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Challenging PC Treatment Biases – Is Nothing Sacred?

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Most prostate cancer (PC) patients have acquired quite a bit of knowledge regarding the “best” way to administer hormone blockade. The answer to this question is obvious… whether you choose continuous androgen blockade (CAB) or intermittent androgen blockade (IAB) is determined by whichever way you and/or your doctor decide is best. Other less opinionated patients might chain themselves to their internet portal device and try to quickly read a few million cholesterol but what is surprising is that men gain a lot of fat quickly if they do NOT AGGRESSIVELY EXERCISE WHEN ON HORMONE THERAPY! In the Dr. Moyad world no one receives hormone therapy unless they agree to exercise daily and lift weights twice a week (as long as they get doctor clearance and do not have bone metastasis).

-Abstract 43 was a great review of the cheap blood test C-reactive protein (CRP), which appears to have some ability to predict overall survival in men with metastatic prostate cancer from preliminary research (higher values are more concerning), but a large prospective study is needed and it is interesting work.

WHAT ELSE DO I NEED TO KNOW?
I have written too much for this issue and my fingers hurt. I need to take a 3-month break before writing again. However, I love you all like family and I will see you soon!

THAT IS ALL FOLKS!
See you this SUMMER, when I will write about many other serious issues and give timeless advice in the next newsletter, such as: why it is never smart to drink 2 gallons of water wearing really tight jeans on a 4-hour airplane flight with the airplane bathroom out of service or why it is not smart to live in Michigan in the winter (especially during 2014) and forget to buy 20 pairs of 10-inch thick thermal underwear! HAPPY SUMMER - SOON I HOPE!
to go back on HB. And if you are ever urged to start another cycle of HB, you should instead insist on being treated with my 3-Pronged treatment protocol. It is my opinion that this is clearly the most effective and best way to use HB and always remember my first rule: “Everyone is entitled to their own opinion. Their own WRONG opinion.” Corollary: “Especially me.”

As I explained in the last issue of PAACT, in my very strong opinion, the longer you are on HB, the more your illness is evolving into CRPC. Each month on HB brings you 1 month closer to CRPC and a shortened survival. The definition of CRPC is a rising PSA while you are on HB. If your doctor can find effective treatments that can delay or better yet, prevent the need to go back on HB, then by definition, you will not evolve into CRPC, since a rising PSA with normal or elevated testosterone levels is not CRPC. Every month a prostate cancer patient survives with a normal or even better supraphysiologic level of testosterone (T), is one additional month of survival… as opposed to when he has a rising PSA on HB, which, in my opinion, will shorten his survival one month.

Until the past several years, the near universal opinion of academic prostate cancer experts, along with almost the same percentage of clinicians (or at least that is what they wrote and said) was that IAB should be considered experimental and should not be used outside of an experimental (Institutional Review Board {IRB} approved) study.

In the late 1990’s, I was honored to be an invited speaker and panel participant at the annual Massachusetts Prostate Cancer Symposium. Some of the other panelists included Dr. Marc Garnick, A professor at Harvard Medical School whose predominant interest is urologic oncology, with a specialization in clinical investigation related to prostate cancer. We both had spent time (he still does) at the Harvard Medical School affiliated Beth Israel Medical Center. Other panel members included a family practitioner; a patient care advocate who was a prostate cancer survivor; a well-known, highly regarded academic urologist; a few other members that I sincerely apologize to because I have forgotten their names. Most impressive to me, our panel was privileged to have Dr. Anthony V. D’Amico, MD PhD, participate. He is, without doubt, one of the absolutely most brilliant and nicest people I have ever been blessed to know. He very likely is among a handful of the “all-time best” radiation therapists in the world; he is affiliated with Dana Farber/Harvard Cancer Center as well as Brigham and Women's Hospital (both Harvard affiliated and I had the privilege to spend 6 months of my fellowship at these institutions). Dr. D’Amico has been a major contributor in countless ways helping to better treatment and control cancer along the entire spectrum of malignant disorders. His research in PC therapy is one of his major areas of expertise, resulting in major advances in patient care, as well as in the basic science of PC. One of his major PC contributions is known as the D’Amico classification scheme dividing new patients with prostate cancer into 3 separate, well-defined prognostic categories: Low Risk, Intermediate Risk, and High Risk. Yes!!! That D’Amico – impressive, huh?

The final panelist, equally as impressive to me, was also our moderator, Dr. Philip W. Kantoff. Like many of the other panelists, he is a professor in the Department of Medicine of Harvard Medical School. He was also the Director of the Lank Center for Genitourinary Oncology at Dana-Farber Cancer Center, and is one of the most respected and knowledgeable prostate cancer experts in the world.

The Symposium started with each panelist delivering their prepared talks and slide presentations. Following this, Dr. Kantoff, as moderator, lead us to discuss a number of controversial issues based on an imaginary (or actual) prostate cancer patient from his clinic who required a treatment recommendation at various stages of his illness. My most vivid memory involved Dr. Kantoff asking us about the type and manner of HB that we recommend for our patients.

1) “Who would treat this patient with IAB? Who would advise CAB??”

Never being shy, my hand did not even wait for the entire question to be asked or even for my brain to select an answer before it shot upward, almost pulling me off my chair.

“IAB” my hand seemed to force my mouth to yell out. The rest of the panel absolutely and unanimously disagreed with my hand and my mouth.

Next question:
1) “What type of patient on hormone blockade, in your practice, do you believe is a candidate to be treated with IAB?”

That same hand acted without hesitation, and Dr. Kantoff allowed me (reluctantly?) to answer:

“All of them!” Surprisingly, none of the panelists shared this belief and once again they unanimously chose the exact opposite answer.

2) “Does anyone have any patient in their practice on IAB?”

Hand – yes

Everyone else – no!!!

And finally,
3) “Does anyone believe that at any future time they will ever use IAB in their practice?”
Only my hand rose. The unanimous opposition party that comprised all of the panelists, except Dr. Bob, only raised their hands when the offered choice was “No”; they cannot conceive of a time when they would ever treat any patient in their practices with IAB, instead they confirmed that they would always advise their patients to use CAB, and never to use IAB.

About 4-5 years ago, I was reading a medical journal that published the authoritative National Comprehensive Cancer Network (NCCN) treatment guidelines for various cancers and that issue addressed the use of hormone blockade (HB) for prostate cancer patients. One of the authors was Dr. Kantoff. In spite of any differences of opinion we have had, he and I both know that he is far more intelligent than I am; that he has devoted his life to determining and proving scientifically, exactly which treatments are most effective and/or least toxic for every stage of prostate cancer, as well as a large number of other types and stages of cancer. His efforts benefit prostate cancer (and other types of cancer) patients everywhere; he advances scientific knowledge benefitting society by following the scientific method; leaving nothing to chance; proving each and every step by creating treatment protocols, participating in them, supervising them, analyzing their results, and then presenting the results at conferences and/or publishing these results in peer reviewed journals, textbooks, symposiums, while always ensuring that the rights and privacy of every patient remain his primary concern. I am sure that I omitted countless other major contributions that were, are and will be made by Dr. Kantoff, but not intentionally (it is 2am).

Back to the NCCN guidelines for using HB to treat prostate cancer that I believe appeared in an April edition; they gave the exact same recommendation that had been articulated by a panel at the ASCO Prostate Cancer meeting in February of that same year (and Dr. Kantoff had expressed that same opinion). “CAB should be considered the standard of practice for prostate cancer patients requiring HB. IAB should be considered experimental and should not be given outside the context of an IRB approved clinical trial.”

Nothing (yet) had changed for more than 15 years. But about 3 months later, I was reading (I think) a newspaper-type journal, probably “Oncology Times,” and I noticed a picture of Dr. Kantoff along with an article about HB. The author quoted Dr. Kantoff and I paraphrase:

“Intermittent Androgen Blockade is at least as effective as CAB; and probably better.”

Shocked but ecstatic and so pleased, I immediately wrote a letter to Dr. Kantoff asking him to please let me know if the article was accurately quoting him regarding the type of HB he advises. He promptly wrote back to me saying that in general the article was accurate, although in a few uncommon HB settings, he might have some reservations about using IAB.

Around 1995, I had written that I believed IAB would eventually be shown to be superior to CAB, and in either 2008 or 2009, I was advised by Dr. Kantoff and others that soon to be reported studies were able to conclude that IAB should no longer be considered investigational. Over the next few years, IAB was generally considered the “standard of practice” method to prescribe HB. In January 2014, at the ASCO prostate cancer conference in San Francisco, more than 90% of the audience of physicians agreed that IAB should be the preferred way to use HB, rather than CAB. Please remember that it takes an extraordinarily long time for doctors to change their treatment preferences/prejudices.

Later in this paper, I will present case reports from our own practice that will provide some insight into my choice for the title of this article. I used this same title in 2003 at the annual Massachusetts Prostate Cancer Symposium. The Symposium was sponsored by Massachusetts General Hospital Cancer Center, Dana-Farber Cancer Institute, Beth Israel Deaconess Medical Center, Dana-Farber/Harvard Cancer Center, American Cancer Society, Tufts-New England Medical Center, Massachusetts Prostate Cancer Coalition, Massachusetts Department of Public Health, New England Coalition for Cancer Survivorship, American Foundation of Urologic Disease, and several more. There were two invited keynote speakers for this meeting: Dr. Philip Kantoff and myself (“Dr. Bob” Leibowitz.) This was the first national conference where I had the privilege to be a keynote speaker and I felt that this was the ideal format to present my interpretation and analysis of the medical literature regarding testosterone and its interactions in PC patients at different times in their evolution, from hormone sensitive disease to hormone refractory and maybe back towards hormone sensitive again. This evolution results in HB betraying you and becoming a Benedict Arnold as it switches from killing PC cells to helping PC cells, and to seemingly becoming invincible – fortunately enormous advances in understanding these changes continue to result in more FDA approved effective treatments to help men to defeat their own evil Benedict Arnolds. We cannot cure metastatic PC, but our increasingly realistic goal is to change it to a chronic disease (like high blood pressure or adult onset diabetes mellitus) that you can live with and die with, but not die from. At Compassionate Oncology Medical Group (COMG), we continue to make extraordinary, compelling and impressive progress, as we endeavor daily to make even more effective advances for each of our patients along this path. We design individualized treatments; we never use institutionalized, rigid, recipe-book-type (“cookie-cutter”) fixed protocol approaches that force the participating study doctors to become robotic, and not allowing carefully crafted and studied creative innovations.
The standard of practice protocols that are FDA approved only improve the median survival of PC patients by 2.5 months compared to placebo. The standards of practice that were used before the approval of Taxotere® in May, 2004 to treat PC patients had never been found to prolong survival in PC. Prior to May 2004, no treatment for PC ever prolonged survival. I began to exclusively use Taxotere® to treat all my PC patients who needed chemotherapy beginning in 1997, seven years before the FDA approved it for PC. Our use of Taxotere® as part of my 3-Pronged protocol and our own modifications to reduce side effects, while markedly improving its effectiveness, is a major reason that patients continue to travel literally thousands of miles to see us. Please see our map on our Compassionate Oncology website that identifies the various countries and states that are home to our patients. More than 75% of our patients are not living in Los Angeles.

Authors of numerous medical articles that were published in the 1940's, 1950's, 1960's and literally through today, reported that testosterone in some patients and at some stages of PC stimulated cells to grow, while in other situations, testosterone inhibited the growth of PC cells; and in the lab, the effect of T on PC cells follows a bell shaped curve...low levels of T stimulate PC cells to grow while high levels of T inhibit the growth of PC cells and the higher the level of T, the greater inhibitory effects on PC cell growth. This effect follows the classic example of a bell shaped curve. The same effect is seen when breast cancer cells are exposed to varying concentrations of estrogen. Low levels of estrogen stimulate breast cancer cells to grow, but high levels inhibit the growth of breast cancer cells; the higher the level of estrogen, the greater the amount of inhibition.

To find the specific medical references that confirm these “claims of mine” and will convince my loudest and most skeptical critics, please read the articles that I have posted on our Compassionate Oncology website, including “High Dose Testosterone & Prostate Cancer: Wait until you read this update,” “High-dose Testosterone Replacement Therapy and Prostate Cancer,” “TRT Case Reports: High-Dose Testosterone Replacement Therapy (TRT) and Prostate Cancer (CaP),” and “Testosterone Replacement in Prostate Cancer Survivors with Hypogonadal Symptoms” (BJU article May 2010; coauthored with Dr. Tanya Dorff, et al.). Also, see “Hormone Blockade: Continuous, Intermittent or?” and for 3-Pronged Approach case studies, read “Compassionate Oncology’s Latest Three-Pronged Approach Patient Case Studies.” You can also find them in the various DVD lectures that I have given (available FREE (only pay S&H) by calling our office or ordering on our website): DVD #4 (high-dose TRT), DVD #5 (IAB and high dose TRT), DVD #6 (high dose TRT and 3-Pronged), DVD #7 (high-dose TRT and AAC), DVD #8 (3-Pronged), and DVD #9 (high-dose TRT and 3-Pronged). Our latest DVD will be coming out very soon – you can call our office to preorder your copy today.

At the January 2014 ASCO prostate cancer conference in San Francisco, CA, there was a poster presentation by Dr. Samuel Denmeade, Professor of Urology and Pharmacology at Johns Hopkins. His paper reported on their ongoing study that investigates the effect of rapid cycles of very high levels of T followed by a cycle of HB with castrate levels of T. Their study tries to determine if PC growth might respond to their unique and previously untested theories. The poster describes their approach and results:

- Men with CRPC could respond to rapid cycling between polar extremes of supraphysiologic and castrate T levels [Bipolar Androgen Therapy (BAT)].
- Rapid cycling disrupts adaptive auto-regulation of AR.
- They call this “The Love Study”
- Eligibility criteria:
  - Must be on continuous androgen deprivation therapy (ADT) for greater than or equal to 1 year.
  - Rising PSA
  - Less than or equal to 5 total bone metastases and less than or equal to 10 total lymph node or soft tissue metastases.
  - No worrisome lesions (high risk), e.g., spinal cord compression, urinary tract obstruction
  - Prior second line hormone therapy and/or prior chemotherapy allowed
  - No pain

Men were started on T injections to achieve supraphysiologic levels of T above 1500 ng/ml (“normal” is usually about 300-800 in many labs).

A TRT Case Report from COMG:

S. B.

12/95: 52 years old; GS 3+3/6 at John Hopkins Hospital; PSA = 7.3
5 mos. 2-drug hormone blockade
Then saw Dr. Bob and was treated with 9 mos. Triple Hormone Blockade®, followed by Proscar® alone (Finasteride Maintenance® Therapy)
7/03: Started high dose TRT; later added in some Anti-Angiogenic Cocktail (AAC)

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Eleven years after his diagnosis of PC, he never received local treatment. His treatment was one 14-month cycle of HB and 3 years of high-dose TRT, along with some AAC. He expired unexpectedly, apparently in his sleep, and was found by his sister when he failed to show up at a restaurant where they planned to meet.

Excerpts from his autopsy report:

“Mr. B--- was diagnosed with moderately differentiated adenocarcinoma of the prostate gland circa 1996 and he has been under treatment since that time. At autopsy, there is no evidence of recurrent or residual tumor. The prostate gland demonstrates only benign stromal and glandular hyperplasia with no evidence of malignant tumor.”

“In this case, Mr. B--- had 90% and 85% luminal compromise of the right and left coronary artery systems, resulting in greatly reduced oxygenated blood flow to the heart muscle (myocardium), and this in concert with hypertension placed him at great risk for a sudden, irreversible, fatal cardiac arrhythmia or clinical heart attack.”

“Forensic Elements and Consultations: … Medical records: Limited records, primarily medication lists and records from Dr. Leibowitz office are received, reviewed, and retained in the autopsy file.”

I spoke to the pathologist before he started to do this patient’s autopsy. He understood that the reason we asked for an autopsy was to determine if there was any evidence of PC:

1) In this man’s prostate gland – he said that normally they would cut the prostate into 2 equal parts – like an opened oyster with a top and a bottom. Instead he cut the entire prostate gland into 1 mm slices. This is the same technique that is done with a radical prostatectomy specimen. The finding: no PC anywhere in the prostate.

2) All of the lymph nodes that drain the prostate were sliced like salami. The finding: no PC cells.

3) Knowing that PC spreads to bone preferentially and especially to the vertebra of the spine, he carefully sectioned each vertebral body longitudinally trying to identify anything that could be metastatic PC. The finding: absolutely no evidence of any PC cells anywhere in this patient’s body.

The cause of death was severe advanced bilateral coronary artery disease with 90% obstruction of the right coronary artery and 85% obstruction of the left coronary artery. These narrowed coronary arteries caused either a sudden fatal rhythm disturbance of the heart (like ventricular fibrillation) or a clinical heart attack (myocardial infarction).

This is a case of low-risk PC treated without any local therapy. The patient only received 14 months of HB and later the Anti-Angiogenic Cocktail (AAC). The autopsy confirmed that he had a pathologic complete response to these medicines alone.

Please note that I (Dr. Bob) have been using high-dose Testosterone Replacement Therapy (TRT) on select PC patients in our practice since the late 1990’s. I vividly recall my first PC patient starting on TRT; my target T range was only 100-200. Over the next 6 years or so, I slowly raised the target T level, while always requiring oral and written, informed consent detailing all risks/benefits and treatment options. We also ordered extremely frequent labs, as well as scans and office visits. When a patient was started on TRT, we initially required weekly labs, including PSA and T levels. If there were not any problems, we gradually lengthened the intervals between their blood tests, but even today, the least often that labs are checked is monthly. We were surprised to find that for most patients, PSA levels did not increase in spite of rising T levels. However, in patients who still had an intact prostate gland, their T levels began to rise after HB was stopped or if they were being treated with TRT, the T would always stimulate their normal prostate gland cells to make PSA. HB does not kill normal prostate cells. Everyone with a normal prostate gland will have their PSA’s increase, usually starting about 2-5 months after HB is stopped. The levels of PSA rise in what I describe as a “step and plateau” pattern. Can HB cure PC? It certainly did for this patient.

Part three of this article will be printed in the Summer 2014 issue of the PAACT Newsletter.

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