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LONG-TERM TREATMENT WITH ANTIANDROGENS

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Summary—Since the first report in 1966 by Scott and Schirmer on the clinical use of antiandrogens in patients with prostatic cancer, several studies have been published. Most of these deal with short-term treatment and include only a limited number of patients.

Steroid antiandrogens have demonstrable progestational and antigonadotrophic effects, whereas the non-steroid "pure" antiandrogens mainly act peripherally on androgen-dependent accessory genital organs and thus preserve libido and sexual potency in most patients.

Short-term treatment with antiandrogens have exerted responses similar to those achieved with conventional endocrine therapy. Because of relatively fewer side effects of these drugs, there is an increasing interest in assessment of the long-term effect, and some studies have been initiated.

It is well-known that antiandrogens act by competitive inhibition of the binding of dihydrotestosterone to the nuclear receptor in target cells.

There are two different groups of antiandrogens, the steroidal and the non-steroidal, so-called pure antiandrogens (Table 1). Steroidal antiandrogens have, in addition to their antiandrogenic property, progestational and antigonadotrophic effects. They cause a decrease in the concentration of testosterone almost to castration level. Contrary to this, treatment with pure antiandrogens has a stimulating effect on the hypothalamus–pituitary–gonadal axis, leading to increased secretion of LH and testosterone.

Cyproterone acetate (CPA) was the first antiandrogen which was used clinically [1]. The effect has been demonstrated to resemble that of oestrogens and orchiectomy [2, 3]. Bracci and DiSilverio used CPA in combination with orchiectomy. They published their first results in 1972 [4] and that was, in fact, the first report on the so-called total androgen blockade.

Some clinical studies dealing with CPA treatment of prostatic cancer are listed in Table 2. When response figures in different phase II studies are compared, it is important to remember that eligibility criteria as well as response criteria may vary greatly from study to study.

The EORTC study 30761 [8] has been published on several occasions; 210 eligible patients were included. The patients were allocated to treatment with either DES, CPA or medroxyprogesterone (MPA). Those treated with MPA had a higher progression rate and shorter survival than the patients in the other two groups. However, in that study a lower dose of MPA was used. From studies in women with breast carcinoma it is known that the clinical and hormonal effects of MPA are dose dependent. The patients treated with CPA had fewer side effects than the other two groups. The most frequent side effects of CPA are impotence and gynaecomastia.

Megestrol acetate has not been used widely in prostatic cancer patients. The effects seem to resemble those of CPA.

The non-steroidal antiandrogens differ fundamentally from CPA and the other steroidal drugs. Pure antiandrogens are devoid of progestational and gonadotrophic properties, which means that the patients theoretically preserve libido and sexual potency.

Flutamide was introduced clinically by Irwin and Prout [5] in 1973. The principal active metabolite is 2-hydroxyflutamide.

Several phase II studies have been published. Some phase III studies are indicated in Table 3. Lund and Rasmussen [12] allocated 40 patients

Table 1. Antiandrogens

Steroidal	Pure
Cyproterone acetate	Cyproterone
Megestrol acetate	Flutamide
Medroxyprogesterone acetate	Anandron
Chlormadinone acetate	Casodex

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Table 2. Cyproterone acetate studies

Phase II—untreated patients:	Scott and Schirmer [1]
	Wein and Murphy [5]
	Tveter *et al.* [6]
Phase II—relapsed patients:	Smith *et al.* [7]
	Wein and Murphy [5]
Phase III—untreated patients:	Jacobi *et al.* [2]
	Varenhorst [3]
	EORTC 30761 [8]

to either treatment with flutamide 750 mg or DES 3 mg daily. The two groups were comparable with respect to age and the different pretreatment criteria. The patients were followed during 12 months. The effect of flutamide was at least equal to that of DES. There was one case of hepatic toxicity in the flutamide group. This is a well-known side effect, which usually is reversible. Like other antiandrogens, flutamide has fewer side effects than DES. Gastrointestinal discomfort is relatively frequent. It has been postulated that diarrhoea is caused by the capsule itself and not by flutamide. This is refuted in the NCI multicenter study published by Crawford *et al.* [15]. The only significant difference in side effects between the two groups was the amount of diarrhoea, which was more frequent in the group treated with leuprolide + flutamide compared to the patients getting leuprolide + placebo. The capsules were exactly identical in the two groups.

A rise in serum testosterone is common in patients treated with pure antiandrogens. It appears that the concentration reverts to normal levels within a year.

The general impression from phase III studies is that the effect of flutamide is comparable to that of conventional endocrine therapy. There seems to be fewer side effects, especially no cardiovascular complications.

Casodex is a new non-steroidal antiandrogen which in rats has been found to act exclusively peripherally. However, in man it has been demonstrated that casodex resembles other pure antiandrogens, which block the negative feedback effect at the hypothalamic centres and thus result in elevation of serum testosterone. The drug has a relatively long half-life, allowing only one daily dose.

Published studies on the effect of pure antiandrogens are generally of limited size and duration. It has been suggested that the rise in serum testosterone may finally overcome the blocking effect of the antiandrogen, resulting in failure of the treatment. If this is a real problem can only be proven in larger and longer studies. There are some ongoing phase III studies with flutamide, and three large multicenter studies comparing casodex with orchiectomy are about to start.

Table 3. Flutamide phase III studies

Jacobo *et al.* [10]	Flutamide vs DES
Kassem *et al.* [11]	Flutamide vs DES
Lund and Rasmussen [12]	Flutamide vs DES
Johansson *et al.* [13]	Flutamide vs Estracyt
deKernion *et al.* [14]	Flutamide vs Estracyt

Fifty years after Huggins' appearance in the field, orchiectomy is still considered the golden standard in treatment of advanced prostatic cancer. No new drug has been proven to be significantly better concerning survival or relief of symptoms. When advocating treatment policy it is therefore absolutely necessary to consider quality of life. If the pure antiandrogens can be proven to be equally effective in long-term treatment of prostatic cancer, possibly they should replace orchiectomy, especially when libido and potency are important to the patient.

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