Leuprorelin depot injection: patient considerations in the management of prostatic cancer

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Abstract: Hormone therapy is well established for treating patients with prostate cancer and remains the mainstay of the treatment of metastatic and locally advanced disease, this article reviews the rationale for its use, its different forms, and complications and controversies still surrounding some of its modalities. Availability of long-acting synthetic luteinizing hormone-releasing hormone (LHRH) agonists revolutionized the hormonal treatment of prostate cancer, and helped to avoid the emotional and psychological effects related to surgical castration. The depot formula has gained wide acceptance from both patients and physicians. This review emphasizes the newer, long-acting formula, leuprorelin (leuprolide acetate), especially the 6-month formula, its advantage over over shorter-acting depot products, and its potential to become a standard of care for patients eligible for androgen deprivation therapy.

Keywords: prostate cancer, androgen deprivation therapy (adt), leuprorelin

Introduction

In the post prostate-specific antigen (PSA) era, screening for prostate cancer has not only led to a stage migration, but also to a higher incidence of the disease. Such a trend has decreased the incidence of metastatic disease at diagnosis and paralleled the decrease in the mortality rate from prostate cancer.

The incidence of metastatic disease was only 1.6% of patients enrolled in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), diagnosed between 1998 and 2003 (Ryan et al 2006). On the other hand the population failing the initial treatment is increasing, and 40% of the patients treated with curative intent eventually end up with PSA recurrence (Ward and Moul 2005), raising the question of whether there is any evidence that aggressive intervention in these patients may result in cure.

Because many patients with T3 disease or local lymph node metastases progress to distant metastases, some authors recommended that the concept of advanced prostate cancer should also include stages C and D1 (Moul 2004) (T3, T4, and any T N1).

Today, in addition to its well-established role in treating patient with metastatic disease, androgen deprivation therapy (ADT) is sometimes used to treat patients with biochemical failure even without evidence of local or systemic recurrence. This therapy is also used as an adjunct to radiation for high risk localized disease.

The treatment of locally advanced and metastatic prostate cancer is only palliative, and most patients who respond initially to ADT ultimately evolve towards hormone refractory disease within 2 years, and at this stage, unfortunately, alternative modalities such as chemotherapy become of limited value, with a survival of only 18–24 months.

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This inevitable evolution led to new strategies being explored for delaying progression to androgen independence, which may involve targeting of anti-apoptotic factors, use of chemotherapy at the time of androgen ablation, or blockage or down-regulation of androgen receptor (AR) activity (Petrylak 2005). Among those novel options is a broad range of promising strategies such as targeting signal transduction pathways, cell cycle regulation and differentiation, and angiogenesis (Cavarretta et al 2005).

Prostate cancer: a hormone sensitive malignancy

The prostate – testis relationship has been known since the 18th century when John Hunter (Androutsos 1998) demonstrated in 1786 that castration in young male animals prevented further growth of the prostate, whereas in the adult it caused atrophy. Hunter also observed that aging eunuchs never suffered from symptoms of a hypertrophied prostate (Home 1811).

The second half of the 19th century marked a growing interest in orchiectomy for the treatment of prostatic hyperplasia, particularly urinary retention. Symptomatic improvement in over half of patients with an enlarged prostate treated with castration was reported by William White in 1895 and 1904 (White 1895, 1904).

The development of prostate cancer requires the presence of a prostate gland and a source of androgens. It has been shown that androgens produced elsewhere can be activated in the prostatic tissue, as prostate cancer never occurs in those with testicular feminization syndrome and in patients with 5-alfa reductase deficiency (Newling 1996).

Before 1940s there was no effective treatment for advanced prostate cancer. In 1939 Charles Huggins, aware of androgens sensitivity of the prostate gland, proposed orchiectomy to control prostate cancer. He demonstrated that castration decreased the height of prostatic epithelial cells in normal prostatic tissue, and that testosterone administration stimulated the secretory activity of dogs' prostatic cells (Huggins and Clark 1940); furthermore, he proved that castration produced clinical pain relief and a stabilization or regression of metastatic osseous lesions (Huggins et al 1941) and reduction in acid phosphatase level (Huggins and Hodges 1941). Huggins soon realized, however, that the same results could be achieved by the less drastic procedure of the administration of female sex hormones to neutralize the effect of androgens produced by the testicles. Consequently, in 1941 he began to inject his patients with the hormones stilbestrol and hexestrol.

Other forms of castration have been developed, such as the technique of radio-orchiectomy (Keyes and Ferguson 1936), consisting of irradiation of the testis in patients with advanced prostate cancer.

Ninety to 95% of the androgens are produced by the testes and only 5%–10% by the adrenals. These small amounts of androgens continue to support tumor growth.

The involvement of the adrenal gland in hormonal control of prostate malignancies was supported by reports of an increase in the urinary concentration of 17-keto-steroids in patients after castration (Satterthwaite et al 1941; Schröder 2002). The recognition of the role of adrenal androgens in prostate cancer led to the development of the therapeutic strategy known as combined androgen blockade.

The early form of this approach combined orchiectomy and bilateral adrenalectomy. The first procedure in a patient with prostate cancer was carried out by Huggins and William Wallace Scott in 1945 (Huggins and Scott 1945), who demonstrated a clinical benefit of such procedure in men with disease recurrence after orchiectomy.

The initial success of hormonal therapy led on the one hand to less interest in radical surgical and radiation treatment, even for localized disease. On the other hand, it led to a tendency to remove sound organs with vital functions such as adrenals (adrenalectomy) and the pituitary gland (surgical ablation [Silverberg and Britt 1979]) and external irradiation (Murphy and Schwippert 1951) of the pituitary gland, as well as the implantation of radioactive material (Fergusson 1957), in hope of completely suppressing androgens and therefore curing or slowing disease progression.

Schally and associates (1971) purified the decapeptide gonadotropin-releasing hormone, referred to as LHRH. The availability of long-acting synthetic luteinizing hormone-releasing hormone (LHRH) agonists in the 1980s revolutionized the hormonal treatment of prostate cancer, enabling many men to avoid the emotional and psychological effects of surgical castration (McLeod 2003).

Anti-androgens block testosterone action in target tissues by interfering with testosterone or dihydrotesterone (DHT) binding to the steroid-binding domain of the androgen receptor. Steroidal anti-androgens, such as cyproterone acetate, also have some ability to block luteinizing hormone (LH) secretion, and are therefore associated with many of the sexual effects seen with LHRH agonists (See 2003).

By contrast, the non-steroidal anti-androgens have been associated with a far more beneficial sexual side effect profile. Non-steroidal anti-androgens, such as flutamide, were first used in the mid 1970s (Sogani et al 1975) and steroidal

anti-androgens such as cyproterone acetate were approved for use in the 1980s (Jacobi 1983).

The gonadotropin-releasing hormone (GnRH) antagonists represent the newest class of agents introduced for the hormonal treatment of prostate cancer. The advantages of GnRH antagonists are that they do not cause the initial surge in testosterone associated with LHRH agonists and they rapidly achieve castrate androgen levels.

In clinical trials, monotherapy with abarelix was shown to achieve medical castration more rapidly than leuprorelin (leuprolide acetate) alone or in combination with bicalutamide and without an early surge in testosterone (Trachtenberg et al 2002).

Physiology: hypothalamus – pituitary – testis axis

LHRH, also known as GnRH, is secreted in a pulsatile fashion by the hypothalamus. The increase in LHRH stimulates the anterior pituitary to secrete LH and follicle-stimulating hormone into the systemic circulation (Denmeade and Isaacs 2004). LH stimulates the Leydig cells of the testes to secrete testosterone.

Testosterone is converted into a more potent compound, DHT. Conversion occurs in the cytoplasm of prostatic cells by the enzyme 5-alfa reductase. In addition to testosterone, adrenal androgens may be converted to DHT (Sandow et al 1988). In the cytosol, DHT binds to the androgen receptor and crosses into the nucleus. The activated androgen receptor binds to specific DNA sequences that influence gene expression, stimulate the synthesis of specific proteins such as PSA, and trigger cell proliferation.

In the normal prostate, androgen is the major growth factor through two mechanisms: on the one hand, it stimulates cellular proliferation of prostatic epithelial cells; on the other, it blocks the potentially high apoptotic rate of epithelial cells. The net balance determines the overall number of prostate cells (Isaacs 1984, 1994).

Testosterone-lowering strategies (Table 1)

The first method of permanent castration was bilateral orchiectomy, and the first reversible method was diethylstilbestrol (DES) (Byar and Corle 1988).

Therapeutic approaches to interrupt the production and/or block the action of testosterone include:

(1) Suppression of testosterone via surgical removal of the testes or use of estrogens;

Table 1 Methods to interrupt the production of and/or block the action of testosterone

Methods	Action	Side effects
Orchiectomy	Surgical suppression of testicular male hormones leading to immediate drop in testosterone (Iversen 1998)	Limitations include its irreversible nature causing erectile dysfunction, occasional post-operative complications, and associated psychological factors (Cassileth 1989)
Estrogens	The negative feedback on the hypothalamus afforded by estrogen. Suppression of LHRH release and subsequent decrease not only of LH but also of FSH (Brawer 2001)	Cardiovascular complications. gynecomastia is a common complaint
LHRH agonists	Over-stimulation of the LHRH receptors, followed by subsequent drop due to the loss the pulsatile secretion pattern (LSG 1984); the net effect is a reduction of testosterone to castration levels within 2–4 weeks	Testosterone surge and potential for clinical flare
LHRH antagonists	Inhibition of LHRH and subsequent rapid time to testosterone suppression with a higher rate of medical castration (Debruyne 2004)	- Safety of abarelix is comparable to that of LHRH agonists with or without anti-androgen - Cost - Increased liver enzymes
Anti-androgens	Block the binding of DHT to the androgen receptors in the prostate (Iversen 2001)	Gynecomastia, breast pain Diarrhea,visual disturbances
Inhibitors of alfa-reductase	Inhibit 5-alfa reductase conversion of testosterone to DHT in the prostate	Gynecomastia, breast pain, anemia
Ketoconazole	In high dose is able to produce castrate levels of androgens (both testicular and adrenal) within 4–8 h of the first dose (Lowe 1990)	Gastrointestinal disturbances and suppression of cortisol production which resulted in subsequent Addisonian crisis and sudden death (Pont 1987)

Abbreviations: DHT, dihydrotesterone; LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone; FSH, follicle-stimulating hormone.

(2) LHRH agonists to down-regulate the pituitary and prevent release of LH or by using LHRH antagonists to directly suppress LH release;
(3) Inhibition of 5-alfa reductase conversion of testosterone to DHT in the prostate;
(4) Blocking the binding of DHT to the androgen receptors in the prostate.

These strategies can be used individually or in various combinations.

In 1983, ketoconazole in high dose was identified as able to produce castrate levels of androgens within 4–8 h of the first dose (Trachtenberg and Point 1983), and represents an alternative treatment where urgent androgen ablation is required (Lowe and Bamberger 1990).

Biological effects of androgen deprivation

Anterior pituitary – testis axis

With longer-term administration, a resetting of the anterior pituitary receptor occurs, with subsequent reduction in LH along with follicle-stimulating hormone (FSH) release, resulting in achievement of castrate levels of testosterone (Conn et al 1984). Chronic exposure to LHRH ultimately suppressed testosterone by desensitizing pituitary cells through down-regulation of the LHRH receptors (Van Loenen et al 2002).

Castration, the time-honored frontline treatment for metastatic prostate cancer, was previously defined by induction of a serum testosterone level of <50 ng/mL (Coppage and Cooner 1965; Young and Kent 1968). Recent literature redefines this upper limit as <20 ng/mL (Oefelein et al 2000).

Prostate cell level

Effects of androgen deprivation include apoptosis of both cancer cells and benign prostatic epithelium (Denmead et al 1996; Buttyan et al 2000). One of the earliest events, occurring prior to the initiation of epithelial apoptosis, is degeneration of the prostatic vasculature. This has been observed in animal models as well as in the human prostate (Franck-Lissbrant et al 1998; Shabisgh et al 1999). A recent study has shown that in patients on complete androgen blockade therapy (CAB), there were morphological changes within the prostatic tissues as early as 7 days after initiating ADT, similar to the response to castration. These changes induce significant involution within prostatic tissues over 7–28 days, but allow the persistence of some viable tumor cells capable of proliferation (Mercader et al 2007). This event is mediated at least in part by decreased expression of vascular endothelial growth factor (VEGF), an androgen-regulated gene, in the prostatic epithelium and stroma (Burchardt et al 2000). This phenomenon of apoptosis does not affect basal cells which remain intact. A high percentage of androgen-independent cancers appear to maintain expression of the AR gene, but many have genetic alterations that change receptor activity. Altered expression of AR co-activators may occur in recurrent cancer, and AR mutations may occur in as many as 40%–50% of such cancers. Proteins involved in cell survival and resistance to apoptosis are over-expressed in androgen-independent prostate cancer cells or tumors (Peehl 2001).

Indication of ADT in prostate cancer

Today, in addition to its well-established role in treating patients with metastatic disease, ADT is sometimes used to treat patients with biochemical failure even without evidence of local or systemic recurrence. This therapy is also used as an adjunct in patients undergoing radiation for high-risk localized disease.

Controversies around hormonal therapy

Several controversies still surround the modalities of this therapy (Table 2):

- Monotherapy or CAB?
- Early versus delayed?
- Continuous or intermittent?
- Adjuvant or neoadjuvant?
- Secondary manipulation after failure of initial hormonal therapy?
- Hormone after PSA recurrence?
- Hormone for localized prostate cancer.
- Role of anti-androgens alone?
- Role of anti-5AR + antiandrogens?

LHRH agonists flare issue

During the initial 1–2 weeks the LHRH receptor is overstimulated, initially resulting in testosterone surge and potential for clinical flare. There is a delay in testosterone reduction and a surge in testosterone and dihydro-testerone as well as elevation of PSA. Symptomatic flare may result. The impact of the increase in FSH is only now undergoing evaluation, but this too may have an untoward effect on prostatic carcinoma. 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 anti-androgen, which inhibits the

Table 2 Controversies around hormonal therapy for prostate cancer

HT modality	Argument for	Argument against
Early vs delayed HT	The appropriate time to initiate hormonal therapy for prostate cancer remains a matter of debate. Two recent studies provide convincing clinical evidence supporting the early treatment of advanced prostate cancer (Kirk 2000; Messing 1999). The randomized trial reported by the Medical Research Council (MRC) has shown more rapid local and distant disease progression in the deferred treatment group, increase in serious complications, such as pathologic fractures, spinal cord compression, and there was clear survival advantages associated with early hormone therapy for high risk malignancies (MRC 1997). Also in Eastern Cooperative Oncology Group (ECOG)/SWOG Stage D1 (N+) study (Messing 1999), the survival in the delayed therapy and immediate therapy arms was 65% and 85%, respectively.	Arguments for early hormonal therapy are countered, however, by a number of factors, including: • The long natural history for most men of rising PSA levels before clinical metastases and death • No randomized controlled clinical trials to confirm the survival advantage or to document the long-term effects of such therapy. The side effects of hormone therapy, particularly for younger men • Cost of hormone treatment, particularly if over a long period of time. Studer et al (2006) has shown that there is no benefit in early versus delayed treatment in patients with clinically localized prostate cancer not suitable for radical therapy.
CAB	From 1980 to 1991, approximately 36 prospective, randomized studies were performed, 27 of them being reasonably well designed with at least 1 year of therapy. Of these, only 3 showed a statistically significant improvement in overall survival (Crawford 1989; Denis 1998). Although the overall benefit of MAB may be small, some patients will likely show a more substantial improvement in survival compared with androgen suppression alone. Should remain a reasonable option when discussing treatments for metastatic prostate cancer (Messing 1999). A recent Japanese study showed that first-line combination LHRH-agonists therapy with bicalutamide 80 mg in patients with advanced prostate cancer offered significant benefits over LHRH-A alone, with respect to TTTF, TTP, although the difference in the interim overall survival was not statistically significant (Usami 2007).	The lack of benefit in any of the other 24 studies led to much debate about the overall benefit of MAB in men with metastatic disease. The survival benefit for MAB of only 3% has led many experts to believe that the benefit is overshadowed by the therapy cost and side effects (Chodak 2004, 2005).
	This option became feasible only when medical castration became available. Advantages include reduction of side effects from therapy such as the physiological changes associated with castration, reduction of cost, and potentially delayed emergence of hormone refractoriness as evidenced by laboratory data (Sandford 1984).	Controversy remains as to which patients might benefit the most from intermittent hormonal therapy, when to start hormonal therapy, how long to treat before stopping, and when to restart subsequent cycles.
Intermittent hormone therapy	The most recent evidence is the mature experience of phase II trial from Ottawa group. Intermittent AS therapy was initiated in prostate-cancer patients to delay hormone resistance and minimize potential side effects of androgen-deprivation therapy (Malone 2007). Intermittent AS has also the potential to reduce side effects, including recovery of hemoglobin level, return of sexual function and absence of weight gain at the end of the study period (Malone 2005). Its use in D1 and D2 prostate cancer patients appears to be safe and feasible. Off treatment periods are >40% and contribute to patients' quality of life (Miller 2007).	
Anti-androgen alone	Monotherapy with bicalutamide 150 mg once daily provides a survival outcome that is not significantly different to that of castration in men with locally advanced, non-metastatic disease, while conferring significant advantages for sexual interest and physical capacity (Boccon-Gibod 1997; Pavone-Macaluso 1994).	The most common side effects of non-steroidal anti-androgen monotherapy are gynecomastia and male breast pain. These events occur more frequently than with castration alone (McLeod 1997; Migliari 1999).

(*Continued*)

Table 2 (Continued)

HT modality	Argument for	Argument against
	The administration of low-dose flutamide (125 mg) was clinically effective in treating PSA recurrence after definitive treatments for prostate cancer, and was well tolerated (Barqawi 2003).	
Anti-androgen and Inhibition of 5-alfa reductase	The combination of finasteride and flutamide showed a moderate efficacy in patients with PSA-only recurrence after definitive therapy. The efficacy appears to be greater in patients who can achieve a PSA nadir of 0.1 ng/mL or less after the start of treatment (Barqawi 2003). This combination is also regarded as a potency-sparing 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. Although it offers modest activity, it represents an alternative to early use of chemotherapy in patients with androgen independent disease.	Although the side effects are low, combined finasteride and flutamide therapy significantly lowers hemoglobin and haematocrit levels in men with advanced prostate cancer (Ornstein 1999).
Secondary HT	The strategy can be summarized as follow either the adjunction second-line non-steroidal anti-androgens or its withdrawal in case of initial CAB, the use of inhibitors of adrenal androgen production such as ketoconazole (Scholz 2005). The future direction would involve the development of molecules that effectively inhibit androgen receptor through changes in the ligand binding complex activating conformational changes or co-factor recruitment (Small 2006). Preclinical evidence supports the hypothesis that FSH signaling contributes to progression of AIPC. Patients on LHRH agonists have modestly reduced but detectable FSH levels, whereas patients treated with orchiectomy have significantly elevated FSH levels. Abarelix suppresses FSH more effectively than LHRH agonists when used as front-line hormonal therapy (Beer 2004).	Longevity following progression has historically been short, with a reported median of 6–9 months, given the lack of efficacious treatment options (Taneja 2003). With the development of potentially efficacious chemotherapeutic regimens, particularly taxane-based chemotherapies, secondary manipulation may delay therapy (Petrylak 2007).
PSA-only Recurence after Radical Prostatectomy	Moul et al in a large retrospective multi-center study, found that delayed hormonal therapy in high-risk disease (GS $>$ 7 and PSA DT $<$ 12 months) was associated with an approximately 2-fold increased risk of metastasis (Moul 2004). Whoever this study has the limitations of retrospective studies and requires validation to reach a meaningful result (Freedland 2005).	Retrospective study, revealed that patients with PSA recurrence who did not undergo hormonal deprivation therapy had a median actuarial time to metastasis of 8 years after PSA rise, only 34% had apparent metastases (Pound 1999). HT provides no benefit or might even harm men with low-risk/local disease (Leibovitz 2001).
Androgen deprivation as monotheraphy for localized prostate cancer	Primary ADT has long been the treatment of choice for localized and locally advanced prostate cancer in Japan and more evidence of its efficacy is accumulating. This trend is also on the rise in clinical practice in the USA (Akaza 2006). More evidence has been accumulating that progression of prostate cancer was retarded by primary hormone therapy in men with localized or locally advanced prostate cancer (Akaza et al 2006). Some authors described that triple androgen blockade (LHRH agonist+anti-androgens) therapy followed by finasteride maintenance appears to be a promising for management of localized prostate cancer (Labrie 2002), and long-term and continuous CAB offers the possibility of long-term control or possible cure of localized prostate cancer (Janoff 2005).	ADT resulted in poor control of localized prostate cancer. In particular, younger patients and those with Gleason $\geq$ 6 cancers were at higher risk of treatment failure. And the toxicity, principally in the form of bone fractures, was high (Janoff 2005). Androgen deprivation as a primary therapy for localized prostate cancer provided modest disease control, but toxicity was high. Younger men with tumors of Gleason score $\geq$6 had a higher risk of biochemical progression (Kirk 2006).

(*Continued*)

Table 2 (Continued)

HT modality	Argument for	Argument against
Adjuvant HT	NAS can reduce the number of tumor clonogens prior to radiation, thus increasing the tumor control probability. Also, NAS may sensitize tumor cells to radiation if cell kill by both modalities follows a common pathway. The timing and sequence of NAS and radiation are important, with radiation being most effective if given at the point of maximal tumor regression (Zietman 2000; Hall 2000). Pilepich showed that the incidence of local failure at 10 years was 23% in the adjuvant arm, compared with 38% in the radiation alone The 10-year rate of distant metastases was 24% in the adjuvant arm, compared with 39% in the control arm ($p < 0.0001$) and concluded that adjuvant androgen suppression reduces disease progression and improves survival in patients with unfavorable-risk, high-grade prostate cancer treated with radiotherapy (Pilepich 2005).	The 5-year bRFS rate for patients with unfavorable tumors who received radiation doses of 72 Gy or greater vs less than 72 Gy was 75% and 41 %, respectively; thus the benefit might not be due to adding hormone to higher radiation dose (Lyons 2000). There appeared to be little if any benefit of adding neoadjuvant AS before high intensity focused ultrasound for men with presumed organ-confined prostate cancer (Uchida 2006). Neo-adjuvant and adjuvant HT before radical prostatectomy showed a significant reduction in the positive surgical margin rate, from 23% to 12% ($p = 0.01$) for patients who received 3 vs 8 months of neoadjuvant AST, but no cancer control outcomes (Gleave 2001). A recent study to evaluate NHT prior to radical prostatectomy for high-risk prostate cancer, showed that biochemical failure was frequent after this combined treatment, even in a pT0 ca which questions the use of modality in this category of patients (Tabata 2006).

Abbreviations: ADT, androgen deprivation therapy; AIPC, androgen-independent prostate cancer; AS, androgen suppression; DHT, dihydrotesterone; CAB, complete androgen blockade; HT, hormone therapy; LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone; FSH, follicle-stimulating hormone; MAB, maximum androgen blockade; NAS, neoadjuvant androgen suppression; NHT, neoadjuvant hormonal therapy; PSA, prostate-specific antigen; TTTF,. time-to-treatment failure; TTP, time-to-disease progression.

stimulatory effect of the testosterone surge at the level of the androgen receptor (Thompson 2001).

Patients with symptomatic advanced prostate cancer such as those with significant obstructive voiding symptoms merit a flare-free induction of hormonal therapy, as do patients with significant back pain and early neurologic sequelae: both urinary retention and paraplegia are side effects to be avoided.

Optimal blockade is achieved by pretreatment with an appropriate agent (eg, anti-androgen), or for the patient in whom maximum blockade is desirable immediately, consideration could be given to the use of ketoconazole, which dramatically reduces testosterone in only a matter of hours.

Failure to achieve castrate level

A small but potentially important subgroup of men on depot LHRH agonist therapy fail to achieve or maintain a castrate level of testosterone (Oefeien and Comum 2000), a finding that supports the need for monitoring testicular response during LHRH agonist therapy (Morote et al 2006).

Cost of treatment

For an individual patient the cost of LHRH agonist treatment surpassed the cost of surgery at less than 4.2–5.3 months, and for combined androgen blockade (LHRH agonists and non-steroidal anti-androgens) at less than 2.7–3.4 months (Mariani et al 2001). Except for patients with short anticipated survival, current medical androgen suppressive treatment options are more costly than bilateral orchiectomy.

For men who accept it, bilateral orchiectomy is likely to be the most cost-effective androgen suppression strategy. Combined androgen blockade is the least economically attractive option, yielding small health benefits at high relative costs (Bayoumi et al 2000).

Complications of hormonal therapy

The common side effects of hormonal manipulation are hot flushes. Changes in the hormonal balance induced by hormonal manipulation in men with prostate cancer can increase the likelihood of gynecomastia, which usually resolves spontaneously after cessation of hormonal manipulation during the first year (Kumar et al 2005).

Men with prostate cancer who are initiating ADT have a 5- to 10-fold increased loss of bone density at multiple skeletal sites compared with either healthy controls or men with prostate cancer who are not on ADT. Bone loss is maximal in the first year after initiation of ADT, suggesting initiation

of early preventive therapy (Greenspan et al 2005; Shahinian et al 2005). Hormone therapy does not appear to cause clinically significant changes in depression among men with locally advanced prostate cancer. However, fatigue increased significantly over the study period (Koupparis et al 2004).

The current data suggest that men with prostate cancer who are receiving long-term ADT are at risk for developing insulin resistance, hyperglycemia (Basaria et al 2006), and the occurrence of metabolic syndrome (Braga-Basari et al 2006), thus leading to an increased risk of cardiovascular complications.

Compared with normal men, total and free testosterone levels during treatment were 1.8-fold and 2.3-fold higher in obese men. These differences may contribute to the association between obesity and increased prostate cancer mortality (Smith 2007), loss of sexual desire, erectile dysfunction, and anemia.

Pituitary adenomas (Massoud et al 2006) together with subcutaneous granulomas (Whitaker et al 2002) mimicking metastatic metastatic nodules have also been described with ADT.

Leuprorelin

Chemical composition and different formulas

Natural LHRH was first isolated and identified in 1971 (Schally et al 1971). Leuprorelin (leuprolide acetate) was first synthesized in 1974 by Takeda Chemical Industries, Japan (Fujino et al 1974).

Leuprorelin is a synthetic non-peptide analogue of naturally occurring porcine LHRH. It has a longer half-life than natural LHRH due to its enhanced binding affinity and increased resistance to peptidase degradation. At least two alterations in chemical structure serve to enhance the biologic activity of GnRH. These alterations include substitution of a D-amino acid for the glycine molecule at position 6 and deletion of the glycine molecule at position 10, and usually replacement by an N-ethylamide group (Monahan et al 1973). Leuprorelin is 80 times more potent than natural LHRH (Chrisp and Sorkin 1991).

Leuprorelin is orally inactive and originally was generally given subcutaneously or intramuscularly; leuprorelin 1 mg was given by daily injection. However, a depot formulation was soon developed to enable convenient subcutaneous or intramuscular injection at 1-month intervals. The clinical benefit of treating prostate cancer with LHRH analogues was reported from 1982 (Tolis et al 1982).

Leuprorelin was initially administered subcutaneously to men with metastatic prostate cancer as a daily 1-mg injection, starting in 1985.

The monthly depot was first launched in Europe in France in April 1989, and now is well established as the leading LHRH analogue. Since the publication of earlier reviews (eg, Chrisp and Sorkin 1991), new formulations have also been developed to maximize flexibility and convenience of administration for both doctor and patient.

Microsphere technology enables leuprorelin to be given as a depot formulation. Leuprorelin microspheres range in mean diameter between 10 and 20 mm for the 1-month depot and between 10 and 30 mm for the 3-month depot. Clinically, this means that leuprorelin can be given as a liquid injection through a fine-gauge needle using conventional injection techniques.

Sustained-release parenteral depot formulations, in which the hydrophilic leuprorelin is entrapped in biodegradable highly lipophilic synthetic polymer microspheres, have been developed to avoid daily injections (Sharifi et al 1997; Periti et al 2002). In-situ forming drug delivery systems are prepared by dissolving a drug and a biodegradable polymer (poly (D, L-lactide-co-glycolide; PLGA) in a biocompatible organic solvent. In clinical studies of prostatic cancer, use of the depot formulation has effectively reduced the dose required to as low as one-eighth of that needed for administration by daily injection (Togushi 1992).

Three- and 4-month formulations of leuprorelin were approved by the FDA for this indication in 2002 and 2003. Within a few years of its introduction, the 3-month depot accounted for 45% of the LHRH agonist market, and the 4-month formulation accounted for 40% of the market in its first year.

The development of depot forms of the LHRH agonists provided a well accepted approach to effective castration. Current formulations of 3- or 4-month (or longer) preparations are widely utilized; the most recent addition is the 6-month formula. Other benefits of the LHRH agonists include no cardiovascular toxicity and the fact that the "castration" is reversible.

Subcutaneous implants have been developed; the implant is designed to be removed after 12 months, and then another implant can be inserted for continued therapy.

Implants require a surgical incision and have greater injection site reactions; however, patients avoid multiple injections. The leuprorelin implant (Viadur®) effectively suppressed testosterone concentrations to less than the castrate threshold and maintained that suppression throughout

the study period (Fowler et al 2000a). Some authors claimed testosterone suppression to the castrate range of 100% (Fowler et al 2000b; Mark 2003).

Histrelin acetate 50 mg subdermal implant (Vantas®) also seems to achieve similar results in men with advanced prostatic cancer. The hydrogel implant provided consistent delivery of histrelin over 1 year. Testosterone suppression was maintained throughout the 52 weeks after implantation in more than 99% of patients. No testosterone or LH surge was observed with re-implantation. PSA, a secondary end point for effectiveness, was also suppressed significantly from baseline (Schlegel 2006).

Pharmacokinetics

After injection of the 1-month depot formulation of leuprorelin 3.75 mg, peak serum levels are achieved within 1 hour, followed by a rapid fall over the next 24 hours. A dose-dependent plateau is maintained over at least 5 weeks, representing a constant rate of release of leuprorelin from the copolymer (Mazzei et al 1990).

As with the 1-month injection, the 3-month injection (11.25 mg), results in an initial rise in serum levels of leuprorelin, followed by continuous linear release. A serum level of about 200–287 pg/mL is maintained over at least 3 months (Wechsel et al 1996) (equivalent to that achieved with a 1-month dose of 3.75 mg after repeated injections).

Mechanism of action

Leuprorelin acts as a potent inhibitor of gonadotropin secretion when given continuously in therapeutic doses. Animal and human studies indicate that after an initial stimulation as with other LHRH analogues (3–4 days), chronic administration of leuprorelin suppresses testicular and ovarian steroidogenesis. In humans, administration of leuprorelin initially increases circulating levels of LH and FSH, leading to a transient increase in levels of the gonadal steroids. However, continuous administration of leuprorelin decreases levels of LH and FSH, and subsequently reduces testosterone. These decreases occur within 2–4 weeks after initiation of treatment.

To obtain optimal therapeutic effect against androgen-dependent tumor cells, serum testosterone levels must be reduced to castrate levels (=50 ng/dL) (Fergusson 1957). This level can be achieved by a 1-month depot injection of 3.75 mg leuprorelin (Whitaker et al 2002) or by at 3-month depot injection of 11.25 mg (Khan and O'Brien 1998), or other new depot formulations.

GnRH agonist administration was shown by Redding and Schally to reduce the growth of prostate tumors in rats (Redding and Schally 1983). Early clinical studies in metastatic or advanced prostate cancer established the efficacy of daily s.c. injection of leuprorelin (1–20 mg) in suppressing testosterone levels, delaying tumor progression, and alleviating symptoms of locally advanced and metastatic prostate cancer (Trachtenberg 1983; Yamanak et al 1984). This effect is reversible upon discontinuation of drug therapy and this therapeutic approach has now replaced surgical castration.

Comparative studies on other androgen suppression modalities (Table 3): comparison of different depot formulas

The US Food and Drug Administration (FDA) has emphasized the importance of testosterone in prostate cancer therapy by utilizing decrease in testosterone associated with ADT as a surrogate endpoint for prostate cancer treatment (Brawerr 2001). It is intriguing that the agency uses testosterone and not PSA level in this regard. Therapies directed at treating prostate cancer on a hormonal basis need only to demonstrate achievement of castrate levels of testosterone for approval by the FDA.

Another requirement of GnRH agonists and other endocrine therapies for prostate cancer is the ability to maintain castration levels of testosterone while on long-term therapy. Different formulas have been proven to be meet those criteria (Table 4). Selecting the best product may be based on: patient comfort, side effects or injection-site reactions, ease of use such as patient preparation, time, and staffing required for administration.

Six-month formulation of leuprorelin depot (Eligard® 45-mg)

Six-month leuprorelin acetate (Eligard® 45-mg; Atrix Laboratories) is a new formulation for the palliative treatment of advanced prostate cancer.

In recent study conducted by Crawford et al (2006), the 6-month depot formulation of leuprorelin 45-mg (Eligard®) was evaluated clinically in a 12-month, open-label, multicenter study in patients with prostate cancer. The mean time required to reach castrate T levels (<50 ng/dL) was 21 days, 99% had 12-month testosterone (T) levels <50 ng/dL, and 88% patients had T levels <20 ng/dL. Mean PSA levels decreased from 39.8 ± 21.5 ng/mL at baseline to 1.2 ± 0.3 ng/mL at 12 months.

Table 3 Leuprorelin: comparative studies to other androgen suppression modalities

	Testosterone lowering/ blocking method	Comment	Reference
Leuprorelin	Orchietomy	Equivalent, orchiectomy, cost effective but associated with psychological complications	(Parmar 1985; Cassileth 1989; Iversen 1998; McLeod 2003)
	Estrogens (DES 3 mg) vs 1 mg/day leuprorelin	Equivalent, less cardiovascular side effects with leuprorelin.	(LSG 1984)
	Other LHRH agonists	No meaningful difference among the various approved GnRH agonists.	(Seidenfeld 2000)
	LHRH antagonists (aberalix)	Short time to testosterone suppression. No testosterone surge with aberalix. Safety is comparable to that of LHRH agonists with or without anti-androgens.	(McLeod 2001; Debruyne 2004)

Abbreviation: LHRH, luteinizing hormone-releasing hormone.

The 6-month formula of leuprorelin is the new addition which has a number of advantages over shorter-acting depot products, while reducing the need to schedule actual treatment time to only twice yearly.

Patients who may benefit from include those who:

- Are stable and well controlled on palliative therapy
- Travel for extended periods of time
- Have difficulty getting to the physician's office (eg, due to limited mobility or long travel distance)
- Receive an LHRH agonist as neoadjuvant therapy.

Moreover, the change in Medicare reimbursement (Painter 2005) for injections to "budget neutral" removes any incentive for favoring a formulation that is given more often over one that is given every 6 months. Of the urologists polled, 77% said that they were likely to use a 6-month depot rather than the shorter treatment regimens currently available. This novel delivery system allows for a low-volume injection, with very small changes in volume with increased dosage.

The Atrigel® Delivery System is composed of a biodegradable polymer (DL-lactide-coglycolide) dissolved in a biocompatible liquid solvent (N-methyl-2-pyrrolidone, or NMP). Because of its larger volume, leuprorelin depot is typically injected into the buttocks, necessitating the use of a treatment room. Patients receiving Lupron® Depot may experience pain at the injection site lasting up to 2 days, large abscesses, and bruising. However, there was no statistically significant difference in pain experienced on injection of goserelin and leuprorelin when patients were unaware of needle size (Montgomery et al 2005).

Conclusion

After seven decades, ADT has stood the test of time and gained its place as the mainstay of treatment for advanced and metastatic prostate cancer. It has relieved the symptoms and prolonged the life of many patients. Its discovery and refinement have brought two Nobel prizes to the medical community, first with the seminal work of Charles Higgins on the influence of the endocrine system on the development of a human malignancy in 1966, and then in 1977 with Andrew Schally's work on the hypothalamic hormones.

ADT went through several steps and refinement processes to reach its current status. In the 1940s the only option available was the irreversible castration through orchiectomy or the administration of female hormones, today the options are myriad.

The availability of long-acting synthetic LHRH agonists in the 1980s revolutionized the hormonal treatment of

Table 4 Leuprorelin formulas and testosterone suppression

Leuprorelin formula	Injection volume (mL)	Testosterone castrate level		Authors
		50 ng/dL	20 ng/dL	
7.5 mg monthly	0.250	100.0%	97.5%	Perez-Mareno 2002
22.5 (3 month)	0.375	98%		Berges 2006
		98%	84%	Chu 2002
30 mg (4 month)	0.500	96%		Sharifi 1998
45.0 mg (6 month)	0.375	99%	88%	Crawford 2006

prostate cancer, enabling many men to avoid the emotional and psychological effects of surgical castration. The depot formulas have gained wide acceptance from both patients and physicians.

The 6-month formula of leuprorelin represents a new addition to the armentarium that has a number of advantages over shorter-acting depot products. It suppresses the testosterone to the castrate level in the majority of patients completing treatment without any breakthrough responses.

Compared with a 3-month depot, the 6-month depot is associated with two rather than four opportunities for patients to lose therapeutic effect if they delay their injection beyond the formulation's normal duration, thus improving the patient's compliance to therapy and quality of life.

The limited number of injections reduces the anxiety due to physician's office visit and fear of pain; injection takes minimal time which is the most desirable option from the nursing standpoint. The drug is well tolerated while maintaining a side effect profile comparable to other products in its class.

These advantages coupled with the recent change to Medicare legislation will make long-duration formulation an attractive option for physicians, and will certainly tip the balance in favor of this option in treating prostate cancer patients fulfilling the criteria for receiving such products.

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