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Prostate Cancer

A Randomized Phase 1 Study of Testosterone Replacement for Patients with Low-Risk Castration-Resistant Prostate Cancer

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Article info

Article history:
Accepted February 16, 2009
Published online ahead of print on February 27, 2009

Keywords:
Prostate cancer
Castrate resistant
Androgens
Hormonal therapy
Testosterone

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Abstract

Background: Even in castration-resistant prostate cancer (CRPC), the androgen pathway remains biologically relevant. In preclinical models, androgen therapy for CRPC leads to growth arrest, apoptosis, and tumor shrinkage.
Objective: This study sought to determine the toxicity and feasibility of a testosterone therapy in early CRPC.
Design, setting, and participants: Prostate cancer patients with progressive disease following androgen ablation, antiandrogen therapy, and withdrawal and no to minimal metastatic disease who were followed at the University of Chicago were randomized to treatment with three doses of transdermal testosterone.
Intervention: Patients were treated with transdermal testosterone at 2.5, 5.0, or 7.5 mg/day.
Measurements: Toxicity, prostate-specific antigen (PSA), imaging, quality of life (QoL), and strength were monitored. Treatment was discontinued for significant toxicity, clinical progression, or a 3-fold increase in PSA.
Results and limitations: Fifteen men with a median age of 73 yr (range: 62–92) and a median PSA of 11.1 ng/ml (range: 5.2–63.6) were treated. Testosterone increased from castrate to median concentrations of 305 ng/dl, 308 ng/dl, and 297 ng/dl for dosages of 2.5 mg/day ($n = 4$), 5.0 mg/day ($n = 5$), and 7.5 mg/day ($n = 5$), respectively. One patient was taken off of the study at 53 wk due to grade 4 cardiac toxicity. There were no other grade 3 or 4 toxicities related to the study medication, and the grade 2 toxicities were minimal. Only one patient experienced symptomatic progression, and three (20%) patients demonstrated a decrease in PSA (largest was 43%). Median time to progression was 9 wk (range: 2–96), with no detectable difference in the three dose cohorts. There was no significant improvement in QoL, and there was a borderline statistically significant improvement in hand-grip strength with treatment. The study was limited by sample size, single arm, and variability of baseline patient characteristics.
Conclusions: Testosterone is a feasible and reasonably well-tolerated therapy for men with early CRPC. A larger, randomized trial is under way to further characterize efficacy and impact on QoL measures.

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1. Introduction

Since the seminal work by Huggins and Hodges in the 1940s, it has been well known that prostate cancer (PCa) is driven by androgens and can be treated with androgen ablation [1]. As such, medical or surgical castration aimed at lowering systemic testosterone levels is the mainstay for initial management of systemic PCa [2]. Although typically effective initially, hormone responsiveness is finite in most cases and patients typically fail first-line androgen deprivation within 2–3 yr, progressing to castration-resistant prostate cancer (CRPC). The only therapy for CRPC that has demonstrated a clear survival benefit is docetaxel [3]. Nonetheless, there is significant controversy as to whether this potentially toxic therapy should be administered to the growing number of patients with early CRPC characterized by rising prostate-specific antigen (PSA) without radiologic evidence of metastases. Furthermore, androgen ablation is associated with significant side effects and diminished overall quality of life (QoL) [4].

The mechanisms for development of CRPC have been extensively investigated. Most important, upregulation of androgen receptor (AR) expression has been linked to progression from hormones sensitive to CRPC under selective pressure from androgen ablation [5]. It is postulated that this amplification can make PCa more sensitive to extremely low levels of circulating or intratumoral androgens and, in some instances, can lead to antiandrogens acting paradoxically as AR agonists [6]. Interestingly, this AR upregulation may lead to recapitulation of normal prostate epithelial cell growth arrest following androgen exposure [7]. Moreover, several investigators have demonstrated that certain androgen-insensitive human PCa cell lines adapted to androgen deprivation are inhibited by physiologic levels of androgen both in vitro and in vivo [8,9]. Additionally, there have been reports of PCa patients responding to exogenous testosterone; in a retrospective analysis of 52 patients with metastatic PCa treated with testosterone, a small subset (13%) achieved symptomatic benefit [10,11]. Theoretically, intermittent androgen deprivation therapy (IADT) could be used to assess the value of androgens in early castration-resistant disease, but this is complicated by the fact that most patients receiving IADT are not truly castration resistant and by the highly variable rate and extent of testosterone recovery after cessation of luteinizing hormone-releasing hormone agonist therapy. Clinical evaluation of the hypothesis raised by preclinical data that androgen therapy of early CRPC may be growth inhibitory is thus indicated.

Despite the theoretical appeal of this concept, especially with regard to amelioration of androgen deprivation toxicities as well as potential delay of other toxic therapies, androgen replacement in prostate cancer is highly controversial. Specifically, testosterone therapy has the potential to accelerate disease progression, and several trials in more advanced disease have shown that some patients will develop serious and even fatal tumor flair [11,12]. The advent of transdermal testosterone products with pharmacologic effects that can be terminated rapidly in comparison with older intramuscular preparations, and the identification of a patient cohort with early CRPC who would be at lower clinical risk if exogenous testosterone were to accelerate the disease process provide the opportunity to reevaluate the safety of testosterone therapy in this disease state. Such an evaluation in a small cohort of patients is prudent prior to embarking on larger randomized trials evaluating the antitumor effect of testosterone in CRPC.

2. Methods

2.1. Patient eligibility

Eligible patients were men $\geq$18 yr with Eastern Cooperative Oncology Group (ECOG) performance status of $\leq$2 and PCa displaying evidence of castration resistance (rising PSAs after antiandrogen and antiandrogen withdrawal in the setting of castrate testosterone levels), with a minimum absolute PSA value of 3.0 ng/ml. At enrollment, there could be no evidence of visceral metastasis and no more than minimal bone metastases (bone scan index of $\leq$1.4%) [13]. Previous cytotoxic or radionuclide therapy was prohibited. All patients provided written informed consent and were informed of possible risks with this therapy, including the potential for disease acceleration. The clinical trial was approved by the institutional review board of the University of Chicago Medical Center.

2.2. Treatment plan

Castration therapy was continued throughout the study to ensure that systemic testosterone levels were solely influenced by exogenous testosterone administration. Patients were treated with transdermal testosterone patches and were randomized to dosages of 2.5 mg/day, 5.0 mg/day, or 7.5 mg/day. Testosterone patches were used based on short half-life in comparison with intramuscular injections, the only other available formulation at the time of study initiation, to allow for rapid discontinuation of the study drug in case of toxicity [14]. The dosages were chosen based on pharmacokinetic data from hypogonadal men [15]. Triamcinolone acetatonide cream (0.1%) was provided with the testosterone patches to decrease skin irritation.

2.3. Patient monitoring and response evaluation

All patients had baseline laboratory testing, including hormone levels, PSA, basic chemistry, liver function, and blood counts, which were repeated at regular intervals. Imaging studies (computed tomography scans of chest/abdomen/pelvis, bone scan) were performed within 4 wk of study initiation and were repeated every 8 wk. Patients underwent clinical examination with toxicity evaluation every 2–4 wk. All adverse events were graded according to the revised US National Cancer Institute (NCI) Common Toxicity Criteria v.3.0.

Patients were continued on the study until disease progression, either by PSA or imaging; unacceptable adverse events; or patient withdrawal of consent. Patients could also be taken off of the study at the physician's discretion for clinical progression of disease. Because androgen was expected to increase PSA levels, even in the absence of any effect on tumor burden, a study-specific definition of PSA progression as an increase in level to three times the nadir PSA was used. All other PSA end points were defined per standard criteria [16]. If patients developed unequivocal new lesions on imaging, they were considered to have progressive disease and were taken off of the study.

Additionally, QoL and strength were monitored throughout the study. QoL measures used included the University of California Los

Angeles (UCLA) Prostate Cancer Index and the Rand SF-36 survey [17,18]. Muscle strength was tested using hand-grip strength evaluation [19].

2.4. Statistical analysis

Subjects were randomly assigned to the three dosing levels of Androderm in a 1:1:1 fashion. A total of 18 patients (6 per dose group) were to be entered into the trial. The primary objective was to determine the safety of testosterone treatment at these dosing levels. A dose level was considered to have acceptable safety if one or no patient experienced a dose limiting toxicity, defined as NCI Common Terminology Criteria for Adverse Events grade $\geq$3 toxicity, or the inability to administer the study medication due to toxicity for >7 consecutive days. The first of two secondary aims was to determine the effect of transdermal testosterone patches on serum testosterone levels. Based on a coefficient of variation in measured testosterone of 45%, there was a 94% power to detect a hypothesized testosterone level of 300 ng/dl in the 2.5-mg group, compared with 600 ng/dl in the 7.5-mg group, assuming standard deviations of 150 ng/dl (1-sided, $\alpha = 0.05$). The effects of transdermal testosterone on QoL, sexual function, and muscle strength were tabulated, and changes from baseline to treatment were analyzed using a paired *t* test. Additionally, changes from baseline were compared between dose groups using a linear regression analysis, and the effects of dose on time to disease progression were assessed using Cox regression analysis.

3. Results

Because another study reported testosterone replacement to be safe [20], 16 of the planned 18 patients consented to participate between August 2004 and March 2007. One patient withdrew consent prior to initiating treatment and was not included in the analysis, leaving 15 patients randomized to the three treatment arms (2.5 mg/day, $n = 4$; 5.0 mg/day, $n = 5$; 7.5 mg/day, $n = 6$) (Table 1). The median patient age was 73 yr (range: 61–92), and the average number of prior hormonal therapies was 2.8. The median PSA at enrollment was 11.1 ng/ml (5.3–63.6), and 6 of 15 patients had evidence of bone metastases prior to enrollment. On treatment, the serum testosterone increased from castrate levels (<30 ng/dl) to median concentrations of 291 ng/dl (94–468), 308 ng/dl (164–824), and 271 ng/dl (191–599) for dosages of 2.5 mg/day, 5.0 mg/day, and 7.5 mg/day, respectively (Fig. 1). One patient in the 7.5-mg/day group had no available posttreatment level. Using a linear regression model, there was no significant dose response ($R^2 = 0.018$, $p = 0.65$). Despite slight variations in sex hormone binding globulin (SHBG) and albumin, calculation of free testosterone levels generated similar results ($R^2 = 0.117$, $p = 0.20$).

Overall, testosterone therapy was well tolerated at all doses tested. There was one grade 4 cardiac toxicity, a myocardial infarction in the 7.5-mg/day group at week 53, that was deemed possibly related to study medication. There were no other grade 3 or 4 toxicities reported throughout the trial. The grade 2 toxicities were minimal and included hot flashes ($n = 2$), hyperglycemia ($n = 2$), skin rash ($n = 1$), and hypertension ($n = 1$). None of these toxicities required medical intervention or dose adjustment.

The majority of patients were taken off of the study due to progression of disease by either PSA ($n = 9$) criteria or for both imaging and PSA ($n = 3$). In addition to the patient who was taken off the study due to his cardiac event, one patient was taken off of the study due to insurance issues precluding follow-up and one patient was taken off of the study due to a decline in performance status, possibly due to symptomatic progression of disease. The median time to progression (TTP) was 9 wk (range: 2–96). Per dosing level, the median TTPs were 10 wk (3–14), 4 wk (2–9), and 45 wk (2–96; two censored at 30 wk and 53 wk) for dosages of 2.5 mg/day, 5.0 mg/day, and 7.5 mg/day, respectively (Fig. 2). There was no statistically significant relationship between dose or testosterone level and TTP using a Cox proportional hazards model ($p = 0.072$ and $p = 0.14$, respectively). Baseline PSA and presence or absence of bone metastases were not associated with TTP ($p = 0.59$ and $p = 0.13$, respectively).

Three patients demonstrated a decrease in PSA while on treatment (decline of 16%, 20%, 43%), with the largest decrease being from 41.3 ng/ml to 23.4 ng/ml. Of these, one had an initial PSA increase of 69% (8.5 ng/ml to 12.3 ng/ml),

Table 1 – Baseline characteristics

	2.5 mg/d ($n = 4$)	5.0 mg/d ($n = 5$)	7.5 mg/d ($n = 6$)	Total† ($n = 15$)
Median age, yr (range)	66.5 (61–81)	81 (69–81)	72.5 (62–92)	73 (61–92)
Median PSA, ng/ml (range)	8.4 (5.2–23.6)	14.3 (7.0–63.6)	13.2 (5.3–46.4)	17.7 (5.3–63.6)
Mean prior hormonal therapies* (range)	2.75 (2–3)	3.0 (2–3)	3.0 (2–4)	2.8 (2–4)
Bicalutamide	3	4	5	12
Flutamide	1	0	2	3
Nilutamide	1	2	1	4
Ketoconazole	1	1	2	4
Finasteride**	1	1	1	3
Diethylsilbestrol	0	1	0	1
Baseline testosterone, nd/dl (range)	19 (<10–22)	16 (<10–23)	17 (<10–20)	18 (<10–23)
No. with bone metastases	3	3	0	6

PSA = prostate-specific antigen.
† Of 18 planned patients, 16 consented (1 withdrew consent prior to therapy) when study closed due to presentation of similarly designed phase 1 trial showing safety and opening of phase 2 trial.
* Including castration (not listed separately and common to all patients); not counting antiandrogen withdrawal.
** In combination with an antiandrogen.

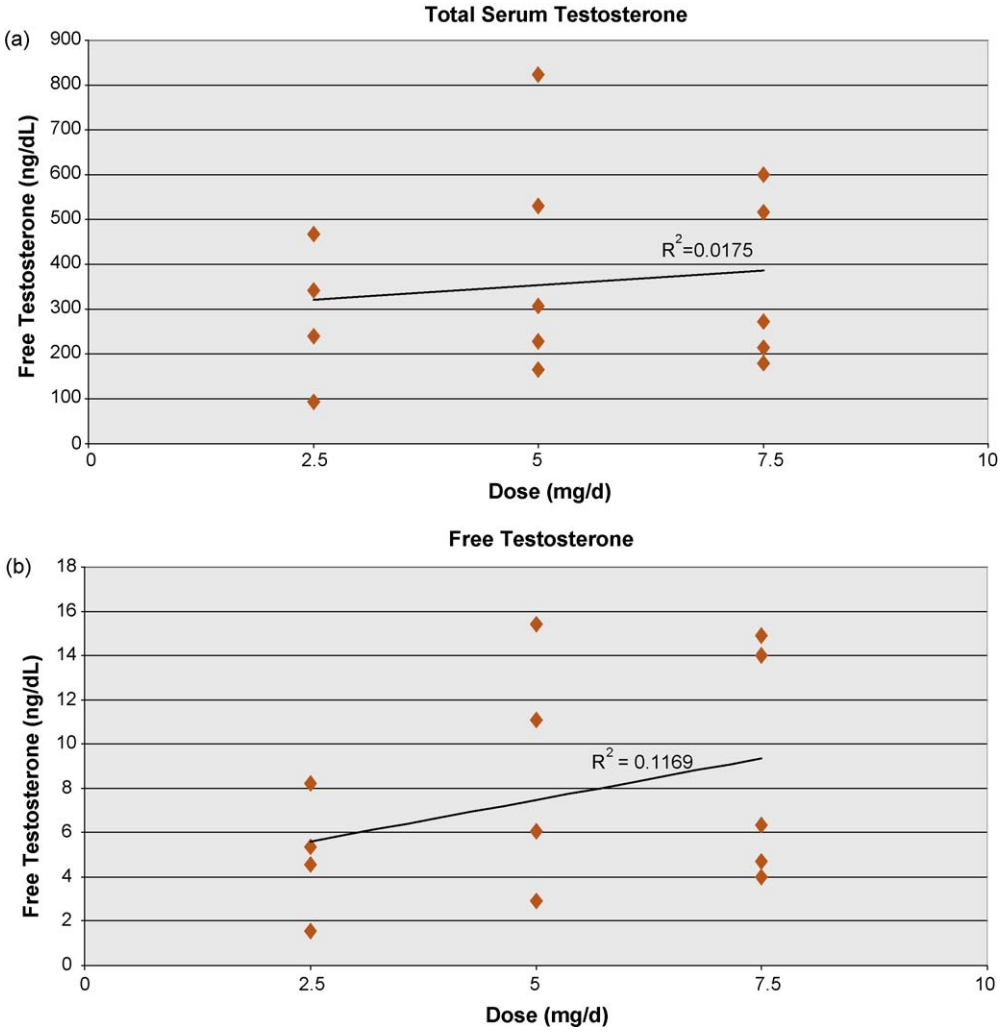

Fig. 1 – Testosterone levels on treatment by treatment group. Total (a) and free (b) testosterone levels for all patients on the study who had at least one posttreatment level. Using a linear regression model, there was no significant dose response for either total ($p = 0.65$) or free ($p = 0.20$) testosterone on treatment.

followed by a decrease of 55% (12.3 ng/ml to 6.75 ng/ml). Additionally, seven patients without a PSA decline remained on treatment for at least 8 wk, with the longest duration of therapy in this group being 53 wk. One of these patients had an initial rise in PSA of 68% (from 10.6 ng/ml to 15.5 ng/ml), followed by at 44% decline, after which the PSA fluctuated from 12 ng/ml to 18 ng/ml for another 47 wk (Fig. 3). In 12 of the 14 patients with available follow-up PSA measurements, the PSA fell after cessation of study medication, with a median percent decline of 47% (range: 14–71%). Likewise, testosterone levels returned to castrate levels in all 13 patients with available posttherapy levels. Only one patient returned to his pretreatment PSA after cessation of study medication.

QoL was measured along with muscle strength throughout the study. As shown in Fig. 4, when all patients treated are analyzed together, the measures of QoL varied from baseline to first assessment posttreatment. There were no significant changes seen in role limitations due to emotional health ($p = 0.26$), social functioning ($p = 0.17$), mental

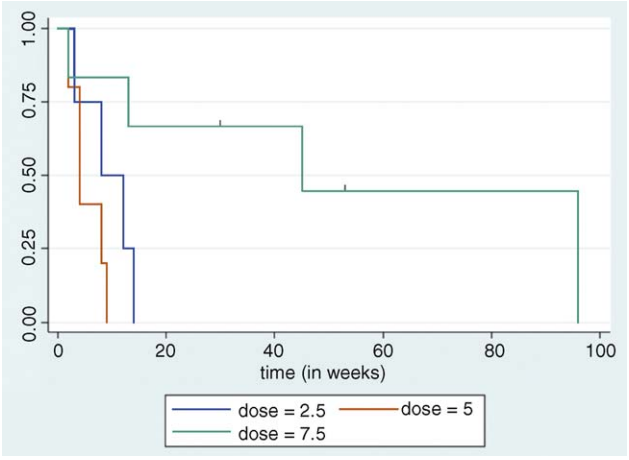

Fig. 2 – Time to progression (TTP) by treatment group (milligrams per day). Kaplan-Meier curve showing TTP on treatment for each treatment dose group. Using a Cox proportional hazards model, the relationship between dose and TTP was not statistically significant ($p = 0.072$).

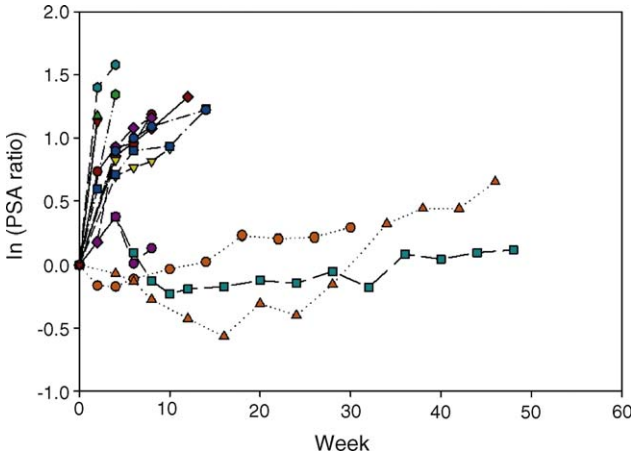

Fig. 3 – Natural log of prostate-specific antigen (PSA) changes over time on the study, with each line representing a patient enrolled in the trial.

health ($p = 0.14$), general health ($p = 0.31$), physical functioning ($p = 0.56$), bowel bother ($p = 0.10$), urinary bother ($p = 0.17$), sexual function ($p = 0.11$), urinary function ($p = 0.33$), vitality ($p = 0.55$), bodily pain ($p = 0.71$), bowel function ($p = 0.19$), or sexual bother ($p = 0.35$). There was a statistically significant decline in role limitations due to physical health (mean: −18.25%; 95% confidence interval [CI]: −32.3–−4.3; $p = 0.015$). Only five patients had grip strength measured pre- and posttreatment. The mean percent change in grip strength was 3.3% (range: 0.7–6%). While this reached statistical significance ($p = 0.042$), the result could be biased due to missing data for 10 of the patients.

4. Discussion

This study represents the second trial of testosterone treatment for castration-resistant PCa in the current era of PSA monitoring and improved imaging modalities, the other study being the phase I trial by Morris et al [21]. Men with

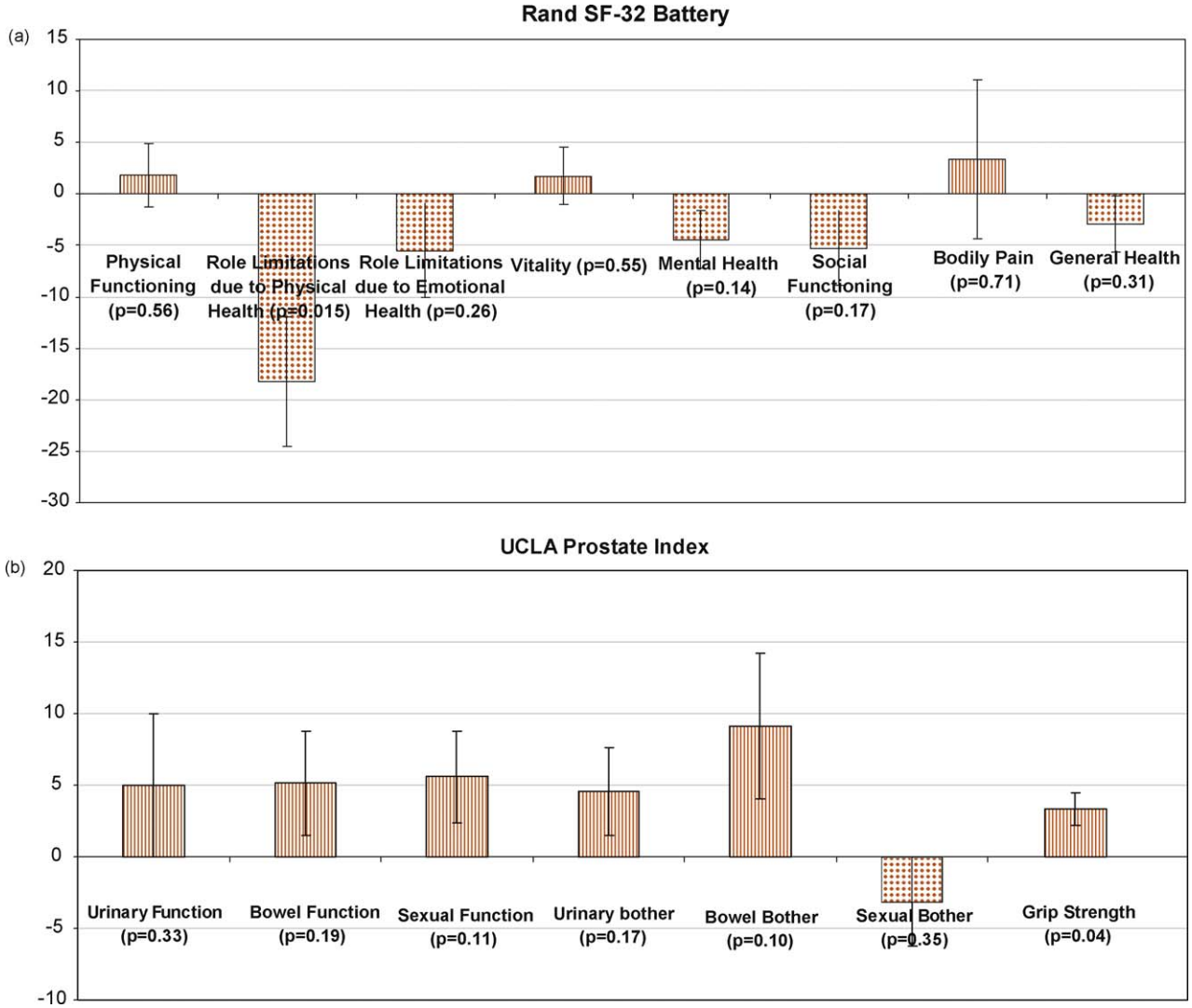

Fig. 4 – Quality of life (QoL) using (a) the Rand SF-32 survey and (b) the University of California Los Angeles (UCLA) Prostate Cancer Index. Graphs depict cumulative mean change in QoL from baseline to first assessment 2–4 wk on treatment with standard error bars.

early, low-burden, castration-resistant disease were treated with three different doses of transdermal testosterone, with the primary objective of determining the toxicity and feasibility of testosterone therapy in this patient population. As described, the therapy was very well tolerated. There was one grade 4 cardiac event possibly related to the study drug and one possible symptomatic disease progression. Cardiovascular disease is the most common cause of death in men with PCa who do not die of the cancer itself. Furthermore, there is a growing body of evidence that androgen deprivation therapy is associated with increased cardiovascular events [22]. As all of our patients were on long-term androgen suppression, it is possible that androgen deprivation, along with the common cardiovascular risks associated with elderly men, contributed to the cause of this patient's myocardial infarction.

This trial used three escalating doses of transdermal testosterone with the hypothesis that there would be a dose response effect in measured serum testosterone levels. Based on pharmacokinetic studies of transdermal testosterone patches, it is known that measured serum testosterone levels can vary greatly depending on time of patch application, time of blood draw, and metabolism. Peak levels are typically achieved 4–6 h after application, after which testosterone levels fall steadily [14]. Although patients were instructed to apply the patch at night, variations in timing of patch application and blood draw could have accounted for the lack of dose response of testosterone levels seen.

There was no statistically significant correlation of measured testosterone level with TTP, but this is not unexpected for such a small trial in which TTP was dominated by prognostic disease characteristics, even if the underlying hypothesis of testosterone being growth inhibitory in certain patients was true. Interestingly, the relationship between dose and TTP approached significance ($p = 0.072$) with delayed progression in the high-dose group, but this should be interpreted cautiously, again due to the small sample size. These results are further limited by the variability in prior hormonal therapy, which may affect outcomes of a hormonally based treatment, and by bone metastasis status at baseline (see Table 1), although neither variable was associated with changes in TTP when analyzed separately. Furthermore, the study population was primarily an older cohort, with 6 of 15 patients $\geq$80 yr old, and both the TTP and toxicity profiles may be different in younger men.

In support of the underlying hypothesis that testosterone may have growth inhibitory effects in patients with castration-resistant disease, there were three men whose PSA declined and several others who had apparent disease stability while on the study, with four patients staying on the study for >6 mo. These results are similar to a preliminary report of a phase 1 trial of testosterone therapy in castration-resistant metastatic PCa from Memorial Sloan-Kettering Cancer Center [20]. This observation is particularly interesting because PSA is an androgen-regulated gene and would thus be expected to rise in response to increased testosterone levels. Nevertheless, PSA changes in the context of an uncontrolled trial must be interpreted with caution and cannot be definitively linked to patient benefit.

There was no statistically significant change in QoL noted with testosterone treatment in this trial, except for a slight decline in the physical role limitations scale. Whether this is due to the small study size, the insensitivity of the measurement instruments, or lack of testosterone effect in patients with long-term prior androgen ablation cannot be determined at this time. It is expected that QoL measures would decline in an untreated control group with progressive PCa on continuous androgen deprivation. A controlled study will be necessary to determine whether testosterone could minimize or ameliorate such a decline. Grip strength did improve, but this was assessed in only five of the men and a bias due to missing data cannot be ruled out. Furthermore, it will be interesting to note any changes in these measures in patients who remain on testosterone therapy for longer time periods.

5. Conclusions

This phase 1 trial of testosterone treatment in low-risk CRPC demonstrates that the therapy is well tolerated and safe. A larger, placebo-controlled, randomized study of testosterone in CRPC patients without evidence of metastases has been initiated to determine the effects of testosterone on disease progression and QoL.

Author contributions: Russell Szmulewitz 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: Stadler, Mohile, Posadas.
Acquisition of data: Manchen, Szmulewitz.
Analysis and interpretation of data: Szmulewitz, Stadler.
Drafting of the manuscript: Szmulewitz, Stadler.
Critical revision of the manuscript for important intellectual content: Szmulewitz, Mohile, Posadas, Stadler.
Statistical analysis: Karrison, Kunnavakkam.
Obtaining funding: Stadler.
Administrative, technical, or material support: Manchen.
Supervision: None.
Other (specify): None.

Financial disclosures: I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/ affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: The University of Chicago had a role in the design and conduct of the study, in the management of the data, and in the review and approval of the manuscript.

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Editorial Comment on: A Randomized Phase 1 Study of Testosterone Replacement for Patients with Low-Risk Castration-Resistant Prostate Cancer

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Androgen dependence of prostate cancer (PCa) cells was set in a new light with the recent findings on androgen receptor alterations and expression as well as local testosterone production in PCa [1]. The role of estrogen receptors α and β in PCa progression further increased complexity of the mechanisms [2].

It is clearly novel and counterintuitive to use testosterone in the management of men with seemingly hormone-independent PCa, although randomization in a phase 1 trial is somewhat unusual [1]. Intermittent androgen ablation studies showed an improved quality of life (QoL) during off-treatment intervals, supporting the notion that androgen resuppletion may improve QoL in these men. It seems evident that within physiologic levels, testosterone suppletion is not associated with an increased risk of PCa [3], yet in men with androgen-independent PCa, based on above-mentioned results, one may assume a higher sensitivity of cells to even lower levels of androgens. Careful titration of androgens in these men is essential, and I would personally prefer histologic analysis of data such as androgen receptor levels or mutations to possibly predict the tumor-promoting effects of testosterone prior to treatment initiation. These data should be made available in any future study plan.

The fact that one man experienced a myocardial infarction urges us to be extremely careful with the suggested use of testosterone in these patients. It cannot be ignored that (local) aromatase activity converting testosterone into estrogens plays a role in the prostate-specific antigen effects observed in these men, and it is far from clear whether these increased estrogen levels are, by definition, beneficial [4,5]. More than ever, these data [1] should be interpreted with great care.

Thorough evaluation of tumor characteristics and response criteria are required before we become tempted to treat hormone-refractory PCa patients with androgens. Then again, new insight into the mechanisms of hormone-refractory PCa is desperately needed, and studies like this one will help us to further it.

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DOI: 10.1016/j.eururo.2009.02.023

DOI of original article: 10.1016/j.eururo.2009.02.022