Expanding Androgen- and Androgen Receptor Signaling–Directed Therapies for Castration-Resistant Prostate Cancer

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This article reviews the most recent advances in androgen receptor-directed therapies for castration-resistant prostate cancer, and new agents under development.

Source:

Introduction

Over the past decade, there have been major advances in the management of metastatic prostate cancer, based on growing knowledge of biologic mechanisms of prostate cancer proliferation and survival. Nonetheless, prostate cancer is an important cause of cancer mortality in men, with an estimated 250,000 deaths yearly worldwide.[1]

Since the discovery by Huggins and Hodges in 1941 that prostate cancer is an androgen-dependent disease,[2] the mainstay of therapy for advanced disease has been androgen deprivation therapy (ADT). Unfortunately, after a variable period of time on ADT, patients eventually progress to the lethal form of prostate cancer in the setting of castrate levels of testosterone. During the past several years, it has become recognized through laboratory models and molecular profiling studies that reactivation of the androgen signaling axis is a key driver of disease progression.[3-7] The findings of a rising prostate-specific antigen (PSA) level; an androgen receptor (AR)-responsive gene; responses to second-line hormonal agents, such as ketoconazole and hydrocortisone, that further lower androgen levels; and reports of response to discontinuation of anti-androgens and other agents that bind to the receptor, all validate the molecular findings.

Prostate Cancer Clinical States

The full disease spectrum of prostate cancer from diagnosis to death is best described by a series of clinical states proposed by Scher and Heller in 2000.[8] Patients are categorized based on the extent of disease, hormonal status, and absence or presence of metastases on imaging studies (Figure).[8] Each state represents a clinically significant clinical milestone in the disease continuum, easily recognized by patients and physicians, for which the therapeutic objectives differ. In the clinic, patients may progress from one state to another but cannot
move backwards. It follows that maintaining a patient in a state with persistent disease but with no symptoms and no progression, such as the state of a rising PSA with no evidence of metastatic disease, can be tantamount to cure.

The androgen receptor axis

The androgen receptor. The human AR gene is a steroid hormone receptor found in both benign and malignant prostate epithelial cells. The AR is a ligand-activated transcription factor with three distinct domains: DNA-binding domain (DBD); C-terminal ligand-binding domain (LBD); and N-terminal transactivation domain (NTD), which drives transcriptional activity.[9,10] In the absence of androgen, the AR associates with heat shock proteins, which act as chaperones to prevent the AR from degradation through ubiquitination, also preventing it from entering the nucleus and thereby maintaining the ligand-binding conformation.[11,12] When dihydrotestosterone (DHT) binds to the AR LBD, a conformational change of the receptor occurs enabling dimerization, which is followed by nuclear translocation, DNA binding, and ultimately gene transcription of androgen-dependent genes.[3,9,13]

The androgen metabolic pathway

Depletion of androgens, either surgically or medically, to produce a castrate state is the standard first-line treatment. This initiates an apoptotic response in a proportion of cells within the tumor mass that is followed by a decrease in PSA; an improvement in disease-related symptoms, if present; and tumor shrinkage. Notably, this approach does not fully deplete androgens within the tumor itself, nor does it affect adrenal androgen synthesis. What follows is a period of stability during which the tumor does not proliferate and PSA levels do not change. Unfortunately, after a variable period of time, AR reactivation occurs, PSA levels rise, and tumor proliferation resumes. This castration-resistant phenotype is associated with a number of oncogenic changes in the AR and in AR signaling, including upregulation of androgen biosynthetic machinery in the tumor itself and AR overexpression.[14-16]

The critical steps in androgen biosynthesis include CYP17 enzyme complex conversion of pregnenolone-like steroids into androgens and the conversion of testosterone and other steroids into 5α-dihydrotestosterone (DHT) by 5α-reductase and other enzymes, respectively. The CYP17 enzyme complex (17α-hydroxylase and 17,20-lyase) is a member of the cytochrome P450 family, expressed in testicular, adrenal, and normal prostatic tissue, as well as in prostate cancer cells. Inhibitors of CYP17 suppress the adrenal androgens dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S) and androstenedione, preventing expression of high-affinity AR ligands in the prostate cancer tissue.[17]

Treatment Perspective in 2014

Until 2009, docetaxel was the only drug for treatment of CRPC whose approval was based on a survival benefit.[18,19] Since then, there has been a dramatic evolution in the treatment of CRPC, and five additional agents with diverse mechanisms of action have been approved: sipuleucel-T[20] and cabazitaxel[21] in 2010, abiraterone acetate plus prednisone[22,23] in 2011, enzalutamide[24] in 2012, and radium-223[25] in 2013. More important, several other agents with promising activity in phase II trials are now in late-stage development, with final survival analyses anticipated soon.[26-30]

Androgen-directed targeted therapy
First-generation AR antagonists. The first-generation nonsteroidal anti-androgens flutamide, bicalutamide, and nilutamide are reversible inhibitors that bind the AR LBD with low affinity and do not inhibit AR target gene transcription completely.[7] These agents have been used for the treatment of CRPC for several decades and yield a PSA decline of 50% or greater in 20% to 25% of patients that is generally of short duration.[31-33] The main limitation of these agents is their weak affinity for the AR and the agonist potential after long-term use. It is well recognized that in the setting of AR overexpression, approximately 15% to 30% of patients will eventually develop AR mutations and tumor progression.[34,35]

Enzalutamide, a second-generation anti-androgen. Enzalutamide has a high binding affinity for the AR. It is distinct from the previously available anti-androgens in that it inhibits nuclear translocation, recruitment of coactivator peptide, and DNA binding of the AR by inducing a conformational change in the receptor. Preclinical data demonstrated that it has a five- to eightfold greater affinity for the AR compared with bicalutamide, and it did not cause increased AR target gene activity indicative of agonist potential.[36] Enzalutamide was evaluated in a phase I/II trial in patients with CRPC both pre- and post-chemotherapy, and showed evidence of activity at all tested doses, with a plateau between 150 mg and 240 mg.[37] The drug was generally well tolerated, and the most common adverse event was fatigue. Two patients treated with doses of 360 mg daily and higher presented with seizures. This serious adverse event is a potential class-related side effect possibly mediated by inhibition of γ-aminobutyric type A (GABA-A).[38]

The promising preliminary results in the phase I/II trial led to the pivotal AFFIRM trial, a phase III multinational double-blind study in which 1,199 men with CRPC following docetaxel-based chemotherapy were randomized in a 2:1 ratio to receive enzalutamide or placebo (Table).[24] The study was unblinded by an independent data safety monitoring committee in November 2011, when a planned interim analysis at 520 events demonstrated a 37% reduction in the risk of death in the enzalutamide arm as compared with placebo (hazard ratio [HR] for death = 0.63; 95% confidence interval [CI], 0.53–0.75; P < .001). The median overall survival (OS) was 18.4 months vs 13.6 months, in favor of enzalutamide. Treatment with enzalutamide was also superior in all secondary endpoints, including PSA decline of 50% or greater, soft-tissue response rate, radiographic progression-free survival (rPFS), time to PSA progression, and patients’ response to a quality-of-life questionnaire. Seizure-related events were observed in less than 1% of patients receiving enzalutamide (n = 5).[24] Based on these results, enzalutamide was approved by the US Food and Drug Administration (FDA) in September 2012 for use after docetaxel-based chemotherapy in patients with CRPC. Recently, the results of the PREVAIL randomized phase III trial of enzalutamide vs placebo in 1,717 patients with chemotherapy-naïve CRPC were presented.[39,40] This study was halted at the interim analysis based on a statistically significant benefit in OS (HR = 0.706; P < .0001) and rPFS (HR = 0.186; P < .0001). Further support of the activity of the drug was shown by the improvement in overall soft-tissue response rate (58.8% vs 4.9%; P < .0001) and the rate of a post-therapy PSA decline of 50% or greater (78% vs 3.5%; P < .0001).

ARN-509, a next-generation anti-androgen. ARN-509 binds directly to the LBD of the AR with high affinity, inhibiting its nuclear import and DNA-binding capacity. There are important preclinical properties that distinguish ARN-509 from enzalutamide: greater antitumor activity at a lower dose and exposure, higher tumor/plasma ratio, and fourfold lower drug levels in the brain compared with enzalutamide.[41] Preliminary results of a multicenter phase II study were presented for 46 patients with metastatic CRPC and 47 patients with high-risk nonmetastatic CRPC treated with ARN-509.[42,43] The most common treatment-related adverse events were fatigue and gastrointestinal events. At 12 weeks, the percentages of patients demonstrating ≥ 50% decline in PSA from baseline were 91%, 88%, and 29% for nonmetastatic, treatment-naive metastatic, and post-abiraterone metastatic patients,
respectively. The final analysis is ongoing, with evidence of promising preliminary activity in patients with high-risk nonmetastatic and metastatic chemotherapy-naive CRPC, both before and after treatment with abiraterone.

**Androgen synthesis inhibitors**

**Ketoconazole.** This imidazole antifungal drug inhibits adrenal androgen synthesis through inhibition of the CYP17 enzyme complex.\[44\] It has been used as a second-line hormonal treatment for CRPC for many years with variable degrees of response and variable patient tolerance. Adequate absorption required that the drug be taken with orange juice three times daily, and the agent has been replaced largely by abiraterone acetate, a more specific and less toxic CYP17 inhibitor.

**Abiraterone.** This first-in-class next-generation cytochrome P450 17 alpha (17 alpha-hydroxylase-C17, 20-lyase) inhibitor has been shown in preclinical studies to have an approximately 10-fold higher inhibitory potency compared with ketoconazole.\[45\] Phase I/II studies demonstrated that abiraterone was well tolerated and had significant antitumor activity in CRPC.\[46,47\] Although no patient developed clinical adrenocortical insufficiency, the main toxicities reported were related to secondary mineralocorticoid excess (hypertension, hypokalemia, and fluid retention); therefore, in subsequent studies the addition of prednisone at a dosage of 10 mg daily was suggested to prevent these side effects.

Initial efficacy results demonstrated PSA decline of 50% or greater in 67% of patients and an objective response rate of 37.5%.\[47\] Based on these very promising results, two phase III trials comparing abiraterone against placebo in both the pre- and post-chemotherapy settings were conducted (Table). The COU-AA-301 trial included 1,195 men with CRPC who had disease progression after docetaxel-based chemotherapy. The patients were randomized in a 2:1 ratio to receive abiraterone plus prednisone vs placebo plus prednisone.\[22\] In this pivotal trial, men treated with the abiraterone regimen demonstrated increased survival time (14.8 months vs 10.9 months with placebo; HR = 0.65; 95% CI, 0.54–0.77; \(P < .001\)) and had improved outcomes in all secondary endpoints compared with the placebo group, including time to PSA progression (10.2 months vs 6.6 months; \(P < .001\)), PFS (5.6 months vs 3.6 months; \(P < .001\)), and PSA decline of 50% or greater (29% vs 6%; \(P < .001\)). Based on these results, abiraterone was approved by the FDA in April 2011 for use in patients with CRPC who have progressive disease after docetaxel-based therapy.

The COU-AA-302 study enrolled 1,088 chemotherapy-naive patients with CRPC to be randomized to abiraterone plus prednisone vs placebo plus prednisone (Table).\[23\] The study was unblinded after a second planned interim analysis, when 43% of expected deaths had occurred. The co-primary endpoint, median rPFS, was significantly improved in the abiraterone arm (16.5 months vs 8.3 months in the placebo arm; HR = 0.53; 95% CI, 0.45–0.62; \(P < .001\)). There was a 25% decrease in the risk of death in the abiraterone-prednisone group (HR = 0.75; 95% CI, 0.61–0.93; \(P = .01\)), which indicated a strong trend towards improved survival but did not meet the prespecified significance level (of \(P < .001\)). Furthermore, abiraterone demonstrated improved secondary endpoints, including time to initiation of cytotoxic chemotherapy, opiate use for cancer-related pain, PSA progression, and decline in performance status. In September 2012, the FDA approved abiraterone for treatment of chemotherapy-naive CRPC.

Currently, there is a great interest in evaluating abiraterone acetate plus prednisone in earlier disease states, alone and in combination with a variety of drugs.

In CRPC, combinations under evaluation include phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) inhibitors; a poly (ADP-ribose) polymerase
(PARP) inhibitor; dasatinib, an Src inhibitor; an AKT inhibitor; heat shock protein (Hsp27 and Hsp90) inhibitors[48]; antiangiogenic agents; sipuleucel-T; and cabazitaxel.

Orteronel (TAK-700). This novel androgen synthesis inhibitor has an increased selectivity for 17,20 lyase over 17-hydroxylase, in terms of enzyme activity inhibition. Despite this higher selectivity, sparing the first blockade of 17-hydroxylase, the need to test higher doses mandated concomitant use of steroids in the clinical trials conducted with orteronel. Based on very promising results of a phase I/II study,[28] two phase III clinical trials have been conducted, in both chemotherapy-naive and post-chemotherapy patients (Table). The results of the ELM-PC 5 trial, evaluating orteronel vs placebo for patients with CRPC in the post-docetaxel setting, were presented at the 2014 Genitourinary Cancers Symposium.[49] In this study, 1,099 patients were randomized in a 2:1 ratio to receive orteronel at 400 mg twice daily plus prednisone or placebo plus prednisone. The study was unblinded at the second interim analysis after the prespecified futility boundary for OS was reached. The median OS was 17.0 months vs 15.2 months in the orteronel and placebo arms, respectively (HR = 0.886; \(P = .189\)), and there was a significant benefit in terms of rPFS (8.3 months vs 5.7 months; HR = 0.76; \(P = .00038\)), overall response rate (17% vs 3%; \(P < .0001\)), and PSA decline of 50% or greater (25% vs 10%; \(P < .0001\)). While this study did not meet its primary endpoint, notable rPFS and response rate differences were observed, favoring the orteronel arm. In the non-European/North American population of the trial, a significant OS benefit was observed (HR = 0.709; \(P = .019\)), possibly due to lesser use of subsequent therapies, including abiraterone, and lack of access to enzalutamide.

Recently, the results of the pre-chemotherapy phase III trial (ELM-PC 4) of orteronel plus prednisone vs placebo plus prednisone were presented.[50] This study included 1,560 patients, and although there was a statistically significant improvement in the co-primary endpoint rPFS, favoring the orteronel group (13.8 vs 8.7 months; HR = 0.7; 95% CI, 0.6–0.8; \(P < .00001\)), no survival benefit was demonstrated (31.4 months vs 29.5 months; \(P = .314\)). Importantly, in this trial there were no notable regional differences in terms of survival, and post-study treatments were fairly similar between the groups. Based on these results, no further development is planned.

Cross-resistance between the currently approved agents

It is currently uncertain whether patient benefit would be optimized by using the available agents in combination or in sequence, and if the latter, in what order. Thus, an area of great interest is the evaluation of different sequences of the newer-generation AR-directed agents. So far, the available evidence, largely retrospective in nature, suggests that these agents may have partial cross-resistance when used sequentially. In one series, the efficacy of enzalutamide after abiraterone failure and vice-versa was evaluated, with modest results evidenced by a PSA decline ranging from 8% to 45% and time to PSA progression ranging from 2.7 months to 4.9 months.[51-56] In these retrospective studies, the quality of response to one agent was not predictive of response to the other agent. The only prospective data in this setting are from a phase II trial of ARN-509 in 21 patients with CRPC previously treated with abiraterone, in which an encouraging 29% rate of PSA decline of 50% or greater was demonstrated.[42]

Another approach is to use the agents in combination, in effect co-targeting AR and paracrine androgen synthesis. A recent study evaluated 60 patients with CRPC treated with abiraterone and enzalutamide in combination.[57] The combination was well tolerated with no significant drug interactions and encouraging effects on PSA, including a PSA decline of 50% or greater in 75% of cases. Potential escape mechanisms observed with these drugs when used as single agents were not identified by serial blood and bone marrow evaluation during this study.
Further test studies are necessary to assess the efficacy of these agents used either sequentially or in combination; one phase III trial being conducted by the Alliance for Clinical Trials in Oncology Foundation is studying enzalutamide alone or in combination with abiraterone. The primary endpoint is OS.

**Mechanisms of Resistance to AR-Targeted Therapy**

Despite the recent success of new agents targeting the androgen signaling axis, with studies demonstrating improved clinical outcomes and patient survival, most men with CRPC will eventually die of progressive metastatic disease. Three patterns of response have been described: dramatic declines in PSA with durable radiographic control, an intermediate response characterized by a slowly rising PSA, and rapid disease progression despite therapy.[58]

**Androgen biosynthesis pathway**

One proposed mechanism for progression after treatment with CYP17 inhibitors is related to selection of cells with upregulated CYP17 or the presence of other steroidogenic enzymes within the tumor microenvironment after abiraterone therapy.[59,60] Other escape pathways likely to be associated with disease progression in this setting are under investigation, including AR-dependent and -independent mechanisms. A study evaluating patients with progressive disease on abiraterone demonstrated undetectable levels of testosterone and DHT in the bone marrow aspirate obtained on treatment discontinuation, suggesting that resistance to CYP17 inhibition is not primarily related to persistent intratumoral androgen production.[61] Another interesting finding is that exogenous steroids can cause mutations that allow promiscuous AR activation, and that mineralocorticoid receptor antagonists (such as spironolactone and eplerenone) can activate AR signaling.[62]

**AR-related mechanisms of resistance**

AR mutations and amplification can be identified mainly in patients with castration-resistant disease, suggesting an adaptive mechanism for cell survival after ADT. AR mutations are present in 10% to 20% of prostate cancers, and these mutations may result in agonist activity for standard anti-androgens such as bicalutamide and flutamide. Recently, a novel mutation (F876L) has been reported to convert enzalutamide into an AR agonist and may represent an important mechanism of resistance to the new AR antagonists.[63] Another potential mechanism of resistance to new-generation AR-targeted therapy may be the AR splice variants, which represent constitutionally active AR lacking LBD.[64] The AR splice variant-7 (AR-V7) is one of the most frequently identified, and its expression is significantly increased in the castration-resistant state. Recently, a prospective biomarker study that included 62 patients evaluated the presence of AR-V7 in samples of circulating tumor cells (CTCs) from patients treated with enzalutamide (n = 31) or abiraterone (n = 31).[65] AR-V7 was detected in the CTCs of about 20% to 38% of patients with heavily pretreated CRPC. Remarkably, none of the patients with AR-V7 demonstrated a PSA response to either abiraterone or enzalutamide, whereas patients with no AR-V7 detected through CTCs demonstrated PSA responses ranging from 52.6% to 68%. Moreover, there was a significant difference in PFS, favoring patients with AR-V7–negative CTCs. Although these data need to be independently confirmed in a larger cohort of patients, these results strongly suggest that AR-V7 might be associated with both primary and acquired resistance to AR-directed therapy in patients with CRPC. In this case, development of drugs targeting the NTD instead of LBD could potentially overcome the resistance mediated by AR splice variants.[10]
Other potential mechanisms for resistance to AR-targeted therapy

Alternative pathways have been implicated in resistance to next-generation AR-targeted therapies. Since the recognition that the reciprocal feedback between AR and PI3K/mTOR pathways may be related to cell survival and progression, there has been an increasing interest in developing strategies for dual inhibition, in an attempt to overcome resistance. [66,67] Recently, another potential mechanism of resistance to AR blockade has been described that involves activation of AR target genes through the glucocorticoid receptor (GR).[68] In this preclinical study, GR expression was commonly identified in AR-resistant cells and was able to activate a similar set of AR target genes, leading to manifestation of the resistant phenotype. Moreover, use of a GR agonist conferred resistance to enzalutamide, and restoration of sensitivity was achieved with the use of a GR antagonist.

Conclusions

Based on a better understanding of the molecular basis of prostate cancer progression and the main role of AR activation in the castration-resistant disease state, novel agents targeting the androgen-signaling axis have changed the landscape of treatment for CRPC. Androgen synthesis inhibitors such as abiraterone and next-generation AR antagonists such as enzalutamide represent major therapeutic advances that validate the approach of understanding and targeting the underlying molecular mechanisms of disease progression. Now, intensive efforts are focused on understanding the mechanisms of resistance to these novel agents and developing new strategies to target them. Also needed are validated predictive biomarkers to better inform treatment selection, and surrogate endpoints for survival that can better enable drug approvals.

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