

Gn-RH Antagonist Possible Response, After Gn-RH Agonist Failure in a Man with Metastatic Prostate Cancer

B. ROCCO¹, M. FERRARI², E. SCARDINO¹, D.V. MATEI¹,
F. VERWEIJ¹, R. VARELA¹ and O. DE COBELLI¹

¹Division Of Urology, European Institute of Oncology, Milan;
²Division of Endocrinology, Istituti Clinici Humanitas, Milan, Italy

Abstract. Gn-RH agonists or surgical castration are considered standard treatment for patients affected by metastatic prostate cancer. Despite greater cost, chemical castration is often considered the treatment of choice as it is psychologically better tolerated. We report our experience of one patient undergoing treatment with Gn-RH agonist who developed an early resistance to the administered drug, with serum testosterone levels within the range of normality.

The effects of castration in prostate cancer treatment were described by Huggins in 1940.

More recently, in the seventies, the introduction of LH-RH agonists allowed the wide development in clinical practice of chemical castration. This is more expensive, but psychologically better tolerated. We report the case of one patient presenting resistance to LH-RH agonists.

Case Report

A 76-year-old man with hormone-naïve bone metastatic prostate cancer had shown ECOG performance status 0, and initial PSA of 49.72 ng/ml in November 2003. Since then, the patient underwent treatment with Flutamide 750 mg daily, triptorelin 11.25 mg every 3 months and zoledronic acid 4 mg every 4 weeks. In January 2004, PSA reached nadir level (6.1 ng/ml), whereas in March it increased to 11.3 ng/ml with serum testosterone levels above the range of castration (875 ng/dl).

Endocrine tests revealed FT3 (34.4 pmol/L), FT4 (13.6 pmol/L), TSH (0.6 mU/L), inhibin-B (173 pg/ml), SHBG (60

nmol/L), prolactin (180 mIU/L), ACTH (46 ng/L), cortisol (520 nmol/L), DHEA-S (8 mmol/L), SHBG (50 nmol/L), androstenedion (8 nmol/L) and 17 OH progesterone (2.4 nmol/L), all within the ranges of normality.

Basal LH (6.8 mIU/mL), FSH (7.0 mIU/mL) and testosterone (875 ng/ml) levels were normal. Oral etinilestasradiol 1 mg was given, with significant reduction of gonadotropin and serum testosterone levels; a further test was performed with LH-RH antagonist (Cetrorelix 0.25 s.c.), showing again a significant decrease of gonadotropin and serum testosterone levels.

Gn-RH antagonists are not available in Italy for prostate cancer treatment; the patient was administered leuprorelin 3.75 mg every 4 weeks. Bone scan and abdomen CT scan were stable. Successive PSA was 32.65 ng/ml with castrate serum testosterone levels (< 50 ng/ml); one month later, PSA was 41.65 ng/ml and the serum testosterone reached normal levels. Following this, the patient developed pain in the right lower limb, requiring strong narcotics (morphine-based therapy) and a worsening of ECOG performance status, with a PSA level of 51.2 ng/ml. Bilateral orchiectomy was thus performed at the end of June 2004.

After the procedure, the patient became asymptomatic, the PSA value decreased to 44 ng/ml and testosterone to castrate levels.

Discussion

Recently, case reports regarding LH-RH agonists resistance have been published (1,2) showing their involvement in monitoring serum testosterone levels in patients treated with these drugs. However, there is a lack of evidence about risks factors or mechanisms of resistance. In our case, the non testicular origin of serum testosterone level, functional pathologies of the Hypophysis or alteration of the LH-RH-Gonadotropins-testis pathway have been excluded.

Correspondence to: Bernardo Rocco, MD, Division of Urology, European Institute of Oncology, Milan, Italy. Tel: +39 02 57 48 99 33, Fax: + 39 02 57 48 97 85, e-mail: bernardo.rocco@ieo.it

Key Words: Gn-RH agonist, prostate cancer, leuprorelin, triptorelin, drug resistance.

To our knowledge, this is the first time that the LH-FSH pathway has been tested (using ethinylestradiol and LH-RH antagonists), in a LH-RH agonist-resistant hormone-naïve prostate cancer patient. It appears that both ethinylestradiol and LH-RH antagonists effectively inhibit testosterone production, albeit that further studies are needed to confirm the therapeutic role of these drugs in Gn-RH non-responders.

In these patients, the experimental use of LH-RH antagonists might be studied before definitive orchiectomy in order to reach stable castration levels of testosterone.

References

- 1 Smith MR and Mc Gover FJ: Gonadotropin – releasing hormone agonist failure in man with prostate cancer. *J Urol* 166: 211, 2001.
- 2 Curry EA and Sweeney CJ: Resistance to luteinizing hormone releasing hormone agonist therapy for metastatic prostate cancer. *J Urol* 168: 193, 2001.

Received July 27, 2004
Accepted December 30, 2004