

Development of GnRH Antagonists for Prostate Cancer: New Approaches to Treatment

TERRY COOK, WILLIAM P. SHERIDAN

Amgen Inc., Thousand Oaks, California, USA

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ABSTRACT

Prostate cancer has become the most common cancer among American men and is second only to lung cancer as a cause of male cancer-related death.

Several treatment options exist for different stages of prostate cancer including observation, prostatectomy, radiation therapy, chemotherapy, and hormone therapy. Hormone therapy has evolved from the use of estrogens to gonadotropin-releasing hormone (GnRH) agonists and recently, investigational GnRH antagonists.

GnRH receptor agonists such as leuprolide, bruserelin and goserelin have been used for the treatment of prostate cancer. These agonists eventually cause the inhibition of lutenizing hormone production, which in turn causes a suppression of testosterone and dihydrotestosterone, on which continued growth of prostate cancer cells depend.

Several comparative studies of leuporelin administered as daily injections or monthly depot injections have been reported. Disease progression was prevented in more than 72% of men administered daily leuporelin, and in 82% to 89% of those receiving monthly depots. Another synthetic GnRH analog, goserelin, has been studied in a similar population of men with daily injections producing partial responses in 60% to 80% of men with previously untreated prostate cancer. Abarelix, a peptide antagonist of GnRH receptor, is also being studied for the treatment of prostate cancer.

The discovery and development of GnRH antagonists may provide an important advance for patients with prostate cancer. Clearly the studies described herein, as well as many others, outline an exciting era of research to define the optimal use of hormonal therapy in prostate cancer. *The Oncologist* 2000;5:162-168

INTRODUCTION

Prostate cancer has become the most common cancer among American men and is second only to lung cancer as a cause of male cancer-related deaths [1, 2]. The age-specific mortality rate has increased slowly over the past 50 years [3]. Prostate cancer is responsible for almost 3% of deaths in men older than 55 years [1]. Because the incidence of prostate cancer increases more rapidly with age than the incidence of any other cancer, and because the average age of American men is increasing, the number of patients with prostate cancer is expected to increase steadily

over the next decade [2]. The annual rate of increase worldwide has been estimated at 2% to 3%. In addition, if the prevalence of prostate cancer includes those patients alive at five years after diagnosis, this would result in over one million patients alive and requiring medical care—not an insignificant burden [4].

Currently the American Cancer Society estimates an incidence rate of 185,000 with approximately 40,000 deaths per year from prostate cancer. Prostate cancer is becoming a major public health concern, due to a convergence of factors such as an increased life expectancy leading to more cases of

Correspondence: William P. Sheridan, M.D., Amgen Inc., One Amgen Center Drive, Thousand Oaks, California 91320-1799, USA. Telephone: 805-447-3844; Fax: 805-498-1425; e-mail: sheridan@amgen.com Received July 23, 1999; accepted for publication February 8, 2000. ©AlphaMed Press 1083-7159/2000/\$5.00/0

prostate cancer being diagnosed, the absence of any marked improvement in treatment, and prevention by lifestyle changes only beginning to be discussed. An increase worldwide in mortality from prostate cancer has resulted, and drives a demand for better understanding of the molecular biology of the disease as a means to generate improved treatments for cancer of the prostate.

Several treatment options exist for different stages of prostate cancer including observation, prostatectomy, radiation therapy, chemotherapy, and hormonal therapy. Hormonal therapy for the treatment of more advanced disease has evolved from the use of estrogens [5] to gonadotropin-releasing hormone (GnRH) agonists and recently, investigational GnRH antagonists.

PHYSIOLOGICAL ROLE OF ANDROGENS

GnRH (also known as luteinizing hormone-releasing hormone or LHRH) is produced in the hypothalamic area of the brain under the influence of norepinephrine, dopamine, histamine, and other neurotransmitters (Fig. 1). GnRH is produced in a pulsatile fashion, with the pulses occurring at 60 to 90 minutes [6]. GnRH enters the hypothalamic-hypophyseal portal blood system, travels to the anterior pituitary gland, and

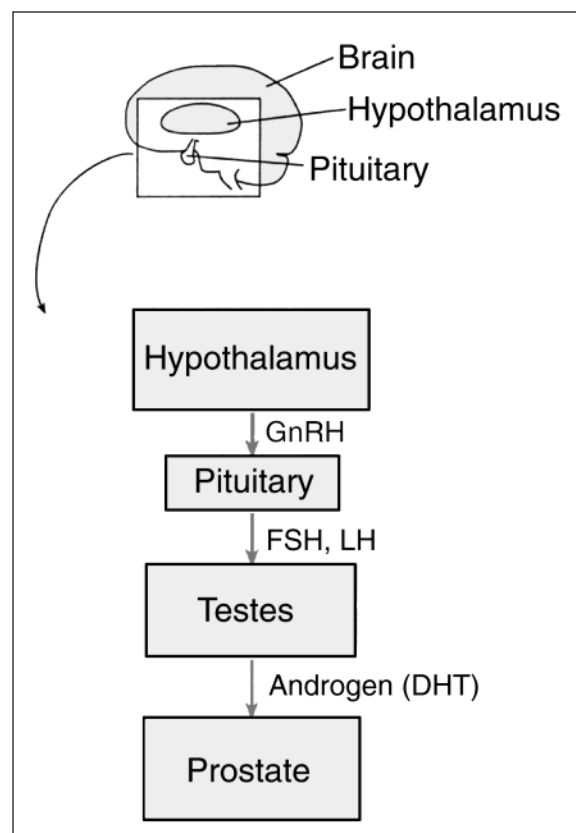


Figure 1. Interactions of hypothalamus, pituitary, and testes, and the production of the androgen, testosterone.

binds to specific plasma membrane receptors on pituitary gonadotroph cells. This binding stimulates the gonadotrophs to secrete gonadotrophins, LH, and follicle-stimulating hormone (FSH). The same GnRH stimulates release of both LH and FSH. Once LH enters the general circulation, it can then act on the gonads to stimulate production of androgens (including testosterone and dihydrotestosterone [DHT]) in men and estrogens in women. Androgens, of course, are necessary for male sexual maturation, and maintenance and function of the prostate gland. Prostate gland development is initiated by androgens produced by the fetal testes and is completed at the end of puberty. However, growth of the prostate is unique in that it continues throughout life with the size of a prostate gland in men 65 years or older on average two to three times larger than that of a 20-year-old man [7]. Thus androgens can favor the development of carcinogenesis simply by promoting repeated rounds of cell division. Tissue growth, both normal and malignant, depends on an intricate balance between the rate of cell proliferation and programmed cell death, or apoptosis. Although androgens are important mitogenic factors within the prostate, necessary for cell proliferation, there is a growing body of evidence suggesting that they do not directly stimulate epithelial cell proliferation in culture. Epithelial cells also respond to a range of polypeptide growth factors. Of these, three growth factor families have been studied extensively including epidermal growth factor, transforming growth factor- β and heparin-binding (fibroblast) growth factor family [8]. Secreted hormones, e.g., androgens, are transported to the prostate. These extrinsic factors then regulate the growth regulatory factors (intrinsic) produced by the prostate cells. The polypeptide growth regulatory factors act through paracrine effects on adjacent, different cell types, by an autocrine action on the same type of cell from which the growth factor is produced, or by an intracellular intracrine effect within the cell of origin [9]. A large body of animal data provides definitive support for a role of androgens in the development of prostate cancer. Chronic treatment of rats with testosterone produces a high incidence of carcinomas after administration of carcinogens; however, short-term exposure to chemical carcinogens alone produces an incidence of 5% to 15% [10]. Direct and indirect clinical evidence also suggests a role for androgens in the genesis of human prostate cancer. Prostate cancer is rare in androgen-deprived men (eunuchs). In addition, nearly 50 years ago surgical or medical castration was shown to cause tumor regression [5].

DEVELOPMENT OF CANCER

Although the carcinogenic process is not completely understood for any human malignancy, the current belief is that development of a fully malignant cancer from a normal cell requires multiple transformation events. These transformation events generally involve two general classes of

cellular genes: oncogenes and tumor-suppressor genes. Oncogenes function to enhance the net accumulation of cells whereas tumor-suppressor genes operate to inhibit the tumorigenicity of cells. Homeostasis within the complex intracellular milieu of the prostate gland is maintained by a balance between the actions of growth stimulatory factors and growth-restraining factors; androgens promote the former, but exhibit an antagonistic effect on apoptosis [7]. Thus, prostate cancer develops in the setting of decades-long interaction of prostatic epithelial cells with circulating androgens. In addition, the smooth muscle of the male genital tract depends on androgens for differentiation and maintenance of its phenotype in adulthood [11]. *Hayward et al.* proposed that reciprocal smooth muscle:epithelial cell interactions regulate both normal and malignant prostatic epithelial proliferation. At some point the epithelium suffers genetic damage and the epithelial cells begin to drift from the normal phenotype, creating an abnormal signal between epithelial cells and smooth muscle. This abnormal signaling may actively promote the carcinogenic process or allow the progression to anaplasia through the loss of normal homeostatic growth-inhibitory regulation. Although the exact role of androgens in this complex process remains an enigma, the fact that tumors regress as a result of androgen ablation suggests that androgens play a significant part in the development of prostate cancer.

AGONISTS

Agonist drugs have an affinity for and stimulate physiologic activity at cellular receptors normally stimulated by endogenous ligands. Literally thousands of GnRH derivatives have been synthesized in an effort to develop potent therapeutic compounds [6]. GnRH agonists are similar in structure and function to natural GnRH, but are as much as 60 times more potent than the natural hormone [12].

GnRH receptor agonists such as leuprolide, bruserelin, and goserelin (with or without an antiandrogen) have been used for the treatment of prostate cancer [2, 13]. These agonists eventually cause the inhibition of LH production, which in turn causes a suppression of testosterone and DHT, on which continued growth of prostate cancer cells depends. Initially, however, GnRH agonists stimulate LH production, which in turn causes a surge of testosterone and DHT for 5 to 12 days before inhibition of LH [2]. This androgen surge of male hormones can cause a flare reaction ("clinical flare") [2, 14, 15]. Clinical flare is often painful and always dangerous. Flare can precipitate such clinical symptoms as bone pain, compression of a nerve root, spinal cord compression, or blockage of one or both ureters. Spinal cord compression can often lead to paralysis and, if the lymph nodes near the ureters are involved, flare can increase the size of the nodes and cause

compression of one or both ureters. Ureteral compression involving both sides results in kidney failure or uremia. Thus, clinical flare often leads to medical emergencies. The extent of the effect of the testosterone surge observed after initiation of an LHRH agonist on prostate cancer cell proliferation has not been fully examined, however, the adverse clinical sequelae observed warrant significant caution in the use of agonists in many patients [16].

Antiandrogens, such as flutamide or cyproterone acetate, are often used in an attempt to limit the clinical sequelae produced by this hormonal surge [17]. However, antiandrogens are associated with undesirable side effects of diarrhea, liver function abnormalities (including rare instances of fatal hepatotoxicity), pulmonary fibrosis, or visual disturbances, and do not alter the biochemical surge in LH testosterone, or DHT [18]. GnRH receptor agonists are contraindicated in patients at risk of significant complications from bone metastases or ureteric obstruction.

ANTAGONISTS

Antagonist drugs tend to nullify the action of endogenous mediators by binding to a cellular receptor without eliciting a response. Pure antagonists are devoid of any agonist activity. The synthesis of GnRH receptor antagonists posed greater problems than those associated with the synthesis of GnRH agonists [6]. Problems including insufficient potency and lack of solubility were encountered with many of these compounds and others failed in early development due to unacceptable histamine-release properties. Incorporation of sufficient quantities of antagonist peptide into candidate-sustained duration formulations was also a challenge [6].

GnRH receptor antagonists would be expected to be devoid of the initial androgen-stimulation characteristics of GnRH agonists [19]. Abarelix is the first GnRH receptor antagonist in a sustained-duration formulation to progress through clinical studies [19]. This antagonist blocks GnRH and inhibits LH production, which in turn causes a suppression of testosterone and DHT. Unlike GnRH agonists, however, GnRH antagonists, including abarelix, do not cause an initial stimulation of LH production, testosterone, or DHT [2]. This lack of testosterone surge prevents a temporary worsening of the cancer.

CLINICAL EXPERIENCE

Agonists

Several noncomparative studies of leuprolide (leuprolide acetate) administered as a daily injection or monthly depot injection have been reported [20-31]. Patients enrolled in these clinical trials had previously untreated histologically confirmed metastatic or locally advanced disease.

Disease progression was prevented in >72% of men administered daily leuporelin 1, 10, or 20 mg/kg s.c., and in 82% to 89% of men receiving s.c. or i.m. depots of 3.75, 7.5, or 15 mg every 28 days. Approximately 88% of patients achieved disease stabilization, although complete responses were rare. No significant differences between the responses to 1 or 10 mg/day were noted [20, 23] or to 3.75 or 7.5 mg depot each month [27, 29, 30]. The median response duration was between 10 and 18 months, and the median survival was about two years. Leuporelin alleviated bone pain in 64.5% of affected patients and relieved urinary symptoms of 80% of patients.

Men who received leuporelin after previous hormonal manipulation showed only minimal evidence of response with 5% having partial response, 43% having disease stabilization, and 52% having disease progression [20].

A large, randomized, double-blind clinical trial demonstrated no significant difference in response rates of previously untreated patients with metastatic disease receiving daily leuporelin with or without flutamide [32]. However, progression-free and overall survival were slightly, but significantly greater in patients receiving the antiandrogen (52 months and 52 months compared with 19 months and 40 months, respectively, in the combination and leuporelin alone groups, respectively).

Another synthetic GnRH analog, goserelin, has been studied in a similar population of men. Daily s.c. injections of goserelin 250 µg produced partial responses in 60% to 80% of men with previously untreated prostate cancer [33-36]. The median duration of response in 10 patients was 25 months [37].

A sustained-release formulation was developed and adopted for use at 3.6 mg every four weeks. Complete or partial responses were achieved after three months in 64% of patients receiving 0.9 mg depot monthly, 48% receiving 1.8 mg, and 68% receiving 3.6 mg; disease stabilized in 23%, 35%, and 20% of patients, respectively [38, 39]. Bone pain was alleviated in 69% of patients (all doses combined).

Antagonists

Abarelix, a peptide antagonist of GnRH receptor, is being studied for the treatment of prostate cancer. Results from one study indicate that prostate gland volume significantly decreased (median, 35%) over the course of treatment with abarelix 1 mg [19]. Serum concentrations of testosterone and prostate-specific antibody (PSA) were decreased: testosterone to chemically castrate values (<50 ng/dl) by day 15 for 34 of 36 patients, and PSA to <4.0 ng/ml for 29 of 36 patients. When abarelix treatment was discontinued, PSA concentrations remained low, but testosterone concentrations recovered to greater than castrate values within four to five weeks for most patients.

Results from a phase II study have been reported in abstract form [40, 41]. This study compared the abarelix depot formulation with the depot formulations of two agonists, with or without concomitant antiandrogen use. In the first study, 209 patients were treated with abarelix depot 100 mg on days 1 and 15, and then at 50 to 100 mg every four weeks. A concurrent control group of 33 patients was treated with leuporelin or goserelin with or without an antiandrogen (bicalutamide) orally on a daily basis. Data for the first 12 weeks were reported [40]. Abarelix induced rapid chemical castration (day 8) in 76% of patients compared with 0% of the leuporelin- or goserelin-treated patients. Testosterone surge occurred in all leuporelin- or goserelin-treated patients but in none of the abarelix-treated patients.

FUTURE DIRECTIONS

The use of hormonal therapy in the form of agonists was a significant advance for patients with prostate cancer, as it meant that estrogens or orchiectomy were no longer the only therapeutic options. The discovery and development of GnRH antagonists may provide another advance for patients with prostate cancer. GnRH receptor antagonists are devoid of the initial androgen-stimulation characteristics of GnRH agonists. The use of GnRH antagonist may avoid the need for antiandrogens that have their own side effects.

Despite being considered the standard of care for treatment of advanced prostate cancer, the optimal form of hormonal treatment remains to be elucidated. Of critical concern are the timing, duration, and long-term side effects of androgen-deprivation therapy. A survey of clinical trials looking at total androgen blockade (TAB) over the past decade outlines the current controversy (Table 1). Although several trials have demonstrated a significant survival benefit, others have failed to find a difference. However, many outstanding questions surround these studies, not the least of which is which group of patients stands to benefit from hormonal treatment, as well as when to initiate hormonal treatment and for how long. In addition, several meta-analyses of studies using TAB have also been unable to resolve this issue of long-term benefit. Hormonal therapy is considered palliative treatment for prostate cancer, however long-term disease-free survival in some patients exceeds 10 years and many of these may even be "cured" [32].

Several recent studies have reported improved local control and survival after radiotherapy in combination with hormonal therapy [42, 43]. However, as with TAB, the timing and duration of hormonal treatment in combination with radiation therapy remain to be determined. An article from the Medical Research Council [44] supports the use of early treatment. A large randomized study reported significant overall survival in those patients treated immediately [44]. A population-based registry study in Denmark indicates that localized prostate

Table 1. Survey of clinical trials examining the use of total androgen blockade

Ref. n	Treatment	n of Patients	PFS (mo)	OS (mo)	Comments
32	Lu + Flu versus Lu + Pbo	603	13.9 versus 16.5	28.3 versus 35.6	TAB arm significantly improved PFS & OS
48	Orch versus Gos + Flu	327	19.6 versus 30.7	27.1 versus 34.4	TAB arm significantly improved PFS & OS
49	Gos versus Gos + Flu	304	17 versus 24	No difference	No difference in PFS or OS
50	Gos versus Gos + Flu	571	No difference	37.7 versus 42.2	No difference in PFS or OS
51	Orch versus Gos + Flu	262	16.8 versus 16.5	27.6 versus 22.7	No difference in PFS or OS
52	Orch + Pbo versus Orch + Flu	1,371	18.6 versus 20.4	29.9 versus 33.5	No difference in PFS or OS
53	Orch + Pbo versus Orch + Nilut	457	21.2 versus 14.7	37 versus 29.8	TAB arm significantly improved PFS & OS

Lu = lupron; Flu = flutamide; Pbo = placebo; gos = goserlin; Orch = orchiectomy; Nilut = nilutamide; TAB = total androgen blockade; PFS = progression-free survival; OS = overall survival.

cancer is not a harmless disease once diagnosed and emphasizes that cure may indeed be necessary in those for whom cure is likely to be possible [45]. Patients 55 to 74 years old with clinically localized prostate cancer exhibited greater mortality and increased percentage of prostate cancer-related deaths when treated with deferred hormonal therapy. A small study reported the outcome of deferred treatment in patients with locally advanced, nonmetastatic disease [46]. In terms of survival, delayed treatment appears to be a viable option only in cases with nonpoorly differentiated tumors extending beyond the prostate capsule, no metastases and a life span greater than 10 years. Most recently, *Messing et al.* [47] report a significant survival benefit of immediate androgen-ablation after radical prostatectomy. The cancer-specific survival rate

in men in the immediate-therapy group was 77% compared with only 43% in the observation group. Although these findings are encouraging, larger prospective randomized trials need to be conducted to confirm and elaborate the results.

Clearly the studies described above, as well as many others, outline an exciting era of research to define the optimal use of hormonal therapy in prostate cancer. Additional studies to determine the time of hormonal therapy initiation, the optimal duration as well as patients most likely to benefit from these regimens are urgently needed.

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