‘Hot flush’, an unpleasant symptom accompanying antiandrogen therapy of prostatic cancer and its treatment by cyproterone acetate

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Abstract. From 1995 to 1997 the authors have assessed 31 patients with histologically verified advanced carcinoma of the prostate (CaP) and the ensuing symptom of ‘hot flush’. Patients underwent transurethral resection of the prostate (TURP), bilateral orchiectomy (OE) and combined androgen blockade (CAB) by the administration of non-steroid antiandrogens. The authors present the mechanism of the genesis of the ‘hot flush’ symptom as well as its subjective manifestations, methods of laboratory monitoring as well as their experience with the treatment of this symptom. 50 mg tablets cyproterone acetate administered twice daily or Androcur depot 300 mg i.m. inj. once in 14 days were the main factors in the treatment of ‘hot flushes’ which reduced subjective difficulties in 80.6% of the patients studied.

Key words: Carcinoma of the prostate, ‘Hot flush’, Androgens, Hypothalamus, Hypophysis catecholamines, Centre of termoregulation

Introduction

Practically all over the world carcinoma of the prostate (CaP) is the most frequent oncological affliction of the urogenital tract of the male population. The trend of prolongation of the average life-span in the male population also causes a higher incidence of the disease [1–3]. In 1941, Huggins et al. [4] have objectively confirmed the direct dependence of the prostatic cell on the level of androgens. This dependence was and is predominantly used as the basis of the treatment of advanced metastatic CaP. Testosterone (TST) production in the Leydig cells of the testicles and of androgens in the suprarenal gland are determined by the co-operative activity and simultaneous control of the hypothysis and of the hypothalamus and their mutual feedback. According to Walsh [5], 90% of the testicular TST is produced under the influence of LH and FSH and 10% originate in the suprarenal gland stimulated by ACTH. According to Debruyne et al. [6], the most frequent and at the same time the most economical endocrine therapy is surgical orchiectomy which is considered to be the optimal approach resulting in a pronounced decrease of the TST level in the serum within 24 hours after surgery. Another possibility of a ‘chemical’ or ‘pharmacological castration’ is the treatment with LH-RH agonists. With this therapy 90–95% of TST and its conversion product, dihydrotestosterone (DTS) provoking growth factors in the prostatic tissue are removed from the circulating plasma. Suprarenal androgens with estrogens probably increase their activity and act synergically on the growth factors of the prostatic cell [1–3, 7]. Their blockade can be achieved predominantly by antiandrogenic substances [1–3, 9].

Estrogens (diethylstilbestrol) were one of the first to be known to have an antiandrogen effect. Lately Estracyt (estramustin phosphate) is known to have an antimitotic activity and the released estrogens have antigonadotropic effects. Successively steroid antiandrogens were discovered of which we know Flutamide (flucinom), Anandron (nilutamidium), Casodex (bicalutamide). Apart from the antiandrogens listed also blockers of testicular and suprarenal androgen synthesis exist. Ketokonazol and Liarozol are representatives of this group of substances which are success-
fully applied in the treatment of hormonally resistant CaP. As a concomitant effect of antiandrogen treatment, mainly after surgical or medicamental castration, where the greatest amount of androgens is removed, as well as in combined treatment by non-steroid antiandrogen preparates, in 70% of the patients a defect of termoregulation known as ‘hot flush’ can be observed [3, 7, 8].

Most often ‘hot flush’ (HF) comprise of rushes of warmth in the facial region and proceeding to the neck and thorax combined and alternating with intense perspiration lasting from several seconds to several minutes. These sensations are combined with a feeling of weakness, fear, apathy and even depression. The loss of libido, potency and gynecomastia – as well as osteoporosis in later stages are very common.

Patients and methods

At the Department of Urology and Andrology of the University Hospital in Bratislava we have treated 31 patients with HF manifestation within three years from 1995 to the end of 1997. The patients underwent either bilateral OE or medicamental castration with combined androgen blockade (CAB) by non-steroid antiandrogens. Questionnaires were used to evaluate the number, intensity and duration of HF the profusion of perspiration during the day and night, their correlation with TST, protein, PSA and alkaline phosphatase levels in the serum, with the results of hepatal tests and with the consumption of alcoholic beverages. We have also assessed psychical depression.

The age-span of patients reached from 60 to 87 years (median: 72.8 years). The onset of HF symptoms was registered from two weeks to 7 months after OE or CAB. In one patient (80 years) subjective discomfort set on only 1 year after surgical castration.

We have divided the patients into two groups: the lighter group A (12 patients) and the more severe group B (19 patients). Patients not having more than 3 hot flushes and bouts of perspiration per day and not more than one per night were considered to have the light form of HF patients with a higher incidence of these symptoms were classified as belonging to the more severe group B. Gynecomastia was observed in 26 patients (83.8%) and decrease of libido was registered by 29 out of 31 patients (93.5%). Depressions and other psychical changes were recorded in 20 patients (64.5%). In the lighter group A, serum TST levels ranging from 0.10 to 1.0 ng/ml were assessed.

We have found that the levels of PSA, ALP and results of hepatal tests could not be significantly correlated with the subjective discomfort of patients and with objective manifestations of HF. On the other hand hypoproteinemia and hyperglykemia worsened the negative physical and psychical symptoms of patients. Especially in the more severe group B, spicy food and even more so, consumption of alcohol had very pronounced negative effects on patients. Patients with the lighter form of HF symptoms we administered Lexaurin (bromazepanum) 1.5 or 3 mg tablet. Three times daily or Xanax (alprazolanum) 1.0 mg 3 times daily. Patients not responding to this treatment or suffering from the more severe form of HF were then given either the steroid preparate Cyproterone acetate (androcure) twice daily per 50 mg tablet p.o. or androcure depot 1 amp. per 300 mg i. m. once per two weeks. If the effect of this treatment was unsatisfactory we have added Prednisone (prednisonum) one 5 mg tablet daily. The described treatment resulted in the reduction of subjective difficulties in 80.6% of the patients and we consider this to be a favourable achievement.

Discussion

A low level of TST decreases the formation of opioid peptides in the blood serum. In the hypothalamus more catecholamines are released, these are important neurotransmitter stimulators for the production of LH-RH and later in the production of gonadotropins in the hypophysis. In the hypothalamus neurons of the thermoregulation center and neurons monitoring LH-RH production are located anatomically close to each other and thus an increased level of catecholamines could affect them both with a massive ensuing vasodilatation of the periphery [3, 8]. According to Labrie [9], after bilateral OE or treatment with a LH-RH agonist the TST level in the prostate decreased by 95% whereas DHT was only decreased to 40% of its normal level. Metabolites of androgens, including those originating in the suprarenal gland, are decreased only to 50–60%. This indicates that after OE conversion of high levels of suprarenal precursors to DHT takes place in the prostate. According to Tomaskin et al. [7] HF exist in 71% of patients not only after bilateral OE or after treatment with LH-RH agonists but also as a result of combined treatment by non-steroid antiandrogens. Buchholz et al. [10] pointed out that whereas in patients not older than 75