BJUI
BJU INTERNATIONAL

Effect of testosterone administration to men with prostate cancer is unpredictable: a word of caution and suggestions for a registry

Alvaro Morales

Centre for Applied Urological Research, Queen's University, Kingston, ON, Canada

Accepted for publication 19 January 2010

To assess the evidence for the concept that the androgen receptor of prostate cancer (PCa) cells becomes saturated when testosterone values exceed castrate levels, so that testosterone administration in hypogonadal men with untreated PCa does not stimulate tumour growth. To propose basic criteria for administration of testosterone to untreated patients with PCa and, as this is a rare clinical situation, to encourage the establishment of an international registry for these patients. Men with a diagnosis of PCa and symptomatic testosterone deficiency received testosterone therapy (TTh). Patients were assessed quarterly. Prostate-specific antigen (PSA) velocity was used as the criterion to discontinue therapy and a return to nadir PSA levels allowed re-initiation of testosterone supplementation. The responses to testosterone supplementation were varied according to each individual and were unpredictable. While some men showed little change after years of treatment, others exhibited a rapid and significant increase in PSA levels. In others, the use of intermittent therapy resulted in synchronous changes in PSA levels. Interruption of TTh invariably translated into a decrease in PSA to pre-therapy levels. Available evidence regarding the effect of testosterone administration to hypogonadal men with untreated PCa is too limited to be considered reliable. In addition, the response to this treatment appears to be varied and unpredictable. Hypogonadism associated with untreated PCa is not common, therefore, we propose the establishment of an international registry as the quickest way to establish the basic parameters for consideration of TTh in this situation and recommendations for follow-up. Until credible evidence becomes available, the current restrictions regarding the administration of testosterone to men with PCa should remain in place.

What's known on the subject? and What does the study add?

Very little is known on the effect of T in men with untreated PCa. There are only two small series (including the present one) available that comprise less than 25 men with PCs receiving TTh.

It raises a warning that testosterone administration to men with PCa is not always safe, that current precautions should be maintained, and that only an international registry would provide prompt answers to these issues.

KEYWORDS

prostate cancer, testosterone, androgens, prostate safety

INTRODUCTION

The prostate cell population is heterogeneous and comprises, among others, epithelial, basal, neuroendocrine and stem cells, as well as stroma and tissue matrix. The effect of androgens in some cells (i.e. stem cells) is paradoxical: deprivation does not affect them but restoration of testosterone levels increases their proliferation. Complicating matters, stromal–epithelial interactions are regulated not only by androgens, oestrogens [1] and prolactin, but also by a number of growth factors that work through endocrine, paracrine or intracrine mechanisms, which remain only partially elucidated. The relationship between the prostate and testosterone is therefore complex and can be favourable or detrimental to the host, depending, to a large extent, on his individual characteristics. For instance, Parsons *et al.* [2] reported a curious dichotomy found in the Rancho Bernardo Study: community-dwelling men with higher mid-life testosterone:dihydrotestosterone (DHT) ratios are at a decreased risk of developing BPH, while those with higher DHT levels are at a higher risk. This information supports other studies showing that higher testosterone and lower DHT levels are protective against BPH. The mechanisms of androgen–oestrogen synergism in the adult are incompletely understood but, in the prostate gland specifically, it was shown that oestrogens increase the nuclear androgen receptor (AR) cellular content and that the length of CAG repeats of the AR influence both androgen and oestrogen action [3]. Lakshman *et al.* [4] recently showed that administration of testosterone results in an age differential in the aromatization of testosterone to oestrogen. It is also well established that the two isoforms of 5 α-reductase exhibit divergent kinetic values in human tissues, depending on age. Finally, progress is being made, but we haven't quite yet understood how AR regulates growth-promoting genes in prostate cancer (PCa) cells in the absence of binding of its physiological ligand DHT. The lack of prostatic uptake of exogenous testosterone [5] and the 'hard-wiring' changes occurring in the AR signalling pathways during prostate carcinogenesis and PCa invasiveness [6] complicate matters further. These findings point to significant inter-individual responses to changes in the hormonal milieu in men harbouring PCa.

The seminal work of Huggins and Hodges [7] in the first-half of the 20th century provided invaluable insights into the mechanisms of androgen dependency of the prostate and PCa. It led to the wide acceptance of the concept that testosterone stimulates growth of PCa. Recently, however, there has been a challenge to long-held views on testosterone and PCa, as it was found that (i) the levels of endogenous testosterone do not influence the development of Pca [8]; (ii) the levels of androgens in the prostate are discordant from those in peripheral blood [9]; and, most importantly, (iii) the AR has a finite ability to bind to androgens and that when that ability is fulfilled, higher testosterone concentrations have no further effect on prostate growth [10]. Despite the lack of conclusive studies regarding the concept of saturation of the AR and only a handful of clinical cases, there is a growing tendency to accept that testosterone therapy (TTh) for men with testosterone deficiency syndrome (TDS) and PCa is intrinsically safe.

We have explored the effect of TTh on men with both TDS and PCa. Herein we report cases in our experience indicating that the responses to TTh in these men are highly variable and largely unpredictable. We are of the opinion that liberalizing current guidelines is premature.

METHODS

This is an observational series of men with histological diagnosis of PCa and a clinical picture compatible with a diagnosis of TDS supported by biochemical confirmation of serum testosterone levels below normal ranges (10 nmol/L total testosterone) and who were considered suitable for TTh because of symptoms affecting their health-related quality of life. Baseline and follow-up assessments included PSA level, DRE and serum total testosterone levels at quarterly intervals for the first year and six-monthly thereafter. All biochemical investigations were carried out at the Queen's University Affiliated Hospitals Clinical Chemistry Laboratories, Kingston, ON, Canada [11].

In the absence of any guidelines, we followed the recommendations of Bhasin *et al.* [12], although they were based on observations made in hypogonadal men without PCa. It was agreed with the patients that an increase in PSA level >1 ug/mL quarterly or a doubling of PSA level within 12 months of onset of TTh would be reason for discontinuation of TTh, while a return to pretreatment PSA levels would permit re-initiation of TTh.

TABLE 1 Patient characteristics

Patient age	PSA level at entry	Total testosterone at entry	Formulation	Duration, months	Grade/% involvement
73	4.03	8.7	Testosterone enanthate	33	3 + 3/<15
54	1.7	8.3	Testosterone enanthate	96	3 + 3/<5
68	5.8	9.6	Testosterone enanthate	6	4 + 4/30
75	13.4	9.5	Testosterone enanthate	Intermittent	
63	2.6	8.5	Testosterone enanthate	51	3 + 3/25
84	7.3	8.5	Testosterone gel	Intermittent	3 + 3/N.S.
59	4.8	9.8	Oral undecanoate	6	3 + 3/25

FIG. 1. Changes in PSA levels (blue line) in a patient with PCa receiving TTh (red line) over 4 years. After an initial increase the levels have remained stable on testosterone supplementation.

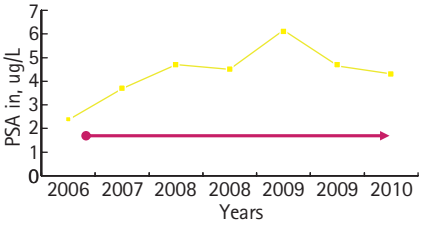


FIG. 2. Another patient in whom, after a stable period, there was an increase in PSA values with return to the pre-treatment nadir upon interruption of TTh. Re-initiation of TTh caused a rapid increase in PSA followed by a precipitous decline after TTh was discontinued.

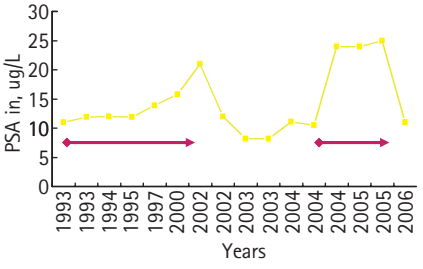


FIG. 3. Another patient in whom the onset of TTh resulted in a prompt and marked increase in PSA levels. This patient opted for definitive surgery with good early biochemical results.

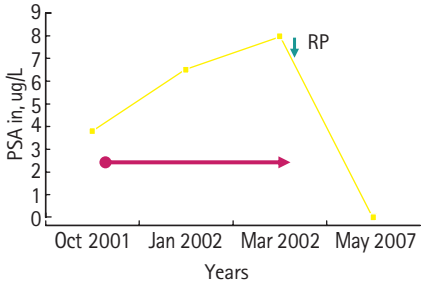
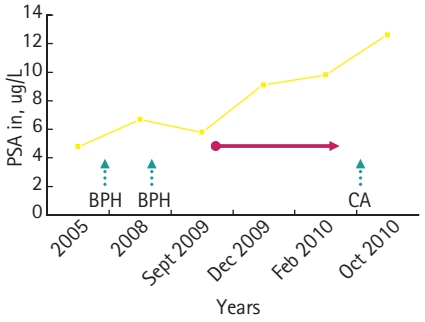


FIG. 4. In this patient a sub-clinical PCa was discovered. Two previous biopsies (arrows) were negative for PCa. After TTh the values of PSA increased promptly, leading to a new biopsy showing the presence of PCa.



RESULTS

To date, seven patients with PCa and serum testosterone levels below the normal ranges in our laboratory have been treated and followed up. Their mean (range) age is 68 (54– 84) years. The lowest PSA level at the beginning of the study was 1.7 ug/L while the highest was 13.4 ug/L. With one exception, all of the patients initially had T1c PCa (diagnosed by needle biopsy because of an elevated PSA level) and no patient had ≥T2c PCa at any time. None had evidence of metastatic disease. Patient characteristics are shown in Table 1.

The responses to TTh have been variable (Figs 1–4). Figure 1 shows an example of modest increases in PSA level during a long

period of TTh; this patient continues to receive treatment. Figure 2 shows the lack of an initial elevation in serum PSA level in another patient, with a fairly rapid increase after 36 months of treatment, followed by a rapid decline after discontinuation of TTh which was maintained until TTh was reinitiated. At this point the increase in PSA level was rapid but its decrease was equally rapid once TTh was discontinued. This patient died 2 years later of causes unrelated to PCa. Figure 3 shows prompt acceleration in PSA velocity in a relatively young patient. TTh was discontinued according to the pre-treatment agreement. The patient decided to undergo a radical prostatectomy. Figure 4 illustrates a different potential benefit of TTh in men with undiagnosed PCa: there was a rapid increase in PSA level after the onset of TTh and biopsies showed PCa despite two previous ones being negative for PCa.

DISCUSSION

The challenging of long-standing medical notions is always welcome. But the challenge needs to involve a credible scientific methodology and evidence superior to that shown by the challenged concept. The hypothesis of the saturation model is very appealing but the available evidence is too frail to be disseminated as a new standard.

From the outset, two issues need to be considered in any discussion on the use of androgens in men with untreated PCa: (i) the complexity of the tumour's biological behaviour in relation to gonadal steroids and (ii) the use of PSA level as a surrogate measure of such behaviour. The first can be addressed by the extensive studies being carried out on the PCa cell line LNCaP, which has been a valuable model for studies on the effect of hormones in prostate malignancies. Chuu *et al.* [13], working with athymic mice and using xenografts of LNCaP, showed that cells that become rich AR-positive androgen-independent cells can be reverted by testosterone administration to androgen dependency. This clearly shows the complex interactions between gonadal steroids and the AR in PCa. The second issue centres on the accuracy of PSA as a measure of tumour progression. Although measurement of PSA may be not be a totally reliable biomarker, currently no other surrogate test offers its universal availability and accuracy as an indicator of tumour response to gonadal steroids. It is the best available early warning for discontinuation of TTh. Currently, there is a scarcity of information as to levels for interruption or re-initiation of TTh in these men and clinicians would be forced to rely on extrapolations from studies not necessarily equivalent to this situation.

The proponents of TTh in men with PCa cite studies going back several decades showing little tumour progression after TTh. Most of those studies, however, did not use TTh alone. The present author and colleagues reported long ago [14] on a group of men with metastatic PCa primed with testosterone before receiving i.v. radioactive phosphorus. The majority of these men experienced an exacerbation of the PCa, although a small number (14%) had a temporary remission when receiving testosterone alone. Even then, this was not new. As far back as 1950 Trunell and Duffy [15] reported that the disease was exacerbated in only 30% of men with PCa who were receiving TTh. Prout and Brewer [16] reported that a patient improved after receiving TTh. More recently Morgentaler *et al.* [17] reported on a small group of men who received TTh while on active surveillance for PCa and in whom there was no evidence of progression of their malignancy. A common characteristic of these patients was the presence of low-grade disease.

Against this rather small group of reports involving a few patients there is an array of extensively documented and contrary information spanning several decades and showing that TTh in patients with PCa can be detrimental. It includes the sporadic reporting of rapid increases in PSA level after TTh [18], a situation more common than is recognised, as the isolated case is no longer considered a publishable experience. The nearly universal and impressive response of PCa observed after surgical or medical castration. The well documented 'flare' that occurs with the increase in testosterone after administration of GnRH agonists in eugonadal men is perhaps the most common and concerning. The new GnRh antagonists are touted as an improvement in treatment because they do not produce the initial flare and also prevent microsurges in testosterone production which are reported to be detrimental in men with PCa during treatment [19]. The frequent increase in PSA level in men on intermittent androgen deprivation therapy further supports the theory that not all men with PCa experience a lack of tumour growth after normalization of endogenous testosterone levels. The large prostate cancer prevention trial (PCPT) describes the beneficial effect of depriving prostate cells of androgens. The saturation model indicates that such saturation occurs at low androgen concentrations of 2–3 nM (close to castrate values), a phenomenon seldom seen in clinical practice where most men are within a borderline range [11]. It should also be noted that evidence exists that is incompatible with this saturation model in an acute study where TTh in eugonadal men without evidence of PCa resulted in a 30% increase in PSA level in those men in whom PCa was subsequently diagnosed [20] Pertinent scientific societies recommend against the use of testosterone in these men [21] or consider its use an absolute contraindication. National regulatory agencies equally discourage the use of testosterone in this situation. However, there is undoubtedly a population of men with both PCa and hypogonadism in whom the administration of testosterone does not appear to bring detrimental consequences. Unfortunately such a population has not been identified and no guides exist to help the clinician in deciding which patients might benefit from TTh and those who might not. In view of the spreading theory that TTh can be used with impunity in men with PCa, the present paper reports on a limited experience indicating that the biological behaviour of PCa in relation to the internal hormonal environment is poorly understood and cannot yet be universalized.

Because of the extremely meagre experience worldwide with this limited population, a number of suggestions are offered. It is important to establish the distinction between men with PCa receiving TTh and those with a remote history of PCa treated successfully. Of the latter, currently there are <200 cases reported in the English literature [22]. Symptomatic hypogonadal men also harbouring PCa are even more rare, and ideally a global registry should be established to follow them with a straightforward and universally accessible assessment protocol to clarify the basic criteria as to which hypogonadal men with PCa might be candidates for TTh. A plan for their long-term follow-up and standards for initiation and discontinuation of treatment should also be established. Table 2 shows the most basic criteria to consider in choosing candidates for TTh. Initially, men with high grade (Gleason sum >8) and metastatic disease should be

- A treating physician who is competent, qualified and interested
- Patient able and willing to provide informed consent
- Clinical picture compatible with diagnosis of TDS
- Serum testosterone levels supporting the diagnosis of TDS
- Histological grade (Gleason sum) ≤7
- Disease confined to the pelvis (<T2c)
- Absence of significant LUTS (IPSS <19)
- Other contraindications for TTh (erythrocitosis, sleep apnoea, CHF)

TABLE 2
Criteria to consider before intiating TTh in a patient with TDS and PCa

TABLE 3 Factors to be assessed at onset of TTh and/or at quarterly intervals, and during follow-up

- Age
- Race
- Gleason grade and % involvement in prostate biopsies (at entry only)
- DRE
- PSA velocity (increase/decrease/no change)
- PSA doubling time from nadir if TTh is intermittent
- Serum testosterone (total and measured or calculated bioavailable testosterone)
- LH
- Haemoglobin
- Haematocrit
- IPSS
- Previous treatments for PCa
- Standard investigations for men receiving TTh

During follow-up:

- Adverse events related to TTh (related/unrelated; degree of severity)
- New medications or treatments

excluded. Candidates for TTh should be willing and able to adhere to a strict follow-up (quarterly for the first 2 years and bi-annually thereafter if they are stable). They should also be willing to discontinue therapy if, in the judgment of the treating physician, there is evidence of PCa progression. Table 3 lists the most indispensable features to be included in the registry.

The innovative idea of using androgen supplementation in men with TDS and untreated or unsuccessfully treated PCa is worth exploring. It should be done, however, with a great deal of caution. The whole field of male hypogonadism and its treatment has, historically, been plagued by controversy. After more than seven decades of testosterone use, we should be able to appropriately investigate the one issue that most concerns physicians and patients alike: prostate safety. It has been established that endogenous testosterone does not induce Pca [8]. There is increasing evidence that men successfully treated for PCa can safely receive TTh under certain circumstances [22]. We should now define which men bear prostate malignancies that do not prosper during testosterone substitution and which men experience an improvement in health-related quality of life with such treatment. The issue needs to be addressed from a medical, ethical and scientific perspective. The establishment of a registry should address these important issues and provide reliable answers in a prompt manner.

CONFLICT OF INTEREST

None declared. Source of funding: Centre for Applied Urological Research.

REFERENCES

1 **Hudson DL.** Epithelial stem cells in human prostate growth and disease. *Prostate Cancer Prostatic Dis* 2004; **7**: 188–94
2 **Parsons JK, Palazzi-Churas K, Bergstrom J, Barrett-Connor E.** Prospective study of serum dehydrotestosterone and the subsequent risk of benign prostatic hyperplasia in community dwelling men: the Rancho Bernardo Study. *J Urol* 2010; **184**: 1040–4
3 **Huhtaniemi I, Pye SR, Limer K *et al.*** Increased estrogen rather than decreased androgen action is associated with longer androgen receptor CAG repeats. *J Clin Endocrinol Metab* 2009; **94**: 277–84
4 **Lakshman KM, Kaplan B, Travison TG *et al.*** The effect of injected testosterone dose and age in the conversion of testosterone to estradiol and dihydrotestosterone in young and older men. *J Clin Endocrinol Metab* 2010; **95**: 3955–64
5 **Marks LS, Mazer NA, Mostaghel E *et al.*** Effect of testosterone replacement in therapy of prostate tissue in men with late onset hypogonadism. *JAMA* 2006; **296**: 2351–62
6 **Litvinov I, De Marzo AM, Isaacs JT.** The Achilles heel for prostate cancer therapy a gain of function in androgen receptor signaling? *J Clin Endocrinol Metab* 2003; **88**: 2972–82
7 **Huggins C, Hodges CV.** Studies on prostatic cancer 1. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res* 1941; **1**: 293–7
8 **Endogenous Hormones and Prostate Cancer Collaborative Group, Roddam AW, Allen NE, Appleby P, Key TJ.** Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. *J Natl Cancer Inst* 2008; **100**: 170–83
9 **Marks LS, Mostaghel EA, Nelson PS.** Prostate tissue androgens: history and current clinical relevance. *Urology* 2008; **72**: 247–54
10 **Morgentaler A.** Testosterone therapy in men with prostate cancer: scientific and ethical considerations. *J Urol* 2009; **181**: 972–9
11 **Collier CP, Morales A, Clark A, Lam M, Wynne-Edwards K, Black A.** The significance of biological variation in the diagnosis of testosterone deficiency and consideration of the relevance of total, free and bioavailable testosterone determinations. *J Urol* 2010; **183**: 2294–9

12 **Bhasin S, Singh AB, Mac RP, Bellentine C, Martin IL, Cunningham GR.** Managing the risks of prostate disease during testosterone replacement therapy in older men: recommendations for a standardized monitoring plan. *J Androl* 2003; **24**: 299–311
13 **Chuu CP, Hiipakka RA, Fukuchi J, Kokontis JM, Liao S.** Androgen causes growth suppression and reversion of androgen-independent prostate cancer xenografts in androgen-stimulated phenotype in athymic mice. *Cancer Res* 2005; **65**: 2082–4
14 **Morales A, Connolly JG, Bruce AW.** Androgen therapy in advanced carcinoma of the prostate. *Can Med Assoc J* 1971; **105**: 71–3
15 **Trunnel JB, Duffy BJ Jr.** The influence of certain steroids on the behavior of human prostatic cancer. *Trans N Y Acad Sci* 1950; **12**: 238–41
16 **Prout GR, Brewer WR.** Response of men with advanced prostate cancer to exogenous administration of testosterone. *Cancer* 1967; **20**: 1871–8
17 **Morgentaler A, Sweeney M, Bennett R, Avila D, Khera M, Lipshultz LI.** PSA and follow-up biopsy results in men who received testosterone therapy while on active surveillance for prostate cancer. *J Urol* 2010; **183** (Suppl. 4): e531; Abstr. 1376
18 **Curran MJ, Bihrle W III.** Dramatic rise in prostatic specific antigen after androgen replacement in a hypogonadal man with occult adenocarcinoma of the prostate. *Urology* 1999; **53**: 423–4
19 **Klotz L, Boccon-Gibod L, Shore ND *et al.*** The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel group phase III study in patients with prostate cancer. *BJU Int* 2008; **102**: 1531–8
20 **Svatek RS, Schulman MJ, Benaim EA, Rogers TE, Margulis E.** Change in prostate specific antigen following androgen stimulation is an independent predictor of prostate cancer diagnosis. *J Urol* 2008; **179**: 2192–5
21 **Bhasin S, Cunningham G, Hayes F *et al.*** Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2010; **95**: 2536–59
22 **Morales A, Black AM, Emerson LE.** Testosterone administration to men with testosterone deficiency syndrome after external beam radiotherapy for localized prostate cancer: preliminary observations. *BJU Int* 2009; **103**: 62–4

Correspondence: Alvaro Morales, Centre for Applied Urological Research, 62 Barrie Street, Kingston, ON, Canada, K7L 3J7.
e-mail: moralesa@queensu.ca

Abbreviations: **PCa**, prostate cancer; **DHT**, dihydrotestosterone; **AR**, androgen receptor; **TTh**, testosterone therapy; **TDS**, testosterone deficiency syndrome.