



**HORMONE BLOCKADE; CONTINUOUS, INTERMITTENT, OR?
UPDATE ON ANTIANGIOGENIC COCKTAIL**

Dr. Bob is convinced that the most effective way to use hormone blockade is neither continuous, nor intermittent, since both of these methods encourage evolution to hormone resistant/refractory prostate cancer. The "best" way to use hormone blockade (opinion) is to treat with one 13-month cycle of triple hormone blockade®/Leibowitz protocol for patients presenting with previously untreated, low-risk or intermediate-risk, clinically localized prostate cancer. For men who have previously been treated with hormone blockade, my approach to controlling their prostate cancer is to use all effective medications to postpone, or hopefully prevent, the need to go back on another cycle of hormone blockade. You cannot develop hormone resistant or hormone refractory prostate cancer unless you are re-treated with another cycle of hormone blockade, since the definition of those conditions is a rising PSA while on hormone blockade. If we can find effective, non-hormone blocking medicines to control a rising PSA, then you can remain off hormone blockade. **I am certain that the longer you are off hormone blockade, the much longer you will live** (opinion, but the logic, to me, is essentially irrefutable, and the only possible interpretation). Every time you are treated with another cycle of hormone blockade, your time on hormone blockade lengthens, and your time off hormone blockade shortens. You can recognize this pattern as evolving hormone resistant prostate cancer.

Continuous hormone blockade is the worst way to use hormone blockade since it essentially always evolves to hormone resistant/refractory prostate cancer (HRPC). Intermittent androgen blockade (IAB) is far superior to continuous androgen blockade (CAB), if for no other reason than the fact that when you are off hormone blockade, your quality of life markedly improves. This is fact, not opinion. Studies are being conducted to determine whether survival with IAB is equal to CAB, or superior. I believe that IAB will be found to prolong survival compared to CAB. Eventually, other investigators will agree with me that the most effective form of hormone blockade is a single cycle of effective HB (13 months THB/LP) followed by finasteride maintenance® therapy. For those patients whose clinical course dictates, they would also be treated with a number of the medications in my antiangiogenic cocktail to

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postpone, and possibly prevent, the need to be treated with another cycle of HB.

Since 1994, I have written that IAB will be found to be far more effective than CAB. At the Sixth Annual Massachusetts Prostate Cancer Symposium on May 21, 2003, I was one of two keynote speakers. The sponsors included Massachusetts General Hospital Cancer Center, Dana-Farber/ Harvard Cancer Center, Tufts-New England Cancer Center, Beth Israel Deaconess Medical Center (also a Harvard Hospital), the American Cancer Society, and others. I was the only doctor at the Symposium who expressed the opinion that intermittent androgen blockade was superior to continuous androgen blockade. A few years earlier, at the same conference, I was one of many prostate cancer specialists that participated in a panel discussion on IAB versus CAB. Some of the other participants included Dr. Philip Kantoff, moderator; Dr. Anthony D'Amico, a Harvard radiation therapist; Dr. Glen Bubbly, a Harvard oncologist; Dr. Mark Garnick, a medical oncologist; at least one Harvard urologist, and a number of other nationally acknowledged prostate cancer experts. Dr. Kantoff, the moderator, asked the panelists whether they recommended IAB. Everyone said no, except for Dr. Bob. Dr. Kantoff then asked the panelists to predict whether ongoing or future studies would prove CAB or IAB superior. Not being shy, I spoke first, and stated that I was certain that treatment with IAB prolongs survival compared to CAB. When polled by Dr. Kantoff, every one of the other panelists stated that CAB would be found superior. As I always maintain, "Everyone is entitled to their own (wrong) opinion." Even me!

If a man's clinical situation does necessitate starting another cycle of hormone blockade, my essential goal of therapy is to do everything I can do to ensure that this will be the last cycle of hormone blockade necessary. Some of the tools I use to accomplish this goal include never giving an antiandrogen a second time (like Casodex, flutamide and/or nilutamide), since this category of hormone blockade medicines eventually become agonists, and actually stimulate prostate cancer cells to grow. Instead of an antiandrogen, I use an adrenolytic medication such as ketoconazole or Cytadren, or whenever possible, ethinylestradiol which, in my opinion, is far and away the most effective form of hormone blockade. All patients are also treated with an LH-RH agonist and Proscar.

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In addition to hormone blockade, patients starting on a new cycle of hormone blockade are treated with 15 doses of low-dose, weekly Taxotere/Emcyt/carboplatinum (T/E/C) chemotherapy. This T/E/C protocol is one that I pioneered and have been using since 1998. These specific medications, doses, and this particular schedule make this protocol extraordinarily easy to tolerate. Patients essentially never report nausea or vomiting. Only about 15% of patients have significant hair loss which is always temporary and always reversible. The average layperson believes that when you are treated with chemotherapy, you feel sick and terrible; you throw up; you lose your hair, and then you die. This is the reputation that layperson believe chemotherapy has "earned." However, the **practice** of medicine is both an art and a science. The science is knowing what types of chemotherapy are most effective; the art is knowing how to administer these medicines in a manner that maximizes effectiveness, but makes the medicines easy to tolerate with side effects that do not disrupt your ability to enjoy an excellent quality of life, even while you are being treated with T/E/C. Compassionate Oncology takes great pride that we have succeeded in accomplishing these goals for virtually all of our prostate cancer patients. We have a list of patient volunteers that you can call to discuss how well they tolerated their chemotherapy. You will be very pleasantly surprised to discover that my descriptions of treatment side effects are honest and accurate. After you complete your treatment, you will wonder why other doctors have not discovered these techniques.

As soon as each individual patient's clinical status permits, I begin adding a number of the ingredients in my prostate cancer antiangiogenic cocktail to their ongoing prostate cancer treatment. These agents include Proscar, Aredia/Zometa, thalidomide, but since late January 2006, Revlimid (second-generation thalidomide), Celebrex, Leukine (GM-CSF), as well as anticoagulation to help prevent blood clots. Our preferred anticoagulant is the use of one of the low-molecular weight heparins (LMWH), which include medicines such as Lovenox or Innohep. LMWH anticoagulants are self-injected at bedtime under the skin of your belly - with a tiny needle that anyone can easily self-administer. LMWH anticoagulants have antiangiogenic effects, and direct anticancer benefits, in addition to thinning the blood. Because of these additional benefits, which the anticoagulant pill Coumadin (warfarin)

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lacks, I try to convince all of my patients to use LMWH rather than Coumadin.

I usually add metronomic dosing of cyclophosphamide (Cytoxan) pills, which targets and attacks the cells that line blood vessel walls - thus, it is yet another antiangiogenic agent. Cytoxan is a type of chemotherapy treatment. The highest dose of Cytoxan that I have ever used is 13,000 mg, administered over 48 hours, to a patient with lymphoma. The dose in my AAC is 12.5 mg, once or twice a day. This dose is only one one-thousandth of the dose given to the lymphoma patient. (By the way, this lymphoma patient was treated in the late 1990's, and remains in remission.) Thus, we are not utilizing Cytoxan as chemotherapy, but as an antiangiogenic agent. This mini, mini-dose of Cytoxan does not cause nausea or vomiting, and does not significantly suppress blood counts.

The most effective antiangiogenic medication may be Avastin, which targets a growth factor on the surface of cancer cells. Avastin has been shown to prolong survival for patients with metastatic colon, breast, and lung cancers. These studies compared chemotherapy treatment alone to the same chemotherapy plus Avastin. In patients with metastatic prostate cancer, Avastin plus Taxotere chemotherapy seemed to improve response rates compared to historical controls treated with Taxotere alone. Currently, prospective randomized studies comparing chemotherapy treatment with and without Avastin are being conducted in patients with metastatic prostate cancer. I believe these studies will confirm that Avastin also benefits patients with metastatic prostate cancer. Remember, there are very few anticancer medicines that prolong survival in three diverse types of disease such as colon, breast, and lung cancer. Avastin resulted in statistically significant prolongation of survival in all three of those types of cancer. I believe that treatment with chemotherapy plus Avastin will soon be found to prolong survival in metastatic prostate cancer patients compared to the same chemotherapy alone.

Another two of the most effective agents in the prostate cancer antiangiogenic cocktail (PCAAC) are Leukine and thalidomide. Leukine (generic name, sargramostim) is also often referred to as GM-CSF, since it stimulates the bone marrow to increase production of two different types of white blood cells (WBC). The two types of WBCs are granulocytes (G), also known as polys, which fight off bacterial infections, and monocytes (M),

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which are part of your immune system. Thus, Leukine enhances the ability of your immune system to recognize and kill cancer cells.

Before taking your first dose, it is necessary for you to please call our physician assistant, Mary. She will tell you when to start taking Leukine and what dose to take. Ignore the dosing instructions on the prescription, and only follow what our PA's tell you to do. If you take the amount of Leukine the prescription instructs, it will almost certainly cause nasty side effects. Do not take more than the PA's instruct you to take. They will also instruct you to take Tylenol, 650 mg; Benadryl, 50 mg, and Zantac, 150 mg as premedications 5 to 15 minutes before you take your shots of Leukine. These premedications help to reduce the risk for developing side effects and/or reduce the severity of them. The most common side effects from Leukine are the possibility to develop flu-like symptoms such as chills, fever and/or muscle aches. These symptoms may begin one to several hours after an injection, and are almost always mild and self-limiting. Lowering the dose of Leukine reduces the severity of this or any side effect.

When you get the flu and have these symptoms, the cause for them is not a poison from the virus, but rather your immune system fighting back. Leukine stimulates these same types of chemicals; hence, it can cause these same symptoms. By taking your Leukine at bedtime, and by first taking all three premedications (Tylenol, Benadryl, and Zantac), side effects generally are mild. Over a relatively short period of time, side effect symptoms disappear completely in almost 100% of patients.

Zantac is not being prescribed to help your stomach. There are two different antihistamine receptors in the body. Benadryl and most antihistamine medications block one receptor only. Zantac blocks the second type of antihistamine receptor. Therefore, we are using Zantac for its antihistamine benefits.

If Benadryl causes problems with your ability to urinate, or if it is too sedating, we can switch to Zyrtec, which may not cause those side effects. Since Benadryl is taken at bedtime, some patients like the sedative effects it produces.

If you develop any symptoms such as fever, chills, or muscle aches, we recommend that you take two Extra-Strength Tylenol or

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three regular-strength Tylenol and, in addition to Tylenol, you should also take two Advil (or ibuprofen or Motrin) every four hours, but only as needed. Rarely, Leukine can cause bone pain, particularly if it raises your white count too high. Ibuprofen is quite effective to relieve bone pain. After the first several weeks of treatment with Leukine, if you are not experiencing any side effects, you can begin to reduce the number of premedications you take. Initially, you take two each of Benadryl, Tylenol and Zantac, a total of six pills. After several weeks, you can begin to taper down to five pills by stopping one Tylenol, one Benadryl, **or** one Zantac. The next week, you can reduce one of the two other medicines that you are still taking two pills each night (if you cut Tylenol the first week, reduce Zantac or Benadryl from two to one the next week). One week later, reduce to just three pills per night (one of each). Continue to reduce one pill per week. If side effects return, you can increase your premedications up to two of each (six total).

The only other common side effect from Leukine is a local reaction at the site of the injection. Leukine revs up your immune system locally at the injection site. You may develop a bump that may itch or cause some minor local discomfort. Taking all six premedication pills limits this side effect. Other effective measures to reduce injection site reactions include ignoring the directions from the manufacturer and only following our PA's advice. The picture that comes with your Leukine prescription instructs you to inject the medicine into your belly and/or thighs. Do not inject into your thighs since the reactions are usually much worse there. The directions also tell you to pinch your skin. Do not pinch your skin. Mary will explain the procedure we find works best for our patients. Applying a reusable ice pack to the injection site for five minutes after each injection also helps to reduce any local reaction.

One type of white blood cell count that Leukine increases is usually referred to as polys, but may also be called granulocytes. If a person on Leukine goes to an emergency room, and a doctor orders a CBC (complete blood count), the results will almost always show an elevated white blood cell count (WBC). The CBC will also show an elevation in polys which are the type of white cells that suggest to the emergency room doctor that you have an active bacterial infection. Most doctors are not familiar with the effects Leukine has on your

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white blood cells. It is important for you to inform the doctor that Leukine raises the total white cell count, **and** also the polys. Polys suggest bacterial infection to a doctor. If you do not inform your doctor about being on Leukine and how it affects your white blood cells, and specifically your polys, you might be treated for a disease that you do not have. This could result in your receiving unnecessary medications that could cause serious side effects. Remember to tell any doctor you see for any reason that you are being treated with Leukine. The Leukine effects on white blood cells completely go away 48-72 hours after your last dose.

There are a significant number of articles in our recent medical literature that report excellent PSA responses following treatment with Leukine, either alone or, as we prefer, in combination with other medicines in our antiangiogenic cocktail. In the January 2003 issue of the *Journal of Clinical Oncology*, Rini, Brian, et al., reported on 29 patients who had rising PSAs following local therapy. Prior to treatment with Leukine, their PSA doubling time was approximately 8.4 months. While on Leukine, their PSA doubling time prolonged to 15 months, meaning it took twice as long for their PSA to double on Leukine compared to pre-Leukine.

In one of his other publications, Rini reported a dramatic PSA response in a patient whose pretreatment PSA doubling time was four months. Following treatment with Leukine, his doubling time increased to approximately 74 months.

At the February 2005 ASCO Prostate Cancer Symposium, held in Orlando, Florida, Rini, B., et al., reported that seven of the 29 patients evaluated in their study (24%) continued to remain on GM-CSF, without evidence of disease progression after a median of 4.4 years. That duration of PSA control is absolutely phenomenal. I do not believe any other non-chemotherapy or non-hormone blocking medication has been shown to exert control over prostate cancer for this long a period of time. I believe it is possible that by combining thalidomide or Revlimid with Leukine, we might be able to significantly improve upon these already impressive results. Leukine is also active against several other types of cancer.

As far back as July 1999, Small, Eric, et al., *Clinical Cancer Research*, Volume 5, July 1999, pages 1738-1744, had reported on two series of patients treated with Leukine, and all patients

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in Dr. Small's study had metastatic, hormone refractory disease. Twelve out of 13 patients in his second cohort experienced a decline in their PSA, with a median decline of 32%, and one patient had over a 99% decline in PSA, as well as improvement in his bone scan. This response continued for 14+ months, and was ongoing at the time this paper was published.

Beginning in 1998, Dr. Bob began treating prostate cancer patients with thalidomide as a potent antiangiogenic agent that also enhances the immune response. He published a letter to the editor of the journal, *Oncology*, in September of 2002, Volume 16, Number 9, pages 1146-1148, reporting on some of his prostate cancer patients and their anecdotal responses to thalidomide. William Figg at the National Cancer Institute had reported that thalidomide was effective treatment for men even with metastatic, hormone refractory prostate cancer. In a personal discussion with Dr. Figg, both Dr. Bob and he have noted response rates as high as 80% when prostate cancer patients who are hormone sensitive or hormone naive are treated with thalidomide as a single agent.

At Compassionate Oncology Medical Group, Dr. Bob first combined Leukine with low-dose thalidomide beginning in 2002. At the International Conference on Molecular Targets and Cancer Therapeutics in November of 2005, held in Philadelphia, Pennsylvania, an abstract was presented by Dr. Robert J. Amato. This conference was organized jointly by the American Association for Cancer Research, the National Cancer Institute, and the European Organization for Research and Treatment of Cancer. In Dr. Amato's paper, eighteen prostate cancer patients were treated with Leukine and thalidomide. All had rising PSAs following local therapy, and had not previously been treated with hormone blockade. My experience using Leukine and thalidomide had independently verified the same remarkable response rates that Dr. Amato reported. All of the men in his study had at least a 26% reduction in their level of PSA, with a median reduction of 59%. His response rate was 100%. One of the nicest things about this regimen is that both of these medications enhance the immune system. Many cancer patients are concerned that chemotherapy can adversely affect their immune response; with Leukine and thalidomide, the opposite occurs. Neither Leukine nor thalidomide lower testosterone levels, and thus they do not have any hormone blockade effects.

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In summary, we have a very effective treatment option that is not chemotherapy; is not hormone blockade, and enhances your immune system. Isn't this exactly what you have been searching for?

In January of 2006, the eagerly awaited, second-generation **thalidomide** product, **Revlimid** (lenalidomide), received FDA approval to treat one type of MDS or myelodysplastic syndrome. In essence, MDS is a type of smoldering leukemia, or advanced preleukemic syndrome. Using Revlimid for any medical condition other than to treat one subcategory of MDS means using it "off-label." Thus, treating prostate cancer patients with Revlimid is an off-label indication. It is legal to use a medicine off-label, as long as the doctor explains the risks, benefits, and alternatives. As an aside, the only FDA approved indication for using thalidomide is for treating a type of leprosy!!

Unlike thalidomide, use of Revlimid is not supposed to be associated with drowsiness or symptoms of peripheral neuropathy. Both thalidomide and Revlimid are associated with an increased risk of blood clots. We routinely anticoagulate our patients with aspirin, or much more commonly with blood thinners, especially with a low-molecular weight heparin (LMWH), which we believe to have anticancer benefits, as well.

Revlimid is also associated with the possibility to have a decrease in your platelet count. Platelets help the blood to clot. However, patients treated with Revlimid had a preleukemic syndrome which almost always is associated with low platelet counts. It is possible that in patients with normal bone marrows, perhaps Revlimid will not affect platelet counts. The FDA requires us to check your platelet count weekly for the first eight weeks after starting Revlimid. If your platelet count drops, stopping Revlimid almost always quickly restores your count to normal. To date, we have not yet seen any problem with platelet counts, but remember, Revlimid only became available in mid-January 2006. Since Revlimid is related to Thalomid, the same precautions regarding the risk of fetal abnormalities are appropriately FDA mandated.

There are side effects associated with all medicines, and the reader is reminded to discuss the risks, benefits, and alternatives of every medication with their prescribing doctor before taking any medicine. I believe there is a high

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probability that the combination of Leukine plus Revlimid will be better tolerated, and probably even more effective, than Leukine plus thalidomide, but this is my opinion, not fact.

In January 2006, Compassionate Oncology Medical Group began evaluating the effects of Revlimid alone, in combination with Leukine, and as part of our various treatment protocols. Our very early observations confirm the ability of Revlimid to lower PSA levels in at least some of our patients. I believe it is highly probable that Revlimid will be proven to be one of the most active medications in our prostate cancer antiangiogenic cocktail. For those patients currently being treated with thalidomide, if insurance coverage permits, you should consider changing to Revlimid. For those men who had to discontinue thalidomide because of symptoms of peripheral neuropathy, you should consider taking Revlimid.

When hormone blockade is completed, then we evaluate patients to see whether high-dose testosterone can be considered. (See my papers, "High-Dose Testosterone Replacement Therapy and Prostate Cancer" (2006) and "High-Dose Testosterone Replacement Therapy" (2004) and/or watch my recorded lectures from 2004 and 2005). For men who are hormone naive, the first cycle of hormone blockade lasts for 13 months. Almost without exception, for all subsequent cycles of hormone blockade, I only treat for nine months.

Prostate cancer is exceptionally and almost universally responsive to treatment. While metastatic prostate cancer cannot be cured, it is highly treatable and controllable. The goal of treating patients with metastatic prostate cancer is to turn their illness into a chronic disease, much like hypertension or diabetes. You don't cure those diseases, you successfully treat and control them. It is not necessary to cure most patients with metastatic prostate cancer in order for them to live a normal lifespan. Our goal is to make prostate cancer cells "hibernate;" to make them **dormant**. Remember that 80% of men in their 80's have prostate cancer, but only 2-3% of men die from prostate cancer. Most of us live with prostate cancer and die **with** it, not **from** it. Our realistic, achievable goal is to control metastatic prostate cancer. For almost all of the patients treated at Compassionate Oncology Medical Group, this goal continues to be successfully accomplished.

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As always --

Be happy,
 Be well,
 Live long and prosper,

DR. BOB

Dr. Bob's Birthday 2006

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