Novel hormonal therapy for castration-resistant prostate cancer

C. N. Sternberg
Department of Medical Oncology, San Camillo Forlanini Hospital, Rome, Italy

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Introduction

Prostate cancer is the most common cancer in European men and the second leading cause of death [1]. For patients who relapse after treatment of organ-confined disease or those who have initial metastatic disease, testosterone suppression is the mainstay of therapy. Manipulating the androgen receptor (AR) axis was the first method discovered, which could actively control prostate cancer. In fact, the AR represents the most relevant target even in patients with metastatic castration-resistant prostate cancer (CRPC). While this disease has been referred to as ‘hormone refractory’ or ‘androgen independent’ in the past, there is now recognition that the AR axis is functional in most patients throughout the natural history of prostate cancer from diagnosis to death, and therefore represents a therapeutic target that is relevant even in the final phases of the disease. The mechanisms of tumor escape through castration—defined as a testosterone level of <50 ng/dL—are multiple, with each mechanism representing a therapeutic opportunity. Some of these approaches have recently shown to improve both survival and quality of life. Others are in advanced stages of development. Although, metastatic CRPC is a significant challenge, research has resulted in five new treatments in the past few years. Immunotherapy with sipulecel-T, cabazitaxel chemotherapy, the androgen biosynthesis inhibitor abiraterone acetate, the radioisotope alpharadon and the antiandrogen MDV-3100 (Enzalutamide) have all been shown to improve overall survival (OS) in large-scale well-conducted phase III randomized clinical trials [2–6]. Bone-targeted therapy has also shown improvements [7]. This review will focus upon novel hormonal therapies for metastatic CRPC.

Advances in targeting AR signaling

The foundation of treatment of advanced prostate cancer is the suppression of gonadal androgens, which invariably leads to the development of castration-resistant disease. Several mechanisms have been identified to explain persistent androgen signaling in CRPC including increased AR gene expression and mutations in the AR gene. In addition, many enzymes involved in androgen synthesis are highly upregulated in CRPC compared with androgen-sensitive prostate cancer.

Until recently, there were very few data evaluating hormonal therapy in patients post-chemotherapy (Figure 1) [8, 9]. The arena has dramatically changed with the discovery and clinical development of novel agents that block testosterone synthesis and AR signaling (Table 1). The success of abiraterone acetate and MDV-3100 (Enzalutamide) in the post-docetaxel (Taxotere®, Sanofi-Aventis) and now the prechemotherapy setting has been of major significance.

Inhibitors of CYP117

Persistent androgen-axis signaling mediated by adrenal, testicular and intratumoral androgen synthesis, and AR amplification and mutations in driving tumor growth have been increasingly acknowledged. This comes with the recognition that prostate epithelial cells upregulate internal expression and activity of biosynthetic enzymes to produce androgens from precursors [10]. In addition, cytochrome P450 enzyme 17 (CYP17) has an important role in the production of androgenic and estrogenic steroids. The anti-fungal ketoconazole was the first CYP17 inhibitor to be used in clinical practice for CRPC primarily before chemotherapy [11]. Although it has often been used, it has never been shown in a clinical trial to clearly improve survival and its side-effects have been prohibitive.

Abiraterone acetate

Abiraterone acetate (Zytiga, Johnson and Johnson) is an oral inhibitor of CYP17, which is essential for androgen biosynthesis. Abiraterone inhibits 17α-hydroxylase/C17,20 lyase (CYP17A1), an enzyme which is expressed in testicular, adrenal and prostatic tumor tissues. CYP17 catalyzes two sequential reactions: (a) the conversion of pregnenolone and progesterone to their 17α-hydroxyl derivatives by its 17α-hydroxylase activity, and (b) the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively, by its C17, 20 lyase activity. DHEA and androstenedione are androgens and precursors of testosterone. Inhibition of CYP17 activity by abiraterone thus decreases circulating levels of testosterone, the most important ligand for the AR. Abiraterone acetate depletes blood and bone marrow
aspire testosterone and DHT concentrations to less than pg/ml levels [12].

After oral administration of abiraterone acetate, the prodrug form present in the commercial preparation is converted into the active form, abiraterone. This conversion is likely to be esterase-mediated and not CYP-mediated. The oral prodrug is well absorbed and rapidly deacetylated in the liver. Administration along with food increases absorption of the drug and has the potential to result in increased and highly variable exposures. The drug should, therefore, be consumed on an empty stomach. The drug is highly protein bound (>99%), and is metabolized in the liver by CYP3A4 and SULT2A1 to inactive metabolites. Approximately 88% of abiraterone is excreted in the feces and ~5% in the urine with a half-life of 12 ± 5 h.

There were four phase I/II studies, which showed impressive decreases in serum prostate-specific antigen (PSA) of ≥50% that contributed to the development of abiraterone both before chemotherapy [13, 14], after chemotherapy [15] and after ketoconazole administration [16]. Reductions in circulating tumor cells (CTCs) and radiological responses were also seen.

Abiraterone leads to a rebound increase in luteinizing hormone and adrenocorticotropic hormone. The observation that addition of low-dose corticosteroid resulted in normalization of mineralocorticoid levels and improvement in side-effects led investigators to recommend that prednisone was included in its development.

The pivotal trial leading to the approval of abiraterone was the COU-AA-301 phase III randomized, double-blind, placebo-controlled trial involving 1195 patients with metastatic CRPC who had failed one to two prior chemotherapy regimens (one with docetaxel) and were randomly assigned (2:1) to abiraterone acetate (1000 mg) and prednisone (5 mg twice daily) or placebo and prednisone. The primary end-point was OS and secondary end-points included time to PSA progression, radiological progression-free survival (PFS) and PSA response. The majority of patients had radiographic evidence of disease progression before study entry. At a median follow-up of 12.8 months, OS was longer in the abiraterone and prednisone arm than in the placebo and prednisone group (14.8 versus 10.9 months, HR 0.65, 95% CI 0.54–0.77) [4]. The study was stopped by the independent data monitoring committee (IDMC) at the time of the interim analysis. All secondary end-points were superior in the abiraterone-treated patients; time to PSA progression (10.2 versus 6.6 months, P<0.001), PFS (5.6 versus 3.6 months, P<0.001) and PSA response rate (29% versus 6%, P<0.001). In all subgroups analyzed, the abiraterone arm was favored...
Although the confidence levels were much less impressive in patients with a PS of 2. Abiraterone was very well tolerated although mineralocorticoid-related adverse events were somewhat more frequent. In an update of these results with 20.2 months follow-up, the median OS increased from 3.9 to 4.6 months and OS was longer in the abiraterone and prednisone group 15.8 versus 11.2 months (HR 0.74, 0.64–0.86; P<0.0001) [17, 18]. An intervention with little or no toxicity compared with chemotherapy for treatment of asymptomatic or mildly symptomatic CRPC is highly desirable. The aim is to prevent or delay the onset of pain related to metastatic disease and disease progression and also to prolong survival.

COU-AA-302 was a phase III randomized, double-blind and placebo-controlled trial in chemo-naïve patients with asymptomatic or mildly symptomatic metastatic CRPC randomly assigned (1:1) to abiraterone and prednisone versus placebo and prednisone (Table 2). The co-primary end-points were OS and PFS (clinicaltrials.gov. NCT00887198). The study completed accrual of 1088 patients and was terminated early by an IDMC decision. The results were presented at ASCO 2012 by Ryan et al. [19]. The difference in radiological PFS was highly statistically significant, with median survival of patients on abiraterone not yet reached when compared with 8.3 months for patients on the placebo arm [HR 0.43 (95% CI 0.35–0.52); P<0.0001]. The difference in OS constituted a ‘strong trend’ with a median not yet reached in the abiraterone arm when compared with 27.2 months in the placebo and prednisone arm [HR 0.75 (95% CI 0.61–0.93); P=0.0097].

In both the post-chemotherapy and the prechemotherapy studies, the eligibility criteria included a serum testosterone level of <50 ng/day (<2.0 nM) and LHRH analog was continued in those patients who had not received surgical castration. Abiraterone further decreases the intracrine testosterone produced by the testis, adrenal glands and the prostate tumor cancer cells themselves. These studies have demonstrated an important breakthrough in our knowledge of the continued hormonal dependence of prostate cancer after castration.

Abiraterone is now being evaluated in earlier-stage hormone sensitive men beginning LHRH analogs (clinicaltrials.gov NCT01088529 and NCT00924469) and during definitive radiation therapy (clinicaltrials.gov NCT01023061).

### Table 2. Ongoing trials with novel hormonal therapies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Phase</th>
<th>Patients</th>
<th>Primary end-point(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAK-700 (NCT01193244)</td>
<td>III</td>
<td>n = 1454, chemotherapy-naive mCRPC</td>
<td>Overall survival (OS), progression-free survival (PFS)</td>
</tr>
<tr>
<td>Abiraterone (NCT00887198)</td>
<td>III</td>
<td>n = 1000, chemotherapy-naive mCRPC</td>
<td>OS, PFS</td>
</tr>
<tr>
<td>ARN-509 (NCT01171988)</td>
<td>I/II</td>
<td>n = 123, progressive advanced CRPC</td>
<td>Prostate-specific antigen (PSA) response</td>
</tr>
<tr>
<td>TOK-001 (NCT00959959)</td>
<td>I</td>
<td>n = 49, chemotherapy-naive CRPC</td>
<td>Safety and tolerability</td>
</tr>
<tr>
<td>EZN-4176 (NCT01337518)</td>
<td>I</td>
<td>n = 150, chemotherapy-naive mCRPC</td>
<td>Maximum tolerated dose (MTD)</td>
</tr>
<tr>
<td>ODM-201 (NCT01317641)</td>
<td>I/II</td>
<td>n = 54, mCRPC</td>
<td>Safety and tolerability</td>
</tr>
<tr>
<td>AZD-3514 (NCT01622395)</td>
<td>I</td>
<td>n = 150, CRPC</td>
<td>OS, PFS</td>
</tr>
<tr>
<td>MDV-3100 (NCT01212991)</td>
<td>III</td>
<td>N = 1680 chemotherapy-naive mCRPC</td>
<td></td>
</tr>
<tr>
<td>MDV-3100 (NCT01288911)</td>
<td>II</td>
<td>N = 570 hormone responsive, chemotherapy naive</td>
<td>PFS</td>
</tr>
</tbody>
</table>

### CYP17 inhibitors in development

Other agents are in clinical development, which target the AR signaling pathway through CYP17 inhibition. TAK-700 (Oreteronel) has a similar mechanism of action to abiraterone; a non-steroidal CYP17 inhibitor with potentially greater 17,20 lyase selectivity (i.e. for androgen as opposed to corticosteroid synthesis). In a phase I/II trial, 96 chemo-naïve patients with metastatic CRPC were treated in four TAK-700 dose cohorts. The results, reported at the ASCO 2012 annual meeting, revealed encouraging activity +/- prednisone, profound reductions in testosterone and adrenal androgens, PSA response rates of ≥50% at 12 weeks in 54% and 63% who had not received prior ketoconazole with a concomitant decline in serum androgens and mean CTC numbers [20]. Currently, TAK-700 is being evaluated in two large placebo-controlled phase III trials (with prednisone in both the arms) in men with progressive metastatic CRPC, who are either chemotherapy-naïve (clinicaltrials.gov. NCT01193244) or post-docetaxel (clinicaltrials.gov. NCT01193257) as well as in phase II trials in men with rising PSA and no evidence of metastatic disease (M0) (clinicaltrials.gov. NCT01046916) and in combination with docetaxel (clinicaltrials.gov. NCT01084655). Another randomized phase II study with the EORTC GU Cancer Group is planned.

Other agents are in earlier stages of development such as TAK-001 (Galetorene), which inhibits prostate cancer growth by multiple mechanisms. In addition to inhibiting CYP17, it directly antagonizes the AR and also down regulates AR protein expression. A phase I/II trial of TAK-001 has been initiated in chemo-naïve patients with CRPC (clinicaltrials.gov. NCT00959959).

### AR antagonists

**MDV-3100**

MDV-3100 (Enzalutamide, generic name, Medivation and Astellas) is a novel AR antagonist that binds the AR with a higher affinity than bicalutamide, prevents nuclear translocation and DNA binding, induces apoptosis and has no agonist activity when the AR is overexpressed [21]. MDV-3100 is also active on castration-resistant splice variants of the AR [22].

In a phase I/II trial of 140 patients with progressive metastatic CRPC, antitumor activity was noted at all doses, including declines in serum PSA level ≥50% in 56% of...
patients, responses in soft tissue in 22%, stabilization of bone disease in 56% and conversion from unfavorable to favorable CTGs in 49% [23]. These data led to the phase III AFFIRM study of MDV-3100 versus placebo (prednisone was not required) of 1199 patients with CRPC who have progressed after one to two prior chemotherapy regimens, including docetaxel chemotherapy. A planned interim analysis of the study after 520 events led the IDMC to unblind the study as it showed a 4.8-month improvement in median OS compared with placebo (18.4 versus 13.6 months, HR 0.631, P < 0.00001) [5, 24]. A survival benefit was observed in all subgroups, although less benefit was seen in those with PS of 2, similar to what was observed in the abiraterone trial. The side-effects were minimal. Confirmed PSA decline of >50% was seen in 54.0% when compared with 15.7% (P < 0.0001) of placebo patients. The median time to PSA progression was 8.3 when compared with 3 months (HR 0.248, P < 0.00001).

The PREVAIL study is a phase III randomized, double-blind, placebo-controlled trial in chemo-naïve patients with metastatic CRPC (Table 2). The co-primary end-points are OS and PFS (clinicaltrials.gov. NCT01212991). The study was closed to accrual in March 2012 and had planned to accrue ~1680 patients. The phase II TERRAIN trial comparing MDV-3100 with bicalutamide (n = 370) is currently enrolling men who have progressed while on LHRH analog therapy or following surgical castration (clinicaltrials.gov. NCT01288911). PFS is the primary end-point. A phase II trial evaluating MDV-3100 monotherapy (n = 60) is also enrolling hormone-naïve patients (clinicaltrials.gov. NCT01302041). ARN-509 has a similar mechanism of activity and is undergoing phase I/II evaluation. ARN-509 exhibits lower brain levels per unit dose than MDV-3100, which may lead to a higher therapeutic Index (Table 2) [25].

mechanisms of resistance to abiraterone and enzalutamide in prostate cancer

Studies are starting to elucidate mechanisms of resistance to abiraterone, which may be mediated by amplification of CYP17 (indicating possibly a role for dose escalation of abiraterone) [26, 27]. In tumor models and patient tumor tissue, there is evidence of up-regulation of biosynthetic intracrine androgen enzymes resulting in increased production of androgens. Efstathiou et al. reported on 57 patients with CRPC treated with abiraterone who had bone marrow aspiration taken before therapy. Uniform and intense tumor nuclear AR expression, coupled with cytoplasmic CYP17 expression, is linked to lack of primary resistance to abiraterone acetate. Pretreatment bone marrow aspirate testosterone levels and tumor CYP17 expression appear correlated [12]. As mentioned earlier, abiraterone acetate depletes blood and bone marrow aspirate testosterone and DHT concentrations to less than pg/ml levels, and this depletion is sustained at treatment discontinuation. The progression observed in the presence of a depleted testosterone environment leads one to propose that native ligand-independent mechanisms are likely to drive progression during treatment with androgen biosynthesis inhibitors. This does not exclude the possibility that altered steroid biosynthesis in the tumor microenvironment accounts for progression in a testosterone-depleted environment.

Likewise, in a phase II trial in which patients with CRPC were treated with MDV-3100 and underwent bone marrow biopsies, responders to MDV-3100 had increased pretreatment levels of testosterone and CYP17A, and a post-treatment decrease in nuclear AR translocation [28]. Non-responders correlated with increased AR copy number and greater activation of Src kinase. AR inhibition correlated with increased serum and bone marrow levels of testosterone.

Carver et al. have evaluated escape from MDV-3100 [29]. Reciprocal feedback regulation between the AR and PI3K/ADT signaling that supports CRPC cell survival was found. Inhibition of the androgen axis with MDV-3100 downregulates the androgen regulated immunophilin FKBP5, a chaperone for the AKT phosphatase PHLPP. As a result, PI3K/AKT signaling is activated to support cell survival. When an inhibitor to the PI3K/AKT axis is used alone, androgen signaling is upregulated relieving feedback inhibition of HER kinases. This suggests that MDV-3100 in combination with a PI3K/AKT inhibitor may induce better tumor regression.

PSA

It has become increasingly clear that PSA alone is not a reliable surrogate end-point for OS in clinical trials. As part of the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) guidelines, it is recommended that early changes in PSA should not be acted upon without other clear radiographic evidence of disease progression. For this reason, in most current clinical studies treatment is continued for at least 12 weeks to ensure adequate drug exposure before PSA is measured [30].

conclusions

Persistent androgen signaling is implicated in the progression of CRPC and can now be targeted therapeutically. Improved radiological PFS and OS in CRPC patients with abiraterone before and after chemotherapy and improved OS with MDV-3100 after chemotherapy in well-conducted phase III trials have been impressive. The excellent safety profile with both these drugs has been important. Improved PFS and OS in the prechemotherapy setting will change the way in which patients with metastatic CRPC are treated and evaluated. As improved understanding of the mechanisms of castration resistance in prostate cancer is elucidated, further therapeutic opportunities will become available.

disclosure

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references


