period of observation of the enzalutamide group was more than twice that of the placebo group, rates of adverse events were similar in the two groups, and the median time to a grade 3 or higher adverse event was 12.6 months in the enzalutamide group, compared with 4.2 months in the placebo group. The most common adverse events in the enzalutamide group included fatigue, diarrhoea, and hot flashes. Convulsions are a dose-dependent toxic effect of enzalutamide and occurred in 0.9% of treated patients. Since August 2012, enzalutamide is approved in North America, and awaiting approval by EMA in Europe.

NEW IMMUNE THERAPY: SIPULEUCEL-T

Immune therapy with the vaccine sipuleucel-T (Provenge®) stimulates the immune system to lyse prostate tumour cells. Over 95% of prostate cancers express prostate acid phosphatase (PAP). The vaccine sipuleucel-T is made of autologous dendritic cells that are stimulated *in vitro* with a fusion protein (PA2024: PAP and granulocyte-macrophage colony stimulating factor). After reinfusion in the patient this vaccine induces native T cells to recognise and kill PAP-expressing prostate cancer cells in an antigen-dependent manner.

The IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment) study included 512 patients with asymptomatic or minimal symptomatic mCRPC (median age of patients 71 years, PS 0-1, Gleason ≤7, no known visceral metastases).[16] Of the included patients, 18% had used docetaxel therapy before. Patients received a sipuleucel-T infusion or placebo at T=0, 2 and 4 weeks. The median survival was 4.1 months longer in the sipuleucel-T group (25.8 *vs* 21.7 months; HR 0.78; 95% CI 0.61-0.98; p=0.03). Sipuleucel-T is the first immune therapy showing improvement of overall survival in mCRPC patients in a phase 3 randomised controlled trial. This immune therapy has been available in North America since 2010.

NEW RADIOPHARMACEUTICAL THERAPY: RADIUM-223

Radium-223 dichloride (Ra-223, Alpharadin®) is a new bone-seeking (first-in-class) alpha-emitter radionuclide. Radium-223 is a calcium mimetic that naturally targets new bone growth in and around bone metastases. It kills cancer cells through alpha radiation from the decay of radium-223, inducing double-strand DNA breaks in adjacent tumour cells. In the ALSYMPCA (ALpharadin in SYMptomatic Prostate Cancer) trial, radium-223 was tested against placebo in 921 patients with mCRPC and cancer-related bone pain who had previously received or were ineligible for docetaxel (2:1 allocation ratio, mean age of patients 70.5 years; PS 0-2) (clinical trial NCT00699751).[17] The primary endpoint was overall survival. Six intravenous administrations (50 kilo Becquerel/kg body weight) at four weekly intervals were given. At the planned interim analysis, Ra-223 significantly improved overall survival (median overall survival 14.9 *vs* 11.3 months (HR 0.7; 95% CI 0.58-0.83; p=0.001) and time to secondary endpoints (PSA progression and time to first skeletal-related event) as well as quality of life. These data still await publication in a peer-reviewed journal. This drug has not been approved by the FDA yet.

CHANGING TREATMENT PARADIGM FOR METASTATIC CRPC PATIENTS

After an era of little improvement in therapeutic options for mCRPC patients progressive on or after docetaxel treatment, several drugs have recently shown clinically relevant survival advantages and improvement in palliative care, such as delay of bone pain and first skeletal-related event. Since 2011, the cytotoxic drug cabazitaxel and the new anti-androgen abiraterone are available for Dutch mCRPC patients. The new anti-androgen enzalutamide will probably follow soon, as will the radiopharmaceutical radium-223. Immune therapy with sipuleucel-T is available in North America; other vaccines are currently being tested in clinical trials, also in Europe.

Patients with advanced prostate cancer are usually treated by urologists with first-line androgen ablation therapy. With the arrival of additional chemotherapy and new anti-androgens that need close monitoring, the role in treatment of patients with metastatic prostate cancer by medical oncologists becomes more important.[18] Since especially patients with a good WHO performance status have been shown to benefit from recently described treatment options (before or after docetaxel therapy), early referral is important.

Further studies need to investigate what the optimal treatment sequence for patients with mCRPC is. Currently, is seems reasonable to start early with docetaxel in fit patients with progressive mCRPC. For patients who are not candidates for chemotherapy, abiraterone, instead of docetaxel, is an option. Fit patients (PS 0-1) with progressive disease on or after docetaxel could be offered cabazitaxel as second-line therapy. Abiraterone and enzalutamide have shown to be effective after one and two lines of chemotherapy, and can be a third-line therapy.[14,15]

Over the past three years, five differently acting drugs have become available for patients with mCRPC, as a result of the development of further insight into the pathophysiology of advanced prostate cancer. These new treatment options for patients with mCRPC offer a significant extension of overall survival and improvement of palliative care.

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