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REVIEW

THE ROLE OF PARENTERAL POLYESTRADIOL PHOSPHATE IN THE TREATMENT OF ADVANCED PROSTATIC CANCER ON THE THRESHOLD OF THE NEW MILLENIUM

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ABSTRACT

Orchiectomy and estrogens have been used for over 50 years in the treatment of advanced prostatic cancer. Although orchiectomy is a simple procedure, it may cause psychological stress. Oral estrogen therapy is as effective as orchiectomy in terms of cancer inhibitory effect, but its acceptance as primary hormonal treatment is overshadowed by an increased risk of cardiovascular complications. Parenteral estrogen, polyestradiol phosphate (PEP), is effective, but also associated with cardiovascular complications, although to a lesser extent. During the last 20 years, well tolerated luteinizing hormone releasing hormone (LHRH) analogues have been replacing orchiectomy and estrogens. Efforts have been made to increase the efficacy of the treatment by adding antiandrogens to LHRH analogues and also to orchiectomy (combined androgen blockade, CAB). However, the efficacy of LHRH analogues and CAB has not proved to be superior to that of simple orchiectomy and, moreover, they are expensive treatment modalities. Orchiectomy and LHRH analogues are associated with negative effects on bone mass and may cause osteoporosis, whereas PEP treatment has an opposite effect. Parenteral polyestradiol phosphate is still a cheap potential treatment for advanced prostatic cancer, but further studies should be conducted to establish its future role, e.g. combining acetylsalicylic acid to prevent cardiovascular complications.

Key words: Prostatic cancer; estrogen therapy; cardiovascular complication; expenditure

INTRODUCTION

Androgen dependence of prostatic cancer was discovered more than half a century ago, and orchiectomy and estrogen therapy have since then been used in the treatment of advanced prostatic cancer (1). During the last 20 years the use of luteinizing hormone releasing hormone (LHRH) analogues have gain ground as an effective treatment with few side-effects. The efficacy of the treatment has been tried to improve by adding antiandrogens to LHRH analogues and also to orchiectomy (combined androgen blockade, CAB). The inhibition of the effect of testosterone on prostatic cancer tissue has been the goal of all treatment modalities. Orchiectomy decreases the serum testosterone concentration to a castration level. Estrogens and LHRH analogues decrease the testosterone to a castration level via the hypophyseal-pituitary axis. Antiandrogens inhibit the effect of testosterone on prostate cells. Orchiectomy has been "the gold standard" to which any other treatment modalities have been compared in terms of cancer inhibitory effect and complications. Oral estrogens are as effective as orchiectomy in inhibiting the progression of the cancer (2–3), but the risk of cardiovascular complications is significantly higher (4). Parenteral estrogen, polyestradiol phosphate (PEP, Estradurin ®) is as effective as orchiectomy, but the

risk of cardiovascular complications is lower than with oral estrogens although higher than with orchiectomy (5, 6, 7).

POLYESTRADIOL PHOSPHATE

Parenteral polyestradiol phosphate, combined with oral estrogen, ethinylestradiol (EE), was introduced nearly 30 years ago (8). The cancer inhibitory effect of this combination (PEP 160 mg initially, followed by 80 mg/month and EE 1 mg/day for 2 weeks, followed by 0.15 mg/day) was even better than that of orchiectomy (9), but the combination was associated with a significantly higher risk of cardiovascular complications (10). In addition to decreasing the serum testosterone to castration level, estrogens may have a direct cytotoxic effect on prostatic cancer tissue (11). To avoid the complications of oral estrogen, parenteral PEP has been used alone at higher doses. PEP 160 mg/month was not associated with an increased risk of cardiovascular complications (12). In fact, the cardiovascular mortality rate was lower than in orchiectomized patients and even in the standard population (13). However, the efficacy of this PEP dose did not reach the cancer inhibiting effect of orchiectomy (14). The higher initial PEP dose of 320 mg followed by 240 mg/month, was as effective as orchiectomy in inhibiting the disease progression but, like oral estrogens, also this dose of PEP was associated with a significantly higher risk of cardiovascular complications, especially during the first year of treatment, but not during the second (5). However, the proportion of complications was lower than in patients treated with the combination of PEP and EE (5,10).

Because of the extensive first-pass metabolism of estrogens, a higher oral dose of estrogen is required compared to parenteral administration to achieve the same therapeutic effect. PEP treatment alone is associated only with a slight increase in sex hormone binding globulin (SHBG) level, whereas the combination of PEP and EE yields a greater increase in SHBG level (15). This stronger effect of oral estrogens on liver metabolism probably explains the higher risk of cardiovascular complications.

It is generally accepted that a low high-density lipoprotein (HDL) cholesterol level and a high low-density lipoprotein (LDL) cholesterol level are risk factors for coronary heart disease (16, 17). PEP therapy is associated with a significant increase in serum HDL cholesterol and a decrease in serum LDL cholesterol levels, whereas in orchiectomized patients there are no significant changes in HDL or LDL cholesterol levels (18, 19). An increase in serum HDL cholesterol and a decrease in serum LDL cholesterol levels have been associated also with the combination of EE and PEP (20). Thus the effect of estrogens on liver lipid metabolism does not explain the higher risk of cardiovascular complications associated with oral estrogens.

Estrogens influence also the coagulation system. It was observed that oral estrogen (21) induced a significant increase in factor VII level and a decrease in antithrombin III (AT III) level, whereas PEP 160 mg (22) or 320 mg (23) monthly was associated with a significant decrease in AT III without any change in factor VII level. It is possible that the lack of increase in factor VII during PEP therapy is one reason for the smaller number of cardiovascular complications as compared to oral estrogens. Increasing the dose of PEP from 160 mg/month to 240 mg/month may overshadow the protective effect of the increase in HDL and decrease in LDL on cardiovascular complications by the unfavorable dose-dependent effects on hemostatic parameters towards a hypercoagulable state. The decreased AT III level during PEP therapy might indicate a potential risk of cardiovascular complications. It seems that a positive long- term effect (decreased risk of cardiovascular morbidity) of PEP is associated with the alteration of the liver lipid metabolism and acute dose-dependent negative effect (thromboembolic complications) with the alteration of the coagulation factors.

A frequently appearing side-effect of PEP is painful gynecomastia, but this can be prevented effectively by pretreatment breast irradiation (24). However, sometimes the PEP treatment has to be changed because of the hyperplasia and pain of the mammary glands (5).

Further information about the efficacy and complications of PEP treatment will be obtained from the ongoing SPCG-5 (Scandinavian Prostatic Cancer Group) study. SPCG-5 has recently completed recruitment of 917 patients with previously untreated metastatic prostatic cancer. The study randomized patients between 240 mg of PEP every 4 weeks (every 2 weeks for the first 8 weeks) and surgical or pharmacological castration (2.75 mg of decapeptyl every 4 weeks) plus 250 mg of flutamide three times daily. This study is giving special attention to cardiovascular events.

ORCHIECTOMY, LHRH ANALOGUES, ANTIANDROGENS, CAB AND INTERMITTENT ANDROGEN DEPRIVATION

Orchiectomy is a cheap and simple procedure to block the testosterone secretion in the testes. The castration level is reached within 24 hours. Orchiectomy is the best treatment modality when a rapid decrease of testosterone is desired for example in patients with metastatic spinal compression or severe pain. It is also suitable for patients with poor compliance in taking regular medication or injections. About half of the orchiectomized patients suffer from hot flushes (25), which can be treated effectively with antiandrogens. Although most patients accept orchiectomy, the concrete partial loss of manhood may cause psychological stress in many patients.

The castration level of testosterone is achieved by LHRH analogues (medical castration) within 2–4 weeks after injection (26). The interval between injections is one to three months. During the first week of treatment with LHRH analogues the "flare phenomenon" can occur, because LHRH analogues stimulate testosterone production during the first few

days of the treatment. Thereafter the testosterone level falls by the negative feed-back mechanism. The "flare phenomenon" can be prevented with antiandrogens. Otherwise LHRH analogues are well tolerated. Orchiectomy and LHRH analogues seem to be equal with regard to efficacy and other side-effects (27,28).

The efficacy of antiandrogens alone is poorer than that of orchiectomy. Unlike PEP, orchiectomy, and LHRH analogues, which lead to impotence (with few exceptions), monotherapy with antiandrogens may retain a patient's potency. On this basis, if the patient insists on retaining his potency, but still wishes to go ahead with the therapy, although less effective, antiandrogen monotherapy can be used. Great expectations have been associated with CAB, i.e. antiandrogens combined with surgical or medical castration. However, it was found that the efficacy of the combination of orchiectomy and the antiandrogen flutamide was not better than that of orchiectomy and placebo (29). In a large meta-analysis on 22 trials and 5710 patients, no statistically significant difference in survival was observed when CAB was compared with orchiectomy or LHRH analogues alone (30).

In intermittent androgen deprivation therapy, LHRH analogues are interrupted and restarted again, when the disease is reactivated. Intermittent androgen deprivation therapy has been shown to prolong the hormone sensitivity of the cancer. However, in preliminary studies, no increase in survival has been detected (31,32). Intermittent treatment may improve the quality of life due to recovery of sexual functions during the off-treatment period, and the cost of treatment is lower. Further studies are in progress also in Finland.

OSTEOPOROSIS

Both medical and surgical castration may result in osteoporosis, especially in patients surviving long. It has been observed that the treatment with LHRH analogues is associated with negative effects on bone mass (33,34). In a previous study, a significant decrease in bone mineral content by 5 % in the distal radius was found one year after orchiectomy, while no decrease was observed in the estrogen treated (PEP + EE) patients (35). Another study showed that orchiectomy induces changes in serum bone and collagen markers, indicating an increased bone turnover, whereas the opposite pattern was found in the PEP treated patients, indicating a reduced turnover (36).

EXPENDITURE

Prostatic cancer is the most common malignancy in males in most Western countries (37), which makes the mode of treatment an important economic issue. In Finland, the cost of a monthly dose of PEP (240 mg) is only about 15 % of the cost of a monthly dose of LHRH agonists, 7.5 % of a LHRH agonist plus an antiandrogen and 15 % of the cost of an antiandrogen alone.

CONCLUSION

According to the present knowledge, parenteral estrogen, polyestradiol phosphate, at a dose of 240 mg/month, is as effective as orchiectomy in the treatment of advanced prostatic cancer. Combined androgen blockade has not proved to be superior to surgical or medical castration alone. Although the risk of cardiovascular complications is increased in patients treated by parenteral polyestradiol phosphate, we believe that this treatment modality should not yet be abandoned, but further studies should be conducted to establish its future role, e.g. combining acetylsalicylic acid to prevent cardiovascular complications. On the other hand, estrogens seem to protect patients from osteoporosis and osteoporotic fractures as opposed to orchiectomy and LHRH agonists. In addition, parenteral polyestradiol phosphate therapy is cheap as compared with other pharmacotherapics.

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