July 1997
April 2004

(Revised)

INTERMITTENT ANDROGEN BLOCKADE
(Formerly "THE FUTURE IS NOW!!" - Part II)

Intermittent androgen blockade (IAB) has come of age. The future is now.

At our recently completed 1997 American Society of Clinical Oncology presentations, there was a program on hormone refractory prostate cancer (HRPC).

We all know this is our dreaded enemy. That elusive devil of a term. That mysterious evil, powerful foe that may lie within us, waiting to declare itself. It holds us in terror as we wait for our next PSA; hoping and praying that we have not become hormone refractory.

Our strategy must be to figure out how to prevent or at least delay the onset of hormone resistant or, even worse, hormone refractory prostate cancer.

At one of our educational and poster sessions on HRPC, the speaker's slides listed strategies to delay or prevent the HRPC state. For the first time ever, IAB was listed as one of the more "promising options" that we have. This is the first time that I have heard a speaker lecture so positively about IAB. In the past, whenever IAB was mentioned, the tone was neutral to negative. At last a speaker at ASCO dares to suggest that IAB might be a promising approach to prolong survival, that IAB might be superior to continuous blockade. We already have proven IAB is associated with improved quality of life (during the off periods). Finally, a speaker dares to suggest it may also prolong life.

This is exactly what I believe. I comfortably and confidently predict that IAB will soon be proven to be clearly more effective than continuous androgen blockade. The future is now. I admit how uncomfortable it has been for me to be viciously attacked for daring to believe that we could challenge the "established dogma" that continuous hormone blockade is obviously the superior and only way. If

continuous blockade is not the best form of hormone blockade, then orchiectomy must not be allowed; men should be allowed to keep open their option for IAB. Orchiectomy is not reversible.

But let me inform, warn and educate you. There are many IAB formulas. It seems that like the rest of the field of prostate cancer, we have many more opinions than answers. Again, I remind all of us:

"Everyone is entitled to their own wrong opinions."

Let me expand on my observations and interpretations of this newest field of study, IAB.

Publications are beginning to appear as early experiences are reported. We all owe the greatest debt to the Vancouver, Canada group who, I believe, first studied and reported on the use of IAB for their prostate cancer patients. They personally, and Nick Bruchovsky in particular, have been my sources of inspiration.

It seems that most of the studies have utilized double or combined hormone blockade; usually an LHRH agonist, but the choice of the antiandrogen has differed in the few studies reported to date. What stands out to me, however, is that most studies utilize hormone blockade for about six to nine months. Typically they treat until the PSA reaches "normal;" or until the PSA plateaus. This is called the "on" treatment period. At this point the two drugs are discontinued and thus begins the "off" treatment interval.

These studies report that patients are "off" treatment for an average of five to nine months. Therefore, the off periods average from 38 to 50% of the time, usually 40%; the "on" is about 60% of the time or as low as 50% in one report. Double hormone blockade is usually restarted whenever the individual patient's PSA reaches some predetermined (but arbitrary rather than scientifically calculated) level. None of us know what the "ideal" level of PSA to re-treat actually is.

My own personal experience has been different and far superior to the reported literature.

As my readers know, I have been recommending what I have termed "Triple Hormone Blockade" or triple androgen blockade. This consists of:

> An LHRH agonist -- either Zoladex or Lupron every 28 to 30 days; plus flutamide (Eulexin), 250 mg every 8 hours (rather than 50 mg of Casodex, or nilutamide, or cyproterone acetate); plus Proscar, 5 mg once a day. Beginning later in 1997, I always recommended 3 Casodex per day all at one time. If a man could not afford 3 Casodex per day, I advised 2 flutamide three times a day. I never recommend taking 1 or 2 Casodex a day.

I treat for 13 months, then utilize Proscar, 5 mg once a day, so-called finasteride maintenance therapy. The interested reader may request my references on why I recommend Proscar.

Therefore, the differences in my practice compared to the reported medical literature is that I use <u>triple</u> hormone blockade, not two drug blockade; treating for 13 months, not six to nine months; and I add Proscar (finasteride) during the 13 months, just Proscar, 5 mg once a day, so-called finasteride maintenance therapy. I also usually require an unmeasurable PSA for about nine months (later found not to be important). An unmeasurable PSA is arbitrarily defined by me as a PSA of <0.1 —- it is not truly unmeasurable but below the usual laboratory level that they call unmeasurable. (The newest ultrasensitive PSA's can detect a PSA as low as .001.) If a man has his prostate gland, it will make some PSA that would be detected by future assays.

Usually my patients enjoy off treatment intervals of more than 65 to 75% of the time (later this off treatment period is 84% and still increasing). Is this apparent improved result from a combination of all three different approaches that I utilize? Don't ask me, not <u>yet</u>. (Later, the answer is yes, and with a major contribution from Proscar or finasteride maintenance therapy.)

I am often asked if you can use IAB even in men with far advanced disease. The answer is **<u>yes</u>**; **<u>yes</u>**; **<u>yes</u>**. Mr. R.W., aged 52, came to see me in 1995 when his PSA was 2,700; his bone scan showed at least 30 metastatic deposits (not bone cancer but prostate cancer cells in the bone); his CT scan of the chest showed "too many to count" metastatic islands

of prostate cancer cells and also showed "diffuse interstitial changes" -- like a honeycomb or spider web appearance -- all from prostate cancer cells that were in the lung.

He was treated with one year of triple hormone blockade and then maintained on Proscar alone.

Today his CT scan of the chest is normal; his bone scan is normal. (This does not mean that the bones and lungs are cured; it merely means the leftover seeds are too small to be detected by the scans.) The limits of resolution of our scans cannot detect what is left. (This helps explain why a so-called normal bone scan is worthless when a patient is considering whether to allow a radical prostatectomy.)

Mr. R.W.'s PSA has been slowly rising since he stopped triple blockade in February 1996. It is 11 this month; was 10 last month; 8 two months ago; and 6 four to six months ago. He will need to be treated again at some time in the future, but he was on treatment for 13 months and off treatment about 16 months, so far. He has no symptoms from his disease. If triple hormone blockade works this well against prostate cancer cells that were so aggressive they caused his markedly abnormal bone scan and CT scan of his lungs, and a PSA of 2,700; imagine how much better this treatment works in patients with clinically confined prostate cancer and a PSA of less than 10. (As of May 2004, he is still alive and well with a PSA of less than 0.1. He has been off hormone blockade for more months than on hormone blockade. He has received some low-dose, weekly, easily tolerated chemotherapy at times. His scans are still normal.)

Studies reported this year at ASCO confirm that the average response time to continuous hormone blockade in men with extensive metastatic prostate cancer is only 12-18 months. After that time, in spite of being on hormone blockade, the PSA begins to rise. This means they have developed hormone resistant or refractory prostate cancer. Mr. R.W. began treatment 28 months ago. His PSA is rising but he is off hormone blockade with a normal testosterone level. Whenever we restart triple hormone blockade he has essentially a 100% probability that his PSA will fall. That means he has hormone responsive or hormone sensitive prostate cancer. By using IAB, he has already exceeded the 12-18 month typical

response time for continuous blockade by more than one year and he still has hormone sensitive not hormone resistant disease.

I have concluded something that sounds so obvious that it might, at first glance, seem to be a circular argument or foregone conclusion. But I believe it has major implications. Please follow this logic for patients with recurrent or metastatic prostate cancer:

The longer you are off hormone blockade, the much longer you will ultimately remain hormone responsive, and by implication, the longer you will live.
I believe that each time you are forced to go back on treatment, the less effective our medicines will probably be. **If**, as animal models suggest, hormone sensitive cells preferentially regrow during the off treatment cycle, then by not rushing back to start cycle 2 too soon, you might be able to repopulate with additional hormone sensitive cells. Later, I would recommend using a number of supportive medicines to postpone or hopefully prevent the need to go back on hormone blockade. In future papers, I explain that the best treatment is one single, 13-month cycle of triple hormone blockade followed by finasteride maintenance therapy. If you ever have to go back on hormone blockade, I never recommend using Casodex, flutamide, or nilutamide; instead use ketoconazole or aminoglutethimide. (See future papers and videos.)

In order to achieve a prolonged off treatment interval, use your strongest and most effective agents up front, (triple hormone blockade plus Proscar maintenance is what I believe to be most effective) -- use triple blockade for 13 months, not less. I have not yet re-treated Mr. R.W; his PSA is not explosively rising; it is drifting up slowly.

I am also now strongly considering that when I do restart his triple androgen blockade, I will almost certainly also utilize a three or four month course of chemotherapy along with the triple blockade. The triple hormone blockade will continue for about nine to 12 months. Cancer is aggressive; I am compassionate. I believe in treating prostate cancer aggressively, especially the first time you have to re-treat someone. This new approach may not apply to men who only have clinically confined prostate cancer.

This treatment option is being explored at a few other centers; earlier intervention with chemotherapy combined with hormone blockade.

I believe that at the start of the first re-treatment with triple hormone blockade, we already expect a major percent cell kill against our prostate cancer cell enemies. But instead of just hitting them with medicines they previously were exposed to and managed to survive (or else you wouldn't have a rising PSA), add brand new weapons to the attack that kill prostate cancer cells in a totally new and different way. But you also combine your new weapons with triple hormone blockade.

This approach is not a standard approach and I do not recommend it to others. I am merely stating my views, my opinions and describing my constantly evolving approach for treating prostate cancer patients in my private practice.

When I have utilized triple hormone blockade for 13 months for men with clinically localized prostate cancer followed by finasteride maintenance, I still have not had to re-treat any one of them. My longest off period is about four years, so far. (More recent updates are available.)

I have used IAB for patients who either presented with metastatic prostate cancer or with recurrent disease following failure of radical prostatectomy, radiation therapy, seed implants and/or cryotherapy. I note anecdotally that patients who had brief prior exposure to monotherapy or two drug hormone blockade therapy seem to have shorter off periods. Men who have received three to six month prior hormone blockade, I believe, are at greater risk for developing hormone resistant or refractory disease. The most common situation I am describing is a patient who received three to four months of one or two drug hormone blockade at the time of their primary form of radical local treatment. Many of these well-intentioned doctors had tried to "downsize" prostate glands involved by locally advanced disease in order to then be able to justify treatment with their particular local modality. I think this exposure to short-term, inadequate (not triple blockade) treatment may be shown in the future to hasten the

time to hormone resistant or refractory prostate cancer.

When dealing with various types of cancer, I have found that the best approach is to always use your most powerful weapons up front. You never "save" some of your arsenal. Cancer cells are most vulnerable to the first attack. You must kill the greatest number of them on your first try. That leaves the fewest number of them left to try to mutate and become more aggressive. Triple hormone blockade for 13 months is the most potent form of attack today, in my opinion.

I hope that the addition of finasteride maintenance alone (after the year of triple hormone blockade has reduced the total body tumor burden of prostate cancer cells), can further enhance and prolong control of this disease, and perhaps even prolong survival. I am in the process of writing a paper on why I recommend Proscar.

As an aside, I never recommend saw palmetto while patients are on hormone blockade because I don't want the saw palmetto to compete with the other effective medicines and perhaps bind to the same receptors on prostate cancer cells. If a man is <u>not</u> on hormone blockade then I don't have a bias against saw palmetto. Don't add an unknown (saw palmetto) that conceivably could reduce the effectiveness of, or the absorption of, known prostate cancer killing medicines.

Bruchovsky and his group have shown that PSA's continue to decline often for eight months or more in men with metastatic prostate cancer. Even beyond eight months of treatment, 20% of their patients still had falling PSA's. I have treated an occasional patient who had metastatic prostate cancer for over 18 months since his PSA fell every month. I continued to treat him beyond my usual 13 months because his PSA had not reached its nadir. Therefore my standard 13 month treatment plan does <u>not</u> apply to all men who present with metastatic disease. (Later, I began to add up-front chemotherapy for patients with metastatic disease and stopped hormone blockade after 13 months in everyone.)

There are no simple all inclusive formulas. Each patient deserves his own treatment plan, not some unalterable recipe. My standard of 13 months of treatment is not biblically inspired. Future studies may show that longer

periods of treatment may be more effective, but longer treatments are more likely to cause permanent testicular suppression. This would prevent the IAB concept since your male hormone levels might not recover. Since February 1993, I have never recommended less than or more than 13 months of triple hormone blockade.

There is only one patient of mine whose testosterone level has failed to recover after the 13 months of triple hormone blockade.

Unfortunately, I did not obtain a baseline testosterone level on him before treatment started so I can't tell if the low testosterone level today is a complication of his hormone blockade, or whether it was a pre-existing condition. This is one of the reasons I urge that a pretreatment testosterone level be obtained on everyone.

Another concern with prolonged hormone blockade is the development of osteoporosis. This is a real concern. Orchiectomy will cause osteopenia or even osteoporosis in more than half of all men, if not all men who survive for more than a number of years. If a man has a pretreatment low testosterone, he might already have osteopenia, or even osteoporosis. I would order a baseline bone densitometry study on all men. Calcium and vitamin D supplements, specifically Citracal with D, two twice a day with food, should be taken by all men. Treatment with Aredia or Zometa are the most effective medications to treat or prevent osteopenia or osteoporosis.

I am impressed with a newer medicine Aredia, or pamidronate. Studies with this intravenous medicine seem to show that it helps patients who have metastatic cancer cells to their bones, at least in breast cancer and multiple myeloma. There is some emerging evidence it may have this effect in men with established bone metastases from prostate cancer. Besides relieving pain, there are tantalizing suggestions it has the potential to decrease PSA or <u>possibly</u> prolong remissions. <u>Eventually</u> it is hoped it might even be able to prolong survival, but this is <u>not at all</u> a certainty. Later studies did not show prolongation of remission or survival.

I have used Aredia in patients with advanced hormone refractory prostate cancer, who were also on chemotherapy.

I am now going to be using it earlier in patients with metastatic disease, but this is my **opinion only**. I do not recommend it to other doctors or other patients and I am not using it in clinically localized prostate cancer and feel it would be wrong to do so. Aredia is not a form of chemotherapy. Later, we recommended Aredia at least every one to three months to prevent and/or treat osteoporosis.

For patients who have HRPC, I am becoming impressed with a number of promising treatment options. It seems there are at least five or ten different regimens available that will cause PSA declines of over 50% in more than one-half of men treated. I am excited about Taxotere in combination regimens, but this is very preliminary and cannot be recommended except in controlled situations. Taxotere is related to Taxol, the drug from the bark of the Pacific yew tree. Taxotere comes from the needles of the European yew tree.

It bothers me when some patients call me and tell me their doctor informs them that nothing helps hormone refractory prostate cancer. That is just not true. What is true, is that when dealing with a systemic disease, I believe a board certified oncologist would, in general, know more about emerging new systemic treatments than a surgeon (urologist). There are, to be sure, a number of extraordinarily bright, interested urologists who do keep up with emerging literature on various treatments for HRPC. However, very few actually administer chemotherapy. The average community urologist specializes in treating localized disease. His or her expertise is not as a cancer doctor. They do perform cancer operations; but they are not oncologists. Community urologists often know much about hormone blockade, but in my opinion, hormone blockade is systemic treatment, and an oncologist is the expert for treating systemic disease.

I wish to emphasize that there are exceptional urologists who design and implement and are experts at treating with systemic therapies (almost always hormone therapies) and these usually academic urologists, practice far above the level of their peers -- by peers I mean urologists and most community medical oncologists. Just being a medical oncologist does not make one an expert in prostate cancer.

In the not too distant future, as more articles are

published on effective therapies for HRPC, more community oncologists will acquire the necessary skills and expertise. This will make it easier for patients to find doctors specializing in the care and treatment of patients with prostate cancer.

And finally a request, plea and/or explanation. I am informed that there are those who criticize me because I have not published my results, except through patient oriented publications (see *Oncologist* and ASCO Abstracts).

I have been a practicing medical oncologist for 22 years. I have subspecialized in prostate cancer for the past eight years. I was an original member of the National Prostate Cancer Study Group in the 1970's. I was the only medical oncologist in the 1980's and 1990's who had access to free compassionate use of cyproterone acetate through the generosity of Berlex labs. I was an original Casodex investigator. I was also the physician for the sixth patient in this country treated with Zoladex.

But in 1995, I became disabled and had to leave practice for almost one year. That office practice was taken over by another doctor. All of my prior patient records are in his possession. I have complete records on any patient who returned to my care when I opened my new office. There are 91 cartons of patient records from my Sherman Oaks (prior practice) office. Unfortunately the computer program that I used at that time did not have the capability of identifying the patients by disease classification. I am not able to generate a list of each prostate cancer patient that I saw prior to May 1995.

If any prostate cancer fund or organization wishes to pay for a nurse or investigator to go through all of those 91 cartons, pull the charts of every prostate cancer patient and extract the pertinent data, then an independent audit can be done and we will all know my exact treatment results. I have utilized hormone blockade alone for treatment of clinically localized prostate cancer since 1991; I have treated all “local” recurrences after radical prostatectomy, radiation therapy, cryotherapy or seed implant therapy with triple hormone blockade alone without any additional local treatment. Later this recommendation would change. I have used finasteride maintenance since around 1992; I have used

intermittent androgen blockade since 1991. The data is there. I don't want to be paid anything, but I need someone to fund the entire project. I will assist, but I don't have the time or office space to complete this project. There is office space available adjacent to my office so this might be an ideal, unique opportunity to collect, analyze and then publish this important useful information.

Rather than criticize me, help me -- make it possible to publish this important useful information. Help make it possible to share this information rather than have me continue to have to say, "in my experience," but not have the hard data to quote exactly. I believe that these clinical results need to be tabulated and published, because if prostate cancer patients treated by me have done better than expected (which is what I believe), then this information begs to be published so that other doctors and patients can evaluate it and decide for themselves whether their standard approaches to prostate cancer patients should be modified.

And as always –-

Be happy,
Be well,
Live long and prosper,

BOB LEIBOWITZ, M.D., AKA DR. BOB