

Journal für
Urologie und Urogynäkologie

Zeitschrift für Urologie und Urogynäkologie in Klinik und Praxis

Leuprorelin Acetate in Prostate

Cancer: a European Update

Persad R

Journal für Urologie und

Urogynäkologie 2002; 9 (Sonderheft

3) (Ausgabe für Österreich), 16-26

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Krause & Pachernegg GmbH · VERLAG für MEDIZIN und WIRTSCHAFT · A-3003 Gablitz

P. b. b. 022031116M, Verlagspostamt: 3002 Purkersdorf, Erscheinungsort: 3003 Gablitz

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LEUPRORELIN ACETATE IN PROSTATE CANCER: A EUROPEAN UPDATE*

Summary

This review provides an update on leuprorelin acetate, the world's most widely prescribed depot luteinising hormone-releasing hormone analogue. Leuprorelin acetate has been in clinical use in the palliative treatment of prostate cancer for more than 20 years, but advances continue to be made in terms of convenience and flexibility of administration, and in the incorporation of leuprorelin acetate into novel treatment regimens. The drug is administered in the form of a depot injection containing leuprorelin acetate microspheres, and is at least as effective in suppressing testosterone secretion as orchietomy. In patients with prostate cancer, serum testosterone levels are reduced to castrate levels (= 50 ng/dl) within 2–3 weeks of the first one-

month depot injection of 3.75 mg or three-month depot injection of 11.25 mg. Both the one-month and three-month formulations are effective in delaying tumour progression and alleviating symptoms of locally advanced and metastatic prostate cancer. Tolerability is generally good, with side-effects reflecting effective testosterone suppression. Recent studies have investigated the place of leuprorelin acetate as part of continuous or intermittent maximal androgen blockade (MAB) and in neoadjuvant therapy (ie, to reduce the size of the prostate and downsize the tumour before radiotherapy). Additional formulations and presentations are in development, including a six-month injection, with the aim of adding to the clinical flexibility and patient acceptability of this important palliative treatment for prostate cancer.

Cancer of the prostate is the most common malignancy in elderly men (> 65 years) and the second most common cause of death in this age group [1]. In recent years, screening programmes using prostate-specific antigen (PSA) levels have increased detection rates for early-stage disease, which is treatable with radical prostatectomy or radiation therapy [2]. Many cases remain undiagnosed, however, until the disease finally becomes symptomatic, by which time it is usually already locally advanced or metastatic. For these patients, and for those with recurrent cancer after radical prostatectomy or radiation, androgen suppression using hormonal therapy is now the standard palliative treatment [2].

The earliest forms of hormonal therapy used oestrogens, such as diethylstilboestrol (DES). However, because of their cardiovascular toxicity, oestrogens are generally no longer widely used in prostate cancer [3]. Orchiectomy, although an effective means of androgen

suppression, is psychologically difficult for patients to accept [4]. Most patients prefer one-month or quarterly injections of luteinising hormone-releasing hormone (LHRH) analogues – the current mainstay of therapy for locally advanced or metastatic prostate cancer [3].

LHRH analogues such as leuprorelin acetate, goserelin, triptorelin and busserelin work by inhibiting LH production. This in turn suppresses production of testosterone and dihydrotestosterone, on which the growth of hormone-dependent cancer cells depends [5]. Androgen suppression delays clinical progression and palliates symptoms of metastatic disease such as bone pain [6]. LHRH analogues do not cure prostate cancer or prolong median survival (which is about 24 months in metastatic prostate cancer) [7]. They do, however, improve symptoms in 60–80% of patients. Relapse eventually occurs despite the sustained suppression of testosterone with growth of androgen-independent tumour cells.

Meta-analysis has shown that survival after therapy with an LHRH analogue is equivalent to that after orchietomy [6]. Survival rates with LHRH analogues appear to be higher in advanced disease, and treatment withdrawals less common, than with non-steroidal antiandrogens used as monotherapy [6]. The current trend is towards initiating LHRH analogue therapy early – as soon as metastatic or locally advanced prostate cancer is diagnosed – rather than waiting until the onset of symptoms. A Medical Research Council trial in the UK found that, compared with deferred treatment, immediate androgen suppression reduced progression and complications due to the disease and delayed the development of metastatic pain [8].

Leuprorelin acetate as a one-month 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 [7, 9, 10], new studies have contributed to our understanding of the role of leuprorelin in prostate cancer. New formulations have also been developed to maximise flexibility and convenience of administration for both doctor and patient. This review aims to provide an up-to-date summary of the clinical profile of an established but still evolving treatment.

CHEMISTRY AND PHARMACY

Natural LHRH was first isolated and identified in 1971 [11]. Leuprorelin was first synthesised in 1974 by Takeda Chemical Industries, Japan, [12] and is a synthetic non-peptide analogue of naturally occurring porcine LHRH [13]. It has a longer half-life than natural LHRH due to its enhanced binding affinity and increased resistance to peptidase degradation, associated with amino

*Nachdruck mit Genehmigung aus: Int J Clin Pract 2002; 56: 389–96

acid substitutions at positions 6 and 10 of porcine LHRH. Leuprorelin is 80 times more potent than natural LHRH [9]. Sustained occupation of pituitary GnRH receptors by leuprorelin results in desensitisation and/or downregulation of receptors in the anterior pituitary, thereby suppressing gonadotrophin release and reducing testosterone release by the human testes to castrate levels [13]. There is also evidence that leuprorelin may act directly on cell growth in human prostatic cancer cells, behaving like a negative growth factor [14].

Leuprorelin is inactive when given orally, as it is poorly absorbed from the gastrointestinal mucosa. It therefore has to be given by injection [15]. Originally, leuprorelin 1 mg was given by daily injection. However, a depot formulation was soon developed to enable convenient subcutaneous or intramuscular injection at one-month intervals. Now, there is also the option of a three-month subcutaneous injection. The depot formulation enables leuprorelin to be given less often.

MICROSPHERE TECHNOLOGY

Microsphere technology is what makes it possible to give leuprorelin as a depot formulation. Microsphere technology is also used for depot formulations of triptorelin, whereas buserelin and goserelin are used as a solid implant. For the one-month depot formulation of leuprorelin, a biodegradable co-polymer composed of lactic and glycolic acids (PLGA) was chosen as the release-controlling substance. PLGA is used in surgical sutures and has a known safety profile. A co-polymer with a molecular weight of 14,000 and a lactic acid/glycolic acid ratio of 75/25 was found to have the most satisfactory releasing properties. Clinical studies showed that the one-

month depot preparation reduced the total dose of leuprorelin required to achieve castrate testosterone levels to one-eighth of that needed when injected daily [15].

A sophisticated manufacturing system was developed, yielding a product with predictable controlled-release characteristics [16]. The three-month depot injection differs from the one-month depot injection in that during microencapsulation, only D, L-poly-(lactic acid) acts as the vehicle instead of the PLGA co-polymer, and the product does not include gelatin [17].

The properties of leuprorelin microspheres have been compared with those of the microcapsule formulation of triptorelin [18]. Both products had similar pharmacological potency in rats. The leuprorelin depot had higher drug content and lower residual impurities (solvents and metals) than the triptorelin depot. Leuprorelin microcapsules were smaller, and had a slower sedimentation rate after dispersion in the vehicle. These differences appear to be a result of the methods used to produce the biodegradable matrices and microcapsules of each product. Leuprorelin microspheres range in mean diameter between 10 and 20 µm for the one-month depot and between 10 and 30 µm for the three-month depot. Clinically, this means that leuprorelin can be given as a liquid injection through a fine gauge needle using conventional injection techniques. Leuprorelin does not require the concurrent administration of a local anaesthetic or a special injection technique (as is required for the administration of some other LHRH analogue implant formulations).

PHARMACOKINETICS

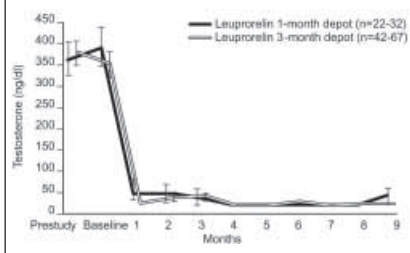
After injection of the one-month depot formulation of leuprorelin 3.75 mg, peak serum levels are achieved within one hour, followed by a rapid fall over the next 24 hours. A dose-dependent plateau is maintained over at least five weeks, representing a constant rate of release of leuprorelin from the co-polymer [15]. Injections can be given at intervals of either four weeks or one month, at the convenience of the patient and the physician. Over an extended 45 month treatment period of repeated monthly injections, leuprorelin remains at a constant therapeutic level and there is no evidence of accumulation following the depot injection [19].

As with the one-month injection, the three-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 three months (equivalent to that achieved with a one-month dose of 3.75 mg after repeated injections) [17]. Following injection, the plateau phase is reached at about 7 days, and persists for about 117 days. This clearly demonstrates that leuprorelin three-month injection will yield sufficient levels of leuprorelin to suppress testosterone production for at least the intended three-month treatment period. As with the one-month depot injection, there is no evidence of long-term accumulation with the three-month depot injection [17].

Effects on testosterone levels

To obtain optimal therapeutic effect against androgen-dependent tumour cells, serum testosterone levels must be reduced to castrate levels (= 50 ng/dl) [20]. This level can be achieved by a one-month depot injection of 3.75 mg leuprorelin [9] or by a

Figure 1. Suppression of plasma testosterone by leuporelin depot injection, 3.75 mg one-month or 11.25 mg three-month injection, over nine months [17].



three-month depot injection of 11.25 mg (Figure 1) [17, 21, 22]. As with other LHRH analogues, a rise in testosterone levels is seen after the first leuporelin injection only (see below), but castrate levels are achieved within 2–4 weeks and maintained for the duration of treatment.

The effects of leuporelin in suppressing testosterone secretion appear to be equivalent to those of other widely used LHRH analogues. A study in 64 previously untreated patients with metastatic prostate cancer compared one-month depot injections of leuporelin, goserelin and triptorelin. Histology, histochemistry and immunohistochemistry showed that the effects of all three LHRH analogues were similar to those of castration. All had similar effects on testosterone levels, and numbers of progressions and deaths were similar in the three groups, although at 3 and 6 months patients treated with leuporelin showed significantly lower serum PSA levels than the other two groups [23].

Clinical efficacy

Early studies in metastatic or advanced prostate cancer established the efficacy of daily s.c. injection of leuporelin (1–20 mg) [24–29] in suppressing testosterone levels, delaying tumour progression and alleviating symptoms of locally

Table 1. Major studies of the 1-month and 3-month formulations of leuporelin in prostate cancer

Study	n	Regimen	Duration (months)	Objective response* (%)
Akaza 1990 [30]	81	3.75 or 7.5 mg 1-month	3	86
Bischoff 1990 [36]	190	3.75 or 7.5 mg 1-month	1–15	88
O'Brien 1990 [35]	48	3.75 or 7.5 mg 1-month	3	90
Navratil 1990 [32]	18	3.75 mg 1-month	7	83
Rizzo 1990 [31]	43	3.75, 7.5, 15 or 30 mg 1-month	12	88
Wechsel 1996 [17]	80	3.75 mg 1-month	9	81
Wechsel 1996 [17]	157	11.25 mg 1-month	9	80

*no change, partial response or complete response

advanced and metastatic prostate cancer. Most studies, however, have been carried out with the one-month and three-month depot formulations.

Monthly injection

Open label studies of depot injections given at intervals of four weeks or one month in patients with metastatic or locally advanced prostate cancer (Table 1) [19, 30–36] found that serum testosterone fell to castrate levels within the first month and stayed at this level for the duration of therapy (up to 63 months) [19]. Where reported, bone pain [30, 31, 34, 36] and urinary symptoms [30, 31, 34, 35] were reduced, and performance status improved or stabilised [33, 35, 37]. The tumour marker PSA was markedly decreased [34]. Over follow-up periods of 3–24 months, disease progression was prevented in up to 95 % of patients [19, 30–36].

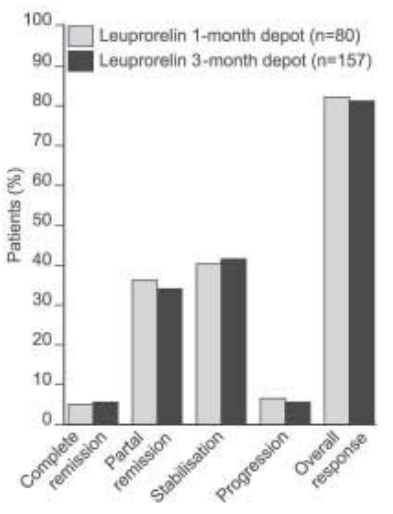
Although doses used for one-month injection in clinical trials have varied from 3.75 to 7.5 mg [33] a dose of 3.75 mg has been demonstrated to suppress gonadal testosterone synthesis to castrate levels [15]. There is

no difference in the effects of s.c. or i.m. administration [36]. For this reason, the European recommended dose for one-month depot injection is 3.75 mg administered as a single s.c. or i.m. injection at one-month intervals. After two days, the pharmacokinetic curves after the s.c. and i.m. injections are the same. The only practical difference between the two routes is that s.c. injection in the forearm may sometimes be more convenient.

Three-month injection

The availability of a choice of injection frequencies (one-month or three-month) offers more individualised, patient-orientated treatment [38]. The three-month depot formulation of leuporelin is given by s.c. injection. The three-month injection reduces the total number of injections to four per year, and can be timed to coincide with a typical schedule of three-month or six-month check-ups [38]. This may reduce the number of doctor visits required. A reduction in the number of injections may also reduce stress on patients, who are often elderly with multiple illnesses [38].

Figure 2. Best response during the course of a nine-month study comparing leuprorelin depot, 3.75 mg one-month and 11.25 mg three-month injections.



In a randomised open-label comparative study of the efficacy, safety and tolerability of leuprorelin one-month and three-month depot in patients with advanced prostatic cancer a single three-month dose of 11.25 mg has been shown to be therapeutically aequivalent to a one-month dose of 3.75 mg injected three times (Table 1, Figure 1) [17, 21, 39]. This study included 237 patients with locally advanced or metastatic prostate cancer, treated for nine months with

either the one-month 3.75 mg formulation (n = 80) or the three-month 11.25 mg formulation (n = 157). The two formulations of leuprorelin were similar in terms of clinical response and tolerability. Comparing one-month with three-month injections (Figure 2), complete remission occurred in 5.0 % versus 5.7 % of patients, partial remission in 36.3 % versus 33.8 % and stabilisation in 40.0 % versus 40.8 % (ie, efficacy was comparable). The two formulations produced virtually identical endocrine effects, with a pronounced fall in testosterone and gonadotrophin serum levels and a marked reduction in PSA levels (Figure 3). After nine months of treatment, PSA was normalised (< or = 4 ng/ml) in 65.2 % of patients receiving one-month injections and 66.1 % of those receiving three-month injections [17].

Thirty-seven patients entered a long-term follow-up study, in which they received treatment with the three-month formulation for up to 43 months (Figure 4) [38]. Suppression of serum testosterone to castrate levels was maintained throughout the study. The nature and severity of adverse events was similar to that observed previously. This follow-up study also provided prospective data on median survival time for 63 patients receiving three-month treatment only. The median survival time from the beginning of treatment

was 3.1 years, with a median time to tumour progression of 2.8 years [38].

Comparison with other LHRH analogues

Few studies have compared different LHRH analogues. A meta-analysis suggests there is little or no clinical difference between leuprorelin, goserelin and buserelin in terms of clinical response [6] though different formulations may differ in their acceptability to patients [40]. Although both leuprorelin and triptorelin make use of microcapsule technology, goserelin is administered in the form of an implant rather than an injection. Anecdotally, patients have been reported to prefer leuprorelin injection to goserelin implants, because of the smaller gauge of needle required [40].

One open-label randomised study has compared one-month s.c. injection with leuprorelin 3.75 mg with triptorelin 3.75 mg. Both treatments were equally effective in reducing serum testosterone to castrate levels over a six-month period, although plasma testosterone fell more rapidly with leuprorelin [41].

Comparison with DES

DES (3 mg daily) and leuprorelin (1 mg daily s.c. injection) have been shown to be equally effective in

Figure 3. Effect of leuprorelin depot injection, 3.75 mg one-month or 11.25 mg three-month, on PSA levels over nine months [17].

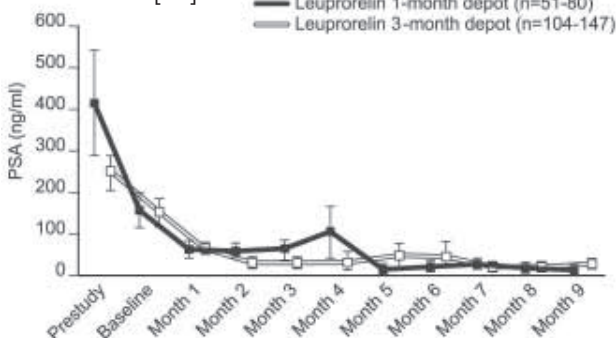
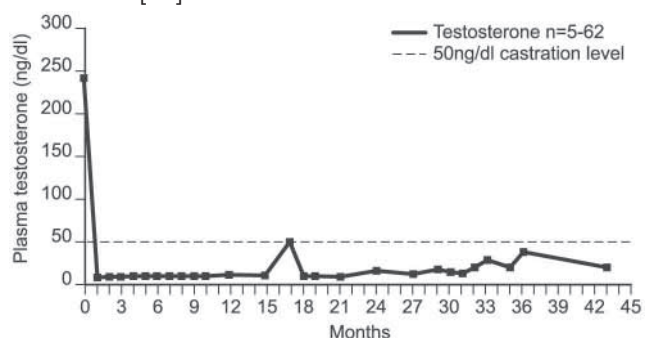


Figure 4. Median plasma concentrations of testosterone with three-month leuprorelin depot injection, 11.25 mg over 43 months [38].



reducing serum testosterone below castrate levels in patients with metastatic prostate cancer [42, 43]. Objective and subjective responses, and survival and duration of response were comparable [42, 43]. However, leuprorelin was better tolerated [42, 43] leading to fewer treatment withdrawals than with DES [43]. Fewer adverse cardiovascular events occurred with leuprorelin than with DES [42]. In a crossover study, patients reported that their general health and social life were better with leuprorelin than with DES [44].

Deferred versus immediate therapy

Whether hormonal therapy should be initiated immediately or deferred in patients who suffer biochemical relapse following radiotherapy or surgery for the primary tumour remains a topic for debate. The potential to prolong survival and delay the development of clinical symptoms are arguments for early treatment. Several studies have now shown that early hormonal treatment can delay the time to progression and reduce the rate of cancer-related complications such as urinary obstruction and bone fractures [45, 46].

For example, a large study by the UK Medical Research Council in 938 patients with locally advanced or asymptomatic metastatic prostate cancer compared immediate treatment (orchiectomy or LHRH analogue) and the same treatment deferred until an indication occurred [8]. Progression from M0 to M1 disease and development of metastatic pain occurred more rapidly in deferred patients, and transurethral resection for local progression was more likely to be performed in deferred patients. Pathological fracture, spinal cord compression, ureteric obstruction and development of extraskeletal metastases were twice as common in deferred patients. Significantly more patients died from prostate cancer in the deferred arm; the difference was

seen largely in M0 patients. The authors conclude that the data "provide consistent support for the benefits of immediate treatment".

A further study by the Eastern Cooperative Oncology Group (ECOG) was conducted in 98 patients who had undergone radical prostatectomy and had pelvic lymph node metastases (D1) [47]. Compared with deferred therapy, immediate antiandrogen therapy improved survival and reduced the risk of recurrence [47].

Other data also support immediate treatment versus deferred treatment in advanced disease [45, 46], including Study 30846 of the European Organisation for Research and Treatment of Cancer (EORTC) [46]. This prospective randomised study included 412 patients with positive lymph nodes who did not undergo a previously planned radical prostatectomy, but were instead randomised to immediate or deferred hormone therapy. Early data from 84 patients indicate that time to distant metastases was prolonged by immediate therapy.

Leuprorelin in maximal androgen blockade (MAB)

LHRH analogues such as leuprorelin block only testicular testosterone. They have no effect on the 10 % of testosterone produced by the adrenal glands. Thus, even with maximally effective doses of LHRH analogues, some testosterone will remain, which could have a stimulatory effect on hormone-sensitive prostatic cancer cells. MAB has been developed in an attempt to reduce residual testosterone from the adrenal glands, combining an LHRH analogue with an antiandrogen such as flutamide, nilutamide or bicalutamide, or cyproterone acetate [48].

The usefulness of MAB is controversial and may vary among patient groups. A recent meta-analysis of

data from trials in 8275 men with metastatic or locally advanced prostate cancer indicated that survival was increased by 2–3 % by the addition of an antiandrogen to an LHRH analogue or orchiectomy [48]. However, the range of uncertainty regarding the true size of the benefit ranged from 0 % to about 5 %.

Nevertheless, some studies using leuprorelin as a daily injection alongside antiandrogens indicate beneficial effects of MAB on progression and survival [49–53]. The largest of these was a double-blind randomised comparative study in 603 men with metastatic prostate cancer [51–53]. Patients who received leuprorelin and flutamide had longer progression-free survival than those who received leuprorelin alone (16.5 vs 13.9 months; $p = 0.039$). The median length of survival was also greater in patients who received MAB (35.6 vs 28.3 months; $p = 0.035$). The differences between the treatments were particularly evident for men with minimal metastatic disease (vertebrae only) and good performance status [51–53].

However, a randomised multicentre study [54] in 241 men, in which leuprorelin was compared with leuprorelin plus flutamide in advanced prostate cancer found no significant differences in time to progression or survival. The authors concluded that the benefits of MAB in this study were "at best marginal".

A further 160-week randomised, multicentre, open-label trial in 813 patients assessed the efficacy and tolerability of two antiandrogens, bicalutamide and flutamide, each combined with one-month depot preparations of leuprorelin or goserelin, in patients with stage D2 prostate cancer. The percentages of patients whose tumours progressed or who died during the study were similar for goserelin plus antiandrogen and leuprorelin plus antiandrogen therapies [55]. There was no long-term

difference between flutamide and bicalutamide in terms of survival, quality of life or subjective response [56].

Leuprorelin in intermittent MAB

Continuous androgen ablation produces hormonal independence of some tumour cells; these then become dominant in the tumour and lead to progression. It is argued that intermittent MAB will delay occurrence of hormone resistance. It could also preserve quality of life while off therapy and re-increase bone mineral content [57], allowing libido and potency to return [3]. Studies in animal models suggest that, when androgen suppression is cycled, there appears to be recovery of apoptosis and subsequent slower progression to an androgen-independent state [58]. However, intermittent MAB is at present still an experimental therapy.

Several phase II and III clinical trials of intermittent MAB in clinically localised or metastatic prostate cancer have recently been reported [57–67]. Typically, MAB was given for lead-in treatment intervals of about 6–9 months. Off-treatment intervals were of variable length, using PSA levels as a surrogate marker of disease reactivation [58]. These phase II–III studies have demonstrated that repeat responses to androgen deprivation are possible, with off-treatment intervals of varying length. Several suggest that quality of life is improved during off-treatment intervals [67].

For example, an open, non-randomised, prospective pilot study was conducted in 44 patients with early prostate cancer and rising PSA after transurethral resection of the prostate or radical prostatectomy [63]. Leuprorelin (one-month depot) and cyproterone were used to achieve MAB for nine-month cycles, interspersed with variable treatment-free intervals determined by serum PSA. Over an

observation period of 48 months, the mean cumulative treatment-free period was 27 months. During the treatment-free intervals, patients reported a decline in side-effects, improvement in their general well-being and an increase in libido, which was correlated with a return to normal serum testosterone levels.

However, phase II studies should be regarded mainly as a demonstration of the feasibility of the approach. Several phase III studies are currently comparing tumour progression, safety and quality of life with intermittent or continuous MAB in patients with metastatic prostate cancer [58, 68].

Adjuvant and neoadjuvant therapy

Traditionally, the use of LHRH analogues has been confined to palliative therapy for locally advanced or metastatic prostate cancer. However, they may also be used to enhance the efficacy of surgical or radiological ablation of the prostate. Adjuvant LHRH analogues have been shown to improve both local control and survival after radiotherapy [69, 70]. In one five-year follow-up study, patients with clinically localised prostate cancer with poor prognostic features who received short-term hormonal treatment in addition to radiotherapy were more likely to show no biochemical evidence of disease than those who received radiotherapy without short-term adjuvant treatment [71]. There was also a trend towards better distant metastasis-free survival in patients treated with short-term adjuvant hormones.

Recently, there have been studies of the use of neoadjuvant treatment with LHRH analogues to reduce the size of the prostate and downsize the tumour before radiotherapy or surgery. Leuprorelin has been used in a number of such studies, usually alongside antiandrogens [72–84]. So far, there are no conclusive data on

the influence on survival of neoadjuvant treatment given before surgery, and further data are required before definite conclusions can be drawn on the role of this treatment [82].

With regard to radiotherapy, neoadjuvant hormonal therapy is used for decreasing the size of prostatic tumours and optimising the geometry of the target volume. This allows the volume of normal tissues exposed to high radiation doses to be reduced, thus limiting the morbidity caused by treatment. It might also allow safe delivery of higher radiation doses to restricted tissue areas [83]. This approach may result in an improvement in the therapeutic ratio. In patients with localised prostate cancer, down-sizing of the prostate with leuprorelin treatment has been shown to reduce the volume of bladder and rectum receiving high radiation doses [80, 84]. However, as with surgery, follow-up studies are needed to determine whether neoadjuvant therapy before radiotherapy has any effect on long-term outcome.

Safety and tolerability

LHRH analogues are, in general, well tolerated, with withdrawal rates in clinical studies of only 0–4 %, compared with 4–10 % for non-steroidal antiandrogens [6]. A progressive decrease in bone density occurs with increasing duration of androgen deprivation therapy [84], although there is evidence that LHRH agonists lead to less treatment-induced bone demineralisation than orchiectomy [85, 86]. Pamidronate has been shown to prevent bone loss in the hip and lumbar spine in men receiving treatment with leuprorelin for prostate cancer [87].

Clinical trials on leuprorelin indicate good tolerability for both the one-month [19, 31–36] and three-month depot injection [17, 21, 39]. The tolerability of the one-month and three-month formulations is similar (Table 2) [17, 21, 39]: 87.5 % of

Table 2. Side-effects experienced by patients receiving leuprorelin depot injection, 3.75 mg one-month or 11.25 mg three-month, over nine months [17]

Side-effect (% patients)	3.75 mg 1-month (n = 80)	11.25 mg 3-month (n = 157)
Hot flushes	60.0	47.8
Increased sweating	42.5	36.3
Decreased libido	28.8	23.6
Atrophy of testicles	30.0	21.0
Impotence	23.8	22.3
Skeletal pain	12.5	14.0
Muscle weakness	15.0	10.8
Urinary tract infection	16.3	8.9
Fatigue	10.0	12.1
Nocturia	10.0	11.5
Anorexia	7.5	11.5
Dysuria	10.0	8.3

patients receiving one-month depot injections and 83.4 % of those receiving three-month depot injections assessed their medication as "well tolerated" or "very well tolerated" [17].

As with other LHRH analogues, first administration of leuprorelin is associated with an initial transient elevation in testosterone levels, which may lead to an exacerbation of symptoms in 10–30 % of patients [35, 42, 88, 89]. This "flare" subsides on continuation of therapy. Administration of an antiandrogen is commonly used to reduce the risk of tumour flare [32, 52].

Most of the other side-effects of leuprorelin are related to its therapeutic effects in reducing serum testosterone, and include hot flushes, increased sweating, decreased libido, atrophy of testicles and impotence [17]. Gynaecomastia has been reported occasionally. Other adverse events reported infrequently include peripheral oedema, fatigue, nausea, headache, arthralgia, dizziness, insomnia, paraesthesia, visual disturbances, weight changes and irritation at the injection site.

Most adverse reactions observed in clinical trials have been mild to mo-

derate and withdrawal rates have been low. Local reactions at the injection site occur in only about 3 % of patients [35, 36]. In a study comparing leuprorelin plus flutamide with leuprorelin as a single agent, the only side-effect more common in the combination group was diarrhoea, almost certainly due to flutamide [51, 52].

NEW TREATMENT MODALITIES

New formulations of leuprorelin are in development, and recent research suggests ways in which further flexibility may be added to an already very adaptable administration schedule. The injection system for leuprorelin allows selected patients to learn and practise self-injection, depending on local country product presentations [89]. This may lead to increased independence for patients, offering them extra choices, and may also involve them more in their own treatment. However, given that patients with prostate cancer are likely to see a doctor for regular check-ups, the number of patients wishing to self-inject is likely to be limited.

A six-month formulation is in development. A change in the current six-month depot formulation is required to extend the release of leuprorelin from the microcapsules beyond three months. The biodegradable polymer technology has been changed to achieve a six-month release of leuprorelin, using recognised excipients. Pharmacokinetic studies in dogs have confirmed the release profile of leuprorelin over a six-month period, and patient studies are now planned.

A 12-month leuprorelin implant as a titan capsule has been approved in the US: a slow-release device that delivers leuprorelin continuously for up to one year. It is surgically placed under the skin of the upper inner arm, and an osmotic device inside the implant releases the drug at a constant rate. In a two-year open-label trial involving 107 men, the implant maintained castrate levels of serum testosterone for one year [91]. However, patient acceptance of the 12-month implant has been poor, because the capsule has to be removed by surgery after one year.

CONCLUSION

Today, LHRH analogues are the mainstay of the treatment for locally advanced and metastatic prostate cancer, and are usually preferred to orchiectomy or oestrogens. The efficacy of all the available LHRH analogues in suppressing serum testosterone to castrate levels appears to be similar, but leuprorelin has the advantage being administered by depot injection rather than implant, with the option of one-month or three-month administration.

Unlike implants, leuprorelin one-month or three-month injection can usually be given by either a physician or other member of the healthcare team, depending on local product

presentations. The choice of injection frequency enables more individualised, patient-orientated treatment, which can be given at home or in the office, and timed to coincide with regular check-ups. The use of a liquid injection, which can be given through a fine 23-gauge needle, minimises patient discomfort and reduces injection site trauma (especially important in patients receiving anticoagulants).

Although LHRH analogues have now been in use for more than 15 years, their place in therapy continues to develop. Leuprorelin acetate is now the world's most widely prescribed depot LHRH analogue. Its place alongside other agents in MAB (continuous or intermittent) continues to be explored, as does its use as neoadjuvant and adjuvant therapy in patients undergoing radical prostatectomy and/or radiotherapy. Meanwhile, ongoing research offers the imminent prospect of additional formulations, adding to the flexibility and potential patient-friendliness of this important palliative treatment for prostate cancer.

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