TITLE: Chemical Or Surgical Castration? Is This Still An Important Question?

SUBTITLE: Chemical Or Surgical Castration?

AUTHORS: Michael Kolinsky BSc, MD[1,2], Pasquale Rescigno MD[1,2], Johann S. de Bono MB ChB, MSc, FRCP, PhD, FMedSci [1,2,*].

AFFILIATIONS:

1. The Institute of Cancer Research, London, United Kingdom; 2. The Royal Marsden NHS Foundation Trust, London, United Kingdom;

*CORRESPONDING AUTHOR:

Professor Johann S. de Bono, MB ChB, MSc, FRCP, PhD, FMedSci

Professor of Experimental Cancer Medicine

Division of Clinical Studies, The Institute of Cancer Research

Drug Development Unit, The Royal Marsden NHS Foundation Trust

Downs Rd

Sutton, Surrey SM2 5PT

United Kingdom

Telephone: +44 (0)2087224028

Fax: +44 (0)2086427979

Email: johann.de-bono@icr.ac.uk

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Androgen deprivation therapy (ADT) remains a mainstay in the treatment of prostate cancer (PCa) since the discovery 70 years ago by Charles Huggins that castration results in regression of prostate cancer (PCa)[1]. ADT can be achieved either surgically (orchiectomy) or pharmacologically with gonadotropin-releasing hormone (GnRH) analogues. Alternatively, some patients wishing to maintain sexual potency may elect for treatment with anti-androgens (AA), recognizing that outcomes are inferior to ADT in the metastatic setting[2].

GnRH agonists (GnRHa) have largely replaced orchiectomy due to their ease of administration, reversibility, the avoidance of disfiguring surgery, and likely (at least in part) to the financial incentive afforded to prescribing physicians[3]. With an established role in the treatment of high risk, locally advanced, and metastatic disease, ADT is frequently prescribed to patients suffering from prostate cancer. However, ADT is not free of risk: In addition to the well known side effects of fatigue, hot flushes, decreased libido and sexual potency, gynecomastia, and reduced penile and testicular size, prospective studies have shown decreased bone mineral density, weight gain, decreased insulin sensitivity, and increases in fasting glucose, LDL cholesterol, and triglycerides[4]. Of even greater concern is that a number of observational studies have found an increased risk of fractures, diabetes mellitus (DM), peripheral arterial disease (PAD), venous thromboembolism (VTE), and cardiovascular disease (CVD)[4-6]. While this has not been supported by data from randomized controlled trials, these data prompted the FDA to mandate changes to GnRHa labelling to include a warning of the increased risk of DM and CVD.

In the article that accompanies this editorial[7], Sun et al report interesting findings. Using the Surveillance, Epidemiology and End Results (SEER) program of cancer registries matched to Medi-

care data, the authors investigated the risk of fracture, PAD, VTE, cardiac-related complications, DM and cognitive disorders in patients with metastatic PCa treated with GhRHa, or bilateral orchiectomy between 1995 and 2009 and compared the expenditures within the first 12 months after diagnosis of PCa. In adjusted analyses, they report that patients who were treated with bilateral orchiectomy had a lower risk of fractures (HR 0.77), PAD (HR 0.65), and cardiac-related complication (HR 0.74) compared to patients receiving GnRHa. However, no statistical differences were noted between the treatments in term of risk of DM and cognitive disorders, except patients receiving ≥35 months of GnRHa had a higher risk of DM compared to patients undergoing orchiectomy. Moreover, they report no significant difference in expenditures between the two groups 12 months after Pca diagnosis.

Sun and colleagues should be lauded for their contribution to this subject. Most publications addressing the adverse effects of ADT have involved either exclusively or predominately non-metastatic PCa patients, and therefore have been written with the undercurrent of "do no harm". However for patients with metastatic PCa, ADT remains essential and therefore the question becomes: Can we do less harm? Prior studies have suggested a lower risk of adverse events with orchiectomy compared to GnRHa, however definitive conclusions could not be drawn because of the lack of a direct comparison[6,8]. The current study has used the GnRHa group as the reference to which the orchiectomy group is compared, allowing for a critically important direct comparison between the two forms of ADT. Focusing on these patients results in a smaller, but more homogenous group than other observational studies. Importantly, patients who received AA as well as those with a baseline condition were excluded from this study to reduce the risk of bias. Use of AA could represent a confounding variable as they may influence the risk of CV events.

While this study has many strengths, one must be conscious of its limitations. Attempts were made to account for the differences between the groups analyzed, but there may be other key variables unaccounted for despite the propensity analysis. These include the use of bone anti-resorptive agents, corticosteroids, and diethyilstilboestrol, which are are commonly used in the treatment of metastatic PCa and impact the risk of fractures, diabetes and VTE. Furthermore, patients treated with GnRHa were stratified based on time on treatment, yet the same stratification was not pursued for the other groups. This may be relevant since some endpoints such as of fractures, CVD, and cognitive decline are associated with advancing age. Caution must also be exercised when interpreting studies of cognitive function, as it is difficult to measure even under ideal circumstances. Relying on diagnostic codes in a Medicare database has limited utility in detecting the frequently subtle symptoms that patients experience. Surprisingly, the effect of ADT on cognitive function is not well established; the largest randomized controlled trial addressing the subject showed no consistent adverse effect after 12 months of ADT in prostate cancer patients, compared to both prostate cancer patients not receiving ADT and healthy controls[9]. And while the expenditures analysis is an important addition, the 12-month time window evaluated likely does not provide an accurate assessment of the cost differences associated with the two forms of ADT: patients undergoing orchiectomy are faced with the up-front cost of a surgical procedure, while patients who chose GnRHa face continuing drug and administration costs. Furthermore, if patients who receive GnRHa have higher rates of complications, the medical costs of those will increase over time.

That orchiectomy may be associated with a lower risk of CVD compared to GnRHa is not altogether surprising, although controversial. Some studies have found that GnRHa, but not orchiectomy, are associated with excess CVD risk compared to non-ADT treated controls[6,8]; while a recent meta-analysis of observational studies has found an increased risk of CVD with both GnRHa and orchiectomy[10]. Nevertheless, the lower risk of fracture is unexpected as a large observational study found orchiectomy to be associated with a similar if not higher risk of fracture compared to GnRHa[11]. Overall, it remains possible that no true difference exists between orchiectomy and GnRH agonists. Indeed, the number of patients undergoing orchiectomy in this study is relatively small and observational study bias due to unmeasured differences between the treatment groups is a significant risk. For this reason prospective trials are warranted.

If a true difference between these forms of ADT exists, GnRHa may play a direct role in the pathogenesis of these adverse events. GnRH receptors are present on many extra-pituitary tissues, including the heart, with some evidence that GnRHa directly mediate cardiac contractility and intracellular calcium concentration[12]. GnRH receptors are also present on T-lymphocytes, with agonists possibly promoting inflammation and contributing to the destabilization of atherosclerotic plaques, increasing the risk of plaque rupture and thrombotic events[13]. Studies in mice have shown that the GnRHa leuprolide causes atherosclerotic plaque instability, while the GnRH antagonist degarelix does not[14]. Interestingly, a meta-analysis of trials comparing degarelix to GnRH agonists showed a lower incidence of cardiac events within 1 year of initiating treatment in men with pre-existing CV disease[15].

Despite their retrospective nature, studies such as this are critically important, as they increase awareness of these concerns. As men with metastatic PCa are living longer than ever, it is imperative that we minimize the risk of harm from therapies. Physicians treating PCa patients must familiarize themselves with how to prevent and manage these complications (see Nguyen 2015 for a review of the subject[4]). The current article by Sun adds fuel to an already controversial debate, and the discredit brought by the reimbursement issues. When there is more than one reasonable option, clinical decisions must be guided by the patient's values and preferences. In the absence of clear evidence to the contrary, patients are likely to continue to overwhelmingly favour GnRHa over orchiectomy.

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