**FORUM**

**E VOLUTION OF ANDROGEN DEPRIVATION THERAPY**

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**Abstract**

The androgen signalling axis is critical for the development and progression of prostate cancer. Therefore, the mainstay treatments for metastatic disease are hormonal manipulations aimed at reducing androgen levels and/or blocking the androgen receptor, collectively termed androgen deprivation therapy. This review will discuss the evolution of androgen deprivation therapy since it was instigated more than 70 years ago, and outline the key mechanisms underlying its inevitable failure. We will also briefly introduce potential new androgen signalling-targeted therapies in clinical development.

Prostate cancer is the most common cancer and the second most common cause of cancer mortality in men. In Australia alone, there are >21,000 new diagnoses and >3200 deaths per annum.1 Metastasis to the bone, lymph nodes, lung, liver or brain is primarily responsible for mortality from prostate cancer. Some patients are diagnosed with metastatic disease at their initial evaluation, while others develop metastases after failing primary surgical or radiation therapy.

Huggins and Hodges demonstrated in 1941 that prostate cancer is driven by the male sex steroid hormones, androgens.2 Androgens are produced through a pathway involving the hypothalamus, pituitary, testes and adrenal glands and mediate their action by binding to the androgen receptor. Both androgens and the androgen receptors are located in almost every body tissue and have distinct roles in each organ.3 Testosterone is the major circulating androgen, with 90-95% secreted by the testes and 5-10% secreted by the adrenal glands. Almost all circulating testosterone is bound to sex hormone binding globulin, which prevents it from diffusing into cells. After passively entering prostatic epithelial cells, free testosterone is converted to the more potent androgen 5α-dihydrotestosterone (DHT) through the action of 5α-reductase. Subsequent binding of DHT by the androgen receptor causes it to move from the cytoplasm to the nucleus of the cell. Once in the nucleus, the androgen receptor binds to DNA and regulates the expression of hundreds to thousands of genes.4 Genes regulated by the androgen receptor are enriched for those involved in processes like cellular proliferation, differentiation, metabolism and steroid biosynthesis.4,5 The prototypical androgen-regulated gene is KLK3, which encodes prostate specific antigen (PSA). Induction of PSA expression by enhanced androgen receptor activity in prostate cancer is evidenced by increased serum PSA levels in patients, which is used to diagnose disease and to identify recurrence following therapies.

**Castration-sensitive prostate cancer**

The androgen axis is the first and primary target for patients with locally-advanced or metastatic castrate-sensitive disease. Hormonal manipulation to decrease circulating androgen levels, commonly referred to as androgen deprivation therapy (ADT), reduces circulating testosterone levels by 90-95%. ADT causes cancer regression and a decrease in serum PSA in the vast majority of men; this therapy-responsive disease state is referred to as castrate-sensitive prostate cancer. An overview of the evolution of ADT for castration-sensitive prostate cancer is outlined below.

Since the primary source of androgens is the testes, surgical castration via removal of the testes (orchiectomy) was initially the intervention of choice. While surgical castration achieves very effective ADT, it is associated with debilitating physical, emotional and psychological side-effects. In the 1960s, ‘medical castration’ using synthetic estrogens such as diethylstilbestrol (DES) became a common alternative. Although direct beneficial effects of DES in the prostate have been described, DES primarily acts by inhibiting luteinizing-hormone-releasing hormone (LHRH) through negative feedback on the hypothalamic-pituitary axis. DES proved effective in achieving castrate levels of circulating testosterone, and was used therapeutically for a long time, but fell out of favour because it caused cardiovascular complications, including increased rates of mortality from cardiac events.6

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1. Adapted from Australian Prostate Cancer Action Network.2. Adapted from American Urological Association.3. Adapted from U.S. National Library of Medicine.4,5. Adapted from Cancer Genome Atlas.6. Adapted from D communism.
The 1970s saw the advent of agents that block androgen binding to the androgen receptor, referred to as anti-androgens (figure 1). Anti-androgens can be classified as steroidal (e.g. cyproterone acetate, medroxyprogesterone acetate) and non-steroidal (e.g. flutamide, nilutamide and bicalutamide); the latter are preferable since they preserve potency and libido in most cases.

Long-acting synthetic LHRH agonists became available in the 1980s and, given that they achieved castrate levels of circulating androgens while sparing men surgery and the associated psychological effects, as well as eliminating the use of DES, represented a revolutionary new form of ADT. LHRH agonists such as leuprolide and goserelin are now generally the first-line ADT, being administered subcutaneously in a slow-release form approximately every 3-6 months. LHRH agonists initially activate the pituitary, causing luteinising hormone release and a subsequent rise in androgens. After persistent stimulation, the pituitary becomes desensitised and LHRH receptors are reduced, causing a concomitant decline in serum androgen levels. LHRH agonists target androgen production both in the testes and the adrenals and, like other forms of ADT, cause disease regression in most patients, but for variable lengths of time. The initial rise in androgens driven by luteinising hormone release can cause ‘flare’ or worsening symptoms of metastatic disease. In these patients, non-steroidal anti-androgens are often administered prior to LHRH agonists to prevent symptomatic flare by inhibiting the action of the androgen receptor.

The imidazole antifungal agent ketoconazole also became available as a treatment of advanced prostate cancer in the 1980s. Ketoconazole exerts its therapeutic effect in prostate cancer primarily by inhibiting the activity of multiple cytochrome P450 enzymes, including CYP17A1. By doing so, ketoconazole inhibits the conversion of cholesterol to pregnenolone and thus suppresses a key step in steroidogenesis, inhibiting testicular, adrenal and intratumoral androgen biosynthesis. Until quite recently (circa 2013), ketoconazole continued to be employed therapeutically with some success to treat advanced prostate cancer. However, serious liver toxicity associated with ketoconazole has led to its discontinuation for the treatment of prostate cancer in Australia and most other countries.

Dutasteride is a drug used to treat benign prostatic hyperplasia, an androgen-driven condition characterised by an enlarged prostate. It acts by inhibiting both Type 1 (found throughout most tissues, including skin, liver and prostate) and type 2 (expressed predominantly in prostate and reproductive organs) 5-reductases. Given its inhibitory effect on DHT production, dutasteride was assessed for the chemoprevention of prostate cancer in clinical trials in the early 2000s. Despite the observation of a slight overall reduction in prostate cancer incidence in the dutasteride treated group, there was an overall increase in higher grade prostate cancer associated with dutasteride treatment, making dutasteride inappropriate in a chemoprevention setting. A more recent study of dutasteride demonstrated its efficacy in reducing cancer recurrence in an active surveillance cohort of men with low-risk, localised disease, and there was no evidence for it causing more aggressive disease in this cohort (REDEEM study; HR 0.62, 95% CI 0.43–0.89). Given these data, the chemopreventative utility of dutasteride is questionable. However, it could prove more useful in the setting of aggressive disease in combination with other agents; indeed, it is now being tested in combination with abiraterone in a clinical trial (NCT01393730).

Degarelix and other gonadotropin-releasing hormone (GnRH) antagonists have been developed more recently and are alternatives to LHRH agonists and anti-androgens. GnRH antagonists block receptors in the pituitary and result in decreased levels of luteinizing hormone, follicle stimulating hormone and testosterone production. A key advantage of GnRH antagonists is that they do not cause flare, while a disadvantage is that they require monthly subcutaneous administration.

The recognition that intra-prostate levels of DHT remain relatively high even in men with castrate levels of circulating testosterone, led to the development of a therapeutic strategy known as combined androgen blockade. This approach combines an LHRH agonist or orchiectomy with either a steroidal or a nonsteroidal antiandrogen to block androgens of both adrenal and testicular origin. While initial studies on combined androgen blockade were positive, other studies do not support the superiority of this strategy over monotherapy.

Potential side-effects from the aforementioned androgen deprivation therapies include decreased libido, impotence, hot flashes, gynecomastia, breast tenderness, osteoporosis, anemia, weight gain and increased cholesterol. Since these side-effects have a significant impact on the quality of life of men undergoing long-term ADT, there is wide-spread interest in developing selective androgen receptor modulators that abrogate the growth promoting activity of androgens in prostate tumour cells, while maintaining their beneficial effects in other tissues.

Castration-resistant prostate cancer

The vast majority of patients with prostate cancer will initially respond to ADT for a variable period of 2-15 years. However, the ongoing selective pressure placed on prostate cancer cells in an androgen deprived environment drives the development of resistance, after which time the prostate cancer invariably recurs and continued growth ensues, as evidenced by rising PSA levels. At this stage, the disease progresses despite the maintenance of castrate levels of serum testosterone and is referred to as castration-resistant prostate cancer (CRPC).

The totality of research over the past decade has revealed that the most common event associated with failure of ADT is the inappropriate activation or
maintenance of androgen signalling. Many androgen signalling-dependent mechanisms have been identified as drivers of the development of castration resistance, most of which involve direct changes to the androgen receptor. First, the androgen receptor is frequently overexpressed in CRPC, often as a result of increased copies of the androgen receptor gene, and this can result in the receptor being activated by castrate levels of androgens (‘hypersensitive signalling’). Second, gain-of-function mutations of the androgen receptor have been reported in a minority of CRPC cases. Mutant receptors typically exhibit one of two main phenotypes: increased promiscuity of activation by non-classical ligands (including the conversion of antiandrogens from antagonists to agonists), or greater transactivation capacity via altered interaction with co-regulators. Third, deregulation of androgen biosynthesis also contributes to sustained androgen receptor signalling in CRPC. Mechanisms of deregulation include the conversion of non-testicular (i.e. adrenal) androgens or other steroid hormones to more potent androgens in peripheral tissues, including the prostate, and the overexpression of enzymes essential for androgen biosynthesis. Thus, serum testosterone levels may not accurately mirror the intraprostatic environment. Fourth, the presence of truncated versions of the androgen receptor that typically lack the majority of the ligand binding domain and are constitutively active proteins, are frequently enriched in CRPC samples and can drive androgen-independent cancer growth in pre-clinical models. Importantly, a recent study found that mRNA of the AR-V7 variant predicted lack of response to the androgen signalling inhibitors abiraterone and enzalutamide. Fifth, emerging evidence suggests that inappropriate expression of androgen receptor co-regulators also contributes to the development of castration-resistant disease. We and others have demonstrated that the transcriptional output of androgen signalling is heavily dictated by a complex system comprising over 200 co-regulator proteins, and their expression and function is often altered in response to ADT and during the development and progression of CRPC. Lastly, there is extensive interplay between androgen signalling and other growth factor signalling pathways in prostate cancer. This interplay, which often causes changes in the post-translational modifications of the androgen receptor (i.e. phosphorylation, ubiquitylation, acetylation and sumoylation), can stimulate activity of the receptor in the castrate environment.

### Improved targeting of the androgen receptor in CRPC

Since 2010, several new drugs have been approved by the Federal Drug Administration, including abiraterone and enzalutamide. These drugs enable more effective inhibition of intra-prostatic androgen production or the androgen receptor itself (figure 1).

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**Figure 1**: Current agents (red) and agents in clinical development (blue and in brackets) that target the androgen signalling axis in prostate cancer (5α-R, 5α-reductase; AR = androgen receptor; DHT = 5α-dihydrotestosterone; GnRH, gonadotropin-releasing hormone; LHRH, luteinizing-hormone-releasing hormone; T = testosterone).
Blocking androgen production

Abiraterone decreases androgen and glucocorticoid production by inhibiting the 17-β-hydroxylase and 17,20-lyase activities of CYP17, a key enzyme involved in androgen synthesis.\textsuperscript{43,44} Abiraterone received FDA approval in 2010.\textsuperscript{45,46} In the COU-301 study, patients with CRPC treated with abiraterone had longer median overall survival (OS) compared to the placebo group (15.8 months vs 11.2 months; HR 0.74; 95% CI 0.64-0.86). Importantly, abiraterone produced a greater OS benefit for patients than the original (now discontinued) CPY17 inhibitor, ketoconazole (19 months vs 11 months; HR 0.53).\textsuperscript{48} Abiraterone toxicity was low, with the most common adverse events being fatigue, anemia, back pain, bone pain and fluid retention or edema. Since the inhibitory effect of abiraterone on both the 17-β-hydroxylase and 17,20-lyase activities of CYP17 results in an accumulation of mineralocorticoids, its administration requires concomitant use of steroids. This side-effect may be minimised with the newer CYP17 inhibitors orteronel (TAK-700) and galeterone (TOK-001), which do not inhibit 17-β hydroxylase.\textsuperscript{47,48} However, orteronel plus prednisone failed to meet the primary endpoint of improved median OS over the placebo arm in patients with CRPC (17.0 vs 15.2 months; HR: 0.89; 95% CI 0.74-1.06).\textsuperscript{49} Galeterone is currently undergoing phase II evaluation in patients with CRPC (NCT01709734).\textsuperscript{48}

Blocking the androgen receptor

Enzalutamide is a second-generation anti-androgen that binds to the ligand binding domain of androgen receptor with an affinity higher than the first-generation agent bicalutamide. In addition to blocking DHT binding, it impairs androgen receptor nuclear translocation, co-activator recruitment and interaction with DNA.\textsuperscript{50} Enzalutamide received FDA approval in 2012 following a clinical trial demonstrating its positive effects on overall survival in the post-chemotherapy setting (18.4 months in the enzalutamide arm versus 13.6 months in the placebo arm; HR 0.63; 95% CI 0.53-0.75).\textsuperscript{51} Interim analysis of a more recent clinical trial has now shown that enzalutamide also elicits a small increase in overall survival in the setting of chemotherapy-naïve CRPC (32.4 months in the enzalutamide arm versus 30.2 months in the placebo arm; HR 0.71; 95% CI 0.60 to 0.84).\textsuperscript{52} Enzalutamide is relatively well tolerated, with common side-effects including fatigue, diarrhoea and hot flushes. However, seizures occurred in 1% of patients.

Targeting the androgen signalling axis: the future

The therapeutic landscape for prostate cancer has been transformed in recent years, particularly in the context of metastatic CRPC. In addition to abiraterone and enzalutamide, the last decade has seen approval of chemotherapies (docetaxel and cabazitaxel), the bone-targeted agent denosumab, the immunotherapy sipuleucel-T, and the radiopharmaceutical radium-223. However, these agents have only a modest effect on overall survival, generally in the order of 3-6 months.\textsuperscript{45,46,51,53-55} Two non-mutually exclusive means to improve outcomes for men with advanced prostate cancer are on the horizon. First, better sequencing and/or combinations of the currently approved agents will undoubtedly enhance therapeutic efficacy. Unfortunately, clinical evidence to guide either sequencing or combinatorial therapies is lacking, with treatment decisions being based primarily on predicted toxicity and tolerability. The identification of predictive biomarkers that can enable personalised treatment regimens are urgently required in this context. One emerging example of such a biomarker is the AR-V7 splice variant, which may predict lack of response to abiraterone and enzalutamide.\textsuperscript{58} Second, new agents that more effectively inhibit the progression of prostate cancer will likely become available in the near future (figure 1). In terms of agents targeting the androgen signalling axis, new agents of note in clinical development include: the next-generation anti-androgens APN-509 (which appear to have greater anti-tumour activity, better pharmacological traits and improved patient tolerability than enzalutamide);\textsuperscript{56,57} and ODM-201, which has a higher affinity for the androgen receptor than enzalutamide, inhibits androgen receptor nuclear translocation and CRPC growth in preclinical assays, and has shown promise in phase I/II clinical trials;\textsuperscript{58} and the aforementioned CYP17 inhibitors (orteronel, galeterone).

Conclusion

The androgen signalling axis drives prostate cancer and is a central target in prostate cancer therapy. The transition period from the initiation of ADT to the onset of CRPC is a crucial time for intervention. While recent advances in targeting androgen receptor signalling in CRPC have improved outcomes, until a cure or more effective drugs against prostate cancer are developed, an estimated 3300 Australian men will continue to die from this disease each year.

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