Castrate-resistant prostate cancer: the future of antiandrogens

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Several promising new treatment options for men with castrate-resistant prostate cancer have become available recently. The authors look at developments in this rapidly progressing area.

Prostate cancer is the most common non-cutaneous cancer in North American and European men and the second leading cause of male cancer-related death. The lifetime probability of developing prostate cancer in the UK is 14 per cent and in 2010 there were 40,975 new cases, accounting for 10,721 deaths.

Prostate cancer is associated with many risk factors, including age, family history, ethnicity, diet and weight. Although it is estimated that not more than 5 per cent of all prostate cancer cases are hereditary, family history is appropriately considered a relevant risk factor. Many genetic changes have been associated with prostate cancer, including mutations in \( P53, P21, P73 \) and tumour-suppressor genes.

For early-stage disease, surgery and/or radiotherapy with or sometimes without adjuvant hormone therapy are used, though even in an area as common as this there remains controversy about who and when to treat, and duration of therapy. Many patients with localised prostate cancer, and virtually all patients with advanced disease, relapse.
ANDROGEN DEPRIVATION THERAPY
Since the discovery of the benefits of androgen deprivation for patients with metastatic prostate cancer by Huggins and Hodges in 1941, targeting of androgens – androgen deprivation therapy (ADT) – has become a major paradigm of prostate cancer treatment (Figure 1).

Androgen deprivation targets the synthesis of gonadal androgens and is achieved through luteinising hormone-releasing hormone (LHRH) agonists, alternatively called gonadotrophin-releasing hormone (GnRH) antagonists. ADT has been the first-line therapy for patients who progress following local treatment and for those who present with metastatic disease; the majority of these patients are initially sensitive to it.

Importantly, androgen deprivation does not suppress adrenal androgens or androgens produced by prostate cancer cells, so does not typically lead to a total ablation. Therefore, prostate cancer progressing on androgen deprivation is termed ‘castrate-resistant prostate cancer’ (CRPC) rather than ‘hormone-refractory’ disease, although these are interchangeable in the clinic.

COMBINED ANDROGEN BLOCKADE
Small-molecule androgen receptor (AR) antagonists (eg the steroidal AR antagonist cyproterone acetate or the non-steroidal compounds flutamide, nilutamide and bicalutamide), with or without androgen deprivation, are used for patients with rising PSA levels or clinical progression on castration. This regimen is called combined androgen blockade; however, its benefits over chemical castration alone have been unimpressive. The major reasons for this failure may rest with a combination of conversion of AR antagonists to AR partial agonists by prostate cancer cells, increased AR expression or AR mutation; it results in the ‘antiandrogen withdrawal syndrome’.

DOCETAXEL CHEMOTHERAPY
Currently docetaxel chemotherapy is the gold-standard treatment for CRPC. However, the median survival in the first-line setting of CRPC is approximately 20 months and docetaxel provides a small survival advantage with a median period of less than three months. It is typically prescribed with prednisolone, which is a reasonable therapy in itself in this setting, and docetaxel is undoubtedly toxic.

NEW TREATMENT OPTIONS
In the past two years, several new drugs have become or are about to become available, so treatment options for patients with CRPC have expanded, signifying the move towards the ‘post-docetaxel’ era. These include cabazitaxel (Jevtana), sipuleucel-T (Provenge), radium-223 dichloride (Xofigo), abiraterone acetate (Zytiga) and enzalutamide (Xtandi).
**Cabazitaxel**

The microtubule inhibitor cabazitaxel is a novel semi-synthetic derivative of a natural taxoid and the fourth taxane that has been approved for cancer treatment. It has antitumour activity in docetaxel-refractory prostate cancer and provides a three-month extension of median survival over mitoxantrone as a second-line therapy, although it is not known for its lack of toxicity.11

**Sipuleucel-T**

Sipuleucel-T is the first immunotherapy approved for cancer treatment. It is an activated product of the patient’s own antigen-presenting cells incubated with a fusion protein consisting of prostatic acid phosphatase (present in 95 per cent of prostate cancer cells) and granulocyte macrophage–colony-stimulating factor (PAP/GM-CSF). The data from the IMPACT phase 3 trial demonstrated a survival benefit of sipuleucel-T treatment of 4.5 months over placebo for asymptomatic or minimally symptomatic CRPC.12 Sipuleucel-T remains an alternative to docetaxel; however, it is very expensive and its benefits have been questioned.

**Radium-223 dichloride**

Radium-223 dichloride is an alpha-emitting agent. A phase 3 study in patients with symptomatic metastatic (specifically to bone) CRPC pre- or post-docetaxel chemotherapy showed a three-month survival advantage over placebo.13 In November 2013 it was approved for use in the European Union for the treatment of patients with CRPC, symptomatic bone metastases and no known visceral metastatic disease.

**Abiraterone acetate**

Abiraterone acetate is an irreversible inhibitor of 17α-hydroxylase/C17,20 lyase (CYP17A1), a key enzyme in androgen synthesis, which is expressed in testicular, adrenal and prostatic tumour tissues. Discovered in the early 1990s in a Cancer Research UK laboratory, it did not find its immediate use until a paradigm shift led to a radical idea that CRPC remains dependent on the AR signalling.7 The clinical confirmation of that came with the randomised phase 3 study, which demonstrated improved overall survival in abiraterone-treated patients with disease progression following first-line docetaxel chemotherapy.14 It is now licensed in the US in the pre-chemotherapy setting and, like docetaxel, it requires steroids to be taken concomitantly to help ameliorate certain side-effects. Overall, these therapies have led to a median survival in the post-docetaxel setting of about 15 months. However, the benefits of these drugs are incremental and do not provide a radical solution for treatment of CRPC.

**Enzalutamide**

Following the success of abiraterone, several other molecules targeting AR signalling are currently in clinical development (orteronel, ARN-509, AZD3514, TOK-001 and EZN4176). Probably the most developed of these new-generation drugs is enzalutamide, a novel AR antagonist that binds to the AR more avidly than currently available antiandrogens. Enzalutamide is a synthetic small-molecule AR antagonist. In CRPC cells, it has a five- to eight-fold greater affinity to AR compared with bicalutamide, which is the most widely used antiandrogen on the market.15 Importantly, in prostate cancer cells expressing mutated AR that were isolated from a patient with acquired resistance to bicalutamide (and where bicalutamide was acting as an agonist), enzalutamide showed no agonist activity.15 Enzalutamide has been further shown to impair nuclear translocation of the AR, DNA binding and co-activator recruitment.16 Antitumour activity and safety of enzalutamide were investigated in a phase 1–2 study in 140 patients with progressive, metastatic CRPC in five US centres. Enzalutamide was given orally, with the daily doses ranging from 30 to 600mg. All doses produced antitumour effects, including decreases in serum PSA by 50 per cent or more in 56 per cent of patients, responses in soft tissue in 22 per cent, stabilised bone disease in 56 per cent, and conversion from unfavourable to favourable circulating tumour cell counts in 49 per cent.17

Following this success, 1199 men with CRPC who had progressed following docetaxel chemotherapy were recruited in a phase 3, double-blind, placebo-controlled trial (AFFIRM) and assigned 160mg/day oral enzalutamide or placebo.18 A planned interim analysis at the time of 520 deaths showed a 4.8-month improvement in median overall survival at 18.4 months versus 13.6 months, respectively.

Enzalutamide has also shown numerous advantages with respect to all secondary end points: reduction in the serum PSA level by 50 per cent or more (54 versus 2 per cent), responses in soft tissue (29 versus 4 per cent), the quality-of-life response rate (43 versus 18 per cent), the time to PSA progression (8.3 versus 3.0 months), radiographic progression-free survival (8.3 versus 2.9 months), and the time to the first skeletal-related event (16.7 versus 13.3 months). In this trial, rates of fatigue, diarrhoea and hot flashes were higher in the enzalutamide group compared with placebo. Enzalutamide can cross the blood–brain barrier and seizures were reported in five patients (0.6 per cent) receiving enzalutamide, although this point is confounded by the presence of brain metastases.18

**THE FUTURE**

Overall, both abiraterone and enzalutamide are next-generation, well-tolerated, orally
available antiandrogens of the post-docetaxel setting, and are moving into the pre-chemotherapy setting too. It is tempting to speculate that in five years time, these two drugs will be major weapons in our fight against prostate cancer following standard hormonal therapy. It is possible that the biggest impact of drugs such as enzalutamide will come in the early-stage setting, where they have the potential to replace bicalutamide as the antiandrogen of choice. This will be clarified in ongoing clinical trials.

The potential advances in treatment of CRPC do not stop there. Currently 27 clinical trials in the UK are investigating new therapies for men with CRPC. First, in preparation for the ‘post-abiraterone’ era, there are studies testing abiraterone in combination with phosphoinositol-3 kinase inhibitors (BEZ235 or BKM120) or a heat-shock protein 90 inhibitor (AT13387). A therapeutic cancer vaccine (PROSTVAC), alone or in combination with GM-CSF, is being tested for prolonging overall survival in men with few or no symptoms of CRPC. A new antiandrogen (ODM-201) and a new protein kinase B inhibitor (AZD5363) are being tested for safety, tolerability, pharmacokinetics and antitumour activity in CRPC patients who have progressed after chemotherapy. An orally active specific endothelin-A antagonist (ZD4054) and a poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor (olaparib) are also being tested in phase 2 trials in patients with advanced CRPC. These all appear to be better tolerated than chemotherapy, and may be more effective in certain settings, but the role of chemotherapy should not be diminished.

Patients are now living with advanced prostate cancer for longer, with improved quality of life and better palliation of symptoms. With the advent of so many new treatment options, we are recognising advanced prostate cancer as a chronic disease rather than a fatal one. Several new promising therapies have recently become available for treatment of castrate-refractory disease and more are currently undergoing clinical trials; their sequencing and use in combination will be crucial. Enzalutamide and abiraterone have particular potential in view of their impressive phase 3 data, favourable toxicity profiles and potential for use earlier in the treatment pathway, cost considerations notwithstanding.

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**REFERENCES**