Re: Nadir Testosterone Within First Year of Androgen-Deprivation Therapy (ADT) Predicts for Time to Castration-Resistant Progression: A Secondary Analysis of the PR-7 Trial of Intermittent Versus Continuous ADT
Klotz L, O’Callaghan C, Ding K, et al.
J Clin Oncol 2015;33:1151–6

Experts’ summary:
In a post hoc analysis of the landmark phase III randomized PR-7 clinical trial, Klotz et al assessed the impact of testosterone levels in the first year of androgen deprivation therapy (ADT) on clinical outcome. The PR-7 study was designed to prospectively compare outcomes of continuous versus intermittent ADT in men with nonmetastatic biochemically recurrent prostate cancer (PCa) after surgery and/or radiation therapy. In this study, 696 patients were assigned to continuous androgen deprivation (CAD) with evaluation of serum testosterone and prostate-specific antigen every 2 mo and a nadir of the testosterone value < 1.7 nmol/l (50 ng/dl) in the first year of CAD was associated with longer time to development of castration-resistant PCa (CRPC) and better cancer specific survival compared with higher serum testosterone levels. Spikes of serum testosterone > 1.7 nmol/l (50 ng/dl) also predicted time to CRPC and PCa mortality; however, testosterone levels at start of therapy did not.

Experts’ comments:
Men with biochemical recurrence (BCR) after radiation therapy or radical prostatectomy represent a heterogeneous population with highly variable outcomes [1]. Although ADT timing and type in these patients are still controversial, the objective is to provide deep castration to delay PCa progression and CRPC. In a significant subset of patients, serum testosterone response to luteinizing hormone–releasing hormone analogs does not reach the expected castrate levels, which have been set arbitrarily at an upper limit that ranges between 0.7 and 1.7 nmol/l. Despite initial response and observance, men will also experience spikes of testosterone. The clinical impact of these incomplete and variable responses remains controversial and poorly studied, specifically, in nonmetastatic PCa patients. Klotz et al, based on data from a prior randomized clinical trial, highlight that subcastrate nadir and spikes of testosterone during the first year of ADT in men with hormone-sensitive nonmetastatic PCa are associated with shorter time to CRPC and worse cancer-specific survival.

This study has several implications that are increasingly based on cumulative evidence. Testosterone-level monitoring seems useful to help identify patients who may benefit from additional early therapies. Indeed, few prognosticators have been identified to help physicians with patient counseling and clinical decision making. Recently, a retrospective study in a large cohort of patients treated with external beam radiotherapy demonstrated that, except for Gleason score, established clinicopathologic features were not independent predictors for the development of CRPC [2]. It is likely that PCa progression and castration resistance relate to adverse biological and molecular features rather than baseline clinicopathologic characteristics alone. Testosterone levels were not associated with established clinicopathologic features of tumor aggressiveness in the current study. Consequently, response to ADT may reflect informative tumor and patient biological characteristics. In the era of personalized and tailored medicine, integration of such markers in predictive models is needed to identify patients who are more likely to experience short-term development of CRPC and thus may enter clinical trials that assess the role of ADT combination or intensification.

The critical issue of the therapeutic decision when facing subcastrate patients still remains. No evidence shows that efforts to achieve early and continuous testosterone castrate levels would affect the outcome. The early introduction of ADT in nonmetastatic patients has not yet proven beneficial in terms of survival. The PR-7 study, according to its primary end point, demonstrated that intermittent androgen deprivation, which leads to reincrease of testosterone in most patients, is not inferior to CAD [3]. Although it makes sense to discuss ADT manipulation, such as whether to switch to another type of ADT or add a new antiandrogen treatment to reach “supercastrate” levels in selected patients, results from ongoing clinical trials that address the benefit of these treatment modalities are still needed before any recommendation can be formalized.

We have to mention some limitations, as outlined in the accompanying editorial [4]. First, the analyses did not assess overall survival. Competing risks and potential metabolic complications due to deeper castration levels may have limited the marginal benefit of cancer-specific survival,
resulting in a lack of difference in overall survival. Second, assessing the association between testosterone levels and outcomes at different times during follow-up would have been helpful to determine the consistency of prognostic value of testosterone levels, specifically at the time of CRPC. Finally, investigations regarding the impact of clinical patient characteristics, type of ADT, and androgen metabolism on the testosterone response might have been helpful to identify potential confounders that contributed to castration failure.

Despite these limitations, we believe that this study represents a first step toward the identification of predictors and prognosticators for the selection of patients with BCR who may benefit from early and intensive systemic therapy.

Conflicts of interest: The authors have nothing to disclose.

References

Re: Effect of Bipolar Androgen Therapy for Asymptomatic Men with Castration-resistant Prostate Cancer: Results from a Pilot Clinical Study
Sci Transl Med 2015;7;269ra2

Experts’ summary:
Schweizer et al recently conducted a pilot clinical study evaluating the effects of bipolar androgen therapy (BAT) on castration-resistant prostate cancer (CRPC). Sixteen men with CRPC and a low metastatic burden who were currently receiving ADT were treated with supraphysiologic levels of testosterone (>1500 ng/dl) and etoposide over three 28-d cycles. ADT was continued during these cycles, increasing the rate of testosterone reduction to castration levels following injection. BAT was ceased after three cycles if prostate-specific antigen (PSA) did not show a decline below prestudy baseline or a downward trend. Of the 16 patients, 7 had PSA levels that showed response to BAT. All 7 patients who responded to BAT had significantly higher prestudy PSA levels (159.7 vs 13.9, p = 0.019). For all patients who responded to BAT, a return to increasing PSA levels was eventually observed after a median of 221 d (range: 95–451 d). Of these 7 patients, 5 exhibited a lack of radiographic progression, and 1 patient showed complete response. Following BAT, testosterone levels of all patients fell to castration levels. Patients received second-line ADT after PSA progression.

Experts’ comments:
ADT has been the standard of care for metastatic prostate cancer for >70 yr and results in significant palliative benefit [1]; however, prostate cancer will eventually progress and develop a castration-resistant state in every patient receiving ADT. This progression is due both to cells’ increasing levels of androgen receptor (AR) and to production of ligand-independent AR in response to low serum androgens. The inevitable progression to CRPC has led to the continued development of new ADTs (eg, androgen receptor blockers and new gonadotropin-releasing hormone antagonists). Intermittent ADT (IADT) has been proposed as an alternative to continuous ADT [2]. Patients receiving IADT will continue therapy until reduction in PSA levels are noticed, and then ADT is discontinued. Once PSA levels begin to rise, ADT is reintiated. The goal of IADT is to prevent the adaptation of cancer cells to reduced levels of androgens. However, testosterone levels can take months to recover to precastration levels, giving cancer cells enough time to adapt to normal testosterone levels and AR expression [1,2]. Consequently, the efficacy of IADT is minimal outside of the reduction of symptoms from ADT.

The focus of this study is on the long-standing knowledge that CRPC cell lines can be inhibited be supraphysiologic levels of androgen [3]. Schweizer et al examined cultured CRPC cells in vitro and showed that overexpressing AR exhibited increased cell death when exposed to supraphysiologic levels of synthetic androgen. With BAT, there is a rapid change from supraphysiologic levels of testosterone to castration levels. This rapid change in testosterone levels limits the response time available to cancer cells to change AR expression. In addition, the function of AR in DNA replication is to help repair double-strand breaks. Binding of testosterone to AR could prevent its normal function of repairing double-strand breaks. For the cells to progress through the cell cycle following replication, AR expression must be reduced; otherwise, apoptotic pathways are activated [3]. It is theorized that in the presence of supraphysiologic levels of testosterone, increased levels of stable, ligand-bound AR are available that, in turn, can lead to cell cycle failure and programmed cell death.

Although the results of this study are intriguing, ADT remains the standard of care. At present, BAT can be implemented as an option for treatment of CRPC only in the setting of a clinical trial. The small sample size of this study...