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Opinion

Orchiectomy – A Surgical Procedure in which One or both Testicles are Removed – is it Sufficient to Inhibit Androgen (Testosterone) from Access to Prostate Cancer Cells?

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A compilation of information by Charles (Chuck) Maack – Prostate Cancer Continuing Patient, activist, and Mentor - regarding anticipated testosterone level results following Orchiectomy, and reminding that testosterone is also produced by other sources than testicular.

I provided information below as a response to a prostate cancer patient in Australia with a testosterone level of 1.7nmol (50ng/dl) and still rising PSA post bilateral orchiectomy. The testosterone level 50ng/dl used to be considered castrate level but no longer so. 20ng/dl (0.68nmol/L) is the level considered castration level that has been achieved with testosterone deprivation medications to reduce the testosterone level of active testicular/Leydig Cell production. With bilateral orchiectomy, testosterone, on average, more often falls to 15 ng/dL (0.5 nmol/L). This patient's orchiectomy had not sufficiently lowered testosterone to suppress PSA elevation and requires further testosterone deprivation therapy. Apparently, testosterone produced from other sources (adrenal glands and testosterone that can be produced with cancer cells) continue to feed his cancer. With such PSA rising, and no evidence of metastasis (non-metastatic castration-resistant prostate cancer (nmCRPC), his Prolactin level should be checked and if high, treated with reasoning explained here: https://tinyurl.com/7w5omeo. Next, determine if dihydrotestosterone (DHT) level is elevated as the result of these other testosterone production sources. If so, an antiandrogen such as bicalutamide/generic of Casodex might suppress adrenal gland produced testosterone from coming in contact with 5 Alpha Reductase (5AR) enzymes on cancer cells wherein, if not blocked, that testosterone would be converted to the stronger stimulant to cancer cell growth, dihydrotestosterone/DHT. Also to be considered and might serve to inhibit any testosterone not suppressed by the antiandrogen while enroute to 5AR and bring PSA down and manageable, would be the 5AR inhibitor dutasteride/Avodart to inhibit that conversion.

Additionally, to be considered, and recently approved by the FDA for nmCRPC to add to ADT, is enzalutamide/Xtandi, a much more powerful androgen receptor blocking medication than the usual antiandrogen, to block any T or DHT access to 5AR and/or the multitude of androgen receptors on cancer cells. Another for alternate consideration recently approved by the FDA is apalutamide/Erleada to add to the ADT, since this is also a "next step" medication for nmCRPC pre-chemotherapy prostate cancer. On the near horizon will likely be darolutamide/ODM-201, on the verge of approval by the FDA, for pre-chemotherapy nmCRPC.

What would likely be yet another medication preferred, but unfortunately only approved by the FDA for pre-chemotherapy "metastasis evident" castration-resistant prostate cancer (mCRPC), would be abiraterone acetate/Zytiga that shuts down the three locations of T production (testicular, adrenal glands, and that which cancer cells can produce within themselves)

Since enzalutamide and apalutamide are expensive medications, it would be important that they are covered under one's government or private health insurance plan. Please note that I am only describing considerations to discuss with your treating physician (preferably a Medical Oncologist).

Testosterone from other sources than testicular

Despite testicular shut down of testosterone production either by GnRH agonists or antagonist – or by orchiectomy - the adrenal glands still secrete precursors to androgens such as testosterone and prostate cancer cells acquire the ability to synthesize androgens thus castration and inhibition of testosterone production in the testes may not achieve androgen deficiency in prostate cancer cells, particularly those in advanced stages of the disease. (MY NOTE: Though the below reference goes into detail as to how androgen can be produced from other sources (adrenal glands - and cancer cells can produce testosterone within themselves which is

derived from cholesterol) to fuel androgen "independent" cancer cells - the same can occur to continue to fuel androgen "dependent" cancer cells.) http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2802176/.

Of further note regarding effects of orchiectomy vs ADT, this paper https://tinyurl.com/y77762w4 concludes that a consequence of orchiectomy is greater increases in fat accumulation and increase in insulin resistance than similar effect from ADT medications.

In summary, and depending on the patient's financial situation, ADT appears preferable to orchiectomy for androgen/testosterone control and management.

PLEASE NOTE: Medications involved in Androgen Deprivation Therapy (ADT) are known to increase cardiovascular risk. Thus, IT IS IMPORTANT that prior to prescribing any form of ADT medication the patient's other health issues, that would include already present cardiovascular issues, are determined. As noted in:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4516188/

"Androgen deprivation therapy (ADT) has been the mainstay of treatment for advanced prostate cancer for decades and has been shown to control disease and improve symptoms. In addition, for men with high-risk localized or locally advanced prostate cancer, short-course ADT in combination with radiotherapy improves survival. There is evidence that ADT increases cardiovascular risk, particularly in men with preexisting cardiovascular disease. This increased risk may apply even with short-course ADT. In an individual patient, the benefits of ADT should be balanced against the risk, and patients who require ADT should have risk factors for cardiovascular disease optimized. There is some evidence to suggest that more contemporary methods of delivering ADT may reduce cardiovascular risk".

Dr. Matthew Roe, a Professor of Medicine at Duke University's Clinical Research Institute (DCRI), the Faculty Director of the Global Outcomes Commercial MegaTrials program, and the Director of their Fellowship Program, remarks: "If a patient who has advanced prostate cancer and known cardiovascular disease is being considered for androgen deprivation therapy, it is important that he speak with his cardiologist. (Presumably, both a cardiologist or cardiovascular specialist and an urologist or oncologist would treat him.) He needs to ensure that all the providers have a discussion about what the best and safest treatment would be before therapy begins. Obviously, this trial (the PRONOUNCE trial regarding which is safer for patients with cardiovascular issues, the GnRH agonist Lupron or antagonist Firmagon (or neither?) https://tinyurl.com/yxnw5kb6) is not completed yet so we don't have any answers. In the meantime, it is certainly in the patient's best interest to ensure that his providers are communicating and trying to jointly determine the right approach.

Disclaimer

Please recognize that I am not a Medical Doctor. Rather, I do consider myself a medical detective. I have been an avid student researching and studying prostate cancer as a survivor and continuing patient since 1992. I have dedicated my retirement years to continued deep research and study of prostate cancer to serve as an advocate for prostate cancer awareness, and, from an activist patient's viewpoint, as a mentor to voluntarily help patients, caregivers, and others interested develop an understanding of this insidious men's disease, its treatment options, and the treatment of the side effects that often accompany treatment. There is absolutely no charge for my mentoring – I provide this free service as one who has been there and hoping to make their journey one with better understanding and knowledge than was available to me when I was diagnosed so many years ago. IMPORTANTLY, readers of medical information I may provide are provided this "disclaimer" to make certain they understand that the comments or recommendations I make are not intended to be the procedure to blindly follow; rather, they are to be reviewed as MY OPINION, then used for further personal research, study, and subsequent discussion with the medical professional/physician providing their prostate cancer care.

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