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European Association of Urology

Prostate Cancer

Failure to Achieve Castration Levels in Patients Using Leuprolide Acetate in Locally Advanced Prostate Cancer

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Article info

Article history:
Accepted September 5, 2005
Published online ahead of print on November 15, 2005

Keywords:
Prostate cancer
LHRH analogues
Antiandrogens
Serum testosterone

Abstract

Objective: In a cross-sectional, retrospective, non-randomised study to investigate the possibility that some patients treated with luteinizing hormone releasing hormone analogues (LHRH analogues) fail to reach castration levels of serum testosterone.

Methods: 40 patients treated with a 3-monthly formulation of leuprolide acetate and continuous use of an oral antiandrogen (''Leu group'') and 25 patients treated with a 3-monthly formulation of goserelin acetate and an oral antiandrogen for one month (''Gos group'') were identified from our hospital's registry. Serum testosterone was measured during treatment with the respective LHRH-analogue and compared between the two groups. In the Leu group, serum testosterone was measured during week 11 or 12 of treatment. In the Gos group, serum testosterone was assessed during week 23 or 24.

Results: Four patients (10%) treated with leuprolide acetate failed to reach the castration level of serum testosterone after treatment with one injection of a three-monthly formulation of leuprolide acetate. All patients treated with goserelin acetate achieved the castration level.

Conclusion: Although the overwhelming majority of prostate cancer patients during treatment of LHRH analogue achieve serum testosterone values within the castration range, individual patients may fail to reach this therapeutic goal, probably more often during treatment with leuprolide acetate than with goserelin acetate.

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0302-2838/$ – see front matter © 2005 Elsevier B.V. All rights reserved. doi:10.1016/j.eururo.2005.09.009

1. Introduction

Androgen deprivation is considered the treatment of choice in patients with newly diagnosed metastatic prostate cancer and has an important role in the adjuvant treatment of locoregionally advanced prostate cancer [1,2]. Analogues of luteinizing hormone releasing hormones (LHRH analogues) have taken the leading role for the achievement of androgen deprivation and result in similar outcome as surgical castration if evaluated by means of serum testosterone. LHRH analogues are in most countries available as 1-monthly and 3-monthly formulations. In general, maximal Leydig cell suppression is achieved within the first month after start of the 1- or 3-monthly depot preparations of LHRH analogues available today.

In Norway, three LHRH analogues are available: Buserelin acetate (Suprefact®, Aventis Pharma, Goserelin acetate (Zoladex®, Astra Zeneca) and leuprolide acetate (Procren®, Abbott and Enanton®, Orion). Goserelin acetate and leuprolide acetate are on the market for monthly and 3-monthly use. Buserelin and another formulation of LHRHa, tryptorelin, are not registered in Norway and will not be considered in this report.

During the recent years several authors have suggested that serum testosterone is not always suppressed below the upper limit of the castration range in prostate cancer patients using leuprolide acetate [3–5]. On the other hand, except for one case report [6], the authors of the present study are not aware of any published reports dealing with insufficient testosterone suppression using goserelin acetate if the drug is adequately administered. After having seen two patients in our clinic who were referred to us for hormone-resistant prostate cancer (HRPC) but did not display castration levels of serum testosterone during their treatment with leuprolide acetate [7], we initiated the present study which in cohorts of patients compare serum testosterone levels 3 to 6 months after start of treatment with either leuprolide acetate or goserelin acetate.

2. Patients and methods

Based on the hospital's patient registry we identified men with locally advanced non-metastatic prostate cancer in whom serum testosterone was recorded before start of treatment with LHRH analogue therapy and during the last two weeks after receiving one or two injections of a 3-monthly formulation of the drug. One group of these eligible patients represented patients included in a phase III trial which assesses the role of radiotherapy in locoregionally confined prostate cancer (the SPCG-7-Study [8]). These patients received a single injection of a three-month depot formulation of 11.25 mg leuprolide acetate (Procren®, Abbott) and an oral antiandrogen (Eulexin®, Schering-Plough) 750 mg per day, given continuously (''Leu group''). After closing this trial in 1998 similar patients were treated with two injections of goserelin acetate 10.8 mg s.c. (Zoladex®, Astra Zeneca) applied with an interval of 3 months together with Casodex® (Astra Zeneca) 50 mg orally daily during the first four weeks (''Gos group'') before they started high-dose radiotherapy to the prostate.

In these patients, serum testosterone was routinely measured before start of hormone treatment and once during the last two weeks of a three-month cycle, before radiotherapy was started. In the Leu group, serum testosterone was measured during week 11 or 12 of treatment. In the Gos group, serum testosterone was assessed during week 23 or 24. Serum testosterone was measured with a Spectria coated tube (Orion Diagnostica, Turku, Finland, coefficient of variation less than 8%). In the present study we defined the upper limit of the castration range at 2.8 nmol/l (0.81 ng/ml), which in our laboratory is the upper limit of the female range of serum testosterone. This level has in a previous study been shown to be a valid cut-off value for achievement of clinical improvement in patients with insufficient androgen deprivation undergoing secondary orchiectomy [9].

Statistics: Descriptive methods were used whenever appropriate (means ± standard deviations, medians ± ranges) ranges) with *t*-test, Wilcoxon test or chi-square test for comparisons. A *p*-value of less than 0.05 was considered to be statistically significant.

3. Results

There were 40 patients in the Leu group and 25 patients in the Gos group. Their mean age was 66 and 65 years, respectively. In the Leu group the median level of serum testosterone prior to hormone treatment was 16.5 nmol/l (range: 9.4–31.6). After 3 months the median level of serum testosterone was 0.6 nmol/l (range: 0.5–9.4). Four patients (10%) from the Leu group failed to reach castration levels after 3 months. In the Gos group median serum testosterone prior to hormone treatment was 16.2 nmol/l (range: 11.2–29.6). At the end of the second 3-month interval during treatment with goserelin acetate the median serum testosterone was 0.9 nmol/l (range: 0.5–2.2). All patients in the Gos group reached castration levels of serum testosterone. (Fig. 1). The difference of the serum testosterone values between the two groups were statistically not significant ($p = 0.16$).

4. Discussion

In 4 out of 40 patients (10%) treated with one 3-monthly injection of leuprolide acetate (11.25 mg),

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