Serum follicle-stimulating hormone levels predict time to development of castration-resistant prostate cancer

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Abstract

Introduction: Treatment of advancing prostate cancer focuses on blocking the activation of the androgen receptor with resultant prolonged perturbation of the hypothalamic-pituitary-gonadal axis. Androgen deprivation therapy (ADT) is marked, however, by eventual progression to castration- resistant prostate cancer (CRPC). Emerging evidence has postulated that follicle-stimulating hormone (FSH) may lead to proliferative and mutagenic responses of prostate cancer. We investigated the association of serum FSH and time to castration resistance.

Methods: This was a single-centre retrospective study assessing serum FSH levels of patients undergoing ADT for advancing prostate cancer. The primary outcome was time of ADT initiation to the development of CRPC. For each patient on treatment and with castrate levels of testosterone, the maximum FSH value between ADT commencement and CRPC was identified and recorded. FSH was analyzed as a continuous and categorical variable. Cox multivariate regression in a step-wise fashion was used to explore the association between FSH levels and time to CRPC.

Results: From a database of 323 prostate cancer patients actively managed with ADT, 103 men had a documented FSH value while castrate, with 45 men progressing to CRPC. The mean ± standard deviation maximum FSH value of these patients was 6.66 ± 4.22 mIU/mL (range: 1.5–28.1). The mean duration from ADT commencement to CRPC was 3.03 ± 0.34 years (range: 0.36–9.71). Univariate analysis suggested a trend of a negative correlation between FSH values and time to castrate resistance. A FSH value of less than or equal to the lowest tertile (4.8 mIU/mL) was associated with a longer time to CRPC (hazard ratio 0.46; $p = 0.006$). In the Cox regression analysis, elevated FSH was associated with a shorter duration time to CRPC ($p = 0.03$).

Conclusions: This retrospective, single-centre study would suggest there may be an association between serum FSH levels and time to CRPC for men treated palliatively with ADT for advancing prostate cancer. Further clinical investigation in a larger cohort of men is required to determine any clinical utility of FSH as a biomarker of progression or target for therapy.

Introduction

Prostate cancer is the most commonly diagnosed solid organ malignancy in men; about 1 in 8 Canadian men will be diagnosed with it throughout their lifetime.[1] Despite advances in the detection and management of localized disease, with subsequent evidence of reduced prostate cancer mortality,[1] many men still require systemic therapies for recurrent or metastatic disease. The mainstay for palliation of advancing prostate cancer remains androgen deprivation therapy (ADT).[2] The vast majority of these patients will be managed with medical castration through manipulation of the hypothalamic-pituitary-gonadal axis with gonadotropin-releasing hormone (GnRH) agonists or antagonists.[3] These agents lead to decreased pituitary secretion of luteinizing (LH), and subsequent inhibition of the testosterone synthesis cascade within Leydig cells in the testes.[4] The effect of ADT on the other pituitary gonadotropin, follicle-stimulating hormones (FSH), appears to be variable between patients and approaches to castration.[5,6]

Although most patients are initially responsive, ADT for advanced disease is marked by eventual progression to castration resistant prostate cancer (CRPC), with an ensuing median survival of less than 3 years.[7,8] One of the most studied mechanisms of progression despite castrate levels of circulating androgens are the intracellular and adrenal sources of testosterone, which appear to be important drivers of progression.[7,9,10] These observations suggest that adrenal and intracrine contributions to the tumour androgen signaling axis represent important targets for further hormonal modulation of prostate cancer.[8,10,11] Despite this increasing understanding of androgen-receptor mediated prostate cancer progression, there are a number of other non-androgen mediated factors involved in progression to CRPC.[10,12]

FSH has been shown recently to have a functional role in a number of genitourinary malignancies, including a role in angiogenesis in both benign and pathologic microenvi-

ronments.[13-17] Interestingly, the prostate has long been recognized as a potential source of extra-pituitary FSH and up-regulated in the face of prostate pathology.[16,17] Ben-Josef and colleagues have proposed the presence of an FSH/FSH receptor (FSHR) autocrine loop, postulating that FSH could stimulate the transition from a hormone-sensitive to a hormone-independent state.[18] More recent studies have verified the presence of up-regulated FSH and FSHR in pathological prostatic states, and implicate these molecules in the tumorogenic milieu.[19-21] Given the preclinical evidence supporting the hypothesis that FSH may contribute to progression of androgen-independent prostate cancer, we sought to investigate if FSH levels in men on ADT could predict time to CRPC.

Methods

This single-centre retrospective review was drawn from a database of advanced prostate cancer patients managed through the Centre for Applied Urological Research of Queen's University between 2001 and 2014. A total of 323 patients were evaluated for eligibility in our study. Patients were included if they had received any method of castration for metastatic or non-metastatic prostate cancer and had at least one recorded FSH value while on ADT. Clinical parameters collected included: age at diagnosis, age at initiation of ADT and at time of documented CRPC, original Gleason score, primary treatment as well as prostate-specific antigen (PSA) and the presence of metastases at ADT initiation. Given the lack of clinically significant outcome differences between intermittent and continuous ADT in most patients, it was decided to include both of these cohorts in this exploratory study.[22]

Serum testosterone measurements for men managed with ADT were routinely obtained during this time frame and patients included in this study had to maintain castrate levels of testosterone (<1.7 nmol/L) while on treatment. To be included in this study cohort, serum FSH levels were required to be taken at the same time that patients had castrate levels of testosterone and patients must have been castrate for at least 6 months. The primary outcome of interest was the duration of time between initiation of ADT and the development of CRPC. Castrate resistance was defined as 3 consecutive rises in PSA, separated by at least 2 weeks, with simultaneous castrate levels of testosterone regardless of therapy.

FSH was analyzed as both a continuous and categorical variable. Spearman correlation coefficients, unpaired T tests and the Mann-Whitney U were used to analyze clinical parameters. Univariate survival curves were analyzed using the Log-Rank test for statistical significance. A Cox multivariate analysis was performed to evaluate the potential interface between FSH and a number of pathological and clinical factors on time to CRPC. These variables included age, initial Gleason score, original primary prostate cancer management (watchful waiting vs. curative intent surgery or radiotherapy) and the presence/absence of metastases upon presentation. The Omnibus Tests of Model Coefficients was used to evaluate the statistical significance of this logistical regression. A p value of <0.05 was considered statistically significant. Analyses were performed using SPSS (SAS Institute, Cary, NC). This study was approved by the Institutional Review Board of Queen's University.

Results

From a database of 323 prostate cancer patients actively managed with ADT between 2001 and 2014, 103 men had a documented FSH value while castrate. Of these 103 patients, most had ADT initiated because of progressing disease on watchful waiting or for a new presentation of metastatic disease with no local therapy (n = 56). The remaining patients started ADT after failure of primary therapy with either radical prostatectomy (n = 19) or curative intent radiotherapy (n = 28).

As of December 2013, 45 patients (44%) had progressed to CRPC, of which 34 patients (67%) had died of their disease. The mean age at original diagnosis of the 45 patients with CRPC was 69.7 ± 1.48 and the mean age at the time of CRPC was 74.9 ± 1.41 years. Only 13 (29%) of this final cohort had metastatic disease on imaging prior to starting ADT. The vast majority of patients received a GnRH agonist, with only a few receiving an antagonist during their management of advanced prostate cancer. Most men received goserelin acetate (56%), with the remaining patients being treated with leuprolide acetate (32%), buserelin acetate (5%); 3 patients (7%) had several different GNRH agonists or antagonists prescribed over time. No patients were concomitantly receiving anti-androgen therapy during this time period while responding to the ADT.

The median number of serum FSH values identified in the entire cohort while on treatment was 4 (mean 3.70 ± 2.55, range: 1–11). Of the 45 patients who had gone on to develop CRPC, the mean maximum serum FSH level recorded was 6.66 ± 4.22 mIU/mL (range: 1.5–28.1). The dataset did not capture which GnRH agonist or antagonist was used at the time of this maximum reading. The mean time from ADT commencement to CRPC was 3.03 ± 0.34 years, with a median of 2.32 years (range: 0.36–9.71). Initial analysis of FSH as a continuous variable revealed a trend to negative correlation with time to castrate resistance (Spearman correlation coefficient, r = -0.246; unpaired T test, p = 0.104) (Fig. 1).

In an analysis to define cut-points of maximal FSH values predicting time to CRPC, we categorized values into tertiles. The range of values created a tertile distribution of 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 in the lowest tertile (Q1) were

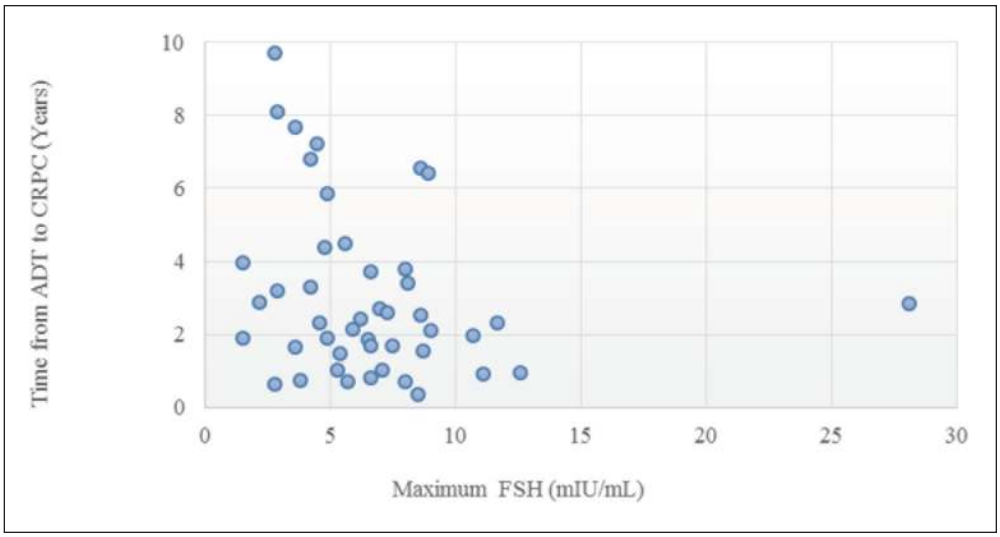

Fig. 1. Scatter plot of the correlation between maximum follicle-stimulating hormone (FSH) while on androgen deprivation therapy (ADT) with the development of castration-resistant prostate cancer (CRPC). Spearman correlation coefficient *(r* = -0.246, *p* = 0.104).

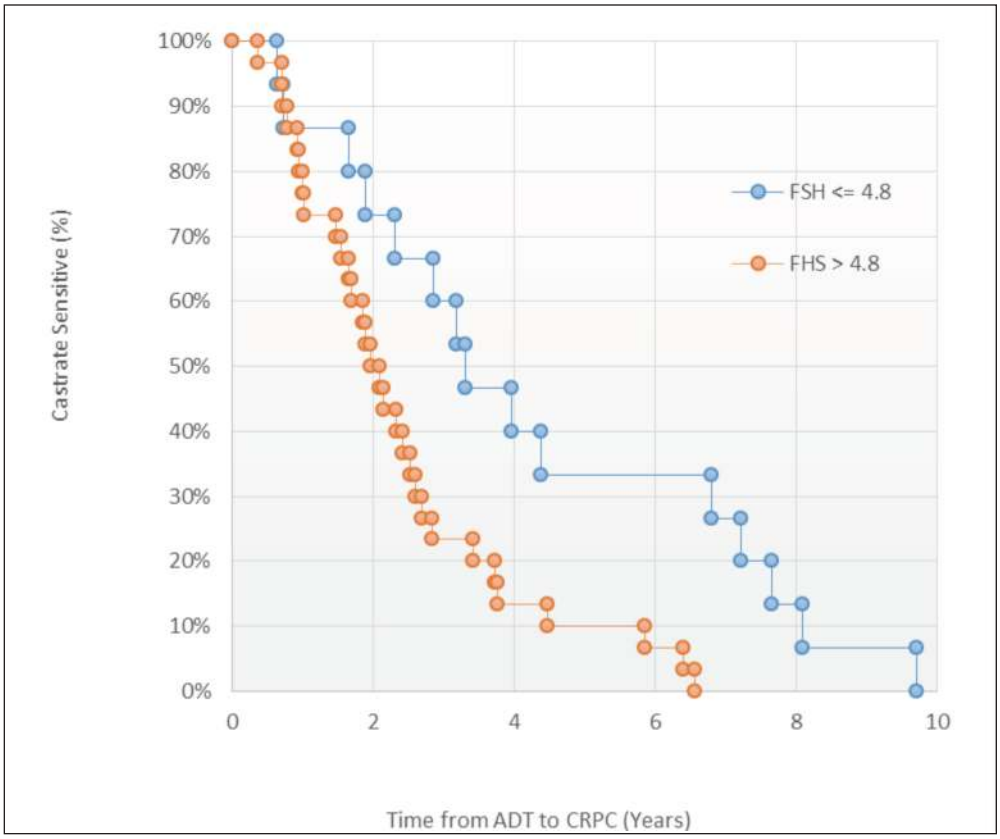

Fig. 2. Kaplan-Meier survival analysis of time to castration-resistant prostate cancer (CRPC) by maximum serum follicle-stimulating hormone (FSH) values. Significant difference in time to CRPC was seen for those patients with a maximum serum FSH ≤4.8, hazard ratio 0.46 (95% confidence interval 0.23–0.73, *p* = 0.006).

then compared to patients in the combined upper two tertiles (Q2+Q3). Patients within this lower tertile, with a FSH ≤4.8 mIU/mL advanced to CRPC at a significantly reduced rate when compared to those above this threshold (hazard ratio 0.46; 95% confidence interval 0.23–0.73; log-rank test $p = 0.006$) (Table 1, Fig. 2).

Table 1. Comparison of age and time to castrate-resistance between patients with a maximum FSH value above or below the lowest tertile (4.8 mIU/mL)

	FSH ≤4.8 mIU/mL	FSH >4.8 mIU/mL	*p* value
Sample (n)	15	30	
Mean age at ADT ± SEM	69.81 ± 2.34	73.03 ± 1.77	0.28*
Mean age at CRPC ± SEM	74.04 ± 2.42	75.40 ± 1.76	0.65*
Mean years ADT to CRPC ± SEM	4.28 ± 0.75	2.41 ± 0.30	0.03*
Median years ADT to CRPC (range)	3.29 (0.63–9.71)	2.02 (0.36–6.55)	0.03**
HR (95% CI)	0.46 (0.23–0.73)	2.18 (1.38–4.43)	0.006***

FSH: follicle-stimulating hormone; ADT: androgen deprivation therapy; SEM: standard error of the mean; CRPC: castration-resistant prostate cancer; HR: hazard ratio; CI: confidence interval. *T test with Welch's correction for parametric, unpaired from two groups, two-tailed p value; **Mann-Whitney U Test for non-parametric, unpaired medians from two groups, two-tailed p value; ***Log-rank Test for non-parametric, unpaired hazard functions from two groups, two-tailed p value.

A Cox multivariate analysis was performed to further elucidate the relationship between FSH and the development of castrate resistance. A series of regressions were conducted using a manual, stepwise approach. Within this cohort, several clinical variables, including age at diagnosis and presence of metastases, were eventually excluded as they were found to be non-contributory to the outcome and because of the limited sample within the cohort. The final model was therefore composed of maximum FSH, dichotomized Gleason score (greater than vs. less/equal to 7) and primary treatment status (watchful waiting vs. prior curative-intent therapy). The resultant Omnibus Test of Model Coefficients suggested that increasing FSH, high-grade disease (Gleason 8 or above), and the use of a primary curative treatment lead to a shorter duration from ADT to castrate resistance (Chi-square 9.01; df = 3; $p = 0.029$) (Table 2).

Discussion

In this retrospective, single-centre study we have documented serum levels of FSH in men on ADT for advancing prostate cancer and investigated the association of FSH levels on time to CRPC. As far as we are aware, this is the first clinical study to suggest that higher serum FSH levels in medically-castrate prostate cancer patients may predict shorter time to CRPC. Multivariate analysis suggested time to CRPC for this small cohort of men on ADT was associated with serum FSH levels. Exploratory analyses to determine potential FSH cut-points suggest that patients with levels greater than the lowest tertile, 4.8 mIU/m, have a significantly shorter time to CRPC.

Prostate cancer patients with higher risk, recurrent or metastatic disease have a poor prognosis despite significant long-term remissions with ADT as they will inevitably progress to CRPC. Castration resistance has been used synonymously with other terms, such as androgen-insensitive or hormone-refractory disease. However, CRPC is a more clinically accurate term as many men with a rising PSA on ADT will respond to further therapies that ablate or block prostate cancer androgen-dependent growth.[10] In this early stage of castration resistance, clinical or biochemical progression may result from constitutively active autocrine/paracrine androgen loops with neoplastic cells acquiring the ability to express androgen-synthesizing enzymes circumventing low levels of serum androgens.[7,9,10] Furthermore, numerous mutations to the androgen-receptor, capable of amplifying and augmenting activity, have been proposed to accentuate local steroidogenesis.[23-25] The increasing understanding of this biologic basis for progression while on ADT has led to a number of novel therapeutics that have significant benefits. CRPC is however a heterogeneous disease, with eventual progression to a mostly androgen-independent state. The mechanisms that are involved in androgen-independent growth of prostate cancer cells can be divided into those that are mediated by the androgen receptor (amplified, promiscuous, hypersensitive) and others that bypass the androgen receptor completely.[26] Many of these have been elucidated and targeted for drug development, including multiple pathways to malignant proliferation, invasion, angiogenesis, metastases, and avoidance of immune surveillance.[10,12]

The anterior pituitary hormone FSH is the dominant regulator promoting ovarian follicle growth in women. In males, FSH induces Sertoli cells to secrete androgen-binding proteins as well as stimulate primary spermatocytes to undergo the first division of meiosis.[27] FSH has also been implicated

Table 2. Results of Cox multivariate analysis of time from ADT commencement to the development of CRPC

	β	SE	Wald	df	*p* value	HR	95.0% CI for HR	
							Lower	Upper
Maximum FSH	0.186	0.081	5.238	1	0.022	1.205	1.027	1.413
Gleason score >7 or ≤7	0.771	0.473	2.658	1	0.103	2.161	0.856	5.457
Prior curative treatment	1.000	0.461	4.711	1	0.030	2.719	1.102	6.711

FSH: follicle-stimulating hormone; ADT: androgen deprivation therapy; SE: standard error; HR: hazard ratio; CI: confidence interval.

in cancer progression, through binding of its receptor in the endothelia of tumour vasculature, leading to neovascularization via both VEGF-dependent and -independent mechanisms.[14] It has been postulated for many years that FSH may have a functional role within the prostate and in prostate cancer biology. Not only do prostate cells express the FSHR, the prostate has long been recognized as a source of extra-pituitary FSH production.[16,17] Several clinical studies have suggested a relationship of elevated FSH levels and a prostate cancer diagnosis and this may predict higher stage after radical prostatectomy.[19,20] Recently, Mariani and colleagues evaluated FSHR up-regulation and subsequent response to FSH in prostate cancer cell lines, suggesting an association with androgen sensitivity.[21] This pre-clinical data would appear to support the findings of this study that FSH may have a predictive, and potentially functional, role in the development of CRPC.

Prostate cancer patients who progress after castration are destined to die of their disease, although the prognosis of any individual man on ADT is variable. The ability to predict the course of the disease and to predict response to future therapeutic interventions is important to patients as well as to clinicians. Several prognostic clinical-pathologic variables and serum biomarkers have been described for men with CRPC.[28] The results of this study would suggest that serum FSH levels for men on ADT may represent a novel biomarker to aid in the prediction of time to biochemical progression. Furthermore, our findings, supported by other pre-clinical data, are also evocative in that the manipulation of FSH and its binding to its receptor may have therapeutic benefit in prostate cancer patients. Men on ADT with GnRH agonists have incomplete reduction of serum FSH levels compared to GnRH antagonists, which lead to a more immediate and sustained decrease.[6,29] In a phase III extension trial with a one-arm crossover, Crawford and colleagues reported a signal of superior PSA progression-free survival for men treated with a GNRH antagonist compared to an agonist.[6] It is possible that even low, incompletely suppressed levels of FSH in the castrate tumour microenvironment may contribute to the development of CRPC. However, to our knowledge there has been no direct clinical evidence that targeting FSH suppression leads to improved survival for patients with androgen-dependent or -independent prostate cancer.[30] Although the results are evocative, our present study is unable to further evaluate the differential effect of the various agents used for ADT given the limited cohort size.

Our results suggesting a potential prognostic ability of serum FSH levels are limited by the retrospective nature of study, as well as the relatively small cohort of men that progressed to CRPC. The discontinuous nature of measurement of FSH, as well as the limited clinical-pathological information for the multivariate analysis, could have led to a positive finding by chance or by confounding of unrecognized variables. There is good evidence from randomized controlled studies that local treatment may be additive to ADT for men with advanced prostate cancer and the extent of metastases may also be prognostic. Although previous curative therapy and Gleason score appeared to be significantly associated with time to CRPC in our final model as expected, the presence of metastases at ADT initiation was not associated with the outcomes. These observations likely underscore the limitations of the retrospective nature of the study, as well as the small sample size. For example, the extent of metastatic disease at the time of ADT initiation was not captured and most in the cohort were non-metastatic. Finally, due to the nature of the study and its limited power, more clinically relevant outcomes of clinical progression or survival were not investigated.

Conclusion

This retrospective, single-centre study would suggest there may be an association between serum FSH levels and time to CRPC for men with advancing prostate cancer. However further clinical investigation in a larger cohort of men, preferably collected in a prospective fashion, is required to determine any clinical utility of FSH as a biomarker of progression or target for therapy.

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