Luteinizing hormone-releasing hormone analogues and hormone ablation for prostate cancer: state of the art

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INTRODUCTION

Prostate cancer is the most common noncutaneous malignant tumour in men, and androgen-dependent prostate cancer constitutes ≈70% of all cases of prostate neoplasms [1]. The present methods for treating advanced prostate cancer are palliative and based on androgen deprivation. Endocrine therapy for adenocarcinoma of the prostate has included bilateral orchidectomy, administration of oestrogens and antiandrogens, and even hypophysectomy and adrenalectomy. However, surgical castration is associated with a psychological and social impact, oestrogens have serious cardiovascular, hepatic and mammothropic side-effects, and antiandrogens can be toxic to the liver. Our approach is based on agonistic analogues of LHRH [1]:

- Carcinoma of the prostate is androgen-dependent in ≈70% of cases.
- The management of advanced prostate cancer is palliative and is based on therapies that induce androgen deprivation.
- Chronic administration of LHRH agonists with or without an antiandrogen and orchidectomy are standard therapies for advanced disease.

In 1971, my laboratory was the first to isolate, structurally elucidate and synthesize hypothalamic LHRH [2,3]. We were also the first to show that natural and synthetic LHRH released LH and FSH in humans [3]. Because natural and synthetic LHRH has substantial FSH-releasing and LH-releasing activity, we suggested that one hypothalamic hormone, designated LHRH/FSHR or simply GnRH, controls the secretion of both gonadotrophins [2–4]. Although LHRH is now accepted as the main FSH-releasing hormone, the abbreviation LHRH is still recommended for naming its analogues. The abbreviation GnRH causes confusion because of its similarity to growth hormone-releasing hormone (GHRH).

AGONISTIC ANALOGUES OF LHRH

In the past 34 years, >3000 analogues of LHRH have been synthesized. This intense activity was caused by the need to synthesize super-active analogues that would be more therapeutically useful than LHRH itself, and to develop antagonistic analogues for gynaecological and oncological use [5].

Substitution at positions 6 and 10 can result in super-active analogues. Therefore, several LHRH analogues substituted at position 6, 10, or both are much more active than LHRH and have prolonged activity [5]. Of these analogues, the most important are [D-Trp⁶]LHRH (triptorelin), [D-Leu⁶,Pro⁹,Pro¹⁰,NHET]LHRH (leuprolide), [D-Ser(Bu)⁶,Pro⁹,NHET]LHRH (buserelin), and [D-Ser(Bu)⁶,Aza-Gly⁹]LHRH (goserelin), which are 50–100 times more potent than LHRH itself. This greater biological activity of the analogues is due to increased resistance to enzymatic degradation and increased receptor affinity.

ONCOLOGICAL AND GYNAECOLOGICAL USES OF LHRH AGONISTS

Although an acute injection with super-active agonists of LHRH induces a marked and sustained release of LH and FSH, chronic administration produces inhibitory effects [5]. Continuous stimulation of the pituitary by chronic administration of LHRH agonists results in inhibition of the hypophyseal-gonadal axis through a process involving down-regulation of pituitary receptors for LHRH, a decrease in expression of the LHRH receptor gene, desensitization of the pituitary gonadotrophs, and suppression of circulating levels of LH and FSH. This state is reversible and termed ‘selective medical hypophysectomy’. The decrease in circulating LH and FSH results in complete inhibition of testicular or ovarian function. This state, characterized by suppression of sex-steroid levels, is called chemical or medical castration.

The key advantage of medical castration achieved by LHRH agonists is its reversibility.

These processes, which can be induced by repeated administration or depot preparations of LHRH agonists, have important clinical applications [5]. The use of LHRH agonists to treat central precocious puberty and in in vitro fertilization and embryo-transfer programmes is based on their suppression of gonadotrophin secretion. Therapy for sex hormone-dependent malignant neoplasms, which are typified by prostate and breast cancer, as well as other conditions such as BPH, uterine leiomyomas and endometriosis, is based on reversible medical castration and the creation of a state of sex-steroid deprivation [5].

USE OF LHRH AGONISTS TO TREAT PROSTATE CANCER

Endocrine therapy for prostate cancer, which is based on agonistic analogues of LHRH, was developed by my laboratory in 1980 [1,5–7] after we had established the principles of this approach in experimental studies [6]. We found that long-term administration of [D-Trp⁶]LHRH can inhibit prostate tumour growth in rat models [8]. When rats bearing the Dunning R-3327H prostate adenocarcinoma were treated with [D-Trp⁶]LHRH, tumour volume and weight decreased, and tumour-cell doubling time increased. Serum LH, FSH and testosterone levels were significantly reduced after treatment. This study showed for the first time the potential clinical efficacy of [D-Trp⁶]LHRH in the treatment of prostate carcinoma in men [6].

CLINICAL STUDIES OF LHRH AGONISTS IN MEN WITH PROSTATE CANCER

The first successful palliation of advanced prostatic carcinoma by agonistic analogues of LHRH was shown in a collaborative trial. Ten patients with advanced prostatic carcinoma...
received treatment from 6 weeks to 12 months with agonistic analogues of LHRH. [D-Trp<sup>6</sup>]LHRH was given s.c. once daily at a dose of 100 µg, and buserelin was given s.c. at a dose of 50 µg once daily or intranasally at a dose of 500 µg twice daily [7]. In all patients, mean plasma testosterone levels decreased by 75% by the third week of treatment and remained at castration values thereafter. This event was followed by a decrease or normalization of serum acid phosphatase levels. In patients with stage C disease who had urinary obstruction at diagnosis, clinical improvement was noticeable and a decrease in the size of the prostate was confirmed by ultrasonography. Patients with stage D disease manifested by diffuse bone metastases had relief of bone pain; the improvement was documented by radioisotope bone imaging. The only side-effects were a decrease in libido and climacteric-like vasomotor phenomena. This trial showed for the first time that superactive agonistic LHRH analogues might be effective in patients with androgen-sensitive prostatic adenocarcinoma [7]. Our findings suggested that treatment with agonistic analogues of LHRH might eliminate the need for surgical orchidectomy or oestrogens in treating prostate cancer [7].

These findings were confirmed by other clinical trials of LHRH agonists in patients with prostate cancer in Europe and North America [1,5,8]. The LHRH analogues used clinically to treat advanced prostate cancer include triptorelin, buserelin, leuprolide and goserelin. Medical castration produced by chronic administration of LHRH analogues accounts for most of the benefit of this treatment, but LHRH agonists and antagonists can also exert direct effects on prostate tumour cells [1,5].

Initially, agonists of LHRH were given daily s.c. or intranasally. Subsequently, we developed a long-acting delivery system for [D-Trp<sup>6</sup>]LHRH in microspheres of poly(D-lactide-co-glycolide). This system was designed to release a controlled dose of the peptide over 30 days [1,5]; its efficacy in the treatment of advanced prostatic carcinoma was shown in clinical trials [9,10]. In one, we obtained a reduction in LH, FSH and testosterone in men with prostate cancer treated with the microspheres, and the objective response was 87% in the microsphere-treated group vs 81% after total orchidectomy [10]. The use of sustained-release formulations, which can be administered once per month or even once every 3–6 months, makes the treatment of prostate cancer more convenient, practical and effective [1,5,9,10]. These regimens also ensure better patient compliance than is obtained with daily injections. Side-effects of chronic administration of LHRH agonists (e.g. erectile dysfunction, loss of libido, hot flushes) are caused by androgen deficiency [1,5]. Occasional ‘flare’ in the disease with an increase in bone pain during the first week of administration of LHRH agonists was reported in ≈10% of patients, but such flares can be prevented by administration of an antiandrogen before and for 2–4 weeks after the first injection with the agonist [1,5].

The acceptance of LHRH analogues is excellent. Therapy with agonists of LHRH is presently the preferred method of primary treatment for men with advanced prostate cancer, and recent surveys indicate that LHRH agonists are selected for primary treatment in ≈70% of cases [1,5].

More recently, LHRH agonists with or without antiandrogens have been used before or after various local treatments in patients with clinically localized prostate cancer. Treatment with LHRH agonists is now recommended in patients who have an increasing PSA level after surgery or radiotherapy [11].

**LHRH ANTAGONISTS**

Potent antagonists of LHRH such as cetrorelix have also been synthesized [1,5]. Experimental and clinical data indicate that LHRH antagonists can be useful in the treatment of prostate cancer and BPH [1,5]. LHRH antagonists induce competitive blockade of LHRH receptors, and they down-regulate these receptors. The advantage of the antagonists is based on the fact that they inhibit LH, FSH and sex-steroid secretion from the start of their administration, and thus greatly reduce the time to onset of therapeutic effects. Clinical studies of the antagonism cetrorelix in patients with advanced prostate cancer and BPH showed a lowering of serum testosterone levels to castration values, a decrease in elevated PSA levels, and a marked clinical improvement [1,5]. Cetrorelix is being evaluated in clinical trials in men with BPH. Sustained-release formulations of cetrorelix pamoate have been developed. Cetrorelix and other LHRH antagonists are used in *in vitro* fertilization and embryo transfer.

**PERSPECTIVES FOR TREATING ANDROGEN–INDEPENDENT PROSTATE CANCER**

For all hormonal methods of treatment aimed at androgen deprivation, including LHRH analogues, the duration of remission in patients with prostate cancer is limited, and relapse eventually occurs. The relapse is attributed to a proliferation of androgen-independent cancer cells [1,5]. The prognosis for patients with androgen-independent prostate cancer is very poor, and no effective treatment exists at present [1,5].

Growth factors, including epidermal growth factor, IGF-I and -II, bombesin and GHRH, might be involved in the growth, neoplastic transformation and progression of prostate cancer. Several studies indicate an association between serum IGF-I levels and risk of prostate cancer [1,5]. Interference with endogenous growth factors and their receptors could inhibit the growth of androgen-independent prostate cancers [1,5].

Recent investigation of many specimens of human prostate adenocarcinoma showed that 86% of cancers have high-affinity binding sites for LHRH and express mRNA for LHRH receptors [12]. Prostate cancers also contain a high percentage (63–65%) of binding sites for somatostatin and bombesin, and express mRNA for somatostatin and bombesin receptor subtypes [1]. Receptors for LHRH, somatostatin or bombesin can be used to target the respective cytotoxic peptide analogues [1,12].

Thus, we developed a new class of targeted cytotoxic antitumour drug by linking doxorubicin or its derivative AN-201 to analogues of LHRH, somatostatin and bombesin [13]. The cytotoxic LHRH analogue AN-152 comprises [D-Lys<sup>6</sup>]LHRH linked to DOX-14-O-hemiglutarate, whereas AN-207 contains 2-pyrrolino-DOX (AN-201), also conjugated to [D-Lys<sup>6</sup>]LHRH. AN-152 and AN-207 inhibit the growth of experimental prostate cancers [13]. In castrated nude mice bearing androgen-sensitive human LNCaP tumours, treatment with AN-152 enhanced the tumour-inhibitory effect of androgen ablation by 83% [13]. Clinical phase I trials of AN-152 are in progress in Germany. AN-207 inhibited the growth of androgen-independent DU-145 human prostate cancers [1,13].
Our work supports the concept that targeted chemotherapy based on cytotoxic LHRH analogues should be more effective and less toxic than the current systemic chemotherapeutic regimens. Targeted cytotoxic analogues of LHRH might be considered for treating advanced prostate cancer after relapse [1,13]. Cytotoxic analogues of somatostatin and bombesin also inhibit the growth of experimental androgen-independent human prostate cancers [1,13].

Expression of mRNA for GHRH and the existence of splice variants of pituitary GHRHR receptors in various human tumours, including prostate cancer, suggest that GHRH can function as an autocrine growth factor [14]. Some of the antiproliferative effects of GHRH antagonists on prostate cancer cells appear to be exerted by a direct interference with the tumoral GHRHR system. In nude mice, the combination of castration or triptorelin with GHRH antagonists inhibited the growth of xenografted androgen-sensitive MDA-PCa-2b and LNCaP human prostate cancers and reduced PSA secretion [14]. Thus, GHRH antagonists enhance the inhibitory effects of androgen deprivation on the growth of prostate tumours. In androgen-independent PC-3 and DU-145 human prostate cancers, GHRH antagonists alone can inhibit tumour growth [1,14,15].

CONCLUSION

LHRH agonists such as triptorelin provide an effective palliative therapy for advanced prostate cancer:

- they are the preferred alternative to surgical castration or oestrogen therapy for advanced prostate cancer;
- they provide effective palliative therapy that results in objective stable disease or partial remission;
- the development of new treatment methods based on GHRH antagonists and bombesin or gastrin-releasing peptide antagonists could prevent or delay relapse;
- the use of cytotoxic analogues of LHRH, somatostatin, and bombesin that can be targeted to prostate tumours might also lead to improvements in treatment.

The use of bombesin/gastrin-releasing peptide antagonists and GHRH antagonists might improve the present therapy, prevent or delay relapse in patients with advanced prostate cancer treated by androgen deprivation, and prolong survival. The development of cytotoxic analogues of LHRH that can be targeted at prostate cancers could also provide new methods for the clinical management of prostate cancer.

REFERENCES


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Abbreviation: GHRH, growth hormone-releasing hormone.