Androgen Deprivation Therapy in the Treatment of Advanced Prostate Cancer

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This article reviews the issues and controversies relevant to the treatment of advanced prostate cancer with androgen deprivation therapy. Initially, diethylstilbestrol was used for achieving androgen deprivation, but was replaced by luteinizing hormone-releasing hormone (LHRH). Adverse events associated with LHRH agonists include the flare phenomenon, hot flashes, loss of libido, erectile dysfunction, depression, muscle wasting, anemia, and osteoporosis. Intermittent therapy has been advocated to reduce morbidity of treatment. The addition of an antiandrogen provides maximum androgen blockade. There remains controversy regarding the timing of the addition of an antiandrogen. Secondary hormonal therapies include antiandrogens, adrenal androgen inhibitors, and estrogens.

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The role of androgen deprivation therapy (ADT) in the management of prostate cancer is highly controversial. The beneficial clinical effects of ADT in men with symptomatic metastatic prostate cancer are rapid and dramatic.[1] ADT is universally accepted as first-line treatment of symptomatic metastatic prostate cancer.[2] There is also compelling evidence that neoadjuvant ADT increases disease-specific and overall survival in men with high-grade, clinically localized prostate cancer who undergo radiotherapy.[3,4] Although ADT

is indicated by the US Food and Drug Administration only for the palliation of symptomatic metastases and as neoadjuvant therapy for radiation therapy, ADT is widely used in the community setting to treat men with clinically localized prostate cancer, biochemical (prostate-specific antigen [PSA]) recurrence after radical prostatectomy, locally advanced disease, lymph node metastases, and asymptomatic metastatic disease. The benefits of ADT for these unapproved indications have not been definitively ascertained owing to the requirement for performance of large-scale, multicenter, randomized trials with long-term follow-up.

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Today, the time to initiate ADT, the benefits of maximum androgen blockade (MAB), the management of adverse events associated with ADT, the role of intermittent ADT, and the benefits of secondary hormonal therapies remain unresolved. This article will focus on these issues and on controversies relevant to the treatment of advanced prostate cancer with ADT.

Historical Overview

Huggins and Hodges first reported the dramatic clinical effects of suppressing serum testosterone levels in men with advanced prostate cancer in 1941.[1] ADT was achieved by surgical castration or suppression of luteinizing hormone-releasing hormone (LHRH) production at the level of the hypothalamus with diethylstilbestrol (DES). Both surgical and pharmacologic castration resulted in dramatic palliation of painful bony metastases, decreases in the postvoid residual urine, and improved quality of life. Within a short period, hormonal therapy became widely accepted as the treatment of advanced prostate cancer. Huggins and Hodges were awarded the Nobel Prize in 1967 for this pioneering work.

The Veterans Administrative Cooperative Urological Research Group (VACURG) was initiated in 1959 with the goal of investigating the role of ADT in the treatment of prostate cancer, using randomized clinical trials.[5] The major conclusions of VACURG were as follows: 5 mg of DES was associated with significant cardiovascular toxicity; orchiectomy plus DES provided no benefit over DES alone; 1 mg and 5 mg of DES had equivalent effects on prostate cancer survival; 1 mg of DES was associated with reduced cardiovascular toxicity; 1 mg of DES did not reliably achieve castrate levels of testosterone; and there was no survival advantage of early versus delayed initiation of hormonal therapy in advanced disease. A post hoc analysis of the VACURG survival data suggested that there was a survival advantage for early initiation of ADT in men with high-grade disease.[6] The primary objectives of ADT for advanced prostate cancer were to avoid surgical castration, achieve castrate levels of testosterone, and minimize cardiovascular toxicity. A daily dose of 3 mg DES was thought to best achieve these objectives and ultimately became the accepted regimen for pharmacologic castration.

Schally and associates[7] purified the decapeptide gonadotropin-releasing hormone, also referred to as LHRH, in 1971. Chronic exposure to LHRH ultimately suppressed testosterone by desensitizing pituitary cells through downregulation of the LHRH receptors.[8] Substitutions at the sixth amino acid position of LHRH resulted in significantly more potent LHRH agonists.[9] The monthly depot of leuprolide was the first LHRH agonist evaluated as a treatment for advanced prostate cancer. In a randomized clinical trial, leuprolide was equivalent to 3 mg of DES in reducing serum testosterone to castrate levels.[10] The advantage of leuprolide was a lower incidence of cardiovascular toxicity. Leuprolide ultimately replaced DES and orchiectomy as the preferred approach to androgen deprivation.

Over the next 30 years, substitutions at the sixth amino acid position yielded goserelin, triptorelin, and histrelin, which are the commercially available LHRH agonists in the United States (Table 1).[11] LHRH agonists are

Table 1
Hormonal Therapies Available in the United States

LHRH Agonists	Antiandrogens	Adrenal Androgen Inhibitors	Estrogens
Leuprolide	Flutamide	Ketoconazole	Diethylstilbesterol
Goserelin	Bicalutamide	Corticosteroids	Estradiol
Triptorelin	Nilutamide	Aminoglutethimide	Polyestradiol phosphate
Histrelin			Premarin®*

* (Wyeth-Ayerst; Philadelphia, PA)
From Lepor H.[11]

differentiated by their route of administration (intramuscular injection vs subcutaneous injection vs subcutaneous implant) and frequency of administration (1-12 months). All of these LHRH agonists seem to have similar side effect profiles and the ability to lower serum testosterone to castrate levels. There has only been 1 study directly comparing different LHRH agonists.[12] Overall survival was significantly greater with triptorelin compared with leuprolide, 97% vs 90.5% survival at 9 months, respectively ($P = .033$). Although not statistically significant, there was a trend for triptorelin to better maintain castrate levels of testosterone over a 9-month interval.

Adverse Events of LHRH Agonists

The adverse events associated with LHRH agonists can be categorized as immediate, acute, and chronic. The optimal use of ADT requires an effort to prevent or treat these adverse events.

One of the limitations of LHRH agonists is the initial "flare" phenomenon, which is attributed to a surge of serum testosterone levels due to the initial stimulation of LHRH receptors.[13] The flare phenomenon may be life threatening if an LHRH agonist is administered to men with high-volume metastatic disease. The clinical consequence of the flare is prevented by pretreatment with an antiandrogen, which inhibits the stimulatory effect of the testosterone surge at the level of the androgen receptor.[14]

The acute adverse events associated with LHRH agonists become evident a few weeks after initiation of therapy and coincide with the achievement of castrate levels of testosterone. These acute adverse events include hot flashes, loss of libido, and erectile dysfunction.[15] Hot flashes can be effectively treated with hormonal agents, including low-dose estrogens, megestrol acetate, medroxyprogesterone acetate, and cyproterone acetate.[15] Approximately 60% of men will experience significant hot flashes.[11] The overwhelming majority of men taking LHRH agonists will develop erectile dysfunction. Erectile dysfunction can be treated with phosphodiesterase inhibitors, vacuum devices, or intracavernous therapy. Although these pharmacologic and mechanical approaches may restore the ability to achieve an erection, the lack of libido often limits patients' enthusiasm for pursuing treatment to restore erections.

The chronic adverse events associated with LHRH agonists include musculoskeletal, hematologic, and cardiovascular events. There is increasing awareness that men are prone to developing osteoporosis and related fractures with advancing age.[16] Several investigators have reported significantly increased risk of fractures in men undergoing androgen deprivation therapy compared with controls.[17,18] All men taking LHRH agonists should be advised to modify their lifestyle to prevent or minimize osteoporosis. Lifestyle modifications include cessation of smoking, decreasing alcohol consumption, performance of resistance exercises, and taking calcium supplementation. Bone mineral density should be monitored at least annually.[18] If bone mineral density significantly decreases, treatment options include bisphosphonates.[19] Estrogens and selective estrogen-receptor modulators have also been shown to protect against the osteoporotic side effects of ADT.[20,21] Advanced prostate cancer directly predisposes men to the development of fractures due to skeletal metastases. It is therefore important to prevent or minimize the osteoporotic effects of LHRH agonists to decrease the risk of fractures.

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Men with advanced prostate cancer are also predisposed to developing anemia due to hematuria from locally advanced prostate cancer and to bone marrow infiltration by metastatic disease. Testosterone increases production of erythrogenesis-stimulating proteins.[22] Therefore, LHRH agonists may cause or exacerbate anemia by indirectly inhibiting erythrogenesis.

Progressive muscle loss has been associated with declining testosterone levels in men.[15] Men receiving LHRH agonists for prostate cancer demonstrate significant increases in muscle fatigue.[23] Resistance exercises may limit the consequences of LHRH agonists on muscle function.

Hormonal therapy has also been shown to cause neurologic impairment, manifested by decreased cognitive function.[15] There is some evidence that hormonal ADT may also cause depression.[15]

Keating and colleagues[24] recently reported increased cardiovascular morbidity and mortality associated with LHRH agonists. The increased cardiovascular toxicity was hypothesized to be mediated through changes in lipoproteins, arterial stiffness, and QT interval prolongation.

In summary, men with advanced prostate cancer are predisposed to developing osteoporosis, anemia, muscle wasting, and depression as a direct consequence of their metastatic disease. LHRH agonists may directly exacerbate these problems, resulting in significant morbidity and mortality.

Every effort should be made to recognize and correct these conditions to optimize the treatment of men with advanced prostate cancer.

Owing to the adverse events associated with ADT, intermittent therapy has been advocated as a measure to reduce morbidity of treatment.[25] It is reasonable to assume that both the acute and chronic complications of LHRH agonists would be minimized by intermittent therapy. Several large studies have demonstrated the return of potency and resolution of anemia with an intermittent ADT regimen.[26,27] The unresolved issue is whether prostate cancer survival is negatively impacted by intermittent therapy. Currently there are 3 phase III trials directly comparing continuous and intermittent hormonal therapy regimens. One of these phase III trials (Southwest Oncology Group 9346) is comparing intermittent ADT with continuous ADT in men with newly diagnosed metastatic prostate cancer.[25]

Maximum Androgen Blockade

Androgens are produced by the testes and the adrenal glands. Ninety to 95 percent of the androgens are produced by the testes and only 5% to 10% by the adrenals.[28] LHRH agonists reduce testosterone to castrate levels by suppressing only androgens produced by the testes. The impact of the adrenal androgens on prostate cancer in men with LHRH agonists is highly controversial. Huggins and Scott[29] demonstrated a clinical benefit of surgical adrenalectomy in men with disease recurrence after orchiectomy.

MAB can be achieved pharmacologically by combining an LHRH agonist with an antiandrogen. The antiandrogens flutamide, bicalutamide, and nilutamide block the effects of adrenal androgens at the androgen receptor. There is a general consensus that MAB has a role in the treatment of advanced prostate cancer.[30] The controversy is whether MAB should be the initial form of ADT or whether the antiandrogen should be offered after the patient has had disease progression with LHRH agonist treatment.

Three randomized studies have demonstrated the advantage of initiating MAB at the time of diagnosis for metastatic prostate cancer.[31-33] The mean increase in overall survival attributable to MAB demonstrated in these studies was approximately 7 months. This modest increase in survival far exceeds that attributable to cytotoxic agents, such as the combination of docetaxel and estramustine, initiated for androgen-independent prostate cancer.[34] It is also important to recognize that several studies have failed to show an advantage of MAB initiated at the time of diagnosis for metastatic prostate disease.[35]

Secondary Hormonal Therapy

It is inevitable that the overwhelming majority of men treated with pharmacologic or surgical castration will develop disease progression due to development and propagation of androgen-independent prostate cancer cells. The first step is to measure the serum testosterone level in those men taking LHRH agonists, to ensure that castrate levels of testosterone are being achieved.

Second-line nonsteroidal antiandrogens are typically administered at the time of biochemical disease progression.[36] For men who were initially treated with MAB, the antiandrogen should be withdrawn.[37] Approximately 15% to 30% of men will exhibit a greater than 50% decline in serum PSA level simply by withdrawal of the antiandrogen.[37-39] Unfortunately, the serum PSA decline is short lived—generally between 3 and 5 months.[37-39] When the PSA level begins to rise after antiandrogen withdrawal, it is reasonable to initiate treatment with a second-line antiandrogen.[40] This intervention is often associated with clinical, biochemical, and radiographic responses.

Inhibitors of adrenal androgen production include ketoconazole, corticosteroids, and aminoglutethimide.[41] Ketoconazole is the preferred agent for secondary hormonal therapy because of its better tolerability.[41] Approximately 50% of men exhibiting disease progression while taking LHRH and antiandrogen therapy will exhibit up to a 50% reduction in PSA level, with a median response of 30 weeks after initiation of treatment with an inhibitor of adrenal androgens.

Estrogen therapy was the initial mainstay of hormonal therapy and then lost favor after reports of significant cardiovascular toxicity. Recently, there has been renewed interest in this approach to achieving androgen deprivation. In 2005, Ockrim and colleagues[42] reported no cardiovascular events in 20 men treated with transdermal estradiol for locally advanced or metastatic prostate cancer over a 2-year period. Furthermore, this study showed an improvement in coagulation factor levels from baseline, suggesting protection against thrombotic events.

Approximately 15% to 30% of MAB-treated men will exhibit a greater than 50% decline in serum PSA level simply by withdrawal of the antiandrogen.

Ultimately, men will develop disease that is refractory to all hormonal manipulations. This is termed androgen-independent prostate cancer. There is no consensus as to whether LHRH agonists should be

withdrawn at this time. The rationale for withdrawing the LHRH agonist would be to improve quality of life and possibly diminish any osteoporosis, muscle wasting, anemia, and depression that might be associated with the LHRH agonist. ■

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Main Points

- Androgen deprivation therapy (ADT) is widely used in the community setting to treat men with clinically localized prostate cancer, biochemical recurrence after radical prostatectomy, locally advanced disease, lymph node metastases, and asymptomatic metastatic disease. The benefits of ADT for these unapproved indications have not been definitively ascertained.
- The dramatic clinical effects of suppressing serum testosterone levels in men with advanced prostate cancer were first reported in 1941. A daily dose of 3 mg diethylstilbestrol (DES) eventually became the accepted regimen for pharmacologic castration.
- The monthly depot of leuprolide was the first luteinizing hormone-releasing hormone (LHRH) agonist evaluated as a treatment for advanced prostate cancer. Leuprolide ultimately replaced DES and orchiectomy as the preferred approach to androgen deprivation.
- Leuprolide, goserelin, triptorelin, and histrelin are the commercially available LHRH agonists in the United States and are differentiated by the route and frequency of administration. All of these LHRH agonists seem to have similar side effect profiles and the ability to lower serum testosterone to castrate levels.
- Adverse events associated with LHRH agonists can be categorized as immediate (initial "flare" phenomenon), acute (hot flashes, loss of libido, and erectile dysfunction), and chronic (musculoskeletal, hematologic, and cardiovascular events). Owing to the adverse events associated with ADT, intermittent therapy has been advocated as a measure to reduce morbidity of treatment.
- There is a general consensus that maximum androgen blockade (MAB) has a role in the treatment of advanced prostate cancer. The controversy is whether MAB should be the initial form of ADT or whether the antiandrogen should be offered after the patient has had disease progression with LHRH agonist monotherapy.
- Ultimately, men will develop disease that is refractory to all hormonal manipulations (androgen-independent prostate cancer). There is no consensus as to whether LHRH agonists should be withdrawn at this time.

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