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Role of Luteinising Hormone Releasing Hormone (LHRH) Agonists and Hormonal Treatment in the Management of Prostate Cancer

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Abstract

The use of luteinising hormone releasing hormone (LHRH) agonists has increasingly evolved during the past 10 years. This review paper aims to discuss the role of LHRH agonists in patients with prostate cancer, a leading cause of cancer death in men.

To retrieve the most relevant randomised clinical trials (RCTs), a Medline search was performed in the last quarter of 2004. Only fully published studies in English language with at least 25 patients per treatment arm and those frequently cited in review articles were included in the current review. This review does not claim to have included every single study with the selected treatment options, but aimed at including the most important trials performed and fully published with these treatments. The retrieved studies are discussed and put into perspective of the EAU guidelines.

Initially, LHRH agonists were part of the treatment strategy for patients with advanced or metastatic disease. Currently, LHRH agonists are increasingly used as a treatment option in a neoadjuvant and/or adjuvant setting for patients with early or localised disease. LHRH analogues are used as adjuvant hormonal therapy after radical prostatectomy, and as neoadjuvant and adjuvant treatment to radiotherapy. Patients with early or localised disease and a low Gleason score may experience clinical benefit from the neoadjuvant addition of LHRH agonists to radiotherapy. In patients with a high Gleason score and positive lymph nodes, adjuvant LHRH agonist treatment is considered standard therapy.

In patients with rising prostate specific antigen (PSA) after radical treatment, hormonal therapy is often applied in an intermittent way, but results remain inconclusive.

Maximum androgen blockade (MAB), a combination of a LHRH agonist and an antiandrogen, has been applied in advanced prostate cancer. However, due to the increased incidence of side effects and very modest survival benefits, there are few arguments to offer this treatment strategy to patients with prostate cancer.

In summary, LHRH agonist therapy is important in the treatment of both early and advanced prostate cancer. Additional studies are needed to further define the optimal use of LHRH agonists within various patient risk groups.

Keywords: Prostate cancer; LHRH agonists; Adjuvant therapy; Neoadjuvant therapy; Early prostate cancer; Advanced prostate cancer; Metastatic prostate cancer; Biochemical recurrence; Review

1. Introduction

Following Huggins and Hodges observation that prostate cancer (PCa) growth is dependent on the presence of androgens, testosterone suppression or deprivation by orchiectomy or oestrogens became the standard treatment for advanced PCa [1]. However, both forms of castration have problems. The irreversibility of orchiectomy limits its use to advanced PCa. Oestrogen treatment is associated with significant cardiovascular morbidity and mortality [2]. Therefore, new ways of non-surgical castration were needed.

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In 1971, Schally and Guillemin discovered the luteinising hormone releasing hormone (LHRH) which led to the development of LHRH agonists as chemical castration strategy.

1.1. Rational for LHRH agonist therapy

The hypothalamus secretes LHRH, also referred to as gonadotropin releasing hormone (GnRH), in a pulsatile pattern. This small peptide has a very short half-life because of peptidase degradation. This is an elegant effect, as it has only to remain active for a short time in the hypophyseal portal circulation. Via this circulation, LHRH travels to the anterior pituitary gland where it binds to the LHRH-receptor and stimulates the synthesis and secretion of both luteinising hormone (LH) and follicle stimulating hormone (FSH). Circulating LH enters the systemic circulation and interacts with receptors on the interstitial Leydig cells of the testis. This interaction activates intracellular mechanisms leading to the synthesis and release of testosterone. More than 90% of this testosterone circulates in the bloodstream bound to the sex hormone binding globulin (SHBG) or to albumin. Only a small percentage ($\pm$10%) is unbound and through this, available for cellular activation. If the testosterone level increases, testosterone itself regulates the negative feedback loop and inhibits the release of LHRH from the hypothalamus as well as the release of LH from the pituitary. As a result, this decreases the synthesis and release of testosterone from the Leydig cells [3–5].

Testosterone produced by the Leydig cells is transported by the systemic circulation to other organs, including the prostate. In the prostatic cells, testosterone is converted by 5α-reductase into dihydrotestosterone (DHT). DHT has a higher affinity for the intracellular androgen receptor than testosterone. After binding of DHT to the androgen receptor on the cell nucleus, this complex binds to the promotor of the hormone-responsive element, which finally results in protein synthesis of prostate specific antigen (PSA) and growth factors [3–5].

The adrenal glands are a second source of androgens, accounting for approximately 5% of total androgen production. The adrenocorticotropic hormone (ACTH) stimulates the adrenal glands to produce the androgens androstenedione and dehydroepiandrosterone. Both androgens will be converted to testosterone in peripheral tissues and in the prostate gland itself [3–6].

When given for the first time, LHRH agonists induce a transient rise in pituitary LH. Simultaneously, there is a surge in testosterone plasma levels to concentrations far above pre-treatment values (flare phenomenon) [7]. In the clinical setting this flare can be avoided by short-term co-treatment with antiandrogens [8].

After an average of 3–4 weeks, LHRH receptors in the pituitary will be down-regulated, resulting in a decline of serum testosterone levels towards the castration level of 50 ng/dL [7,9–11]. Two factors appear to be important in this down-regulation; first, the continuous administration of LHRH agonists as compared to the natural occurring pulsatile pattern and second, the overstimulation of the receptors by maintaining the LHRH agonist blood level constant on $>$100 pg/mL [12].

1.2. LHRH agonists applied in different stages of prostate cancer

Because of the reversibility of the castration and the favourable side effects profile, LHRH agonists are currently used in both early and advanced disease [13,14].

This article will focus on the literature, defining the use of LHRH agonists in:

- Adjuvant therapy to radical prostatectomy
- Neoadjuvant and adjuvant therapy to radiotherapy
- Hormonal therapy after biochemical recurrence
- Hormonal therapy for advanced disease
- Hormonal therapy for metastatic disease

It also briefly reviews their side effect profile.

2. LHRH agonists as a treatment option in early disease

2.1. Rationale

As a consequence of the introduction of PSA as a marker for PCa, awareness of both patients and physicians has increased. PCa is nowadays often diagnosed at earlier stages, younger ages ($<$60 years), and in men with lower PSA and testosterone levels [15,16].

Staging of PCa in early disease is not straight forward, as 50% of cancers diagnosed as clinical stage T2 are often found to be pT3 after radical prostatectomy [17]. Conceptually, early PCa can be cured, meaning that patients diagnosed at this stage, can have a 5-year survival rate of 100% [18].

Radical treatment, either radical prostatectomy (and other treatment modalities such as high-intensity focused ultrasound (HIFU)) and/or radiotherapy (external beam radiation therapy (EBRT) and brachytherapy), is the standard therapy for patients with early disease (Fig. 1) [19–21].

Radical prostatectomy can be considered as curative, if surgical margins are negative. However, surgery