

Castrate resistant prostate cancer: the future of anti-androgens.

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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 [1]. The lifetime probability of developing prostate cancer in the UK is 14% [1] and in 2010 there were 40,975 new cases, accounting for 10,721 deaths [2]. Prostate cancer is associated with many risk factors, including age, family history, ethnicity, diet, and weight and although it is estimated that not more than 5% 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*, and *P73* and tumour suppressor genes [3].

For early stage disease surgery and/or radiotherapy with or sometimes without adjuvant hormone therapy are used [4], though even in an area as common as this there remains controversy on who to treat, when and duration of therapy. Many patients with localised prostate cancer, and virtually all patients with advanced disease, relapse [5]. Since the discovery of the benefits of androgen deprivation for patients with metastatic prostate cancer by Huggins and Hodges in 1941 [6], targeting of androgens (androgen deprivation therapy (ADT)) became a major paradigm of prostate cancer treatment. 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 and 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 [7] and therefore does not typically lead to a total ablation. Therefore, prostate cancer progressing on androgen deprivation is termed "castration resistant prostate cancer" rather than "hormone-refractory" disease, though these are interchangeable in the clinic.

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 prostate specific antigen (PSA) 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 of 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 and results in the "antiandrogen withdrawal syndrome" [8].

Currently docetaxel chemotherapy is the gold standard treatment for castration resistant prostate cancer. However, the median survival in the first-line setting of castration resistant prostate cancer is approximately 20 months and docetaxel provides a small survival advantage with a median period of less than 3 months [9, 10]; it is typically prescribed with prednisolone which is a reasonable therapy in itself in this setting, and docetaxel is undoubtedly toxic.

In the last 2 years, with several new drugs have become or are about to become available and with this treatment options for patients with castration resistant prostate cancer have expanded, signifying the move towards the "post docetaxel" era. These include: cabazitaxel, sipuleucel-T, alpharadin, abiraterone acetate and most recently enzalutamide).

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 3 months extension of median survival over mitoxantrone as a second line therapy, although it is not known for its lack of toxicity either [11].

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

Alpharadin is an alpha-emitting radium-223 chloride. A phase III study in patients with symptomatic metastatic (specifically to bone) castration resistant prostate cancer pre- or post-docetaxel chemotherapy showed a 3 months survival advantage over placebo [13] and its role in the clinic is awaited when its approval occurs.

Abiraterone acetate is an irreversible inhibitor of 17 α -hydroxylase/C17,20 lyase (CYP17A1), a key enzyme in androgen synthesis, which is expressed in testicular, adrenal, and prostatic tumour tissues. Discovered in early 1990s in a CRUK laboratory, it didn't find its immediate use until a paradigm shift led to a radical idea that castration resistant prostate cancer remains dependent on the AR signalling [7]. The clinical confirmation of that came with the randomised phase III 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 lead 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 castration resistant prostate cancer.

Following abiraterone success, 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. It has at least a 30-fold lower affinity for the AR compared with dihydrotestosterone (DHT), the natural ligand of the AR, and bicalutamide, which is the most widely used antiandrogen on the market. In castration resistant prostate cancer cells, enzalutamide had 5-8 fold greater affinity to AR compared with bicalutamide. 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 was investigated in a phase I-II study in 140 patients with progressive, metastatic, castration-resistant prostate cancer in five US centres. Enzalutamide was given orally with the daily doses ranging from 30 mg to 600 mg. All doses produced antitumour effects, including decreases in serum PSA by 50% or more in 56% of patients, responses in soft tissue in 22%, stabilised bone disease in 56%, and conversion from unfavourable to favourable circulating tumour cell counts in 49% [17].

Following this success, 1199 men with castration resistant prostate cancer who had progressed following docetaxel chemotherapy were recruited in a phase III, double-blind, placebo-controlled trial (AFFIRM) and assigned 160 mg/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 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% or more (54% vs. 2%), responses in soft-tissue (29% vs. 4%), the quality-of-life response rate (43% vs. 18%), the time to PSA progression (8.3 vs. 3.0 months), radiographic progression-free survival (8.3 vs. 2.9 months), and the time to the first skeletal-related event (16.7 vs. 13.3 months). In this trial rates of fatigue, diarrhoea, and hot flashes were higher in the enzalutamide group in comparison to placebo. Enzalutamide can cross the blood brain barrier and seizures were reported in five patients (0.6%) receiving enzalutamide though this point is confounded by brain metastases being present [18].

Overall, both abiraterone and enzalutamide are next generation well-tolerated, orally available antiandrogens in a post-docetaxel setting, and are moving into the pre-chemotherapy setting too. It is tempting to speculate that in 5 years time, these 2 drugs will be our major weapons in our fight against prostate cancer following standard hormonal therapy. It is possible that the biggest impact of drugs like enzalutamide will come in the early stage setting where enzalutamide has the potential to replace bicalutamide as the antiandrogen of choice. This will be clarified in the ongoing clinical trials.

The potential advances in treatment of castration resistant prostate cancer don't stop there. Currently 27 clinical trials in the UK investigate new therapies for men with castration resistant prostate cancer. Firstly, in the preparation for the "post-abiraterone" era, there are studies testing abiraterone in combination with phosphoinositol-3 kinase (PI3K) inhibitors BEZ235 or BKM120 or heat-shock protein 90 (HSP90) inhibitor AT13387. A therapeutic cancer vaccine PROSTVAC alone or in combination with GM-CSF is tested for prolonging overall survival in men with few or no symptoms castration resistant prostate cancer. A new antiandrogen ODM-201 and new protein kinase B (PKB/Akt) inhibitor AZD5363 are being tested for safety, tolerability, pharmacokinetics and anti-tumour activity in castration resistant prostate cancer patients who have progressed after chemotherapy. An orally active specific endothelin-A antagonist ZD4054 and Poly(adenosine diphosphate-ribose) polymerase (Parp) inhibitor Olaparib is also being tested in phase II trials in patients with advanced castration resistant prostate cancer. 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 [19].

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 a view of their very impressive phase 3 data, favourable toxicity profiles and potential for use earlier in the treatment pathway, cost considerations notwithstanding.

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