

ENDOCRINE THERAPY OF PROSTATE CANCER: OPTIMAL FORM AND TIMING

The best known and unanimously recognized characteristic of prostate cancer is its high sensitivity to androgen deprivation. In fact, among all hormone-sensitive cancers, prostate cancer is the one showing the best response to endocrine therapy. Accordingly, for more than 50 yr, the exclusive treatment of advanced metastatic disease has been androgen deprivation (1). The two most relevant questions concerning endocrine therapy are: 1) what is the best endocrine therapy; and 2) when should treatment start? It should be mentioned that the results of recent clinical trials indicate good reasons to believe that hormone therapy, in addition to remaining the first-line treatment of advanced disease, could well become part of any treatment of early stage disease; endocrine therapy would thus be the single therapy or part of therapy of any patient treated for prostate cancer.

What is the best endocrine therapy for prostate cancer?

What are the sources of androgens regulating prostatic growth? Before discussing the best therapy for prostate cancer, it is essential to summarize the most recent information on the sources and mechanisms of formation of androgens in the prostate. Until recently, it was believed that 95% of androgens were of testicular origin (2). This opinion was based on

the correct but misleading observation that plasma levels of testosterone are 95% reduced following orchiectomy (1) or treatment with an LHRH agonist (3). The physicians responsible for the treatment of prostate cancer were thus led to believe that a 95% decrease in serum testosterone was equivalent to the elimination of 95% of all androgens. With the information then available, it was logical but erroneous to conclude that a treatment having a 95% rate of success in correcting a biochemical parameter (serum testosterone) was acceptable, and it was even suggested and generally believed that castration was going as far as one could expect in the endocrine therapy of prostate cancer.

As will be clearly indicated in more detail later, measurement of serum testosterone alone is not a reliable indicator of the impact of androgens in an individual. Moreover, it should be mentioned that although castration leads to a positive response in 60–80% of patients with advanced prostate cancer, thus improving quality of life, it has never been proven to prolong life (4).

Relative role of testicular testosterone and adrenal dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEA-S). Although the presence of DHEA in the circulation in man was reported 35 years ago (5), the role of this steroid secreted in very large quantities by the human adrenals has so far remained largely unknown. In fact, DHEA-S, the sulfated form of DHEA, is the most abundant steroid in the circulation in man, its concentration ranging between 1000–5000 ng/mL in adult men, while plasma cortisol, the second most abundant steroid, has a 10–50 times lower concentration. The secretion of DHEA and DHEA-S by the adrenals increases at puberty to reach maximal levels at the age of 25 to 30 yr, before declining progressively thereafter.

Although castration (orchiectomy or treatment with a luteinizing hormone-releasing hormone [LHRH] superagonist) causes a 95% reduction in serum testosterone concentration, a much smaller effect is seen on the only meaningful indicator of androgenic action in the prostatic tissue, namely the intraprostatic concentration of dihydrotestosterone (DHT). In fact, after elimination of testicular androgens by medical or surgical castration, the intraprostatic concentration of DHT remains at about 40% of that measured in intact men (Fig. 1A). As another measure of the importance of adrenal androgens in adult men, the serum levels of the main metabolites of androgens [5α -androstane- 3α , 17β -diol (3α -diol), androsterone (ADT), and their glucuronidated derivatives] are reduced by only 50–70% following castration, thus reflecting the high level of adrenal precursor steroids converted into DHT in peripheral tissues (including the prostate) in castrated men (Fig. 1B). Contrary to the wrong belief that the testes are responsible for 95% of total androgen production in men, as suggested by simple measurement of circulating serum testosterone (2), it is now well demonstrated that the prostatic tissue efficiently transforms the inactive steroid precursors DHEA-S and DHEA, into the active androgen DHT. In fact, the prostate synthesizes its own androgens from adrenal precursors in quantities comparable to those of testicular origin.

It is important to recognize that although LHRH superagonists offer a more acceptable method of castration that is

free of the important side effects of high doses of estrogens, we cannot expect to improve the prognosis of prostate cancer beyond the results achieved with orchiectomy because the effects of LHRH superagonists are also limited to blockade of testicular androgens.

Which genes for steroidogenic enzymes are expressed in the human prostate? To stimulate prostatic growth, the adrenal steroid precursors DHEA-S and DHEA, must be taken up by the prostatic tissue and be locally metabolized into active androgens. As illustrated in Fig. 2, the formation of the active androgen DHT from DHEA involves three enzymatic activities: 3β -hydroxysteroid dehydrogenase/ Δ^5 - Δ^4 isomerase (3β -HSD), 17β -hydroxysteroid dehydrogenase (17β -HSD), and 5α -reductase. Alternatively, DHEA can be transformed into androst-5-ene- 3β , 17β -diol (Δ^5 -diol) by 17β -HSD, whereas 3β -HSD catalyzes the conversion of the latter into testosterone.

The structure of two 3β -HSD, three 17β -HSD and two 5α -reductase human genes has been elucidated (6). The expression of genes specific for each of these enzymatic activities has been demonstrated in the human prostate, thus providing the explanation for the high level of DHT formation from DHEA in this tissue (6). This new field of endocrinology has been called intracrinology (7). This area of great promise for future therapeutical developments relates to the formation of active steroids in peripheral (intracrine) tissues from inactive precursors, these steroids acting directly in the cells where their synthesis took place without being released in the extracellular compartment. These intracrine tissues, such as the human prostate, can thus control the synthesis and inactivation of androgens according to the local needs (7).

Combination therapy: simultaneous blockade of androgens of testicular and adrenal origin as first-line therapy. Based on the knowledge that both the testes and the adrenals contribute about equally to androgen formation in men, combination therapy was developed to block simultaneously testicular and adrenal androgens at start of therapy in advanced prostate cancer (8) (Fig. 2). The benefits of combination therapy first described in 1982 have been confirmed by all four large-scale, double-blind, and placebo-controlled randomized studies (9–12) (Table 1). In fact, these pivotal studies have confirmed and demonstrated the important advantages of combination therapy using a pure antiandrogen on all the objective and subjective parameters measured. Of particular importance is the observation that the simple addition of Flutamide added, on average, 7.3 (10) and 15.1 (11) months of life, while the use of an analog of Flutamide, namely, Anandron, added 5.4 (9) and 7.3 (12) months of life, respectively (Table 1). Studies that have not shown a benefit of combination therapy have had methodological problems, such as too small number of patients, inclusion of other than stage D₂ patients, and no double-blind or placebo control (13, 14).

In three of the combination therapy studies (8, 11, 12), the antiandrogen was added to the control arm at the time of progression, this addition leading to little or no significant benefit. Such results clearly demonstrate the need to use combination therapy at start of treatment instead of at the time of relapse, following failure of standard therapy.

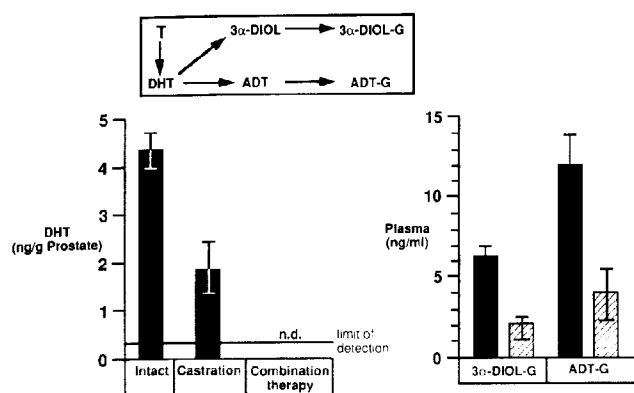


FIG. 1. *Left panel:* Effect of orchietomy and combination therapy (addition of Flutamide to orchietomy or treatment with a LHRH superagonist) on the concentration of dihydrotestosterone (DHT) in human prostatic cancer tissue. Note that orchietomy has only a partial inhibitory effect (approximately 60% reduction), whereas the addition of Flutamide decreases intraprostatic DHT to undetectable levels. The lower limit of sensitivity of DHT measurement is 0.2 ng DHT/g tissue. About 40% of DHT is left in the prostatic cancer after castration, thus illustrating the need to block such a high level of androgens of adrenal origin left free to stimulate growth of prostate cancer after castration. *Right panel:* Effect of castration on serum levels of the main metabolites of DHT, namely, androsterone (ADT) and androstane-3 α ,17 β -diol (3 α -diol) and their respective glucuronated derivatives. *Black boxes:* intact, *hatched boxes:* castrated.

The above indicated observations argue strongly against a two-step approach in the treatment of prostate cancer. It is clear that combination therapy should always be applied as first-line therapy, because the same treatment loses most or all of its efficacy when used as second-line at the time of relapse following monotherapy. This approach of maximal androgen blockade at start of therapy is supported by the well-known observation that patients relapsing after castration or treatment with estrogens, LHRH superagonists, or an antiandrogen alone have a poor or no response to adrenalectomy, hypophysectomy, or Flutamide. Moreover, as strong support for the harmful effect of exposure of prostate cancer cells to low androgen levels is the observation that low serum testosterone levels are associated with shorter survival following androgen deprivation (15). In fact, low pre-treatment serum testosterone levels before the start of endocrine therapy are associated with a poor prognosis, this variable being even more important than the extent of bone metastases (15). Such clinical data are well supported by the laboratory findings that low levels of androgens, comparable to those found after castration in men, induce the development of androgen-hypersensitive tumors that are resistant to antihormonal therapy (16). In agreement with numerous previous studies, EORTC Trial 30853 showed no difference between orchietomy and orchietomy associated with cyproterone acetate (17), thus demonstrating the absolute requirement to use a pure antiandrogen (Flutamide or one of its analogs) in combination therapy instead of a mixed agonist-antagonist of androgen action such as cyproterone acetate.

Such dramatic and negative effects of partial blockade of androgens, which leads to shorter survival (8 - 12), make un-

ethical the use of any therapy having lower androgen-blocking capacity than the combination therapy using a pure antiandrogen in association with surgical or medical castration. In fact, it was judged unacceptable by the participants at the 1993 Geneva meeting on prostate cancer to treat men suffering from prostate cancer with any treatment exerting a blockade of androgens inferior to that achieved by combination therapy (18).

When to start combination therapy?

An important observation made in all studies of stage D2 patients who received the combination therapy as initial or first-line

Combination therapy with a LHRH superagonist and a pure antiandrogen

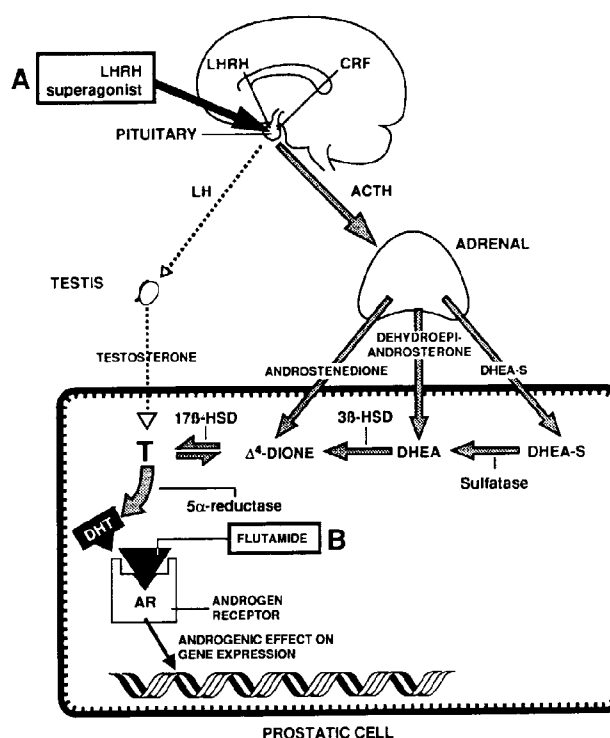


FIG. 2. Schematic representation of the effect of combination therapy with a LHRH superagonist and a pure antiandrogen (Flutamide) on prostate cancer growth and of the biosynthetic steps involved in the formation of the active androgen dihydrotestosterone (DHT) from testicular testosterone as well as from the adrenal precursors dehydroepiandrosterone (DHEA), DHEA-sulfate (DHEA-S), and androstenedione (Δ^4 -dione) in human prostatic tissue. 17 β -HSD = 17 β -hydroxysteroid dehydrogenase; 3 β -HSD = 3 β -hydroxysteroid dehydrogenase/ Δ^5 - Δ^4 -isomerase. The testis secretes testosterone (T) which is transformed into the more potent androgen dihydrotestosterone (DHT) by 5 α -reductase in the prostate. Instead of secreting T or DHT directly, the adrenal secretes very large amounts of DHEA and DHEA-S which are transported in the blood to the prostate and other peripheral tissues. These inactive precursors are then transformed locally into the active androgens T and DHT. The genes encoding DHEA sulfatase, 3 β -HSD, 17 β -HSD, and 5 α -reductase, are all expressed in the prostatic cells, thus providing 40% of total DHT in this tissue. The antiandrogen blocks the access of DHT to the androgen receptor, thus greatly reducing the influence of androgens on genetic expression and prostate cancer cell growth, while testicular testosterone secretion is completely blocked by the LHRH superagonist or surgical castration (orchietomy).

TABLE 1. Combination therapy with a pure antiandrogen and castration in double-blind, randomized, placebo-controlled and prospective studies of stage D₂ disease

Study	No. of patients	Best response	No response	Pain improvement	PSA or PAP normalization	Duration of response (months)	Death due to cancer (months)	Death from all causes (months)
Béland <i>et al.</i> (9)*	194	46% vs. 20% <i>P</i> < 0.01	20% vs. 38% <i>P</i> < 0.01	<i>P</i> < 0.05	<i>P</i> < 0.05	Positive trend		24.3 vs. 18.9 (5.4) <i>P</i> < 0.05
National Cancer Institute (10)†	602	<i>P</i> < 0.05		<i>P</i> < 0.05	<i>P</i> < 0.05	16.9 vs. 13.8 (3.1) <i>P</i> < 0.05		35.6 vs. 28.3 (7.3) <i>P</i> < 0.05
Janknegt <i>et al.</i> (12)*,‡	423	41% vs. 24% <i>P</i> < 0.001	22% vs. 36% <i>P</i> < 0.002	<i>P</i> < 0.05	<i>P</i> < 0.05	19.0 vs. 14.9 (4.1) <i>P</i> = 0.006	37.1 vs. 29.8 (7.3)	27.3 vs. 24.2 (4.1)
European Organization for Research and Treatment of Cancer (11)‡	327			<i>P</i> < 0.05	<i>P</i> < 0.05	30.7 vs. 19.6 (11.1) <i>P</i> = 0.008	43.9 vs. 29.9 (15.1) <i>P</i> = 0.007	34.4 vs. 27.1 (7.3) <i>P</i> = 0.02

* Nilutamide and orchiectomy vs. orchiectomy as control. † Flutamide and luteinizing hormone-releasing hormone (LHRH) agonist vs. LHRH agonist as control. ‡ Flutamide and LHRH agonist vs. orchiectomy as control. NS, not significant; PAP, prostatic acid phosphatase; PSA, prostate-specific antigen.

treatment is that prostate cancer is rapidly and extremely well-controlled at the level of the prostate. Moreover, when progression of the disease occurs after an initial response, reappearance of the cancer takes place in the bones in about 98% of cases, whereas progression at the level of the prostate is rare (2%). Such findings clearly indicate that combination therapy is most efficient in blocking cancer growth at the level of the prostate: in other words, the problem in achieving control of prostate cancer by androgen deprivation is with metastatic and not with localized disease. Such data strongly suggest that major efforts should be directed toward treatment of the disease still localized to the prostatic area.

In fact, it is well-recognized that the only opportunity for a curative therapy of prostate cancer is at an early stage when the disease is still localized. There have been important efforts devoted to the development of an efficient strategy for the diagnosis of prostate cancer at an early stage, when the disease is curable (19, 20). Despite the recognized potential of early treatment of prostate cancer, the acceptance of radical prostatectomy has been controversial, due mainly to the observation that prostate cancer presumed to be organ-confined at diagnosis is found to be at a more advanced stage at histopathological analysis of the surgical specimen in 50–60% of cases, while overstaging occurs in up to 30% of cases. The patients overstaged are thus denied the opportunity of a curative therapy while those understaged have a prostatectomy of no benefit, which simply adds side effects to their situation.

Neoadjuvant endocrine therapy before radical prostatectomy. Because it is known that patients having organ-confined prostate cancer and treated by radical prostatectomy have a life expectancy comparable to that of men having no prostate cancer (21, 22), the main objective in the prostate cancer field should be early diagnosis (23) and treatment of organ-confined disease. Unfortunately, not all men who are thought to have organ-confined prostate cancer at diagnosis are found to have organ-confined disease at surgery. In fact, as mentioned above, in 50–60% of cases, the pathological analysis of the specimen obtained at radical prostatectomy shows that the cancer is more advanced than originally predicted at diagnosis (24). Since the prognosis of stage C or D₁ prostate

cancer is poor, the risk that 50–60% of prostate cancers expected to be localized at diagnosis are found to be not curable at surgery can easily explain the lack of enthusiasm for radical prostatectomy and the controversies surrounding the diagnosis and treatment of early stage prostate cancer.

A possible means of improving the proportion of patients with organ-confined disease and cancer negative margins at surgery was clearly suggested by the observation that patients with metastatic disease who are treated by combination therapy using a pure antiandrogen associated with medical or surgical castration show a much more rapid and marked regression of their cancer in the prostatic area compared to distant metastatic disease (8). Moreover, it is well-recognized that, when recurrence of the disease occurs, progression of the cancer at the level of the prostate is a rare event, while instead, the bones are the usual site of progression. Since prostate cancer localized in the prostatic area is so highly sensitive to androgen deprivation, it appears logical to use combination therapy to downstage prostate cancer in men diagnosed as having localized disease before performing radical prostatectomy.

Following an encouraging preliminary study (25), we conducted a prospective and randomized clinical trial in order to precisely assess the potential advantages of neoadjuvant combination therapy with the pure antiandrogen Flutamide and an LHRH agonist administered for three months before radical prostatectomy compared with surgery alone (26).

In this study, after only three months of neoadjuvant combination therapy with Flutamide and an LHRH agonist, cancer-positive surgical margins decreased from 33.8% to only 7.8% while organ-confined disease increased from 45.1% to 73.3% (26). Although the long term effects of androgen deprivation achieved by neoadjuvant combination therapy on survival remain to be assessed by long-term follow-up of the patients, the present data show that prostate cancer cell death or apoptosis occurs at a relatively high rate in the prostatic area, under the influence of combination therapy: such cancer cell death leads to a relatively rapid downstaging of the disease.

The success of the present approach relies, to a large extent, on the availability of an efficient, low-cost, and widely ac-

ceptable strategy to detect early stage prostate cancer in the general population (23). It is reasonable to expect that patients with localized disease at final histopathological staging following radical prostatectomy should have a life expectancy not unlike that of men of similar age with no prostate cancer.

Neoadjuvant combination therapy with radiotherapy. The rationale for combination therapy before radiotherapy is to reduce the number of stem cells to be inactivated by radiation therapy and possibly to increase sensitivity to radiation. In the Radiation Therapy Oncology Group (RTOG) 8610 trial, where combination therapy with Flutamide and Zoladex was given for two months before and two months during radiotherapy *versus* radiotherapy alone, the clear advantages of combination therapy, with three years of follow-up, are indicated by disease-free survivals of 46% *versus* 26%, respectively ($P = 0.0001$). In fact, in the RTOG trial, the combined therapy of Flutamide + Goserelin has become the standard arm against which other modalities will be compared (27).

Can combination endocrine therapy be used alone in localized disease? What are the options for a man diagnosed as having localized prostate cancer with a tumor having a largest diameter over 0.75 cm. As mentioned and demonstrated above, early stage prostate cancer is exquisitely sensitive to androgen deprivation. Detection of prostate cancer at an early stage, before the cancer spreads to the bones, does not imply that all cancers should be treated or even less that all cancers should be treated by radical prostatectomy or radiation therapy. The age and health status are important factors. For a man younger than 70 yr, with a life expectancy of 10 yr or more, the choice is between radical prostatectomy and radiation therapy. In any case, the recent data strongly suggest that either procedure should be preceded by at least three months of combination therapy in order to increase the proportion of organ-confined disease.

For men aged 70 yr or more or those having a life expectancy of less than 10 yr, our recent data show that combination therapy alone can efficiently control the disease and should prevent death from prostate cancer. In addition to overall survival benefits, combination therapy alone in older men prevents the complications of local recurrence, including urinary tract obstruction and other signs and symptoms related to enlargement of the prostate, thus adding important benefits to the quality of life. It is unlikely that a patient having localized prostate cancer and treated by combination therapy will have progression of his disease during a 10-yr period. It seems reasonable, therefore, to administer combination therapy alone to these patients, thus avoiding the side-effects and risks of radical prostatectomy and radiotherapy. Studies are in progress to determine the efficacy of intermittent administration of combination therapy to these patients using serum PSA as indicator of prostate cancer control.

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