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FROM THE DEPARTMENTS OF UROLOGY, ONCOLOGY AND CLINICAL CHEMISTRY, UNIVERSITY HOSPITAL, S-581 83 LINKÖPING, AND DEPARTMENT OF SURGERY, CENTRAL HOSPITAL, S-601 82 NORRKÖPING, SWEDEN.

TREATMENT OF PROSTATIC CANCER BY MONTHLY INJECTIONS OF AN LHRH-ANALOGUE DEPOT

H. HJERTBERG, E. VARENHORST, M. SVENSSON, B. KÅGEDAL AND B. NORDENSKJÖLD

Abstract

Thirty-six patients with advanced prostatic cancer were treated by monthly depot injections of a luteinizing-hormone releasing hormone analogue (LHRH-a). Five of these patients were also pretreated for 14 days with cyproterone acetate (CPA) in order to counteract initial increase in testosterone concentration. Two weeks after the initial depot injection the serum testosterone had been reduced to and was maintained at castrate level. Luteinizing hormone and follicle stimulating hormone were also significantly reduced. Of the 31 patients 23 showed objective regression at 3 months, 9 had stable disease and none showed progression. At 3 months 22 patients reported subjective improvement. At 12 months 18 showed objective regression, 7 had withdrawn from therapy and 6 showed progression. Side effects were acceptable and comparable to those following surgical castration. It is shown that CPA counteracts the initial increase in testosterone concentration at initiation of LHRH-a treatment. We conclude that depot preparations of LHRH-analogues, both with and without pretreatment with CPA, are useful in the treatment of patients with advanced prostatic cancer.

Key words: Prostate, neoplasms; advanced carcinoma, LHRH-analogue, cyproterone.

Endocrine therapy of prostatic cancer was introduced by Huggins & Hodges in 1941 (11). Endocrine treatment by castration or with oestrogen prevents androgens from reaching the cell nucleus and stimulating tumour cell replication. In most patients it causes regression of symptoms. Surgical castration involves psychological trauma that some men have difficulty in coping with. Oestrogen treatment leads to feminization and increased risk of cardiovascular complications (10, 23).

Treatment with luteinizing-hormone releasing hormone analogue (LHRH-a) is effective in advanced prostatic cancer (1, 13, 15, 24). The purpose of the present phase II study was to assess the endocrinological effect, clinical efficacy, and safety of a depot preparation (Zoladex, LHRH-analogue, ICI-118630) in previously untreated patients with advanced cancer of the prostate. In some patients also cyproterone acetate (Androcur, Schering) was given in order to counteract initial increase in testosterone level.

Material and Methods

Zoladex depot is a synthetic decapeptide analogue of the naturally occurring luteinizing-hormone releasing hormone. The depot consisted of a solid cylinder of a biodegradable 50:50 lactic-glucolic acid copolymer containing 20% of the analogue by weight and allowing continuous, sustained release of the polypeptide over a period of approximately 28 days (2, 19, 21). The skin of the abdomen was cleansed, lignocaine was infiltrated and 3.6 mg of the LHRH-a was injected subcutaneously through a 16 gauge needle. Five patients also received cyproterone acetate (CPA) orally, 100 mg twice daily, for 2 weeks before the first depot injection of LHRH-a, and for another 2 weeks afterwards.

The diagnosis of prostatic cancer was made by fine-needle aspiration biopsy in all cases. No patient had previously received any hormone therapy, radiotherapy, or chemotherapy.

Thirty-six patients aged 51–85 years (mean 72) with advanced prostatic cancer were included in the study; 21 had skeletal metastases and 23 elevated prostatic acid phosphatase (PAP). Thirty-five patients had a primary tumour of category T3 or T4 (UICC 1978) and one patient had a T2 tumour with lymph node metastases. Five patients had a well differentiated tumour (grade 1), 21 a moderately differentiated tumour (grade 2) and 10 a poorly differentiated tumour (grade 3) as determined by cytological examination.

Treatment was continued until progression of the disease was found or until the patient for other reasons wished to withdraw. The mean treatment period was 13.6 months (range 7–24).

Before starting therapy the primary tumour was as-

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Table 1

Mean value of serum testosterone, serum LH and serum FSH before and during treatment with LHRH-a depot only

Months of treatment	Testosterone nM/l (± SD)	LH IU/l (± SD)	FSH IU/l (± SD)	n
0	14.25 (±5.64)	10.26 (±6.61)	9.11 (±8.73)	31
1	0.99 (±0.40)***	5.09 (±2.17)***	3.56 (±1.42)***	31
2	0.99 (±0.38)***	4.72 (±1.42)***	5.02 (±1.74)*	31
3	1.04 (±0.55)***	4.87 (±1.48)***	5.43 (±1.63)***	31
6	1.36 (±1.07)***	5.04 (±1.54)***	6.11 (±1.97) NS	30
12	0.97 (±0.36)***	4.43 (±1.19)**	Not done	12

*** $p<0.001$, ** $p<0.01$, * $p<0.05$

Table 2

Testosterone concentrations (n mol/l) during treatment with CPA, starting 15 days before initiation of LHRH-a treatment

Patient No.	Days in relation to LHRH-a initiation						
	−15	−8	0	+4	+8	+15	+28
1	23.0	5.7	2.3	5.9	2.1	0.8	0.8
2	15.0	6.3	3.9	4.9	2.5	2.4	2.2
3	22.0	5.6	2.4	11.0	4.3	0.8	0.8
4	21.0	3.9	2.1	12.0	2.8	1.6	1.4
5	14.0	4.0	2.4	14.0	3.9	1.1	0.8
Mean ± SD	19.0	5.1	2.62	9.56	3.12	1.34	1.2
	4.2	1.1	0.7	3.9	0.9	0.6	0.6

sessed clinically. Presence and extent of bone metastasis were surveyed by radionuclide scan and, if necessary, by radiography. Laboratory tests included routine haematological and biochemical investigations. Serum concentrations of prostatic acid phosphatase (PAP), luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone (T) were determined by radioimmunoassay.

Our criteria for objective and subjective response were based on those of the British Prostate Group (5). The degree of prostatic obstruction was evaluated clinically.

The endocrinological response was assessed on the basis of suppressed testosterone and gonadotrophin.

History, clinical examination, and blood analyses were repeated with 3 months' intervals, and skeletal radionuclide scans were done every 6 months.

Statistics: t-values were obtained by paired analysis.

Results

Endocrinological response. After 4 weeks of treatment T levels were suppressed in all 31 patients to values found in surgically castrated or oestrogen treated men. LH and FSH fell significantly below pretreatment values but were within the normal range for men. All values remained suppresssed during treatment (Table 1).

All 5 patients in the CPA treated group had suppressed, T, LH, and FSH values after 1 and 2 weeks of CPA treatment. Four days after administration of the LHRH-analogue the mean T values showed only a slight increase to 50% of the pretreatment values. Castrate levels were achieved 10 days later (Table 2). PAP decreased continuously.

Clinical effects. The objective response is shown in Table 3. Of the 31 patients treated with LHRH-a only, 23 (74%) achieved objective regression at 3 months, none showed progression, and all 31 complied fully with the directions. In the 21 who showed elevated PAP the values were reduced within 1–3 months; in 19 the reduction was more than 80% below pretreatment values and this reduction persisted at 6 months. On skeletal radionuclide scan 6 patients (5.1%) showed regression of metastases and on CT scan 1 (3.2%) showed regression of retroperitoneal lymph node metastases.

At 12 months regression was still seen in 18 patients (58%); but in 6 (19.4%) the disease had progressed, and in these patients therapy was stopped. Further 5 patients withdrew for social reasons, 1 owing to hot flushes, and 1 owing to other disease (Table 3).

Subjective response. Twenty-one patients developed urethral obstruction and a further 8 required an indwelling catheter. At 3 months 22 showed improvement in the obstructional symptoms, and only 3 patients still needed a catheter. Two patients underwent transurethral resection.

Six patients had severe skeletal pain owing to metasta-

Table 3

Objective response in 31 patients with advanced prostatic cancer during treatment with LHRH-analogue depot only

	3 months	12 months
Complete regression	0	0
Objective regression	23	18
Stable disease	9	0
Progression	0	6
Withdrawn from therapy for reasons other than progression	0	7
Total	31	31
Objective response in the group also treated with CPA		
Complete regression	0	0
Objective regression	4	4
Stable disease	1	0
Progression	0	1
Withdrawn from therapy for reasons other than progression	0	0

ses; at 3 months 4 were free from pain. In 8 patients general condition was impaired; all 8 had improved at 3 months.

In the CPA-treated group of 5 patients, 4 achieved objective response at 3 months and none showed progression. Two patients with elevated PAP had a reduction of more than 80% below pretreatment values which persisted at 12 months. At 12 months regression was also seen in 4 patients, but one had progression of the disease and died. None of the 4 withdrew from therapy.

One patient in the CPA group developed urethral obstruction and a further 2 required indwelling catheter. None had indwelling catheter at 12 months, and one had undergone transurethral resection.

Undesirable side effects. Only 12 patients of 36 were potent before the start of treatment and 11 of them became impotent. Hot flushes occurred in 23 (63.8%) patients but tended to diminish during treatment. Gynaecomastia was not seen in any patient.

One patient withdrew from therapy owing to severe hot flushes. Another patient experienced increased symptoms, including bone pain, for 2 weeks after starting therapy, but was subsequently free from pain; this patient was not treated with CPA.

No systemic or local allergic reactions and no thromboembolic or cardiovascular manifestations were noted.

Five patients withdrew from treatment after 7–9 months of therapy owing to the long travelling time for monthly administration of the LHRH-analogue.

Discussion

LHRH-analogues are decapeptides with substitution of aminoacids at positions 6 and 10. Intranasal treatment or daily injections result in paradoxal inhibition of gonadotrophins and testosterone secretion after transient stimulation (20).

The details in this paradoxal effect are obscure. Several explanations have been proposed.

1) Abolishment of gonadal steroidogenesis owing to loss of gonadotrophin receptors in the testis caused by the initial high circulating levels of endogenous gonadotrophins (3). Evidence against this theory is the fact that LHRH-a treatment does not reduce the total amount of LH receptors (12).

2) Desensitization at the pituitary level induced by LHRH-analogues, with ensuing reduced secretion of the gonadotrophic hormones has also been discussed (4). The present investigation and others (16) have shown decreasing serum gonadotrophins, however still remaining within normal limits. This suggests that decreased gonadotrophines owing to desensitization of the pituitary gland cannot alone explain the action of the LHRH-analogue.

3) During continuous administration of the LHRH-analogue, inhibition of testosterone biosyntheses has been suggested as a result of disturbed normal pulsatile pattern of gonadotrophin secretion, which in turn might induce decreased response at the testicular level (12).

4) Direct inhibition of gonadal steroidogenesis through specific LHRH receptors in the Leydig's cells has also been proposed (7) and contradicted (6).

The transient stimulation of the gonadotrophins gives rise to a flare, i.e. an increase in testosterone concentration during approximately 1 week with a maximum on the 4th day. This increase in testosterone can be inhibited and counteracted by pretreatment with antiandrogens. In the absence of antiandrogens the testosterone increase may aggravate symptoms (8). For patients with signs of ureteral obstruction or compression of the spinal cord, this may be deleterious. One of our patients experienced a flare with increase in bone pain for 2 weeks, but was subsequently free from pain. No serious complications occurred. Pretreatment with CPA might reduce the potential risk of this flare and increase in testosterone concentration.

Unlike oestrogen treatment, LHRH-analogue has the advantage of not giving rise to cardiovascular complications, gynaecomastia or other feminizing side effects. Patients are spared the distress of operative castration. Both surgical castration and LHRH-therapy cause hot flushes and sexual impotence in most patients, whereas the response and survival seem to be identical (14). Hot flushes can be reduced by adding CPA (9). The objective and subjective results of treatment with LHRH-analogue are comparable to those of surgical castration and oestrogen treatment (13, 15, 17, 24).

The present findings show that continuous suppression of testosterone can be achieved with LHRH-analogue in a depot form. The biological effects resemble those of surgical castration. The effect is reversible (20) even after long-term treatment for up to 12 months (18), but it is not known whether the reversibility persists after longer treatment.

The *advantages* of LHRH-analogue can be summarized thus.

1. Oestrogenic side effects are not seen (22, 23).
2. Operation and in-patient treatment are obviated.
3. There is no psychological trauma as sometimes seen after surgical castration.
4. Reversibility can be an advantage while testing the hormone dependency of a tumour or if volume reduction of a prostate cancer is desired in preparation for radical prostatectomy where potency after the operation is always desired.

Disadvantages of LHRH-analogue.

1. The monthly injections are tedious.
2. Exceeding the interval between injections by more than a few days involves a risk of testosterone flare.
3. There is an initial rise in testosterone concentration at the start of treatment which, however, can be counteracted using an antiandrogen.
4. No cost-benefit analysis comparing surgical castration with LHRH-analogue treatment has been done but it is reasonable to assume that the cost of the monthly attendances at the hospital and the cost of the actual LHRH-depot will exceed that of operation, in-patient care and post-operative examinations.

Request for reprints: Dr Hans Hjertberg, Department of Urology, University Hospital, S-581 85 Linköping, Sweden.

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