

Addressing the pressing issues related to testosterone administration to men with prostate cancer

Alvaro Morales, MD, CM, FRCSC, FACS

Department of Urology, Queen's University, Kingston, ON, Canada

Cite as: *Can Urol Assoc J* 2016;10(5-6):185-6. <http://dx.doi.org/10.5489/cuaj.3824>

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By a wide margin, urologists treat the majority of men with a current or remote diagnosis of prostate cancer (PCa) and are consulted or take primary responsibility for managing those who, in addition are affected by testosterone deficiency syndrome (TDS). Thus, the paper by Millar et al¹ is important and timely. Important because, with relatively little evidence, there has been a drive to shift the long-established concept that administration of androgens to men with PCa has been wrong. It is also timely because it is apparent that there is a significant amount of confusion and inconsistency among clinicians as to the appropriateness and safety of testosterone administration in general and to men with a history of PCa in particular.²

There are two important distinctions regarding the administration of testosterone to hypogonadal men with PCa: 1) those who have been treated with curative intent; and 2) those on active surveillance. For the former, limited but accumulating evidence indicates that judicious administration of testosterone is safe.³⁻⁸ As shown by the results of the survey, embracing this notion is preponderant among Canadian urologists. In regard to those men on active surveillance, it is encouraging and rewarding to find the sensible (if somewhat incongruent) skepticism expressed by responders to questions 4 to 8 (Table 1 in Millar et al). It is intriguing that almost one-half of those who feel it is safe to treat patients on active surveillance (question 4) still do not offer this option. Is it because they have not had the opportunity to do so or because they lack the confidence in tackling the situation?

The much-touted saturation model remains appealing, but speculative.⁹ More significantly, the proponents have not yet produced algorithms with clear parameters as to which levels of serum testosterone are appropriate or how to follow those patients (i.e., frequency of testosterone and prostate-specific antigen [PSA] measurements, biopsies,

time for cessation of therapy, etc.). By the same token, it is not clear who is or who is not a candidate for testosterone administration (e.g., only those with low-grade tumours or only those with severe hypogonadism?) Until such issues are clearly defined, it is incumbent to the practitioners to exercise a great deal of caution and restraint.

Beyond the original studies of Huggins and Hodges,¹⁰ the paradoxical response of PCa to testosterone administration in advanced PCa has been recognized for decades; in most cases it translates into rapid progression,¹¹ but occasionally such treatment appears beneficial.^{12,13} Similar observations have been reported in patients with cancers confined to the gland.^{14,15} The reasons remain conjectural, but range from the effect of estrogens (due to an age-related differential) in the aromatization of testosterone on the nuclear androgen receptor (AR) and the length of the CAG repeats to the lack of prostatic uptake of exogenous testosterone. The relevant point here is that there may be substantial inter-individual responses to changes in the hormonal environment of men with PCa and we should be wary of oversimplifications and generalizations.

Millar et al aptly recognized the limitations of their survey, particularly the disappointing response rate despite a second mailing. However, it is clear that there are significant gaps in knowledge regarding the management of TDS, as also shown by a recent needs assessment.² The gaps are certainly profounder for clinicians dealing with hypogonadal men and a history of PCa. This challenge is not unique to Canada.^{16,17}

The stated purpose of the survey is to eventually develop a Canadian registry of hypogonadal men with a history PCa and receiving testosterone treatment. It is evident that only a countrywide registry would provide the power to address some of the pressing issues related to testosterone administration to men with PCa. A wider effort, such as a North American (or even better, a global registry)¹⁵ offers a better opportunity to reach credible conclusions within a shorter time context. Randomized, placebo-controlled studies,¹⁸ although ideal, at this time remain utopian.

Competing interests: Dr. Morales has received grants/honoraria from Telesta Therapeutics.

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Correspondence: Dr. Alvaro Morales, Queen's University, Kingston, ON, Canada; moralesa@queensu.ca