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POLYESTRADIOL PHOSPHATE (160 MG/MONTH) OR LHRH ANALOG (BUSERELIN DEPOT) IN THE TREATMENT OF LOCALLY ADVANCED OR METASTASIZED PROSTATIC CANCER

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ABSTRACT

The clinical efficacy, cardiovascular complications and mortality of polyestradiol phosphate (PEP) 160 mg/month i.m. were compared with the luteinizing hormone releasing hormone (LHRH) analog, buserelin, in a prospective, randomised multicentre study including 147 patients with prostatic cancer. The cumulative non-progression rate at three years was 0.53 in the PEP group and 0.70 in the LHRH group. The mortality from cardiovascular diseases was the same in the two treatment groups. The parenterally given PEP was not associated with an increased risk of cardiovascular complications. The dosage of PEP 160 mg monthly seems, however, to be insufficient in the treatment of prostatic cancer.

KEY WORDS: PROSTATIC CANCER; ESTROGENS; LHRH ANALOGS

Since the demonstration of androgen dependence of prostatic cancer by Huggins and Hodges (15) in 1941, orchiectomy and estrogens have been widely accepted primary treatments for palliation in prostatic cancer. Orchiectomy can have a psychologic impact and some men refuse this therapy modality. The acceptance of estrogen therapy has been shadowed by the increased risk of cardiovascular complications (3, 5, 9, 11, 12, 30, 31). Most of these complications occur during the first months of treatment, when estrogen is given orally (3, 5, 6, 9, 11, 12, 31). During recent years polyestradiol phosphate (PEP), which is given parenterally, has been an extensively used estrogen in the Nordic countries. It seems that this form of estrogen therapy is not associated with an increased risk of cardiovascular complications (2, 4). An alternative to androgen deprivation therapy involves the use of analogs of the naturally occurring luteinizing hormone releasing hormone (LHRH). Since the elucidation of its structure in 1971 by Schally et al. (23), a number of LHRH analogs have been synthesized and studied. It has been shown in a large number of clinical trials that the efficacy of LHRH analogs in the treatment of prostatic cancer is the same as that of surgical castration. The side effects are also similar.

The purpose of the present report is to compare the clinical efficacy of polyestradiol phosphate and a GnRH agonist, buserelin, in patients with prostatic cancer, and further to evaluate the cardiovascular complications and mortality associated with these treatments.

PATIENTS AND METHODS

In a Finnish multicentre study (Finnprostate IV), 147 patients with locally advanced (T3 or more) or metastasized (M1) prostatic adenocarcinoma were prospectively randomized with envelopes coded for each treatment arm into two treatment groups, PEP or LHRH analog. The diagnosis was confirmed histologically and/or cytologically. The exclusion criteria were: previously diagnosed and hormonally or radiologically treated prostatic cancer, history of other malignancy, history of acute thromboembolic episode, myocardial infarction during the past year, treatment-resistant decom-

TABLE 1

Extent of primary tumor (T classification), presence of distant metastases (M classification) and differentiation grade (G classification) in patients with prostatic cancer by treatment group (number of patients given).

		T0–2		T3–4		M0		M1		G1		G2		G3	
	n	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
PEP	70	6	(9)	64	(91)	41	(59)	29	(41)	16	(23)	37	(53)	17	(24)
LHRH	77	7	(9)	70	(91)	47	(61)	30	(39)	16	(21)	55	(71)	6	(8)

n = number of patients
T = extent of primary tumor
M = distant metastases
G = differentiation grade
PEP = intramuscular polyestradiol phosphate
LHRH = LHRH analog, buserelin depot

pensated cardiac insufficiency, known severe liver disease, senility or mental disturbance. At the time of diagnosis there were no significant differences between the treatment groups in terms of local extent of tumour, presence of metastases (based on bone scan), and grade of malignancy (Table 1) (29).

The PEP therapy group consisted of 70 patients (mean age 71.9 years, range 54.8–86.3) and the LHRH analog group of 77 patients (mean age 72.6 years, range 46.9–87.0). The PEP therapy consisted of monthly intramuscular injections of PEP (Estradurin^{R}) 160 mg each. Local irradiation was given to prevent gynaecomastia at least two weeks before the start of treatment (1). The LHRH analog, buserelin (Suprefact^{R}), was given at intervals of eight weeks. The implant contains a dose of 6.6 mg buserelin and consists of a polyactide/glycolide copolymer, molar ratio 75:25. Implantations were performed by s.c. injection into the adipose tissue in the abdominal region laterally to the rectus abdominis muscle. The implants were biodegradable and were left *in situ*. One week before the start of buserelin treatment, cyproterone acetate (Androcur^{R}) was instituted at a dosage of 100 mg t.i.d. perorally to prevent an eventual flare-up reaction. This treatment was continued for two weeks after the beginning of buserelin treatment.

The patients were examined at 2 or 3, 6 and 12 months after the beginning of treatment and thereafter every six months. Apart from regular assessment visits, examinations were performed whenever symptoms indicated progression. Progression of the disease was evaluated according to the SPCG criteria (Scandinavian Prostatic Cancer Group), a modification of the EORTC criteria (24), which we have used in our earlier study (4). Progression was defined as an increase in prostatic tumour size of more than 25 % and/or an increase in the size of metastases of more than 25 % or the appearance of a new metastasis. Changes in prostatic acid phosphatase/prostatic specific antigen or performance status only were not recorded as progression. Cardiovascular complications included myocardial infarction, cerebrovascular complications, pulmonary embolism and deep vein thrombosis.

Statistical analysis of proportions was done using the chi-square test and the test for linear trend. Survival analyses were performed by the product limit method. The term "non-progression" indicates period when no criteria of progression can be found.

RESULTS

The cumulative non-progression rate at three years was 0.53 in the PEP group and 0.70 in the LHRH group (Fig. 1). There was a significant difference in the cumulative non-progression rates between the PEP group and the LHRH analog group ($P < 0.001$). The numbers of carciovascular deaths and cardiovascular complications not leading to death were similar in both groups (Table 2).

DISCUSSION

Parenteral estrogen, polyestradiol phosphate (PEP), or orchiectomy have been the most used therapeutic modalities for advanced prostatic carcinoma in the Nordic countries. The LHRH analogs have still a minor role in palliative treatment.

In a previous Finnish multicentre study (Finnprostate II), the clinical efficacy of orchiectomy and PEP (160 mg/month) was compared in patients with advanced prostatic cancer (10). The cumulative non-progression rate at two years was about 0.8 in the orchiectomy group, about the same as in this study in the LHRH analog group. The results of these two studies indicate that buserelin and

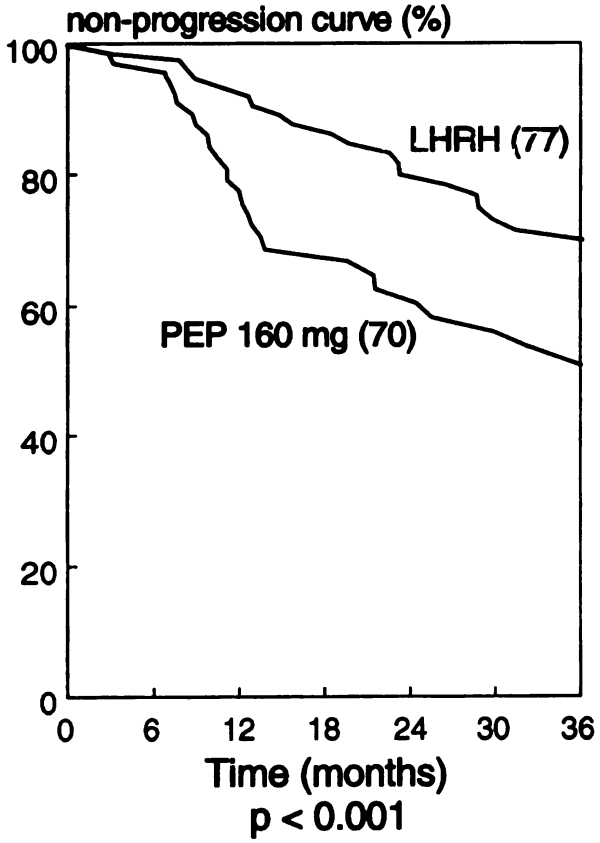

Fig. 1. Cumulative non-progression curves of patients with prostatic carcinoma treated by polyestradiol phosphate (PEP) or LHRH analog.

TABLE 2

Cardiovascular deaths and cardiovascular complications not leading to death by treatment group.

Treatment (*n*)	Cardiovascular deaths	Cardiovascular complications
PEP (70)	4	1
LHRH (77)	4	2

PEP = intramuscular polyestradiol phosphate
LHRH = LHRH analog, buserelin depot

orchiectomy are equally effective treatment modalities. The cumulative non-progression rate was significantly lower in both of these studies in patients treated with PEP (160 mg/month).

Estrogen therapy is claimed to be as effective as orchiectomy in terms of the cancer inhibitory effect (22, 25, 28). It has been proposed that the estrogen effect is based not only on the decrease of the androgen production but also on a direct cytotoxic effect on prostatic cancer cells (8, 27). However, according to McConnell, evidence of a direct cytotoxic effect on the cell is lacking (18). This study confirms with a larger number of patients and a longer follow-up time the previous finding (10) that at least the dose of PEP used (160 mg/month) seems to be insufficient in the treatment of prostatic cancer. In the study of Norlén and co-workers the steady-state concentrations of testosterone were about 45, 25, and 15 % of the pretreatment values when PEP was given 80, 160 or 240 mg every four weeks for at least six months (19).

Estrogen treatment in prostatic carcinoma has a bad reputation because of the increased risk of cardiovascular complications (5, 9, 11, 12, 30, 31). Most of these complications appear during the first months of treatment, when estrogen is given orally (3, 5, 9, 11, 12, 31). The combination estrogen therapy consisting of intramuscular polyestradiol phosphate (PEP) and oral ethinyl estradiol has been a widely used treatment modality in Scandinavia and in Finland during the past 10 years. This combination estrogen therapy has been shown to involve an increased risk of cardiovascular complications (2, 3, 11, 12, 13). It seems that the parenterally given PEP monotherapy is not associated with an increased risk of cardiovascular complications (2, 4, 14, 26). This is the finding also in the present study. The mortality from cardiovascular diseases was the same in the two treatment groups.

LHRH agonists appear to be as effective as orally given diethylstilbestrol or orchiectomy in the treatment of advanced prostatic cancer (7, 17, 20, 21). The advantage of using these agents is that they lack the cardiovascular side effects associated with oral estrogens and the surgical and psychologic complications of orchiectomy. The initial stimulatory effect of LHRH analogs causing an increase in serum testosterone may cause a "flare" reaction, a transient exacerbation of disease symptoms (16). In our material, three weeks of cyproterone acetate seemed to prevent the "flare" reaction.

In the choice of treatment modality, the individual patient compliance and the overall costs have to be taken into consideration. In LHRH agonist and PEP therapy monthly injections are needed, whereas orchiectomy is a once-only procedure. Orchiectomy is relativ-

ely cheap. PEP therapy is inexpensive, too, whereas LHRH agonists are much more expensive.

The advantage of PEP over orally given estrogens seems to be that there is no risk of cardiovascular complications. The dosage of 160 mg monthly, however, is not sufficient. These results as well as the findings of Stege and co-workers (26) have prompted us to use higher doses of PEP in our ongoing studies.

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