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Urologic Oncology: Seminars and Original Investigations 33 (2015) 322–328

UROLOGIC ONCOLOGY

Review article

Gonadotropin-releasing hormone antagonist: A real advantage?

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Received 18 February 2015; received in revised form 2 April 2015; accepted 23 April 2015

Abstract

Degarelix is a gonadotropin-releasing hormone (GnRH) antagonist that is approved for the treatment of prostate cancer. GnRH antagonists bind directly to and block GnRH receptors, without causing the initial testosterone surge associated with GnRH agonists. A pivotal phase III study indicated that degarelix induced significantly faster reduction of testosterone and prostate-specific antigen level than GnRH agonist does. In addition, its 5-year extension trial suggested that patients could be safely switched from GnRH agonist to degarelix treatment with sustained efficacy, as measured by biochemical markers. Possible benefits of GnRH antagonists over agonists were suggested especially in patients with advanced prostate cancer with metastatic and symptomatic disease. Moreover, the recent reports including pooled data analyses on degarelix suggest improved disease control, quality of life, and lower urinary tract symptoms and decreased risk of cardiovascular diseases when compared with GnRH agonists. However, interpretation of these reports should be conducted cautiously because of the potential biases involved. This article critically reviews the results of the clinical trials and subsequent analyses and evaluates the points and counterpoints of the conclusions.

Keywords: Degarelix; Prostate cancer; GnRH antagonist; Oncological outcome; Cardiovascular disease

1. Introduction

Since Huggins and Hodges demonstrated the clinical benefits of surgical castration for prostate cancer (PCa), androgen deprivation therapy (ADT) has been the cornerstone of management for metastatic PCa. Now ADT is also taking on an increasingly important role in earlier stages of PCa. It is widely used in combination, or as a salvage option, with radiation therapy or surgery. The most prevalent form of ADT currently relies on gonadotropin-releasing hormone (GnRH) agonists. However, GnRH agonists stimulate pituitary GnRH receptors, resulting in prompt secretion of luteinizing hormone (LH), which in turn causes a surge of testosterone that delays the onset of ADT and is potentially tumor promoting [1]. This can cause clinical flare in patients with advanced disease, exacerbating clinical symptoms such as skeletal pain, ureteral obstruction, and spinal cord compression [2]. These phenomena can be minimized by concomitant antiandrogens that negate the effects at the testosterone receptor level. But antiandrogens do not remove the risk of clinical flare completely.

The development of the GnRH antagonists was inspired by the counterintuitive testosterone surge associated with GnRH agonist therapy. GnRH antagonists bind directly to and block GnRH receptors, without causing the initial testosterone surge and flare associated with agonists [3,4]. Degarelix is a clinically effective third-generation GnRH antagonist developed to obtain potent GnRH antagonists that are characterized by low histamine-release properties, long-lasting biological activity, and high solubility [5]. A pivotal phase III study—CS21—and its 5-year extension trial—CS21a—indicated that degarelix induced significantly faster reduction of testosterone and prostate-specific antigen (PSA) levels than leuprolide did [6,7]. Possible benefits of GnRH antagonists over agonists were suggested especially in patients with advanced PCa with baseline PSA levels >20 mg/ml and metastatic or symptomatic disease or both. Moreover, recent reports, including pooled data analyses, suggested that degarelix improved disease control, quality of life (QOL), and lower urinary tract

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http://dx.doi.org/10.1016/j.urolonc.2015.04.013
1078-1439/

symptoms (LUTS) and decreased the risk of cardiovascular diseases (CVD), when compared with GnRH agonists. The immediate onset of action of degarelix makes it a favored ADT option in men with a high tumor burden and risk of acute onset of problems, such as urinary tract symptoms, pain, or spinal cord compression.

This article critically reviews the results of the clinical trials and subsequent analyses and evaluates the points and counterpoints of the conclusions.

2. Basic mechanisms of GnRH agonist and antagonist

2.1. Different mechanisms for the induction of chemical castration by GnRH agonist and antagonist

Agonist-induced overstimulation overcomes the pulsatile GnRH control of the pituitary by constantly stimulating the organ. This leads to desensitization or down-regulation of pituitary GnRH receptors, a reduction in LH (and follicle-stimulating hormone [FSH]) production, and the desired result—suppression of testosterone to castration levels [1]. However, approximately 10% of patients treated with GnRH agonists fail to achieve those castration levels [7]. In contrast, the GnRH antagonists bind directly to GnRH receptors in the pituitary gland, leading to a rapid decrease in LH, FSH, and testosterone levels without any flare [8].

2.2. Testosterone surge and microsurges

The most expected advantage of GnRH antagonist when compared with GnRH agonist was the inhibition of testosterone surge and microsurges owing to immediate suppression of testosterone. The intense initial stimulation of release of LH and FSH by GnRH agonists can lead to a transient rise or surge in testosterone levels, resulting in exacerbation of clinical symptoms (flare effects) in advanced disease [9,2]. This risk is not completely removed with the introduction of a concomitant antiandrogen, because the antiandrogen does not suppress testosterone. In CS21 phase III randomized trials, of 23 patients who received leuprolide with bicalutamide, 17 (74%) experienced a testosterone surge [6]. Microsurges, elevation in testosterone from less than to greater than the castrate level, occurred in 17.7% to 27.0% of the patients who received 1 or more repeat injections of GnRH agonist, even though no patient with a testosterone surge had clinical symptoms of a tumor flare reaction [10].

2.3. Other potentially important mechanisms

After administration of degarelix, the median LH and FSH levels also decreased rapidly and remained suppressed until the end of the CS21 phase III study [6]. In contrast, patients in the leuprolide group showed an increase in median LH and FSH levels at the beginning of treatment, and FSH levels did not decrease to the same extent as they did in the degarelix groups. At the end of the study, mean FSH levels had decreased from baseline by 54.8% in the leuprolide group compared with 88.5% to 89.0% in the degarelix groups. This phenomenon was reported as “FSH escape” in 1994 [11]. A possible mechanism has been proposed, associated with FSH escape or increased FSH, but the clinical relevance of the phenomenon is not yet fully understood. Both direct and indirect mechanisms may be involved for growth of PCa. FSH receptor is selectively expressed on the surface of the blood vessels of a wide range of tumors and metastatic sites including PCa [12,13], and it appears that FSH receptors and their ligands may play a role in the regulation of PCa growth. FSH receptor is also expressed in bone, where they accelerate bone resorption [14]. Because degarelix acts to block FSH levels, it may be beneficial in limiting the growth of tumors.

3. Clinical trials of degarelix

3.1. Phase III trials

The Table summarizes phase III trials. There are 7 phase III studies, including 2 unpublished ones. The primary end point varies from study to study. Of those, 2 studies use the change of testosterone level as the primary end point (CS21 and CS35), 2 studies use the change in PSA level (CS29 and CS37), 2 studies use the change in prostatic volume (PV) (CS30 and CS31), and the remaining 1 use the change in the International Prostatic Symptom Score (CS28). Of these studies, 2 lacked control arms of GnRH agonist as the comparator. Treatment was administered as neoadjuvant before definitive radiotherapy (RT) in 1 study.

3.2. Pivotal phase III trial (CS21)

To evaluate the efficacy of degarelix with the GnRH agonist leuprolide, a randomized, open-label phase III trial (CS21) was conducted [6]. The primary end point was the probability of patients having testosterone levels <0.5 ng/ml from days 28 through to 364 of treatment.

Degarelix at doses of 240/80 and 240/160 mg were both effective and noninferior to leuprolide in suppressing testosterone levels for up to 12 months; the treatment response rate was 97.2% in recipients of degarelix at a dose of 240/80 mg, 98.3% in recipients of degarelix at a dose of 240/160 mg, and 96.4% in recipients of leuprolide. Testosterone suppression was more rapid in the degarelix recipients. Testosterone surge (defined as an increase in testosterone level of $>15\%$ from baseline on any 2 days during the initial 2 weeks of treatment) occurred in 80% of patients in the leuprolide group and 0% in the degarelix groups. This surge was noted in 81% of patients (144/178) receiving leuprolide without bicalutamide compared with