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Original article

Insulin-like growth factor-1 is associated with regulation of the luteinizing hormone production in men receiving androgen deprivation therapy with gonadotropin-releasing hormone analogues for localized prostate cancer☆

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Abstract

Background: Luteinizing hormone (LH) during androgen-deprivation therapy (ADT) with gonadotropin-releasing hormone analogues (GnRHa) has been thought to be biologically inactive, and the regulation of LH during ADT with GnRHa is thus unknown. Insulin-like growth factor-1 (IGF-1) is involved in the regulation of cell proliferation and differentiation, and IGF-1 production in the liver is dependent on growth hormone (GH) secretion from the anterior pituitary. Despite the presence of IGF-1 receptors in the gonadotroph, associations between the GH/IGF-1 and pituitary-gonadal axes, e.g., whether IGF-1 elicits the LH secretion, remain unclear.

Methods: Seventy-one patients with localized prostate cancer, who received ADT with GnRHa, were prospectively studied based on their blood samples before treatment and after ADT for 6 months. We employed highly sensitive assays for measurement of serum testosterone (electrochemiluminescence immunoassay), GH/IGF-1 (radioimmunoassay), adrenocorticotropic hormone (ACTH: immunoradiometric assay), LH (chemiluminescent immunoassay), and dehydroepiandrosterone sulfate (DHEA-S: chemiluminescent enzyme immunoassay).

Results: No correlation was noted between the pretreatment LH and IGF-1 levels; after ADT, the serum LH level was closely correlated with the IGF-1 concentration [Spearman's correlation coefficient (rs) = 0.370, $P = 0.001$]. The serum levels of androgens and gonadotropins reduced following ADT ($P < 0.001$ in all). The serum IGF-1 level increased (22 ± 6 nmol/L) compared with that at the baseline (19 ± 5 nmol/L) ($P < 0.001$), but no change was observed in the serum GH concentration between before and after ADT (1.4 ± 2.3 vs. 0.9 ± 0.9 μg/L, respectively, $P = 0.691$). The serum testosterone level was not correlated with the LH level either before or after ADT. The testosterone and DHEA-S levels after ADT were correlated with ACTH concentration (rs = 0.367, $P = 0.002$ and rs = 0.354, $P = 0.002$, respectively). We did not identify any correlations between the serum IGF-1 concentration and Gleason score, PSA value, or androgen levels.

Conclusions: During ADT with GnRHa, IGF-1 possibly promotes LH production, although its role is unclear. Associations among pituitary-gonadal, pituitary-adrenal, and GH/IGF-1 axes represented by IGF-1-mediated LH secretion and ACTH-mediated androgen synthesis are of interest, since both prostate epithelium proliferation and male anabolic activity are involved in these 3 axes. Assessment of oncologic outcomes is warranted for their significance in patients with prostate cancer.

Keywords: Androgen deprivation therapy; GH/IGF-1 axis; Pituitary-gonadal axis

1. Introduction

Treatment involving androgen deprivation has become the therapeutic mainstay for patients with metastatic prostate cancer or non-metastatic disease to prevent recurrence. Androgen deprivation therapy (ADT) has recently been used in about 30% of patients with localized or locally

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advanced prostate cancer, mainly combined with radiotherapy for intermediate- to high-risk disease [1,2]. ADT has also been associated with unfavorable events such as blood hemoglobin decrease and bone metabolic disorder [3–5], however, many phenomena regarding the impact of ADT on the hormonal milieu in vivo have not been elucidated thus far.

The hypothalamic-pituitary-gonadal axis is essential for the endocrine regulation of gametogenesis in mammals. The pituitary gonadotropins such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH) play a central role in this endocrine communication. Gonadotropin-releasing hormone (GnRH), also known as LH-releasing hormone, induces the pituitary secretion of FSH and LH in normal female cyclicity, which is critical for regulating the gonadal and reproductive functions [6]. In men, FSH and LH stimulate intracellular signal transduction by binding to each receptor, and coordinately regulate androgenic activities such as testicular growth and spermatogenesis [7]. Since the 1980s, GnRH analogues (GnRHa) have been widespread for contraception and treatment of various endocrinologic disorders such as precocious puberty or ovarian hyperstimulation mainly by the suppression of endogenous LH, and they have also been applied for patients with sex-steroid-dependent disease including endometriosis, breast cancer, and prostate cancer [7,8]. Clinical outcomes with mentioned evidence have strongly supported the utility of chemical hypophysectomy by GnRHa. GnRHa does not completely repress the secretion of LH, although LH in men receiving ADT with GnRHa has been thought biologically inactive [6,7]. Thus, the regulatory mechanism and significance of LH during ADT with GnRHa are unknown.

Insulin-like growth factor-1 (IGF-1) is a peptide involved in the regulation of cell proliferation and differentiation, and exerts multiple effects on glucose, fat, and protein metabolisms, bone synthesis, and hematopoiesis [9]. Although several tissues secrete IGF-1, more than 90% of IGF-1 in the serum is synthesized in the liver [9]. The production of IGF-1 in the liver is predominantly dependent on growth hormone (GH) secretion from the anterior pituitary. GH secretion declines with aging, and in the so-called somatopause state, the reduced IGF-1 level accelerates age-related physiological changes represented by osteoporosis and blood hemoglobin loss [10,11]. In contrast, the impact of ADT on the GH/IGF-1 axis has barely been studied.

All subtypes of the endocrine cells in the pituitary, including gonadotroph cells, have recently been reported to express IGF-1 receptors in the mammalian [12,13], suggesting a relationship between the GH/IGF-1 and pituitary-gonadal axes. However, it remains unknown whether IGF-1/IGF-receptor interaction elicits or regulates the secretion of gonadotropins in vivo, and the influence of ADT with GnRHa on these endocrine alliances important for growth and aging is of interest. In the present study, we examined the influence of ADT on androgens and pituitary hormones not only by measuring each hormone level but also in terms of endocrine axes, and focused on the pituitary-gonadal and GH/IGF-1 axes by analyzing blood sample data prospectively obtained from patients who received ADT for localized prostate cancer to elucidate (1) regulation of LH during ADT with GnRHa; (2) crosslink between the 2 axes and the influence of ADT on their relationship.

Table 1
Patients' characteristics (n = 71)

Age at diagnosis, mean (range)	68.9 (54–79)
PSA at diagnosis (μg/L)	No. of patients (%)
<4.0	0
4.0–10.0	22 (31.0)
10.1–20.0	27 (38.0)
20.1–50.0	20 (28.2)
≤50.1	2 (2.8)
Gleason score	No. of patients (%)
≤6	19 (26.8)
7	29 (40.8)
≤8	23 (32.4)

PSA = prostate-specific antigen.

2. Materials and methods

2.1. Patients

Men with liver dysfunction or renal insufficiency were excluded, and in total, 71 consecutive patients who were treated with radiotherapy for localized or locally advanced prostate cancer (cT1c–3 N0 M0) at the Department of Urology, Niigata University Hospital, were enrolled between May 2004 and December 2006 (Table 1). Therapeutic criteria were: patients with high-risk disease (Gleason score of ≥8 and/or serum PSA levels of ≥20 ng/ml and/or cT2c or more advanced stage) and those with intermediate-risk disease (Gleason score of 7 and/or PSA levels of 10–20 ng/ml and/or cT2b disease). Mean patient age at diagnosis was 69 years old (range 54–79). Mean PSA at diagnosis was 17.9 ng/ml (range 5.2–100.9) and mean Gleason score was 7.1 (range 5–9). Twenty-two patients had hypertension, and 2 and 3 patients had been diagnosed as having diabetes that was well-controlled by oral hypoglycemic agents and alimentary therapy, respectively. The patients received a subcutaneous injection of a GnRHa, goserelin acetate (3.6 mg, every 4 weeks), and peroral non-steroidal anti-androgen flutamide (375 mg/d) for 6 months, prior to radiotherapy. Patients' demographics are shown in Table 1. The study was prospectively designed, and the procedure for this research project was approved by the Ethics Committee of our institution. Informed consent was obtained from all patients.

2.2. Blood sampling and analytical measurements

In all patients, blood samples were evaluated at the baseline as well as after ADT for 6 months. All blood