



Compassionate

Oncology Medical Group

Bob Leibowitz, M.D.

DIPLOMATE
AMERICAN BOARDS OF INTERNAL MEDICINE
AND SUBSPECIALTIES OF
MEDICAL ONCOLOGY AND HEMATOLOGY

October 1997

April 2004

(Revised)

ANGIOSTATIN AND WHY LOCAL THERAPY FAILS

TO CURE SO MANY MEN

(Formerly "THE TRANSITIONAL ZONE ERA")

1997 marks the end of the radical prostatectomy era as it is known today. No longer can urologists confidently recommend radical prostatectomy with the intention to cure their new patients. Surgery alone just does not work for up to 75% of men. I have had a number of urologists admit to me that they no longer believe radical prostatectomy can cure prostate cancer for the vast majority of patients today. One urologist confided:

"Bob, I no longer can look a new patient in the eye and tell him he needs a radical prostatectomy."

This is earth shattering news. I have just attended two major prostate cancer meetings this past week; one in New York and one in San Diego.

Shocked!!

I am shocked at what I heard and saw.

Local therapies don't work!!!

Urologists admit that radical prostatectomy alone does not work; you need to add systemic hormone ablation (triple hormone blockade) mostly before surgery, but also perhaps after surgery -- a total treatment time of about one year is what they advised for best results. Remember, many urologists have been warning patients not to take hormone blockade before surgery because it could delay the only treatment they believed could help you (radical surgery). And some warned that somehow this hormone blockade might detract from the benefit of surgery.

Radical radiation therapy alone does not work. Bolla, as reported and described in my recent paper, "The Capitulation of Radiation Therapy," showed that unless you also give hormone blockade to patients treated with radiation therapy, you have fewer patients alive a few years later. The radiation therapy speakers at these two conferences now advocate adding hormone blockade (once again, triple hormone blockade works best) to radiation therapy.

2080 Century Park East, Suite 1005 • Los Angeles, California 90067 • 310.229.3555 • Fax 310.229.3554

<http://www.compassionateoncology.org>

ANGIOSTATIN

Page 2

I listened to proponents of cryotherapy. I personally am terribly disappointed by emerging results with cryotherapy treatment and feel that all it does is debulk prostate cancer, not cure it. I believe cryotherapy alone will not cure more than 10 to 15 percent of patients, at best. When the group that developed this procedure reports that two years after cryotherapy 53% of men biopsied still show viable living prostate tissue, it is obvious this treatment does not come close to sterilizing the prostate. If you don't eliminate all prostate tissue, how can you kill all prostate cancer cells? Additionally, as I have emphasized, I believe prostate cancer is a systemic disease in most men by the time we diagnose it, and any disease outside the prostate is not going to be controlled by cryotherapy given to the prostate.

I have written that if you cannot cure a patient with any radical local treatment, do not attempt your local treatment. Debulking even 99%+ of local prostate cancer in the presence of distant metastases is not beneficial (no study has ever shown debulking surgery for prostate cancer to be beneficial) and, in my very strong opinion, I believe it is harmful. I confidently predict that future studies will show that inadequate local treatments actually shorten the lives of patients with occult, undiagnosed metastatic disease.

In the Bolla Study, more men who received radiation alone died compared to those men who were treated with hormone blockade plus radiation. The radiation therapy only arm may have been harmed by this treatment. These men would have been far better off receiving hormone blockade alone, rather than radiation therapy alone. If you are trying to choose between accepting only local treatment versus only systemic treatment, I urge systemic treatment. Men die because of prostate cancer cells outside their prostate; not prostate cancer cells limited to the prostate. Many prostate cancer studies show that radiation therapy shortens survival compared to a no treatment arm. In my opinion, hormone blockade prolongs survival. Choose systemic therapy. A woman does not die from breast cancer cells in the breast; only from the cells that escape away from the breast. We have shown that all subcategories of breast cancer have improved cure rates when you give systemic therapy (hormone therapy and/or chemotherapy). The systemic therapy can kill the cells that already escaped from the breast. Prostate cancer patients need systemic therapy, too.

ANGIOSTATIN

Page 3

An article in the August *Journal of Urology* by John Connolly, Volume 158, pp. 515-518, August 1997, "Accelerated Tumor Proliferation Rates in Locally Recurrent Prostate Cancer After Radical Prostatectomy," concludes that the growth rate (doubling times or proliferative rates) of tumors that recur locally after radical prostatectomy are higher than from the parent tumor. The article also emphasizes that "increased PSA doubling times, which presumably reflect tumor growth, have been reported in patients with locally recurrent cancer following radiation therapy." My recent paper, "The Capitulation of Radiation Therapy," references some of the work from Judah Folkman and his group that shows a possible explanation for these observances. Dr. Folkman's papers mention:

"There is now considerable direct evidence that tumor growth is angiogenesis dependent. Angiostatin inhibits angiogenesis and can induce dormancy (hibernation) of metastases. If you remove angiostatin, the metastases begin growing again within a few weeks. Angiostatin inhibits the growth of human prostate cancer cells by almost 100% (in his animal model systems)" (*Nature Medicine*, Volume 2, Number 6, June 1996).

"By potentially inhibiting angiogenesis, angiostatin can cause human carcinomas to regress to a dormant state" where there is balanced cell growth (proliferation) and cell death (apoptosis). The mechanism by which angiostatin leads to an increase in tumor cell apoptosis is unknown, although some reasonable possibilities are mentioned (loss of paracrine growth factors, for example). This is fascinating new information. Most of us thought that tumor metastases were dormant and not growing. Dr. Folkman shows us that these cells grow three times faster than normal cells, but because of mechanisms like apoptosis (programmed cell death), they are being killed three times faster. The state of dormancy exists because of this delicate balance. If you remove the factors that kill these cancer cells, you are left with cells growing three times faster than the normal cells in your body.

Another Dr. Folkman article (*Nature Medicine*, Volume 1, Number 2, February 1995) points out that:

"In cancer patients, dormant micrometastases are often asymptomatic and clinically undetectable, for months or years, until relapse.....However, tumor cells of dormant metastases exhibited a more than threefold higher incidence of apoptosis."

ANGIOSTATIN

Page 4

These data show that, in my opinion, there is balanced tumor cell proliferation and an equivalent rate of cell death, and I suggest that angiostatin controls metastatic growth by increasing apoptosis in cancer cells. Angiostatin inhibits cancer cell growth by suppressing tumor angiogenesis.

In *Cancer Research*, Volume 56, pp. 4887-4890, November 1, 1996, Dr. Stephan Gately reported that human prostate cancer cells express an enzyme that converts human plasminogen into....angiostatin. This helps to show us that angiostatin isn't just important to laboratory mice experiments, but to human prostate cancer cells, as well.

I am simply using the above three medical references to illustrate my point that if you fail to cure a patient with any form of local treatment, you could end up doing far more harm because your local therapy might remove the only source of angiostatin. If the patient already has metastases (dormant or otherwise) you could cause an exponential increase in the growth rate of those metastases by removing (or radiating and implanting or freezing) his prostate. This could also help explain why I believe debulking local treatments have the potential to shorten a man's life. If you cannot cure a patient with local treatment, don't think you are helping him by getting rid of almost all of his cancer. I believe you are doing far more harm than is currently understood.

As of October 1997, no patient of mine, who presented with clinically localized prostate cancer and who has been treated only with hormone blockade has had to be re-treated with hormone blockade. Obviously, by definition, none has become hormone refractory, and none have died (from prostate cancer). I submit that local therapy often hastens death in those men who have unsuspected, untreated metastases.

There are those cryotherapy enthusiasts who claim you don't need to kill all the cancer cells with cryotherapy; the cryotherapy activates the immune system and your immune system will kill the leftover cancer cells. This is a great fairy tale that we all would love to believe. Seems to me I remember something similar for radiation therapy at one time; I also remember how if you debulk cancer then there are fewer cells left so your immune system can work more effectively, etc. Great for dreamers but the reality is that all of these local treatments have failed us.

ANGIOSTATIN

Page 5

So what did the cryotherapy experts recommend at these conferences?? You need to take (triple) androgen blockade in addition to the cryotherapy; about one year of triple hormone blockade. Starting to sense a pattern emerge, aren't you?

Radiation seeds, implants or brachytherapy; their proponents were also at these bicoastal conferences. What did they have in common with the other prostate cancer specialists (or, as we prefer to be called, experts)?

As recently as this past year, many (most) seed implant specialists told their patients that they did not want them to receive any neoadjuvant hormone blockade -- (neoadjuvant means giving the hormone blockade before the local treatment is administered). The usual explanation was that they did not want anything to interfere with the known benefit of their local treatment. For seed implanters, they did not want the hormone blockade to change the prostate cancer tissue and somehow diminish the effectiveness of the implant.

This sounds familiar. It should, because cryotherapy specialists usually (almost always, but with some notable exceptions) told their patients the same thing. Don't take any hormone blockade before your cryotherapy because we don't want it to "screw up" our results.

It has frustrated me these past few years as I would hear from patient after patient how their radiation therapist, cryotherapist, or implant specialist told them absolutely not to receive hormone blockade before their local treatment.

But at these two recent conferences, the message seemed to be universally changing. Now seed implant candidates are being advised to do something in addition to seed implant; usually hormone blockade (although to be fair and complete, some centers combine external beam radiation with implants). But my message is patients should receive systemic therapy (hormone blockade) for 13 months and avoid any type of local treatment.

And for those who advocate the most radical treatment of all -- radical prostatectomy --

What do they say about hormone blockade?

In the October 1997 *Journal of Urology*, Dr. Anthony D'Amico (from Harvard), Dr. Alan Wein (University of Pennsylvania), and others state:

ANGIOSTATIN

Page 6

Vol. 158, p. 1425: "...patients....may benefit....
from....the addition of a traditional systemic
therapy (that is, androgen ablation) to
definitive local therapy."

When given before radical prostatectomy, this is called neoadjuvant hormone blockade. How long should you treat? I have addressed this in prior papers, but briefly we know that three months of hormone blockade is far too little. The PSA misleads us here. The average PSA falls over 95% in the first three months of hormone blockade (often falling 99%). We forget that this early decline in PSA is not due to cell death. As soon as androgens are withdrawn, the rapid decline in PSA is almost entirely a result of shutting off the cell's ability to synthesize PSA. The cell does not die; it simply stops making PSA. Three months of double hormone blockade results in less than five% pathologic complete remission (all prostate cancer cells killed in the prostate, as found at radical prostatectomy).

Six to eight months of double hormone blockade prior to planned (and performed) radical prostatectomy causes a 20% pathologic complete response (personal communications and statements made at lecture by Dr. Stan Brosman, urologist). Later, special stains would show a much lower percent.

Goldenberg, Gleave, Bruchovsky, et al. showed that after nine months of hormone blockade, the PSA was still falling in 20% of men. Hence, hormone blockade needs to be given for at least one year (13 months is my recommendation).

To be sure, the optimal duration of blockade may ultimately be shown to be 18, 24 or 36 months, but I believe 13 months is the ideal duration of triple hormone blockade. Also, longer blockade will almost certainly result in more men developing permanent testicular suppression and this would prevent intermittent androgen blockade from being possible. In my own practice, I have two metastatic prostate cancer patients who were treated with five years of hormone blockade; four and a half years later, their testosterone is still suppressed. Permanent testicular suppression is medical castration and should be avoided.

And so we have entered a new era in prostate cancer treatment. No longer are we being ridiculed for suggesting that prostate cancer is a systemic disease for many (in my opinion, most) men

ANGIOSTATIN

Page 7

diagnosed using today's crude methods. The future will undoubtedly help us identify through molecular biology those of us destined to develop biologically aggressive disease and help determine who needs treatment and who does not. But for now, if you are going to be treated for prostate cancer with any local treatment --

either radical prostatectomy (150,000 this year),
or radical radiation (about 50,000 this year),
or implant (about 15,000 this year),
or cryotherapy (about 5,000 this year),

start first with triple hormone blockade for 13 months. Then decide whether you want local treatment. I do not recommend any local therapy.

Remember, I don't claim that men should not consider local treatment after their one year of triple hormone blockade. I do state unequivocally that radical local treatment, either alone or first, is absolutely not appropriate for most patients today. And until radical local treatment is shown to be necessary and effective, I prefer to utilize systemic therapy alone. I still believe that hormone blockade works best in the prostate. If after 13 months of triple hormone blockade you still have prostate cancer cells surviving in the prostate, I believe most of these men will also have prostate cancer cells in distant sites (bones, etc.); thus, local treatment to the prostate after the 13 months of triple blockade is not likely to be of benefit.

However, I clearly acknowledge that this point should be addressed in a study. All new patients should start with 13 months of triple hormone blockade and then decide whether they want any form of local treatment. You could biopsy the prostate after the year of triple hormone blockade, but as pointed out, most (I hope and pray) all biopsies might come out benign. This is no guarantee of cure since a sampling error could exist and you might miss pockets of prostate cancer cells. Furthermore, if cancer is still in the prostate, I believe that almost always there will be cancer cells in the bones and/or lymph nodes. However, I am not so arrogant to believe I know this to be factual, and how grateful we all would be if CapCure or some other entity sponsors this study and proves me right or wrong.

ANGIOSTATIN

Page 8

Because if all men would first be treated with 13 months of triple hormone blockade, I am confident and arrogant enough to believe that lives will be saved; men will live longer than the era that is just now closing.....where men were primarily treated with local therapies alone. Local therapy alone has too many permanent bad side effects, and far too few true cures. Its' time has passed. A new era is beginning. I call this the Transitional Zone Era because I hope we ultimately transition to systemic therapy alone.

I desperately call on and plead with my prostate cancer colleagues to come forward now; today. Strongly support this stance. Tell everyone; write it in articles and in consults; tell friends, peers and patients that starting today, it is no longer appropriate not to **offer** systemic hormone blockade to every patient who is considering any form of prostate cancer treatment. We must make it the standard of practice to consider each new patient a candidate for systemic hormone blockade and must discuss this option with each patient.

Let us join together in this effort at changing the standard of practice. Think of how many lives will be saved or lengthened if every prostate cancer doctor considers every new prostate cancer patient a candidate for systemic therapy.

As Captain Jean Luc Picard from "Star Trek, The Next Generation" says:

"Make It So!!!"

As Dr. Bob says:

"Today is the best day to start to make it so!"

And I look to the future with a renewed sense of cautious optimism. I am so pleased to see proponents of local treatment begin to recommend systemic treatment. The addition of systemic hormone blockade will improve survival and that is our ultimate goal.

If the future also shows us that systemic therapy alone is sufficient for most men with prostate cancer, then I would smile and feel even better. But if some men benefit from the addition of local treatment to their 13 months of triple hormone blockade, then I would smile even more and say:

"I was wrong."

ANGIOSTATIN

Page 9

May we all live and be well and see those future days; and get our answers; and know we did our best to help our patients live well, live long, and prosper.

Less startling and less earth-shattering is the news that Dr. Charles "Snuffy" Myers, noted prostate cancer expert, and author of the very well respected monthly publication,

"Prostate Forum,"

has stated publicly that he believes Proscar is an effective treatment for prostate cancer and that it should be used. This same support for Proscar was also voiced by Dr. Paul Geller, a urologist, and support for Proscar was also expressed by Dr. Mack Roach.

As I have explained in my paper, "Proscar Greetings on Father's Day," I believe Proscar is one of the major reasons for the successful results my patients are enjoying. I urge others to read this paper and utilize Proscar as described. The Proscar band wagon is already moving down Main Street, U.S.A. and the world, too, and triple hormone blockade along with finasteride maintenance is here to stay. In fact, I believe that finasteride maintenance will soon be the standard of practice. I doubt that there will be much more resistance before this concept is accepted by most experts. It will be interesting to see how much more difficult it will be to accept Proscar as the third drug in the triple hormone blockade recipe. But as for maintenance finasteride, I already project "Victory." Exit polls have already projected this emerging trend.

And as always --

Be happy,
Be well,
Live long and prosper,

BOB LEIBOWITZ, M.D. AKA DR. BOB