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Sex Hormones and Prostate Cancer

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Abstract

The prostate is an androgen-dependent organ that develops only in male mammals. Prostate cancer is the most common nonskin malignancy in men and the second leading cause of cancer deaths. Metastatic prostate cancer initially retains its androgen dependence, and androgen-deprivation therapy often leads to disease control; however, the cancer inevitably progresses despite treatment as castration-resistant prostate cancer, the lethal form of the disease. Although it was assumed that the cancer became androgen independent during this transition, studies over the last two decades have shown that these tumors evade treatment via mechanisms that augment acquisition of androgens from circulating precursors, increase sensitivity to androgens and androgen precursors, bypass the androgen receptor, or a combination of these mechanisms. This review summarizes the history of prostate cancer research leading to the contemporary view of androgen dependence for prostate cancers and the current treatment approaches based on this modern paradigm.

INTRODUCTION

ADT: androgen-deprivation therapy

GnRH: gonadotropin-releasing hormone

PSA: prostate-specific antigen

CRPC: castration-resistant prostate cancer

LH: luteinizing hormone

T: testosterone

AR: androgen receptor

ER: estrogen receptor

Prostate cancer is the most common nonskin malignancy in men, with over 174,000 new cases estimated per year. Prostate cancer is second only to lung cancer as the leading cause of cancer-associated death. About 90% of prostate cancers are confined to the prostate and adjacent tissues, and for these cases, the prognosis is quite good. Management of localized prostate cancer consists primarily of surgery, radiation, or active surveillance. For the remaining 10% of cases with metastatic disease, the disease is generally incurable. In addition, prostate cancer has a predilection for bone metastases, which cause significant pain and morbidity.

The prostate is an androgen-dependent organ found only in men, and most prostate cancers maintain this androgen dependence, at least initially. Consequently, treatment of metastatic prostate cancer had been androgen-deprivation therapy (ADT), typically medical castration with a gonadotropin-releasing hormone (GnRH) antagonist (degarelix) or long-acting agonists (leuprolide, goserelin, triptorelin, and histrelin). Responses to ADT are generally good, as reflected in reduced prostate-specific antigen (PSA) in the circulation, improved bone pain, and stabilization of tumor burden. Over time, the response to ADT wanes, and the cancer progresses as castration-resistant prostate cancer (CRPC). CRPC accounts for most prostate cancer deaths, and for this reason, CRPC has been the focus of intense basic research and pharmaceutical development in the past several years.

This review summarizes the work leading to the traditional views of how hormones regulate prostate cancer progression, the key studies that altered these views, our current understanding of hormonal regulation in CRPC, the successful treatment strategies that have emerged from this knowledge, and the current directions of research in the field.

EARLY STUDIES AND FALSE ASSUMPTIONS

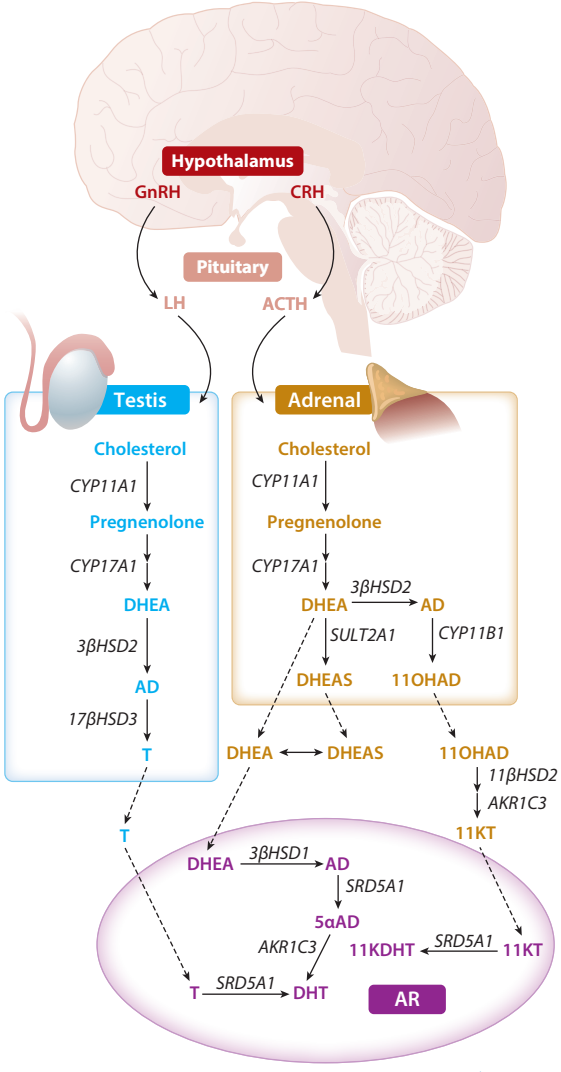
The first form of ADT was surgical castration, for which Huggins and Hodges received the 1966 Nobel Prize in Physiology or Medicine (1). The dramatic responses represented proof of the androgen dependence, and the surgical approach positioned prostate cancer treatment in the realm of urology. This treatment paradigm is based on the assumption that removal of testicular androgens is sufficient to treat prostate cancer. Consequently, subsequent strategies to introduce medical therapies were based on the hypothalamic-pituitary-testicular axis and its regulation. In the arcuate nucleus of the hypothalamus, GnRH is released in a pulsatile fashion every 90–120 min under complex regulation from higher brain centers and physiologic cues, including caloric sufficiency and sleep stages. Every pulse of GnRH results in pulses of luteinizing hormone (LH) and follicle-stimulating hormone from the gonadotrophs in the pituitary gland. LH acts on the Leydig cells of the testes to stimulate the acute synthesis of testosterone (T) and the long-term maintenance of steroidogenic capacity, meaning expression of the enzymes and other necessary proteins as well as the supply of cholesterol substrate for T synthesis (**Figure 1**).

T is also produced in pulses, but unlike peptide hormones, T is not stored for secretion but acutely generated from cholesterol by an enzymatic cascade. T released into the circulation is almost all bound to plasma proteins, about 60% tightly bound to sex-hormone-binding globulin and 40% weakly bound to albumin. This protein binding dampens the fluctuations in circulating T concentrations derived from pulsatile synthesis and substantially delays clearance compared to LH. T exerts negative feedback on both GnRH and LH release through its binding to the androgen receptor (AR), and through the binding of its downstream metabolite, estradiol, to the estrogen receptor (ER). Based on this physiology, medical therapies were designed to "trick" the male gonadal axis to shut off T production (2). The first approaches were to enhance the negative feedback with estrogens such as diethylstilbestrol, but predictable side effects such as

gynecomastia and thromboembolic complications limited this option. Subsequently, the long-acting GnRH agonists were used to downregulate GnRH receptors via continuous rather than the normal pulsatile activation. Following an initial transient rise, LH and T suppress to castrate levels during these therapies, and outcomes are equivalent to surgical castration (3).

DHT: 5α-dihydrotestosterone

Throughout the development of these treatments in the 1970s and 1980s, T was measured using immunoassays designed to function best in the normal adult male range, roughly 300–600 ng/dl (10–20 nmol/L). Medical or surgical castration lowered T to the lower limit of the assay, <50 ng/dl (<1.7 nmol/L), in a range where quantitation is very inaccurate. Upon progression to CRPC, circulating T remained low, suggesting that the recurrence was not due to failure of T suppression but rather due to transition to a state of androgen independence. Curiously, early studies demonstrated that intratumoral 5α-dihydrotestosterone (DHT), the most potent endogenous androgen, declined modestly despite the dramatic reductions in circulating T during ADT



(*Caption appears on following page*)

Figure 1 (*Figure appears on preceding page*)

Androgen synthesis and its regulation in the human male testes and adrenals. For the testes, GnRH pulses stimulate LH release from the pituitary, and LH drives T synthesis. The major testicular androgen is T, which is taken up in CRPC cells (*purple shaded oval* at bottom) and converted to DHT. In parallel, CRH stimulates pituitary secretion of ACTH, which drives not only cortisol production but also synthesis of adrenal-derived androgens and androgen precursors. The major adrenal-derived androgen precursors are DHEA, DHEAS (which to some extent are interconverted peripherally, as *double-headed arrow* indicates), and 11OHAD, which is peripherally converted to 11KT. Circulating DHEA and 11KT are converted in CRPC cells to DHT and 11KDHT, respectively, via the indicated pathways. The three major sources of androgens and androgen precursors in the circulation that appear to be most relevant for CRPC are highlighted: testicular T synthesis and adrenal production of DHEA and 11OHAD. Other pathways also exist. For example, circulating AD derived directly from the adrenal or from peripheral metabolism of DHEA can also serve as a source of DHT, and 11OHAD can be metabolized to 11KDHT in prostate cancer cell lines. Abbreviations: 5αAD, 5α-androstanedione; 11KT, 11-ketotestosterone; 11KDHT, 11-ketodihydrotestosterone; 11OHAD, 11β-hydroxyandrostenedione; ACTH, adrenocorticotropin; AD, androstenedione; CRH, corticotropin-releasing hormone; CRPC, castration-resistant prostate cancer; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; DHT, 5α-dihydrotestosterone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; T, testosterone.

(4). This paradox was the first suggestion that CRPC tumor cells have the capacity to synthesize androgens; however, which androgens, how much, and from what precursors remained unknown. In addition, the clinical significance of this finding was unclear given the prevailing notion that it was the circulating gonadal androgens that fueled prostate cancer growth.

RECOGNITION THAT ANDROGEN-RESPONSIVE GENES DRIVE CASTRATION-RESISTANT PROSTATE CANCER

For decades after the work of Huggins & Hodges (1), prostate cancer that becomes resistant to castration was referred to as androgen-independent prostate cancer (AIPC) or hormone-refractory prostate cancer (5, 6). Over time, however, these labels were proven to be misnomers that did not explain clinical responses to other therapies (7).

Ketoconazole, one of the first azole-based antifungal drugs, was developed for the treatment of superficial and systemic candidiasis and not as a prostate cancer drug. Ketoconazole inhibits lanosterol demethylase (CYP51A1), which is required for ergosterol synthesis, a critical component of the fungal cell membrane. Serendipitously, ketoconazole was found also to inhibit several steroidogenic cytochrome P450 enzymes necessary for cortisol and T synthesis both in vitro and in vivo. In particular, ketoconazole in doses higher than those used to treat fungal infections (200–400 mg t.i.d.) rapidly lowers circulating T to castrate or near-castrate levels. Thus, in the early 1980s, ketoconazole was shown to be an effective alternative to LH suppression strategies for treating prostate cancer (8). When long-acting GnRH agonists were first used in the mid-1980s, addition of ketoconazole could block the initial T rise and disease flare that occurred immediately after the first dose prior to LH suppression. Initially, ketoconazole was assumed to be equivalent to LH suppression, blocking all testicular T production, but in the late 1980s, ketoconazole was studied in patients who failed conventional ADT (9). Curiously, a substantial fraction of these patients then experienced a second disease remission, which did not fit the existing model of AIPC. Early-generation nonsteroidal AR antagonists such as flutamide were also employed to block the GnRH-agonist-induced flare, but AR antagonists did not dramatically improve survival when used along with ADT or after ADT failure (10). Nevertheless, the concept of "maximum androgen blockade" or "combined androgen blockade" surfaced in the 1980s, and small studies suggested improved survival when androgens were brought as low as possible with combination

AIPC: androgen-independent prostate cancer

therapy (11). Thus, mounting evidence suggested that the difference between androgen-sensitive and "androgen-independent" disease was quantitative rather than absolute.

Molecular genetics studies further illustrated the participation of AR in prostate cancer. PSA is a circulating protease expressed almost exclusively in the prostate. PSA expression is exquisitely sensitive to androgens, and serum PSA has long been used as a tumor marker for monitoring treatment of prostate cancer. In CRPC, it was recognized that after being suppressed by castration, expression of AR-responsive genes re-emerges (12, 13). The most fundamental observation is that a rise in serum PSA protein, which is androgen-responsive and declines with castration, is often the first signal for the development of resistance. Frequently, the PSA rise probably is also indicative of a resurrection of AR stimulation. Another prostate-derived serine protease, TMPRSS2, is also expressed in an androgen-dependent manner. AR-driven hybrid oncogenes containing the 5′-regulatory region of the *TMPRSS2* gene fused to proto-oncogenes such as *ERG*, *ETS*, and *ETV1* are pathologic genetic alterations that are commonly found in prostate cancers and explain the androgen dependence (14). A rise in PSA during ADT heralds the conversion to CRPC, and the *TMPRSS2*-fusion oncogenes are also expressed in CRPC. The consistent re-expression of androgen-dependent genes in the evolution of CRPC introduced a conceptual revolution, in that the tumor progression was once again AR-driven (15). Subsequently, the poor responses to first- and second-generation AR antagonists was attributed to the relatively modest affinities of these drugs compared to the endogenous ligands T and DHT, which bind AR at nanomolar concentrations.

DHEA: dehydroepiandrosterone

A commonly used experimental paradigm of CRPC also represented a stumbling block to accepting the clinical dogma regarding the mechanisms for "androgen independence." In this model, male nude mice are xenografted with an androgen-dependent human prostate cancer cell line. Over time, the tumor grows, and castration leads to regression of the tumor. Subsequently, tumor growth resumes, and the assumption has been that the cells have acquired androgen independence, given the absence of testes and the inability of the mouse adrenal to synthesize androgen precursors. In some strains of mice, however, castration and resultant elevated gonadotropins lead to the expression of the *Cyp17a1* gene encoding the steroid 17-hydroxylase/17,20-lyase (cytochrome P450 17A1) in the adrenals and the capacity to synthesize adrenal-derived androgens. Moreover, the mouse model can be "humanized" with dehydroepiandrosterone (DHEA) supplementation, to mimic at least in part the androgenic component of the human adrenal (16).

MECHANISMS IN CASTRATION-RESISTANT PROSTATE CANCER TO EVADE ANDROGEN-DEPRIVATION THERAPY

Overexpression and Mutations of Androgen Receptor

This recognition of the androgen dependence of CRPC and the critical adrenal contribution to androgen economy led to intense study of the mechanisms that tumors employ to restore androgen responsiveness. In breast cancer, ER expression and stimulation are biomarkers that guide therapy. In prostate cancer, increased expression of AR has been observed in CRPC specimens during ADT. In addition, the AR ligand-binding domain mutations, such as T877A (revised numbering, T878A), which reduces the specificity of androgen binding to allow activation by other steroids, and even the AR antagonist flutamide, have been found in up to 10% of CRPC tumors, particularly in patients receiving AR antagonists (17, 18). AR overexpression by way of gene amplification and other mechanisms were noted to occur almost entirely after treatment selection with medical castration (15), and AR mutations were discovered after treatment with AR antagonists (18). Perturbations in AR coregulators have also been widely described that may result in AR stimulation (7, 19). Other promiscuous AR mutations have been identified in CRPC, and AR

splice variants pose yet another mechanism. The AR-V7 and other variants lack a ligand-binding domain and appear to exhibit constitutive transcriptional activity even in the absence of ligand, which may also limit response to AR antagonist therapies (20–22). Nevertheless, the majority of CRPC tumors contain wild-type AR and remain vulnerable to treatments that either remove the AR ligands or antagonize AR with sufficiently high affinity to out-compete residual androgens (23). These resistance mechanisms might explain the surprising observation that intratumoral T and DHT concentrations from clinical CRPC tissues were found to be elevated to physiologically significant levels despite ADT (4, 24, 25). The clinical activities and survival benefit conferred by ketoconazole and next-generation hormonal therapies that block the synthesis or effects of intratumoral T and DHT now provide unequivocal clinical evidence that potent androgens synthesized from extragonadal precursor steroids drive the development and progression of CRPC (26).

The compelling results with ketoconazole therapy validated the concept that further lowering of androgens could treat CRPC, but the observation begged the question of where the androgens were coming from. Serum T remained in the castrate range of <50 ng/dl (<1.7 nmol/L) and LH suppressed, making it unlikely that the testes were the source of androgen. Medical castration, in contrast, does not affect the production of adrenal-derived androgens (**Figure 1**). While the adrenals produce very little T directly, they produce significant amounts of androstenedione (AD) and vast amounts of DHEA and its sulfate (DHEAS), which circulate at concentrations over 100 ng/dl (3.5 nmol/L) and 100 μg/dl (2,700 nmol/L), respectively. Therefore, if only 10% of circulating DHEA or 0.1% of circulating DHEAS were converted to T or DHT in the prostate cancer cell, the androgen delivery would be enough to overcome ADT. Not surprisingly, the expression of enzymes required for metabolism of DHEA to T and DHT is increased in CRPC cells compared to normal prostate (27, 28). Prostate cancer cell lines that more efficiently metabolize DHEA to active androgens exhibit more rapid progression in xenograft models that are "humanized" with DHEA supplementation. Thus, the adrenal shifts from a trivial source of androgens in eugonadal men to the critical androgen source in men failing ADT during progression to CRPC. More importantly, the enzymes and pathways responsible for utilization of adrenal-derived androgens have become topics of intense investigation and potential therapeutic targets.

Dysregulation of 3βHSD1

An essential step that is absolutely required for the synthesis of T or DHT from extragonadal precursor steroids—whether tumors utilize de novo steroidogenesis, the adrenal 5α-androstanedione pathway, or the canonical adrenal pathway—is 3β-hydroxysteroid dehydrogenase/isomerase (3βHSD). 3βHSD catalyzes two reactions that are together effectively irreversible. The first is 3β-hydroxyl to 3-keto oxidation, and the second is Δ^5 to Δ^4 isomerization (29, 30). This enzymatic step converts DHEA to AD, Δ^5-androstenediol to T, pregnenolone to progesterone, and 17-hydroxypregnenolone to 17-hydroxyprogesterone (31). Two human genes encode 3βHSD isoenzymes. *HSD3B2* encodes the isoenzyme expressed in the gonads and adrenals, and *HSD3B1* is primarily expressed in peripheral tissues, including the prostate, skin, breast, and placenta (32, 33).

HSD3B1 has a common missense-encoding germline variant that regulates metabolic flux mediated by 3βHSD1. *HSD3B1*(1245A) is the adrenal restrictive allele that encodes a protein that limits conversion from DHEA to AD, whereas *HSD3B1*(1245C) is the adrenal permissive allele that encodes an enzyme that enables increased synthesis of AD and downstream steroids (34, 35). Remarkably, germline inheritance of the adrenal permissive allele confers more rapid clinical resistance to ADT and shorter time to development of clinical endpoints related to CRPC for men with advanced prostate cancer (36). These findings have been independently replicated in multiple

cohorts in the United States, Japan, and Spain (37–40), and most recently have been additionally validated in low-volume metastatic castration-sensitive prostate cancer in a phase III clinical trial of ADT versus ADT + antimitotic docetaxel (41). These results demonstrate that inheritance of the adrenal permissive allele allows prostate cancers to more quickly dissociate from dependence on gonadal T by more readily engaging extragonadal precursor steroids for synthesis of T and DHT. Inheritance of the adrenal-permissive *HSD3B1* allele is also associated with longer duration of CRPC response to ablation of extragonadal androgen synthesis (e.g., CYP17A1 inhibition)—thus suggesting that it confers an "addiction" to extragonadal androgens such that this mechanism of resistance to castration also reveals a pharmacologic vulnerability to blocking the synthesis or possibly effects of extragonadal androgens (42). Together, these data provide genetic evidence for the role of extragonadal androgens in promoting prostate cancer progression and that *HSD3B1* is a predictive rather than prognostic biomarker (35). A caveat for the use of the CYP17A1 inhibitor, abiraterone, specifically in the context of the adrenal-permissive *HSD3B1* allele is that this genetic context also allows for greater circulating levels of an abiraterone metabolite that has partial AR agonist activity, as discussed in the following section on strategies to manage advanced CRPC (43).

GR: glucocorticoid receptor

Steroid Receptor and Steroid Metabolism Switches

Frequently, when potent AR antagonists such as enzalutamide and apalutamide effectively block AR, glucocorticoid receptor (GR) emerges as a compensatory mechanism that drives the expression of a subset of genes that otherwise are normally AR regulated, thereby promoting AR antagonist resistance (44–46). Furthermore, there is evidence that GR stimulation may have other tumor-promoting effects that are unrelated to the AR transcriptional program (47). Just as perturbations in androgen metabolism are clearly implicated in generating T and DHT to stimulate AR, evidence exists for intratumoral alterations in glucocorticoid metabolism that enable GR stimulation. In normal physiology, 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) serves to limit GR stimulation in peripheral tissues by 11β-hydroxyl oxidation to 11-keto and converting cortisol (which stimulates GR) to cortisone (which is inactive) (48). The AR to GR switch that occurs with AR antagonist resistance is accompanied by a loss in tumor 11βHSD2 expression, which retards conversion from cortisol to cortisone, raising tumor tissue concentrations of active glucocorticoids and effectively increasing GR stimulation (49). In mouse xenograft models, forced expression of 11βHSD2 results in reversal of enzalutamide resistance, thereby illustrating that sufficient tumor tissue cortisol concentrations are indeed required for GR stimulation and tumor resistance to next-generation AR antagonists.

Adrenal-Derived 11-Oxyandrogens

While DHEAS is recognized as the archetypal and most abundant adrenal-derived 19-carbon steroid, the coexistence of CYP17A1 and CYP11B1 (steroid 11β-hydroxylase) in the human adrenal enables the synthesis of 11-oxygenated metabolites of A4 and T. In teleost (bony) fishes, the testes also co-express these enzymes, and the major reproductive androgen in male fish is not T but 11-ketotestosterone (11KT). In fact, the third most abundant known steroid in human adrenal vein samples is 11β-hydroxyandrostenedione (11OHAD), and circulating concentrations of 11OHAD generally exceed those of AD. Furthermore, circulating concentrations of 11KT exceed those of T in children and most women—and, initial results suggest, also in men during ADT. 11KT is nearly as potent an agonist of human AR as T, and 11KT is metabolized via steroid 5α-reductase type 1 (SRD5A1) to its more potent 5α-reduced metabolite (50–53). Thus, initial studies of CRPC that focused on the traditional androgens and precursors DHEA, AD, T, and

DHT neglected an entire parallel and even more robust source of adrenal-derived androgens with comparable potencies.

The pathway of 11OHAD metabolism to 11KT is first 11βHSD2-catalyzed oxidation to 11-ketoandrostenedione (11KAD) and then reduction via the 17β-hydroxysteroid dehydrogenase activity of aldo-keto reductase 1C3 AKR1C3 (17βHSD5), which also catalyzes most extragonadal conversion of AD to T. 11KAD is a much better substrate for AKR1C3 than AD itself, whereas 11OHAD is a poor substrate. Therefore, tumors that downregulate 11βHSD2 expression favor cortisol preservation and GR activation but thwart the conversion of 11OHAD to 11KT (54, 55). The LNCaP cell line metabolizes 11OHAD to 11KT, and 11-oxyandrogens have been found in tumor tissue of a few patients with prostate cancer during ADT. The contributions of 11-oxyandrogens to CRPC progression, prognosis, and response to treatment have not been adequately studied in a large number of diverse CRPC patients (56).

STRATEGIES TO MANAGE ADVANCED CASTRATION-RESISTANT PROSTATE CANCER

Generally, there are two therapeutic approaches to blocking mechanisms that enable the development of extragonadal-androgen-mediated CRPC. The first is inhibition of the synthesis of intratumoral T and DHT from extragonadal precursor steroids, and the second is blockade of the AR ligand-binding domain. The prodrug abiraterone acetate is deacetylated after oral administration to abiraterone, a steroidal drug that potently inhibits CYP17A1, with its major site of action being the adrenal. However, CYP17A1 expression has been reported in prostate cancer, potentially implicating de novo androgen synthesis from cholesterol in the tumor itself. There are now three nonsteroidal next-generation AR antagonists that are approved by the US Food and Drug Administration for the treatment of prostate cancer: enzalutamide, apalutamide, and darolutamide. All potently outcompete T and DHT (presumably 11-oxyandrogens as well) for the AR ligand-binding domain.

Abiraterone inhibits CYP17A1 and the synthesis of androgens in the adrenal zona reticularis. Adrenocorticotropin (ACTH) upregulation occurs with abiraterone treatment, leading to an increase in mineralocorticoid synthesis and consequently resulting in hypertension, hypokalemia, and fluid retention, which can be treated with the mineralocorticoid-receptor antagonist eplerenone (57). For this reason, practice-changing clinical trials included concomitant use of glucocorticoids to suppress ACTH and the resultant adverse effects. Phase III clinical trials of abiraterone were conducted first in the post-docetaxel setting and then for docetaxel-naïve patients with CRPC. Together, these studies showed that blocking extragonadal androgen synthesis extends survival in men with CRPC (58, 59). Subsequent studies focused on the question of whether treatment with abiraterone along with upfront initiation of ADT, instead of awaiting the development of CRPC, would also confer a survival benefit. Two phase III clinical trials demonstrated a progression-free survival and overall survival advantage for the group treated with abiraterone + ADT, thereby making upfront gonadal and extragonadal androgen ablation a standard-of-care treatment for metastatic castration-sensitive prostate cancer (60, 61). It is notable that as a steroidal drug that has A/B ring structural identity with DHEA, abiraterone undergoes metabolism by enzymes, including 3βHSD1 and SRD5A, that normally act upon endogenous steroids, and this results in the generation of several steroidal metabolites that have both AR antagonist (Δ^4-abiraterone or D4A) (62) and partial AR agonist activity (5α-abiraterone) (63, 64). Furthermore, the generation of some of these metabolites is known to be regulated by the *HSD3B1*(1245) variant (43). Nevertheless, the ultimate clinical consequences of these metabolites have yet to be clearly determined.

Enzalutamide and apalutamide are both next-generation AR antagonists with activities that are superior to the older drugs, bicalutamide, nilutamide, and flutamide (65–67). Similar to abiraterone, enzalutamide was evaluated in phase III clinical trials in both the post-docetaxel and docetaxel-naïve settings and was shown to confer a survival benefit for men with metastatic CRPC (68, 69). Subsequently, enzalutamide, apalutamide, and darolutamide were tested in the setting of non-metastatic CRPC and shown to prolong metastasis-free survival over treatment with ADT alone in phase III trials (70–72). More recently, enzalutamide and apalutamide have each been tested in combination with ADT in phase III trials in the setting of metastatic castration-sensitive prostate cancer and have demonstrated an improvement in overall survival compared with ADT alone (73, 74).

Together, these data strongly support the current paradigm that blocking the synthesis or activity of extragonadal-derived prostate cancer T or DHT reverses progression of CRPC and delays the development of CRPC when these agents are used upfront along with castration. The evidence is overwhelming that the ultimate effect of treatment with these next-generation hormonal therapy agents is extension of overall survival.

FUTURE DIRECTIONS

We now recognize that CRPC is not AIPC and that AR continues to drive CRPC, at least at its initial development. Although the last several years have seen an explosion of new treatments for CRPC, all of these therapies have drawbacks, and the long-term consequences of early treatment with maximal androgen blockade to men with a new diagnosis of metastatic prostate cancer are not known. New approaches are needed to effectively manage AR-ligand-independent disease, GR-driven disease, and bone metastases with pain refractory to conventional treatments. In addition, the best biomarkers of effective AR blockade and AR ligand synthesis are not known, and combinations of recent treatment advances with other drugs that have distinct mechanisms are under study. Additional potential drug targets have been identified (CYP11A1, 3βHSD1, 11βHSDs, AKR1C3, GR, others). Nevertheless, the remarkable progress made in the last decade has not only improved survival but improved quality of life for men with CRPC, despite the fact that we still have a long way to go before we can consider this disease conquered.

SUMMARY POINTS

1. During the transition to CRPC, androgen-responsive genes are expressed despite ADT.
2. The adrenal is a major source of androgens and androgen precursors for men with CRPC.
3. The major adrenal androgen precursors are DHEA, DHEAS, and 11OHAD.
4. CYP17A1 (steroid 17-hydroxylase/17,20-lyase) is required for all androgen synthesis.
5. The enzymes 3βHSD1, AKR1C3, and SRD5A1 are found in CRPC tissue and participate in pathways of androgen precursor metabolism to potent androgens.
6. A shift from AR to GR dependency is observed in some CRPC tumors during treatment with potent androgen antagonists.

DISCLOSURE STATEMENT

Cleveland Clinic has applied for a patent on HSD3B1 in prostate cancer. R.J.A. is a consultant for Janssen Pharmaceuticals.

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