GUEST EDITORIAL

Bilateral Orchidectomy Should Not Be Considered An Obsolete Alternative For Metastatic Cancer Of The Prostate*

In the treatment of metastatic carcinoma of the prostate, androgen deprivation therapy (ADT) has played a central role since the observations of Huggins and Hodges in the middle of the last century.[1] Orchidectomy became the treatment of choice but it was soon after replaced with the oral administration of estrogenic compounds, primarily diethylstilbestrol (DES) which produces a rapid decrease in serum levels of testosterone (T) and clinical improvement. In the classic large placebo-controlled study, the Veterans Administration Cooperative Research Group (VACURG) compared DES with all other treatments available at the time for men with prostate cancer. It was found that although the disease-specific mortality was lower in the DES cohort, this group exhibited the highest overall mortality.[2] These outcomes were attributed to the large doses of DES used which translated in several adverse and serious cardiovascular events. Although further studies indicated that reduced doses may carry less adverse effects, the use of DES for treatment of metastatic prostate cancer did not regain wide acceptance.

A significant improvement was the introduction of luteinizing hormone releasing hormone (LHRH) or gonadotropin releasing hormone (GnRH) analogs some 3 decades ago. The therapeutic equivalence between bilateral orchidectomy and LHRH analogs has been acknowledged since then.[3] Consensus on the efficacy equivalence though, is not reflected in the choice of treatment which tilts overwhelmingly in favor of the non-surgical approach, primarily to avoid the "mutilating" result of an orchidectomy. However, further studies have shown that the concept of therapeutic correspondence between the two methods of androgen suppression may not be accurate due to an escape phenomenon occurring in a number of men treated with GnRH agonists and translating in an elevation of serum T above castrate levels, potentially leading to unsatisfactory tumor control.[4,5]

Oefelein et al[6] initially challenged the previously accepted "castrate" levels of < 1.73 nmoL/L (< 50 ng/dL), established in the 1960s and proposed a new definition of < 0.7 nmoL/L (< 20 ng/dL) based on the current availability of better analytical biochemical methods for measuring serum T and their findings that surgically castrated men had a median T value of 0.53 nmoL/L or 15 ng/dL (95% confidence interval 0.4 to 0.58 nmoL/L or 12 to 17 ng/dL). The new definition promptly became the standard of practice. The question arose as to whether the surgically castrated group had lower T compared to the group on LHRH agonists. In a subsequent study, Oefelein et al found that only 3 of 35 patients (8.57%) who had been surgically castrated had total testosterone levels above 0.7 nmoL/L[5] while 13% of those medically treated failed to reach castrate T levels.[2] Morote et al found the failure to produce adequate ADT by GnRH agonists to be 12.5%[7] while McLeod reported 18%.[8] Our experience in patients treated with LHRH agonists showed that 21% (10/47) had non-castrate levels of T.[9] Although it is inappropriate to compare results across studies these findings are extraordinarily consistent.

But are these findings clinically important or just an interesting analytical observation? In the papers by Oefelein et al[2,5] as well as in our study,[9] such serum levels of T appears to be a significant correlate of the prostate specific agent (PSA), a fairly reliable surrogate measure of prostate cancer activity: mean, median, minimum and maximum values were all higher for the group with the T > 0.7 nmoL/L (20 ng/dL).

Our study, as well as those of Oefelein[2,5] and Morote,[5] are cross-sectional and do not furnish information as to the time-dependent efficacy of LHRH agonists in achieving the new optimal standard of T nadir. They also fail to provide information regarding time spans at which T levels begin to rise. Only longitudinal evaluations, not yet available, are capable of elucidating this very important aspect of the medical treatment for prostate cancer. It is noteworthy, however, that in the study of Morote et al[5] there were significant differences in survival free of PSA progression between the group with T levels > 50 ng/dL and the one with < 20 ng/dL.

In a recent study, van der Sluis et al[10] found lower levels of serum T in patients treated with LHRH agonists than in those surgically castrated. All patients, however, had a T of < 1.7 nmoL/L (< 50 ng/dL) and 97% reached

castrate levels. The study had significant drawbacks including a small sample (n = 66), its retrospective nature and the fact that a third of the men in the surgical group had the operation as part of a gender re-assignment process and not for prostate cancer. The authors argued that because in their study T was measured by isotope-dilution gas chromatography-mass spectrometry (ID/GC-MS/MS) their results may be more reliable and cite for support a position statement from the Endocrine Society.[11] However, the high laboratory standards endorsed by the Society are in reference to the diagnosis of hypogonadism and not for monitoring of prostate cancer as indicated also in the more recent Endocrine Society Guideline.[12] In addition, Sluis et al quote the paper by Taieb et al[13] to further espouse the argument that immunoassays are not reliable. In fact, Taieb et al expressed the long accepted view that the largest concern relates to the investigation of women and children. It should be kept in mind, that although GC-MS/MS is more specific for T than immunoassays that may register some "noise" from T metabolites, there are always analytical and biological variations for any method employed;[14] therefore, the accuracy of a single determination remains questionable. Currently, the measurement of serum T by ID/GC-MS/MS, although increasingly popular and unquestionably more accurate, is far from universally available and significantly costlier, particularly for monitoring purposes.

In the search for therapeutic agents approaching surgical efficacy, GnRH antagonists (as opposed to the agonists or analogs) were developed and have been commercially available for some time but have not become widely accepted. Abarelix was approved by the Federal Drug Administration (FDA) almost a decade ago and degarelix 5 years ago. The current evidence indicates that the antagonists offered several advantages over the agonists in the treatment of prostate cancer, including the lack of the initial surge and, consequently the need for concomitant anti-androgen treatment. In a comparative study of luprolide versus degarelix, Klotz et al[15] found no "micro-surges" of T levels while these occurred in 6% of the luprolide group. In addition, PSA failures were reported to be lower for patients treated with an antagonist (degarelix) than with an agonist (luprolide).[16] Thus, it appears that the use of GnRH antagonists more closely compare with the efficacy of the therapeutic yardstick, surgical castration.

Issues of comparative oncological efficacy, morbidity, emotional difficulties and financial concerns are important but relatively rarely addressed in the literature. Regarding costs there is a consensus: ADT with LHRH analogs alone was estimated in the United States to be up to 13 times and, when combined with total androgen blockade, up to 21 times the cost of bilateral orchidectomy.[17] A Canadian study[18] reported "orchidectomy likely to be the most cost-effective" option, an opinion supported by a Norwegian study that found orchidectomy to be "the treatment of choice when life expectancy is > 2 years".[19] Anxiety and distress about body image are often quoted for the vast preference for medical treatment. Issa et al[20] dismissed such concerns listing the simplicity of orchidectomy and the preservation of body image with a sub-capsular orchidectomy (or testicular implants), the need for a one-time out-patient procedure under local anesthesia over a lifelong frequent injection therapy at a considerable higher cost as weighty advantages of orchidectomy. On the same vein, a recent German study suggested bilateral sub-capsular orchidectomy to be the first-line of therapy in metastatic prostate cancer due to its efficacy, low morbidity and absence of emotional alterations against the background of the cost explosion in the health care system.[21]

To avoid confusion, it is proposed that a reading > 0.7 nmoL/L (20 ng/dL) of T in men receiving androgen suppression therapy for metastatic cancer of the prostate should be called "sub-optimal T" rather than a "non-castrate" level of T; conversely those with total T levels < 0.7 nmoL/L should be designated has having reached "optimal" T levels of ADT.

The first line of treatment for ADT in men with metastatic prostate cancer remains bilateral orchidectomy. Overwhelmingly, though there is a preference for medical treatment based on the system of drug coverage in Canada and patients' preconceptions regarding esthetics which do not appear justified since sub-capsular orchidectomies leave intra-scrotal volume equivalent to the testicular atrophy resulting from medical ADT. Bilateral orchidectomy should not be considered an obsolete alternative in the treatment of metastatic prostate cancer and should be offered with its virtues and shortcomings clearly explained to patients as a cost effective and therapeutically competitive alternative to medical ADT.

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