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Does Degree of Androgen Suppression Matter in Hormone-Sensitive Prostate Cancer?

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In men with metastatic prostate cancer, androgen-deprivation therapy (ADT) is the mainstay of therapy. Through reduction of serum testosterone from normal levels (approximately 250 to 950 ng/dL [8 to 32 nmol/L]) to castrate levels, ADT has been shown to reduce tumor burden and alleviate symptoms and may improve survival. Although ADT can suppress circulating testosterone levels by 90% to 95%, not all men achieve a testosterone level in the castrate range; others may initially achieve castrate levels but then experience testosterone breakthrough above that level. Castration has historically been defined as serum testosterone of less than 20 ng/dL (0.7 nmol/L), although a threshold of less than 50 ng/dL (1.7 nmol/L) was adopted by the Prostate Cancer Working Group 2 for the purposes of clinical trial accrual.¹ However, this was essentially an arbitrary threshold, and the clinical significance of the testosterone level and the optimal degree of testosterone suppression following ADT remain in question.

In the accompanying article, Klotz et al² report a post hoc analysis of clinical outcomes according to testosterone levels achieved after initiation of first-line ADT among 696 patients treated with continuous ADT in the PR-7 study. This phase III trial randomly assigned men with biochemically recurrent prostate cancer after primary local therapy to either continuous or intermittent ADT (with 8-month treatment cycles). Serum testosterone was measured prospectively every 2 months during the first year on study. In their article, Klotz et al² report that in the continuous ADT arm of the PR-7 trial, men whose testosterone nadir after ADT initiation fell below 20 ng/dL (0.7 nmol/L) fared better in terms of time to castration resistance (defined as three increasing prostate-specific antigen [PSA] values in the setting of serum testosterone < 85 ng/dL [3.0 nmol/L]) and cancer-specific survival

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compared with those who did not achieve this degree of castration. In addition, men whose testosterone spiked above 50 ng/dL during the course of ADT treatment developed castration resistance more quickly than those whose testosterone remained persistently below 20 ng/dL.

The clinical significance of deeper testosterone suppression beyond the conventional castrate level (< 50 ng/dL) has been demonstrated in the context of metastatic castration-resistant prostate cancer. Abiraterone acetate, a CYP17-targeting androgen biosynthesis inhibitor that reduces circulating testosterone levels by approximately 90% beyond that achieved by ADT alone (while also blocking intratumoral androgen production) has resulted in improvements in overall survival in both the pre- and postchemotherapy settings.^{3,4} However, the relevance of the depth of castration in earlier disease states remains unclear. The data from the Klotz et al² study represent some of the strongest evidence to date that failure to achieve deep testosterone suppression after first-line ADT may herald poor outcomes in men with hormone-sensitive nonmetastatic prostate cancer.

Klotz et al state that, for men receiving continuous ADT, achieving a serum testosterone level below 0.7 nmol/L (20 ng/dL) in the first year should be the goal of therapy. Is this conclusion warranted? We believe that there are reasons to be cautious. For one, periods of testosterone normalization are the goal of intermittent hormone therapy. Because the primary analysis of the PR-7 study showed that intermittent hormone therapy was noninferior to continuous therapy with respect to overall survival,⁵ the importance of further testosterone manipulation following ADT is unclear. Moreover, the need for ADT in the setting of nonmetastatic biochemically recurrent prostate cancer remains controversial, regardless of whether it is delivered in continuous or intermittent fashion. Several reports, including a recent analysis of the Cancer of the Prostate Strategic Urologic Research (CaPSURE) registry, have suggested that patients in whom ADT is initiated immediately on PSA relapse might not derive a survival benefit over those in whom ADT is deferred for at least 2 years after biochemical recurrence or until clinical metastasis.⁶ The risk-benefit profile of ADT in this setting, given the well-documented adverse effects related to its use (fatigue, osteoporosis, metabolic syndrome, cardiac and vascular disease, sarcopenia),⁷ remains a concern. A more clinically relevant demonstration of the importance of deeper testosterone suppression might be possible through a similar analysis of the SWOG-9346 (Hormone Therapy in Treating Men With Stage IV Prostate Cancer) trial, which randomly assigned men with metastatic hormone-sensitive prostate cancer to intermittent versus continuous ADT, although testosterone levels were not routinely collected in all patients on this trial.⁸

The relatively soft end points of time to castration resistance and cancer-specific survival used as outcome measures in this post hoc analysis of the PR-7 study also dampen the enthusiasm for the conclusions reached. To this end, the definition of castration resistance used in this study was less stringent than that proposed by the Prostate Cancer Working Group 2, which requires two PSAs increasing by at least 25% and by 2 ng/mL above the nadir (or clinical or radiographic progression) with a serum testosterone level of less than 50 ng/dL.¹ This renders the meaning of time to castration resistance more difficult to interpret here. Furthermore, cancer-specific survival is a challenging end point to ascertain in a population with a relatively long survival and multiple competing causes of mortality. An

analysis of overall survival would have been preferable in this case and could have also accounted for the potential increase in nonprostate cancer–related deaths that may have been attributed to deeper castration over the long term.

If nadir testosterone levels after ADT influence clinical outcomes, what then is the prognostic significance of baseline (pretreatment) testosterone levels? In the study by Klotz et al,² baseline testosterone did not appear to influence time to castration resistance or cancer-specific survival. This is in contrast to a post hoc analysis of the COU-AA-301 (Abiraterone Acetate in Castration-Resistant Prostate Cancer Previously Treated With Docetaxel-Based Chemotherapy) study of abiraterone versus placebo in men with metastatic castration-resistant prostate cancer, in which increased baseline serum androgen levels (testosterone, androstenedione, and dehydroepiandrosterone sulfate) were associated with improved overall survival (in both the placebo and abiraterone arms).⁹ A potential biologic explanation for this phenomenon may be that prostate cancer growth in the setting of very low testosterone levels may represent a more aggressive phenotype. However, this finding may or may not be relevant in the hormone-sensitive setting, given that no correlation between baseline testosterone and time to castration resistance or cancer-specific survival was noted in the study by Klotz et al. An analysis of the effect of testosterone at the time of castration resistance would have been interesting and may have been helpful in reconciling the disparate findings of these two studies.

Why do some men achieve only incomplete testosterone suppression following ADT? Given that approximately 25% of patients who undergo bilateral orchiectomy have serum testosterone above 20 ng/dL,¹⁰ it is likely that adrenal androgen production may play a role. Incomplete testosterone suppression in these men may also represent different intrinsic tumor or host characteristics. Although Klotz et al² report that there was no correlation between baseline testosterone level and either Gleason score or baseline PSA, it is possible that other factors such as age, body mass index, or type of luteinizing hormone-releasing hormone (LHRH) agent used may predict for failure of therapy to achieve castration and it would have been useful to investigate these. There may also be other genetic factors related to androgen metabolism that predict for time to castration resistance, such as germline polymorphisms in the adrenal androgen synthesis pathway (eg, in the *CYP19A1*, *HSD3B1*, and *HSD17B4* genes),¹¹ as well as polymorphisms in the androgen transporter genes *SCLO2B1* and *SLCO1B3*.¹² To this end, measurement of additional circulating androgens (such as dehydroepiandrosterone sulfate and androstenedione) and further investigation of the adrenal axis in this cohort might have been enlightening.

Would further hormonal manipulation in men with hormone-sensitive prostate cancer who fail to achieve deep androgen suppression in response to ADT portend improved outcomes, particularly with respect to overall survival, or is testosterone nadir only of prognostic importance? This is a key question that is not adequately answered by the Klotz et al study. There are some limited but suggestive retrospective data, such as those from Lawrentschuk et al¹³ in which a substantial proportion of men with disease progression on a first-line LHRH agonist experienced a further PSA response after switching to an alternative LHRH agonist. However, only prospective randomized trials comparing standard ADT with more potent androgen suppression in the first-line setting will be able to shed additional light on

this issue. Of note, trials comparing ADT alone versus ADT plus an antiandrogen (ie, combined androgen blockade) have not convincingly demonstrated superiority over ADT alone,¹⁴ although antiandrogens block the androgen receptor rather than further reducing serum testosterone. One trial evaluating the role of deeper testosterone suppression is the ongoing SWOG-1216 study (NCT01809691; S1216, Phase III ADT+TAK-700 vs. ADT+Bicalutamide for Metastatic Prostate Cancer), which randomly assigned men with metastatic hormone-sensitive disease to either standard combined androgen blockade or to a supercastration approach (LHRH agonist plus the CYP17 inhibitor orteronel), with a primary end point of overall survival. An alternative trial design to answer this question would randomly assign men with metastatic hormone-sensitive disease and incomplete testosterone suppression after a period of ADT to either continued ADT alone or ADT plus the addition of a CYP17 inhibitor. Until these or similar results are available, we should not recommend deeper androgen suppression in the first-line setting for men with (metastatic or non-metastatic) hormone-sensitive prostate cancer.

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