Compassionate
Oncology Medical Group

Bob Leibowitz, M.D.
DIPLOMATE
AMERICAN BOARDS OF INTERNAL MEDICINE,
MEDICAL ONCOLOGY AND HEMATOLOGY
Subspecialty of Prostate Cancer

Isaac Gorbaty, M.D.
DIPLOMATE
AMERICAN BOARDS OF INTERNAL MEDICINE
AND NEPHROLOGY
Subspecialty of Prostate Cancer

Mary Duong, P.A.-C.

HIGH-DOSE TESTOSTERONE REPLACEMENT THERAPY AND PROSTATE CANCER

The package insert that accompanies any type of prescription for testosterone replacement products states that testosterone is "contraindicated in men with prostate cancer." This means that you should never use any form of testosterone if you have prostate cancer. 99.9% plus of all physicians believe that if you give testosterone to a patient with prostate cancer, it's "like adding gasoline to a fire." We are taught that testosterone will markedly stimulate the growth of prostate cancer cells, cause widespread metastatic disease, and greatly hasten death. Testosterone replacement therapy has also been reported to cause permanent paralysis.

A number of years ago, I reviewed the medical literature regarding the relationship between testosterone and prostate cancer, especially in men who were previously treated for prostate cancer. I previously discussed this subject in detail in my September 2003 paper, "High-Dose Testosterone Replacement Therapy," and the interested reader is directed to this paper. You can find this paper, as well as all of my papers, at www.compassionateoncology.org. All of the papers may be downloaded at no charge. Since 2002, my recorded (DVD or VCR format) public lectures contain detailed information on testosterone replacement therapy (TRT). Those same lectures show results from patients that I have treated with TRT. You can order them by calling my office.

It is of major interest that the two articles that are quoted as references for substantiating the "contraindication curse" are both by Jackson E. Fowler Jr. and Willet F. Whitmore; one appeared in the *Journal of Urology* (126: 372-375) in 1981 and the other was published in the journal *Cancer* (49:1373-1377) in 1982. Both articles report on the same group of patients. In those articles the authors state that the use of testosterone in patients with prostate cancer should be undertaken with extreme caution. They do not state that testosterone is contraindicated. All of the patients in these articles had metastatic prostate cancer. Four were previously untreated; 14 were on hormone blockade, but were thought to be in remission. However, since we did not have the benefit of PSA's, being in remission just meant that you did not have bone pain. Some of these patients probably had progressive disease, but it had not yet become symptomatic. Thirty-four other patients had progressive, metastatic, hormone refractory prostate cancer, mostly with bone pain.

One of the previously untreated patients remained on testosterone for 310 days. The mean number of days on testosterone for the four untreated patients was 110 days, even though they had metastatic prostate cancer. Of the 14 patients who were thought to be in remission; ten remained on testosterone for at least 50 days. Of these ten, five were able to remain on

testosterone for 120 or more days, including one patient for 245 days, and another for 420 days. The doses of testosterone used were far lower than the doses I believe to be most effective. In spite of using TRT incorrectly (in my opinion) to treat men with metastatic prostate cancer, the reader should be impressed that some men remained on T treatment as long as they did.

I presented this information at a Prostate Cancer Journal Club Meeting on September 14, 2005. The subject I lectured on was high-dose testosterone replacement therapy and prostate cancer. I distributed a copy of the articles referenced below to validate these references.

An editorial by Ana M. Soto and Carlos Sonnenschein appeared in the *Journal of the National Cancer Institute* on November 21, 2001 (93(22):1673-1675). This editorial points out that sex steroids (such as testosterone) are mediators of both cell proliferation and cell death. Low doses of estrogen for breast cancer cell lines, and low testosterone levels with prostate cancer cell lines, increase cell proliferation, whereas high doses inhibit cell proliferation. There is a biphasic response, and high physiologic doses in a bell-shaped curve cause prostate cancer cells to enter a proliferative quiescence. The higher the level of testosterone, the greater the inhibition.

One page of an article by Horace Munger describes a patient who had metastatic, hormone refractory prostate cancer, was felt to be terminal, and was treated with testosterone. He then became free of pain, and rectal examination revealed the prostate bed to be flat, smooth, and no longer having any firmness. He had gained ten pounds in weight, and his anemia had resolved. During the seventh week of testosterone therapy, repeat x-ray studies of the pelvis revealed the **disappearance** of the metastatic lesion in the ilium. How impressive is that? Normalizing a metastatic abnormality on x-ray, and in only seven weeks!!! He was being continued on testosterone at the time of the article. The author stated that, "When a failure is manifest under estrogen suppression, reversal to the opposite extreme of androgen-estrogen balance should be instituted, and observation of its effect recorded." What interested me the most is that this article appeared in the *Transactions of the AUA*, Central Section, pages 100-104, and the article was published in **1947**.

An interesting article by Herbert Brendler and colleagues, commented that, "It appears to us that if continued progress is to be made in the treatment of prostatic cancer, the exact role of androgens in the induction of cancer or the maintenance of cancer growth must be ascertained." The article reports on three patients "for whom the prognosis was regarded as hopeless." Two of the patients improved considerably within two weeks, and in one of these, there was a palpable decrease in the size of the prostate. This shows us that administration of testosterone caused an objective reduction in the size of palpable prostate cancer. The improvement lasted for about five months. The authors state, "Because of the surprising," **but not totally unexpected observations**....telling us that these authors were not surprised that testosterone could benefit prostate cancer patients. This article appeared in the *Archives of Surgery*, (61(3): 433-440), and the year of the publication was **1950**.

In Prout and Brewer's article that appeared in the journal *Cancer* in November, 1967 (20(11):1871-1878), the authors describe a patient that was "unquestionably in a preterminal state when he first received testosterone"[(Pg. 1,878)]. His prostatic acid phosphatase (PAP) levels fell as his general condition improved. This is the blood test that was used to monitor prostate

cancer progression and/or response to treatment. It was the only prostate cancer blood test tumor marker available prior to the development of PSA. Even today, there are some situations where the PAP blood test remains useful. The androgen administered caused dramatic improvement in the patient. The authors state, "We conclude that the effects of exogenous testosterone in patients with advanced prostatic carcinoma, whether previously treated or not, are neither clear-cut nor predictable in many instances."

At the Journal Club, I emphasized that the examples that I had just discussed were from articles published between 1947 and 1967. They clearly demonstrated that the role of testosterone (T) in prostate cancer is not clearly defined. What I believe caused most doctors to believe that TRT is always harmful is that initially, withdrawing T causes metastatic prostate cancer to go into remission for well over 90% of all patients. These responses are rapid and dramatic, and since removing T helps men with metastatic prostate cancer, everyone assumed that adding T would logically make them worse.

However, for men with metastatic disease, the average duration of response to hormone blockade is only 18-20 months; after that, hormone resistant prostate cancer develops. Therefore, if patients are treated with continuous hormone blockade, as was first recommended in the early 1940's, the average duration of remission is only 18-20 months. That is not much to brag about. Treat men with metastatic prostate cancer with the so-called community standard of practice, and your patient will develop hormone resistance in about one and a half years, and die of metastatic prostate cancer, on average, one to two years later.

Rather than accept this terrible "sentence," these pioneer authors expressed the belief that we must study and understand the basic fundamental relationship between testosterone and prostate cancer. The relationship must be understood not just when a patient is hormone naive, but at all subsequent phases of hormone dependence/independence. The authors from these enclosed articles asked these questions more than 50 years ago!! I have simply rediscovered what they too found. Somehow their observations were ignored, while those of Fowler and Whitmore became unchallenged dogma. Imagine how differently we could be treating metastatic prostate cancer patients today if the tables were turned. What these authors are actually stating is that in men who have already been treated for prostate cancer with hormone blockade, and particularly those men who are in remission, the role of testosterone is not at all well defined. That is the opinion these authors first voiced in 1947. I am convinced that absolutely nothing has changed more than one-half century later.

An editorial by Roger Kirby and Duncan Gould, from the Department of Urology, St. George Hospital, London, U.K., appeared in the *British Journal of Urology International* in 2005 (96: 471-476). The article was titled, "Testosterone Replacement Therapy in Hypogonadal Men and Prostate Cancer Risk." The authors state, "The precise role of androgens in terms of carcinogenesis is unclear, as greater than 60 years of worldwide use of testosterone has failed to elicit a signal through case reporting or national adverse – event monitoring."

They are saying that no study has demonstrated that treatment with testosterone is involved in prostate cancer carcinogenesis. In fact, a number of studies where testosterone was administered over 6 to 36 months have shown no increased risk over the background prevalence.

They go on to state, “At present, there appears to be no compelling evidence that testosterone per se has a causative role in prostate cancer. No direct correlation between serum testosterone levels and the risk of developing prostate cancer has been shown and, indeed, high-grade prostate cancer is associated with low levels of testosterone.”

At that September 2005 Prostate Cancer Journal Club Meeting, I presented the clinical details from ten different patients from my practice that I had treated with TRT. If a person believes in intermittent hormone blockade, then when you discontinue hormone blockade, a man’s endogenous testosterone level will recover to its pretreatment range. Since all of my patients are on Proscar, 5 mg once a day (so-called finasteride maintenance® therapy), their testosterone levels on Proscar are significantly higher than they were before they were started on hormone blockade. The average baseline testosterone in my series was 370; on Proscar maintenance, approximately 495. Thus, when off HB, the men in my triple hormone blockade®/Leibowitz protocol series have testosterone levels of just under 500. My target level for T in men that I treat with high-dose TRT is 1,800-3,000. Thus, **the essential question is not whether testosterone is beneficial or harmful to a man with previously treated prostate cancer, but whether a T of 500 is better or worse than a T of 1,800-3,000**. Obviously, that question has never been studied.

Clearly, men on high-dose TRT have a marked improvement in quality of life. Most of them tell me that they feel better, stronger, have an improved overall sense of well-being, and many report an improvement in mental acuity (such as improved memory and/or concentration). Almost all men notice a marked improvement in libido. Different men tell me that they feel like they did in their 20's, 30's, and 40's. All of the men that I have treated with TRT are aware that the only indication for using T in a man with prostate cancer is for quality of life issues.

Of the ten patients that I described at the Journal Club, I think the most dramatic is John H., who presented with a PSA of 3,346 in November 2003; a Gleason 8; multiple bone metastases; a 22-pound weight loss, and pain, etc. After 13 months of hormone blockade, five months of T/E/C chemotherapy, and antiangiogenic cocktail, his hormone blockade was discontinued in January 2005. He started TRT on January 17, 2005. As of August 2005, his testosterone was 5,488; his PSA 0.454. As of November 18, 2005, his testosterone was 3,546; his PSA 0.36. Since that Journal Club meeting, I have tried to update the results from the ten men, and have added other TRT examples, as well.

I have also included a man who had radical prostatectomy in 1994, later radiation therapy, and later hormone blockade. In September 2000, with a testosterone of 113, he was started on high-dose TRT. Almost five years later, his testosterone was 1,395, with a PSA of 1.72**,** and he has commented to me that he feels like he has been given a new life because of the improvement in quality of life associated with high-dose TRT. Before TRT, he had been especially troubled with his marked decline in mental acuity, and felt like he had to quit work. On TRT, he regained all of his lost mental acuity (and then some). He has told me that he feels like he is in his 20's or 30's. He works as an engineer.

I sincerely hope that the reader will be as impressed with this information as I am. Every time that I see a new PSA and testosterone result on these men, I find myself astonished; I usually mumble to myself, or anyone nearby, “miraculous incredible, impossible to believe,” or similar descriptive adjectives. I can only hope that these examples will stimulate scientists (I am anything but a scientist) to study these results and develop the tools that can be used to predict which patient will respond favorably to T, and even what level of T is ideal for them. I have been using testosterone since 1998, and have learned to identify certain prognostic factors that are helpful to predict who may be more likely to do well on TRT, but additional, much more reliable tools need to be discovered. If nothing else, my work with TRT is a very crude beginning. Learning about who may respond may offer hope to some men who until now believed that they would have to remain on hormone blockade for the rest of their lives. Hope is something we all need.

I cannot overemphasize that this paper should not be brought to your doctor along with a request for a testosterone prescription. Testosterone is contraindicated in men with prostate cancer. It has caused the death of some patients (fortunately, no one in my practice); permanent paralysis, increased bone pain, and new metastases. I do **not** recommend use of T for anyone with prostate cancer.

DR. BOB

***** None of the above should be construed as medical advice or consultation, and anything discussed in this paper is meant for information only. All medical treatments, consultations, decisions and recommendations can only be made by the patient and his/her treating physician.

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