LETTER TO THE EDITOR

Hormone levels following surgical and medical castration: defining optimal androgen suppression

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Dear Editor,

In the 1940s, Charles Huggins discovered that surgical castration produced remarkable palliative benefits for men with advanced prostate cancer, an effect we now understand to be mediated through depriving the androgen receptor (AR) from its ligands (i.e., testicular-derived androgens). In the years since, medical forms of androgen deprivation therapy (ADT) have largely replaced orchietomy as the predominant means of achieving castrate testosterone (T) levels, and currently, luteinizing hormone-releasing hormone (LHRH) agonists (e.g., leuprolide) are the most common form of ADT. Importantly, studies have shown that LHRH agonists are clinically efficacious and, similar to surgical castration, drive T below 50 ng dl⁻¹ for most patients.¹

While T <50 ng dl⁻¹ is the most frequently cited definition for what constitutes a castrate level T, it should be recognized that multiple studies have demonstrated better outcomes with lower T levels. For instance, Klotz et al.² reported that, in patients enrolled to the Phase III PR-7 study testing intermittent versus continuous ADT in nonmetastatic biochemically recurrent prostate cancer patients, a total T level <20 ng dl⁻¹ was associated with improved disease-specific survival and time-to-castration resistance compared those with a total T level >20 ng dl⁻¹. This observation has led to the European Association of Urology to recommend that a level of <20 ng dl⁻¹ should be used to define a castrate level of T.

It is important to note that the total serum T levels include both free and protein-bound (e.g., sex hormone-binding globulin, albumin) fractions, while older studies have shown that LHRH agonists suppress total T levels below castrate levels; it is widely understood that free, or unbound, T is the biologically and clinically relevant component.³ That being the case, the therapeutic goal of medical ADT should be to decrease free T levels to those achieved with orchietomy. However, to date, free T has not been well studied in large cohorts of orchietomized men. The purpose of this study was to examine total T and free T levels in men who have undergone orchietomy or received medical ADT in the context of a prospective clinical trial. These determinations will help set expectations for future development of novel agents that effect androgen levels.

Baseline data were utilized from a double-blind, randomized, placebo-controlled trial (G300203) that was designed to determine the capacity of toremifene (a second-generation selective estrogen receptor modulator) to prevent bone fractures in men on ADT. This study included 1389 men from 150 sites in the US and Mexico. Patients were randomized in the ratio of 1:1 to receive toremifene 80 mg by mouth daily or matched placebo. Results from the primary analysis have already been published.⁴ Baseline characteristics, including whether men were on medical ADT or status postorchietomy, were available.

The primary objective of this study is to describe baseline hormone levels in men receiving medical ADT or who underwent orchietomy before initiating toremifene. Hormone levels were determined in a centralized clinical testing facility utilizing an Food and Drug Administration-approved radioimmunoassay (RIA) (Diagnostic Products Corporation, Los Angeles, CA, USA). Free testosterone levels were estimated using RIA and equilibrium dialysis as previously described.⁵ We also evaluated for differences in hormone levels between groups using the Wilcoxon rank-sum test.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committees of the participating institutions. Informed written consent was obtained from all patients before their enrollment in this study.

Between November 2003 and October 2005, 1284 men with prostate cancer receiving ADT were randomized between placebo and toremifene. Of this cohort, castrating therapy was administered as follows: 1191 received an LHRH agonist, 56 underwent bilateral orchietomy, 27 underwent bilateral orchietomy with androgen receptor blockade, and 10 underwent bilateral orchietomy and also received an LHRH agonist. Details for why ten patients received LHRH agonist therapy and orchietomy are not available as these data were gleaned from case report forms which are no longer available for review.

LH levels were significantly lower and estradiol levels were significantly higher in men receiving LHRH agonist therapy. There was no significant difference in total or free T levels between groups (Table 1). However, there was less variability in total and free T levels in orchietomized patients compared to those receiving LHRH agonists. For instance, the total T ranged from 0.69 ng dl⁻¹ to 29.5 ng dl⁻¹ in men receiving LHRH agonist therapy alone compared to 0.69 ng dl⁻¹ to 13.01 ng dl⁻¹ in patients who underwent orchietomy.

To our knowledge, this study is the largest to report free T levels in men who underwent orchietomy. In this cohort, the mean serum-free

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T was approximately 1.9 pg ml⁻¹. This value could be considered to be the optimal suppression of free T with orchiectomy and represents the goal of medical ADT. Reassuringly, there was no difference in free T levels between the orchiectomy cohort and those receiving an LHRH agonist.

An interesting observation from this study was that, while there was no difference in total or free T levels between treatment groups, LH levels were significantly lower and estradiol levels were significantly higher in patients receiving LHRH agonist therapy. Given that LHRH agonists inhibit testicular androgen biosynthesis by impairing LH release from the pituitary gland, it is not surprising that LH levels were lower in men receiving these drugs. Somewhat less clear is why estradiol levels are elevated in men receiving an LHRH agonist compared to other groups. LH receptors are present in the adrenal gland, and it is possible that LH may exert some influence on adrenal estradiol biosynthesis that has yet to be explained.⁶,⁷

Given that mass spectrometry has been demonstrated to be more accurate means to quantitate low hormone levels, a limitation of this analysis was the use of RIA to measure circulating androgen levels.⁸ At the time this study was performed, RIA was considered to be the standard but has since been shown to underestimate free T levels by 20%–60%.⁹,¹⁰ Currently, equilibrium dialysis coupled with LC-MS/MS is the gold standard, but the results from this analysis provide us with increased understanding of the optimal level of free T in treating advanced prostate cancer.

This study provides greater clarity on the effects that LHRH agonists and orchiectomy have on circulating hormone levels. Importantly, as determined by RIA, there is no significant difference in total or free T levels irrespective of whether a man received surgical or medical ADT. These circulating hormone levels should serve as a benchmark for future studies investigating novel forms of medical ADT, with the goal being to meet or exceed this level of free and total T suppression.

AUTHOR CONTRIBUTIONS
This study was designed by MTS, EYY, and RHG. Statistical analysis was performed by MLH and all authors helped to analyze the data. The manuscript was prepared by MTS. All authors read and approved the final manuscript.

COMPETING INTERESTS
MLH and RHG are former employees of GTx, Inc, the sponsor of the clinical trial from which these data were derived. MTS and EYY have no competing interests to declare.

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Table 1: Baseline demographics and hormone levels

|                             | LHRH agonist | Orchiectomy | Orchiectomy + androgen receptor blockade | Orchiectomy + LHRH agonist |
|-----------------------------|--------------|-------------|-----------------------------------------|---------------------------|
| Number of patients (n)      | 1191         | 56          | 27                                      | 10                        |
| The USA                     | 1043         | 20          | 5                                       | 7                         |
| Mexico                      | 148          | 36          | 22                                      | 3                         |
| Age (year, median with range in parentheses) | 76 (48–93) | 76 (61–90) | 74 (62–87) | 75 (51–82) |
| BMI, median (range)         | 27.84 (16.05–46.64) | 27.70 (17.38–38.90) | 26.48 (22.74–42.51) | 24.49 (20.34–30.81) |
| Baseline PSA (ng ml⁻¹, median with range in parentheses) | 0 (0–3.3) | 0 (0–3.9) | 0 (0–3.9) | 0.1 (0–2.6) |
| Gleason score, n (%)        |                |              |                                         |                           |
| ≤6                          | 217 (42.2)   | 1 (3.8)     | 4 (44.4)                                | 2 (66.7)                  |
| ≥7                          | 144 (28.0)   | 11 (42.3)   | 1 (11.1)                                | 0                         |
| ≥8                          | 153 (29.8)   | 14 (53.8)   | 4 (44.4)                                | 1 (33.3)                  |
| LH (mIU ml⁻¹, median with range in parentheses) | 0.1 (0.1–52.6) | 15.9 (3.3–36.9) | 12.9 (2.8–34.9) | 0.1 (0.1–5.8) |
| Estradiol (pmol l⁻¹, median with range in parentheses) | 36.71 (0.330.39) | 29.37 (18.36–187.22) | 25.70 (18.36–62.41) | 34.87 (18.36–69.75) |
| Free testosterone (pg ml⁻¹, median with range in parentheses) | 1.01 (0.17–77.67) | 1.14 (0.35–33.95) | 1.25 (0.35–3.64) | 0.35 (0.35–3.02) |
| Total testosterone (nmol l⁻¹, median with range in parentheses) | 0.69 (0.69–29.50) | 0.69 (0.69–13.01) | 0.69 (0.69–13.01) | 0.75 (0.69–1.21) |

³32 patients had missing Gleason score information. LHRH: luteinizing hormone-releasing hormone; BMI: body mass index; PSA: prostate-specific antigen; LH: luteinizing hormone. P values were determined using the Wilcoxon rank-sum test.