Clinical Interventions in Aging

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Six-month depot formulation of leuprorelin acetate in the treatment of prostate cancer

This article was published in the following Dove Press journal:
Clinical Interventions in Aging
28 May 2009
Number of times this article has been viewed

Rajni Sethi
Nicholas Sanfilippo

Department of Radiation Oncology, New York University Langone Medical Center, New York, NY, USA

Abstract: Hormonal deprivation therapy is well established for the treatment of locally advanced and metastatic prostate cancer, as well as the adjuvant treatment of some patients with localized disease. Long-acting gonadotropin releasing hormone (GnRH) agonists have become a mainstay of androgen deprivation therapy, due to their efficacy, tolerability, and convenience of use. One-month, 3-month, and 4-month depot leuprorelin formulations are well established and widely used to this end. Recently, a 6-month depot leuprorelin has been approved for use in advanced and metastatic prostate cancer patients. With similar efficacy and side effect profiles to earlier formulations, 6-month depot leuprorelin is a convenient treatment option for these patients. This review will highlight the role of GnRH agonists in the treatment of prostate cancer with a focus on the clinical efficacy, pharmacology, and patient-focused outcomes of the newer 6-month 45 mg depot leuprorelin formulation in comparison to available shorter-acting products.

Keywords: prostate cancer, leuprorelin, hormonal deprivation therapy

Prostate cancer is one of the leading causes of cancer deaths among men in the United States. Current treatment options include radical prostatectomy, external beam radiotherapy, brachytherapy, and hormonal therapy. Hormonal therapy has become a mainstay of palliative treatment for patients with locally advanced or metastatic disease. Additionally, androgen deprivation is sometimes integrated with radiotherapy as definitive treatment of patients with localized disease. Selection factors for treatment include patient factors such as age, comorbidities, and patient preference; disease characteristics such as prostate-specific antigen (PSA), Gleason score, and stage; and psychosocial factors such as sexual function. Long-acting gonadotropin releasing hormone (GnRH) agonists have become widely accepted among patients and physicians as an alternative to earlier androgen-deprivation strategies, which included surgical castration and daily GnRH injections. Depot formulations of 1-month, 3-month, and 4-month dosages are well-established in the treatment of prostate cancer. This review will outline the role of hormonal deprivation therapy for prostate cancer patients, with an emphasis on the pharmacologic and clinical profile of a new 6-month depot formulation of leuprorelin acetate, also known as leuprolide acetate.

Therapeutic indications

Androgen suppression therapy is utilized as single-modality therapy for patients with localized disease as well as in conjunction with radiotherapy in patients with locally

Correspondence: Nicholas Sanfilippo
Department of Radiation Oncology, NYU Langone Medical Center, 160 East 34th Street, New York, NY 10016, USA
Tel +1 9212 731-5003
Email nicholas.sanfilippo@nyumc.org

advanced disease or intermediate to high risk localized disease.

The rationale for using androgen deprivation with radiation therapy is based on the principle that cytoreduction through 2 modalities, namely hormones and radiation, may be more effective than local therapy alone. Movement toward this therapy began in patients with adverse tumor features such as bulky tumors, high PSA, and high Gleason score since they carried a poor prognosis with radiation therapy alone. Androgen suppression therapy is usually given in a neoadjuvant and concurrent manner, with additional adjuvant treatment following radiotherapy in those patients requiring longer-term treatment.

Neoadjuvant hormonal therapy could theoretically improve tumor control through 3 mechanisms: (1) Cytoreduction of tumor volume through apoptosis, (2) enhanced tumor cell kill because of radiation induced damage that leads to alternative pathways for apoptosis, or (3) improved radiosensitivity through reduced intra-tumoral hypoxia. While it is unclear which mechanism is most active, the cytoreductive mechanism is most strongly supported by in vitro and in vivo animal experiments and clinical investigations.[1]

Multiple randomized-controlled trials have compared clinical outcomes of radiotherapy with adjuvant hormonal therapy to radiotherapy alone in prostate cancer patients with localized and locally advanced disease as well as patients with regional nodal involvement.[2–11] A meta-analysis of five consecutive Radiation Therapy Oncology Group (RTOG) phase III trials, including 2742 men treated between 1975 and 1992 showed improved outcomes in some groups of patients who received hormonal deprivation therapy. Patients were stratified into four prognostic risk groups based on Gleason score, clinical T-stage, and pelvic nodal involvement. PSA was not included because most patients were treated in the pre-PSA era. While low-risk patients (Gleason score 2–6 and T1–2Nx) did not benefit from adjuvant hormonal therapy, the intermediate- and high-risk groups (T3, N+, or Gleason score $>$ 6) had improved overall survival and 8-year disease-specific survival with the addition of long-term hormonal therapy.[12–13] In the intermediate- and high-risk groups, 8-year overall survival improved from 45% to 61% and 28% to 44%, respectively, and 8-year disease-specific survival improved from 70% to 88% and 42% to 69%, respectively, when long-term hormonal therapy was used.

Many investigators have adopted a combined neoadjuvant-concurrent-adjuvant approach to hormonal therapy. D'Amico and colleagues conducted a prospective randomized trial in intermediate- and high-risk patients. Patients had localized disease but were required to have at least one adverse feature, defined as a PSA of greater than 10, a Gleason score of greater than 7, or radiographic evidence of extraprostatic disease on magnetic resonance imaging. Intermediate-risk patients were those with a Gleason score of 7 and PSA $<$ 20 or with PSA 10–20 and Gleason $\geq$ 6. Patients were randomized to either radiation therapy alone to a dose of 70 Gy in 7 weeks to a localized prostate volume versus the same radiotherapy with 6 months of androgen suppression which was started 2 months before radiation and continued during radiation and then for 2 months after radiation. With a median follow-up of 4.5 years, the authors observed a significantly higher survival (88% vs 78% at 5 years), lower prostate cancer specific mortality (3.8% versus 0% at 5 years), and higher survival free of salvage androgen suppressive therapy (82% vs 57% at 5 years).[14]

The timing and duration of androgen deprivation are still debatable topics, but many investigators believe that 6 months of androgen deprivation is appropriate for intermediate-risk cases while a longer duration (2 to 3 years) is more appropriate for patients with high-risk disease. This neoadjuvant-concurrent-adjuvant approach has also been adopted for longer-term androgen deprivation. Current studies in the RTOG typically employ 2 months of hormone treatment prior to RT and then continue for a total of 2 years in high risk patients. Ongoing studies are also examining whether shorter durations of hormonal therapy will suffice since androgen deprivation can confer significant toxicity.

Androgens and the prostate

Testicular hormone secretion has long been known to influence prostate growth. In the 18th century, surgical castration was noted to cause prostate atrophy in adult animals and halt prostate growth in younger animals.[15] In the late 19th century, castration was utilized to treat urinary retention caused by prostatic hyperplasia. In one early case series published in 1895, over half of the patients experienced improvement of urinary symptoms after surgical castration.[16]

Androgen deprivation therapy (ADT) was first proposed as a treatment for prostate cancer in 1940 when castration was utilized to provide pain relief, stabilize tumor burden, and reduce serum acid phosphatase in prostate cancer patients with osseous metastatic tumors.[17,18]

Given the morbidity of surgical orchiectomy and associated clinical side effects, alternative anti-androgenic measures have been sought. One early approach attempted chemical castration through injection of the female hormones stilbestrol and hexestrol to neutralize the effect of testicular

androgens.[18] The mechanism of this effect was discovered many years later: estrogen inhibits hypothalamic GnRH release through a negative feedback mechanism.[19]

In subsequent decades, the role of the hypothalamic-pituitary axis in controlling testosterone production, namely through the secretion of GnRH, was elucidated. GnRH is secreted in a pulsatile fashion by the hypothalamus. This stimulates the anterior pituitary gland to release gonadotropin, which in turn acts on Leydig cells within the testes to stimulate testosterone production. Testosterone and adrenal androgens can be converted to dihydrotestosterone (DHT), a more potent hormone, within the cytoplasm of prostatic cells by the enzyme 5-alfa-reductase.[20] DHT binds to an androgen receptor within the cytosol, then translocates into the nucleus where it can affect gene synthesis, the production of proteins such as prostate-specific antigen (PSA), and cellular functions such as proliferation, growth, and cell death.

In subsequent years, multiple classes of anti-androgenic drugs have been developed to target the different steps of elucidated androgen regulatory pathways. These drug classes include GnRH agonists, GnRH antagonists, anti-androgens, 5-alfa reductase inhibitors, and the antifungal agent ketoconazole.[21–23] In clinical practice, synthetic GnRH agonists, especially in depot formulations, remain the mainstay of hormonal ablative therapy.

Currently available leuprorelin formulations

In 1971, GnRH was first isolated and characterized in the laboratory.[24] Leuprorelin, a synthetic analogue of GnRH, was first synthesized for clinical use in 1974.[25] Leuprorelin has a longer half-life and is 80 times more potent than naturally occurring GnRH, because of its enhanced binding affinity and increased resistance to degradation by peptidases.[26] Alterations in the chemical structure, including substitution of a D-amino acid for glycine at position 6 and deletion of glycine at position 10 with the insertion of ethylamide, are responsible for these properties.[27]

The clinical benefits of GnRH analogues in prostate cancer patients were first described by Tolis et al in 1982. Ten patients with locally advanced or metastatic prostate cancer were treated with leuprorelin given as daily subcutaneous injections or twice daily intranasal applications for a period of 6 weeks to 12 months. During the treatment period, those patients with urinary obstruction noted improvement in urine flow, and those with osseous metastases reported decreased bone pain.[28]

In 1985, leuprorelin was approved by the US Food and Drug Administration (FDA) for the palliative treatment of advanced prostate cancer.[29] Although the first clinical uses of synthetic GnRH required cumbersome daily injections, usually 1 mg given subcutaneously or intramuscularly, development of this medication revolutionized hormonal ablation therapy by allowing men to avoid the psychological and emotional consequences of surgical castration.

Technological advances have fostered the development of multiple long-acting depot formulations of GnRH in order to improve convenience of use, quality of life, and patient compliance. The first long-acting formulation was a monthly injection approved by the FDA in 1989 for treatment of advanced prostate cancer.[30] In the US, leuprorelin is now available in monthly (7.5 mg), 3-monthly (22.5 mg), 4-monthly (30 mg), and 6-monthly (45 mg) dosages.

The 3-monthly and 4-monthly formulations were approved by the FDA in 2002 and 2003, respectively, for treatment of advanced prostate cancer. They gained wide popularity, and within a year of its release, the 4-monthly formulation accounted for 40% of the market.[31] Most recently, the FDA approved a 45 mg 6-month depot leuprorelin in December 2004 for the palliative treatment of locally advanced or metastatic prostate cancer. These long-acting formulations are easy to use and require less effort on the part of both patient and clinician, which may in turn improve patient compliance, clinical efficacy, and outcomes. Additionally, unlike surgical castration, these medications are reversible, which can protect patients from the long-term consequences of a hypo-androgenic state such as osteopenia and muscle atrophy.

In Europe, a 3.75 mg 1-month depot leuprorelin formulation and an 11.25 mg 3-month depot formulation are available for prostate cancer treatment. In the US, these dosages are FDA approved only for the treatment of endometriosis, fibroids, and precocious puberty, but not for the treatment of prostate cancer. A 6-monthly 30 mg leuprorelin dosage has been developed and tested for efficacy and clinical safety in a recent European multicenter prospective trial.[32]

Sustained release parenteral depot formulations administer hydrophilic leuprorelin that has been entrapped in biodegradable, highly lipophilic synthetic polymer microspheres. The preparation is made by dissolving both the drug and the biodegradable polymer in an organic solvent, with resultant in situ microsphere formation. Leuprorelin is released from the microspheres at a functionally constant rate over 1, 3, 4, or 6 months, depending on the polymer type.[33,34]

The delivery system for the six-month depot formulation utilizes a DL-lactide-co-glycolide polymer, with an 85:15 DL-lactide to glycolide molar ratio.

A12-month subcutaneous implant was developed and briefly available for clinical use after approval by the FDA in 2000 for treatment of locally advanced or metastatic prostate cancer. However, the drug did not gain popularity and was eventually discontinued by the manufacturer in December 2007.[35,36] There may have been less interest in this formulation compared to the depot injections because the 12-month implant entailed a surgical procedure for administration and required good follow-up with patient return for implant removal 12 months later.

Mode of action

Leuprorelin, is a synthetic nonapeptide analogue of naturally occurring GnRH. The chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt).[37]

When given continuously, leuprorelin inhibits pituitary secretion of gonadotropin, which in turn suppresses testicular and ovarian steroidogenesis. Initial administration of leuprorelin causes an increase in gonadotropin levels, which can last for several weeks, leading to a rise in gonadal steroid production during that time. With continuous administration, there is eventual suppression of gonadotropin release within 2 to 4 weeks. In males, testosterone is reduced to a level below the castrate threshold, or ≤50 ng/dL. Upon removal of the drug, this effect is reversible.[33]

Pharmacokinetics of leuprorelin depot

Because it is a peptide, leuprorelin is not active when given orally and is usually administered through a subcutaneous or intramuscular route.

Pharmacokinetic studies showed that mean peak plasma leuprorelin concentrations (C_{max}) were 13.1, 21.8, 47.4, 54.5 and 53 μg/L after injection of 3.75, 7.5, 11.25, 15, and 30 mg depot formulations, respectively, and occurred within 1 to 3 hours of administration. After subcutaneous injection of 1 mg of a non-depot formulation, mean C_{max} was 35 μg/L and occurred 36 to 60 minutes after injection.[39] Following injection of 45 mg 6-month depot formulation, there was an early rise in C_{max} to 82.0 ng/mL 4.5 hours after the initial administration. On the second injection, 6 months after the initial treatment, mean C_{max} was 102 ng/mL and occurred 4.5 hours after the second injection. After these initial increases, mean serum levels remained constant within the 0.2 to 2 ng/mL range.[37]

The mean volume of distribution of leuprolide after bolus administration in a group of healthy male volunteers was 27 L.[39] After a single subcutaneous injection of 1 mg, 3.75 mg, 7.5 mg, or 15 mg leuprorelin, the mean volumes of distribution were 36 L, 33 L, and 27 L, respectively.

Total body clearance and elimination half-life were 9.1 L/hour and 3.6 hours, respectively, after a 1 mg subcutaneous administration. After intravenous bolus, these values were 8.3 L/hour and 2.9 hours, respectively.[33]

To our knowledge, there is no published data documenting the volume of distribution, elimination half-life, or clearance of the 45 mg 6-month depot formulation of leuprorelin. The pharmacokinetics of leuprorelin have not been evaluated in a population of patients with compromised kidney or liver function.

Efficacy

Serum testosterone

The efficacy of the 6-month depot leuprorelin formulation was evaluated in a 12-month, open label, multicenter trial. One hundred eleven patients with prostate adenocarcinoma were enrolled. Inclusion criteria were stage > T1, WHO performance score 0–2, and life expectancy ≥1 year. Patients received leuprorelin 45 mg subcutaneously on days 1 and 168, a six month interval.[38] The primary endpoint of this study was a decrease in serum testosterone to a level equivalent to or below that resulting from surgical castration. Historically, the FDA had established the castrate threshold, or the testosterone level consistent with that obtained after surgical orchiectomy, to be 50 ng/dL.[41] However, this was largely based on the sensitivity of available laboratory assays at the time. With the development of newer assay techniques, substantially lower testosterone levels (15 ng/dL) have been observed in men after bilateral orchiectomy, which has led to reassessment of the historical threshold level by the medical community. The National Comprehensive Cancer Network amended its guidelines to suggest that serum testosterone level ≤ 20 ng/dL reflected optimal control of testosterone after surgical or chemical castration, and several other expert opinions have been published on this matter in agreement.[41,42] In light of this, the 6-month depot leuprorelin efficacy study evaluated the number of patients with serum testosterone level below two separate thresholds: 50 ng/dL and also below 20 ng/dL, measured on at least two occasions at least 1 week apart. Serum PSA and gonadotropin levels and treatment-related toxicity were also assessed.

One hundred three of the 111 enrolled patients received both injections. There was an initial rise in testosterone

level, which increased to a mean level of 588 ng/dL by day 2. By day 28, 108 patients (97%) had achieved a serum testosterone level at or below the castrate threshold (50 ng/dL), and 92 (83%) had achieved optimal control of testosterone (≤20 ng/dL). After 12 months, 102 of the 103 (99%) patients who completed the study had testosterone levels below castrate threshold, and 91 patients (88%) had optimal control of testosterone. Median time to reach castrate level was 21 days.

One patient did not experience castrate level androgen suppression and was removed from the study at day 85. During a follow-up period of 12 months, only 1 patient experienced breakthrough testosterone levels above 50 ng/dL.[38]

In comparison to conventional GnRH agonists, clinical studies indicate that 6-month depot leuprorelin may be more efficacious, although there are no prospective trials comparing these different formulations. Five percent to 17% of patients treated with daily GnRH injections do not reach the historical castrate level (≤50 ng/dL), and 13% to 34% fail to achieve optimal control of testosterone (≤20 ng/dL).[40,43–47]

Six-month depot leuprorelin appears to have similar efficacy to the other available depot formulations. The proportion of patients achieving optimal testosterone control (≤20 ng/dL) after 6 to 8 months of treatment with 6-monthly (45 mg), 4-monthly (30 mg), 3-monthly (22.5 mg), and monthly (7.5 mg) formulations were 94%, 90%, 97.5%, and 94%, respectively.[48–50] Among the different formulations, 98% tp 100% of patients who completed the study had castrate level serum testosterone at study completion.

Transient testosterone escape (level ≥ 50 ng/dL on two separate occasions at least a week apart) was observed in no patients treated with the 7.5 mg monthly or 22.5 mg 3-monthly formulations. Three patients treated with the 30 mg 4-monthly formulation had transient testosterone breakthrough at 4 months, and 1 of these patients had a second breakthrough at 8 months. This patient had a small but clinically insignificant rise in PSA from 2.2 to 2.6 during the first breakthrough response but did not exhibit any other PSA elevations during treatment. One patient treated with the 45 mg 6-monthly formulation had transient testosterone breakthrough.[38,48–50]

Testosterone breakthrough is seen in about 5% of patients treated with conventional, daily leuprorelin injections.[40] There are several theories to explain this phenomenon, including increased GnRH receptor density during treatment, alternate GnRH receptor expression, phosphorylation of the GnRH receptor or its downstream G-protein, and uncoupling of the GnRH receptor and its target G-protein.[51]

A recent European multicenter, prospective randomized trial compared treatment of prostate cancer patients over 12 months with an 11.25 mg 3-monthly formulation (currently approved for use in Europe), with two different 6-month depot formulations: a 22.5 mg dose and a 30 mg dose. One hundred seventy-eight patients with newly diagnosed or relapsed prostate cancer of any grade or stage were enrolled in the trial. Because of inferior response rates and efficacy of the 22.5 mg 6-month depot formulation, it was not selected for submission for approval in European countries, and therefore results from that arm were not published. The remaining two arms had similar efficacy and safety profile. After 12 months of treatment, 100% versus 98% of patients treated with 11.25 mg 3-month depot and 30 mg 6-month depot leuprorelin, respectively, had serum testosterone levels below castrate level (≤50 ng/dL), and 90% versus 81% had optimal testosterone control (≤20 ng/dL), respectively. These differences were not statistically significant.[38] As a result of this study, the 30 mg 6-month depot formulation has been submitted for approval for use in the treatment of prostate cancer patients in Europe.

Several recent studies indicated that depot leuprorelin formulations may be efficacious for longer than the recommended dosing intervals. Pathak et al conducted a prospective study in which 42 patients were treated with 22.5 mg subcutaneous injections of leuprorelin every 3 months, on day 1, after 12 weeks, and after 24 weeks. Serum testosterone levels were monitored at baseline, after 12 weeks, after 24 weeks, and monthly thereafter. If patients were still at castrate levels after 24 weeks, the subsequent injection was withheld until testosterone exceeded 50 ng/dL. After a median follow-up of 18 months, the median dosing interval was 6 months, with a range of 5 to 12 months.[52]

A recent prospective trial by Greil et al evaluated this type of testosterone-based treatment approach in patients treated with the 30 mg 4-month depot leuprorelin formulation. Serum testosterone levels were obtained at baseline and then monthly beginning 4 months after the first injection and 2 months after subsequent injections for a total of 18 months. The median number of days from injection to the first serum testosterone level ≥ 50 ng/dL was 159, 189, and 163 days for the first, second, and third treatment cycle, respectively.[53]

A multicenter randomized controlled trial by Gulley et al assessed time to testosterone recovery in 159 patients treated with two 6-month cycles of GnRH agonist therapy with two 3-month injections of leuprorelin (22.5 mg) or goserelin, another GnRH agonist.[54] Serum testosterone, DHT, and PSA were measured monthly until serum PSA progressed

to a level above 5 ng/mL, at which point a second cycle was administered. Median time to testosterone normalization was 15.4 weeks and 18.3 weeks after cycles 1 and 2 respectively. Median time to DHT normalization was 15.2 weeks and 18.7 weeks after cycles 1 and 2, respectively.

These three studies suggest that patients treated in a testosterone-based manner can achieve sustained efficacy with exposure to fewer injections and lower drug levels, which may improve cost effectiveness and side effect profiles of GnRH agonist therapy. Additionally, periodic monitoring of serum testosterone levels is an important step in identifying patients who fail to achieve castrate levels or have breakthrough rises in testosterone while undergoing androgen deprivation treatment. For these reasons, some physicians are proponents of an individualized approach to hormonal deprivation therapy based upon patient serum testosterone levels as opposed to simply adhering to recommended dosing intervals.

Prostate-specific antigen

In patients treated with 45 mg 6-month depot leuprorelin, the percentage of patients with serum PSA levels within the normal range (<4 ng/mL) at baseline and after treatment was 25% and 96%, respectively. Mean PSA at baseline and after 12 months of treatment was 39.8 ng/mL and 1.2 ng/mL, respectively. This is similar to levels seen in patients treated with 7.5 mg monthly, 22.5 mg 3-monthly, and 30 mg 4-monthly dosages (Table 1).[38,48–50]

Similar PSA levels were seen in the European randomized-controlled trial evaluating the lower dose depot formulations, including 11.25 mg 3-month depot and 30 mg 6-month depot leuprorelin. During months one through 12 of the study, PSA levels ranged from 0.2 to 1.0 ng/mL in the 3-monthly group and from 0.3 to 1.1 ng/dL in the 6-monthly group.

Table 1 Effect of depot leuprorelin on serum prostate-specific antigen (PSA) level[38,48–50]

	Leuprorelin dosage			
	7.5 mg	**22.5 mg**	**30 mg**	**45 mg**
Pretreatment				
Mean PSA	32.9	86.4	13.2	39.8
% patients with PSA <4 ng/mL	25	27	24	33
End of study				
Mean PSA	1.2	1.7	1.3	3.2
% patients with PSA <4 ng/mL	96	93	83	96

Serum gonadotropin

In the European multicenter clinical efficacy trial for 45 mg 6-monthly leuprorelin, there was an initial rise in gonadotropin as a result of leuprorelin's GnRH agonist properties. Eight hours after injection with 45 mg depot leuprorelin, gonadotropin had increased to a mean of 37.9 mIU/mL. By day 7, mean gonadotropin decreased below baseline (6.9 mIU/mL), and it consistently declined over the first 19 weeks to a mean level of 0.1 mIU/mL. After the second injection, there was a transient, small increase in serum gonadotropin level to 0.2 mIU/mL on day 169, and gonadotropin levels remained steady at this level for the remainder of the study.[38]

A similar pattern of gonadotropin surge was seen with administration of 7.5 mg monthly, 22.5 mg 3-monthly, and 30 mg 4-monthly dosages in the respective efficacy trials. Peak gonadotropin levels occurred on days 1 or 2 after leuprorelin administration, and decreased to below baseline between days 10 and 14.

An initial rise in testosterone occurs in parallel with this gonadotropin surge. Mean testosterone increased by 225 ng/dL by day 2, to 588 ng/dL, after the first injection of 6-month depot leuprorelin. A similar effect was seen with the other depot formulations.[55,56] No clinically significant flare reactions in response to the early testosterone rise have been reported.[38,48–50]

Safety and tolerability

The majority of patients undergoing treatment with depot leuprorelin experience mild side effects. Fewer patients experience moderate adverse reactions, and severe toxicity is rarely reported. The most common side effects of leuprorelin are hot flashes, injection site reactions, fatigue, testicular atrophy, and gynecomastia.

After treatment with 45 mg 6-month depot leuprorelin, 82 (74%) of 111 participants reported 211 treatment-related side effects. One event was reported as severe, although the type of adverse reaction was not documented, and the other 210 events were mild to moderate.[38]

Depot leuprorelin 45 mg 6-month has a similar side effect profile to the other depot formulations. Fifty-seven percent of patients treated with 22.5 mg 3-month depot leuprorelin experienced mild side effects, 12% experienced moderate side effects, and no patients experienced severe side effects.[49] Eighty-five percent of patients treated with 30 mg 4-month depot leuprorelin experienced treatment-related side effects, with 97% of these reactions being mild to moderate and 3% documented as severe hot flashes.[50]

Seventy-four percent of patients treated with monthly depot leuprorelin experienced side effects of treatment. Most events were graded as mild to moderate; however 4% were considered severe, including hot flashes in 1 case and injection site burning in 4 instances.[48]

Overall, with the exception of a notably higher rate of mild injection site reactions documented in patients receiving the 22.5 mg dosage, there were no substantial differences between the side effect profile of patients treated with the different depot formulations (Table 2).

No patients stopped treatment with the 45 mg, 22.5 mg, or 7.5 mg dosages due to treatment-related side effects. However, 3% of participants in the 4-month 30 mg depot leuprorelin clinical efficacy trial stopped because of side effects of treatment, although the specific reactions that caused patients to withdraw from the study were not documented.[50]

Treatment compliance of patients enrolled in the above clinical efficacy trials was good. Of the patients enrolled for treatment with 7.5 mg monthly, 22.5 mg 3-monthly, 30 mg 4-monthly, and 45 mg 6-monthly leuprorelin, 98%, 98%, 91%, and 93% completed the 1-year treatment course, respectively.

In the European randomized controlled trial evaluating the lower-dose formulations (11.25 mg 3-month depot and 30 mg 6-month depot leuprorelin), 4% of patients withdrew from the study because of treatment-related adverse events. The most common side effects were hot flashes and injection-site reactions. Hot flashes occurred in 43% versus 34% of patients treated with 3-monthly and 6-monthly injections, respectively, and injection site reactions occurred in 2% and 11% of patients, respectively. About two-thirds of the injection site reactions were considered severe.[32]

In summary, the available depot leuprorelin formulations are convenient and well tolerated with acceptable side effect profiles. Severe adverse events are rare, and patient compliance within published clinical studies is good. Few patients withdrew from the trials because of treatment-related side effects, and over 90% of patients completed the treatment course.

Conclusions

Hormonal deprivation therapy has become the mainstay of treatment for locally advanced and metastatic prostate cancer, as well as for the adjuvant treatment of patients with intermediate-risk or high-risk localized prostate cancer. Androgen deprivation has been shown to improve quality of life and prolong life in many patients who fall within these categories.

Surgical castration was the earliest form of androgen deprivation, but this has been replaced by chemical agents, which potentially have less physical and emotional impact than the surgical alternative. GnRH agonists are potent agents that block testosterone secretion from the testes, which encompasses 90% of the body's testosterone production.[31] While the first synthetic GnRH analogues required daily injections, the introduction of long-acting synthetic GnRH agonists in the 1980s and 1990s revolutionized the hormonal treatment of prostate cancer. With their ease of use, tolerable side effect profile, and good efficacy, the depot formulations have gained wide acceptance from both patients and the medical community alike.

Today, 3-month and 4-month depot leuprorelin formulations are the most commonly used hormonal agents for the treatment of prostate cancer. Treatment with the shorter-acting variations such as 1-month depot and daily formulations presents more opportunities for patients to delay or altogether miss treatments, which can result in testosterone breakthrough and potentially deleterious effects on tumor control and symptom progression. The longer-acting formulations offer clinical benefit on these fronts by limiting the number of treatments involved in a therapeutic course.

Table 2 Treatment-related adverse events of 6-month (45 mg), 4-month (30 mg), 3-month (22.5) mg, and 1-month (7.5 mg) depot leuprorelin[38,48–50]

	Leuprorelin dose			
Adverse event: Mild – Moderate – Severe (%)	**45 mg**	**30 mg**	**22.5 mg**	**7.5 mg**
Hot flashes	33–24–0	59–18–2	49–10–0	44–12–1
Injection site reaction	14–1–0	22–0–0	89–14–0	29–4–1
Fatigue	7–5–0	10–4–0	6–0–0	13–4–0
Testicular atrophy	5–2–0	4–0–0	2–0–0	4–1–0
Gynecomastia	4–0–0	2–0–0	1–0–0	1–1–0

The most recent addition to the hormonal deprivation armament is the 45 mg 6-month depot leuprorelin formulation. Further reducing the number of injections patients receive presents a number of advantages. First, treatment compliance will likely be improved with a decreased number of therapeutic delays or misses resulting in testosterone breakthrough. Second, patients may have fewer clinic visits, which are often anxiety-ridden and disruptive to their daily routine. Finally, since burning at the injection site is one of the most commonly reported treatment-related adverse events, the longer-acting formulations may improve the overall tolerability of the treatment by exposing patients to fewer injections.

In the US, multiple long-acting depot products (7.5 mg monthly, 22.5 mg 3-monthly, 30 mg 4-monthly, and 45 mg 6-monthly formulations) have been approved for use in prostate cancer. In Europe, several additional, lower-dose depot products have been approved for treatment of prostate cancer patients, including 3.75 mg monthly and 11.25 mg 3-monthly formulations.

Two clinical trials have shown that testosterone is often suppressed for longer than the recommended interval for a given depot product.[52,53] Therefore, some physicians are proponents of an individualized, testosterone-based treatment system that utilizes periodic evaluation of serum testosterone levels to guide injection intervals and to detect non-responders and testosterone breakthrough.

In clinical trials thus far, 45 mg 6-month depot leuprorelin has similar clinical efficacy and tolerability, with acceptable rates of mild side effects and low rates of moderate to severe adverse events, compared with preceding shorter-acting depot formulations. The associated benefits of improved convenience, compliance, and tolerability will likely make this formulation popular among physicians and patients alike within the coming years.

Disclosures

The authors declare no conflicts of interest.

References

1. Zietman AL, Nakfoor BM, Prince EA, et al. The effect of androgen deprivation and radiation therapy on an androgensensitive murine tumor: an in vitro and in vivo study. *Cancer J Sci Am*. 1997;3: 31–36.
2. Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): A phase III randomised trial. *Lancet*. 2002;360:103–106.
3. Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med*. 1997;337:295–300.
4. D'Amico AV, Manola J, Loffredo M, et al. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: A randomized controlled trial. *JAMA*. 2004;292:821–827.
5. Denham JW, Steigler A, Lamb DS, et al. Short-term androgen deprivation and radiotherapy for locally advanced prostate cancer: Results from the Trans-Tasman Radiation Oncology Group 96–01 randomised controlled trial. *Lancet Oncol*. 2005;6:841–850.
6. Granfors T, Modig H, Damber JE, et al. Combined orchiectomy and external radiotherapy versus radiotherapy alone for nonmetastatic prostate cancer with or without pelvic lymph node involvement: A prospective randomized study. *J Urol*. 1998;159:2030–2034.
7. Laverdiere J, Nabid A, De Bedoya LD, et al. The efficacy and sequencing of a short course of androgen suppression on freedom from biochemical failure when administered with radiation therapy for T2–T3 prostate cancer. *J Urol*. 2004;171:1137–1140.
8. Pilepich MV, Caplan R, Byhardt RW, et al. Phase III trial of androgen suppression using goserelin in unfavorable-prognosis carcinoma of the prostate treated with definitive radiotherapy: Report of Radiation Therapy Oncology Group protocol 85–31. *J Clin Oncol*. 1997;15:1013–1021.
9. Pilepich MV, Krall JM, al-Sarraf M, et al. Androgen deprivation with radiation therapy compared with radiation therapy alone for locally advanced prostatic carcinoma: A randomized comparative trial of the Radiation Therapy Oncology Group. *Urology*. 1995;45:616–623.
10. Pilepich MV, Winter K, John MJ, et al. Phase III radiation therapy oncology group (RTOG) trial 86–10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. *Int J Radiat Oncol Biol Phys*. 2001;50:1243–1252.
11. Pilepich MV, Winter K, Lawton CA, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma – long-term results of phase III RTOG 85–31. *Int J Radiat Oncol Biol Phys*. 2005;61:1285–1290.
12. Roach M 3rd, Lu J, Pilepich MV, et al. Four prognostic groups predict long-term survival from prostate cancer following radiotherapy alone on Radiation Therapy Oncology Group clinical trials. *Int J Radiat Oncol Biol Phys*. 2000;47:609– 615.
13. Roach M 3rd, Lu J, Pilepich MV, et al. Predicting long-term survival, and the need for hormonal therapy: A meta-analysis of RTOG prostate cancer trials. *Int J Radiat Oncol Biol Phys.* 2000;47:617–627.
14. D'Amico AV, Manola J, Loffredo M, Renshaw AA, DellaCroce A, Kantoff PW. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. *JAMA*. 2004;292(7):821–7.
15. Androustos G. John Hunter (1728–1793): fondateur de la chirugie scientifique etpercurseur de l'urologic. *Prog Urol*. 1998;8:1087–1096.
16. White JW. The results of double castration in hyper-trophy of the prostate. *Ann Surg*. 1895;22:1–3.
17. Huggins C, Hodges CU. Studies on prostate cancer: the effect of castration, of estrogen, and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res*. 1940;1:293.
18. Huggins C, Stevens RE, and Hodges CV. Studies in prostatic cancer. *Arch Surg*. 1941;43:209–223.
19. Brawer MK. The evolution of hormonal therapy for prostatic carcinoma. *Rev Urol*. 2001;3:S1–S11.
20. Sandow J, von Rechenberg W, Engelbart K. Pharmacological studies on androgen suppression in therapy of prostate carcinoma. *Am J Clin Oncol*. 1988;11:S6–S10.
21. Debruyne FMJ. Gonadotropin-releasing hormone antagonist in the management of prostate cancer. *Rev Urol*. 2004;6:S25–S32.
22. Lowe FC, Bamberger MH. Indications for use of ketoconazole in management of metastatic prostate caner. *Urology*. 1990;36:541–545.
23. Iversen P, Melezinek I, Schmidt A. Nonsteroidal antiandrogens: a therapeutic option for patients with advanced prostate cancer who wish to retain sexual interest and function. *BJU Int*. 2001;87:47–56.
24. Schally AV, Arimura A, Baba Y, et al. Isolation and properties of the FSH and LH-releasing hormone. *Biochem Biophys Res Commun*. 1971;43:393–9.

25. Fujino M, Fukuda T, Shinagawa S, et al. Synthetic analogs of lutenizing hormone releasing hormone (LH-RH) substituted in position 6 and 10. *Biochem Biophys Res Commun*. 1974;60:406–413.
26. Chrisp P, Sorkin EM. Leuprorelin: a review of its pharmacology and therapeutic use in prostatic disorders. *Drugs Aging*. 1991;1:487–509.
27. Monahan MW, Amoss MS, Anderson HA, et al. Synthetic analogues of the hypothalamic lutenizing hormone releasing factor with increased agonist or antagonist properties. *Biochemistry*. 1973;12:4616–4620.
28. Tolis G, et al. Tumor growth inhibition in patients with prostatic carcinoma treated with luteinizing hormone-releasing hormone agonists. *Proc Natl Acad Sci U S A*. 1982;79:1658–1662.
29. Santen RJ, Warner B. Evaluation of synthetic agonist analogue of gonadotropin-releasing hormone (leuprolide) on testicular androgen production in patients with carcinoma of prostate. *Urology*. 1985;25(2 Suppl):53–57.
30. Akaza H, Usami M, Koiso K, Kotake T, Aso Y, Nijima T. Long-term clinical study on luteinising hormone-releasing hormone agonist depot formulation in the treatment of stage D prostatic cancer. The TAP-144-SR Study Group. *Jpn J Clin Oncol*. 1992;22:177–184.
31. Abouelfadel Z, Crawford ED. Leuprorelin depot injection: patient considerations in the management of prostatic cancer. *Ther Clin Risk Manag*. 2008;4:513–526.
32. Tunn UW, Wiedey K. Safety and clinical efficacy of a new 6-month depot formulation of leuprorelin acetate in patients with prostate cancer in Europe. *Prostate Cancer Prostatic Dis*. 2009;12:83–87.
33. Periti P, Mazzei T, Mini E. Clinical pharmacokinetics of depot leuprorelin. *Clin Pharmacokinet*. 2002;41:485–504.
34. Sharifi R, Ratanwong C, Jung A, et al. Therapeutic effects of leuprorelin microspheres in prostate cancer. *Adv Drug Deliv Rev*. 1997;28: 121–136.
35. Fowler JE, Flanagan M, Gleason DM, Klimberg IW, Gottesman JE, Sharifi R. Evaluation of an implant that delivers leuprolide for 1 year for the palliative treatment of prostate cancer. *Urology*. 2000;55: 639–642.
36. Fowler JE, Gottelsman JE, Reid CF, et al. Safety and efficacy of an implantable leuprolide delivery system in patients with advanced prostate cancer. *J Urol*. 2000;164:730–734.
37. Eligard.com [homepage on the Internet]. Bridgewater, New Jersey [updated 2008 February; cited 2009 April 15]. Available from: www.eligard.com.
38. Crawford ED, Sartor O, Chu F, Perez R, Karlin G, Garrett JS. A 12-month clinical study of LA-2585 (45.0 mg): a new 6-month subcutaneous delivery system for leuprolide acetate for the treatment of prostate cancer. *J Urol*. 2006;175:533–536.
39. Sennello LT, et al. Single-dose pharmacokinetics of leuprolide in humans following intravenous and subcutaneous administration. *J Pharm Sci*. 1986;75:158–160.
40. Oefelein MG, Cornum R. Failure to achieve castrate levels of testosterone during lutenizing hormone releasing hormone agonist therapy: the case for monitoring serum testosterone and a treatment decision algorithm. *J Urol*. 2000;164:726–729.
41. Millikan R, Logothetis C. Update of the NCCN guidelines for the treatment of prostate cancer. *Oncology*. 1997;11:180–193.
42. Zlotta AR, DeBruyne FM. Expert opinion on optimal testosterone control in prostate cancer. *Eur Urol Suppl*. 2005;4:37–41.
43. McLeod D, Zinner N, Tomera K, et al. A phase 3 multicenter open-label randomized trial of abarelix versus leuprolide acetate in men with prostsate cancer. *Urology*. 2001;58:756–761.
44. Fontana D, Mari M, Martinelli A, et al. 3-month formulation of goserelin acetate ('Zoladex' 10.8-mg depot) in advanced prostate cancer: results from an Italian, open, multicenter trial. *Urol Int*. 2003;70:316–320.
45. Sardosy MF, Schellhammer PF, Soloway MS, et al. Endocrine effects, efficacy and tolerability of a 10.8-mg depot formulation of goserelin acetate administered every 13 weeks to patients with advanced prostate cancer. *BJU Int*. 1999;83:801–806.
46. Sharifi R, Browneller R; Leuprolide Study Group. Serum testosterone suppression and potential for agonistic stimulation during chronic treatment with monthly and 3-month depot formulations of depot leuprolide acetate for advanced prostate cancer. *J Urol*. 2002;168: 1001–1004.
47. Khan MS, O'Brien A. An evaluation of pharmacokinetics and pharmacodynamics of leuprorelin acetate 3M-depot in patients with advanced and metastatic carcinoma of the prostate. *Urol Int*. 1998;60:33–40.
48. Perez-Marreno R, Chu FM, Gleason D, Loizides E, Wachs B, Tyler RC. A six-month, open-label study assessing a new formulation of leuprolide 7.5 mg for suppression of testosterone in patients with prostate cancer. *Clin Ther*. 2002;24:1902–1914.
49. Chu FM, Jayson M, Dineen MK, Perez R, Harkaway R, Tyler RC. A clinical study of 22.5 mg La-2550: a new subcutaneous depot delivery system for leuprolide aceate for the treatment of prostate cancer. *J Urol*. 2002;168:1199–1203.
50. Sartor O, Dineen MK, Perez-Marreno R, Chu FM, Carron GJ, Tyler RC. An eight-month clinical study of LA-2575 30.0 mg: a new 4-month, subcutaneous delivery system for leuprolide acetate in the treatment of prostate cancer. *Urology*. 2003;62:319–23.
51. Ravivarapu HB, Moyer KL, Dunn RL. Parameters affecting the efficacy of a sustained release polymeric implant of leuprolide. *Int J Pharmacol*. 2000;194:181–191.
52. Pathak AS, Pacificar JS, Shapiro CE, Williams SG. Determining dosing intervals for luteinizing hormone releasing hormone agonists based on serum testosterone levels: a prospective study. *J Urol*. 2007;177: 2132–2135.
53. Greil S, Robinson EA, Singal B, Kleer E. Efficacy over time of LHRH analogs in the treatment of PCa-a prospective analysis using serum testosterone to determine dosing intervals. *Urology*. 2009;73:631–634.
54. Gulley JL, et al. Kinetics of serum androgen normalization and factors associated with testosterone reserve after limited androgen deprivation therapy for nonmetastatic prostate cancer. *J Urol*. 2008;180:1432–1437.
55. Sharifi R, Knoll LD, Smith J, Kramolowsky E. Leuprolide acetate (30-mg depot every four months) in the treatment of advanced prostate cancer. *Urology*. 1998;51:271–276.
56. Tunn UW, Bargelloni U, Cosciani S, Fiaccavento G, Guazzieri S, Pagano F. Comparison of LH-RH analogue 1-month and 3-month depot by their hormone levels and pharmacokinetic profile in patients with advanced prostate cancer. *Urol Int Suppl*. 1998;60:9–16.