LUTEINIZING HORMONE–RELEASING HORMONE AGONISTS IN THE TREATMENT OF MEN WITH PROSTATE CANCER: TIMING, ALTERNATIVES, AND THE 1-YEAR IMPLANT

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ABSTRACT
This article reviews the evidence underlying hormone treatment decisions for men with advanced prostate cancer. Luteinizing hormone–releasing hormone (LHRH) analogs are the mainstays of therapy, but 3 areas of LHRH use need clarification: (1) when to start therapy, (2) what alternatives are available, and (3) how to incorporate a long-term strategy for the individual patient. The Medical Research Council (MRC) study, a randomized clinical trial in 938 patients, shows that immediate hormone therapy in men presenting with advanced prostate cancer (stage ≥T3) imparts a survival advantage over a delayed-treatment approach (7.5 years vs 5.8 years, P = 0.0003). LHRH analogs are also widely used (1) along with definitive radiation therapy, (2) when positive lymph nodes are found after radical prostatectomy, and (3) when prostate-specific antigen increases after any primary treatment (biochemical failure). In these situations, timing of therapy is somewhat controversial. Several new developments in hormone therapy are noteworthy, including high-dose antiandrogen monotherapy, a LHRH antagonist (abarelix), transdermal estrogens, and a subcutaneous implant that releases leuprolide acetate at a constant rate for 1 year (Viadur; Bayer Corporation, West Haven, CT). With 4 years of clinical experience with Viadur now available, the long-term data indicate continued, uniform testosterone suppression into the castrate range and a high degree of patient satisfaction. Thus, a long-term strategy—permitting increased patient freedom and decreased dependence on a fixed injection schedule—has for the first time become possible with the Viadur implant in men requiring hormone therapy for prostate cancer.


The salutary effect of androgen deprivation in men with advanced prostate cancer was first recognized >60 years ago.1 Subsequently, potent luteinizing hormone–releasing hormone (LHRH) agonists, originally under development as fertility treatments, were found to paradoxically reduce testosterone levels when administered on a continuous basis. This observation led to clinical evaluation of an LHRH agonist in patients with advanced prostate cancer2 and later to controlled clinical trials of the LHRH agonist leuprolide versus the estrogen diethylstilbestrol (DES).3 Leuprolide is shown to be equivalent to DES in delaying the time to cancer progression, and leuprolide has fewer side effects than DES. In 1985, leuprolide acetate received approval from the US Food and Drug Administration (FDA) for the treatment of metastatic prostate cancer and, subsequently, DES was withdrawn from the US market because of cardiovascular safety concerns. In the following years, the LHRH agonists virtually replaced bilateral orchiectomy in initial androgen deprivation therapy (ADT) because their effects are reversible and they do not cause the emotional stigma associated with surgical castration. A meta-analysis published in 2000 that involved 24 randomized clinical trials and >6600 patients has found that survival with LHRH agonists is equivalent to that after orchiectomy.4 Currently, the LHRH agonists are the most widely used form of hormone therapy, accounting for 70% of the prostate cancer treatment market.5

The optimal timing of hormone therapy in prostate cancer is the subject of considerable debate. Orchiectomy or LHRH agonists with or without antiandrogens are currently approved for use only
OPTIMAL TIMING IN ADVANCED DISEASE

For patients with advanced prostate cancer—stages T3, T4, and metastatic disease—the issue is whether to initiate hormone therapy at diagnosis while a patient is asymptomatic in the hope of prolonging survival or to delay therapy until local or metastatic symptoms occur. To address this issue, the Medical Research Council (MRC) in England conducted a randomized clinical trial from 1985 to 1993. A total of 938 patients with locally advanced or asymptomatic metastatic prostate cancer were randomly assigned to receive immediate hormone therapy (orchietomy or LHRH agonist) within 6 weeks of entry or to defer treatment until an indication for hormone therapy occurred. The choice of orchietomy or LHRH agonist was made by the patient and treating physician.

The MRC study has limitations: bone scans were not performed on all men at baseline and prostate-specific antigen (PSA) monitoring was not done routinely. Nevertheless, this study provides important information on the optimal timing of hormone therapy in advanced disease. Of the 938 patients, 500 (53%) were confirmed to have nonmetastatic disease at enrollment and had follow-up information available. Of these, 256 patients received immediate hormone therapy and 244 patients were randomized to deferred treatment. In the deferred-treatment arm, 29 patients with confirmed nonmetastatic disease died of causes other than prostate cancer before an indication for hormone therapy occurred, and 169 patients ultimately received hormone therapy within a median interval of 27 months. The other 46 patients in this group did not receive hormone therapy. Notably, immediate hormone therapy significantly improved cause-specific survival of patients with confirmed nonmetastatic disease compared with deferred treatment. The median actuarial cause-specific survival duration was 7.5 years for immediate treatment and 5.8 years for deferred treatment ($P = 0.0003$). Moreover, the incidence of tumor-related morbidity, including pathologic fractures, ureteric obstruction, and extraskeletal metastases, was lower with immediate than deferred treatment. The MRC study provides the basis for recommending immediate hormone therapy in patients with advanced disease rather than deferring such treatment until evidence of progressive disease is seen.

OPTIMAL TIMING IN OTHER SETTINGS

Several clinical trials suggest that immediate hormone therapy may also be optimal in other prostate cancer settings. In men with node-positive prostate cancer (T1 to T2 N1 M0), adjuvant hormone therapy (LHRH agonist or orchietomy) after radical prostatectomy and lymphadenectomy significantly improved all-cause ($P = 0.02$) and cause-specific ($P < 0.01$) survival compared with deferred treatment. In patients with high-risk, locally advanced disease (T3 to T4 N0 M0 or T1 to T2 N1 M0), treatment with an LHRH agonist starting during radiotherapy and continuing for 3 years also significantly improved all-cause ($P = 0.0002$) and cause-specific ($P = 0.0001$) survival compared with radiotherapy alone. Many patients in the deferred arm of this study, however, did not receive hormone therapy until evidence of metastatic disease was present. The Radiation Therapy Oncology Group (RTOG) conducted a similar study, except that hormone therapy was continued indefinitely and the control arm received hormone therapy at the time of disease progression. Immediate hormone therapy provided significantly better disease-free survival and disease control than hormone therapy ($P < 0.0001$); however, all-cause and cause-specific survival did not differ significantly between treatments, except in the subgroup of patients with a Gleason score of 8 to 10.

Taken together, these studies support immediate hormone therapy in conjunction with radical prostatectomy or radiotherapy in high-risk patients with locally advanced disease. Despite these findings, some investigators advocate reserving hormone therapy for symptomatic patients and those with clear physical or radiographic evidence of disease progression, arguing that it avoids long-term side effects, minimizes costs, and maintains a palliative option. This position, however, is difficult to support.

Information about the optimal timing of hormone therapy in other prostate cancer settings is not yet available. For example, the role of early hormone therapy in patients with biochemical failure after definitive radiotherapy or prostatectomy remains to be evaluated. The European Organisation for Research and Treatment of Cancer (EORTC) 30943 is a randomized phase 3 study that will compare immediate versus deferred hormone therapy in this setting. Until the results of such studies become available, physicians need to consider each patient on an individual basis. Factors to consider include original tumor characteristics, current PSA doubling time, and patient’s
preferences. In most cases, patients with biochemical recurrence prefer not to delay starting treatment and opt for immediate hormone therapy. Additional information from clinical studies is also needed in other settings, including neoadjuvant therapy with planned radical prostatectomy as well as primary treatment of localized disease.

RECENT DEVELOPMENTS IN HORMONE THERAPY

Several recent developments in hormone therapy are noteworthy. Intermittent hormone therapy and high-dose antiandrogen monotherapy are new treatment methods that may offer quality-of-life advantages over conventional hormone therapy. Intermittent therapy is based on the concept that androgen-dependent cells will repopulate the tumor and compete with androgen-independent cells during periods off treatment. These treatment breaks are associated with fewer adverse events associated with androgen deprivation. Intermittent therapy with a subcutaneous LHRH agonist implant in combination with a nonsteroidal antiandrogen has been reported to provide disease control for a 3-year period without major complications in patients with advanced prostate cancer. It remains to be determined, however, whether survival with intermittent therapy is comparable to that with continuous hormone therapy.

High-dose antiandrogen monotherapy has been evaluated most extensively with bicalutamide. Combined data from 2 large randomized studies did not find a statistically significant difference in overall survival between bicalutamide monotherapy and castration in patients with locally advanced disease. In the metastatic setting, however, castration provided better survival than bicalutamide. Treatment with bicalutamide was associated with significant quality-of-life advantages in terms of sexual interest and physical capacity compared with castration, but it produced breast pain and gynecomastia in nearly half the patients. High-dose bicalutamide therapy is also being evaluated as an adjuvant to standard care with prostatectomy, radiotherapy, or observation. In a combined analysis of 3 controlled clinical studies, adjuvant bicalutamide reduced disease progression compared with standard care alone. The follow-up period is too premature to determine if this approach improves survival.

The gonadotropin-releasing hormone antagonist abarelix is a new agent under investigation for prostate cancer and has been described in a series of articles. Studies by the Veterans Affairs Cooperative Urological Research Group (VACURG) show that cause-specific survival of patients with advanced prostate cancer was somewhat better with DES than with orchiectomy. However, DES is associated with higher cardiovascular mortality, which is attributed to first-pass metabolism in the liver and formation of coagulation factor VII. Administration of estrogens parenterally or transdermally prevents first-pass hepatic metabolism and does not cause thrombogenic side effects. In a randomized trial of patients with advanced prostate cancer, intramuscular polyestradiol phosphate produced a better side-effect profile than orchiectomy or combined LHRH agonist and antiandrogen therapy, but overall survival and cardiovascular mortality did not differ between treatments. In a recent study, transdermal estradiol produces castrate testosterone levels within 3 weeks in patients with advanced prostate cancer, and all patients had biochemical evidence of disease regression. Transdermal estrogen improves quality of life and increases bone mineral density, and it is associated with lower cardiovascular toxicity and side effects than expected with oral estrogens.

As noted previously, an LHRH agonist with or without an antiandrogen is currently the most common form of hormone therapy in prostate cancer. LHRH agonists are water-soluble peptides with poor absorption and relatively short half-lives. They were developed initially for delivery by daily injection, but to achieve and maintain castrate serum testosterone levels, these agents must be delivered continuously. Clinically significant increases in serum testosterone can occur if an LHRH agonist is not administered on schedule. In order to improve patient compliance and overcome issues associated with daily injection, depot formulations and, more recently, an implantable delivery device have been developed. There are 3 LHRH agonists approved by the FDA for the treatment of prostate cancer. These include goserelin acetate implant (Zoladex; Zeneca Pharmaceuticals, Wilmington, DE), triptorelin pamoate sustained-release formulation (Trelstar, Pfizer Inc., New York, NY), and 3 formulations of leuprolide acetate; 2 of these are injectable depot formulations that deliver leuprolide acetate over defined periods of 1 to 4 months (Lupron, TAP Pharmaceuticals, Deerfield, IL; Eligard Atrix Laboratories Inc., Fort Collins, CO) and the other is an implantable delivery system that provides continuous delivery over the course of 1 year (Viadur).

IMPLANTABLE LEUPROLIDE DELIVERY SYSTEM

The leuprolide implant (Figure 1) is a nonbiodegradable, osmotically driven minipump that is de-
signed to deliver leuprolide 120 μg/day at a steady rate for 12 months. Men treated with Viadur achieve castrate levels for an entire year with less leuprolide than depot injections. The implant is designed to be removed after 12 months, and then another implant can be inserted for continued therapy.

CLINICAL STUDIES

The efficacy and safety of the leuprolide implant has been evaluated in 2 open-label multicenter studies. In the first study, 51 patients with advanced prostate cancer were randomly assigned to receive 1 or 2 leuprolide implants for 12 months. Patients completing this study were eligible to receive another implant in a 12-month safety extension phase. In the other study, 80 patients received a single leuprolide implant for 12 months. Subsequently, the implant was removed and another was inserted; patients were observed for 2 additional months. The combined study population included 131 patients with a mean age of 73 (±7.3) years. Most patients were white. A total of 122 patients completed 1 year of treatment; of these, 118 (97%) patients opted to continue treatment by having a new implant inserted for the second year.

A single leuprolide implant produced consistent serum leuprolide concentrations (mean, 0.9 ng/mL) and consistent suppression of serum testosterone to below castrate levels (<50 ng/mL) for the 1-year implantation period (Figure 2). Serum testosterone was suppressed below the castrate threshold within 2 to 4 weeks in 106 (99%) of the 107 patients who received a single implant. In the remaining patient, serum testosterone was suppressed to <50 ng/mL within 4 weeks but did not decrease to <50 ng/mL until 24 weeks. The median serum testosterone level was 6 ng/mL and, in the vast majority, was maintained at <20 ng/mL. Once testosterone was suppressed, it remained suppressed in all patients throughout the 1-year period, and it remained suppressed after removal of the first implant and insertion of a second implant. A flare in serum testosterone was not seen on reimplantation.

Serum luteinizing hormone was suppressed below the lower limit of the normal range in all patients. More importantly, all patients had clinically significant reductions in serum PSA after insertion of the leuprolide implant. The median reduction in PSA was 64% after 4 weeks, 93% after 12 weeks, and 95% after 52 weeks. In the subgroup of 88
patients who had reimplantation, PSA remained reduced by a median of 95.5% after 2 years.

The leuprolide implant was well tolerated. In the pooled data from the 107 patients who received a single implant, adverse events were generally mild, and most were consistent with the physiologic effects of testosterone suppression. The most frequent adverse event considered by the treating physician to be possibly or probably related to treatment was vasodilation (hot flashes), reported by 68% of patients. Other adverse events related to testosterone suppression included sweating (6.5%), gynecomastia (6.5%), testes atrophy or pain (3.7%), breast pain (3.7%), and impotence (2.8%). In addition, several other adverse events were considered by the treating physician to be related to treatment, most commonly asthenia (9.3%), depression (6.5%), ecchymosis (5.6%), and headache (4.7%).

Reactions at the insertion site were mild and transient, and they resolved within 2 weeks of insertion or removal of the implant. The most common local reaction was bruising, which occurred in 33% of the patients. Several (2%) patients had insertion site infections and inflammation that resolved with oral antibiotics. Such mild reactions have been successfully treated with antibiotic therapy, leaving the implant in place.

For the 107 patients receiving a single implant, implantation was considered very easy in 89% of the cases, somewhat easy in 10% of the cases, and somewhat difficult in a single case. Removal of the implant was considered very easy in 68% of the cases, somewhat easy in 18%, somewhat difficult in 13%, and very difficult in a single case. The assessment of reinsertion was consistent with the ease of inserting the first implant. Reinsertion was considered very easy in 91% of cases, somewhat easy in 8%, and somewhat difficult in a single case.

**LONG-TERM SAFETY AND EFFICACY**

In previously unpublished data, long-term safety and efficacy of the leuprolide implant was evaluated in a single-arm, open-label study of patients who wanted to continue treatment for a fourth year. A total of 51 patients were enrolled, and 50 patients were reimplemented. Serum leuprolide levels remained consistent during the fourth year of treatment in the intent-to-treat population, showing a mean change of 0.04 ng/mL from baseline to the end of the treatment period. Similarly, serum testosterone and luteinizing hormone were consistently suppressed, with the mean change of $-1.1$ ng/mL and $-0.01$ U/L from baseline to the end of treatment, respectively.

When a satisfaction survey was administered at the end of the treatment period, most patients during their fourth year of using Viadur responded that they were “extremely satisfied” (66.7%) or “satisfied” (31.1%) with their treatment. Most considered the leuprolide implant to be definitely (86.7%) or probably (8.9%) convenient and found it to be very comfortable (91.3%) or somewhat comfortable (6.5%). In general, patients were able to forget that they had an implant. Moreover, the implant did not affect dressing, bathing, driving, or exercise in any patient, and in the vast majority, it did not affect work or sleep. The satisfaction of patients in this study mirrored the results reported.
for patients during their first year of treatment with the leuprolide implant.34,35

**CANDIDATES FOR LEUPROLIDE IMPLANT**

Patients who need 12 months of androgen deprivation are candidates for Viadur. This group includes those who are hormone-naïve and have been reimplemented, those receiving other types of LHRH agonist delivery forms, or those who dislike intramuscular injections. In addition, patients who seek and require flexible scheduling, such as debilitated patients, nursing home residents, “snowbirds,” and frequent travelers are candidates for the 1-year leuprolide implant. For younger patients, this implant does not affect daily activities, such as work and exercise.

Patients who are receiving other existing hormone therapy may raise the possibility of switching to the 1-year leuprolide implant—the option should be discussed. It is important to recognize that using the leuprolide implant should not change how patients are monitored. Because Viadur may allow less office visit time, as well as provide greater convenience, its use should not be tied into the frequency of office visits. Patients should continue to be seen every 3 to 4 months. As an analogy, patients are observed at regular intervals after orchietomy or radical prostatectomy, and the same practice should be used after insertion of the 1-year implant.

**CONCLUSION**

The optimal timing of hormone therapy continues to be debated, although results from several prospective studies suggest that early therapy may offer a survival advantage in some disease settings: in primary therapy of advanced disease, in adjuvant therapy of node-positive patients after radical prostatectomy, and in neoadjuvant therapy of patients with locally advanced disease undergoing radiotherapy.6–9 The optimal timing of hormone therapy in other disease settings, however, such as PSA-only recurrence, remains controversial because of the absence of carefully conducted prospective clinical trials.

In deciding the optimal timing of hormone therapy, practicing physicians need to consider many factors, including the patient’s age, disease setting, side effects versus expected benefits, and patient characteristics and preferences. For example, is the patient at high risk of recurrence after radical prostatectomy? Is the PSA level the only manifestation of disease after primary therapy? Does early hormone therapy improve survival, reduce risk of recurrence, or delay the time to progression? What are the side effects of hormone therapy, and do they justify the benefit of long-term androgen deprivation? Finally, what are the patient’s preferences? A survey of 80 men with prostate cancer and their partners found that 95% of men wanted to participate in decision making with their physician, and all wanted their partner involved in the process as well.30 After a decision to start hormone therapy is made, the efficacy, planned length of treatment, potential side effects, and patient’s lifestyle and preferences enter the process of choosing which agent is best for that patient. With the evolving role of hormonal therapy, a new implantable leuprolide delivery system may be an appropriate, effective, and convenient method of hormone therapy.

**REFERENCES**


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