Follicle-stimulating hormone: A potential surrogate marker for androgen deprivation therapy oncological and systemic effects

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As urologists prescribing androgen deprivation therapy (ADT) to prostate cancer patients, we all follow the patients' serum PSA levels as surrogacy for oncological response. Accumulating evidences now suggest that periodic measurements of serum testosterone levels is advisable not only as an indicator for adequate castration but also to predict disease progression to castration resistance phase.[1] Can we use other serum markers to predict the inevitable progression to castration resistance prostate cancer (CRPC) in patients treated with ADT?

In this issue, Hoare and colleagues[2] retrospectively investigated their single-centre database of prostate cancer patients treated palliatively with ADT for a potential association between serum follicle-stimulating hormone (FSH) levels and time to CRPC. In total, 103 men had at least one (median 4) documented FSH value while castrate. The vast majority of patients received GnRH agonists, with only a few receiving an antagonist during their management. The mean time from ADT commencement to CRPC was 3.03 ± 0.34 years with a median of 2.32 years. The authors categorized serum FSH levels into tertiles: Q1 = 1.5 to 4.8 mIU/mL; Q2 = 4.8 to 7.3 mIU/mL; and Q3 = 7.3 to 28.1 mIU/mL. Patients within the lower tertile (FSH ≤4.8 mIU/mL) were found to advance to CRPC at a significantly reduced rate when compared to those with serum FSH levels above this threshold (hazard ratio 0.46; 95% confidence interval 0.23–0.73; log-rank test, $p = 0.006$). Despite the inherent limitations of this retrospective small cohort study, its original results deserve further attention and validation.

It is reasonable to suspect that FSH can promote prostate cancer progression. FSH is a trophic hormone that is involved in steroidogenesis, energy and metabolism, angiogenesis, protein synthesis, cell division, growth and differentiation – all key mechanisms in carcinogenesis. Limited preclinical in vitro and in vivo data also suggest its carcinogenic effect in prostate cancer.[3] Importantly, FSH receptors can be documented both in prostate cancer cells and in neovasculature of prostate cancer metastatic foci.[4] Correlation to clinical relevancy however is lagging behind. One previous study that correlated the pathological stage of 250 men undergoing radical prostatectomy to the serum levels of various hormones reported significantly lower levels of serum FSH in patients with localized tumours compared to locally advanced disease.[5] The Hoare study,[1] albeit a small single centre retrospective series, further contributes to the growing understanding that FSH has potential mitogenic effects in prostate cancer.

Interestingly, FSH receptors are highly expressed in cardiac myocytes, adipocytes and skeletal muscle (Pinthus JH, unpublished data, 2015). Accordingly, it has been recently suggested that elevated levels of FSH may facilitate the cardio-metabolic complications of castration.[6] Studies investigating the correlation between serum FSH levels on ADT and cardiometabolic disarrangements and complications are currently underway.

Importantly, different modes of ADT result in completely different serum FSH profile. Orchiectomy induces significant elevation of FSH levels while gonadotropin-releasing hormone (GnRH) agonists inhibit the serum FSH levels, albeit to a significantly lesser extent than GnRH agonists. Although most clinicians intuitively link the effect of GnRH agonists and antagonist on LH levels to that of FSH, the regulation of these two hormones in the anterior pituitary gonadotroph cells by GnRH and other stimulus are very different.[7] Even more so, the effect of adding novel ADT manipulations (such as abiraterone or enzalutamide) which are administrated at the time of CPRP on FSH levels is currently not well-defined. The latter may be important given the potential ability of FSH to promote tumour growth in an androgen receptor independent mechanism.

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Taken together, we need more pre-clinical studies to better define the carcinogenic effects of FSH. Parallel clinical studies investigating the characteristics and performance of FSH as a serum marker for prostate cancer aggressiveness in ADT naïve patients and in ADT+ settings are warranted. The study by Hoare and colleagues[1] certainly lays further rational for this research direction.

Competing interests: Dr. Pinthus is a consultant for Ferring.

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