Mechanisms of Disease Progression and Treatment Resistance in Prostate Cancer

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INTRODUCTION

Prostatic adenocarcinoma is a major health challenge in most Western countries, and the means to durably treat disseminated disease have been elusive. The pioneering work of Huggins and Hodges in the 1940s established the importance of androgens for the growth and development of prostate cancer, and targeting this reliance on androgen action remains the conceptual basis of treatment for advanced disease. Antiandrogen strategies are initially effective in the majority of patients. However, recurrent disease arises due to restoration of androgen activity and/or androgen receptor (AR) signaling, and it is this stage of disease that has proven difficult to treat. This article reviews the underlying basis of disease progression and treatment resistance in prostate cancer, with a focus on the molecular mechanisms that govern recurrent androgen activity and AR signaling in the clinical setting.

EPIDEMIOLOGY

As of 2011, prostate cancer remains the second leading cause of cancer death in men in the United States and the most frequently diagnosed noncutaneous malignancy. It is predicted that in 2012 over 215,000 American men will receive a new diagnosis of prostate cancer; unfortunately, approximately 15% of patients will have metastatic lesions at initial diagnosis, and over 30,000 will die of their cancer. Correct identification of truly organ-confined disease is of significant benefit, since early-stage disease can be effectively treated through surgical resection or via radiation therapy. However, treatment failure is common, and a significant fraction of patients (up to 40%) will develop biochemical relapse and require treatment for non–organ-confined disease. Although the underlying basis remains incompletely defined, prostate cancers that spread beyond the primary site are largely refractory to standard chemotherapeutic agents and antimitotics, and no curative treatment regimen has yet been defined for advanced prostate cancer. As such, determining the basis of disease progression is an area currently under intensive study, and translational discoveries have recently led to approval of promising new therapeutic agents to treat advanced disease.

ROLE OF THE ANDROGEN RECEPTOR IN PROSTATIC ADENOCARCINOMA

OVERVIEW OF AR FUNCTION AND REGULATION

Prostatic adenocarcinomas are noted for their exquisite dependence on and addiction to androgen signaling for growth and survival. Testosterone is the most abundant circulating androgen in the human adult male, and in the context of a normal prostatic epithelial cell or prostatic adenocarcinoma cell, testosterone is converted to the potent androgen dihydrotestosterone (DHT) through the action of a resident enzyme, 5α-reductase. The biological activity of both androgens is mediated through their binding to their cognate receptor, the AR, which serves as a ligand-dependent transcription factor. A part of the nuclear receptor superfamily of transcription factors, AR contains conserved C-terminal functional domains (hinge, DNA-binding domain, and the ligand-binding domain) but harbors a unique N-terminal region. Distinct from many of the other nuclear receptors, the N-terminal region supports the main transcriptional transactivation function of the receptor (activation function 1, AFI). Prior to ligand binding, the AR is present diffusely throughout the cytoplasm and nucleus, and remains inactive due to association with inhibitory chaperone molecules such as heat-shock proteins. Upon ligand (testosterone or DHT) binding, heat shock proteins are released. Subsequently, the receptor undergoes conformational changes that promote transcriptional transactivation functions, forms a homodimer, and rapidly translocates to the nucleus. Activated nuclear AR homodimers bind to DNA at specific DNA sequences (androgen response
Mechanisms of Disease Progression and Treatment Resistance

Figure 1. Androgen receptor function and targeting in prostate cancer progression. The androgen receptor (AR) consists of 3 domains (the DNA-binding domain [DBD]; a hinge region [H]; and a C-terminal ligand-binding domain [LBD]) and a unique N-terminal domain that contains the principle transactivation domain (TAD). Ligand (indicated by circles: testosterone [T] or dihydrotestosterone [DHT]) binding induces homodimerization and rapid nuclear translocation. Active homodimers bind DNA at androgen responsive elements (ARE) within the regulatory regions of target genes, recruit coactivators (Co-Act), and induce a gene expression program that includes activation of prostate-specific antigen (PSA). The AR C-terminal domain is targeted clinically in patients with non–organ confined disease by the use of androgen ablation and direct AR antagonists (indicated by triangles).

elements, or AREs) at the regulatory regions (enhancers and promoters) of target genes and therein recruit a series of coregulators that assist in promoting context-specific and cell-type specific gene expression programs (Figure 1).

In the context of a normal prostate gland, activated AR initiates a gene expression program that is decidedly prodifferentiative, as a number of model systems have demonstrated that AR is required for development and maintenance of differentiated luminal epithelia. Moreover, patients with germline mutations in 5α-reductase or AR that compromise receptor activity fail to develop a functional prostate. Differentiated prostatic epithelia serve to produce and secrete a number of proteases that support prostate function; one of these proteases is encoded by the KLK3 gene and produces a protein marker of clinical relevance for prostate cancer, prostate-specific antigen (PSA). PSA secretion is a hallmark of both prostatic epithelia and prostatic adenocarcinoma cells, which retain some salient features of luminal epithelia. A large body of evidence has demonstrated that KLK3/PSA gene expression is under stringent control of AR, and is arguably one of the best-characterized AR target genes. In both normal prostatic epithelia and prostatic adenocarcinomas, activated AR binds to enhancer and promoter regions of the KLK3 locus and acts as a catalyst to recruit both coactivators that facilitate chromatin opening and basal transcriptional machinery to induce gene expression. Since the resulting protein product is secreted into the sera, PSA levels can serve as a monitor of the number of cells of prostate origin that have the AR pathway engaged. As such, PSA levels are routinely utilized as a means to detect prostate cancer growth and progression.

Despite the commonality of KLK3/PSA as a gene under AR regulation in both normal and cancer cells of the prostate, the biological outcome of AR activation is distinct in the 2 cell types. Whereas AR serves a prodifferentiative role in normal adult prostatic epithelia, a multitude of investigations demonstrate that AR harbors cell-autonomous pro-proliferative and prosurvival functions in prostatic adenocarcinoma. Further, recent findings suggest that the profile of genes controlled by AR continues to change as a function of disease progression, such that AR is rewired in therapy-resistant disease to promote gene expression events that support aggressive tumor phenotypes. As preclinical modeling and clinical investigation strongly support the contention that recurrent AR activity after therapeutic intervention drives progression to the lethal stage of disease, it is critical to define the means
by which AR activity is restored and/or altered in advanced disease, and to develop means to effectively treat this late stage of cancer.

**TARGETING THE AR IN DISSEMINATED DISEASE**

Suppression of androgen synthesis through the use of gonadotropin-releasing hormone agonists currently remains the first line of therapeutic intervention for disseminated prostate cancer.¹ These regimens function to deplete the AR of ligand and thereby suppress receptor activity. Cooperative strategies are often employed in concert, wherein direct AR antagonists such as bicalutamide, nilutamide, or flutamide are given as adjuvant therapies. In general, these agents compete with testosterone or DHT for binding to the AR ligand-binding domain, further suppressing receptor activity. AR antagonists have a second actively suppressive function in that the receptor perceives these first-generation antagonists as a ligand that promotes nuclear entry and DNA binding. Once bound to DNA, bicalutamide-bound receptors can induce recruitment of corepressor molecules such as NCoR (nuclear corepressor) and SMRT (silencing mediator of retinoic acid and thyroid hormone receptors) to actively suppress transcriptional transactivation.²⁶ Whether used in isolation or in combination with AR antagonists, androgen-suppression strategies are highly effective at blocking AR activity, as evidenced by a marked reduction in detectable serum PSA in patients undergoing treatment.²⁷,²⁸

At the cellular level, androgen deprivation leads to either cell death or cell cycle arrest,²¹,²⁹ and tumor remission is observed. Unfortunately, within 2 to 3 years’ median time, recurrent tumors form that can survive and proliferate in the castrate environment, a condition referred to as **castration-resistant prostate cancer** (CRPC). It has long been observed that rising PSA (referred to as “biochemical failure”) almost invariably heralds development of a recurrent tumor that can be detected by radiographic or other means, providing some of the first evidence that the AR pathway has been reactivated despite

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**Figure 2.** Mechanisms of androgen receptor (AR) reactivation in the transition to hormone therapy resistance. Tumors evade hormone therapy through the restoration of AR activity, which can be achieved through multiple mechanisms. Agents designed to target hormone therapy–naïve and recurrent AR activity are shown in red.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Example</th>
</tr>
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<tbody>
<tr>
<td>Depletion of ligand</td>
<td>Testosterone, DHT</td>
</tr>
<tr>
<td>Competitive inhibition</td>
<td>Bicalutamide, nilutamide, flutamide</td>
</tr>
<tr>
<td>Suppression of receptor activity</td>
<td>NCoR, SMRT</td>
</tr>
<tr>
<td>Second actively suppressive function</td>
<td>Bicalutamide-bound receptors</td>
</tr>
</tbody>
</table>

**HORMONE THERAPY**
- GnRH agonists and antagonists
- Anti-androgens
  - Bicalutamide
  - Nilutamide
  - Flutamide
  - Cyperaterone acetate
  - MDV3100

**TARGETING THE AR IN DISSEMINATED DISEASE**

**RESTORED AR ACTIVITY**
- Rising PSA (biochemical failure)
- CRPC tumor growth

**Deregulation**
- Amplification
- Overexpression

**Aberrant Modification**
- GF cytokine pathways
- Src

**Alternative Splicing**
- Constitutively active

**Cofactor Perturbation**
- Gain of function
- CoR loss/dismissal

**Mutation**
- Gain of function
- CoR gain

**Intracrine Androgen Synthesis**
- EPI-001

**Selective pressure**

**Mechanisms of adaptation**

**CRPC development**
the maintenance of therapeutic intervention. Indeed, subsequent clinical investigation and modeling of the disease confirmed that restoration of AR activity can occur through multiple mechanisms (Figure 2), and recurrent AR activity appears to be the major means through which resistance to first-line therapeutic intervention occurs. As such, recurrent AR activity is considered to be critical for progression to the castration-resistant stage.

### THERAPY RESISTANCE AND PROGRESSION TO CASTRATION-RESISTANT PROSTATE CANCER

Restoration of AR activity despite the maintenance of androgen deprivation therapy (ADT) is thought to be the major mechanism of CRPC development.\(^4\)\(^,\)\(^5\)\(^,\)\(^13\) Investigation of the underlying mechanisms continues to be an area of productive discovery that has led to the development of new modes of therapeutic intervention. At present, at least 5 major mechanisms have been identified in the clinical setting and validated in preclinical models that can account for promoting AR-dependent disease progression to CRPC.

### AR Deregulation

It has long been recognized that elevated AR levels predict significantly increased risk of death from prostate cancer,\(^4\)\(^9\) and, in models of human disease, mimicking AR deregulation is sufficient to confer resistance to ADT. For example, elegant studies from Sawyers and colleagues demonstrated that overexpression of the gene encoding AR allowed tumor growth after androgen deprivation in vitro, and rendered human tumor resistant to castration in xenograft models.\(^4\)\(^1\) As would be expected, AR overexpression also resulted in marked upregulation of known target genes in human cells, including PSA. The biochemical means by which excessive AR expression leads to restored activity is thought to be centered on the fact that the receptor retains some basal activity in the castrate environment, and that overproduction of the protein is sufficient to induce AR gene expression programs to the threshold level required to induce tumor growth and survival. In addition, it should be considered that even in the case of effective GnRH agonist–dependent castration, circulating androgens derived from the adrenal gland are not altered by this therapy, and is it known that elevations in AR can sensitize tumor cells to low levels of ligand.\(^4\)\(^1\)\(^2\) Thus, precursors derived from the adrenal glands or other tissues, and/or intracrine–derived androgens (discussed below) are hypothesized to cooperate with high AR levels to sensitize cells to the pro-tumorigenic effects of residual androgens.\(^4\)\(^3\)

In the clinical setting, a significant fraction of CRPC tumors exhibit significant AR elevation, which can be attributed to either amplification of the locus encoding the AR gene or to amplification-independent molecular alterations that lead to overexpression of the AR gene.\(^4\)\(^4\)\(^–\)\(^4\)\(^6\) AR amplification has been reported in up to 30% of CRPCs, suggesting that this is a major means of CRPC development. Amplification-independent mechanisms of AR upregulation can occur in human disease as a result of variant pro-tumorigenic genetic alterations, including loss of the purine-rich element binding (Pur)-alpha corepressor or upregulation of the transcription factor lymphoid-enhancing factor 1 (LEF),\(^4\)\(^7\)\(^–\)\(^4\)\(^8\) both of which impinge upon AR gene expression. Recently, an unexpected link between the retinoblastoma tumor suppressor (RB) and AR expression was identified; as part of RB function as a negative regulator of transcription, it was discovered that RB assembles repressor complexes that dampen AR gene expression.\(^4\)\(^2\) Loss of RB, which was shown to occur with high frequency in human CRPC, proved sufficient through molecular modeling to promote AR overexpression sufficient to induce CRPC both in vitro and in vivo. Accordingly, further investigation of human CRPC showed that not only is RB loss overrepresented in CRPC, but this genetic alteration also inversely correlates with excessive AR expression. These findings identify suppression of AR expression as a major means through which the RB tumor suppressor serves to protect against the transition to CRPC. It is clear that high-level AR expression and output together are sufficient to promote resistance to first-line therapeutic intervention, and that multiple genetic alterations can induce AR levels sufficient to drive CRPC.

### POST-TRANSLATIONAL MODIFICATION AND AR COFACTOR ALTERATIONS

While overexpression of the endogenous, wild-type AR can promote treatment resistance, an emerging body of evidence strongly suggests that altered post-translational modification of the AR and/or aberrant expression of AR cofactors can facilitate this process.\(^4\)\(^6\)\(^,\)\(^4\)\(^9\) The receptor is known to be modified by phosphorylation (both serine/threonine and tyrosine), acetylation, sumoylation, and ubiquitination, and as has been extensively reviewed, these modifications are major modulators of AR activity.\(^5\)\(^0\)\(^–\)\(^5\)\(^3\) Selected modifications have been linked to growth factor pathways relevant to prostate cancer, suggesting that targeting the enzymes that are responsible for post-translational modification
may be of possible clinical benefit. For example, it is known that the Src kinase induces tyrosine phosphorylation of AR, and that this phosphorylation event can promote castration-resistant AR activity. The relevance of this event was further demonstrated through investigation of human tumor specimens that revealed CRPC-specific upregulation of the Src-sensitive phosphorylation event. Importantly, dasatinib (a known Src inhibitor) is in clinical trial to assess its impact on solid tumors, including prostate cancer,54,55 and early findings suggest that this approach may prove effective at suppressing AR activity.56,57 There is a current emphasis in the field on identifying the complex network of enzymes that govern AR post-translational modifications of clinical relevance, and determining whether these pathways could serve as a valid target for therapeutic intervention. Similar interests are directed toward understanding the role of AR cofactors in treatment resistance. Given the observation that alterations which promote excessive AR expression and activity underlie the transition to CRPC, it is not surprising that alterations in transcriptional cofactors that modulate AR function on chromatin have also been observed in the clinical setting. These alterations typically involve loss or dismissal of corepressors that normally serve to keep AR activity in check58 or upregulation of coactivators that facilitate AR function.16 The basis for these alterations can be genetic; for example, loss of the NCoR1 corepressor and gain of the SRC2 coactivator are over-represented events in human CRPC.59 By contrast, AR cofactor alterations can occur as a result of changes in the tumor microenvironment. Exemplifying this, elegant studies showed that macrophage infiltration into the tumor microenvironment results in a signaling cascade that causes dismissal of NCoR1 from the AR complex (thus triggering enhanced AR function sufficient to promote resistance to AR bicalutamide).60 These findings suggest that AR cofactors modulate the response to therapeutic intervention, and that these events should be considered when evaluating how and when to apply novel AR-directed therapeutics.

**AR MUTATION**

Mutation of the AR gene is not typically observed in hormone-therapy–naïve tumors; by contrast, gain-of-function AR mutations are quite common in CRPC, and have been observed in up to 25% of recurrent tumors. These gain-of-function mutations occur most frequently in the AR ligand-binding domain and render the receptor susceptible to an expanded set of ligands as agonists, including both other steroid hormones (eg, estrogen, progesterone, cortisol) and first-generation AR antagonists.51,62 Initial observations supporting the existence of AR mutations were noted by clinical assessment of flutamide withdrawal syndrome,63 wherein an antitumor response was observed upon cessation of flutamide (AR antagonist) treatment, thus indicating that in this subset of tumors, flutamide was serving a pro-tumorigenic role. It was subsequently discovered that tumors associated with flutamide withdrawal syndrome had developed a specific somatic mutation in AR (mutation of threonine 877 to alanine), and that this mutation altered the receptor such that flutamide could function as an agonist that promoted AR function. Recent findings further demonstrated that mutations are selected for during first-line treatment64,65 and that the specific treatment regimens select for a specific subset of AR mutations. The impact of these alterations may go beyond conferring resistance to therapy, but may also be associated with or promote aggressive tumor phenotypes. For example, recent assessment of circulating tumor cells (CTCs) revealed that AR mutations were detected in the CTCs of a large fraction of CRPCs (20 of 35 patients). Moreover, these findings suggest that the frequency of alteration may be higher in cells with metastatic potential.66 How to identify and treat tumors with somatic mutations that expand and alter AR activity remains a major clinical challenge.

**AR SPLICE VARIANTS (TRUNCATED RECEPTORS)**

In addition to therapy-selected AR mutations, new findings show that castration-therapy also selects for expression of “short forms” of the AR that largely result from alternative splicing events. A large number of AR splice variants have been reported, but the majority of these share loss of the sequences encoding the ligand-binding domain of the receptor as a common feature.67-69 Loss of the ligand-binding domain has long been known to result in a weak but constitutively active receptor that is refractory to both agonists and antagonists. Thus, the truncated proteins encoded by AR splice variants are resistant to all currently approved AR-directed therapeutics. Interestingly, the splice-variant–derived proteins appear to promote transcriptional programs distinct from the full-length receptor, and investigation of these gene expression programs further support the contention that the truncated receptors may contribute to castration resistance.70 If correct, developing means to treat tumors expressing significant levels of the truncated receptors may present a major clinical difficulty. Promising new directions were initiated by development of the small molecule EPI-001, which directly binds to the AR transactivation domain instead of the ligand-binding domain and inhibits
protein-protein interactions required for receptor activity. Moreover, EPI001 suppresses association of AR with chromatin-bound regulatory elements,71 and this second function is thought to contribute to the agent’s function in suppressing both long- and short-form AR activity. Consonantly, objective cellular outcomes were observed, wherein EPI001 suppressed CPRC tumor cell growth in vivo without overt host toxicity. These studies are the first to demonstrate feasibility for in vivo suppression of AR using an agent that functions through the AR N-terminus instead of the ligand-binding domain, and they also provide proof-of-principle that agents can likely be developed to treat tumors expressing receptors lacking the ligand-binding domain.

**INTRACRINE ANDROGEN SYNTHESIS**

Recent evidence has shown that in response to castration therapy, tumors develop means to induce intracrine androgen synthesis and therefore restore testosterone levels in the tumor microenvironment. This knowledge resulted in a major terminology shift in the field, wherein use of the term “androgen-independent” cancers was no longer thought to be correct, given evidence that the tumor cells themselves had become factories of androgen production in a castrate patient. Intracrine androgen synthesis occurs via induction of enzymes that convert weak adrenal androgens to testosterone, and the molecular alterations that guide this process can be quite varied.13,14,72 Molecular modeling showed that these events provide levels of agonist sufficient to restore AR activity under castrate conditions.73-78 For example, dehydroepiandrosterone, a steroid precursor of the androgens, can be converted to testosterone and DHT through the function of tumor-derived 3β-hydroxysteroid dehydrogenase (3β-HSD/ketosteroid isomerase type 1 and type 2 [HSD3B1, HSD3B2]), type-5 17β-HSD (aldo- reductase 1C3 [AKR1C3]), and steroid-5α-reductase (SRD5A2). Moreover, HSD3B2, AKR1C3, SRD5A1, and AKR1C2 expression is altered in CRPC, further supporting the postulate that intracrine androgen synthesis is a major contributor to CRPC. Modeling of these events resulted in findings consistent with this hypothesis, as upregulation of genes associated with androgen synthesis from cholesterol was observed after androgen depletion in cell-based models,79,80 and de novo DHT synthesis has been reported in CRPCs. Encouragingly, these findings have been rapidly translated into the clinic and resulted in development of new therapeutic regimens that are showing clinical benefit. As will be discussed below, the CYP17,20-lyase inhibitor abiraterone acetate81,82 targets the intracrine androgen synthesis process, and use of this agent has shown clinical benefit in patients with CRPC.

**IMPACT OF AR-DEPENDENT CHROMOSOMAL TRANSLocations**

The ability of prostate cancer cells to restore AR function after castration therapy as a means to promote disease progression is remarkable, and is reminiscent of oncogene-addiction exemplified in other tumor types. In addition to the ability of AR to orchestrate pro-proliferative and prosurvival gene expression programs in prostate cancer cells, it is now evident that in the presence of DNA damage, AR promotes formation of chromosomal translocations thought to induce aggressive tumor phenotypes.83 Put simply, induction of AR-dependent gene expression is associated with chromatin looping, such that AR binding sites within the proximal promoters and distal enhancers that control AR target gene expression come into close proximity. After genotoxic insult, DNA break resolution is thought to result in AR-dependent chromosomal fusions that can promote tumor cell phenotypes. Resulting gene rearrangements frequently position AR-binding sites upstream and in control of genes whose functions are decidedly pro-tumorigenic, as is exemplified by generation of TMPRSS2:ETS gene fusions.84-90 TMPRSS2 is a well-established AR target gene, and the TMPRSS2:ETS gene rearrangement places ETS gene expression under control of AR. This class of gene rearrangement occurs in approximately 50% of all prostate cancers84,87,88,91-96 and is the most common genetic translocation in any solid malignancy.84,87,97 Modeling of the ETS gene fusions revealed a contribution to carcinogenesis in vivo,84-87,98-103 and these fusions are associated with aggressive phenotypes,86,104 including increased migration and invasive potential.85,86,89,100,105,106 Thus, genetic alterations downstream of and dependent on AR contribute to a cascade of events that promote disease progression.

**ADVANCES IN TARGETING HORMONE THERAPY–RESISTANT DISEASE**

Dramatic advances have been realized over the past 3 years with regard to treatment of metastatic CRPC, made possible through a greater understanding of AR signaling and the molecular basis of treatment resistance. In 2010/2011 alone, 4 different clinical trials reported increased overall survival for new therapeutic agents (abiraterone acetate, cabazitaxel, sipuleucel-T, and radium-223). These new regimens are FDA-
approved, except for radium-223, and each is likely to change the course of treatment for patients with disseminated disease.

**ABIRATERONE ACETATE**

The CYP17,20-lyase inhibitor\(^{81,82}\) abiraterone acetate is a pregnenolone-derived 3-pyridyl steroidal agent that irreversibly inhibits androgen biosynthesis. Phase I/II studies using abiraterone as a single agent resulted in PSA declines of 50% or more in 50% to 60% of patients, and radiological response rates were observed in both the prechemotherapy (37%) and postdocetaxel (27%) settings.\(^{107-110}\) Most importantly, overall survival in a large phase III randomized trial was significantly longer in patients receiving abiraterone (14.8 months) versus placebo (10.9 months).\(^{111}\) This benefit was observed in all subgroups, including patients with a high pain inventory and in men aged 75 years and older. Currently, determining how to sequence abiraterone optimally for treatment of patients with CRPC is of critical importance—trials are currently underway to assess its impact in patients with asymptomatic to mildly symptomatic prechemotherapy CRPC, in combination with antiandrogens, and in both the pre- and postchemotherapy settings (www.clinicaltrials.gov).

**CABAZITAXEL**

The tubulin-binding agent cabazitaxel, approved by the FDA in 2010, shows anticancer activity in model systems resistant to first-generation taxanes (paclitaxel and docetaxel). The agent showed positive results in a phase III randomized trial that compared a cabazitaxel plus prednisone regimen with a mitoxantrone plus prednisone regimen in patients who progressed on or after docetaxel therapy.\(^{112}\) Cabazitaxel increased median overall survival from 12.7 to 15.1 months. Currently, the agent is being evaluated as a first-line chemotherapy for patients who fail hormone therapy.\(^{12}\)

**RADIONUM-223**

Radium-223 is a bone-seeking, alpha-radiation–emitting radioisotope that has preferential uptake in skeletal metastases (versus normal bone).\(^{113}\) As opposed to other bone-targeting radioisotopes (eg, strontium-89 and samarium-153), radium-223 has a high linear energy transfer but a short range of action (approximately 100 \(\mu\)M) and induces double-strand breaks. A randomized, placebo-controlled phase II study of patients with bone metastases of CRPC showed an increase in progression-free survival (26 weeks versus 8 weeks) and prolonged survival (65 weeks versus 46 weeks),\(^{114}\) and the ALSYMPCA phase III trial showed improved overall survival.\(^{12}\) The agent is now on Fast Track designation by the FDA, and may provide a benefit in the postchemotherapy setting.

**SIPULEUCEL-T**

Immunotherapies may offer a new approach for treatment of advanced disease. Sipuleucel-T, an autologous activated dendritic cell therapy, was recently approved by the FDA. A clinical trial of patients who were largely (80%) chemotherapy-naïve showed that the agent rendered an overall survival benefit over placebo of 25.8 versus 21.7 months.\(^{115}\) Current clinical reports suggest that the agent is beneficial most frequently in patients who are asymptomatic.

**NEXT-GENERATION AR ANTAGONISTS**

It is important to note that next-generation AR antagonists may function in a distinct molecular manner, and appear to provide additional clinical benefit. The darythiohydantoin MDV3100 (now known as enzalutamide and approved by the FDA in September 2012) is similar to bicalutamide in structure and binds AR through the ligand-binding domain, but has additional activities.\(^{116}\) These novel functions include the ability to reduce nuclear accumulation of AR, and therefore dampen chromatin association, cofactor recruitment, and AR-dependent transcriptional activation. Interim results of a phase I/II trial involving patients who were either chemo-naïve or post-chemotherapy with progression of CRPC showed that the drug is well tolerated; in addition, almost half of the patients showed at least a 50% PSA decline at week 12, with 38% of evaluable patients showing a partial reduction in tumor volume via radiograph.\(^{117}\) Most recently, enzalutamide was shown in a phase III double-blind, placebo-controlled trial of men with CRPC to significantly prolong survival after chemotherapy (AFFIRM trial).\(^{118}\) Specifically, overall survival was increased from 13.6 to 18.4 months, and all secondary endpoints (reduction in PSA by 50% or more, soft tissue response rate, quality-of-life response rate, time to PSA progression, radiographic progression-free survival, and time to the first skeletal-related event) showed superiority of enzalutamide over placebo. Given these encouraging results, how this novel antiandrogen might alter prostate cancer management is an active area of investigation.

**SUMMARY**

Over the past decade, there has been a remarkable expansion in our understanding of the mechanisms
that drive resistance to first-line therapy for prostate cancer and transition to the stage of castration resistance. Based on the knowledge that CRPC occurs as a result of restored androgen signaling and AR activity, new therapeutic agents have been developed and approved that show some efficacy at treating this late stage of disease. Challenges remain in terms of determining how to stratify patients into the most effective treatment options, and to determine whether complete ablation of AR activity (if achieved) will result in cure or development of adaptive processes that foster tumor recurrence.

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