Testosterone Therapy in Patients with Treated and Untreated Prostate Cancer: Impact on Oncologic Outcomes

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Abbreviations and Acronyms

ADT = androgen deprivation therapy
AS = active surveillance
BCR = biochemical recurrence
CaP = prostate cancer
EBRT = external beam radiation therapy
HIFU = high intensity focused ultrasound
PSA = prostate specific antigen
PSAV = PSA velocity
RP = radical prostatectomy
TT = testosterone therapy
XRT = radiotherapy

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Purpose: Testosterone deficiency and prostate cancer have an increasing prevalence with age. However, because of the relationship between prostate cancer and androgen receptor activation, testosterone therapy among patients with known prostate cancer has been approached with caution.

Materials and Methods: We identified a cohort of 82 hypogonadal men with prostate cancer who were treated with testosterone therapy. They included 50 men treated with radiation therapy, 22 treated with radical prostatectomy, 8 on active surveillance, 1 treated with cryotherapy and 1 who underwent high intensity focused ultrasound. We monitored prostate specific antigen, testosterone, hemoglobin, biochemical recurrence and prostate specific antigen velocity.

Results: Median patient age was 75.5 years and median followup was 41 months. We found an increase in testosterone ($p < 0.001$) and prostate specific antigen ($p = 0.001$) in the entire cohort. Prostate specific antigen increased in patients on active surveillance. However, no patients were upgraded to higher Gleason score on subsequent biopsies and none have yet gone on to definitive treatment. We did not note any biochemical recurrence among patients treated with radical prostatectomy but 3 (6%) treated with radiation therapy experienced biochemical recurrence. It is unclear whether these cases were related to testosterone therapy or reflected the natural biology of the disease. We calculated mean prostate specific antigen velocity as 0.001, 0.12 and 1.1 μg/l per year in the radical prostatectomy, radiation therapy and active surveillance groups, respectively.

Conclusions: In the absence of randomized, placebo controlled trials our study supports the hypothesis that testosterone therapy may be oncologically safe in hypogonadal men after definitive treatment or in those on active surveillance for prostate cancer.

Key Words: prostatic neoplasms; testosterone; risk assessment; prostate-specific antigen; neoplasm recurrence, local

The prevalence of testosterone deficiency, previously known as late onset hypogonadism, is between 3.1% and 7% in men younger than 70 years and 18.4% in those older than 70 years.[1] It is characterized by a low serum testosterone index and a constellation of symptoms and physical changes incrementally related to the degree of deficiency. Several published series confirm the ability of exogenous TT to replenish serum levels of testosterone with an improvement in symptoms.[2] Despite this knowledge the use of TT

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was restricted based on research by Huggins and Hodges in the 1940s indicating that CaP growth was linearly related to the testosterone concentration.[3]

In the last 2 decades evidence has accumulated in opposition to these long held views, bringing TT into the forefront of men's health. In a 2004 review article Rhoden and Morgentaler found no increased risk of CaP in men treated with TT.[4] In 2006 Morgentaler examined the research of Huggins and Hodges,[3] and discovered that there was no scientific evidence to suggest that TT leads to CaP growth.[5] With a growing body of evidence to suggest the safety of TT a new theory, the saturation model, was developed. This model provided an answer to the paradox of why castration effectively reduced PSA while raising testosterone may not worsen CaP or increase PSA. In hypogonadal men it also helped explain why an initial increase in PSA did not necessarily reflect disease progression. The saturation model suggests that testosterone exerts its maximal effect on androgen receptors and CaP growth at low concentrations while having little to no impact at higher concentrations.[6] This new model provides a foundation for TT in men with or at risk for CaP.

In this retrospective review we describe our experience with TT in a cohort of patients with actively treated CaP and those on AS for low risk cancer.

MATERIALS AND METHODS

We searched the electronic medical records at the Vancouver Prostate Center at Vancouver General Hospital and the Victoria General Hospital for the key words, "testosterone replacement; testosterone deficiency; androgel" among patients with active prostate cancer from September 2011 to March 2015. For each patient we documented prostate cancer pathology, D'Amico risk score,[7] testosterone values, type and duration of TT, sequential PSA values, incidence of BCR and overall clinical course. We performed statistical analysis using the paired 2-tailed t-test. Among surgical patients we defined BCR by AUA (American Urological Association) guidelines as postoperative PSA greater than 0.2 μg/l with a second confirmatory PSA of more than 0.2 μg/l.[8] We defined BCR among patients receiving radiation therapy using the PHOENIX criteria, that is a 2 μg/l increase over the posttreatment PSA nadir.[9] We calculated PSAV in patients who had at least 3 PSA measurements. This unfunded study received approval from the University of British Columbia clinical research ethics board.

RESULTS

We identified 166 patients from the electronic medical records under the combined search terms "testosterone" and "prostate cancer." We excluded from analysis 42 men who did not receive TT, 30 who received TT before the CaP diagnosis, 1 who did not have prostate cancer and 11 with incomplete data. Only patients on TT for at least 3 months were included in the study. Information from followup clinic notes were used to document compliance on TT. All men treated with testosterone had presenting symptoms of 1 or more of erectile dysfunction, fatigue, reduced libido, mood changes and weakness. The remaining 82 patients with a diagnosis of CaP and who were on TT are the basis of this report.

Treatment consisted of RP in 22 patients, EBRT in 37, brachytherapy in 13, HIFU in 1 and cryotherapy in 1. We followed 8 men who were treated with AS. The frequency of Gleason 6, 7, 8 and 9 disease was 32, 39, 7 and 4, respectively. In our cohort 21 men received neoadjuvant ADT, including 6 in the RP group and 14 in the XRT group, with the patient who received cryotherapy also receiving neoadjuvant ADT. The table lists the testosterone and PSA characteristics of each of these groups.

Median age of the study group was 75.5 years (IQR 70–82) at the last followup. Median followup after initiating TT was 41 months (IQR 22–57). While on TT, the median Hgb level measured was 149 gm/l (IQR 140–157), which was significantly higher than the median Hgb prior to TT (143 gm/l, IQR 131–149, $p = 0.046$). Median pre-TT testosterone (6.3 mmol/l, IQR 4.55–7.7) increased significantly after TT initiation (13.2 mmol/l, IQR 7.7–20.8, $p < 0.001$). This difference in testosterone remained statistically significant in all risk groups and all treatment groups (fig. 1).

For the entire cohort as well as for treatment and risk groups, PSA values before TT initiation were compared to PSA values at the last followup at a median of 41 months after TT (fig. 2). Overall, PSA was significantly increased after TT ($p = 0.001$). Subgroup analysis of patients treated with RP, XRT and AS showed a significant increase in PSA in each group ($p = 0.048$, 0.028 and 0.003, respectively, figs. 3 to 5). When analyzed by D'Amico risk groups, only patients with low risk CaP had a significant increase in PSA after TT ($p = 0.006$). However, with the removal of AS cases from the overall low risk group there was no significant difference in the PSA increase after TT ($p = 0.37$). Post-TT PSA values did not differ by the route of testosterone delivery, which was transdermal in 54 patients, intramuscular in 8, oral in 5 and mixed (a combination of 2 or more modalities) in 15.

We analyzed BCR and PSAV in all groups. Among the 22 RP patients there was no incidence of BCR. Of the 50 men in the XRT group 3 (6%) experienced BCR, all after EBRT, including 2 with high risk CaP and 1 with intermediate risk CaP. BCR developed an average of 10.7 months (range 3 to 18) after the initiation of TT. In all 3 cases TT