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A New Way to Treat Prostate Cancer: The Development of Abiraterone Acetate

Prostate cancer has overtaken lung cancer to be the most commonly diagnosed cancer in UK men. Annually 37,000 men are diagnosed with the disease and over 10,000 men die from the disease each year [1].

Until recently there were few treatments for men with advanced prostate cancer other than supportive care. Endocrine therapies had been evaluated in men with advanced prostate cancer but none had prolonged survival. Cytotoxic chemotherapy – docetaxel as first line and cabazitaxel as second line – have shown survival benefit, as has active cellular immunotherapy with sipuleucel-T (Provenge®) [2], however over time patients develop resistance to all these drugs, so new therapies are desperately needed.

Abiraterone acetate was discovered at The Institute of Cancer Research (ICR) in the early 1990s, and this year completed the journey from idea to life-extending treatment for men with advanced prostate cancer. The US Food and Drug Administration (FDA) approved the use of abiraterone acetate, now known under the trade name Zytiga™, in men with castration-resistant prostate cancer in April 2011, while the European Commission gave it the green light in September 2011 following the publication of definitive clinical trial results [2].

The concept

In 1941, clinician Dr Charles Huggins suggested that surgical castration would result in depletion of the male sex hormone androgen, which was known to be produced by the testes, and the corresponding regression of prostate cancer [3]. Since then, suppression of androgens by medical or surgical castration remains the main-stay of first line treatment for patients with advanced prostate cancer. Reduction of androgen levels results in a decline in prostate specific antigen (PSA), tumour regression and relief of symptoms for most patients but in time PSA levels increase, indicating tumour progression that invariably proves fatal.

In the 1990s, the ICR's Professor Mike Jarman and colleagues Dr Elaine Barrie and Professor Gerry Potter started to look for drugs that could shut off the production of the male sex hormone androgen. They reasoned that prostate cancers that became resistant to hormonal treatment were in fact accessing androgens from elsewhere in the body to keep growing, including perhaps the tumour itself. If they could disrupt the synthesis of androgen at all sites in the body, not just the testes, perhaps they could develop a new treatment for the disease.

The team noticed that ketoconazole – an antifungal agent – prevented the growth of prostate cancer cells. Ketoconazole is a weak non-specific inhibitor of the enzyme cytochrome P17 (CYP17) with modest anti-tumour activities in advanced prostate cancer but of limited use because of its toxicities. CYP17 catalyses two independently regulated steroid reactions key to androgen and oestrogen synthesis making this enzyme a novel target for drug development.

Using testicular extracts and radiolabelled CYP17 steroid substrates, the team screened for small molecule inhibitors of CYP17. The work led to the design of abiraterone – a potent, selective, irreversible inhibitor of CYP17[4-5]. It is 10- to 30 –fold more potent than the non-selective inhibitor, ketoconazole. However, the parent drug has poor bioavailability and a prodrug, abiraterone acetate was generated. The prodrug is rapidly deacetylated to the active metabolite in vivo [4].

Pre-clinical studies

Preclinical animal studies demonstrated that abiraterone acetate worked as expected, blocking the synthesis of androgen and leading to a decrease in its level in the body and in the size of androgen-dependent organs [4].

Early in the drug's development concerns were raised about the possible side-effects of blocking CYP17. Preventing androgen from being made by blocking this enzyme might lead to adrenal insufficiency – a potentially life-threatening complication. However, characterisation of young adults born with an inherited deficiency of CYP17 showed that they do not suffer from severe adrenal insufficiency [6]. This gave the researchers hope that the issue could be managed.

Early stage clinical trials in prostate cancer patients led by Professor Judson showed that abiraterone was safe and did lower levels of male hormones[7]. However, the developmental progress was hampered at this stage by a lack of interest in hormone treatments for prostate cancer. Part of the problem lay in the name of late stage prostate cancer, which was often referred to as 'refractory' or 'androgen independent' disease, implying that the cancer became resistant to androgens and could progress without them.

Many scientists and clinicians argued that blocking androgen production at this late stage would be ineffective, but mounting evidence challenged this view. Adrenal glands also produce testosterone and studies showing high intratumoural androgens, continued androgen signalling and overexpression of key enzymes in androgen synthesis suggested that some prostate cancers remained hormone dependent and were able to produce their own androgens [8-11].

Clinical trials

Professor Johann de Bono joined the ICR from San Antonio, Texas, in 2003. Through his work as a

clinician treating prostate cancer patients he became interested in abiraterone acetate as a potential new treatment for men with late stage advanced prostate cancer. With support from a partnership with Cougar Pharmaceuticals – now a member of the Janssen Pharmaceutical Companies – Phase I clinical trials to test safety and anti-tumour activity began.

A single centre phase I study conducted at The Royal Marsden Hospital in the UK recruited 21 chemotherapy-naïve patients whose prostate cancer was resistant to multiple hormone therapies. Patients were treated with once daily, continuous abiraterone acetate, which escalated through five doses (250-2,500mg). Abiraterone acetate was well tolerated. PSA levels declined by ≥ 30%, 50% and 90% in 14 (66%), 12 (57%) and 6 (29%) patients respectively. Radiological regression, normalisation of lactate dehydrogenase and improved symptoms with reduction in pain management were documented [12]. The anticipated toxicities attributable to mineralcorticoid excess – namely hypertension, kypokalemia and lower limb oedema – were successfully managed in the trial with a mineralocorticoid receptor antagonist.

Less than a year later, the results of a larger Phase I/II study were reported. The study of 54 chemotherapy-naïve patients confirmed the Phase I results, and showed that up to 70% of men responded to abiraterone acetate. About two-thirds of men experienced significant benefits for an average of eight months, with scans showing their tumours decreasing in size and their PSA levels dropping substantially [13].

Results of a multicentre phase II study in docetaxel-treated patients with castration resistant prostate cancer (CRPC) again showed significant antitumour activity including declines in PSA, partial response and declines in circulating tumour cells (CTCs) [14].

A randomised, double-blind Phase III study was conducted in 147 sites in 13 countries. The 1,195 men who enrolled in the trial had all stopped responding to standard hormone therapy as well as second-line treatments including the chemotherapy drug docetaxel. They were either given abiraterone acetate together with the steroid prednisone (797 men), or prednisone and a placebo (398 men) [2].

Overall survival for men treated with abiraterone acetate and prednisone was 14.8 months versus 10.9 months for those receiving placebo and prednisone. Secondary endpoints of PSA decline, medium time to PSA progression, radiographic progression-free survival all confirmed the superiority of abiraterone acetate and prednisone [2].

Paradigm shift

Abiraterone acetate has changed the way the science community views prostate cancer. It is now clear that continued androgen signalling contributes to disease progression in a subset of men. The research has led to the renaming of hormone refractory, or androgen independent disease, to castration resistant prostate cancer (CRPC).

Abiraterone has shown that therapies that block androgen synthesis by inhibiting CYP17 can produce tumour responses in patients who no longer respond to standard hormonal therapies and doctaxel based chemotherapy. This first-in-class CYP17 inhibitor has led to the development of new therapies (in both early and late stage clinical trials) based on targeting androgen receptor signalling (for review see [15]).

Acknowledgements

Abiraterone was discovered at the ICR in what is now the Cancer Research UK Cancer Therapeutics Unit, in research supported by grants from Cancer Research Campaign (now Cancer Research UK), the Medical Research Council (MRC) and BTG International LTD. Subsequent patient trials and further research on abiraterone was supported by Cougar Biotechnology Inc. / Janssen Pharmaceutical Companies, Cancer Research UK, Experimental Cancer Medicine Centre, the MRC, BTG International Ltd, Prostate Cancer Foundation, Prostate Cancer Research Foundation, The Prostate Cancer Charity, the ICR and The Royal Marsden. Cancer Research Technology assigned abiraterone acetate to BTG International Ltd, who in turn licensed it to Ortho Biotech Oncology Research & Development, a unit of Cougar Biotechnology Inc., now a member of the Janssen Pharmaceutical Companies. ■

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References

1. Cancer Research UK, *Prostate Cancer Statistics.* http://info.cancerresearchuk.org/cancerstats/keyfacts/prostate-cancer/, 2011.
2. de Bono JS, et al. *Abiraterone and increased survival in metastatic prostate cancer.* N Engl J Med. 2011;364(21):1995-2005.
3. Huggins C, Stevens jr RE, and Hodges CV. *Studies on prostatic cancer: ii. The effects of castration on advanced carcinoma of the prostate gland.* Arch Surg, 1941;43(2):209-23.
4. Barrie SE, et al. *Pharmacology of novel steroidal inhibitors of cytochrome P450(17) alpha (17 alpha-hydroxylase/C17-20 lyase).* J Steroid Biochem Mol Biol. 1994;50(5-6):267-73.
5. Potter GA, et al. *Novel steroidal inhibitors of human cytochrome P45017 alpha (17 alpha-hydroxylase-C17,20-lyase): potential agents for the treatment of prostatic cancer.* J Med Chem. 1995;38(13):2463-71.
6. Auchus RJ. *The genetics, pathophysiology, and management of human deficiencies of P450c17.* Endocrinol Metab Clin North Am. 2001;30(1):101-19, vii.
7. O'Donnell A, et al. *Hormonal impact of the 17alpha-hydroxylase/C(17,20)-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer.* Br J Cancer. 2004;90(12):2317-25.
8. Geller J and Candari CD. *Comparison of dihydrotestosterone levels in prostatic cancer metastases and primary prostate cancer.* Prostate, 1989;15(2):171-5.
9. Holzbeierlein J, et al. *Gene expression analysis of human prostate carcinoma during hormonal therapy identifies androgen-responsive genes and mechanisms of therapy resistance.* Am J Pathol. 2004;164(1):217-27.
10. Stanbrough M, et al. *Increased expression of genes converting adrenal androgens to testosterone in androgen-independent prostate cancer.* Cancer Res. 2006;66(5):2815-25.
11. Titus MA, et al. *Testosterone and dihydrotestosterone tissue levels in recurrent prostate cancer.* Clin Cancer Res. 2005;11(13):4653-7.
12. Attard G, et al. *Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven.* J Clin Oncol. 2008;26(28):4563-71.
13. Attard G, et al. *Selective inhibition of CYP17 with abiraterone acetate is highly active in the treatment of castration-resistant prostate cancer.* J Clin Oncol. 2009;27(23):3742-8.
14. Reid AH, et al. *Significant and sustained antitumor activity in post-docetaxel, castration-resistant prostate cancer with the CYP17 inhibitor abiraterone acetate.* J Clin Oncol. 2010;28(9):1489-95.
15. Attard G, Richards J, and de Bono JS, *New strategies in metastatic prostate cancer: targeting the androgen receptor signaling pathway.* Clin Cancer Res. 2011;17(7):1649-57.