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Testosterone replacement in prostate cancer survivors with hypogonadal symptoms

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OBJECTIVE

To describe the clinical outcomes of prostate cancer survivors who were treated with high-dose testosterone-replacement therapy (TRT) for the relief of hypogonadal symptoms.

PATIENTS AND METHODS

We reviewed the records of 96 patients who received TRT after initial management for prostate cancer from 2000 to 2007.

RESULTS

In all, 41 men had prostate-specific antigen (PSA) progression (PSA Working Group) while on TRT, but only seven had radiographic progression of disease. Fifty-six men discontinued TRT due to increasing PSA levels, and 59% of these men had significant reductions in PSA level with no additional intervention. In all, 31 men remain on TRT with no PSA or radiological progression at a median of 36.7 months; nine men stopped TRT for reasons other than progression. Characteristics associated with continuing TRT were radical prostatectomy as primary management, a low PSA level when starting TRT, and concurrent use of dutasteride. Hypogonadal symptoms were alleviated in most cases.

CONCLUSIONS

While most men in this series had increasing PSA levels during TRT, stopping TRT typically resulted in PSA declines. A subset of men were able to remain on TRT for several years without disease progression.

KEYWORDS

prostate cancer, testosterone replacement, PSA, outcome

INTRODUCTION

Prostate cancer is the most common malignancy diagnosed in men, with >186 000 new cases annually in the USA and >500 000 cases annually worldwide; >60% of affected men are aged >70 years [1,2]. The overwhelming majority of these men will achieve long-term survival after receiving treatment for localized disease. This population of elderly survivors is simultaneously at risk of age-related hypogonadism, with manifestations ranging from altered sexual function, cognitive and emotional changes to sarcopenia, decreased bone mineral density, and risk of metabolic syndrome [3]. Testosterone-replacement therapy (TRT) has been shown to improve the symptoms of hypogonadism [4,5], but there is reluctance to prescribe it due to the perceived risk of stimulating prostate cancer progression, particularly in survivors of prostate cancer.

Despite clear evidence that suppression of testosterone induces remission in patients with prostate cancer [6], there are virtually no data indicating that endogenous testosterone or external TRT induces prostate cancer. A pooled analysis of prospective TRT series in men with no history of prostate cancer found a 1.1% rate of prostate cancer incidence, which is no greater than that in the general population [7]. Further, a study of men with prostatic intraepithelial neoplasia found that men treated with TRT for hypogonadism had no increased risk of developing prostate cancer [8]. Several case reports document the safety of TRT; in a small series, five patients were treated with TRT for hypogonadism after initial cancer therapy, including primary androgen-deprivation therapy (ADT), but there was no significant PSA progression [9]. A report of 31 patients treated with TRT for hypogonadism after brachytherapy found that after 5 years of treatment all men had a PSA level of <1 ng/mL and most were <0.1 ng/mL [10]. After radiotherapy, a series of five men who received TRT for symptoms of androgen deprivation reported no PSA progression over 18 months [11].

Prospective, placebo-controlled trials have shown improvements in some aspects of hypogonadism after administration of exogenous testosterone [12]. Specifically, in one study a mean decrease in fat mass of −3.0 kg was reported in men treated with TRT, compared to −0.7 kg in men on placebo [13]. This was coupled with a mean increase in lean mass of 1.9 kg for those receiving TRT, compared to 0.2 kg for placebo. Bone density changes were not statistically significant for the groups as a whole, but in the subgroup of men with the lowest testosterone levels, the effects were more prominent, with a mean gain of 5.9%, compared to just 2.5% on placebo [14]. Cognitive and overall health improvements in men with hypogonadism receiving TRT have not been as clearly

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documented [15], but this is probably partly due to the difficulty in evaluating and quantifying changes in cognitive function. Additional support for the efficacy of TRT in ameliorating hypogonadal symptoms come from studies of intermittent ADT in advanced prostate cancer, which identified significant decrements in quality of life during castrate periods, and improvement in quality of life during testosterone recovery in the off-treatment cycle [16–18].

Given the long lifespan of men after treatment for prostate cancer, and the many negative effects of hypogonadism, we treated selected prostate cancer survivors with TRT, using considerable caution and only after a detailed discussion of risks and benefits. We present a large experience with TRT in a heterogeneously treated population of prostate cancer survivors.

PATIENTS AND METHODS

After approval by the local institutional review board, the charts of 96 patients who received TRT at Compassionate Oncology Medical Group (Los Angeles, CA) during 2000–2007 were reviewed. The TRT administration protocol, monitoring procedures, and adjunctive medications were all designed by R.L; data were abstracted by one investigator (T.B.D.) on a form approved by the institutional review board.

Men received transdermal testosterone, either AndroGel™ (Solvay Pharmaceuticals SA, Brussels, Belgium), or testosterone in pluronic lecithin organogel (20%), except for one who received depot testosterone injections. All men were treated with concurrent inhibition of 5α-reductase using finasteride, dutasteride, or most commonly both. The target serum testosterone level was 1800–3000 ng/dL. Blood samples for the serum analysis of PSA, prostatic acid phosphatase, testosterone, dihydrotestosterone (DHT), and haematology and chemistry, were drawn every 1–2 weeks during the first 2 months, then at least monthly afterwards. Before starting TRT, all patients had a baseline bone scan, MRI or CT of the abdomen/pelvis, a chest X-ray or CT of the chest, and often TRUS with colour Doppler analysis. The disease was re-staged every 6–12 months, and all men who discontinued TRT due to PSA progression had repeat scans within 1 month of discontinuation.

Variable	Mean (range) or *n* (%)
Age at diagnosis, years	61 (46–85)
PSA level at diagnosis, ng/mL	(0.8–6272)
<10	58 (60)
10–20	15 (16)
>20	19 (20)
Missing (pre-PSA)	4 (4)
Stage at diagnosis	
T1c	42 (44)
T2	32 (33)
T3	3 (3)
Node positive (any T)	11 (11)
Distant metastasis	8 (8)
Gleason score (total)	
≤3 + 3 (≤6)	33 (34)
3 + 4, 4 + 3 (7)	17 (18), 22 (23)
4 + 4, 3 + 5 (8)	12 (13), 1 (1)
4 + 5, 5 + 4 (9)	5 (5), 3 (3)
5 + 5 (10)	2 (2)
missing	1 (1)
Primary treatment	
Radical prostatectomy*	24 (25)
External beam radiotherapy*	12 (13)
Brachytherapy*	1 (1)
ADT	59 (61)
Median PSA level before TRT, ng/mL	0.1 (0–97.9)

TABLE 1
Baseline prostate cancer and treatment characteristics of the 96 men

PSA progression, as defined by the PSA Working Group Criteria [19], was analysed statistically, with logistic regression used to assess the prognostic importance of biomarkers and other disease/patient characteristics on the probability of disease progression. Univariate regression identified individual prognostic factors while multiple regression (stepwise selection) identified independent prognostic factors.

RESULTS

The median (range) age of the 96 patients was 61 (46–85) years, and 91 men were Caucasian, four African-American and one Hispanic. The baseline cancer characteristics and initial treatment are summarized in Table 1. Most men had clinically localized disease, had received primary intermittent ADT as initial management after declining surgery or definitive radiotherapy. Radiological evidence of metastatic disease at diagnosis was present in 12% of the men.

The mean (range) serum testosterone level on TRT was 1391 (303–2637) ng/dL. To suppress DHT, all men received a 5α-reductase inhibitor; 35 received finasteride alone, two received dutasteride alone, and 54 received both (data missing for five). Although serum DHT was not measured as routinely as testosterone, the median (range) serum DHT in those who had it measured was 28 (0–194) ng/mL. Several additional pharmacological therapies were used in some patients, concurrently with TRT, or were initiated during the course of TRT due to PSA progression. These included granulocyte macrophage colony-stimulating factor, cyclophosphamide, sorafenib, interferon-α, thalidomide and/or lenalidomide. The heterogeneity of the latter treatment precluded even an exploratory analysis of the effect of these additional medications on the success of TRT.

The clinical outcomes are summarized in Table 2; overall, 41 men (43%) had PSA progression while on TRT [19]; seven of these men were found to have concurrent radiological progression. For 56 men in whom an increasing PSA level triggered discontinuation of TRT, cessation of TRT alone triggered a PSA decline of 30–95% in 33 (59%); the PSA level remained stable in three (5%) patients and continued increasing in six

TABLE 2 The PSA outcomes during and after TRT

Variable	Median (range) or *n* (%)
Duration of TRT, months	15 (1–83)
PSA velocity, ng/mL/year on TRT at time (*n*):	
1–3 months (92)	2.3 (–12.3, 464)
3–6 months (79)	2.0 (–6, 1616)
6–12 months (62)	1.0 (–6.3, 93.6)
2 years (48)	1.1 (–6, 65.4)
3 years (26)	0.5 (–1.9, 84)
Continued TRT	31 (32)
Discontinued TRT for increasing PSA	56 (58)
PSA progression	41 (43)
Radiographic progression on TRT	7
Discontinued TRT for other reason†	9 (9)
PSA trend after TRT discontinuation alone (56):	
>30%	33 (59)
Stable	3 (5)
Continuous increase	6 (11)
Unknown (immediately started ADT ± chemotherapy)	14 (25)
Second cycle of TRT after discontinuation for progression	25
PSA progression lead to discontinuation	18 (72)
Continue on TRT 2nd cycle	7 (28)

**all received ADT adjuvantly or at the time of PSA recurrence. †Included erythrocytosis, noncompliance with follow-up, lack of symptom relief and death from unrelated cause.*

TABLE 3 Logistic regression of disease progression on biomarkers and other disease/patient characteristics

	Odds ratio (95% CI), *P*	
Variable	Univariate	Multiple
RP	0.26 (0.08–0.86), 0.027	0.21 (0.06–0.82), 0.024
Dutasteride	0.34 (0.14–0.82), 0.016	0.23 (0.08–0.67), 0.007
Baseline testosterone*	–, 0.448	0.55 (0.34–0.90), 0.017
Average testosterone*	–, 0.283	–, 0.869
Duration of TRT*	–, 0.182	–, 0.784
Baseline PSA level*	2.07 (1.10–3.92), 0.025	3.04 (1.17–7.87), 0.022
Gleason score	–, 0.531	–, 0.306

**Log-transformation of biomarkers used in regressions.*

(11%). In the remaining 14 men the PSA trend could not be determined due to immediate initiation of ADT, taxane-based chemotherapy, or combination therapy concurrent with TRT withdrawal.

Subsequent evaluation of the 33 men who had PSA progression while on a first cycle of TRT showed that 25 (76%) of them proceeded with a second cycle of TRT, after obtaining a stable PSA nadir on ADT. Ultimately, biochemical progression triggered discontinuation of cycle 2 of TRT in 18 of these men (72%). At the time of analysis, seven of these men remained on TRT with no PSA progression, including two with stable PSA levels at 1 and 4 years into their second course.

Thirty-one men continued on TRT at the end of the study period, with a median (range) duration of 36.7 (2–79) months. Also, nine patients discontinued TRT for reasons other than progression, such as polycythaemia requiring phlebotomy, failure of TRT to relieve symptoms of hypogonadism, death from unrelated cause, and noncompliance.

The statistical analysis of PSA progression comprised the 41 men vs the 55 who had no PSA progression, to identify prognostic factors (Table 3). Univariate analysis modelling the probability of disease progression while receiving TRT identified two factors associated with decreased risk, i.e. initial treatment with radical prostatectomy (RP) ($P = 0.027$) and use of dutasteride ($P = 0.016$), while an elevated baseline PSA level was associated with a greater risk of progression. These three factors in addition to elevated baseline testosterone level (decreased risk) were found to be independent prognostic factors in multiple regression analysis. In univariate and multiple regression analysis Gleason grade, duration of TRT, and level of testosterone achieved during TRT were not prognostic for disease progression.

Hypogonadal symptoms and their response to TRT were not systematically documented in the medical records, precluding a formal statistical analysis, but 63 men had documented hypogonadal symptoms at baseline. The most commonly noted symptoms for which TRT was prescribed were lassitude, fatigue, impairment of overall quality of life or lack of energy, which was noted by 35 (55%). Additional symptoms for which TRT was prescribed included lack of libido in 21 men (33%), cognitive impairment in 18 (29%) anaemia in two men and hot flashes in one. Overall, 62 of the 63 men noticed a significant subjective improvement in one or more symptoms during TRT. There were no reports of new symptoms or worsening symptoms during the treatment and follow-up period.

DISCUSSION

In reviewing our experience with high-dose TRT in hypogonadal survivors of prostate cancer it is evident that for ≈ 40% of patients TRT is not associated with increasing PSA levels, even over a long period. However, nearly 60% of men had increasing PSA levels that triggered discontinuation of TRT. It is reassuring that for most of the patients, biochemical progression on TRT was not associated with clinical or symptomatic disease progression. Further, symptomatic

progression was absent despite the inclusion of men with high-risk high-grade disease, and even patients with metastatic disease at presentation. In most cases, stopping TRT resulted in rapid and dramatic declines in PSA level, such that most men did not need to receive immediate anti-neoplastic therapy.

Further studies to identify the clinical and biological characteristics which increase the likelihood that a man will have safe and successful TRT are critical before pursuing this approach. Our preliminary analyses suggest that men who have previously had RP are less likely to have PSA progression while receiving TRT. This makes intuitive sense, given the absence of viable benign prostatic tissue, which probably contributes to PSA secretion in men with prostate glands in-situ. Most of these patients had no definitive surgery or radiotherapy and received primary ADT only. Thus TRT might have stimulated the residual normal prostate tissue to produce PSA and stopping TRT would probably cause a decline in PSA production and a decline in PSA velocity.

Men who started TRT with lower PSA values had a decreased risk of PSA progression. We hypothesise that these are men who have a very low or absent prostate cancer disease burden at the start of TRT. The men with higher PSA levels at the time of TRT had rapid PSA progression. We assume that TRT stimulated quiescent cancer cells in these men to produce additional PSA, acting as an oncological 'stress test'. This hypothesis also explains the high rate of disease progression reported by Fowler and Whitmore [20], in which men had active disease and were given TRT.

Administration of exogenous androgens achieved supra-physiological levels of serum testosterone in some patients, yet these levels did not correlate with disease progression. A priori, it might have been anticipated that if testosterone initiated disease progression, then higher serum testosterone levels would lead to rapid progression. However, this was not apparent clinically in our experience. Conversely *in vitro* studies have suggested that at high concentrations of testosterone, prostate cancer cells adapted to an androgen-poor environment might be growth-inhibited and possibly undergo apoptosis [21]. However, in the present study we did not identify a clinical association between higher levels of testosterone achieved during TRT and outcome. Specifically, we could not identify patients where the TRT acted as an anticancer therapy.

Concurrent administration of dutasteride was significantly associated with higher chances of successful initial TRT. Previous studies of 5α-reductase inhibitors have shown an effect on PSA progression after RP [22] and on prostate cancer prevention [23]; suppression of DHT by these compounds appears to be the critical step. *In vitro* and animal studies have shown DHT to be far more potent than testosterone at stimulating prostate cancer growth [24]. In patients with prostate cancer, exposure to dutasteride before RP has been shown to dramatically decrease tissue levels of DHT, inducing significant cellular changes such as increased apoptosis and altered gene expression [25,26]. Despite this rationale, our analysis failed to detect a correlation between DHT suppression and disease progression on TRT, although a clear risk reduction was evident with dutasteride therapy. Three possible explanations for this are: (i) our data on DHT levels were inadequate to detect a correlation, as serum evaluation was inconsistent; or (ii) that serum DHT levels do not accurately reflect tissue DHT suppression; or (iii) that dutasteride exerts its protective effect not merely by suppressing DHT formation but by its suppression of 5α-reductase type I, whereas finasteride only affects 5α-reductase type II [27]. An alternative explanation is that dutasteride use was a surrogate marker for a different factor which reduced the risk of progression; most patients on dutasteride were treated after 2002, when anti-angiogenic medications were more commonly used during TRT. While our data are not randomized and certainly not conclusive, we suggest that future studies of TRT incorporate concurrent dutasteride in at least one treatment arm.

Symptoms of hypogonadism, including fatigue, lack of libido, lassitude, and overall dissatisfaction with quality of life, were remedied by TRT, in those for whom symptom data were recorded. While no standardized instrument was used to collect quality-of-life data, responses were frequently dramatic, with many men subjectively expressing strong sentiments, such as feeling their life had been given back to them. Future studies must rigorously capture quality-of-life and symptom data to define the degree of benefit; this would then allow for a complete risk-benefit analysis.

In conclusion, TRT often results in PSA progression but does not cause clinical or symptomatic progression in most patients with prostate cancer who have been previously treated with ADT. While most men enjoy a relief from hypogonadal symptoms, a distinct subset also tolerate TRT with no significant PSA progression, and might be safely treated for years. Additional study is needed to prospectively quantify the risk and identify those patients most likely to receive successful treatment.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **ADT**, androgen-deprivation therapy; **TRT**, testosterone-replacement therapy; **RP**, radical prostatectomy; **DHT**, dihydrotestosterone.