

Multiple intracrine hormonal targets in the prostate: opportunities and challenges

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INTRODUCTION

The finding that the human prostate synthesizes androgens in an amount approximately equivalent to that produced by the testes was a landmark in the field of prostate cancer that led to two key discoveries at Laval University in Québec City. Medical castration with LHRH agonists accompanied by the pure antiandrogen flutamide, bicalutamide or nilutamide (combined androgen blockade, CAB) is now used worldwide. In this combination therapy, LHRH agonists inhibit testicular androgen secretion and thereby suppress serum levels of testosterone. Simultaneously, antiandrogens locally block the interaction between the androgen receptor and the potent androgens made from the inactive precursors dehydroepiandrosterone (DHEA) and DHEA sulphate (DHEA-S) in the peripheral tissues, including the prostate. Treatment with LHRH agonists and antiandrogens together (i.e. CAB) was the first therapy shown to prolong life in patients with prostate cancer in prospective and randomized studies. These early studies focused on patients with advanced or metastatic disease, but our recent data indicate that the same CAB used to treat localized prostate cancer has a much higher efficacy, with a possibility of cure of $\geq 90\%$.

Compared with other cancer therapies, CAB produces remarkable results, although the benefits of this approach have been underestimated in the past. The authors of a recent meta-analysis of all clinical trial data in localized and locally advanced disease largely ascribed the success to follow-up hormone therapy, stating that 'Hormonal treatment as a whole works ridiculously well!' [1]. Considered together, the death rates from all cancers decreased by 1.1% per year from 1993 to 2001, but the death rate for prostate cancer decreased by 3.6% [2]. Improvements in surgery and radiotherapy are likely to have been involved, but a study by Lichtenberg [3], using National Cancer Institute data from 2.1

million patients with cancer in the USA between 1975 and 1995, concluded that 'cancer-fighting drugs improved survival rates, especially for cancer of the prostate, where drug innovations have been the greatest.'

The use of currently available approaches to the early diagnosis and treatment of prostate cancer can virtually eliminate death from this disease. With current techniques, screening can detect prostate cancer at a clinically localized stage in 99% of cases [4]. Radical prostatectomy, radiotherapy or brachytherapy can be instituted immediately, with curative intent, after such early diagnosis. There are data indicating that excellent results can be expected with CAB, particularly in older patients [5]. Most importantly, CAB must be used immediately in patients for whom radical prostatectomy, radiotherapy or brachytherapy fails. It is often erroneously thought that resistance will develop to androgen blockade in localized disease, and that this treatment should therefore be delayed until a later stage of the disease; this is incorrect. The use of CAB to treat localized prostate cancer does not lead to resistance to treatment. However, when treatment is deferred, the possibility of cure is very often lost because of metastasis of the cancer to the bone. In this situation, resistance to treatment cannot then be avoided. It should be appreciated that when prostate cancer is first detected, even by screening, the tumour diameter is $\approx \geq 1$ cm. Immediate treatment is the only treatment that offers a strong hope of cure. When radical prostatectomy, radiotherapy or brachytherapy fails, CAB must be started immediately. CAB can also be used alone as primary therapy with excellent results, as shown in important recent studies [5–9].

MEDICAL CASTRATION WITH LHRH AGONISTS

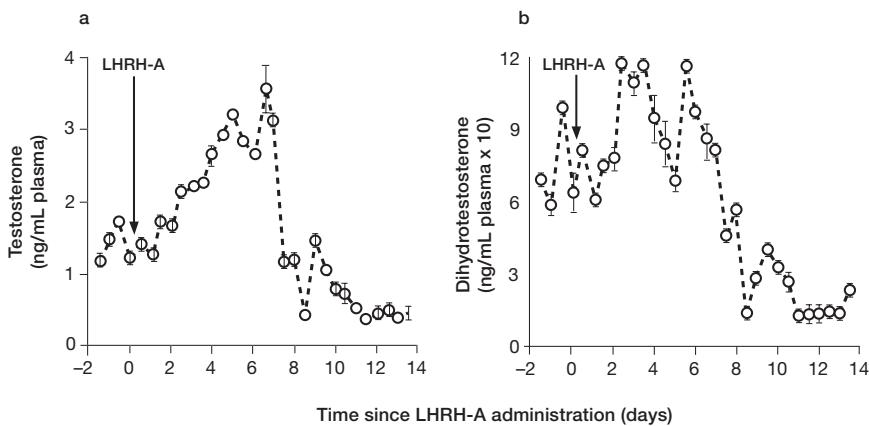
LHRH is a hypothalamic hormone that controls the secretion of LH and FSH by the

anterior pituitary gland. The elucidation of its structure was a major breakthrough [10,11] that offered the opportunity of designing and synthesizing peptides much more potent than LHRH itself. Within 4 years of the determination of its structure, super-agonists of LHRH with 100–200 times its *in vivo* biological activity were available.

When, three decades ago, we first treated experimental animals with an LHRH super-agonist, we expected to see an increase in the weight of the seminal vesicles and prostate. However, we observed the opposite effect; the prostate, seminal vesicles and testicles all became smaller after a few days of treatment. Although experiments with rats suggested that LHRH agonists could have some inhibitory effect on testicular function, we discovered in 1979 at the Laval University Medical Center that complete medical castration is easily achieved in men through chronic administration of LHRH agonists. When we first administered an LHRH agonist to a patient with stage B prostate cancer, there were 70% and 85% reductions in the serum levels of testosterone and dihydrotestosterone, respectively, as early as 2 weeks after starting therapy (Fig. 1) [12]. The LHRH agonist used was buserelin, at a dose of 500 μg , given intranasally. Shortly afterwards, when the effects of various doses of buserelin administered intranasally and s.c. were compared in detail, results showed that the s.c. route should be preferred [13].

Treatment of localized prostate cancer with an LHRH agonist adjuvant to radiotherapy or surgery results in a reduction of at least a third in cancer-related deaths. The reports that medical castration by LHRH agonists is well tolerated soon led to the worldwide acceptance of a well-tolerated hormone therapy for prostate cancer. This development was particularly important for patients with localized disease, who need long-term therapy, and for whom treatment must be easily tolerable. Because LHRH agonists are much more acceptable than orchidectomy or

FIG. 1. Effect of twice-daily intranasal administration of the LHRH agonist (LHRH-A) buserelin on serum levels of **a**, testosterone and **b**, dihydrotestosterone in a patient with stage B prostate cancer. Reproduced with permission from Labrie et al. [12].



and placebo (or no androgen blockade), but between early and late androgen blockade; therefore, the risk of dying from prostate cancer is reduced by more than a third if androgen blockade is started immediately after diagnosis. Results such as these were obtained with partial blockade of androgens or monotherapy alone. These data led Peto and Dalesio [21] to conclude that 'Hormone treatment as a whole works much better than previously thought.'

TWO EQUALLY IMPORTANT SOURCES OF ANDROGENS ARE PRESENT IN MEN

Humans and other primates are unique in having adrenal glands that secrete large amounts of the inactive precursor steroids DHEA and DHEA-S, which are converted into potent androgens in many peripheral tissues, including the prostate (Fig. 2). In adult men, the plasma concentration of DHEA-S secreted by the adrenals is 100–500 times higher than that of testosterone, the main secretory product of the testes [22,23]. There are therefore large circulating amounts of the precursors required for the production of active androgens in the prostate and other peripheral intracrine tissues. The amount of androgen produced in the prostate is comparable to that originating in the testes and transported to the prostate through the circulation.

CAB IN ADVANCED PROSTATE CANCER

As already noted, the combination of a pure antiandrogen (e.g. flutamide, nilutamide or bicalutamide) with an LHRH agonist was the first treatment shown to prolong life for patients with advanced prostate cancer [24–29]. The LHRH agonist blocks androgen secretion by the testes [23], whereas the antiandrogens (also known as nonsteroidal antiandrogens) interfere with the androgen receptor to prevent the prostatic androgens from working [22,24].

The addition of a pure antiandrogen (flutamide or nilutamide) to medical or surgical castration increases overall survival (death from all causes) by an average of 3–6 months [25–29]. This increase corresponds to 6–12 months of life gained, on average, given that about half of those patients will die from causes other than prostate cancer.

TABLE 1 Effect of the use of androgen blockade on prostate cancer death rates

Study	N patients	Advantage	Median follow-up, years	P
EORTC [14]	415	77% decrease in CSD	3.7	0.01
RTOG 85–31 [15]	276	37.5% decrease in CSD for Gleason score 8–10	4.5	0.03
Laval University [16]	21 400	67% decrease in CSD	8	<0.001
Messing et al. [17]	98	81% decrease in CSD	7.1	0.001
Granfors et al. [18]	91	39% decrease in CSD	9.3	0.06
RTOG 92–02 [19]	1 554	59% decrease in CSD for Gleason score 8–10	5	0.007
D'Amico et al. [20]	201	45% decrease in overall death	4.5	0.04

EORTC, European Organization for Research and Treatment of Cancer; RTOG, Radiation Therapy Oncology Group; CSD, cancer-specific death.

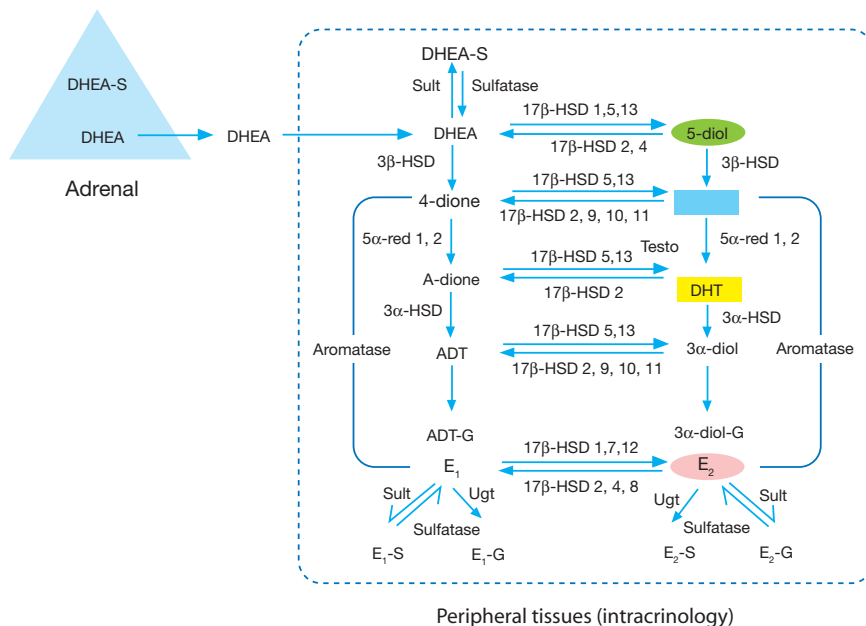
high doses of oestrogens to most patients who have no symptoms or signs of cancer, studies in localized prostate cancer were conducted only with LHRH agonists.

All clinical trials of androgen blockade have shown prolongation of life or a reduced death rate from prostate cancer in patients with localized or locally advanced prostate cancer (Table 1) [14–20]. During 3.7–9.3 years of follow-up, six of these studies showed reductions in deaths from prostate cancer of 37.5–81% [14–19]. A seventh study provided no data on cancer-specific deaths, but a 45% decrease in deaths overall was reported [20].

Following the recent meta-analysis of androgen blockade in localized prostate cancer, Peto and Dalesio [21] stated that

'Prostate cancer is usually treated with surgery or radiation, but a few cancer cells may remain and cause an often-fatal recurrence. Since the mid-80s, oncologists have increasingly followed up with either surgical removal of the testes, or with newer antihormone drugs. The meta-analysis, which assessed several studies involving ≈ 5000 men, showed that 74% of patients who received early hormone monotherapy were still alive 10 years later, compared with 62% of those who did not [1,21]. It was also concluded that the risk of dying from prostate cancer within 10 years decreased by a third if hormonal treatment was given immediately rather than after the disease had progressed [21]. This one-third decrease in the risk of dying from prostate cancer was the result of a comparison not between androgen blockade

FIG. 2. Human steroidogenic and steroid-inactivating enzymes in peripheral intracrine tissues. 3α -diol(-G), 3α -androstenediol (glucuronide); 4-dione, androstenedione; 5-diol, androstenediol; A-dione, androstenedione; ADT(-G), androsterone (glucuronide); DHT, dihydrotestosterone; E_1 , estrone; E_2 , 17β -estradiol; HSD, hydroxysteroid dehydrogenase; red, reductase; Sult, sulphotransferase; Testo, testosterone; Ugt, uridine diphosphate glucuronosyltransferase. Reproduced with permission from Labrie et al. [23]. Copyright 2005, The Endocrine Society.



In comparisons of CAB with monotherapy, CAB prolongs survival, achieves a more rapid and complete decrease in bone pain, and delays progression of the cancer, thereby improving the patients' quality of life. CAB is the only treatment that has been shown to prolong life in patients with advanced disease. In the USA, where 3 million of all men currently alive are expected to die from prostate cancer [2], 6 additional months of life per individual correspond to 1.5 million man-years overall, whereas 12 additional months correspond to 3 million man-years.

CAB IS HIGHLY LIKELY TO CURE LOCALIZED PROSTATE CANCER

LHRH agonist monotherapy in localized prostate cancer has produced important benefits in terms of survival in localized prostate cancer. However, given that half of androgens remain in the prostate after castration alone, it is logical to expect better results from the use of CAB or a combination of an LHRH agonist with a pure antiandrogen. Published data already indicate that the benefit is greater for patients with minimal metastatic disease than for those with

extensive metastatic disease [26,29]. Also, evidence indicates that CAB can achieve long-term control or cure of prostate cancer in at least 90% of patients with localized or locally advanced disease [5–9], provided that treatment is given continuously, uninterrupted, for ≥ 6 years [5]. A series of studies in Japan clearly illustrated the very high efficacy of CAB in localized disease [6–9].

CONCLUSION

The life-saving benefits of androgen blockade in men with prostate cancer have been largely underestimated. LHRH agonists have an important role in the management of prostate cancer because they avoid the psychological problems of surgical castration and the serious side-effects of high doses of oestrogens. However, a pure antiandrogen is required in addition to androgen deprivation to further increase the efficacy of androgen blockade and to obtain a high level of cure [5–9]. Findings from studies of the enzymes involved in the production of androgens in the human prostate (Fig. 2) suggest that 17β -hydroxysteroid dehydrogenase types 5 and 13

could be potential targets for the prevention and treatment of prostate cancer.

CONFLICTS OF INTERESTS

FL has received payment for speaking and has received funding for his work.

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Abbreviations: CAB, combined androgen blockade; DHEA(–S), dehydroepiandrosterone (–sulphate).