The evolution of antiandrogens: MDV3100 comes of age

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Lucy Dumas

Department of Medical Oncology, Bermondsey Wing, Guys Hospital, Great Maze Pond Road, London, SE1 9RT, UK
and
University College Hospital London, Meyerstein Institute of Oncology, 250 Euston Road, London, NW1 2PG, UK

Heather Payne

University College Hospital London, Meyerstein Institute of Oncology, 250 Euston Road, London, NW1 2PG, UK

Simon Chowdhury

Author for correspondence: Department of Medical Oncology, Bermondsey Wing, Guys Hospital, Great Maze Pond Road, London, SE1 9RT, UK
simon.chowdhury@gstt.nhs.uk

> **"…studies have shown that newer, more sophisticated antiandrogens and hormone biosynthesis inhibitors … have significant activity…"**

Since the Nobel Prize-winning discovery by Huggins and Hodges in 1941 [1] that reducing circulating testosterone levels by orchidectomy or exogenous estrogens has a beneficial effect on patients with prostate cancer, androgen-deprivation therapy (ADT) has become the mainstay of treatment for advanced disease. However, most patients will eventually progress on this treatment and develop what has previously been termed 'hormone-refractory' prostate cancer. This is a misnomer as several studies have shown that newer, more sophisticated antiandrogens and hormone biosynthesis inhibitors can continue to have significant activity in a proportion of patients, even at very advanced stages.

Antiandrogens are oral compounds that compete with endogenous ligands for the androgen receptor (AR), and thereby block the biological effects of testosterone and dihydrotestosterone. When bound they induce a conformational change that impedes transcription. These drugs can be broadly split into two categories: steroidal and nonsteroidal. Steroidal antiandrogens, such as cyproterone acetate, were the first to emerge. These are broad-acting drugs, however, and can be associated with a wide range of side effects. This led to the development in the 1970s of nonsteroidal agents, such as flutamide, nilutamide and bicalutamide, which are better tolerated.

Bicalutamide has been extensively investigated in the Early Prostate Cancer program. This multicenter, prospective trial randomized 8113 men with non-metastatic disease to bicalutamide 150 mg or placebo in addition to standard care. Standard care could be with surgery (radical prostatectomy), radical radiotherapy or watchful waiting where appropriate. The fourth and final analysis, with a minimum follow-up of 10 years, showed significant advantages for men with locally advanced disease in terms of progression-free survival [2]. There was also a highly significant improvement in overall survival in favor of bicalutamide when used as an adjuvant to radiotherapy for men with locally advanced prostate cancer.

> **"Patients treated with MDV3100 demonstrated a 4.8-month survival benefit … compared with those receiving placebo…"**

Bicalutamide monotherapy has been shown to be inferior to castration-based treatment with luteinizing hormone-releasing hormone agonists when used to treat metastatic disease [3], but it is commonly used in combination with luteinizing hormone-releasing hormone agonists with good effect. This effect tends to be temporary and patients will ultimately progress on combined androgen blockade. A withdrawal effect is occasionally seen with the cessation of the antiandrogen therapy, demonstrating that they can develop partial agonist activity [4].

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Castrate-refractory prostate cancer (CRPC) is defined as progressive disease in the context of castrate levels of androgens. A proportion of these men will, however, still respond to further lines of hormonal therapy, suggesting that AR signaling continues to be important. This has led to research investigating AR signaling and the mechanisms that occur in 'castrate-resistant' disease in an attempt to develop targeted therapies to interrupt this process. There are several mechanisms by which CRPC manages to overcome androgen-deprivation therapy in order to maintain tumor growth. These include *AR* overexpression [5], AR mutation, which can allow activation by other ligands, for example, progesterone and hydrocortisone [6], ligand-independent activation by growth factor signaling pathways, and upregulation of the enzymes involved in androgen biosynthesis, thus resulting in higher intratumoral androgen concentrations [7].

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Extensive research has been carried out in recent years to develop more specific and efficacious methods of androgen blockade. One of the most significant recent advances has come from Sawyer and colleagues [8]. They screened derivatives of the nonsteroidal AR antagonist RU59063 for pure antagonistic activity. This process produced two drugs, MDV3100 and RD162. These oral compounds both demonstrated five to eight times higher affinity for the AR than bicalutamide without its partial agonist activity. Importantly, MDV3100 in particular does not activate wild-type *AR* receptors or certain mutated *AR*s.

The mechanism of MDV3100 is threefold. First, it has a much stronger affinity for the AR, second it inhibits AR nuclear translocation, and third, it appears to induce a conformational change that impairs binding to DNA and cofactor recruitment. MDV3100 also has no known agonist activity when AR is overexpressed. Preclinical trials have demonstrated the anti-tumor activity of MDV3100 in both *in vitro* and *in vivo* models. In mice with LNCaP/AR xenograft tumors, MDV3100 induced tumor regression where bicalutamide only slowed growth [8].

MDV3100 has been investigated in Phase I and II studies in men with CRPC [9]. One hundred and forty patients with progressive castration-resistant prostate cancer were enrolled, the majority (78%) with metastatic disease and approximately half of whom had received prior chemotherapy. The results demonstrated promising activity with prostate-specific antigen (PSA) declines in serum PSA of 50% or more in over 50% of patients. In addition, two-thirds of patients achieved either a partial response or stable disease radiologically. Better outcomes were seen in the chemotherapy-naive group, with the median time to radiological progression being 47 weeks compared with 29 weeks.

MDV3100 was well tolerated, with the only reported grade 3 or above toxicity being fatigue in 11% of patients. This was only observed at doses of 240 mg or higher. Seizures were reported in three patients, all of whom were taking doses above 360 mg and were also concurrently being treated with other medications that may have contributed to a lower seizure threshold. The maximum tolerated dose was established as 240 mg; no additional anti-tumor effect was observed at greater doses [9]. Subsequent studies have used 160 mg as the dose of MDV3100 to be tested.

This promising activity led to the initiation of two large Phase III studies in metastatic CRPC. The AFFIRM study is a large, double-blind, randomized trial of 1199 men with advanced CRPC who had previously received docetaxel-based chemotherapy. Men were randomized in a 2:1 manner to MDV3100 or placebo. Patients treated with MDV3100 demonstrated a 4.8-month survival benefit (18.4 vs 13.6 months) compared with those receiving placebo ($p < 0.0001$), with a 37% reduction in risk of death. The study was unblinded at interim analysis on the basis of these results and those receiving placebo will be offered MDV3100 [101].

MDV3100 has been shown to be a safe, well-tolerated oral drug that has a significant survival advantage in postchemotherapy patients. This is a major step forward in our understanding of the continuing relevance of the AR and its downstream effects. The second Phase III study in CRPC is the PREVAIL study. This is a large, randomized, placebo-controlled trial in patients with progressive, metastatic castration-resistant prostate cancer who are chemotherapy naive. This study aims to recruit 1680 patients who will be randomized to MDV3011 or placebo on a 1:1 basis. The primary outcomes to be analyzed are overall and progression-free survival.

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Ongoing and extensive research into the field of AR targeting has yielded important developments in the treatment of prostate cancer. In addition to MDV3100, abiraterone acetate, a novel androgen biosynthesis inhibitor, has also been shown to significantly increase the overall survival benefit in men with metastatic CRPC postchemotherapy [10]. The advent of these two new drugs represents a major step forwards in our understanding of the biology and management of this complex disease. The AR remains an increasingly relevant therapeutic target and an important area for current research.

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