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Strategies for Testosterone Therapy in Men with Metastatic Prostate Cancer in Clinical Practice: Introducing Modified Bipolar Androgen Therapy

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Abstract

Purpose: To investigate prostate-specific antigen (PSA) and clinical responses to a variety of treatment strategies involving testosterone therapy (TTh) in men with metastatic prostate cancer (mPCa).

Materials and Methods: Case records were reviewed for three men with advanced PCa treated with TTh for improved quality of life. Two had bone metastases and nephrostomies at baseline. The third had biochemical recurrence, and continued TTh after developing bone metastases. All rejected androgen deprivation therapy, desired improved quality of life with TTh, and accepted the risk of rapid PCa progression and death.

Results: All men experienced substantial symptomatic and health benefits during TTh, including improved strength, vigor, and sexuality. Two reversed substantial weight loss. A 94-year-old man with baseline PSA of 546 ng/mL survived 11 months with continuous TTh, with last PSA of 2493 ng/mL. Two men in their 60s received some form of TTh for 3.5 and 8 years, respectively, and are still alive. None experienced sudden major adverse events. Continuous TTh resulted in progressive rise in PSA to high values. The combination of TTh and enzalutamide provided moderate protection against weakness and fatigue with PSA <10ng/mL for 6 months. PSA values fluctuated from <1.0 to >100 ng/mL within 1–2 months depending on recent androgen status. The most promising strategy appears to be a modified bipolar androgen therapy consisting of repeating cycles of 8 weeks of high-dose TTh followed by 4 weeks of enzalutamide, allowing for prolonged periods of vigor while maintaining PSA control.

Conclusions: These pilot results support explorations of new hormonal strategies involving TTh for men with mPCa.

Keywords: metastatic; modified bipolar androgen therapy; prostate cancer; testosterone; testosterone therapy; androgens

Introduction

Over the last two decades there has been a major re-evaluation of the biology of androgens and prostate cancer (PCa).[1] Whereas it has been long believed that offering testosterone therapy (TTh) to a man with PCa was like "pouring gasoline on a fire,"[2] numerous case series and observational studies have failed to demonstrate increased risk of disease recurrence or progression with TTh after radical prostatectomy,[3] radiation therapy,[4] and even in men on active surveillance.[5,6] This lack of progression may be attributed to saturation, namely, the finite ability of androgens to stimulate PCa growth, with a maximum achieved at a relatively low serum testosterone concentration of ~250 ng/mL.[7] It is now commonplace for health care providers to offer TTh to men after definitive treatment for localized PCa at low risk for recurrence. In 2016, Ory et al. reported low recurrence and progression rates in men with PCa

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who received TTh after surgery, radiation, or on active surveillance, concluding, "…our study supports the hypothesis that testosterone therapy may be oncologically safe in hypogonadal men after definitive treatment or in those on active surveillance for prostate cancer."[8]

However, there is extremely limited clinical experience with TTh among men with metastatic PCa (mPCa), due to the concern that any rise in serum T, even transiently as seen with testosterone flare with luteinizing hormone-releasing hormone agonists, may cause rapid disease progression, with associated morbidity and mortality.[9] Standard treatment for many decades for men with metastatic PCa is androgen deprivation therapy (ADT),[10] with the addition of newer agents as needed that are even more effective at lowering serum T or blocking its actions.[11]

Yet there is evidence to suggest TTh may not be as dangerous as previously believed. *In vitro* and animal experiments have shown growth suppression of androgen-sensitive PCa tumors with high androgen concentrations,[12,13] and androgens have been shown to induce reversion of androgen-sensitive phenotypes in PCa cell lines that have developed androgen insensitivity.[14] Of greatest clinical relevance, landmark studies involving serial cycling of supraphysiological and castrate levels of T within a 4-week period, called bipolar androgen therapy (BAT) in men with castrate-resistant PCa, have shown strong evidence of clinical response.[15,16] These studies suggest a possible role for TTh in men with mPCa.

Presented here are clinical and prostate-specific antigen (PSA) responses to a variety of TTh strategies in three men with mPCa. The most promising of these strategies appears to be a modified BAT (mBAT) protocol to maximize duration of TTh and its associated benefits followed by a shorter period of androgen blockade.

Materials and Methods

Medical records were reviewed for three men with mPCa treated with TTh. Two had previously undergone ADT and found it intolerable. The third repeatedly declined ADT while seeking a more natural form of treatment. All three men had extensively researched their options and understood that TTh was considered an absolute contraindication that could cause rapid morbidity and death. Extensive detailed informed consent was obtained, and all patients provided written consent. Review of these data was performed with approval by the institutional review board for Beth Israel Deaconess Medical Center.

Case 1

This 94-year-old scientist underwent prostate biopsy 2 years earlier for PSA 320 ng/mL, revealing Gleason 9. Bone scan showed diffuse metastases. He was treated with leuprolide for 6 months but discontinued treatment due to severe weakness and fatigue. At time of consultation in July 2015, he had suffered 30 lb (13.6 kg) weight loss and had bilateral nephrostomy tubes for obstruction. Bilateral small pleural effusions were present.

The patient requested TTh so that he could regain enough energy to resume exercise and correspondence with his colleagues. PSA was 546 ng/mL and testosterone was 259 ng/dL. Treatment began with injections of testosterone cypionate 200 mg IM every 2 weeks, with dosage increased to 400 mg every 2 weeks after 5 months of treatment. Results of PSA during TTh are shown in Figure 1. By 1 month, he felt improved and was exercising vigorously three times weekly, fatigue resolved, and he had resumed his correspondence. He no longer required a daily nap, and resumed his scientific work. At 3 months he had gained 10 lbs from initial weight of 108 lbs. He died 11 months after beginning TTh, after developing shortness of breath with prominent pleural effusions. Cytology of aspirated pleural effusion revealed PCa. At no time did he experience bone pain. His last documented PSA was 2493 ng/mL.

Case 2

This 65-year-old businessman was first diagnosed with Gleason 8 PCa in 2011 and had undergone treatment with two courses high-intensity focused ultrasound, external beam radiation, and sipuleucel-T. He had been treated with TTh for >10 years before this. Baseline testosterone without TTh was 134 ng/dL. PSA rose to 31 ng/mL with resumption of T injections in 2012 and became undetectable after treatment with degarelix and enzalutamide. When first seen by me in 2014, his bone scan and CT were negative. He complained of severe fatigue, lack of energy, and absent libido that caused him substantial distress. A number of strategies to improve his quality of life involving androgens were undertaken. PSA results are shown in Figure 2 for several planned strategies involving TTh. In addition, he had experimented with several short-term androgenic strategies to improve his strength, which are as follows.

Oxandrolone. The oral androgen, oxandrolone, was taken for 3 months during degarelix treatment. Workouts improved, but libido did not. Testosterone

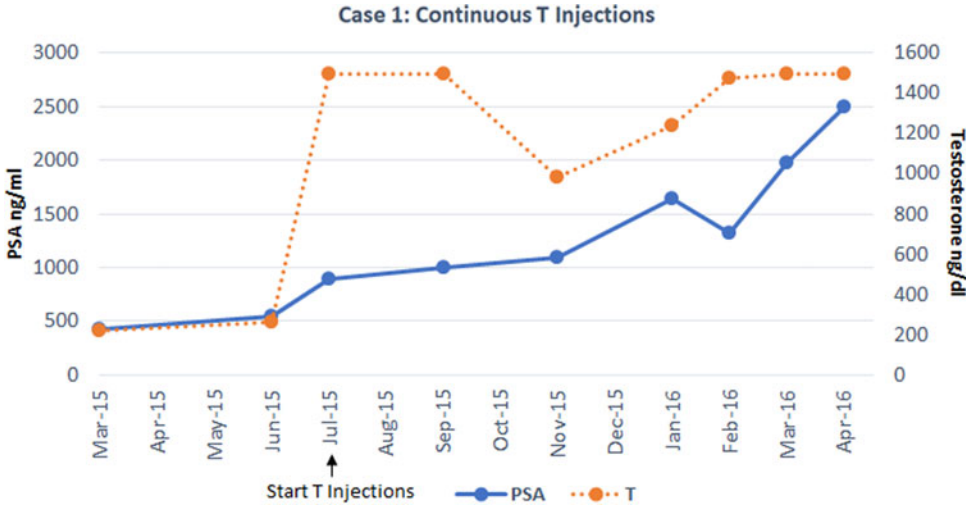

FIG. 1. PSA response to continuous T cypionate injections in a 94-year-old man with diffuse bony metastases and bilateral nephrostomy tubes. Baseline PSA was 546 ng/mL. Testosterone cypionate was administered in doses of 200 mg intramuscularly every 2 weeks. In early February 2016, dose was increased to 400 mg every 2 weeks. He died in late May 2016. Testosterone levels reported as >1500 ng/dL are represented here as 1500 ng/dL. PSA, prostate-specific antigen.

levels were 25–30 ng/dL. PSA rose from 0.03 to 0.64 ng/mL, and dropped to 0.05 ng/mL with discontinuation of oxandrolone.

Selective androgen receptor modulator. A 2-week trial of a noncommercial selective androgen receptor modulator (SARM) resulted in a PSA rise from 21 to 31 ng/mL after 2 weeks, despite a testosterone concentration of only 88 ng/dL.

Short-acting T treatments. Nasal testosterone gel (Natesto™) was applied 30–60 min before exercise. Blood tests obtained immediately before and 1 h after application revealed testosterone concentrations of 182 and 615 ng/dL, respectively. PSA was 0.66 ng/mL at baseline and 0.70 ng/mL at 1 h. No exercise benefit was noted.

Injections of short-acting testosterone propionate 25 mg three times per week provided no symptomatic benefit; however, 75 mg every 4–7 days provided transient improvement in energy and exercise tolerance for 2–3 days. After 3 months, PSA rose from 0.64 to 0.78 ng/mL.

Planned strategies. Bone scan first revealed bone metastases in April 2016. The PSA and clinical response to a number of planned TTh strategies before and after this date are shown in Figure 2, including continuous T injections, combination of TTh with enzalutamide, intermittent use of TTh during enzalutamide treatment, and BAT. Throughout, the goal of adding TTh was to diminish fatigue and weakness and allow for improved quality of life. Additional treatments since development of metastatic disease have included pembrolizumab, and a repurposed drug protocol (doxycycline, metformin). Peak PSA with TTh was 397 ng/mL. Bone marrow biopsy for evaluation of anemia in October 2019 revealed replacement of bone marrow with PCa. At last contact in April 2020, his PSA was slowly declining, with a last value of 51 ng/mL on apalutamide, abiraterone, and prednisone.

Case 3

A 61-year-old consultant was seen in December 2015, 5 years after radical prostatectomy for Gleason 9 PCa with positive lymph nodes. A right nephrostomy was in place for ureteral obstruction from adenopathy. PSA was 31 ng/mL and bone scan revealed metastatic disease in the pelvis. Total testosterone was 181 ng/dL. Symptoms included weight loss, decreased libido, poor erections, weakness, and decreased strength. He was

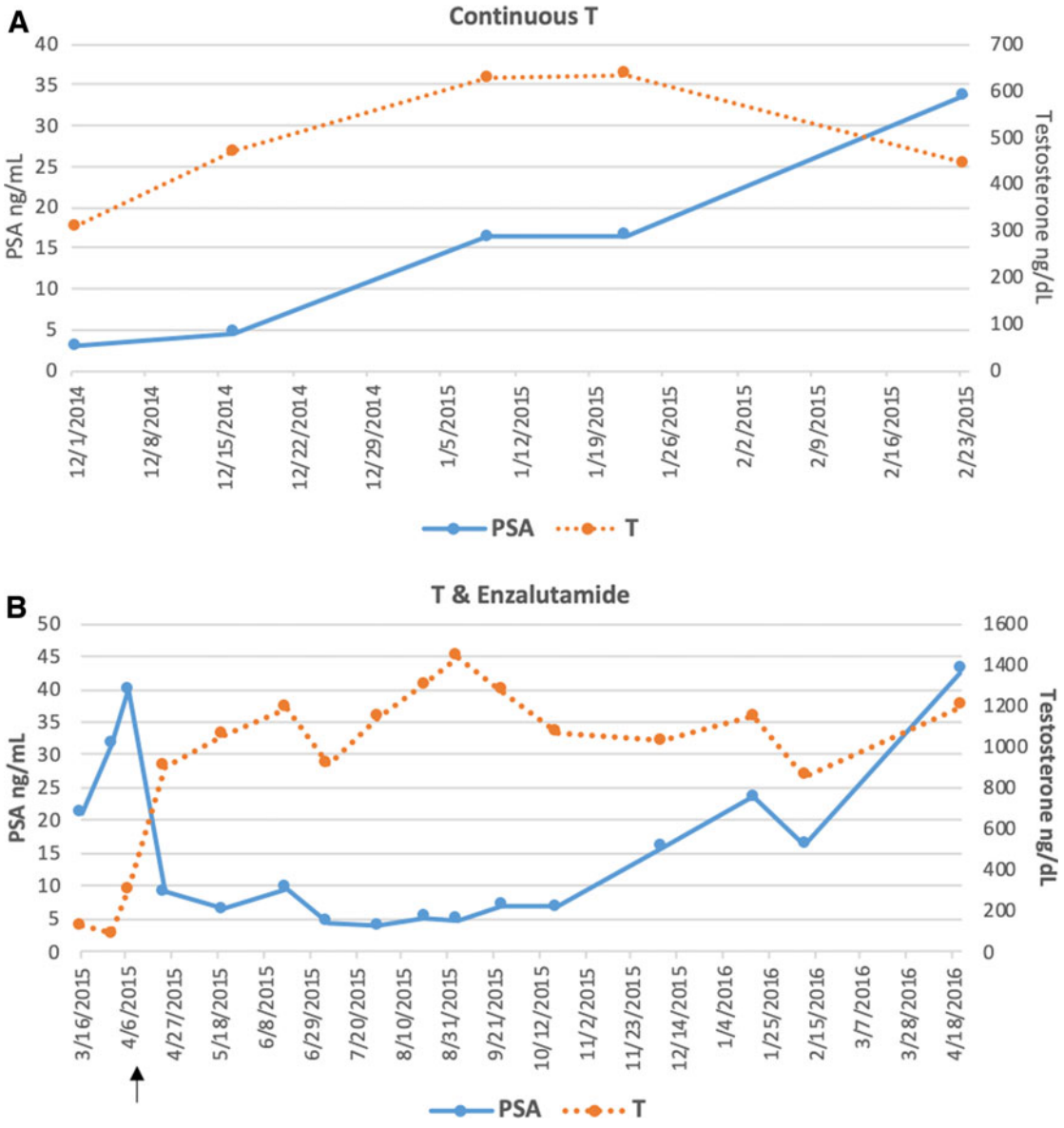

FIG. 2. PSA response to various treatment strategies involving testosterone injections in a 65-year-old man at presentation in December 2014 with biochemical recurrence after high-intensity focused ultrasound, external beam radiation, and sipuleucel-T. Initial PSA was 2.9 ng/mL. Bone metastases were first identified on April 2016. Bone marrow replacement with prostate cancer noted in October 2019. **(A)** Continuous weekly injections of T cypionate 80–120 mg intramuscularly. **(B)** Combination treatment with enzalutamide and testosterone injections. Enzalutamide was taken at 40–160 mg po daily. Testosterone cypionate was administered weekly at 120–200 mg intramuscularly. Arrow indicates beginning of combination treatment. Enzalutamide holidays and reduced doses began on October 2015, accompanied by rising PSA. **(C)** Enzalutamide with infrequent testosterone treatments. Enzalutamide 160 mg taken daily with occasional injections of testosterone cypionate, short-acting testosterone propionate, and nasal testosterone gel. Blood tests taken 2 weeks or longer after injections. **(D)** BAT. Eleven monthly injections of testosterone cypionate 400 mg intramuscularly (arrows) during treatment with leuprolide. Enzalutamide 160 mg added for final 10–14 days of each cycle beginning on May 2017, as indicated. Enzalutamide discontinued after completion of BAT cycle on October 2017, associated with rise in PSA from 12 to 59 ng/mL. BAT, bipolar androgen therapy.

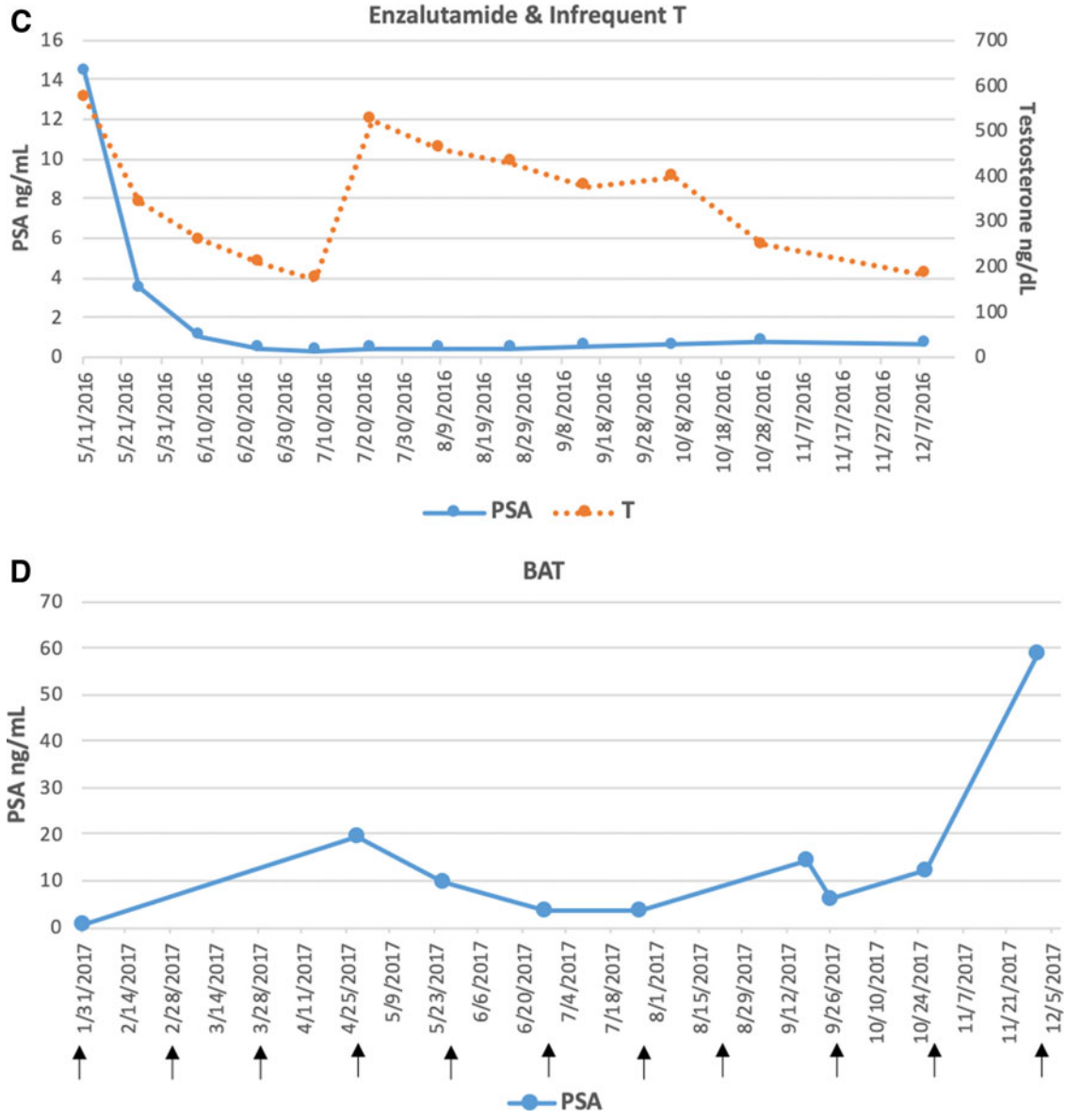

FIG. 2. (*Continued*).

5′8″ and weighed 135 lbs. He had refused ADT, and specifically requested TTh.

Treatment was initiated with injections of T cypionate 400 mg every 2 weeks. Energy, mood, and libido improved. He gained weight, strength, and resumed sexual activity. The PSA response is shown in Figure 3A. He discontinued TTh when PSA reached 185 ng/mL and bone scan revealed extension of bony disease in the pelvis. He denied bone pain. Interestingly, CT 2 months later revealed decreased size of para-aortic adenopathy from 16.7 to 9.8 mm.

In December 2016, bone scan showed a new metastatic focus at the base of the skull, and he agreed to treatment with enzalutamide 160 mg po daily. Although PSA declined to 1.0 ng/mL, he complained of severe weakness and weight loss, and again requested TTh. A mBAT program was developed in response to the patient's request to maximize the time on TTh and minimize the time on antiandrogen therapy. This consisted of testosterone cypionate injections 400 mg every 2 weeks for 8 weeks, followed by 4 weeks of enzalutamide. PSA response is shown in Figure 2B. He rapidly gained

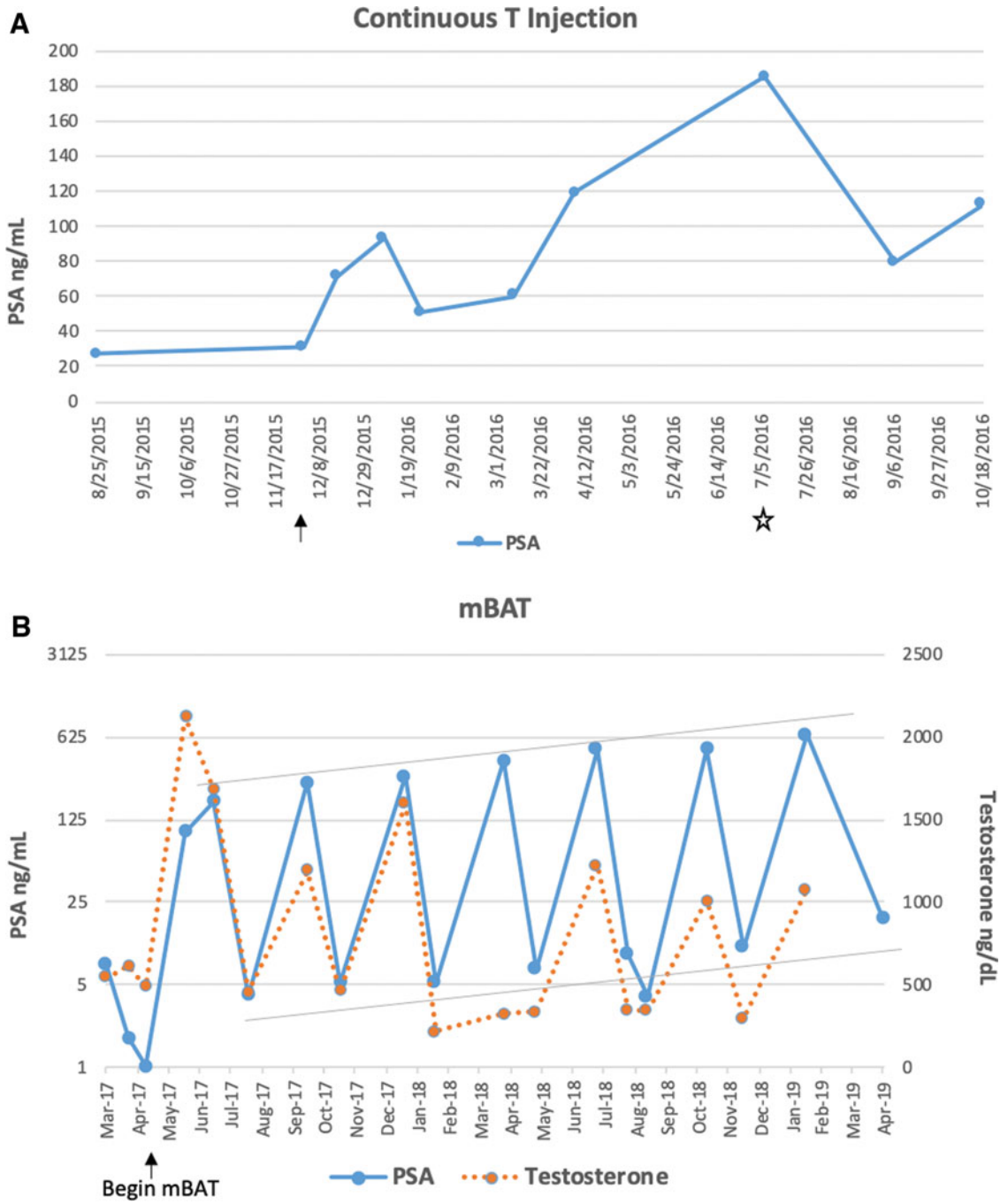

FIG. 3. PSA response to testosterone injections in a 61-year-old man with metastatic prostate cancer and nephrostomy tube, 5 years after radical prostatectomy with positive lymph nodes. PSA at presentation was 31 ng/mL. **(A)** Continuous T injections. Testosterone cypionate injections 400 mg intramuscularly were administered every 2 weeks. Note initial rise to 93 ng/mL with subsequent decline to 51–60 ng/mL for 3–4 months before rising steadily to 185 ng/mL at 7 months. Arrow indicates start of testosterone injections. Star indicates discontinuation of testosterone injections. **(B)** mBAT. Twelve-week cycles were initiated, consisting of 8 weeks of testosterone cypionate 400 mg intramuscularly every 2 weeks, followed by 4 weeks of daily enzalutamide 160 mg orally. Blood tests obtained at end of testosterone and enzalutamide periods. Arrow indicates start of mBAT. PSA shown in log scale to preserve details of PSA values at nadirs. Note upward slope of peaks and nadirs. Imaging studies showed no progression for ~2 years, until April 2019 when new lesions appeared on bone scan and mBAT was discontinued. mBAT, modified BAT.

energy, strength, muscle mass, and resumed sexual activity. PSA levels rose and fell during TTh and enzalutamide periods, respectively, reaching a highest peak of 645 ng/mL after ~2 years. Nadirs were consistently 5–10 ng/mL, gradually increasing with each cycle. Once, when the nadir PSA was 9.2 ng/mL, an additional 2 weeks of enzalutamide reduced PSA to 4.0 ng/mL, after which T injections resumed.

After 2.5 years of stable imaging studies on mBAT, progression was noted on bone scan in May 2019. He discontinued T injections. At last contact, PSA was 4.6 ng/mL in March 2020 after intermittent treatment with enzalutamide alone.

Discussion

After two decades of accumulating evidence of lack of harm with TTh in a variety of circumstances of men with nonmetastatic PCa,[1] it is longer reasonable to assume TTh is universally harmful in men with mPCa. Indeed, several reports suggest that TTh may even be associated with favorable cancer outcomes. Mathew reported stable PSA of ~1 ng/mL during 27 months of TTh in a 78-year-old man with adenopathy after radical prostatectomy.[17] In a study of 850 men who underwent radical prostatectomy, Ahlering et al. recently reported a lower biochemical recurrence rate (7.2%) among 152 men who received postoperative TTh compared with 419 proportionately matched controls who did not receive TTh (12.6%).[18]

The most intriguing evidence for a possible role for TTh in men with mPCa comes from the BAT trials involving rapidly cycling supraphysiological and castrate levels of serum T. These landmark trials demonstrated 50% or greater declines in PSA in 7 of 14 evaluable men with castrate-resistant mPCa and radiographic responses in 5 of 10 evaluable cases.[15] A subsequent trial also re-established androgen sensitivity in men with CRPC. Importantly, BAT was well tolerated despite regular excursions of serum T into the supraphysiological range.

Several immediate observations can be made from this study. First, there are men with mPCa who value quality of life over duration of life, and are willing to accept substantial risk to achieve this. Second, all experienced major benefits from TTh, including increased sense of well-being and physical activity level. Two men reversed substantial weight loss, and two experienced return of sexual desire and ability. Third, none experienced precipitous or unexpected adverse events, such as pathological fracture, spinal cord compression, pulmonary embolus, or disabling bone pain, despite TTh use for 11 months, 3.5 years, and 8 years, respectively. Fourth, there is no indication TTh shortened the lives of these men. One died at 95 years nearly a year after presenting with extensive metastatic disease, and two are still alive and active 4 and 8 years after diagnosis of metastatic disease.

Continuous TTh was associated with an immediate rise in PSA in all men, followed by a plateau period that lasted 2 weeks in one, and 3–4 months in the others, before rising again. Since PSA production is itself androgen dependent, the initial rise was consistent with the saturation model,[7] and it is proposed that the subsequent plateau reflected tumor volume at the time of initiation of TTh, with the subsequent PSA rise representing progressively greater tumor volume over time. The improved health and vigor experienced by these men during continuous TTh argues that such treatment merits formal investigation as a possible treatment option for men for whom quality of life is paramount, and particularly for end of life.

It is noteworthy that PSA rose with all versions of androgen-type therapy, including oxandrolone, and a noncommercial SARM. However, intermittent, short-term, or short-acting TTh failed to cause a rise in PSA, as long as enough time was allowed for T to decline before blood was drawn for PSA testing. Although PSA remained low throughout the period of treatment with enzalutamide combined with infrequent administration of TTh, the patient experienced the chronic bothersome fatigue and absent libido seen with standard ADT or antiandrogen therapy, except for brief periods after testosterone administration. This strategy does demonstrate that in this particular patient, there did not appear to be any lasting adverse PSA effect from occasional testosterone use; however, it was not a successful strategy for improvement in quality of life. The absence of precipitous events in this small group, coupled with eventual return of PSA to low levels here, and with BAT and mBAT, raises the possibility that episodic periods of normal or even elevated testosterone may not cause irreparable harm.

We are unaccustomed to PSA values in advanced PCa with robust T concentrations and without ADT or antiandrogens. The high PSA values seen with continuous T injections were startling and caused two men to discontinue treatment. Any similar studies in the future would require mental recalibration for PSA levels. To illustrate, in one BAT study,[16] median baseline PSA was 39.8 ng/mL, whereas in a 1989 study of men with

mPCa, median PSA in two groups was >10-fold higher at 546 and 678 ng/mL.[19] In the BAT study, all men were already on ADT, and in the 1989 study they were not.

The combination of TTh and enzalutamide was investigated to determine whether this may allay the weakness routinely experienced with ADT. Enzalutamide blocks androgen binding to AR and its subsequent translocation to the nucleus,[11] whereas skeletal muscle contains a second androgenic pathway independent of AR through a G protein-coupled membrane receptor.[20] Patient 2 took this regimen for 11 months, self-adjusting T and enzalutamide doses to optimize energy and minimize fatigue, with moderate subjective benefit. PSA dropped from 40 to 5–10 ng/mL for ~7 months, before rising with reduced dosage of enzalutamide. It appears nearly any PSA within a very wide range can be achieved by manipulating the relative amounts of androgen and antiandrogens, until hormone-insensitivity occurs.

This same patient underwent 11 monthly cycles of BAT once bone metastases were identified.

Enzalutamide was added after the fourth cycle for the last 10–14 days of each cycle to lower the PSA nadir without interfering with the benefits experienced during intervals of high testosterone concentrations. He looked forward to those periods but was frustrated by their short duration.

The most promising of the strategies presented here is mBAT, which provided extended predictable periods of TTh benefits while maintaining PSA control. Whereas BAT proved that repeating cycles of high serum T followed by low serum T could offer therapeutic benefits to men with advanced PCa,[15] the rapid cycles within a 4-week period may not provide an optimal patient experience since the period of normal or even elevated serum T is relatively short. mBAT was developed specifically for clinical use, to improve quality of life due to the prolonged TTh period of 8 weeks, while hopefully providing similar benefits as BAT with regard to cancer control through the bipolar mechanism. A similar peak-and-valley PSA response was seen as with BAT,[15] but in this case occurring for a 3-month interval rather than monthly. Subjectively, patient 3 felt extremely well during his 8 weeks of TTh, and found 4 weeks of enzalutamide tolerable. Enzalutamide was selected for its ability to immediately "quench" the effects of high testosterone; however, other agents could be used to achieve the antiandrogenic effect. Interestingly, both PSA peaks and nadirs gradually rose over time. We surmise the rise in peak values represented increased tumor volume. The rise in the nadir values, in contrast, appears due to the prolonged half-life of PSA, since additional time on enzalutamide at one point resulted in a further drop in PSA. Additional patients have now been treated with mBAT, with promising results. Those cases will be presented when the data are more mature.

It bears comment that an apparent reduction in tumor burden was noted in Case 3, with reduction of para-aortic adenopathy from 16.7 to 9.8 mm after 2 months of continuous high-dose testosterone injections. This is reminiscent of the decreased tumor burden noted in several cases of men treated with BAT,[15] and consistent with *in vitro* studies showing that high androgen concentrations inhibit growth of androgen-sensitive PCa cell lines.[12–14] Clearly, the relationship of testosterone with PCa growth is more complex than previously believed.

These various TTh strategies underscore the limitations of PSA as a marker of disease status in men with advanced PCa. Low values with ADT or antiandrogens may be observed in men with either minimal disease or diffuse metastases. To correctly interpret PSA results, it is necessary to not only know the current testosterone concentration but also its recent history, as changes in PSA concentrations lag behind changes in serum testosterone by at least several days. A high PSA may be seen together with a low serum testosterone, or vice versa, as testosterone is administered or withdrawn. A low PSA in the setting of ADT cannot be interpreted to indicate minimal disease, since the value may soon be in the hundreds with relatively short periods of TTh.

In conclusion, these results suggest a potential role for TTh in selected men with advanced or metastatic PCa, especially for those who prioritize quality of life. Further investigation is warranted to identify treatment strategies that provide adequate cancer control without the full negative impact of ADT on quality of life. Since there are no randomized controlled trials adequately powered to address safety for any of the strategies presented here, no clinical recommendations can be made on the basis of these three patients. Nonetheless, in the absence of an effective cure for mPCa, these results support a personalized approach to hormonal treatment in men with advanced PCa, particularly at end of life.

Author Disclosure Statement

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Abbreviations Used

ADT = androgen deprivation therapy
BAT = bipolar androgen therapy
CT = computed tomography
mBAT = modified bipolar androgen therapy
mPCa = metastatic prostate cancer
PSA = prostate-specific antigen
SARM = selective androgen receptor modulator
TTh = testosterone therapy