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Medical Castration With LHRH Agonists: 25 Years Later With Major Benefits Achieved on Survival in Prostate Cancer

Review

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Prostate cancer is the most frequently diagnosed cancer and the second cause of cancer death in men in North America (Jemal et al, 2003). In fact, one of eight men will be diagnosed with prostate cancer during his lifetime. At such a rate, prostate cancer will kill more than 3 000 000 men among the male population presently living in the United States, whereas more than 200 000 men die annually worldwide from prostate cancer. The medical and social consequences of this disease are comparable to those of breast cancer in women. Prostate cancer is thus a major challenge in urgent need of significant improvement in diagnosis and treatment.

Limitations of Surgical Castration and High Doses of Estrogens

Although it is known today that surgical castration and high-dose estrogen (monotherapy) discovered by Huggins (Huggins and Hodges, 1941) is limited to blockade of the androgens of testicular origin, a long series of reports has shown that such treatment achieves a positive response in as many as 60% to 70% of advanced prostate cancer patients, although for a limited period of time (Nesbit and Baum, 1950; Staubitz et al, 1954; VACURG, 1967; Mettlin et al, 1982; Murphy et al, 1983). As indicated by such a high proportion of positive responses observed after only partial blockade of androgens, prostate cancer is highly sensitive to endocrine therapy. In fact, prostate cancer is the most sensitive of all hormone-sensitive cancers to endocrine therapy.

The serious and frequently lethal cardiovascular and cerebrovascular complications of estrogens (VACURG, 1967; Robinson and Thomas, 1971; Peeling, 1989), on one hand, and the psychological (Lunglmayr et al, 1988; Cassileth et al, 1989) as well as physical limitations of surgical castration, on the other hand, have generally delayed endocrine treatment until late stages of the disease when pain and debility had developed. Typically, at such a late stage, the large and disseminated tumors show poor and short-lived responses, thus limiting the success of endocrine therapy. In fact, in analogy with all other types of cancers, androgen blockade loses its effectiveness with increasing size of the tumors (Chen et al, 1996).

Partial Inhibitory Effects of Luteinizing Hormone-Releasing Hormone Agonists on the Testicular Axis in Experimental Animals

Some 28 years ago, we were treating rats with a luteinizing hormone-releasing hormone (LHRH) agonist and we were expecting to observe seminal vesicles and a prostate of increased size. On the contrary, most unexpectedly, the opposite observation was made: The prostate, the seminal vesicles, and the testicles had become smaller instead of larger after a few days of treatment with an LHRH agonist (Figure 1) (Auclair et al, 1977a,b). Marked sensitivity differences exist between animal species to the inhibitory effects of LHRH agonists on testicular functions. Thus, male mice and monkeys (Wickings et al, 1981; Resko et al, 1982; Nieschlag et al, 1984; van Steenbrugge et al, 1984) are relatively insensitive to LHRH agonists, whereas rats are moderately sensitive.

First Prostate Cancer Patient Treated With an LHRH Agonist

The discovery that LHRH agonists could achieve medical castration or completely block the activity of the testicles was a completely unexpected scientific finding. In fact, although the experiments performed in the rat were suggestive of an inhibitory effect of LHRH agonists on testicular functions (Auclair et al, 1977a,b; Labrie et al, 1978), we discovered in 1979 (already 25 years ago) that testicular androgen secretion in men is exquisitely sensitive to the inhibitory action of LHRH agonists. As we learned later, humans are the most sensitive of all species to the castration effect of LHRH agonists, thus facilitating

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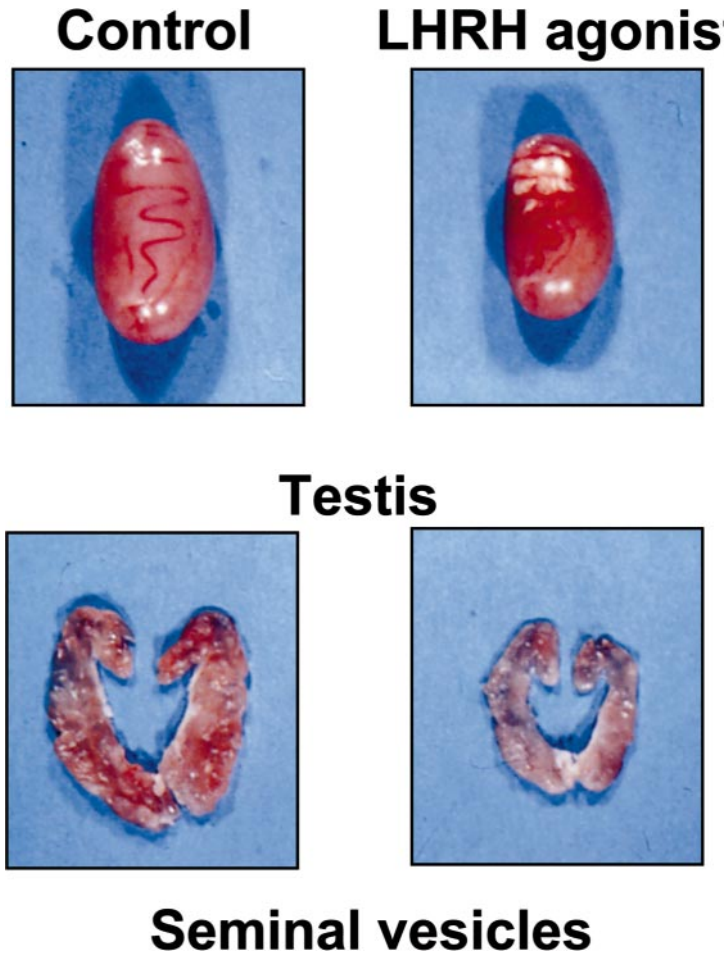

Figure 1. Effect of 2-week treatment of adult male rats with a luteinizing hormone-releasing hormone agonist.

the development of this uniquely efficient and well-tolerated method of castration that is now widely used worldwide and commercially distributed by at least 10 pharmaceutical industries.

This discovery was made by administering the LHRH agonist buserelin to a patient with stage B prostate cancer (Figure 2). Thus, in the first prostate cancer patient treated with an LHRH agonist, the 500-μg dose of the LHRH agonist administered intranasally caused 70% and 85% inhibitions of the serum levels of testosterone and dihydrotestosterone (DHT), respectively, as early as 2 weeks after the start of therapy (Figure 2) (Labrie et al, 1980). This marked inhibition of the serum concentration of both testosterone and DHT followed an initial period of stimulation that lasted approximately 1 week. Most importantly, it can be seen that the serum DHT concentration was decreased even further than that of serum testosterone, thus clearly indicating that treatment of adult men with an LHRH agonist was not accompanied, contrary to what occurs in the rat (Labrie et al, 1980), by a simultaneous increase in the concentration of DHT that would compensate for the inhibition of serum testosterone. Medical castration induced by an LHRH agonist had thus become a clear possibility in men. Further studies determined the optimal dose and route of administration of the LHRH agonist to achieve complete medical castration (Faure et al, 1982; Labrie et al, 1982; Tolis et al, 1982). Medical castration with an LHRH agonist is equivalent to orchiectomy for prostate cancer therapy (Prostate Cancer Triallists' Collaborative Group, 2000). In fact, in 11 trials where an LHRH agonist was used and in 17 trials where orchiectomy was used, no difference was seen on the response or survival rate (PCTCG, 2000).

The availability of a safe and highly efficient method of medical castration with LHRH agonists free of the side effects of estrogens and surgical castration has generated renewed interest in the treatment of prostate cancer and has stimulated an unprecedented number of clinical studies, which rapidly led to the worldwide commercialization of a series of LHRH agonists having equivalent characteristics, mechanisms of action, and efficacy (Figure 3). This marked the end of the requirement for surgical castration, a procedure that is psychologically difficult to accept by the majority of men. Most importantly, this was

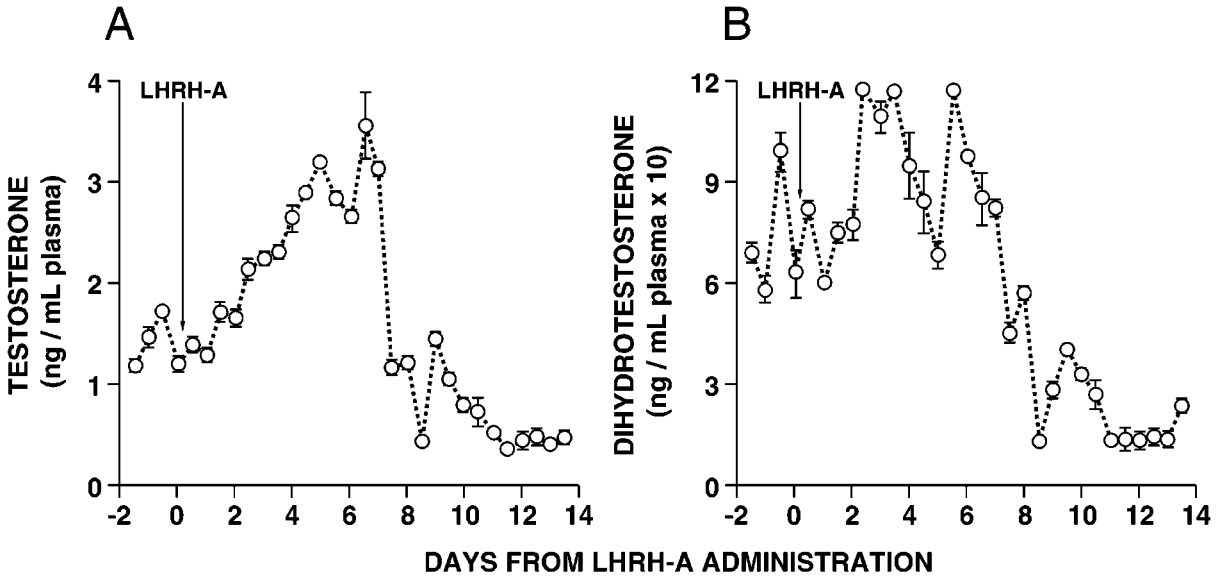

Figure 2. Effect of twice daily intranasal administration of the luteinizing hormone-releasing hormone agonist Buserelin on the serum levels of **(A)** testosterone and **(B)** dihydrotestosterone in a patient with stage B prostate cancer (Labrie et al, 1980).

the end of the need to administer high doses of estrogens to achieve medical castration at the expense of serious cardiovascular effects.

As can be seen in Figure 4, the number of publications on LHRH agonists has been increasing since 1971 to 524 per year in 1989. In 2001, LHRH agonists held nearly half of the market of hormonal cancer drugs with a minimal annual volume of sales of $2.2 billion (US). Such numbers clearly indicate the importance of the LHRH agonists in medicine. In fact, LHRH agonists are now used in 90% of men receiving hormonal therapy for prostate cancer. LHRH agonists have thus been used by millions of prostate cancer patients for more than 20 years with no adverse effect other than those associated with androgen deprivation (Labrie et al, 1996a).

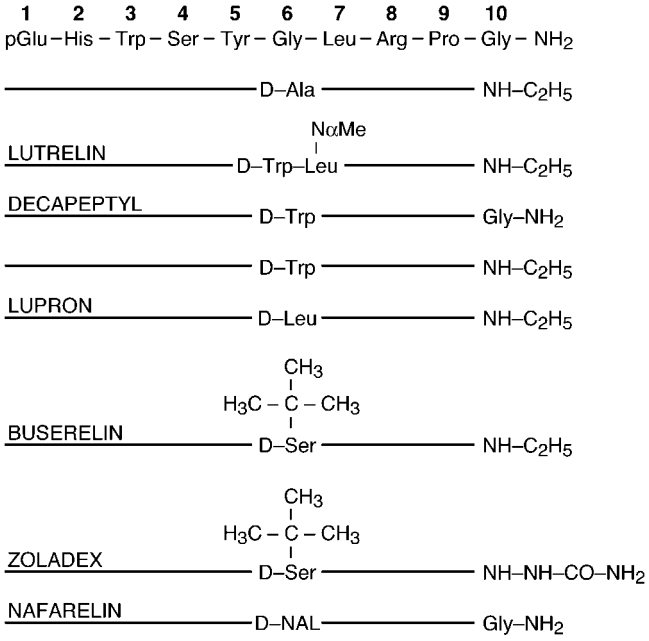

Figure 3. Structure of luteinizing hormone-releasing hormone (LHRH) and 8 of the best-known LHRH agonists.

Mechanisms of Medical Castration by LHRH Agonists

It was only in 1983 that it was discovered that the biological activity of LH was progressively lost during long-term treatment of prostate cancer patients with LHRH agonists (Kelly et al, 1983; St-Arnaud et al, 1986), thus explaining the castration effect of LHRH agonists in men. In fact, in the presence of a greater than 95% inhibition of serum testosterone and DHT levels, serum LH mea-

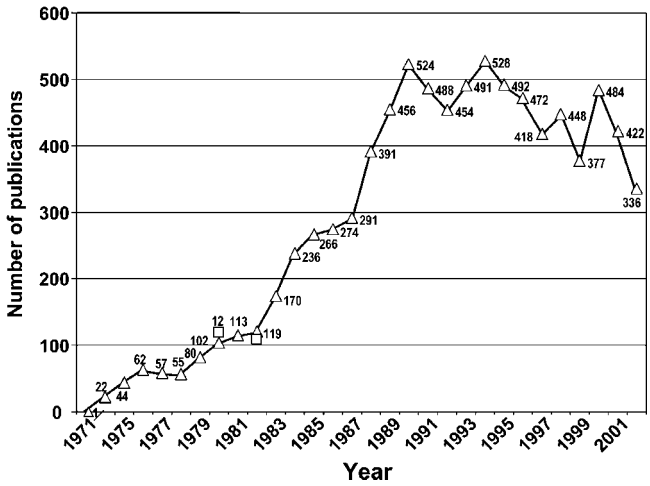

Figure 4. Number of publications on luteinizing hormone-releasing hormone agonists between 1971 and 2002.

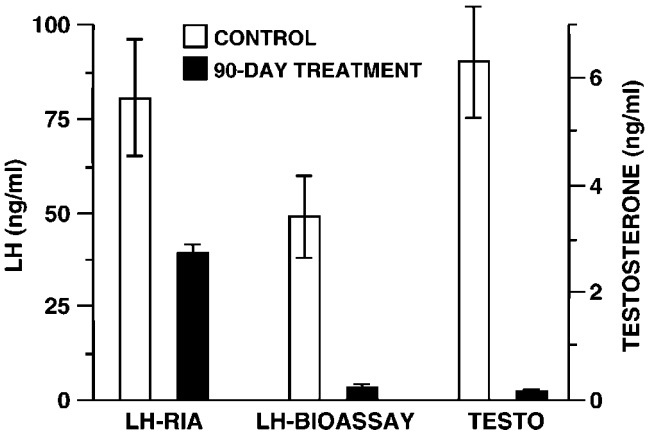

Figure 5. Effect of 1 month of treatment with the luteinizing hormone-releasing hormone (LHRH) agonist Buserelin (500 μg/d, s.c.) and the pure antiandrogen RU-23908 (Anandron; 100 mg, three times daily, p.o.) on serum LH measured by radioimmunoassay and by the mouse Leydig cell bioassay. Also shown is the effect on serum testosterone concentration in patients with advanced cancer of the prostate (Labrie et al, 1985b).

sured by radioimmunoassay (RIA) can remain normal or be only slightly decreased (Faure et al, 1982). Because we had previously found a discrepancy between serum LH measured by RIA and by bioassay in rhesus monkeys treated with a high dose of an LHRH agonist (Resko et al, 1982), we performed a similar study in men. We then observed that although the values of serum LH measured by RIA and bioassay (mouse Leydig cell assay) varied in a parallel manner during the first 2 weeks of treatment, a progressive and marked loss of bioactivity was measured at later time intervals. Thus, after 3 months of treatment, LH bioactivity was reduced to about 5% of control, whereas the radioimmunoassayable LH was reduced by only 40%–50% (Figure 5) (Kelly et al, 1983). These data indicate that the loss of LH bioactivity, rather than testicular desensitization, is the major factor responsible for the complete inhibition of testicular steroidogenesis that occurs after 2 to 3 weeks of treatment with LHRH agonists in men. In men, LHRH agonists thus achieve a medical hypophysectomy selective for gonadotrophs.

Monotherapy With an LHRH Agonist Decreases Cancer Deaths by at Least One-Third in Localized Prostate Cancer

As mentioned above, the exceptionally well-tolerated medical castration achieved with LHRH agonists (Labrie et al, 1980) has opened the way to a much more acceptable hormonal therapy of prostate cancer, especially for localized disease where well-tolerated therapies are particularly important for long-term administration. In fact, only LHRH agonists could permit studies in localized disease. Although equally efficient, orchiectomy is very difficult to accept in the absence of symptoms and signs of cancer.

The major source of controversy concerning early diagnosis and treatment of prostate cancer has been that, until recently, no prospective and randomized trial had shown statistically significant benefits on survival of treatment of localized prostate cancer (Kolata, 1987; Middleton et al, 1995). Such an absence of studies has been erroneously interpreted as being equivalent to the availability of negative data, whereas in fact, negative data have never been obtained concerning the effect of androgen blockade in localized prostate cancer.

Despite the recent advance in the treatment of metastatic prostate cancer using LHRH agonists or surgical castration in association with a pure antiandrogen (Labrie et al, 1982; Crawford et al, 1989; Dijkman et al, 1997; Denis et al, 1998; Bennett et al, 1999), it is well recognized that the only means of achieving an important reduction in prostate cancer mortality is treatment of localized disease (Labrie et al, 1997). In fact, it is reasonable to suggest that the recently observed decline in prostate cancer mortality is due to earlier diagnosis with serum prostate-specific antigen (PSA) and transrectal ultrasound (Lee et al, 1985), coupled with improved treatment of localized disease by surgery, radiotherapy, brachytherapy, and endocrine therapy (Labrie et al, 1994, 1997; Laverdiere et al, 1997).

Most importantly, 6 prospective randomized trials have recently demonstrated that an important prolongation of life is achieved in localized prostate cancer patients treated with androgen blockade (Table 1). In fact, when considering deaths from prostate cancer at 5 years of follow-up, decreases ranging from 37% to 81% were observed in the various studies. In the EORTC (European Organization for Research and Treatment of Cancer) trial performed in stage T_3 patients, overall survival at 5 years was increased from 62% in the group of patients who received radiation therapy alone to 79% (45% difference) in the group of patients who received androgen blockade using an LHRH agonist for 3 years and an antiandrogen for 1 month in association with radiotherapy (Bolla et al, 1997). Death from prostate cancer at 5 years was thus decreased by 77% by androgen blockade (Table 1). On the other hand, a 37% improvement in cancer-specific survival at 5 years had been found in RTOG trial 08351 in the subgroup of high Gleason score patients who received androgen blockade (LHRH agonist) indefinitely or until progression in association with radiotherapy vs radiotherapy alone (Pilepich et al, 1997). In another study, a 54% decrease in cancer-specific death was found in patients with an 8–10 Gleason score who had androgen blockade (Hanks et al, 2000), whereas Granfors et al (1998) found a 39% decrease in cancer-specific death when castration was added to radiotherapy vs radiotherapy alone.

Effect of adrogen blockade on prostate cancer death

Study	Benefits
EORTC (Bolla et al, 1997)	77% decrease in cancer-specific death ($P = 0.01$)
RTOG trial (Pilepich et al, 1997)	37% decrease for Gleason score 8–10 ($P = 0.03$)
Quebec Screening Trial (Labrie et al, 1999a)	64% decrease in cancer-specific death ($P = 0.0002$)
(Messing et al, 1999)	81% decrease ($P = 0.001$)
(Granfors et al, 1998)	39% decrease in cancer-specific death ($P = 0.06$)
(Hanks et al, 2000)	59% decrease for Gleason score 8–10 ($P = 0.007$)

It is thus not surprising that hormone therapy alone is more and more recognized as a highly efficient treatment in localized or locally advanced prostate cancer (Brawer et al, 2001). In fact, prostate cancer growing in the prostate or in the tissue surrounding the prostate is very different from cancer growing in the bones. Localized disease is much easier to treat by androgen blockade because it does not contain androgen-insensitive clones. Moreover, androgen insensitivity does not (or very rarely) develop in localized prostate cancer while the patients are under treatment with androgen blockade, contrary to the situation in metastatic disease where resistance to treatment almost always develops.

It is clear that the lifesaving benefits of androgen blockade in prostate cancer have been largely underestimated. In fact, the results obtained are quite remarkable and are similar or even better than the benefits observed for tamoxifen in breast cancer.

High Probability of Cure of Localized Prostate Cancer by Combined Androgen Blockade

The results obtained in a large series of clinical trials in patients with advanced prostate cancer have demonstrated that combined androgen blockade compared to castration alone has the following advantages: 1) more complete and partial responses, 2) improved control of metastatic pain, 3) longer disease-free survival, and 4) longer survival.

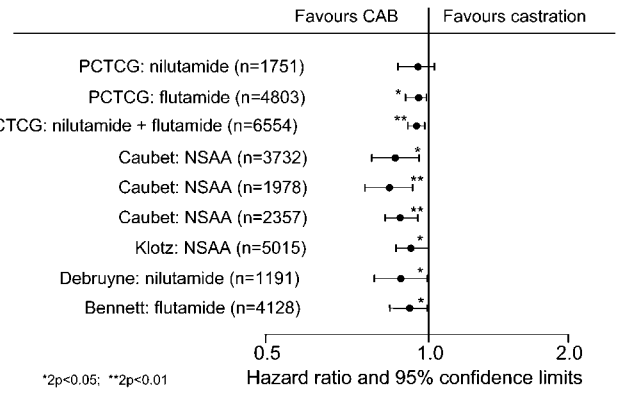

Figure 6. Summary of meta-analyses comparing combined androgen blockade (combination of medical or surgical castration associated with a pure antiandrogen [NSAA], namely Flutamide or Nilutamide) vs medical or surgical castration alone. Adapted from Klotz et al, 2001.

The results of all the meta-analyses of all the studies performed on the comparison of combined androgen blockade and castration show that the risk of dying in advanced disease is reduced by 10% to 20% (Figure 6). Further improvement of the hormonal therapy of metastatic disease is very difficult. By far the best possibility of improvement for the prostate cancer patient is treatment of localized disease. In fact, in analogy with the treatment of all other types of cancers, the beneficial effects are much greater when the same treatment is applied at an earlier stage of the disease.

With long-term treatment of localized prostate cancer by combined androgen blockade (CAB), the evidence recently obtained even indicates that long-term control or cure of the disease can be obtained in the majority of patients (Labrie et al, 2002). Although almost all studies performed so far in localized prostate cancer (Table 1) have used monotherapy (medical or surgical castration) (Bolla et al, 1997; Pilepich et al, 1997; Granfors et al, 1998; Messing et al, 1999; Hanks et al, 2000), there are good reasons to believe that even better results will be obtained with CAB (Labrie et al, 1985a; Caubet et al, 1997; Bennett et al, 1999; Labrie, 2000a,b; Prostate Cancer Triallists' Collaborative Group, 2000; Klotz, 2001, 2003; Aprikian et al, 2003). Since we already had obtained evidence for the high efficacy of long-term and continuous CAB in localized prostate cancer (Labrie et al, 1999b), it was felt important to examine the long-term outcome of these patients as assessed by biochemical failure or PSA rise after cessation of continuous CAB previously administered for periods up to 11.3 years.

The effect of CAB on long-term control or possible cure of prostate cancer was thus evaluated by the absence of biochemical failure or the absence of PSA rise for at least 5 years after cessation of continuous treatment. A total of 57 patients with localized or locally advanced disease received CAB for periods ranging from 1 to 11 years. With a minimum of 5 years of follow-up after cessation of long-term CAB, only two PSA rises occurred among 20 patients with stage T2-T3 cancer who stopped treatment after continuous CAB for more than 6.5 years, for a nonfailure rate of 90% (Figure 7). On the other hand, for the 11 patients who had received CAB for 3.5 to 6.5 years, the nonfailure rate was only 36% while the serum

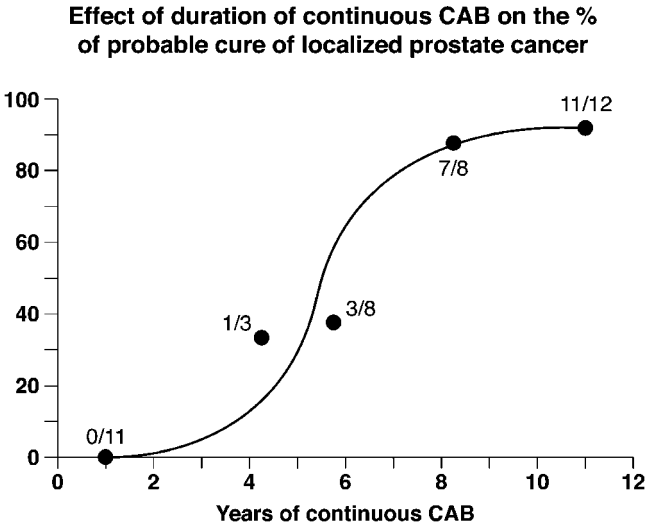

Figure 7. Effect of duration of treatment of localized prostate cancer with continuous combined androgen blockade (CAB) on the probability of long-term control or ''cure of the disease'' illustrated by no recurrence of prostate-specific antigen (PSA) rise for at least 5 years after cessation of CAB. The point at 4.75 years of treatment (33%) refers to the 3 patients treated with CAB for 3.5–5.0 years and followed for at least 5 years, whereas the point at 5.75 years refers to the 8 patients treated continuously with CAB for 5.0–6.5 years before cessation of treatment. The point at 8.25 years refers to the 8 patients treated continuously for 6.5–9.0 years, whereas the point at 11 years refers to the 13 patients treated for 10–11.7 years with continuous CAB before stopping treatment. All patients were followed for at least 5 years after cessation of continuous CAB or until PSA rise. Only 1 patient has died from prostate cancer, whereas 18 have died from other causes (Labrie et al, 2002).

PSA increased within 1 year in all 11 patients with stage B2/T2 treated with CAB for only 1 year, thus indicating that active cancer remained present after short-term androgen blockade despite undetectable PSA levels. Most importantly, in all patients who had biochemical failure after stopping CAB, serum PSA rapidly decreased again to undetectable levels when CAB was restarted; PSA remained at such low levels afterward. Of these patients, only 1 patient had died of prostate cancer at last follow-up (Labrie et al, 2002).

These are remarkable results obtained in patients with localized prostate cancer. Treatment, however, must be continuous, noninterrupted, and should last for many years. An important observation made is that in the patients where PSA increases for a second time after cessation of treatment, administration of CAB was successful in all cases in decreasing PSA to undetectable levels again, thus showing that even after a long duration of treatment, resistance to androgen blockade was not present.

The present results obtained in prostate cancer patients diagnosed with localized prostate cancer and treated continuously for many years with CAB are not too different from the results that we have recently obtained with human breast tumors in nude mice where complete estrogen blockade led to the disappearance or cure of the tumors in 61% of cases within a few months (Roy et al, 2003). In fact, in both breast and prostate cancer, when the estrogens in breast cancer and the androgens in prostate cancer are blocked optimally, cure of the disease can be achieved with hormonal therapy.

The treatment, however, takes a long time before complete apoptosis or total cell death is achieved. Breast and prostate cancers have many characteristics in common and much can be learned from looking at the results obtained in each of them. In fact, when we examine the biology of these two diseases, there are many common features, especially the high level of sensitivity to hormones. Such results clearly indicate that intermittent androgen blockade should remain experimental and should not be used outside clinical trials.

With the knowledge of the above-described data, it seems reasonable to suggest that the minimal duration of continuous CAB in localized prostate cancer should be 6 years, thus providing an approximately 50% probability of long-term or possible cure of the cancer. With longer duration of CAB, the probability increases to about 90% at 8–10 years of treatment. The present data indicate that possible cure of the disease can be obtained in the majority of patients with localized prostate cancer treated continuously with CAB for more than 6 years, thus raising hopes for the successful treatment of patients who fail after surgery, radiotherapy, or brachytherapy where no or minimally effective alternative therapeutic approach exists. Such data clearly indicate the interest of a large-scale randomized study comparing monotherapy vs CAB in the group of patients showing biochemical failure after first therapy with a curative intent. Care should be taken, however, to start treatment early after the rise of serum PSA in order to use androgen blockade at its maximal level of efficacy, namely when the cancer is still localized to the prostate or the prostatic area, before metastases reach the bones when cure becomes an exception.

It is important to indicate that androgen blockade is not only cytostatic, as was previously believed. Androgen blockade is also cytotoxic or tumoricidal. The very high efficacy of CAB with possible cure is observed in localized disease. At the metastatic stage, however, this is not true anymore since cure cannot be achieved in more than 10% to 15% of cases. In localized disease, androgen blockade is extremely efficient and cure can be achieved by apoptosis by simple combined blockade of the two sources of androgens.

It is important to indicate that resistance to androgen blockade does not occur or is extremely rare in localized disease. Resistance to androgen blockade is a phenomenon that accompanies metastatic disease in the bones where the environment is very different and where the growth factors present in large numbers are able to stim-

ulate cancer growth, even in the absence of androgens. This knowledge about the absence of development of resistance to androgen blockade in localized prostate cancer is extremely important. In fact, many physicians wrongly believe that early androgen blockade should not be administered because resistance will develop and one might as well wait to use androgen blockade at a later stage or keep it for later on. In fact, later on can easily be too late because when the cancer has migrated to the bones, resistance will occur automatically. In fact, when prostate cancer is first detected, even by screening, it is not a small cancer and its diameter is of the order of 1 cm or more. This is the most appropriate time to treat with the strong hope of a cure. The results presented today indicate that androgen blockade is probably the most efficient treatment of localized prostate cancer, whereas in metastatic disease, androgen blockade is the only efficient treatment available.

When prostate cancer is diagnosed, it is organ confined in about 40% to 50% of cases. The choice of therapy is then surgery, radiotherapy, brachytherapy, or CAB alone or in combination with surgery, radiotherapy, or brachytherapy. It is important to visualize that prostate cancer takes a long time to develop before it can be detectable by serum PSA, digital rectal examination, or transrectal ultrasonography of the prostate. However, there is a small window during which the cancer can be detected at a stage when it is still curable by the available approaches. It does not take very long, usually, 2, 3, 4, or at most 5 years before the cancer migrates to the bones and then becomes noncurable. If the window of curability of prostate cancer is missed, one faces major problems and the cancer becomes practically impossible to cure. At the advanced stage, the best that can be done is to prolong life.

Conclusion: Death From Prostate Cancer Can Now Be Rare

While showing the particularly high efficacy of hormonal therapy in localized prostate cancer, the present data clearly indicate that long-term treatment with the best available drugs, somewhat similar to the 5 years of tamoxifen in breast cancer, is required for optimal control of prostate cancer. Great caution should be taken, however, when using serum PSA as surrogate marker. In fact, serum PSA rapidly and easily decreases to undetectable levels under androgen blockade although the cancer remains present for much longer periods of time, usually for many years as demonstrated in our recent study (Labrie et al, 2002). For this reason, intermittent therapy should not be recommended outside prospective and randomized clinical trials.

With the present knowledge, it is clear that all available means should be taken to diagnose prostate cancer early and to use efficient therapy immediately to prevent prostate cancer from migrating to the bones where treatment becomes extremely difficult and cure or even long-term control of the disease is an exception. The only means of preventing prostate cancer from migrating to the bones and thus becoming incurable is the application of an efficient treatment at the localized stage of the disease. In fact, since radical prostatectomy, radiotherapy, and brachytherapy (implantation of radioactive seeds in the prostate) can achieve cure in about 50% of cases, these approaches are all equally valid choices as first treatment of localized prostate cancer. Androgen blockade should also be considered as first-line treatment. The most important, however, is to follow closely serum PSA after surgery, radiotherapy, and brachytherapy and to start CAB as soon as signs of recurrence of the cancer appear. It is also clear from the data summarized above that CAB alone could well be the most efficient therapy of localized prostate cancer; it has already been recognized as the best therapy for metastatic disease (Figure 8).

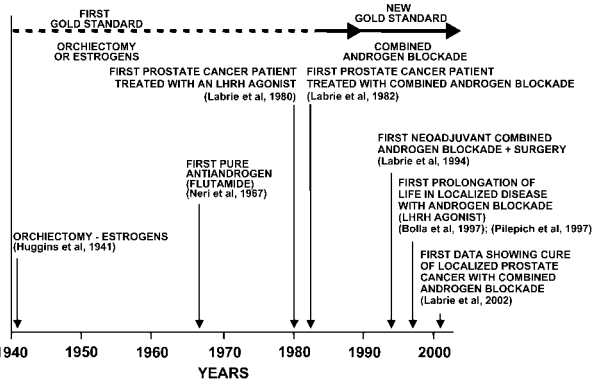

Figure 8. Landmarks in the development of the hormonal therapy of prostate cancer.

Clearly, the rational use of the presently available diagnostic and therapeutic approaches could decrease prostate cancer death by at least 50% (Labrie et al, 1996b, 1999a). As an example, between 1991 and 1999, the death rate from prostate cancer has decreased by 38% in Québec City and its metropolitan area (Candas and Labrie, 2000), whereas the death rate has decreased by 64% in the group of men who have been screened (Table 1).

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