0022-5347/05/1732-0533/0
THE JOURNAL OF UROLOGY®

Vol. 173, 533–536, February 2005
Printed in U.S.A.
DOI: 10.1097/01.ju.0000143942.55896.64

TESTOSTERONE REPLACEMENT THERAPY AFTER PRIMARY TREATMENT FOR PROSTATE CANCER

PIYUSH K. AGARWAL AND MICHAEL G. OEFELEIN*,†

From the Department of Urology, Case Western Reserve University School of Medicine and University Hospitals of Cleveland, Cleveland, Ohio

ABSTRACT

Purpose: A history of prostate cancer has been an absolute contraindication for testosterone supplementation. We studied a cohort of hypogonadal patients treated with radical retropubic prostatectomy (RRP) for organ confined prostate cancer to determine if testosterone replacement therapy (TRT) could be efficacious and administered safely without causing recurrent prostate tumor.

Materials and Methods: Ten hypogonadal patients previously treated with RRP for organ confined prostate cancer were identified. They presented with low serum total testosterone (TT) and symptoms of hypogonadism after RRP. Patients had baseline serum determinations of prostate specific antigen (PSA) and TT, and were started on testosterone supplementation. They were assessed periodically for changes in PSA and TT, and for symptomatic improvement using the hormone domain of the Extended Prostate Inventory Composite Health Related Quality of Life questionnaire.

Results: At a median followup of 19 months no patient had detectable (greater than 0.1 ng/ml) PSA. TT increased significantly after starting TRT from a mean ± SD of 197 ± 67 to 591 ± 180 ng/dl ($p = 0.0002$). The Hormone Domain of the Extended Prostate Inventory Composite Health Related Quality of Life questionnaire increased significantly from 38 ± 5 to 49 ± 3 ($p = 0.00005$), primarily due to a decrease in hot flashes and an increase in energy level.

Conclusions: At a median of 19 months of TRT hypogonadal patients with a history of prostate cancer had no PSA recurrence and had statistically significant improvements in TT and hypogonadal symptoms. In highly select patients after RRP TRT can be administered carefully and with benefit to hypogonadal patients with prostate cancer.

KEY WORDS: prostate, prostatic neoplasms, prostate-specific antigen, prostatectomy, hypogonadism

The entity late onset, idiopathic hypogonadism (andropause) is characterized by low serum testosterone, decreased libido, depression, decreased muscle mass and bone density, anemia and lack of energy.[1] Total testosterone (TT) starts to decrease at age 40 years at a rate of approximately 1% (3.2 ng/dl) yearly.[2] Testosterone supplementation has been shown to counteract these changes by enhancing sexual function, reversing depression, increasing bone mineral density and fat-free mass, stimulating erythropoiesis, and improving strength and energy.[3–5] Based on the potential benefits that testosterone provides many men have been placed on testosterone replacement therapy (TRT) with the number of prescriptions for testosterone products increasing by more than 5-fold since 1993.[6]

Although the relationship between androgens and the development of prostate cancer is still evolving, current data demonstrate a similar risk (approximately 1%) of prostate cancer in men treated with or without testosterone supplementation.[7] TRT may lead to a minor prostate specific antigen (PSA) increases (less than 1 ng/ml) but it does not increase the short-term risk of prostate cancer.[8] Furthermore, in a study of Rhoden and Morgentaler only 1 of 20 hypogonadal men with a history of high grade prostatic intraepithelial neoplasia on prostate biopsy had prostate cancer after 1 year of TRT.[9] This finding would be consistent with the normal progression of prostatic intraepithelial neoplasia toward prostate cancer in the absence of TRT.

Based on limited data TRT in hypogonadal men with a history of prostate cancer is considered to be contraindicated. Specifically the International Consultation on Prostate Cancer recommends that a history of prostate cancer is an absolute contraindication for testosterone supplementation.[10] However, to our knowledge no human studies of the use of TRT after treatment for prostate cancer have ever been performed. The androgen sensitive nature of prostate cancer has been described.[11] In a patient with a history of treated prostate cancer and hypogonadism the concern remains that testosterone supplementation may promote recurrence within remaining tumor foci. This theoretical concern is valid but it has never been adequately explored. We performed a retrospective review of patients with organ confined prostate cancer who were subsequently treated for hypogonadism with testosterone replacement therapy.

MATERIALS AND METHODS

Since 2000, 10 symptomatic hypogonadal men who underwent radical retropubic prostatectomy for prostate cancer between 1993 and 2003 were identified. These 10 patients had no evidence of disease by clinical and PSA criteria. They presented postoperatively with complaints of decreased libido, erectile dysfunction, lack of energy, cognitive impairment and/or hot flashes. Baseline serum determinations of PSA and TT were done to confirm absent recurrent prostate cancer and hypogonadism, respectively. Serum determina-

Submitted for publication July 14, 2004.
* Correspondence: Western Reserve University School of Medicine, University Hospitals of Cleveland, 11100 Euclid Ave., Cleveland, Ohio 44106 (telephone: 216-844-3009; FAX: 216-844-1900; e-mail: michael.oefelein@uhhs.com).
† Financial interest and/or other relationship with Novartis, Sanofi, Ferring and Atrix Laboratories.

tions of TT were done from 6:00 a.m. to 12:00 p.m. Patients were provided appropriate informed consent and were given counseling regarding the potential risk of progression of prostate cancer with TRT. All patients understood the risk and agreed to proceed with testosterone supplementation.

Patients were placed on topical (Androgel 1%, Solvay Pharmaceuticals, Marietta, Georgia or Testim 1%, Auxilium Pharmaceuticals, Norristown, Pennsylvania), transdermal (Androderm patch, Watson Pharmaceuticals, Corona, California) or intramuscular (testosterone cypionate) formulations of testosterone and followed at regular intervals (every 2 months) with determinations of serum PSA and TT. At these visits patients completed the hormone domain of the Extended Prostate Inventory Composite (EPIC) Health Related Quality of Life questionnaire without any assistance from a health care provider.[12] TRT was periodically adjusted at followup visits based on TT and symptomatic response. No patients received any oral formulations of testosterone.

Statistical analysis was performed with a personal computer and commercially available software. Student's t test was used to analyze differences in mean values. All p values were 2-tailed with significance considered at $p < 0.05$.

RESULTS

Ten patients were included in this study. Mean age in the group was 64.3 years. Preoperative mean PSA was 7.0 ng/ml (range 5.8 to 12.6). Preoperative mean TT available in 5 patients was 469 ng/dl. All patients underwent radical retropubic prostatectomy for prostatic adenocarcinoma. Postoperative Gleason scores obtained from the final prostate adenocarcinoma specimen were 6 to 8 with Gleason 6 (3 + 3) disease in 2 patients, Gleason 7 (3 + 4) disease in 5, Gleason 7 (4 + 3) disease in 2 and Gleason 8 (4 + 4) disease in 1. Postoperative mean PSA was less than 0.10 ng/ml and postoperative mean TT was 197 ng/dl. The median duration of TRT was 19 months. During the course of therapy no patient had PSA recurrence. TT increased significantly after starting TRT from a mean of 197 (95% CI 145 to 248) to 591 ng/dl (95% CI 469 to 713) ($p = 0.0002$, fig. 1). The Hormone Domain of the EPIC Health Related Quality of Life questionnaire increased significantly from a mean of 38 to 49, primarily due to a decrease in hot flashes and an increase in energy level ($p = 0.0001$, see table, fig. 2).

Oral formulations of testosterone were not used in any patients. Seven patients used a topical gel formulation of testosterone (Androgel or Testim), 2 used intramuscular injections of testosterone (testosterone cypionate) and 1 used a transdermal formulation of testosterone. Of note, the 2 patients who used intramuscular injections of testosterone had originally been placed on topical gel but they did not achieve appropriate improvement in symptoms and serum TT while on the gel formulation. They improved accordingly after being changed to an intramuscular formulation.

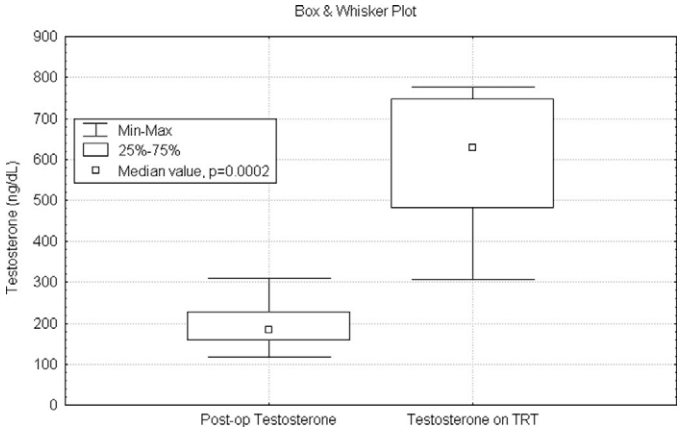

FIG. 1. TT measured postoperatively and after initiating TRT

Patient characteristics

	Mean
No. pts	10
Age (range)	64 (59–69)
TRT duration (95% CI)	19 (9–29)
Ng/ml PSA (95% CI):	
Preop	7.0 (6–9)
Postop	Less than 0.10
Ng/dl TT (95% CI):	
Preop	469 (201–738)
Postop	197 (145–248)
Ng/dl TT on TRT (95% CI)	591 (469–713)
EPIC hormonal domain (95% CI):	
Baseline	38 (32–46)
On TRT	49 (46–54)

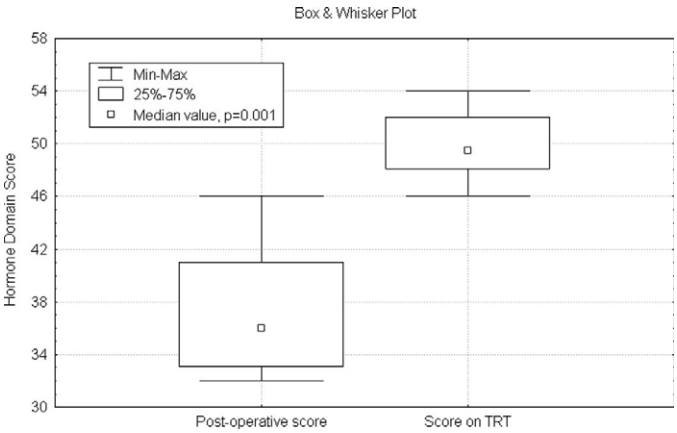

FIG. 2. EPIC hormone domain score postoperatively and after starting TRT.

DISCUSSION

Despite an estimated prevalence of hypogonadism of 2 to 4 million men[13] and numerous potential benefits from TRT many physicians are still reluctant to commence TRT in their patients. They are concerned about the risk of inducing prostate cancer with testosterone supplementation because the age group that would most likely benefit from this therapy is also the group at greatest risk for occult prostate cancer. This concern is rooted in the discovery of Huggins of the androgen responsive regulation of prostate cancer. Based on the theoretical risk of promoting prostate cancer some groups routinely perform prostate biopsies in all patients prior to initiating TRT.[13] However, no compelling evidence exists to suggest that TRT in hypogonadal men can convert occult or precancerous lesions into overt carcinoma or accelerate the natural history of the disease.

A few case reports suggest that short-term TRT can cause an increase in PSA and convert an occult lesion into a clinically apparent one. In 1 such report patient PSA increased from 2.7 to 45.6 ng/ml in a 6-month period while on TRT.[14] Subsequent prostate biopsy revealed Gleason 8 adenocarcinoma of the prostate. Another report demonstrated an increase in PSA from 3.5 to 4.4 ng/ml, also after 6 months of TRT.[15] This patient had organ confined cancer on biopsy. These reports highlight important caveats that must be considered when beginning TRT in a patient. 1) Baseline serum PSA and digital rectal examination must be performed. In addition, baseline serum free and total testosterone should be determined. 2) Patients must be followed more frequently than every 6 months, especially when baseline prostate biopsy is not performed. However, some groups routinely per-