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CLINICAL PROFILE OF A NEW NON-STEROIDAL ANTIANDROGEN

C. MAHLER* and L. DENIS
Departments of Endocrinology and Urology, A.Z. Middelheim, Antwerp, Belgium

Summary—Recently a new non-steroidal antiandrogen (Casodex®) has been shown in animal experiments to possess a potent peripheral antiandrogen effect. In patients with advanced prostatic cancer however, this drug is not peripherally selectively active and blocked central brain androgenreceptors results in a rise of luteinizing hormone (LH) and testosterone (T).

We treated 18 advanced prostatic cancer patients with 50 mg Casodex® daily for a mean period of 42 weeks. There were no complete objective responses but partial responses were seen in a few patients. In 16 patients there was a greater than 50% reduction of pretreatment PSA levels. Endocrine evaluations showed a significant rise in LH, T and oestradiol (E), reaching peak values within the two first months with subsequent lowering of these levels afterwards but without returning to normal. The general tolerance of the drug was good, gynecomastia being the most frequent side-effect. Libido and potency, when present before start of therapy, were maintained in some patients. We conclude that this compound seems as effective as other antiandrogens, but with improved compliance, and shows less side effects in the management of advanced prostatic cancer.

INTRODUCTION

Antiandrogens block the binding of dihydrotestosterone (DHT) to its cytosol receptors and the subsequent translocation of the receptor complex into the nucleus. Unlike steroidal antiandrogens, non-steroidal or pure antiandrogens are completely devoid of any other hormonal effect. Recently a new more potent antiandrogen (Casodex®) has been developed and in animal experiments has been shown to be selectively peripherally active [1]. Clinical experiments in men however, proved that this compound also blocks the central brain androgen receptors which results in an impaired negative feedback of the steroids at the hypothalamic–pituitary level. This induces a rise of LH and T. Peripheral aromatization of the increased androgen levels leads to a significant rise in oestradiol [2].

We have studied the clinical profile of this drug as a first line treatment in a group of men with advanced prostatic cancer and report here our observations.

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*To whom correspondence should be addressed: Professor Ch. Mahler, Department of Endocrinology, A.Z. Middelheim, Lindendreef 1, 2020 Antwerp, Belgium.

PATIENTS AND METHODS

Casodex® (50 mg) was given once daily, for a mean period of 42 weeks (range 8–84 weeks) to 18 previously untreated patients with proven advanced prostatic cancer with good prognostic factors. The mean age of this group was 69.8 yr. Seven patients were staged T_3M_0 and 11 T_3M_+. Clinical, biological and endocrine parameters as well as side effects were evaluated on day 0 and subsequently each 28 days. Serum samples for the endocrine investigations were always taken between 8 and 10 a.m. and kept deep frozen at −20°C. The radioimmunoassays were performed in duplicate at our nuclear medicine laboratory with commercially available kits (Amersham and Pharmacia).

RESULTS

Clinical responses

There were no complete objective responses. In one patient with measurable lymph nodes there was a partial objective response (EORTC criteria) [3]. In 10 patients there was a 50% reduction in prostatic volume. The prostate specific antigen (PSA) levels diminished by more than 50% in 16 out of the 18 evaluable patients. The prostatic acid phosphatases (PAP) that were raised in 8 patients, normalized in 3 and

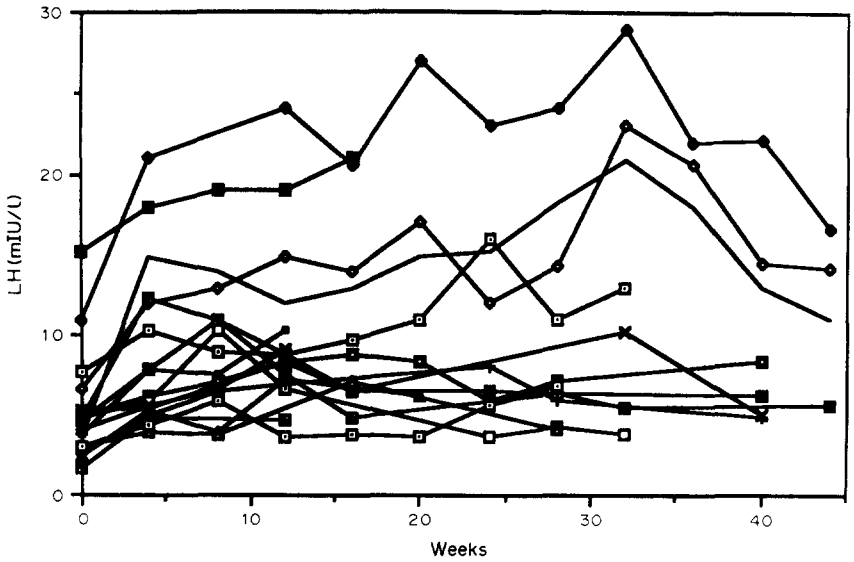

Fig. 1. LH changes during Casodex® therapy.

diminished by more than 50% in 4 of them. Eight patients had an improved miction pattern. As none of those patients had pain this parameter could not be assessed in this group.

Endocrine investigations

LH changes attained values from 2 to 5 times the initial levels. After 12–20 weeks most patients reached a plateau with subsequent progressive lowering of the levels but without returning to pretreatment values (Fig. 1).

The changes for FSH were less impressive with, but for a few patients, a maximal increase of about 50% (Fig. 2).

There was a 50–200% increase of T pretreatment levels. In most patients the highest values were reached within the first 8 weeks. Afterwards the levels fluctuated, returning to normal in some patients but remaining increased (more than 50%) in others after 42 weeks (Fig. 3).

In 16 of the 18 patients there occurred an increase of 30–100% of the initial E values. This rise did not always exactly parallel the rise of T. After a period of about 28 weeks there was a progressive lowering of E levels (Fig. 4).

There were no significant changes in PRL values during the time of treatment.

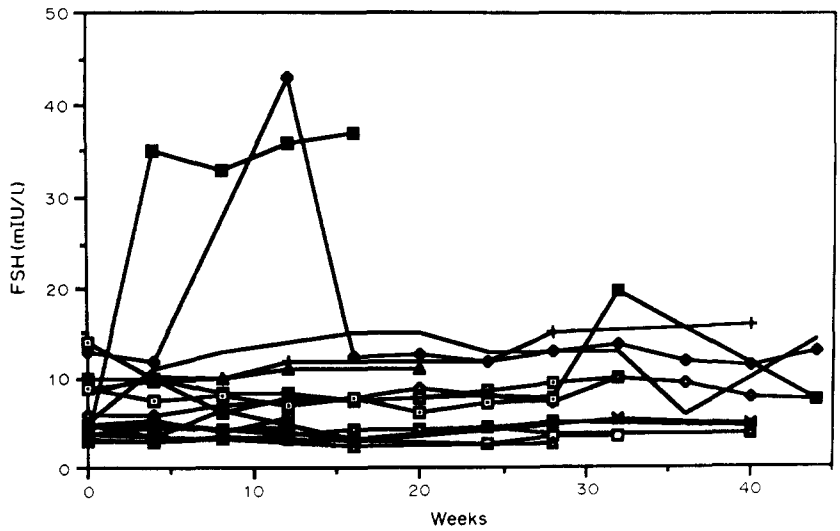

Fig. 2. FSH changes during Casodex® therapy.

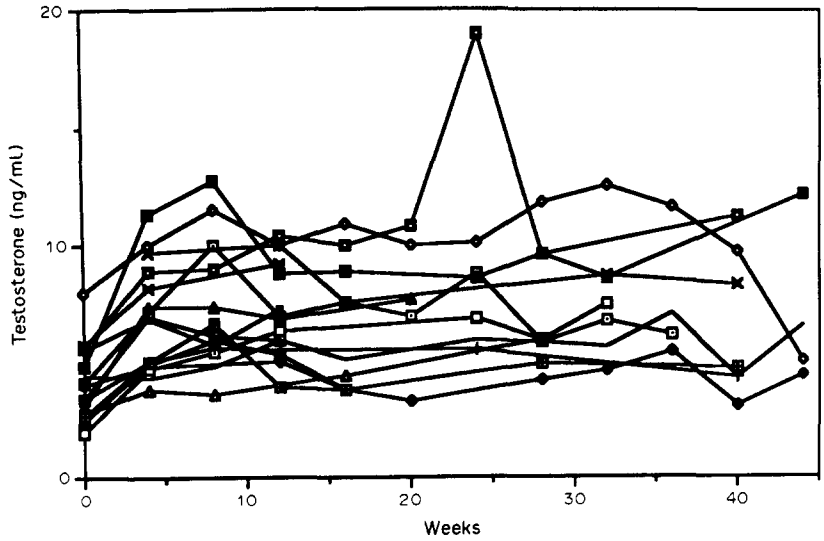

Fig. 3. Testosterone changes during Casodex® therapy.

Toxicity and side effects

No significant biological or biochemical abnormalities were reported. There were no electrocardiographic changes. Drug compliance and general tolerance was excellent. Hot flushes were intermittently noted in one patient. Gynecomastia, from mild to moderate, was the main side effect, occurring in 15 out of the 18 patients.

Libido and potency

From Table 1, showing the sexual status of the patients before and during therapy, it can be concluded that in those patients that still enjoyed a normal sexual life before the start of treatment, libido and potency were maintained during therapy.

Follow up

Six patients were removed from the study. Four because of progression (after 16–32 weeks), one because of suicide and one because gynecomastia. The 12 remaining patients are still on treatment.

DISCUSSION

Our results show beyond any reasonable doubt that Casodex® acts at the peripheral as

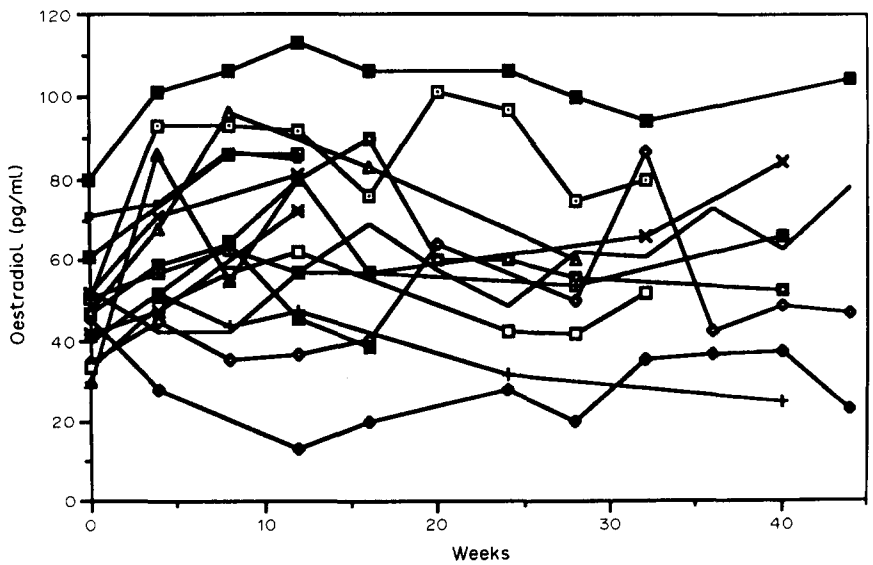

Fig. 4. Oestradiol changes during Casodex® therapy.

Table 1. Evolution of the sexual status of patients during Casodex® therapy

Before therapy	No. of patients	During treatment
Libido+ Erections+	4	No change
Libido+ Erections−	1	No change
Libido− Erections−	11	No change
Libido− Erections+	2	No change in 1 No erections in 1

well as at the central brain level. In this its action is similar to that of other known antiandrogens like flutamide or nilutamide. Used as a monotherapy in advanced prostatic cancer it seems as effective as other compounds but its general tolerance, lack of serious side effects and long half-life, improving compliance, are important contributing factors for an improved quality of life in those patients.

The importance of the raised circulating T levels in the evolution of prostatic cancer treated by antiandrogens remains a point of controversy. The initial apprehension that the reflex increase of T might eventually overcome the blocking effect of the antiandrogens has not been substantiated [4]. It seems reasonable to think that the available amount of antiandrogens is largely sufficient to prevent the effect of the T increase.

Other important questions also remain unanswered. The mechanism that permits a preservation of sexual function is not yet understood. There is also no explanation for the return of gonadotrophins and sexual hormones to lower or even pretreatment levels with continuing therapy. Different factors might be involved. A difference in perfusion rates of the drug in the various sites of the central brain might be one reason. The occurrence of tachyphylaxis an other. Due to increased negative feedback by the significant raised levels of oestradiol there might be a readjustment or resetting of the hypothalamic gonadostat that could be responsible for the modulating pattern of LH, T and E observed in our patients.

Ongoing long-term studies evaluating responses of the hypothalamic–pituitary–gonadal axis to acute challenges by LHRH during antiandrogen therapy and/or the concomitant use of an anti-oestrogen or an aromatase inhibitor might expand our knowledge in this fascinating field.

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