

European Urology Today



OFFICIAL NEWSLETTER OF THE EUROPEAN ASSOCIATION OF UROLOGY *ea*

Volume 3, no 2, June 1993

Present status of endocrine therapy of prostate cancer

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Prostate cancer has become the most frequent cancer and is the second cause of cancer death in men in North America as well as in most European countries. A major problem facing treatment of this disease is the absence of signs or symptoms during many years of cancer growth, thus resulting in the presence of bone metastases at time of first diagnosis in the majority of patients. There is thus a major need for improved diagnostic as well as therapeutic approaches. By far the best known characteristic of prostate cancer is its high degree of sensitivity to androgens. In fact, following the original observations of Huggins and his colleagues in 1941, suppression of testicular androgens has been the cornerstone of the treatment with high doses of estrogens. Since then, endocrine therapy has been the treatment of choice of prostate cancer.

A relatively recent alternative to castration is the use of LHRH agonists that achieve a complete blockade of testicular androgens with an excellent tolerance and no symptom other than those associated with hypoandrogenism. It is however important to recognize that although LHRH agonists offer a more acceptable method of castration free of the important side effects of estrogens, one cannot expect to improve the prognosis of prostate cancer beyond the results already achieved with orchiectomy since the action of LHRH agonists is also limited to the blockade of testicular androgens.

Adrenal androgens

Although castration (orchiectomy or treatment with an LHRH agonist) causes a 90-95% reduction in serum testosterone (T) concentration, a much smaller effect is seen on the only meaningful parameter of androgenic action, namely the intraprostatic concentration of dihydrotestosterone (DHT), the most active androgen. In fact, after elimination of testicular androgens by medical or surgical castration, the intraprostatic concentration of DHT remains at approximately 40% of that measured in intact men. The importance of extratesticular androgens is also well illustrated by the finding that 40-50% of androgen metabolites remain in the circulation after castration in men. Recently, the highly sensitive methods of molecular biology have permitted to elucidate the structure of all the enzymes required for the conversion of the adrenal steroids dehydroepiandrosterone (DHEA) and its sulfate DHEA-S into T and DHT (Fig 1). All these enzymes are expressed in the human prostate, and are responsible for the local formation of DHT.

Various classes of antiandrogens

Since an essential step in the action of androgens in target cells is binding to the androgen receptor (Fig. 1), a logical approach for neutralizing the androgens of adrenal origin is the use of antiandrogens or compounds which prevent the interaction of T and DHT with the androgen receptor. Since prostate cancer is so highly sensitive to androgens, the antiandrogen used should be a compound having high specificity and affinity for the androgen receptor while not possessing any androgenic, estrogenic, progestational, glucocorticoid or any other hormonal and antihormonal activity. In fact, very few compounds meet the criteria of pure antiandrogens and Flutamide was the first pure antiandrogen discovered. Due to the variable efficacy of different antiandrogens, it is essential that the term combination therapy, as originally defined, be limited to the association of medical or surgical castration with a pure antiandrogen, namely Flutamide or its analogues.

Heterogeneity of sensitivity to androgens

Clinical evidence clearly shows a marked heterogeneity of sensitivity to androgens between patients as well as between different tumors in the same patients. In fact, while 20-40% of patients do not show a positive response to standard endocrine therapy (orchiectomy or LHRH agonists), the additional responses obtained in an important proportion of them by the addition of a pure antiandrogen (Table 1) clearly demonstrates that tumors are left growing under standard hormonal therapy while the growth of these tumors can be blocked by the ad-

dition of a pure antiandrogen. There is thus heterogeneity of androgen sensitivity among tumors present in the same patient as well as between tumors present in different patients.

The best model available is the androgen-sensitive Shionogi tumor cell line. In fact, while the original tumor showed a Km value for DHT action at 0.9 nM, the corresponding values in clones A,B and C were calculated at 0.024, 0.15 and 30 nM, respectively. There was thus a 1250-fold difference in sensitivity to DHT between clones A and C obtained from a single tumor.

The influence of progressive blockade of androgens on the growth of tumors having heterogeneous sensitivity to androgens is schematically illustrated in Figure 2. More complete blockade of androgens achieved by the addition of Flutamide results in lower concentrations of free DHT in the prostatic tissue (Fig. 2B), thus causing a more rapid as well as a more complete regression of a larger proportion of tumors. Thus, for the tumors already affected by castration, the addition of Flutamide should cause a more rapid and a greater degree of growth inhibition for a longer time period. Such an interpretation is fully supported by the clinical data summarized in Table 1.

Advantages of combination therapy with a pure antiandrogen

The data recently obtained in the four largest double-blind, placebo-controlled, randomized and prospective studies performed in stage D² prostate cancer patients confirm our original observations and show the important advantages of combination therapy using a pure antiandrogen on all the objective and subjective parameters studied. Of utmost importance is the observation that the simple addition of Flutamide added, on average, 7.3 and 15.0 months of life while the use of Anandron added 5.4 and 7.3 months, respectively.

Since, in three of these studies, the antiandrogen was added to the control arm at the time of progression, the results obtained demonstrate the advantages of using the combination therapy at start of treatment compared to its use at the time of failure to standard therapy. Moreover, since three of these studies had orchietomy as standard therapy, the pooled results obtained in the control arm cannot be explained by an LHRH agonist-induced stimulation of testicular androgen secretion.

Importance of early treatment with combination therapy

At early stages of the disease, the usual choice of therapy is between radical prostatectomy, radiation therapy or no treatment until progression occurs. An important observation made in stage D² as well in stage C patients who receive the combination therapy as first treatment is that prostate cancer is rapidly and extremely well controlled at the level of the prostate. Since the blockade of testicular androgen secretion by an LHRH agonist is fully reversible with no significant side effects, we have investigated, in a preliminary study, the effect of 3-month pretreatment with the combination therapy on the surgical procedure of nerve-sparing radical prostatectomy itself as well as on the short-term clinical follow-up. Combination therapy was continued for 6 months following surgery.

As measured by transrectal ultrasonography and digital rectal examination, prostatic volume was already decreased by approximately 50% three to four months after the start of combination therapy. The volume of prostatic cancer, on the other hand, was reduced to an even greater extent, namely 75%. Most importantly, there was also a marked improvement in the histopathologic grading of the prostatic tissue removed at the time of surgery compared to the biopsy of material obtained at time of diagnosis. The return of normal libido and potency upon cessation of temporary endocrine therapy in all patients who had libido and potency before treatment is an important characteristic of this approach. Using the same strategy, Solomon et al. have found a reduction in the number of positive margins at surgery from 34.6% to 14.3% while our randomized study has shown a decrease in positive margins from 28.6% to 17% (p<0.05). Quite clearly, the best hope of improving survival in prostate cancer is early diagnosis and early treatment.

It is believed that early diagnosis at a time when cancer is still limited to the prostate could allow use of curative techniques which are unavailing at later stages of the disease, especially radical prostatectomy. It is thus of major importance to make available an efficient, cost-effective and well accepted strategy for early diagnosis of prostate cancer in the general population. We have recently found that, when fixing a threshold value at 3.0 µg/L for serum PSA used for prescreening, the efficacy of transrectal ultra-

sound (TRUS) increases from 3.3% to 24%, with one prostate cancer being detected in approximately four examinations, while those not selected for TRUS by PSA prescreening have only a 1.4% chance of having detectable prostate cancer. Since serum PSA is closely correlated with cancer volume, the tumors missed by first PSA prescreening should be of very small size and it is most likely that they will be detected at an early stage by PSA measurements at later annual routine prescreenings. In the first 7000 men screened by the approach, 70% of the cancers were at stage B. Prescreening with serum PSA could thus greatly reduce the number of prostate cancers discovered at an advanced stage and permit curative therapies, thus offering the best chance of improving survival in prostate cancer.

Towards more complete androgen blockade

The presently available antiandrogens have a relatively low affinity for the androgen receptor, thus leaving significant concentrations of intracellular DHT free to interact with the androgen receptor and stimulate cancer growth, especially in androgen-hypersensitive tumors. Since T is converted by 5α-reductase into DHT, a logical site of therapeutic intervention is at this last step in DHT formation in target tissues. Our recent experimental data clearly suggest that further androgen blockade achieved by the addition of a 5α-reductase inhibitor could well improve the efficiency of the present combination therapy.

Despite the demonstrated efficacy of inhibitors of 5α-reductase as blockers of DHT formation, including Proscar, it seems logical to suggest that these compounds should not be administered alone for the treatment of androgen-sensitive diseases, especially prostate cancer. In fact, since T also interacts with the androgen receptor, the well-recognized secondary increase in intraprostatic T induced by the 5α-reductase inhibitor counteracts, to a variable but important extent, the decrease in cellular DHT achieved by the 5α-reductase inhibitor. Most importantly, such low androgen levels are likely to induce the development of tumors hypersensitive to androgens and resistant to endocrine therapy.

(References available by the secretariat upon request).