

ANDROGENS AND PROSTATE CANCER

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Androgens and PCa — Part I

Introduction

During the 1940s Dr. Huggins proved the androgen dependence of prostate cancer. Since then, androgen deprivation has been the mainstream treatment for advanced metastatic prostate cancer. Initially, androgen deprivation was considered a magical cure because of the incredible reversal of symptoms. That enthusiasm was short-lived as in time most patient's disease advanced and symptoms returned. Still, today androgen deprivation remains as the first-line therapy for advanced prostate cancer at diagnosis.

One significant difference today, during the PSA era, is that when advanced prostate cancer is detected at diagnosis, the stage of the disease is usually at a less advanced stage. This has a significant impact in how effective androgen suppression can be. It is medically recognized that the lower the tumor burden at diagnosis the better the response to androgen suppression. This fact is sometimes not recognized by medical practitioners who advocate for saving deprivation for a "rainy day" in detriment of some patients.

The cause of prostate cancer has never been fully defined. It is no doubt a complicated matrix because very rarely younger men develop clinical prostate cancer while older men frequently do. The implication here is that as testosterone levels in older men drop, as a consequence of age, the incidence of clinical prostate cancer tends to increase.

In autopsy studies of men who die of accidents, indolent prostate cancer is commonly found as early as the fourth decade of life (30 to 40 years of age). This should not be ignored when considering models of prostate cancer. As clinical forms of prostate cancer arise as testosterone levels decrease, this could possibly be explained by the slow development of this cancer, environmental and lifestyle factors and last but not least on how the alteration of the hormonal milieu becomes a factor in this process. The key hormone players in this equation are testosterone (T), dihydrotestosterone (DHT) and estradiol (E2). Both androgen and estrogen receptors are involved in this complex matrix. Ed Friedman, PhD (3) proposes

that currently there are two models for prostate cancer that involve these hormones and their receptors in the carcinogenic process. These models are totally opposed to each other.

Model I: Supports the notion that high levels of androgens cause prostate cancer. (1)

Model II: Supports the notion that high levels of androgen prevent prostate cancer and are effective in the treatment of the disease. (2)

At this point in time, of the two models, Model I seems to have more support as a model for prostate cancer. Major support for Model I is the initial work done by Huggins and more recent studies demonstrating both postponement of metastasis development and survival benefits. Few practitioners today are using testosterone supplementation to prevent PCa and fewer YET use it to treat prostate cancer. Still, Model II has supporters and logic behind it because under certain conditions androgens can inhibit cell proliferation and tumor growth. This is an interesting concept that practitioners such as Drs. Leibowitz and Tucker are using to treat prostate cancer in a cohort of men. Both doctors practice in Los Angeles, CA

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Implications of an altered T:E2 ratio

In general, as testosterone (T) levels decrease with age, estradiol levels remain constant. Estradiol (E2), the main female hormone is produced in males by an irreversible enzymatic process of aromatization. This implies that with reduced testosterone and same level of estradiol, the normal testosterone/estradiol (T:E2) ratio that exists in younger men is altered in favor of estradiol in older men.

As mentioned before, if latent (autopsy) forms of prostate cancer exist as early as the second, third and fourth decade of life, these cancers had their origin in men who at that age had not experienced a marked decrease in testosterone production. Is it possible that generation of oxidative species by androgen can cause this initial DNA damage that starts the carcinogenic process?(12,13) These cancers are by no means what clinical cancers are at a latter point. They are usually well differentiated and very small in volume. Still, they are present in relatively high numbers in younger men who were oblivious of their presence and experienced an accidental death.

What causes these cancers to progress to clinical stage cancers in some men and not in others? It is known that men with genetic defects affecting the production of DHT are not affected with prostate diseases such as hypertrophy or PCa. (4) It is also known that estrogen alone or in combination with androgens, can induce aberrant growth and/or malignancy of the prostate gland in animal models using human prostatic epithelium. Squamous metaplasia is an abnormal form of prostatic epithelial differentiation elicited by exogenous estrogen alone. (5)

Can a reduced ratio of testosterone to estradiol (T:E2) be the factor that promotes the progression of these latent prostate cancer cells found in younger men to more poorly differentiated cells? What is the range of such ratio to cause progression? Can testosterone supplementation avoid this causative effect? Can the control of estradiol at an older age have a similar effect as testosterone supplementation in controlling the ratio?

Interesting questions for which I have no immediate or conclusive answer. Since I am not qualified to find an answer, it seems to me that in such complicated matrix, such controls would be too simple to resolve the equation. How does DHT impact this matrix? Would testosterone supplementation or inhibiting its aromatization to

estradiol “fix” this abnormal ratio while DHT is normal or elevated? These and other important questions come to mind.

It is important to think “out of the box” because many times solutions to problems come from the least expected places. Androgen deprivation in the treatment of advanced prostate cancer is well documented. Even after many decades of use the practice is still (rightfully so) not well accepted and medically recognized as non-curative. Androgen supplementation is poorly documented and less used in the treatment of prostate cancer.

Even those using testosterone supplementation are cautious about its use. The evidence in support of this form of treatment is tenuous at best and rejected by the majority of today’s medical practitioners. To the patient, failing current PCa treatments, its use is probably more appealing. Is there risk in this treatment?

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Androgens and PCa — Part III

Testosterone supplementation for prostate cancer

If controlling testosterone to maintain a “normal” T:E2 ratio prevents the development of more aggressive forms of clinical prostate cancer and is a possibility to treat patients who have reach an androgen-independent stage, we need some supporting evidence that this simple maneuver (considering the complexity of the equation) is a potential avenue for many men.

It is important to understand how androgens affect prostate tissues. The main reason androgen suppression is not curative is because the gland is made up of cells that do not need androgen to survive. This compartment of prostate cells is in the minority in quantity, but not in importance. These androgen-independent cells of the prostate are the basal, pluripotent stems cells (mother of all cells) that make up and maintain the functioning of the gland.

How does prostate cancer, which for the most part is so androgen-dependent, get to the point where it does not need androgen to progress? If there are individuals that are androgen-independent at diagnosis, this must be a consequence of a natural adaptation process driven by a lack of androgen or by genetic changes (mutations) that cause the cancer cells to be unstable and to be able to proliferate and grow without their normal androgenic stimulus. At this point the presence of androgen receptors is an important consideration in these individuals.

If for example, the ratio of androgen-dependent cell compartment to the androgen-independent cell compartment of the prostate gland is 80:20, there is a natural progression to androgen-independence by which this ratio is tilted to the independent side. Dr. Bruchovsky (6) contends that when the compartment of stem cells reaches a certain ratio to the number of tumor cells, resistance develops as an initial step to androgen-independence. In other words, the natural progression of prostate cancer to an endpoint seems to be androgen-independence, if given sufficient time.

With this in mind, science is searching for an answer to avoid androgen-independence. Intermittent hormone suppression is a first step in that direction which at the same time provides an improvement in QOL. Under improvements for QOL men with prostate cancer have used testosterone supplementation. The medical literature is very scarce of quality studies that shed a light on this issue. What is the level of risk for a PCa survivor to be treated with testosterone replacement therapy (TRT)? At what stages of the disease is this risk more pronounced?

Dr. Leibowitz is using TRT in prostate cancer patients to improve their QOL. The stage of disease in these patients covers all ranges. Other doctors are reporting TRT after primary PCa treatment in hypogonadal patients (7,8), but in general most urology practices are reluctant to institute this practice in known PCa patients.

Dr. Leibowitz is cautious in its use of TRT when he said: “The only reason to use testosterone replacement therapy is for quality of life issues. Do not use TRT to try to decrease your PSA. If your PSA declines, it is an extra unexpected “bonus benefit.”

This, I suppose it is done for legal issues protection.

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>> Androgens and PCa — Part IV

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>> What are the characteristics of PCa patients that can potentially benefit
>> from TRT?

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>> As we look for studies that had used TRT to treat metastatic PCa in search
>> for results and patient characteristics, the field narrows down to very few

>> studies. The Fowler and Whitmore study (9) is extremely flawed. They treated
>> all patients with the same amount of exogenous testosterone, but neither a
>> baseline nor a post treatment testosterone level was taken. Very few
>> patients responded and then only symptomatically, but wouldn't it be
>> interesting to pursue finding out why this minority responded? No effort
was
>> made to find why this happened.
>>
>> Today's hormone refractory patient is significantly better off than
patients
>> were a few years ago, but still they are left with reduced options. If TRT
>> is another option for some of them it would be good to know (10,11). At
this
>> point, patients considering this form of treatment are left wondering if
>> this approach is valid or not. It is frustrating to find that this
potential
>> avenue has been ignored. The existing studies dating back to the fifties
and
>> sixties do not provide information about who would and who would not
>> benefit. One thing is clear, when hypogonadal men are treated with
>> testosterone supplementation, there is no "explosive" generation of PSA to
>> indicate that the treatment is carcinogenic. In general the use of TRT has
>> generated controversy in spite of benefits.
>> In researching low testosterone as a cause for PCa, there are pending
issues
>> (hurdles to be resolved, at least in my mind)
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>> a. Low incidence of prostate cancer in genetically 5-AR impaired patients.
>> b. Low incidence of PCa in Klinefelter syndrome patients
>> c. Oxidative DNA damage induced by androgen(12,13)
>> d. Testosterone's metabolic rate in PCa patients (14,15)
>> f. Growth factors. IGF, EGF, PDGF, FGF, ILs etc. Involvement in PCa
>> progression
>> g. TRT in the treatment of PCa. What level of testosterone is the minimum
>> level required to induce apoptosis of AI cells?
>> h. Chronic Inflammation and PCa. (16,17)
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Further comments of Ralph Valle:

The action of PCa localized treatments on serum testosterone are not clearly defined. Johns Hopkins reported that men treated by radical prostatectomy(1) have a testosterone elevation a year after surgery. This was a small study and I am not totally convinced of its significance.

In the case of brachytherapy and RT, there is little to report although Mydlo JH reports that "it has been demonstrated in several reports that external-beam radiation therapy is associated with decreased spermatogenesis due to Leydig cell dysfunction and decreased serum testosterone"(2)

Although several reports point to the fact that men with prostate cancer tend to have lower levels of testosterone (not strange considering that the disease is more common in older men) the reality is that when looked at closely there is little statistical difference to imply that lower testosterone is the cause of developing clinical PCa. Meikle AW (3,4) reported that men with PCa have higher production and clearance metabolic rates of testosterone than normal men.

I wish I could be more positive in answering your question, but the bottom line is that at least at this point in time no one has a clear picture of the cause of PCa. Theories and hypothesis are abundant. Still it is always...consumer beware!

RalphV

<http://www.pcainaz.org/phpbb>>www.pcainaz.org/phpbb

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