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HIGH-DOSE TESTOSTERONE & PROSTATE CANCER
WAIT UNTIL YOU READ THIS UPDATE, September 1, 2009

I am pleased and proud to announce that our manuscript has been accepted for publication in an upcoming print and on-line edition of *British Journal of Urology, International*. Our article, written primarily by Dr. Tanya Dorff, reports on results from treating 96 prostate cancer patients from my practice with high-dose Testosterone Replacement Therapy (TRT). Almost all patients were felt to be in remission from their prostate cancer before starting treatment with TRT. In my very strong (as usual) opinion, this is the absolute major explanation for the vastly superior outcomes seen in our patients compared to any other TRT series of prostate cancer patients, many (most) of whom did not have local therapy.

The lead article from the August 2009 *European Urology*, Michael J. Morris, et al., Volume 56 (2009), pages 237-244, and the Editorial that followed, Robert Gardiner, et al., pages 245-246, report and describe results using "High-Dose Testosterone in Patients with Metastatic Castration Resistant Prostate Cancer." I believe that this article is the first time that internationally known and highly respected prostate cancer experts reached conclusions regarding testosterone and prostate cancer that are much more similar to the opinions/beliefs/theories/positions that I have written about on my website, and have been the subject of recorded DVD lectures that I have been giving for almost 10 years regarding the relationship between prostate cancer and testosterone. My ideal target level for testosterone is 1,800-3,000 ng/dl while the patients in this article had levels of about 550-750 ng/dl.

Did you ever believe you would see an article state that using high-dose testosterone to treat men with metastatic castration resistant prostate cancer can be done SAFELY; that preclinical and animal studies show high levels of testosterone can suppress prostate cancer cell growth, but low levels of testosterone can stimulate the growth of prostate cancer cells?

And although no patient required it, this study called for patients who showed evidence of toxicity from testosterone to be treated with 150 mg of Casodex per day, not 50 mg!! So many critics of mine have argued with my recommendation to always use 150 mg of Casodex a day, not 50 mg per day. I started

using this dose in 1997. I believe that this is the first article I have seen (this does not imply that just because I have not seen an article that it does not exist) that advised this dose of Casodex. Now that Casodex is generic, I wonder whether other prostate cancer doctors will find indications for the 150 mg/day dose.

But this article is such sweet **vindication** for me. I am certain that over the past 10 years or so, since I first started to use testosterone on some of my prostate cancer patients, that some rather nasty remarks to describe me personally and professionally have been used. Perhaps some of these critics now need to rethink their positions on the relationship between testosterone and prostate cancer.

What is sweetest of all is that this approach, which I have used on well over 200 patients, provides hope and the possibility that a potentially new and effective treatment approach for some prostate cancer patients may soon be offered to many more men who until very recently have believed that they would never again be allowed to experience the effects of testosterone. And men on high-dose TRT almost always feel incredibly well.

And, as always –

Be happy,
Be well,
Live long and prosper,

Bob Leibowitz

BOB LEIBOWITZ, M.D.

BL:nf

September 1, 2009

** None of the above should be construed as medical advice or consultation, and anything discussed in this paper is meant for information only. All medical treatments, consultations, decisions and recommendations can only be made by the patient and his/her treating physician. There are side effects associated with all medicines, and the reader is reminded to discuss the risks, benefits, and alternatives of every medication with their prescribing doctor before taking any medicine.

Bob Leibowitz MD

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Platinum Priority – Prostate Cancer

Editorial by Robert A. Gardiner, Christopher Sweeney and Wayne D. Tilley on pp. 245–246 of this issue

Phase 1 Trial of High-Dose Exogenous Testosterone in Patients with Castration-Resistant Metastatic Prostate

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Abstract

Background: Growth of selected castration-resistant prostate cancer (CRPC) cell lines and animal models can be repressed by reexposure to androgens. Low doses of androgens, however, can stimulate tumor growth.

Objective: We performed a phase 1 clinical trial to determine the safety of high-dose exogenous testosterone in patients with castration-resistant metastatic prostate cancer (CRMPC).

Design, setting, and participants: Patients with progressive CRMPC who had been castrate for at least 1 yr received three times the standard replacement dose of transdermal testosterone.

Intervention: Cohorts of 3–6 patients received testosterone for 1 wk, 1 mo, or until disease progression.

Measurements: Toxicities, androgen levels, prostate-specific antigen (PSA) assays, computed tomography (CT) scans, bone scintigraphy, positron emission tomography (PET) scans, and metastatic tumor biopsy androgen receptor levels were assessed.

Results and limitations: Twelve patients were treated—three in cohorts 1 and 2 and six in cohort 3. No pain flares were noted. One patient came off study because of epidural disease, which was treated with radiation. Average testosterone levels were within normal limits, although dihydrotestosterone (DHT) levels on average were supraphysiologic in cohort 3. One patient achieved a PSA decline of >50% from baseline. No objective responses were seen. For cohort 3, median time on treatment was 84 d (range: 23–247 d).

Conclusions: We have demonstrated that patients with CRMPC can be safely treated in clinical trials using high-dose exogenous testosterone. Patients did not, on average, achieve sustained supraphysiologic serum testosterone levels. Future studies should employ strategies to maximize testosterone serum levels, use contemporary methods of identifying patients with androgen receptor overexpression, and utilize PSA Working Group II Consensus Criteria clinical trial end points.

Trial registration: ClinicalTrials.gov; NCT00006044.

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1. Introduction

Since the late 1940s, the standard treatment for metastatic prostate cancer (PCa) has been medical or surgical castration [1,2]. Even after patients progress following primary castrating hormonal therapies, secondary or tertiary hormones, or chemotherapy, most still receive androgen-lowering agents. The assumption is that rising testosterone levels stimulate tumor growth, since the androgen receptor remains functional even in castration-resistant patients.

Preclinical data, however, suggest that in select circumstances, there may be a role for testosterone repletion, even in the setting of castration-resistant disease. Androgen-independent cell lines, derived by raising LNCaP and others in androgen-depleted media for several generations, demonstrate growth repression when treated with supraphysiologic levels of exogenous, high-affinity androgens. Growth of these cells, characterized by androgen receptor (AR) overexpression and gene amplification, is inhibited by synthetic androgens at concentrations ≥0.1 nM (normal male testosterone levels: 10–35 nM) [3–6]. Animal models have demonstrated tumor necrosis and regression with testosterone supplementation [7]. Paradoxically, growth can be promoted by androgens at lower concentrations [3,4,8].

Early experiences using testosterone supplementation at Memorial Sloan-Kettering Cancer Center (MSKCC) between 1949 and 1967 resulted in adverse outcomes, including rapid progression. In those analyses, 45 of 52 evaluable patients appeared to suffer with added testosterone. These patients represented mixed clinical states: hormone naïve, castration sensitive, and castration resistant. The latter patients fared the worst, with 94% suffering ill effects from treatment [9]. In separate studies using androgen priming prior to chemotherapy, survival and other clinical outcomes were lower than in patients receiving chemotherapy alone [10,11]. Reports of benefit, particularly in castration-resistant patients, have been isolated and anecdotal [12].

We sought to test whether exogenous testosterone might be safely investigated in a manner that mirrors the successful preclinical data by treating a uniform group of patients with long-term castration-resistant metastatic disease using exogenous androgen at concentrations above an as-yet-unknown threshold of activity. We performed a phase 1 trial to test this hypothesis.

2. Patients and methods

2.1. Eligibility criteria

Patients were >18 yr of age and signed their informed consent. The trial was approved by the institutional review board of MSKCC. Eligible patients had histologically confirmed PCa, which had become progressive, metastatic, and castration resistant. Radiographic progression was defined by World Health Organization (WHO) criteria [13]; new osseous lesions were determined by bone scintigraphy. Biochemical progression was defined as a 25% increase in prostate-specific antigen (PSA) over three tests. Patients were required to be castrated by orchiectomy or by gonadotropin-releasing hormone (GnRH) analogues for a minimum of 1 yr and were required to continue GnRH analogues during treatment if these were their form of castrating therapy. Patients could not receive other anticancer treatments within a month of treatment. Entry was also contingent on a serum testosterone <30 ng/ml, white blood cell count >3500/mm^3, platelet count >100 000/mm^3, bilirubin <2.0 mg/dl, creatinine <2.0 mg/dl or creatinine clearance >60 ml/min, and prothrombin time <14.5 s.

2.2. Treatment

Because preclinical data suggest that high levels of testosterone might arrest growth while lower doses could induce tumor flare, all patients received three times the standard replacement doses of testosterone to minimize the likelihood of falling into the concentration associated with tumor growth. We originally used testosterone 5 mg transdermal patches (Testoderm TTS, ALZA Pharmaceuticals, Palo Alto, CA, USA). This product was discontinued by the manufacturer, so we chose testosterone gel 1% CIII (AndroGel, Unimed Pharmaceuticals, Deerfield, IL, USA) for the remainder of the trial. If any grade 3 or 4 toxicity occurred during testosterone administration, the patient was evaluated to receive 150 mg of bicalutamide (Casodex, AstraZeneca, Wilmington, DE, USA) to counter the effects of testosterone. Tumor flare, defined as an increase in tumor-related symptoms during the first 2 wk of therapy, did not mandate withdrawal from the study unless it represented toxicity of grade ≥3.

The duration of testosterone repletion was escalated by cohort: Cohort 1 received 7 d of treatment, followed by a 4-wk observation period; cohort 2 received 4 wk of treatment, followed by a 4-wk observation period; and cohort 3 was treated until progression (Fig. 1). Cohorts 1 and 2 were designed to hold three to six patients; cohort 3 was intended to hold six patients by design.

2.3. Toxicity

National Cancer Institute Common Toxicity Criteria (NCI-CTC) v.2 were used. A history, physical exam, complete blood count (CBC), and chemistries were done prior to treatment, on days 2 and 4 and every week until study termination.

2.4. Serum drug levels

Serum levels of testosterone, free testosterone (FT), dihydrotestosterone (DHT), and sex-hormone-binding globulin (SHBG) were assayed on day 1, on day 4, and weekly thereafter. Patients applied the testosterone patch or gel on the night of day zero. Serum testosterone was determined by a competitive solid-phase radioimmunoassay (RIA; Coat-A-Count, Siemens Medical Solutions, Tarrytown, NY, USA). Assay imprecision at all concentrations levels was <10%. DHT was determined by a competitive solid-phase RIA. FT was determined by calculation after measuring SHBG, testosterone and albumin. The percent of FT is a function of the concentrations of SHBG, albumin, and testosterone, with the relative concentrations of testosterone and SHBG factoring in the dissociation constants for SHBG and albumin.

2.5. Antitumor effects

Response assessments by PSA, bone scan, and soft-tissue imaging were performed every 8 wk and at study termination except in cohort 1, when repeat imaging was performed at week 5 (Fig. 1). WHO criteria were used for assessing changes in measurable disease. Posttreatment PSA alterations were recorded for all patients. Few assumptions were made regarding the clinical meaning of posttreatment PSA alterations because

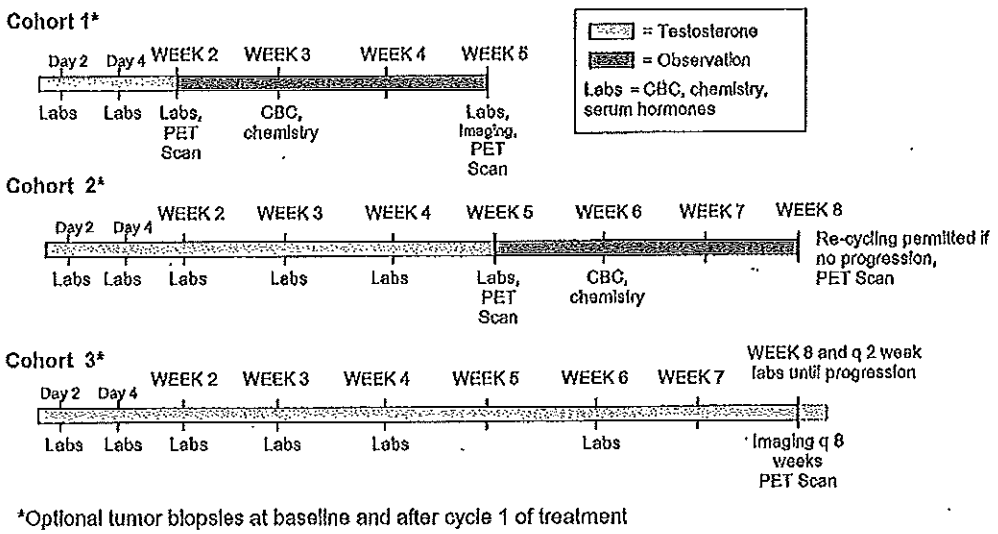

Fig. 1 – Treatment schema. CBC = complete blood count; PET = positron emission tomography.

the treatment directly activates PSA expression. A sustained PSA increase of >50% from baseline over three tests was considered disease progression.

2.6. Correlative studies

Tissue biopsies from metastatic sites were obtained from consenting patients at baseline to determine the correlation between AR expression by immunohistochemistry with clinical outcomes. Primary antibodies (AR; Dako, Carpinteria, CA, USA) were applied to tissue sections at a dilution of 1:50 in 0.5% bovine serum albumin (BSA)/phosphate-buffered saline (PBS) and incubated overnight. The Dako LSAB2 detection system (catalog no. K0675) was used per the manufacturer's instructions, and the signal was developed with diaminobenzidine. Sections were counterstained in Mayer's hematoxylin followed by cover slipping. The cells were stained using immunohistochemistry, and the intensity of AR expression was measured (0, 1+, 2+, 3+).

Additionally, because PSA was felt to be an unreliable measure of treatment effect with this therapy, fluorodeoxyglucose (FDG) positron emission tomography (PET) scanning, shown to be a useful indicator in previous prospective controlled clinical trials [14], was used to demonstrate treatment-related metabolic changes. FDG PET scans were obtained at baseline and at study termination for all cohorts. An FDG PET scan was also obtained during the week following treatment for cohorts 1 and 2 (weeks 2 and 5, respectively). PET scans were read via visual inspection and were categorized as progressing, stable, mildly responding, or responding.

2.7. Biostatistic considerations

The primary end point of the trial was to determine both the safety and the antitumor effects of exogenous high-dose testosterone. Dose-limiting toxicity was defined as grade ≥3 toxicity using NCI-CTC v.2. The maximum tolerated dose was defined as the highest dose level with an observed incidence of dose-limiting toxicity in two of six patients. If the risk of toxicity was 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%, the probability of escalation was predicted to be 98%, 93%, 81%, 71%, 60%, 49%, 40%, 31%, 23%, or 17%, respectively.

3. Results

3.1. Patients

Twelve patients were treated. Table 1 contains demographics, disease status, and prior treatment histories. Eleven of the 12 patients had bone disease, and 3 out of 12 had measurable soft-tissue disease. By definition, all patients were castrate for at least 1 yr; the median number of hormonal manipulations was three. Five patients had progressed through prior taxane-based chemotherapy.

3.2. Treatment

Three patients were treated in both cohorts 1 and 2. Six patients in cohort 3 were treated until progression. All patients in cohorts 1 and 2 were treated with transdermal patches (six patients total), while all patients in cohort 3 were treated with testosterone gel. No patient changed the means of testosterone delivery midtreatment.

3.3. Adverse events

Treatment was well tolerated in all cohorts, with no grade 3–4 episodes of pain. One patient in cohort 3 had a history of epidural disease prior to entering the study and developed low-grade back pain. He was found to have a T4 cord compression without any neurologic findings and experienced a 34% decline in PSA after 21 d on treatment. Follow-up computed tomography (CT) and bone scans after radiation to the spine revealed no new lesions.

Table 2 describes adverse events. Included in the table are all grade 3 or 4 events and any grade 1 or 2 event that affected a total of >25% of patients. Grade 1 and 2 fatigue affected all patients—a frequent finding for patients

Table 1 – Patient characteristics ($n = 12$)

Characteristics	No. of patients
Bone disease only	9
Soft tissue disease only	1
Bone and soft tissue	2
Median age, yr (range)	65 (46–77)
Median Karnofsky PS (range)	90 (80–90)
Median Gleason grade (range)	8 (7–9)
Median PSA (range)	91 (6–2637)
Median no. of prior hormonal regimens (range)	3 (2–5)
One prior regimen	0
Two prior regimens	2
Three prior regimens	8
Four prior regimens	1
Five prior regimens	1
Prior RT	6/12
Primary (prostate)	2/6
Palliative (other sites)	4/6
Prior surgery (prostatectomy)	5/12
Prior chemotherapy	5/12
One prior regimen	0
Two prior regimens	0
Three prior regimens	3
Four prior regimens	2

PS = performance status; PSA = prostate-specific antigen; RT = radiotherapy.

with castration-resistant disease. This was not felt to be the result of treatment, and anecdotally, some patients felt more energized on testosterone than off. Urinary frequency was also frequently seen (67% of patients). Although testosterone has the capacity to induce obstructive symptoms, no patient developed any grade of urinary retention or reported urinary frequency in excess of grade 2 (an increase of twice normal but less than hourly). Other low-grade events such as neuropathy, hyperglycemia, and anemia were likely not caused by treatment and were related to comorbid disease, preexisting conditions, and disease progression. Instances of grade 3 atrial fibrillation, cerebrovascular accident, hyperglycemia, and transaminitis were judged by the patients' treating physicians to be unrelated to treatment. There were no grade 4 adverse events.

3.4. Serum drug levels

Average levels of testosterone, FT, and DHT per patient are summarized in Table 3 and Fig. 2. Cohort 1 had an average testosterone level of 560.5 ng/dl (range: 408.0–853.5) and DHT level of 61.8 ng/dl (range: 45.5–94). Cohort 2 had a higher average testosterone level of 737.2 ng/dl (range: 540.8–876.0) but a comparable DHT level of 63.2 ng/dl (37–105). Cohort 3 had a slightly lower testosterone level than cohort 1 (ie, 530.7 ng/dl [range: 342.5–768.6]) but the highest average DHT level (102.3 ng/dl [range: 79.9–104.4]). Note that all of these values except for the DHT level of cohort 3 are within physiologic range (normal range of DHT: 30–85 ng/dl).

3.5. Prostate-specific antigen levels

Posttreatment PSA nadirs for all patients are shown in the waterfall graph in Fig. 3. A detailed description of every patient's PSA is found in Table 3. In cohort 1, PSA levels increased in all patients during the week of treatment. During the 1-mo observation period, PSA levels declined relative to the treatment period but did not return to baseline for patients A and B, and declined by almost 20% from baseline for patient C. In cohort 2, patients D and E demonstrated minor (<50%) PSA declines, while patient F's PSA rose. All patients demonstrated new lesions on bone scans. The only patient to recycle in cohort 2 was patient D. On day 5 of recycling, the patient presented with grade 2 tumor pain flare and grade 2 fever, and the patient's treating physician opted to stop therapy.

Representative PSA curves for patients in cohort 3 are shown in Fig. 4. Patients G, J, K, and L demonstrated PSA declines of 26%, 50%, 34%, and 12%, respectively. Patients G, J, and L showed no progressive disease on standard scans.

Table 2 – Adverse events

Events		Grade, n (%)			
		1*	2*	3*	4*
Cardiac	Atrial fibrillation	0 (0)	0 (0)	1 (8)	0 (0)
Neurologic	CVA	0 (0)	0 (0)	1 (8)	0 (0)
	Cord compression	0 (0)	0 (0)	1 (8)	0 (0)
	Neuropathy	6 (50)	1 (8)	0 (0)	0 (0)
Hematologic	Anemia	6 (50)	2 (17)	0 (0)	0 (0)
	Leukopenia	1 (8)	1 (8)	0 (0)	0 (0)
Metabolic	Hyperglycemia	6 (50)	1 (8)	1 (8)	0 (0)
Gastrointestinal	Liver toxicity (SGOT)	5 (42)	0 (0)	1 (8)	0 (0)
	Liver toxicity (SGPT)	2 (17)	2 (17)	1 (8)	0 (0)
	Nausea	2 (17)	2 (17)	0 (0)	0 (0)
General	Tumor pain	5 (42)	4 (33)	0 (0)	0 (0)
	Fatigue	9 (75)	3 (25)	0 (0)	0 (0)
	Edema	1 (8)	1 (8)	0 (0)	0 (0)
	Hematuria	0 (0)	3 (25)	0 (0)	0 (0)
	Urinary frequency	6 (50)	2 (17)	0 (0)	0 (0)

CVA = cerebrovascular accident; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.
* Grade 1 and 2 toxicities were reported only for effects observed at a frequency >25%. All grade 3 and 4 events are reported.

Table 3 – Summary of prostate-specific antigen responses and antitumor activity

Patient	Cohort	Days on study	No. of cycles	Average testosterone level on Rx ng/dL	Average FT level on Rx pg/mL	Average DHT level on Rx ng/dL	Pre-Rx PSA ng/dL	Best PSA response ng/dL	Change in PSA %	Soft tissue change	Bone scan	Initial follow-up FDG PET scan	Off-study FDG PET scan
A	1	65	1	420	83.5	46.0	2271	2615.36	5.16[b]	N/A	No new lesions	PD	SD
B	1	46	1	353.5	143.6	94.0	378.66	496.85	31.21[b]	N/A	No new lesions	SD	SD
C	1	121	1	408.0	125.2	45.5	147.52	118.21	−19.87[b]	N/A	New lesions	PD	SD
D	2	57	2	794.3	168.6	105.0	41.12	37.87	−7.9	N/A	New lesions	SD	SD
E	2	52	1	540.8	174.6	37.0	143.88	127.03	−11.71[b]	N/A	New lesions	PD	PD
F	2	57	1	876.0	240.2	47.6	20.63	31.73	53.81[b]	N/A	New lesions	PD	Mild improvement
G	3	109	2	768.6	165.2	79.9	27.22	20.2	−25.79	N/A	No new lesions	PD	Mild improvement
H	3	60	1	342.5	39.4	98.0	64.16	120.2	87.34	PD (54% increase)	New lesions	Mild improvement	N/A
I	3	61	1	622.7	93.5	140.4	108.41	124	14.38	PD (79% increase)	New lesions	PD	N/A
J	3	124	2	489.1	121.8	91.6	5.92	2.98	−49.66	N/A	No new lesions	PD	N/A
K	3	27	1	474.0	89.7	103.0	217.42	143.13	−34.17	N/A[c]	No new lesions[c]	N/A	N/A
L	3	250	4	487.4	84.0	101.0	72.33	63.82	−11.77	SD (24% decrease)	N/A	Mild improvement	N/A

CT = computed tomography; DHT = dihydrotestosterone; FDG = fluorodeoxyglucose; FT = free testosterone; N/A = not applicable; PD = progressive disease; PET = positron emission tomography; RT = radiotherapy; SD = stable disease; Tx = therapy.

[a] Reference values: testosterone 131–758 ng/dL, FT 47–244 pg/mL, DHT 30–85 ng/dL.

[b] During observation.

[c] Only available follow-up CT and bone scan occurred after patient had RT to spine for cord compression.

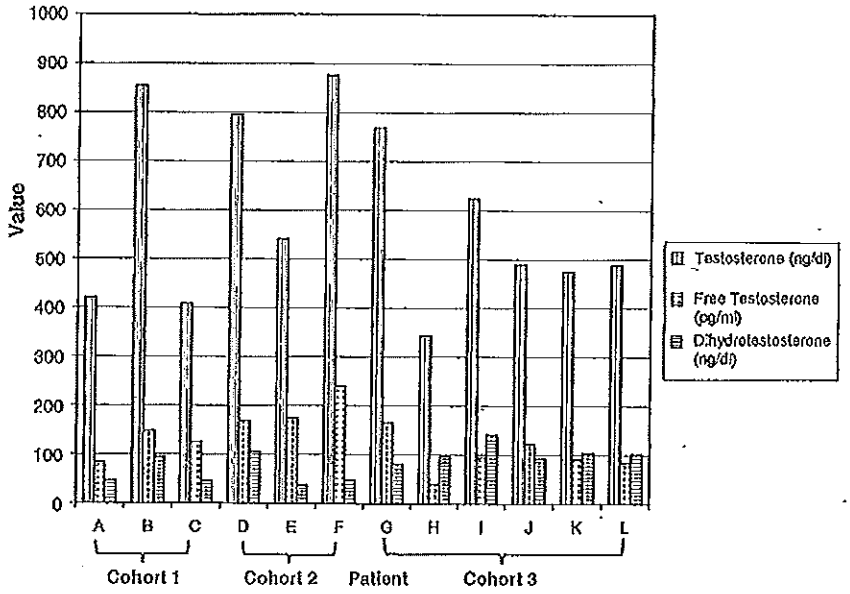

Fig. 2 – Serum androgen levels: Reference ranges for these assays were 181–758 ng/dl for testosterone, 47–244 pg/ml for free testosterone, and 30–85 ng/dl for dihydrotestosterone.

Patient K developed cord compression, as mentioned earlier, and received radiotherapy without neurologic sequelae. Patients H and I sustained PSA rises, with only H reaching the 50% mark. Both patients progressed radiographically.

3.6. *Objective responses*

Three patients had measurable soft tissue disease; no objective responses were seen. In total, 9 of 12 patients (75%) progressed either biochemically or radiographically, 1 (8%) patient demonstrated a PSA decline of 50% without radiographic progression, and 2 patients had "stable" disease (PSA declines of 25% and 12% without radiographic progression). For cohort 3, median time on treatment was 84 d (range: 23–247).

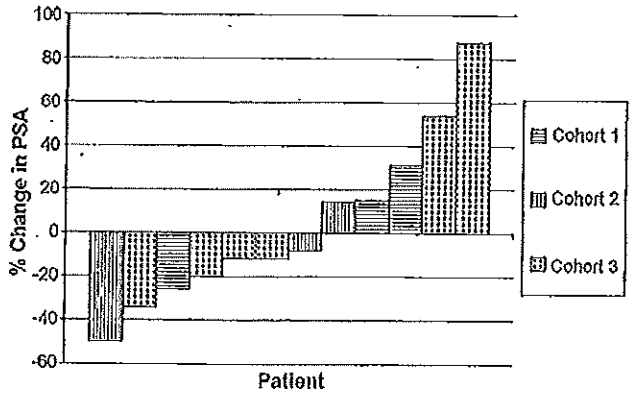

Fig. 3 – Percent change in prostate-specific antigen achieved by all patients while on study. PSA = prostate-specific antigen.

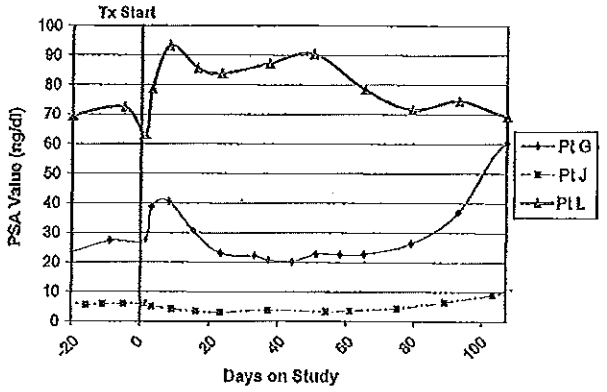

Fig. 4 – Prostate-specific antigen kinetics of representative patients treated to progression as part of cohort 3 (truncated at 109 d of treatment to enhance readability). PSA = prostate-specific antigen; Pt = patient.

3.7. *Positron emission tomography scans*

PET scans were performed to determine whether tumor glucose metabolism might fall despite a rising PSA. We saw no such phenomena. In 4 out of 11 patients with early posttreatment PET scans, PSA declined in the face of worsening PET results. In three patients, the PSA rose as PET scans worsened. Mixed associations were seen in the remaining four patients.

3.8. *Pathology*

A select number of patients elected to have posterior iliac crest bone marrow biopsies for determining tumor AR

expression at baseline and shortly after treatment completion. Patients A, D, E, and H had both pre- and posttreatment biopsies. Patient A had pre- and posttreatment AR expression levels of 1+; patients D and E had pre- and posttreatment levels of 2–3+; patient H had a pretreatment level of 1+ and a posttreatment level of 3+. Patient J had a posttreatment biopsy only, revealing 3+ expression. There were too few specimens and too few responders to draw conclusions regarding the relationship between AR expression and clinical outcome or the success of preselecting the population for tumors with AR overexpression.

4. Discussion

The purpose of this trial was to determine whether exogenous high-dose testosterone was a safe strategy in patients with castration-resistant disease, despite a poor historical safety record. Indeed, our great fear was that we might recapitulate the history of flaring patients' cancers in the process of treating them with testosterone. We hypothesized that selecting patients on the basis of prolonged exposure to castration and treating them with high doses of testosterone would mirror the preclinical milieu that resulted in tumor growth repression and would optimize the likelihood of patient safety (if not benefit). Furthermore, we hypothesized that the use of contemporary safety monitoring would allow a sufficient level of surveillance and early detection of disease progression to minimize patient risk.

Congruent with our hypothesis and expectations, no patient developed an early tumor flare (defined as grade 3 pain) or a new need for opiates or required intervention with high-dose bicalutamide. One patient with an existing spinal bone lesion, however, did develop cord compression after 3 wk on study. The fact that he had preexisting epidural disease strongly suggests that men should undergo a screening magnetic resonance imaging scan of the spine to rule out high-risk lesions prior to initiating treatment. Save for this patient with a presumably preventable problem, patients tolerated therapy well, suggesting that phase 2 investigations of this approach, treating patients to progression, can be performed safely. These data are supported by two other recent clinical trials of patients with metastatic PCa in which exogenous testosterone was administered safely as part of hormonal and chemohormonal therapy in men whose cancer was not castration resistant [15,16].

This trial was only designed to establish preliminary safety data, not efficacy; in fact, cohorts 1 and 2 used such a brief treatment period that treatment effects are not interpretable. Furthermore, too few patients were involved in this study to reach any efficacy-based conclusions. One patient did achieve a PSA decline of 50% without a demonstrable increase in radiographic metastases on standard imaging studies. Although this "responder" may suggest that this study identified patients who mirror the growth repression seen preclinically, this patient was exceptional; however, other patients enjoyed lesser PSA declines. No patients with measurable disease could be characterized as having achieved a partial or complete response.

Given that this approach has proved to be safe, especially if patients are screened for high-risk spinal lesions, several issues are raised relating to future studies. The first regards eligibility. Although all of these patients met the definition of castration-resistant metastatic disease, they likely still represented a biologically heterogeneous group. They had various exposures to prior hormonal therapies and chemotherapy and likely also had variable AR expression. Regarding the latter, when the present study was designed, there were few means by which patients might be selected on the basis of AR overexpression, which, as previously mentioned, predicts for response preclinically. Now, however, such methods exist. Patients with AR-rich tumors, for example, can be identified using fluorinated dihydrotestosterone (FDHT) PET tracers [17,18]. Additionally, circulating PCa cells can be isolated and identified on the basis of AR gene amplification [19]. These techniques as well as further efforts to reduce patient heterogeneity can be used to enrich the patient population for likely responders in future trials. Patient selection is of particular importance in this approach because although testosterone may be beneficial to some patients, it may activate cancer growth in others, representing a deleterious rather than a beneficial effect.

The second modification would be response criteria. PSA Working Group II Consensus Criteria [20] had not been developed when this trial was designed. Posttreatment PSA alterations were generally poorly informative in this study. We anticipated that PSA might rise despite antitumor responses, but patients whose PSA levels rose also progressed radiographically by standard imaging modalities, with no major response seen by PET scanning. PSA declines were also not necessarily indicative of a favorable outcome, as four of six patients in cohorts 2 and 3 whose PSA levels declined also demonstrated disease progression clinically or on scans. For the next trial, we intend to follow PSA Working Group II Consensus Criteria and only use radiographic or clinical progression as an end point, using two new lesions on two successive bone scans as the definition for progression in bone [20].

The final consideration is that of dose. Despite using three times the usual replacement dose of testosterone, serum testosterone levels did not, on average, exceed normal levels. These levels may be a result of inefficient absorption but could also result from metabolism to DHT and other downstream products. Cohort 3 did have supraphysiologic DHT levels. It is not clear from preclinical data whether growth inhibition arises from testosterone or DHT or both, but if indeed supraphysiologic testosterone levels are necessary to repress growth, then it is possible that such levels cannot be achieved without also administering a 5α-reductase inhibitor (5-ARI) [21]. We are exploring this hypothesis in an upcoming clinical trial.

5. Conclusions

In conclusion, this study shows that high-dose exogenous testosterone can be administered safely to patients with castration-resistant disease. We plan to explore this concept further in a study that enriches the castration-

resistant population for AR overexpression using FDHT scans and circulating cells, that utilizes PSA Working Group II response criteria, and that explores maximizing testosterone levels by the addition of a 5-ARI.

Author contributions: Michael J. Morris had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Morris, Kelly.
Acquisition of data: Morris, Kelly, Slovin, Delacruz, Curley, Schwartz, Scher.
Analysis and interpretation of data: Morris, Huang, Kelly, Slovin, Stephenson, Delacruz, Curley, Schwartz, Scher.
Drafting of the manuscript: Morris, Huang, Stephenson.
Critical revision of the manuscript for important intellectual content: Morris, Huang, Kelly, Slovin, Stephenson, Delacruz, Curley, Schwartz, Scher.
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Platinum Priority – Editorial

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Testosterone Therapy in Castrate-Resistant Prostate Cancer: A Possible New Approach

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Manipulation of patients' androgen status pervades so much of the management of prostate cancer (PCa). It commences with neoadjuvant androgen deprivation therapy (ADT) in combination with radiation therapy for intermediate-risk and high-risk organ-confined disease and extends to various modulations of ADT in patients with nonlocalised and metastatic disease. Permutations include continuous and intermittent monotherapy as well as combined androgen blockade for hormone-responsive cancer, with both the addition and subtraction of single therapeutic agents for short-term responses in castrate-resistant PCa (CRPC).

Although initial response to ADT is excellent (>90%), these therapies inevitably fail with the emergence of CRPC. Extensive preclinical and clinical data indicate that the androgen receptor (AR) signalling pathway is not only present but continues to mediate androgen signalling after failure of androgen agonist therapy, despite castrate levels of circulating androgens [1]. AR overexpression, amplification, mutation, and altered coregulator interactions may sensitise the AR to lower levels of ligand, thereby contributing to failure of hormonal therapies. It has been documented recently that intratumoural androgen levels in CRPC are sufficient to stimulate tumour growth [2], indicating that local synthesis of androgens is another mechanism for maintaining AR signalling in the castrate environment. The clinical importance of these findings is highlighted by the recent reports of clinical efficacy of abiraterone acetate, an irreversible inhibitor of 17α-hydroxylase/C17,20 lyase that blocks androgen synthesis in patients with advanced prostate cancer [3].

Thus, in men with CRPC, administration of testosterone seems counterintuitive. In this issue of the journal, however, Morris et al [4] from Memorial Sloan-Kettering Cancer Centre report a phase 1 trial of high-dose exogenous testosterone in patients with castrate-resistant metastatic PCa (CRMPC). Their research is based on preclinical studies of both androgen-independent cell lines [5] and findings in an animal model [6]. Consistent with reports of the safety of exogenous androgen priming to enhance chemotherapeutic efficacy in advanced PCa [7], Morris et al's trial demonstrates that administration of exogenous testosterone to men with CRMPC is safe, provided that very careful monitoring is employed.

Following submission of Morris et al's manuscript to the journal [4], an electronic publication of another study by Szmulewitz et al [8] from the University of Chicago has become available. Their participants, who were at an earlier phase of castrate resistance than those enrolled into Morris et al's study, also used topically administered testosterone. Both studies were designed to assess the safety of the exogenous testosterone administration strategy. Only 1 of 15 patients from Szmulewitz et al's cohorts was withdrawn due to grade 4 cardiac toxicity; the Morris et al trial withdrew one man who had a prior history of epidural disease and developed spinal compression but without neurological symptoms. Because there was an indication of a tumour effect in both studies (with a fall in serum

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prostate-specific antigen in 7 of 12 patients in the Morris et al trial and in 3 of 15 patients [up to 43%] in the Szmulewitz et al trial), these findings pave the way for further studies to examine potential therapeutic benefits from exogenous testosterone therapy in selected CRPC patients.

A notable finding from Morris et al's manuscript is that despite administering three times the usual replacement dose of testosterone, serum levels did not, on average, exceed normal levels [4]. Szmulewitz et al experienced similar findings [8]. This may partially explain the fact that none of the 12 patients in Morris et al's study exhibited an objective response. As pointed out by these authors, PCa growth is stimulated by lower doses of androgens than those that result in growth repression [5]. Thus, while a failure to reach supraphysiological testosterone serum levels may have adversely affected tumour responses in both of these trials, it may have inadvertently served to test the prime objective of safety. Indeed, particularly in Morris et al's report, the oncological therapeutic effect is very difficult to evaluate, since patients were heterogeneous because of different pretrial progression rates (not detailed). Five of 12 patients progressed through previous taxane chemotherapy in addition to different treatment and monitoring regimens pursued for the three cohorts.

Morris et al provide a careful analysis of these and other confounding limitations in their manuscript, with a 5α-reductase inhibitor being proposed as a possible method for bolstering serum testosterone levels. Another alternative would be to deliver testosterone parenterally by intramuscular injections. The most easily available preparations, however, are depot, which provide supraphysiological doses for >14 d, but unlike transdermal daily dosing, depot dosing cannot be *turned off* if a patient encounters testosterone-driven clinical symptomatic progression. This concern could be minimised by only treating patients with no radiographic evidence of disease, and it would address the question of whether pulsed supraphysiological levels are more cytotoxic than continuously released replacement testosterone with the transdermal approach. Of necessity, such an evaluation would need to be done in a formal clinical trial with structured safeguards in place.

Morris et al also suggest strategies to identify patients prior to therapy who may be more likely to respond, so that therapy might be tailored [4]. One proposition, based on the assumption that responders will be those with upregulation of the AR, is the use of fluorinated dihydrotestosterone positron emission tomography tracers to image and to identify patients with upregulation of the AR in CRPC. A further strategy is evaluation of AR gene amplification in circulating CRPC cells, since approximately 40% of patients with progressive CRPC have AR amplification in their circulating tumour cells [9,10].

Clearly, further analyses of perversions of AR signalling in CRPC needs to be undertaken to identify those patients who will benefit from high-dose testosterone therapy and to circumvent the need for a trial-and-error approach to identify responders. Thus, an integrated molecular and clinical research collaboration is required to maximise the potential of this avenue of AR-targeted therapy before translation is recommended to the clinic as a routine treatment.

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