Eur J Cancer Clin Oncol, Vol. 20, No. 4, pp. 483–493, 1984.
Printed in Great Britain.

0277-5379/84$3.00+0.00

LHRH-agonist Treatment in Metastatic Prostate Carcinoma

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Abstract—*Three patients with metastatic prostatic cancer were treated for* 10, 6 *and* 2 months *with the potent LHRH-agonist Buserelin (Hoe* 766*) as a first-line agent. All showed a fall of elevated prostatic acid phosphatase levels (nearly undetectable after treatment in* 2 *patients) parallel to plasma testosterone with a relief of complaints after* 3–4 weeks *of treatment. Two patients had an increment of appetite and body weight. In one patient radiological evidence for objective tumour regression was found by CT scan of the prostate (decrease of* 41% *in prostate volume), skeletal X-rays and bone scan. In this patient plasma alkaline phosphatase showed a transient increase parallel to disappearance of osteolytic bone lesions (indicating new bone formation) followed by a normalization. It is concluded that LHRH-agonist treatment is effective in patients with metastatic prostatic carcinoma in the absence of serious side-effects.*

INTRODUCTION

LUTEINIZING - hormone - releasing - hormone (LHRH) is a hypothalamic decapeptide that induces release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary. These gonadotropins stimulate gonadal steroid production. However, LHRH has a short-lived effect on gonadotrophin secretion. It is therefore not suitable for long-term therapy. To date, many LHRH analogues with marked and prolonged effect have been synthesized and tested [1–4]. A lot of them appeared to have a paradoxical antifertility effect in male and female rats during chronic treatment with pharmacological doses. Effects observed were at the level of the pituitary [1–7], gonads [8, 9] and the target organs of sex steroids [10–12].

Firstly, in the pituitary such long-term treatment with large doses of LHRH analogues causes exhaustion and desensitisation of the gonadotrophic cells [1–4] and further inhibition of prolactin secretion [5–7]. Secondly, after a short-term increase of gonadotrophin secretion down-regulation of gonadal gonadotrophin receptors with decreased steroidogenesis occurred [2, 4, 13, 14]. Further, a direct extrapituitary effect of LHRH at the gonad has also been demonstrated [8, 9]. Clayton *et al.* found a direct inhibition of testicular function by LHRH receptors in interstitial cells [9]. Locally produced LHRH-like peptides in the testis appear to have a regulating function for the testosterone secretions [15, 16]. A third possible important way of action is the recently reported ability of LHRH analogues to antagonize the biological actions of sex steroids [10–12]. The antiandrogenic action of LHRH-agonists appears to be different from cyproterone acetate [11]. Sundaram *et al.* [10] demonstrated that these peptides could block the growth-promoting effect of testosterone on the rat prostate and seminal vesicles. An *in vitro* study suggests that the antiandrogenic activity of LHRH analogues is not due to its ability to compete with androgens for their intracellular receptors [11]. On the other hand, Furr and Nicholson have been unable to show anti-androgenic effects of two analogues in castrated immature rats [17].

The striking fall in plasma sex steroid levels to post-castration values and reduction in weight of secondary sexual organs during chronic treatment with LHRH-analogues [2, 4, 7, 18, 19]

Accepted 10 October 1983.

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suggested a treatment for hormone-dependent tumours [4, 17]. In animals a regression of prostatic [18], mammary [4, 5, 17, 20], pituitary [7] and cartilage tumours [21] (chondrosarcoma) has been shown.

Recently, the first data of LHRH-agonist treatment in small series of patients with prostate [22–28] and breast cancer [29, 30] have been published. After our reports about the results in patients with breast cancer [29, 30], we present in this study detailed data about the effects of long-term LHRH-agonist treatment in three patients with prostate cancer.

MATERIALS AND METHODS

Three patients with metastatic prostate carcinoma gave informed consent to be treated with an LHRH-agonist (Buserelin = Hoe 766). Their relevant data are summarized in Table 1. Patient 3 had received primary radiotherapy and total body irradiation (6 Gy) 3 yr before the occurrence of metastasis, but the patients had undergone no further treatment for either primary or metastatic disease.

They were treated with 3 × 0.5 mg Buserelin subcutaneously for 6 days followed by 3 × 400 μg daily per intranasal spray. In the first week blood samples were taken frequently (Figs 1 and 2) for measurement of LH, FSH, prolactin (PRL), testosterone (T), oestradiol (E_2), alkaline phosphatase, acid phosphatase and specific prostatic acid phosphatase (PAP). Blood sampling has been performed daily before the morning treatment injection, and for LH, FSH and PRL on some days (2–5) 4 hr after the injections. During the follow-up (10, 6 and 2 months respectively) they were measured weekly during the first months, later every 3 weeks. Plasma hormone concentrations were measured by radioimmunoassay as described previously [29, 31]. Alkaline phosphatase was assayed in glycine–NaOH buffer of pH 9.6 at 37°C (normal values 15–38 U/l) and total acid phosphatase in acetate buffer of pH 5.5 at 37°C (normal up to 12.0 U/l). PAP was determined using a solid-phase enzyme immunoassay [32] (normal up to 1.6 U/l).

Before treatment all patients were examined radiologically by total skeletal survey, bone scan and abdominal CAT scan apart from physical and routine laboratory examinations. They were seen every 3 weeks after the start of treatment for physical examinations and recording of complaints. Local bone lesions were evaluated every 6–12 weeks by X-rays and by skeletal survey after 6 months. CT scan of the prostate was repeated after 3 and 6 months.

RESULTS

Endocrine effects

After stimulation of gonadotrophin secretion on the first treatment day plasma LH and FSH levels decreased gradually to below pretreatment values with a plateau level after about 5–8 weeks. After the second treatment day there was no increase of the gonadotrophins in the plasma 4 hr after the subcutaneous Buserelin injections, indicating desensitisation of the pituitary.

Plasma testosterone showed a slight increment in the first week (with peak levels of 158, 148 and 122% of the basal value after 2–3 days of treatment) followed by a clear decrease to near castration levels in 3–9 weeks (1.1–2.4 nmol/l) (Fig. 1). Plasma oestradiol concentration showed changes in parallel with those of plasma

Table 1. Pretreatment patient dates

	Patient 1	Patient 2	Patient 3
Age (yr)	72	65	82
Stage of tumour	$T_2N_xM_1$	$T_2N_0M_1$	$T_{2-3}N_xM_1$
Tumour differentiation	?	high	moderate to poor
Symptoms at presentation	disturbed diabetes mellitus, bone pain, prostatism	prostatism	bone pain, pancytopenia
Weight loss (kg)	8	0	4
Prostatic acid phosphatase (U/l)	32.2	3.2	27.6
Alkaline phosphatase (U/l)	47	23	43
Bone scan	abnormal	abnormal	abnormal
α skeletal-survey	metastasis	arthrosis, metastasis?	metastasis
CT scan (abdomen)	hydronephrosis, enlarged lymph nodes	no lymph nodes	no lymph nodes
Duration of treatment	10 months	6 months	2 months

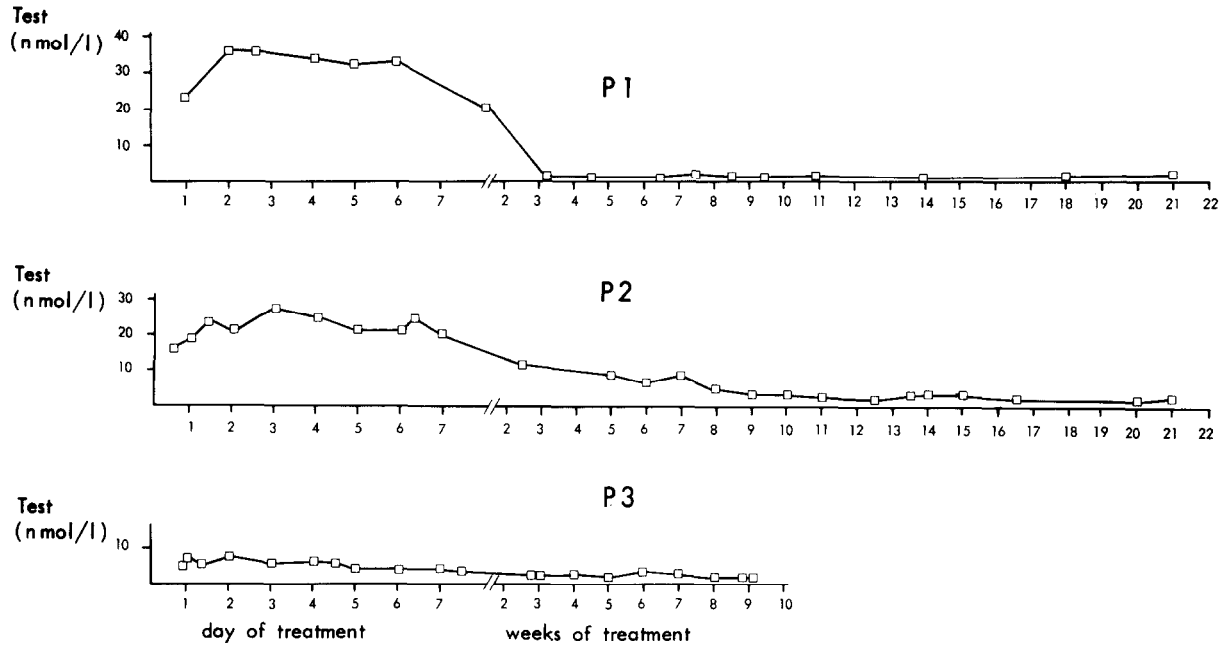

Fig. 1. Changes of plasma testosterone levels in 3 patients during chronic LHRH-agonist (Hoe 766) treatment (p = patient).

testosterone. Mean plasma oestradiol decreased from 117 before treatment to 14 pmol/l after 2 months of treatment. In patient 1, whose detailed data are shown in Fig. 2, plasma prolactin increased in the first week with only a slight decrease later on; the other two patients did not show a decrement.

It has to be noted that patient 3 already had subnormal plasma testosterone values before treatment (5.7 and 7.2 nmol/l) in the presence of elevated LH (54 IU/l) and FSH (43 IU/l) levels. During treatment plasma testosterone decreased to 2.0 nmol/l and the gonadrotrophins to 12.4 and 14.6 respectively.

Antitumour effects

Patient 1. Complaints of prostatism diminished dramatically within 3–4 weeks of treatment. He was again able to make long trips by coach without stopping every half-hour as before treatment. Bone pain and the disturbance of the regulation of his diabetes disappeared; it was no longer necessary to use analgesics. During treatment the appetite increased followed by an increase of 13 kg in body weight.

An objective response has been proven by recalcification of an osteolytic lesion (after 3 months) in the right femur neck (Fig. 3), a clear improvement of the bone scan (Fig. 4), rapid normalisation of acid phosphatase and PAP (Fig. 2), and a decrement in prostatic volume with 41% from 76.0 to 44.6 cm^3 after 3 months (Fig. 5). Thereafter no further significant decrease was observed. Enlarged parailiacal lymph nodes decreased in size. A cloudy osteoblastic vertebral lesion disappeared. On the other hand, a sharp round osteoblastic lesion became visible in the neck of the left femur (Fig. 3), while before treatment the bone scan showed a hot spot locally.

Patient 2. This patient had a more gradual improvement of his prostatism—probably in relation with the slower decrease in plasma testosterone levels—although the CAT scan showed no significant decrement of the prostate volume. A slightly increased PAP before treatment became nearly undetectable (from 3.2 to 0.1 U/l) during treatment, with a normalisation within 6 weeks. The bone scan showed an improvement without changes of the X-rays, which also showed spondylarthrosis of the vertebral column. Faint muscle pain disappeared. His appetite improved and his weight increased by 3.3 kg. He is now free of complaints and feeling well.

Patient 3. This very arteriosclerotic patient had extensive bone metastasis, as indicated by multiple bone lesions and severe pancytopenia. A bone marrow aspiration showed tumour cells. An operation was contraindicated. Buserelin spray was administered every day by his wife or daughter. The acid phosphatase activity in the serum decreased within 9 weeks without significant changes on the X-rays. Concomitantly, the activity of PAP decreased from 27.6 to 5.7 U/l. An elevated plasma LDH activity decreased from 1160 to 459 U/l in the presence of normal plasma bilirubin. He needed a lot of analgesics (aspirin, indomethacin) because of bone pain, which

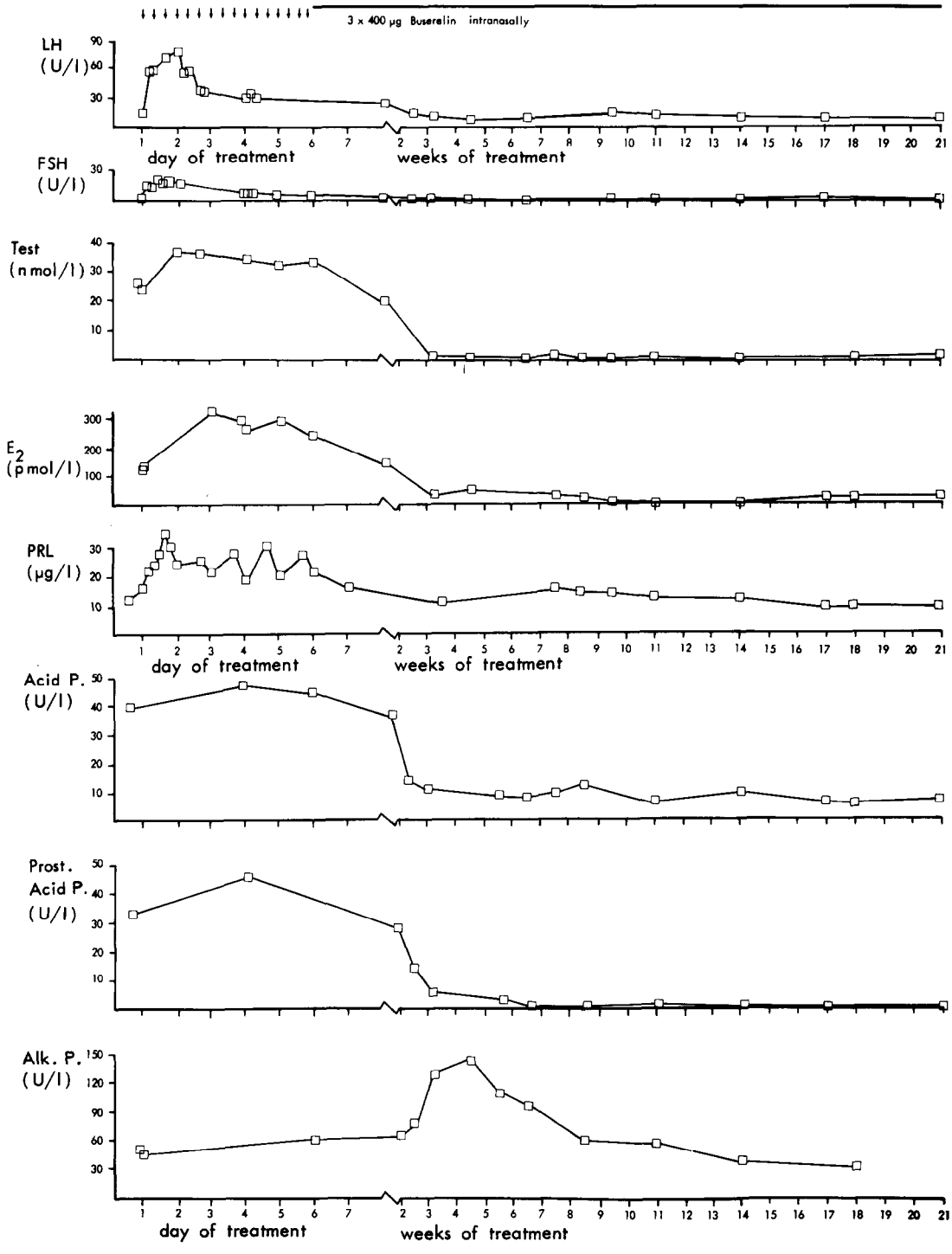

Fig. 2. Changes of plasma hormone levels, and serum alkaline and acid phosphatase activities in patient 1. ↓↓↓ = injections; ⌜ = intranasal administration.

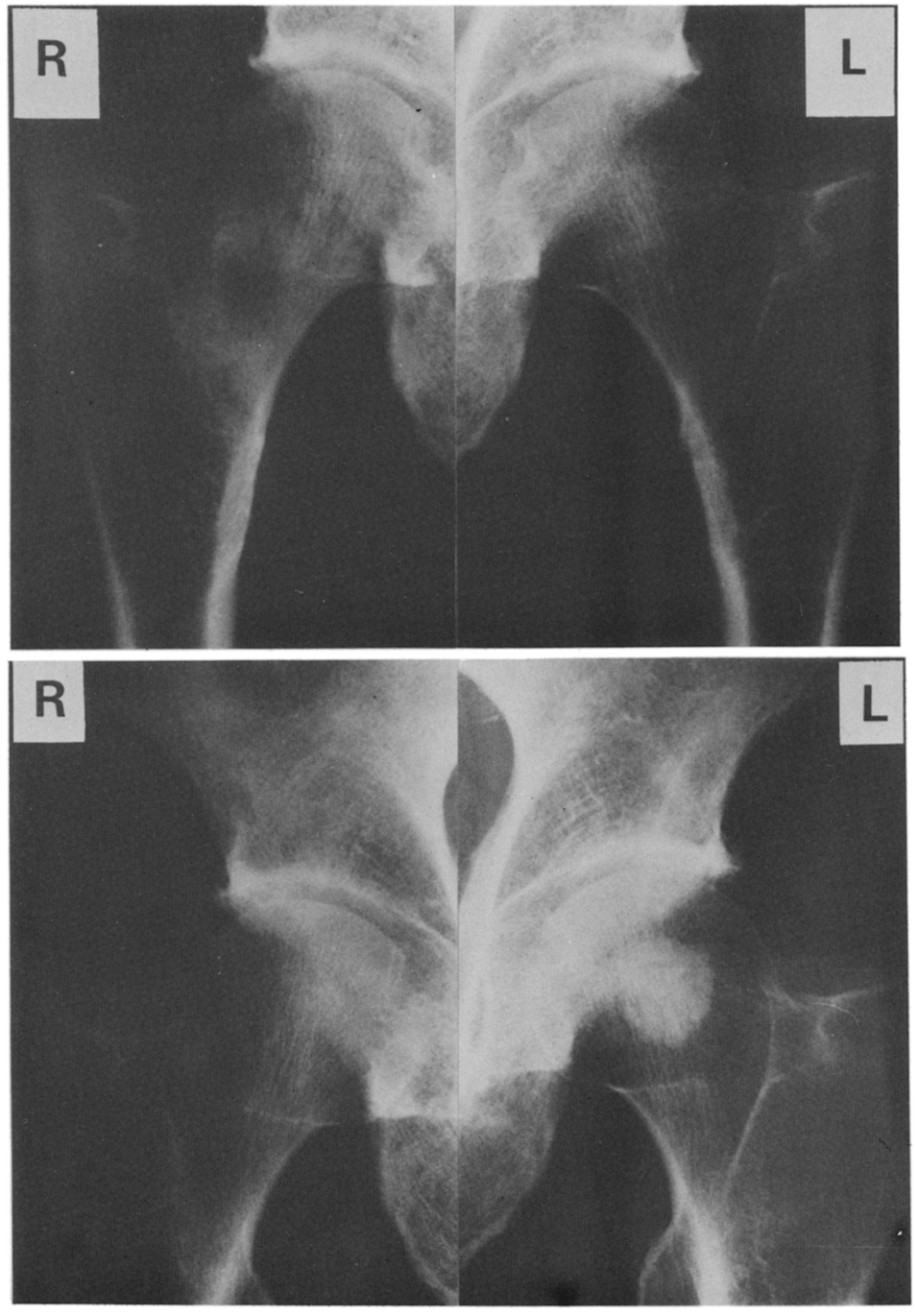

Fig. 3. (A) (upper part) An osteolytic lesion with an osteosclerotic surrounding in the right femur neck of patient 1 before treatment; a minimal sclerotic lesion in the head of the left femur; (b) (lower part) clear improvement in the right femur neck and the appearance of a dense sharp osteoblastic lesion in the left femur head after 3 months of treatment.

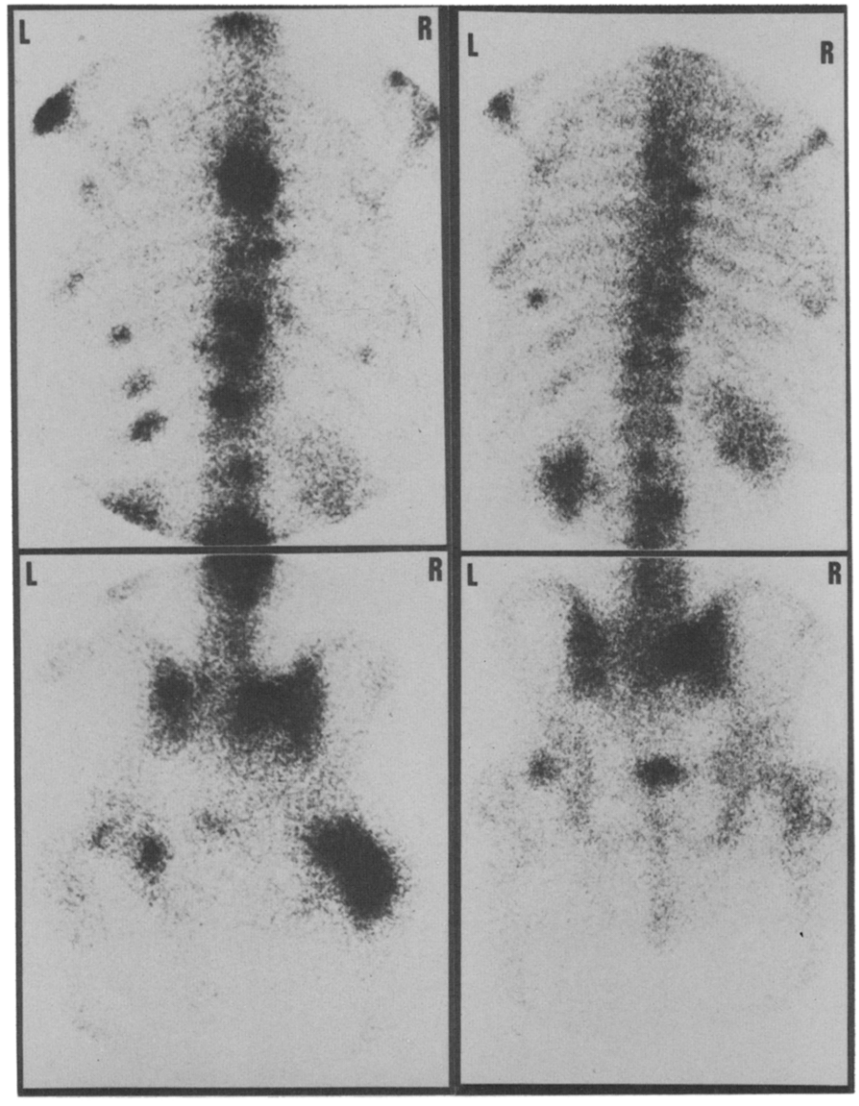

Fig. 4. Bone scintigraphy before treatment (left) and 6 months *after start of treatment (right) in patient* 1.

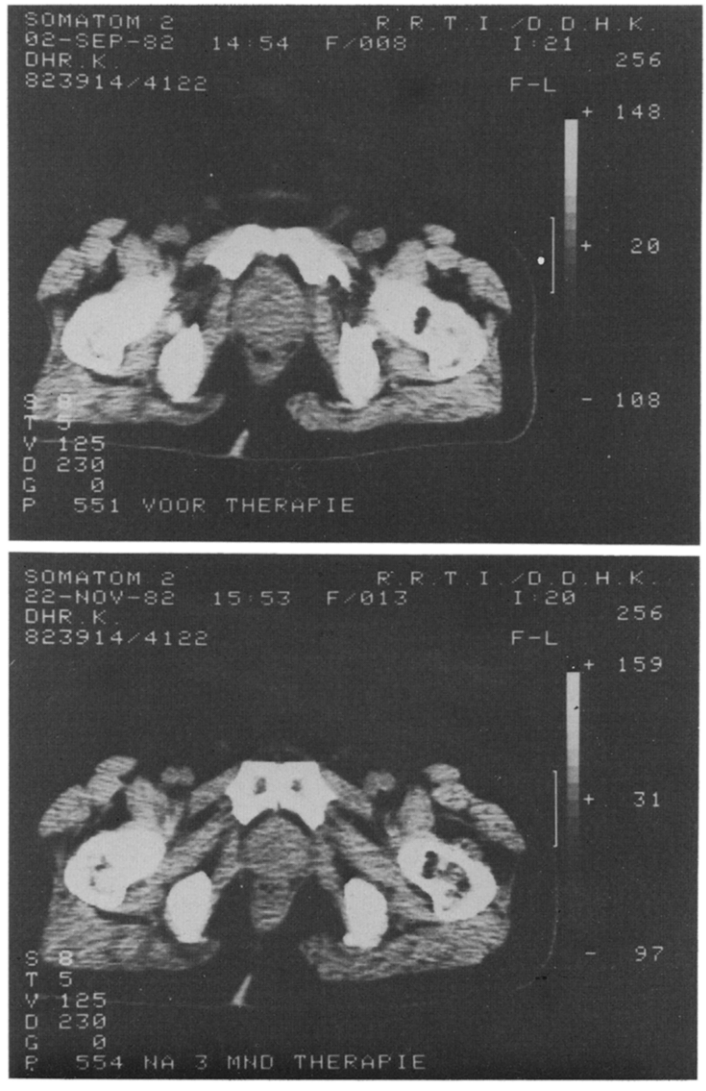

Fig. 5 CAT scan of the prostate before (upper part) and 3 months *after start of treatment (lower part) in patient* 1.

diminished slightly after 8 weeks. At this time he developed pain in the gastric area, which might have been caused by the analgesics. After 9 weeks he died subacutely, possibly by a gastrointestinal bleeding caused by the analgesics in combination with thrombocytopenia.

Side effects

Patient 1 experienced an increase of libido during the first week (no increase of bone pain) followed by a sharp decrease after 3 weeks. Also, in patient 2 libido and potency decreased. Both patients got hot flushes. Patient 3 already had a low sexual activity before treatment. None of the patients showed cardiovascular side-effects in the sense of hypertension, oedema, dyspnoea or thrombosis.

DISCUSSION

Several hormones are involved in the regulation of growth and functions of the prostatic gland, but androgens are the most important ones [33]. The most important androgen is testosterone, mainly (95%) produced in the testis. Other androgens such as androstenedione and dehydroepiandrosterone are also derived from the adrenals.

The major part of prostatic carcinomas are 'hormone-dependent' for their growth [34]. Bilateral orchidectomy appeared effective in the treatment of prostate cancer as well as high-dose oestrogens. The latter treatment, however, caused cardiovascular side-effects in about 40% of the patients [35]. The first preliminary studies with LHRH analogues have shown that this new kind of hormonal treatment, administered subcutaneously or intranasally, decreases plasma testosterone to (nearly) castration levels [22, 23, 27, 28]. Response rates of 70–90% are reported in the absence of serious side-effects. The main mechanism of action is probably a 'chemical castration' [17], but intrinsic antisteroidal effects [10, 11] and inhibition of enzymes (17-hydroxylase, 17-desmolases) involved in steroid synthesis are described [4]. Recently, chronic treatment with LHRH-agonist appeared superior to bilateral orchidectomy in regressing metastatic bone lesions and decreasing plasma PAP in spite of the absence of a significant difference in plasma testosterone levels [36]. This superior effect might be caused by the possible additional antisteroidal properties of LHRH-agonists or by decreased adrenal androgen synthesis. Further, a direct effect of the LHRH-agonist on the tumour cells cannot be excluded since LHRH-receptors were found to be present in an experimental prostatic tumour [37].

All our patients showed subjective improvement and decrement of serum acid phosphatase and PAP, of which the enzyme activity has been shown to be related with tumour mass [38]. Patient 1 also showed radiological evidence for objective tumour regression. Improvement with respect to prostatism can be explained by decrement of primary tumour size, but might be partly due to shrinkage of normal prostate tissue. Remarkable is the close relationship between plasma testosterone and PAP levels. In this patient bone scintigraphy appeared superior in early detection of bone lesions (head of left femur, ribs and spines). Plasma alkaline phosphatase showed a transient increase parallel to the disappearance of osteolytic lesions (indicating new bone formation) followed by a normalisation (Fig. 2). In the head of the left femur a circumscript pronounced osteoblastic lesion, which was scarcely visible on the X-ray before treatment, appeared at the same place as a hot spot was shown on the bone scan before treatment. This can be explained as an abnormal bone reaction that can occur after inhibition of the growth of a spot tumour cells. This sharp, round osteoblastic lesion did not change after 3 months of treatment. So, the events in this patient indicate that an increase of plasma alkaline phosphatase and/or appearance of new osteoblastic bone lesions during the first period of treatment are not a proof for tumour progression.

In conclusion, long-term treatment with the LHRH-agonist Buserelin appeared effective in patients with hormone-dependent metastatic prostate cancer without causing any serious side-effects. Our results are comparable with those reported by other centres using the same or other analogues. After the end of ongoing phase II studies in different countries phase III studies will be needed to indicate which treatment modality will be the most suitable one as a first-line therapy.

Acknowledgements—We thank Hoechst AG, Frankfurt, F.R.G. for supplies of the LHRH-agonist, the medical department of Hoechst Holland N.V. for support and fruitful comments during this study, the nurses for carefully collecting blood samples, H. Portengen for technical assistance, Mrs A. Sugiarsi for administrative help, and Mr J. Vuik and Mr J. Marselje for preparing the graphs.

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