WHITE PAPER

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Consortium for Clinical Science and AI

Machine Learning for Precision Medicine and Drug Development in Prostate Cancer

Part 2: Background on Bicalutamide

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Introduction

This white paper gives general background information on bicalutamide, the most widely used antiandrogen to treat prostate cancer. Bicalutamide is the subject of the research presented in this series.

Bicalutamide, sold under the brand name Casodex among others, is an oral prescription antiandrogen medication, primarily used to treat metastatic prostate cancer. Bicalutamide is used to treat prostate cancer and is sold in more than 80 countries, including most developed countries. It appears on the World Health Organization's List of Essential Medicines.

Bicalutamide is typically used in combination with a gonadotropin-releasing hormone (GnRH) analogue, or. Bicalutamide is also used as a monotherapy in high doses to treat localized advanced prostate cancer (LAPC). Bicalutamide monotherapy is approved in at least 55 countries, but not the US, where it is registered only at low doses and in combination with castration. The negative decision of the FDA (and the withdrawal of approval for bicalutamide for LAPC in some countries) followed the results of a Phase III trial (McCleod et al 2006).

Off-label uses for Bicalutamide include:

- To reduce testosterone 'flares' with the initiation of GnRH agonist therapy
- Skin and hair conditions such as acne, excessive hair growth, and scalp hair loss in women
- High testosterone levels due to polycystic ovary syndrome (PCOS) in women
- Feminizing hormone therapy for transgender women in combination with estrogens
- Early puberty in boys, in combination with an aromatase inhibitor
- Hypersexuality
- Paraphilias in combination with chemical castration

Bicalutamide, and other AR antagonists, have been tested for the treatment of breast cancer (most recently Lu et al 2000) and ovarian cancer (Levine et al 2007). However, it is currently doubtful that bicalutamide will prove to be a viable treatment for these conditions.

Antiandrogens have been suggested as a possible treatment for COVID-19 in men. In May 2020 a study using high-dose bicalutamide as a treatment for COVID-19 was registered with clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT04374279), although at the time of writing no results are available.

History

A timeline of the major points in the development of Bicalutamide is given in the table below:

Table 1: ***Milestones*** *in the development of Bicalutamide.*

1973	Cyproterone acetate becomes the first antiandrogen to be introduced for the treatment of prostate cancer.
1980s	Bicalutamide is developed, being derived from a modification of the bacteriostat flutamide.
1982	Bicalutamide is patented in by Imperial Chemical Industries (ICI), a now defunct British chemical company.
1990	The first a clinical trial results (phase I) for Bicalutamide are reported (Newling, 1990).
1993	The pharmaceutical division of ICI is split into an independent company called Zeneca.
1995	Bicalutamide is launched in the UK.
1995	Bicalutamide is approved by the FDA for advanced prostate cancer in combination with a GnRH analogue.
1999	Zeneca merges with Astra AB to form AstraZeneca.
1990s	Bicalutamide is approved as a monotherapy for localized advanced prostate cancer in Europe, and some other countries.
2009	The patent for Bicalutamide expires and it becomes available as a generic drug.

Brand names

Bicalutamide is marketed by AstraZeneca under the brand names Casodex, Cosudex, Calutide, Calumid, and Kalumid. It is also sold by other manufacturers under other brand names, including Bicadex, Bical, Bicalox, Bicamide and Bicatlon.

Sales

Casodex was a blockbuster drug prior to losing its patent protection in 2007, with its worldwide sales peaking at USD1.3 billion in 2007. In 2014 bicalutamide was still the most commonly prescribed drug for the treatment of metastatic castration-resistant prostate cancer (mCRPC; Campbell, 2014).

Since the expiry of its patent, Casodex still generates significant income for AstraZeneca and worldwide sales were over US$13 billion as of 2018 (2018 AstraZeneca Annual Report).

Patent protection of bicalutamide expired in the US in 2009 and the drug has subsequently been available as a generic at a much lower cost than before patent expiry. The cost of bicalutamide remains lower than other similar medications (typically USD10 for a 30-day supply of once-daily 50 mg tablets).

Pharmacology

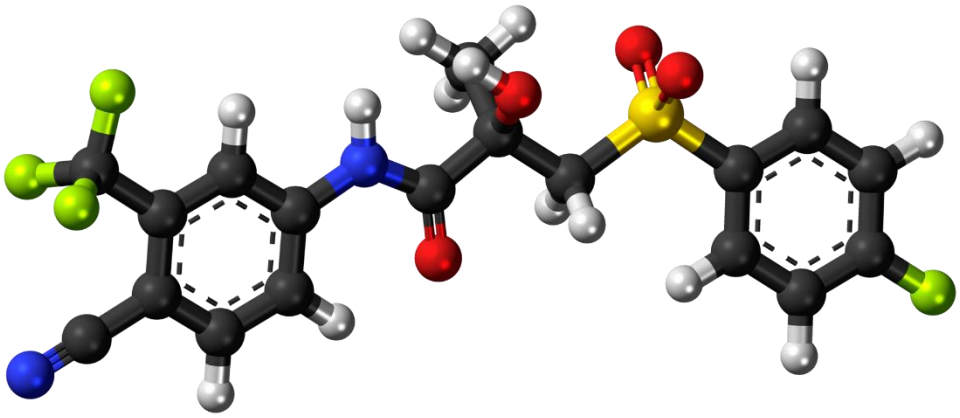

Figure: The Bicalutamide Molecule ($C^{18}H^{14}F^{4}N^{2}O^{4}S$)

Pharmacodynamics

Bicalutamide is a nonsteroidal antiandrogen (NSAA). It does not affect androgen production nor alter androgen levels. It works exclusively by antagonizing/blocking the androgen receptor, the target of the androgens testosterone and dihydrotestosterone (DHT; Dart 2004).

Bicalutamide is a competitive, silent (completely inactive) antagonist of the AR, the major target of testosterone and DHT. Bicalutamide is highly selective i.e. it does not interact significantly with other hormone receptors and has few significant effects on other hormonal systems (e.g., progestogenic, estrogenic, glucocorticoid, antimineralocorticoid). However, bicalutamide has been reported to have a weak antagonistic affinity for the progesterone receptor, and thus could have some antiprogestogenic effects (Ito and Sadar 2018). Also, while bicalutamide does not bind to estrogen receptors, bicalutamide monotherapy can indirectly increase estrogen levels in males, which would be expected to have some estrogen-related effects (Guise 2007).

Bicalutamide is not known to inhibit 5α-reductase or other enzymes involved in androgen production (Furr 1995).

Bicalutamide has a relatively low affinity for the androgen receptor: 30 to 100 times lower than DHT, which is 2- 10 times as potent as testosterone, its main endogenous ligand in the prostate gland (Masielo et al 2002). However, typical dosages of bicalutamide crate circulating levels of the drug thousands of times higher than those of testosterone and DHT, allowing it to provide a comprehensive blocking of the androgen receptor (Furr, 1997).

Bicalutamide blocks androgen receptors in the pituitary gland and hypothalamus, which prevents negative feedback of androgens in the hypothalamic–pituitary–gonadal axis and consequent increase in the production of pituitary luteinizing hormone (Iversen et al 2001). This, in turn, increases the circulating levels of luteinizing hormone and increases the production of testosterone by the testes and the production of estradiol (Eri et al 1995). 150 mg/day bicalutamide monotherapy in men is associated with a 59–97% increase in testosterone levels, a 65–146% increase in estradiol levels, and smaller increases in levels of DHT, sex hormone-binding globulin, and prolactin (Mahler et al 1998).

Bicalutamide monotherapy in men increases gonadotropin hormone levels which then increase androgen levels. However, standard bicalutamide treatment in men combines bicalutamide with anti-gonadotropin agents such as GnRH analogues, estrogens, or progestogen. These maintain negative feedback on the HPG axis (Rao et al 1988) avoiding this increase androgen levels. However, increased levels of estradiol are not countered by the body under any form of bicalutamide treatment and these result in the feminizing side effects in men.

Pharmacokinetics

There is a difference in the speed of absorption between the two bicalutamide isomers, with (R)-bicalutamide levels peaking at around 35 hours after administration, and (S)-bicalutamide being much more rapidly absorbed (Wellington and Keam, 2006).

Steady-state levels of bicalutamide are reached after 4 to 12 weeks of administration, irrespective of dosage (Wellington and Keam, 2006). This long time to steady-state levels results from bicalutamide's long elimination half-life. Despite this long time to reach steady-state levels, bicalutamide has antiandrogenic properties similar to flutamide, which has a much more rapid time to steady-state levels (Blackledge 1996).

Bicalutamide crosses the blood–brain barrier in humans and can therefore potentially affect brain metabolism (Mason 2006), however, these effects are not well characterized.

Bicalutamide is metabolized in the liver. None of the metabolites of bicalutamide are known to be active and their plasma levels are low (Cockshott, 2004). Bicalutamide elimination half-life is about one week. It is eliminated in faeces and urine, and its metabolites are eliminated in urine and bile (Fradet, 2004).

Factors known *not* to affect bicalutamide pharmacokinetics include:

- food consumption
- a person's age
- body weight
- renal impairment
- mild-to-moderate hepatic impairment.[3][165]

Side Effects

Many of the side effects of bicalutamide in men are related to androgen deprivation, resulting in physical feminization/demasculinization (Anderson, 2003). These side effects include:

- reduced body hair
- decreased muscle mass
- feminine changes in composition of body fat
- reduced length of penis
- decreased ejaculate volumes.

Other side effects related to androgen deprivation, include:

- hot flashes
- sexual dysfunction (loss of libido, erectile dysfunction)
- depression
- fatigue
- anemia.

General side effects of bicalutamide include diarrhea, constipation, abdominal pain, nausea, dry skin, itching, and rash. In rare cases, bicalutamide has been associated with liver damage, lung toxicity, and photosensitivity.

The drug is well tolerated at dosages higher than the standard 50 mg/day, with rare additional side effects (Chabner and Longo 2010).

Table 2: Major Side Effects of Bicalutamide

Frequency	Class of effect	Side Effects
Very common (≥10%)	Reproductive and breast disorders	• Breast tenderness • Gynecomastia
Common (1-10%)	General and psychiatric disorders	• Decreased libido • Erectile dysfunction • Hot flushes
	Skin and subcutaneous tissue disorders	Decreased body hair
	Hepato-biliary disorders	Elevated liver enzymes
Uncommon (0.1-1%)	Immune disorders and hypersensitivity	• Angioedema • Hives
Rare (<0.1%)	Respiratory disorders	Lung disease
	Skin and subcutaneous tissue disorders	Sensitivity to light
	Hepato-biliary disorders	Liver toxicity

References

2018 AstraZeneca Annual Report, https://www.astrazeneca.com/content/dam/az/PDF/2018/full-year/Full-Year_2018_Results_announcement.pdf

Anderson, 2003. The role of antiandrogen monotherapy in the treatment of prostate cancer. BJU Int. 91 5: 455–61

Blackledge 1996. Clinical progress with a new antiandrogen, Casodex (bicalutamide). Eur. Urol. 29 Suppl 2: 96–104.

Campbell 2014. Slowing Sales for Johnson & Johnson's Zytiga May Be Good News for Medivation. https://www.fool.com/investing/general/2014/01/22/slowing-sales-for-johnson-johnsons-zytiga-may-be-g.aspx

Chabner 2010. Cancer Chemotherapy and Biotherapy: Principles and Practice. Lippincott Williams & Wilkins. pp. 679–680.

Cockshott 2004. Bicalutamide: clinical pharmacokinetics and metabolism. Clinical Pharmacokinetics. 43 (13): 855–878.

Dart RC 2004. Medical Toxicology. Lippincott Williams & Wilkins. pp. 497, 521.

Eri et al 1995. Effects on the endocrine system of long-term treatment with the non-steroidal anti-androgen Casodex in patients with benign prostatic hyperplasia. British Journal of Urology. 75 (3): 335–40.

Fradet Y 2004. Bicalutamide (Casodex) in the treatment of prostate cancer. Expert Review of Anticancer Therapy. 4 (1): 37–48.

Furr 1995. Casodex: preclinical studies and controversies. Annals of the New York Academy of Sciences. 761 1: 79–96.

Guise et al 2007. Estrogenic side effects of androgen deprivation therapy. Reviews in Urology. 9 4: 163–80.

Iversen et al 2001. Nonsteroidal antiandrogens: a therapeutic option for patients with advanced prostate cancer who wish to retain sexual interest and function. BJU International. 87 1: 47–56.

Ito Y and Sadar 2018. Enzalutamide and blocking androgen receptor in advanced prostate cancer: lessons learnt from the history of drug development of antiandrogens. Res Rep Urol. 10: 23–32.

Levine et al 2007. A phase II evaluation of goserelin and bicalutamide in patients with ovarian cancer in second or higher complete clinical disease remission. Cancer. 110 11: 2448–56.

Lu et al 2020. Bicalutamide plus Aromatase Inhibitor in Patients with Estrogen Receptor-Positive/Androgen Receptor-Positive Advanced Breast Cancer. Oncologist; 251: 21–e15.

Mahler et al 1998. Clinical pharmacokinetics of the antiandrogens and their efficacy in prostate cancer. Clinical Pharmacokinetics. 34 (5): 405–17.

Masiello et al 2002. Bicalutamide functions as an androgen receptor antagonist by assembly of a transcriptionally inactive receptor. The Journal of Biological Chemistry. 277 29: 26321–6.

Mason 2006. What implications do the tolerability profiles of antiandrogens and other commonly used prostate cancer treatments have on patient care? Journal of Cancer Research and Clinical Oncology. 132 Suppl 1: S27-35.

McLeod et al 2006. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. BJU Int; 972:247-54.

Newling DW 1990. The response of advanced prostatic cancer to a new non-steroidal antiandrogen: results of a multicenter open phase II study of Casodex. European/Australian Co-operative Group. European Urology. 18 Suppl 3: 18–21.

Rao et al 1988. Merits and considerations in the use of anti-androgen. Journal of Steroid Biochemistry. 31 (4B): 731–7.

Wellington and Keam 2006. Bicalutamide 150mg: a review of its use in the treatment of locally advanced prostate cancer. Drugs. 66 (6): 837–50.

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Felix Beacher is the founder of Cool Clinical. Felix has a PhD in neuroscience and has worked in drug development and various therapy areas including neurodegeneration and cancer.

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