



Compassionate

Oncology Medical Group

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

**DR. BOB'S (NOT SO) SECRET RECIPE FOR TREATING
METASTATIC, ADVANCED OR RECURRENT PROSTATE CANCER**

Since 2001, I have been recommending a three-pronged approach to treat either recurrent, metastatic and/or advanced prostate cancer. I conceived and pioneered this unique, extraordinarily effective treatment protocol. A useful analogy that I often employ to help patients understand this treatment strategy is to imagine that each prostate cancer (CaP) patient is, in a sense, engaged in a war with the "Bad Guys," also known as prostate cancer cells. Fortunately, we have extremely effective medicines to help you. Instead of thinking three-pronged attack, picture an Army, Navy, and Air Force that are yours to use. These three branches of the military work best when all of them are used together, and are used from the very beginning. Always start using your best weapons right now!! You would not want to initially employ only one or two branches of your military and then later add the other branches. By using your most effective arsenal RIGHT NOW, I am virtually certain that you markedly reduce the risk for the bad cells to grow, mutate, spread and/or begin to develop resistance to our arsenal of weapons. If you only start with one type of treatment, the cancer cells may figure out how to mutate so they develop resistance (like hormone resistant or refractory CaP) and even spread (metastasize). Have **No Mercy** against the Bad Guys. This is the treatment strategy that I have found leads to the best results when treating prostate cancer with systemic therapies such as hormone blockade (HB), chemotherapy and/or my prostate cancer antiangiogenic cocktail (as opposed to local therapies such as radical prostatectomy, radiation therapy, seeds, etc.).

For most of the advanced stages of prostate cancer, I use alternative hormone blockade which you might picture as one branch of our military (e.g., Army). We continue to use Lupron and Proscar, but instead of using an antiandrogen such as Casodex, flutamide, or nilutamide, we most likely will recommend the use of ethinylestradiol (EE) 1 mg per day. This is a form of estrogen. Much less often we use ketoconazole/hydrocortisone. We generally use this alternative hormone blockade for nine months.

For men who only have high-risk disease not previously treated, we usually recommend the hormone blockade protocol that I named, pioneered, and have been using since 1991; 13 months of

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Triple Hormone Blockade® including three Casodex per day, a Lupron-type drug, and one Proscar per day (followed by Proscar, 5 mg once a day, so-called Finasteride Maintenance® Therapy). For men who will be treated with EE, we recommend that they receive three or four doses of radiation to their breasts, hopefully prior to starting EE, and specifically 400 cGy per dose. This may help to prevent breast enlargement and/or tenderness that estrogen almost always causes. Please give the name and phone number of a local radiation therapy doctor to one of our P.A.'s and we will speak to them and ask them to please follow our specific protocol. The radiation therapy doctor should answer any questions that you may have about this treatment.

The second major area of attack is the use of chemotherapy (picture Navy). As far as I know, I was the first to use low-dose weekly Taxotere/Emcyt/ carboplatinum, T/E/C, three weeks on and one week off. I have been using this since 1998. The dose of Taxotere is 25 to 20 mg/M²; maximum dose 50-55 mg. The dose of carboplatinum is 200 mg per week along with the Taxotere if the platelet count is at least 150,000 (lower doses of carboplatinum depending on the platelet count). I only use 2 Emcyt three times a day **with food** the day of Taxotere and the day after only. By using this low dose of Emcyt and taking it with food, nausea rarely, if ever, occurs. We additionally use various post and pre-meds to reduce and usually prevent most side effects. We also use full-dose anticoagulation to prevent blood clots. If you ask most lay-persons what they picture when imagining a patient on chemotherapy, they will usually describe someone who looks and feels sick and terrible; the unfortunate person usually throws up, they lose their hair and then, almost invariably, they soon die. Fortunately, our chemotherapy does not cause these horrible side effects. There is virtually no nausea or vomiting ever; only about one in seven men has temporary but significant hair loss, and about three-quarters have little or no hair loss at all. Patients do not feel "wiped out." In fact, the sicker a patient feels before treatment starts, the better they will feel on therapy. To date, virtually all of our patients who were in pain from metastatic or advanced cancer when they first began their treatment here became pain-free and almost always within one or two weeks. Patients who have been in pain for more than one year and have worsening pain in spite of ever higher doses of narcotics invariably respond this dramatically and rapidly.

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Even patients with weight loss who are mostly confined to bed have enjoyed these incredibly dramatic and favorable responses as well. Almost invariably, they ask us with bewildered looks on their faces: "How is it possible for our protocol to work so well?" They had been told over and over again by their prior doctors that their condition was terminal; that there was not anything further that anyone could do that would help. They were advised to enter a hospice program, accept that they were dying, and not try to fight their inevitable fate. Noting how quickly they have responded, and being even more surprised at the near absence of any side effects, they often state: "If your treatment works this well, why isn't everyone being treated with this "Leibowitz Protocol?" I encourage you to call our office and request a copy of our Patient Volunteer List. More than 75 or 80 patients have volunteered to discuss their experiences when treated with my various protocols.

On our Compassionate Oncology Medical Group website, www.compassionateoncology.org, is an article that I wrote on management of metastatic, castration resistant prostate cancer using Taxotere-based chemotherapy. If you notice at the end of that article, there is a table where I show the percentage of declines in PSA that each patient experienced. It is most impressive. Note also that these are results that I reported in September **1999**. Taxotere did not receive FDA approval to treat prostate cancer until 2004; I have been using it since 1997. If you look at this Table reproduced on the next page, I shall try to explain the details to you. In the first column are the initials of each patient; column #2 their age; then initial PSA prior to our chemotherapy protocol followed by their PSA at the completion of all their chemotherapy. The fifth column refers to the number of doses of Taxotere, Emcyt and Decadron that we gave to that specific patient. Initially, I gave T/E/D until their PSA stabilized, then I added carboplatinum. But within a few months, after observing how well patients tolerated carboplatinum, I treated everyone from the beginning with low-dose weekly Taxotere/Emcyt/carboplatinum (T/E/C), three weeks on and one week off. The next two columns show the month and year chemotherapy started and stopped; the next column shows the number of months on treatment; the next the number of doses of T/E/D where we also administered carboplatinum. For example, the first patient, J.K. received 22 doses of T/E/D chemotherapy, the final 14 doses also included carboplatinum. Thus he received 22 total doses, not 22 plus 14 more doses. The next column is the one that I am most proud of. It shows the percent decline in PSA

HRPC WEEKLY T/E/D ± CARBO
(AS OF SEPTEMBER 1999)

Patient's Initials	Age	Initial PSA	End PSA	Doses T/E/D	Date Started	Date Stopped	# of Months on Treatment	# Doses w/ Carbo	% Decline	# of Prior Hormone Regimens	Prior RT	# of Prior Chemo Regimens	Prior HB and Chemotherapy (see glossary)	Most Recent PSA
JK	59	36.65	3.11	22	Apr-98	Sep-98	6	14	91.5%	6	No	No	F, L, O, C, PcS, N, C+P	8.90
RR	63	31.50	3.13	21	May-98	Sep-98	5	9	90.1%	3	1	No	L, C, F	1.99
RN	76	228.00	10.65	17	Apr-98	Aug-98	5	5	95.3%	4	No	No	O, F, AG, PcS	16.00
RB	66	15.80	13.55	19	Apr-98	Oct-98	7	7	14.2%	4	No	1	CX, DES, L+C, KC	26.67
EK	76	77.00	2.60	20	Jan-98	Jul-98	6	0	96.6%	4	1	No	Z, F+P, C, KC, N, AG	85.90
SM	79	15.50	7.31	17	Apr-98	Sep-98	5	9	52.8%	3	2	No	L+F, P, ME, R, ME	86.00
TI	71	120.00	2.98	22	Apr-98	Aug-98	5	8	97.5%	3	No	No	O, F, C, FW	0.62
KR	69	16.28	1.53	11	Jan-98	Apr-98	3	0	90.6%	3	No	No	Z+C+P, F	0.15
CFH	59	0.84	0.34	12	Mar-98	May-98	2	0	59.5%	2	No	No	FW, TRIPLE BLOCKADE	39.80
AP	69	239.00	7.01	48	Sep-97	Oct-98	13	15	97.1%	3	1	No	L, RI, C, F, P	47.53
JP	58	13.42	0.04	14	Jul-98	Nov-98	5	5	99.7%	3	1	No	L+C, F+P	0.26
CR	74	2.54	0.66	14	Jul-98	Oct-98	4	0	74.0%	3	No	No	O+F, C+P	2.10
DM	73	53.80	5.20	16	Jul-98	Oct-98	4	15	90.3%	3	No	No	L+F, C+P	1.05
LB	69	25.87	1.50	16	Aug-98	Dec-98	4	8	94.2%	3	No	No	L+F+C+P	0.97
NS	55	4.58	5.80	6	Oct-98	Dec-98	2	2	0.0%	2	1	No	L+F+P	14.97

Analysis

Mean PSA for patients off treatment	4.36
% of patients with ≥ 50% Decline	76.5%
% of patients with ≥ 90% Decline	58.8%

Glossary

Code	Description	Code	Description	Code	Description
AG	Aminoglutethimide	KC	Ketoconazol	R	Spot Radiation
C	Casodex	L	Lupron	RI	Radiation Isotope
CX	Cytosan	M	Mitoxantrone	RT	Radiation Therapy
D	Decadron	Me	Megace		to Prostate
Des	Estrogen	N	Nizoral	T	Taxotere
E	Emcyt	O	Orchiectomy	TX	Taxol
F	Flutamide	P	Proscar	V/E	Velban/Emcyt
FW	Flutamide withdrawal	PcS	Pc Spec	Z	Zoladex

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from the day treatment started until the first PSA after chemotherapy was completed. Note under analysis in the left lower part of the page under the Table that over 75% of patients had their PSA decline over 50%, and almost 60% saw their PSA decline at least 90%!! And our results since 2001 are much better, primarily because of the use of AAC as well as alternative hormone blockade. The next column lists the number of prior hormone blockade agents they previously received, and directly below the Table is a glossary that identifies the meaning of the various hormone agents and chemotherapy agents that are listed in the second to last column, and only identified in the column by a letter. The glossary gives the drug name to each letter. The column, "Prior R.T.," refers to any prior radiation therapy, and the next column reports if they received prior chemotherapy. The very last column lists their most recent PSA as of September 1999. Thus patient #1, J.K., had a PSA of 36.65 in April 1998; it was 3.11 in September 1998 when he completed chemotherapy, and one year later, it was less than 9. This PSA was more than 75% lower than his starting PSA almost one and one-half years previously and he was off chemotherapy for the preceding 12 months. Patient #2 had his PSA one year off chemotherapy at 1.99 which was more than 90% lower than pre-chemotherapy, etc. Note that T.I. had his PSA fall from 120 to 2.98 when he went off chemotherapy. Thirteen months later, his PSA was 0.62 - almost 80% lower than when he stopped chemotherapy, and over 99% lower than prior to starting chemotherapy. Thus patients can enjoy extremely prolonged remissions off chemotherapy. Please call some of the volunteers.

Most doctors, perhaps especially oncologists, and especially research oncologists who typically practice in academic centers use "evidence based medicine." This means that they will not alter their treatment approach for any oncology illness unless prospective, randomized, double-blinded studies are completed comparing treatment A to treatment B. In this scenario, treatment A is what the evidence based doctor considers the proven community standard of practice and the "best treatment." In our imaginary example, if treatment B is found more effective and/or less toxic than treatment A, then treatment B becomes his/her new standard of practice.

Additionally, these evidence based doctors insist that your first study compare treatment with a single study medicine to a pill, or capsule, or IV drug that looks, tastes, and smells exactly like the study medicine, but it actually is a placebo

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(a sugar pill or an inert pill). The study must be prospective, randomized, and double-blinded. This means that neither the patient nor the doctor knows which pill (or IV drug) their patient is taking. If the trial determines that the study medicine is more effective than placebo, then a brand new trial begins. In this study, the study medicine from the first trial (call it medicine E) will be compared in a new, randomized, prospective, double-blinded study to the exact same medicine E, but one-half of the patients will also receive a second medicine (call it medicine F). Everyone gets the same dose of E medicine, but half also receive one dose of F medicine while the other half receive a placebo medicine that looks, smells, and tastes like our "real" medicine F, but is inert. Once again, neither the doctor nor the patient know which arm of the study they are on. Are they taking two medicines or one medicine and one placebo?

If the two medicine arm is found more effective, then perhaps a third trial may start. Trial 3 will compare two medicines (E and F) plus placebo to three medicines (E, F and G). This study will be prospective, randomized, and double-blinded. Our evidence based doctors would not allow a study to skip any of these steps. A Maverick Doctor (such as this author) did not want to deprive his prostate cancer patients the use of Taxotere beginning in the summer of 1997 when I began to treat all of my prostate cancer patients who needed chemotherapy with Taxotere. Evidence based doctors would have to wait almost seven more years until May 2004 before studies "proved" Taxotere superior. Dr. Maverick's approach seems to offend and upset evidence based doctors who then seemed to lose respect for Maverick Doctor in spite of the fact that Dr. Maverick is not critical of the way anyone else practices medicine, and is not trying to convince anyone that Dr. Maverick's way is superior to theirs. They should take care of their patients in the manner they believe best, and Dr. Maverick should be allowed to do the same, until and unless it can be proven that the clinical outcome of patients treated by Dr. Maverick was clearly proven to be significantly inferior. However, if evidence based doctors want these rules, are they willing to change their treatment if Dr. Maverick's results are found superior to their results?

I am extremely grateful for the essential contributions made by evidence based doctors and scientists. Their studies may often conclusively prove one treatment superior to another. These studies benefit society. By definition, patients must be

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treated on rigid protocols. Even if your doctor is absolutely convinced that treatment 17 is superior to treatment 18, he/she must still enter you on the protocol comparing treatment 17 to treatment 18, and treat you according to whichever arm you are randomly assigned to by a computer. Our academic, evidence based doctor must utilize the protocols that his institution is supporting or sponsoring.

Having done my Oncology/Hematology fellowship at Harvard, I observed practice patterns, academic pressures, private practice community clinicians, etc. I rotated through the Dana Farber Cancer Center and was exposed to different protocols used to treat essentially every stage of every imaginable cancer. As well, I was exposed to and participated in all phases of studies, Phase I, Phase II, Phase III, and Phase IV studies.

But as soon as I left Harvard and immediately entered into a community oncology practice setting, I chose to change my priorities and approaches to treatment. Rather than put the needs of society first, I found myself a natural patient care advocate. From the very beginning of my first private practice and continuing ever since, I have always tried to "treat each patient the way that I would want to be treated if I were a layperson and had their illness." This means that I endeavor to always try to determine what treatment I believe to be most effective for each individual patient and then treat them that way. Additionally, virtually every time that a patient is seen, their specific treatment protocols are reevaluated. If needed, we adjust, fine tune, or even completely overhaul their treatment. This is truly individualized treatment that is constantly being evaluated and adjusted as needed.

As you can easily predict, our treatment protocols cannot have rigid, inflexible dosages, durations of treatment, etc.

As a result, I believe that our individual patients are able to receive and enjoy near optimal care. In my practice, the needs of each individual patient are far more important to me than the needs of science and society. I accept that this may be considered a selfish way to practice medicine, especially according to academic, evidence based doctors. But this is the only way that I can feel comfortable caring for patients who place their trust in me and expect me to do what is best for them - as individuals, and not do what may be best for society.

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In my 40 years of practice, I have had fewer than a handful of patients feel differently.

The third branch in our military attack analogy, the Air Force, involves the use of my prostate cancer antiangiogenic cocktail (AAC). These drugs turn off the blood supply to cancer cells. Basically, the two most active ingredients in the cocktail are Leukine and a combination of thalidomide/Revlimid.

Since men are being treated concurrently with chemotherapy and antiangiogenic cocktail, you may not be able to recognize that the antiandrogen (like Casodex, flutamide or nilutamide) may be stimulating CaP cells to grow and cause your PSA to rise. Over time, there are a number of different changes that may occur such as mutations in the androgen receptor, increased numbers of androgen receptors, and many others in men who are treated with an antiandrogen. All of these changes lead to the same unfortunate result...instead of the AA killing prostate cancer cells, the AA has turned traitor and is stimulating prostate cancer cells to grow. However, these harmful effects of the AA are masked by the beneficial effects of chemotherapy and AAC which are continuing to lower PSA. Since we cannot tell when the antiandrogen will turn traitor and cannot recognize this deleterious action, I do not use an antiandrogen more than once. I realize that I may be the only prostate cancer specialist who does this, but I have often found myself in this type of situation being the only one -- see my paper, "The Emperor's New Clothes."

We additionally utilize full-dose low-molecular weight heparin (LMWH) because of the risk of deep vein thrombophlebitis (blood clots in veins) with or without pulmonary emboli (blood clots that travel to the lungs) from Taxotere/Emcyt, as well as from estrogen. There is also some significant evidence that LMWH has direct anti-tumor benefit as well as being a superior anticoagulant compared to Coumadin (warfarin) pills. LMWH is also known to be antiangiogenic.

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? The name of this form of treatment is antiangiogenic cocktail (AAC).

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Dr. Judah Folkman, the Harvard Medical School researcher and pediatric oncologic surgeon, was the first to postulate that all forms of cancer shared a common characteristic. In order to grow larger than 2 millimeters, islands of cancer cells had to produce substances that stimulated the growth of new blood vessels (angiogenesis) to bring oxygen and nourishment to the cancer colony. Without new blood vessel formation (neoangiogenesis), cancer cells were unable to grow.

Eventually, Dr. Folkman was able to isolate various proangiogenic substances, and also discovered substances that inhibited the growth of blood vessels - antiangiogenic agents. Dr. Folkman was the pioneer whose brilliant insights along with decades of laboratory and clinical research have resulted in a new and increasingly effective method for controlling cancer - namely turning off the cells that cause blood vessels to form and feed islands of cancer cells. Unfortunately, earlier this year in the Denver Airport, awaiting a transfer of planes on his way to lecture on angiogenesis, he suffered a sudden and unfortunately fatal heart attack. I believe that Heaven and Earth cried out in agony, anguish, and misery with the passing of this irreplaceable giant among Medical Maven giants.

Beginning in 1998, I began treating prostate cancer patients with thalidomide as a potent antiangiogenic agent that also enhances the immune system. I 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 my prostate cancer patients and their anecdotal responses to thalidomide. Dr. William Figg at the National Cancer Institute had reported that thalidomide was effective treatment for some men even with metastatic, hormone refractory prostate cancer. In a personal discussion with Dr. Figg, we both noted response rates as high as 80% when prostate cancer patients who were hormone sensitive or hormone naive were treated with thalidomide as a single agent.

During those first few years using antiangiogenic agents, Compassionate Oncology Medical Group studied and investigated this class of drugs and combinations of drugs in order to more quickly evaluate them for effectiveness as well as toxicities. New insights and discoveries quickly evolved and were incorporated into my various clinical protocols. Until this category of drugs was found to have anti-cancer activity, the target of all chemotherapy drugs was to directly attack cancer cells. Cancer cells have extremely high rates of growth, and

consequently high rates of mutations, as the cells try to find ways to survive the various drugs and treatments that are given in an attempt to cure patients of their malignant diseases. Many of these mutations result in cancer cells acquiring resistance to various types of chemotherapies. The ability of cancer cells to grow rapidly and mutate is one of the mechanisms that they use to acquire resistance to chemotherapy and also to radiation therapy.

While chemotherapies target cancer cells, the target of almost all antiangiogenic agents are the cells that form blood vessels - the vascular endothelial cells. Some cancer cells have doubling times of hours while some vascular cells may only double once or twice a year. These very slow rates of cell growth and cell division result in very low rates of mutations, markedly reducing (but not eliminating) the chance for these cells to develop resistance to antiangiogenic drugs

Over the years, various ingredients in my AAC would appear, but if I was not impressed with their ability to help control prostate cancer (CaP), their inclusion in the AAC was short-lived. However, a few medications have enjoyed charter member status. The two most effective drugs in the AAC are clearly Leukine (GM-CSF) and the combination of thalidomide/Revlimid. For most patients, insurance coverage permitting, we use thalidomide 50 mg one night, alternating with Revlimid 5 mg the next night (or day). We never use both drugs the same day, nor do we ever use more than one total capsule on any day. Thalidomide is the drug that caused severe birth defects in the 1950's and 1960's - flapper limbs, etc. Thalidomide turned off the blood supply to limbs in the developing fetus and this resulted in the birth defects. Turning off the blood supply to cancer cells is the definition of antiangiogenesis. Revlimid is the second-generation thalidomide derivative. It **does** have the same risk to cause birth defects should a woman of child bearing age get exposed to it. Thalidomide/Revlimid can be found in semen; therefore, birth control precautions are mandatory and women of child-bearing age should not physically even touch either medication. Unlike thalidomide, Revlimid does not cause drowsiness, peripheral neuropathy symptoms, constipation, or slow heart rates. Revlimid may lower a patient's platelet count. Platelets help your blood to clot. We monitor blood counts carefully and frequently whenever one of our patients is being treated with Revlimid.

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As of November 2008, I believe (opinion) that 95% of the beneficial results from AAC are due to Leukine and thalidomide/Revlimid. Avastin, when given with T/E/C along with Leukine and thalidomide/Revlimid, is almost certainly a significantly effective antiangiogenic agent that I am convinced (opinion) is the third most potent agent in my AAC. When used in this specific setting, Avastin might account for up to perhaps 25% of the benefit in this AAC with Leukine/thalidomide/Revlimid accounting for 70%+ of the benefit. After we have completed hormone blockade and chemotherapy, our patients are maintained on AAC, but usually without Avastin, although a significant minority of patients are also maintained on Avastin along with the other active AAC drugs.

Some of the minor AAC players that may help our patients include Proscar, Avodart, Celebrex (but only 200 mg once a day to reduce the risk of cardiovascular complications), low-molecular weight heparin (LMWH), and perhaps statins (like Crestor) that also lower cholesterol and reduce the risk of dying from cardiovascular events. A number of studies (still controversial) have found that men on statins who develop prostate cancer have a lower risk of developing advanced or metastatic cancer, as well as a lower risk of dying from metastatic prostate cancer.

Still other minor AAC players include mini-mini-dose alpha interferon, and perhaps vitamin D. We also may use a metronomic schedule of oral cyclophosphamide (Cytoxan) in tiny, tiny mini-doses. At times, we may add another category of drugs called targeted therapy. Currently, our targeted drug of choice is Nexavar, but previously we tried Iressa, Tarceva, Sutent, Gleevec, and rapamycin.

At various times, our drug de jour (not necessarily antiangiogenic) was frozen shark cartilage from one specific Canadian company; curcumin came and went, as did artemisinin, Resveratrol, vitamin C (including extremely high-dose intravenous vitamin C); pomegranate juice, Lyc-O-Mato, Herceptin, Erbitux, Sandostatin, pegylated interferon, oral low-dose methotrexate, Biaxin, Atacand, and Hytrin. I apologize if I have left off any other drugs or medicines that we have tried.

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), which are part of your immune system. Thus, Leukine enhances the ability of your immune system to recognize and kill cancer cells; in part by stimulating dendritic cells.

There are a significant number of articles in 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 prostate cancer (CaP) antiangiogenic cocktail (AAC), particularly thalidomide/Revlimid.

In the January 2003 issue of the *Journal of Clinical Oncology*, Rini, Brian, et al., reported on 29 patients with rising PSA's 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 speculated in the first version of this paper that I believed it possible that by combining thalidomide and/or Revlimid with Leukine, we might be able to significantly improve upon the already impressive results obtained using Leukine as a single agent to treat CaP.

Small, Eric, et al., *Clinical Cancer Research*, Volume 5, July 1999, pages 1738-1744, reported on two series of patients treated with Leukine, and all patients 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%, with one patient having over a 99% decline in PSA, as well as objective improvement in his bone scan. This response continued for 14+ months, and was ongoing at the time this paper was published.

At Compassionate Oncology Medical Group, I first combined Leukine with low-dose thalidomide beginning in 2000. I initially used this combination on men with far advanced disease, but soon utilized these agents to treat men that were still hormone sensitive, and I have even considered using them to treat men who are hormone naive. 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. In Dr. Amato's paper, 18 CaP 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 found that close to 100% of men who were hormone sensitive or naive respond to these two medications. I have also observed that the responses always occur in the first two to four weeks of treatment. This remarkable response rate was also noted by Dr. Amato. All of the men in his study had at least a 26% reduction in 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 system; with Leukine and thalidomide, the opposite occurs. Neither Leukine nor thalidomide lower testosterone levels, and thus they do not have any hormone blockade effects.

In January of 2006, the 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 smouldering leukemia, or advanced preleukemic syndrome. Later Revlimid was FDA approved to treat certain stages of multiple myeloma. Using Revlimid for any medical condition other than an FDA approved indication 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 to their patient. As an aside, until 2006, the only FDA approved indication for using thalidomide was for treating a type of leprosy!! In 2006, thalidomide received FDA approval to treat multiple myeloma, a form of bone cancer.

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 a blood thinner; either Coumadin (warfarin), which is a pill; or much more often, with a self-injection type of medicine known as low-molecular weight heparin (LMWH). We believe that low-molecular weight heparin may have direct anti-cancer benefits, in addition to being a superior blood thinner, especially for cancer patients.

The most common side effect we have seen from Revlimid is the development of a reduced platelet count. Platelets help the blood to clot. 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. We can then usually resume treatment with Revlimid at a reduced dosage. We have not had to give any patient a platelet transfusion. Revlimid is a small molecule derivative of Thalomid. As of November 2008, we have treated several hundred patients with Revlimid, usually alternating it with thalidomide. Patients taking Revlimid almost never report developing symptoms of either peripheral neuropathy or sedation. Because of falling platelet counts, we have had to reduce the dose of Revlimid for a significant percentage of patients, and in some patients, we have to stop Revlimid for a short period of time. Almost all of the patients who developed reduced platelet counts on Revlimid were also taking one or two other medications that can lower platelet counts. We obviously monitor platelet counts very carefully for our Revlimid treated patients, and I would recommend that any patient on Revlimid have their platelet count checked frequently. We have definitely seen excellent PSA responses with Revlimid. In the lab, Revlimid has 100 to 1,000 times more potent anti-cancer effects than thalidomide. Even as of November 2008, I am not convinced that there is a significant difference between Revlimid versus thalidomide regarding their clinical anti-cancer efficacy in our patients. At times, our patients might take thalidomide two nights in a row, Revlimid the next, or vice versa.

"No long-term toxicity from Leukine was observed in a cohort of patients at a median follow-up of 61 months from the start of treatment." There was no evidence of treatment-related blood clots or bleeding. The authors found that these patients had measurable improvements in several different functions of their immune system, consistent with the known beneficial effects of

Leukine on the immune system. The authors concluded that Leukine can provide long-term disease control in patients with androgen-dependent, biochemically relapsed prostate cancer.

Although their Leukine results are good, I am quite certain that at some time in the future, when our academic institutions finally study Leukine alone versus Leukine plus thalidomide/Revlimid, the combination will be found to be significantly more active and effective than Leukine alone.

Effective systemic therapy (medicines) can kill prostate cancer cells anywhere in the body, even if those cells have spread to your bones, lymph nodes, etc. Local treatments like radical prostatectomy or radiation therapy can only kill prostate cancer cells in the prostate and the few nearby lymph nodes that are removed at the time of surgery. Most radiation therapy fields do not include very many lymph nodes. Almost all prostate cancer specialists believe that if prostate cancer cells have spread to several lymph nodes, they have also spread to distant sites, especially multiple bones, even though the bone scan is read as normal. However, a normal scan is worthless for excluding metastatic cancer as I explain in DVD lectures and on my website. Briefly, an x-ray of the spine remains normal until 50-60% of the bone is replaced by cancer cells. A bone scan does not become abnormal until at least 15% of the bone is replaced by cancer cells. An analogy I frequently use is pointing out that my office looks down over Beverly Hills High School and their athletic fields. At any given time, there are usually a number of "guys" playing basketball. However, if you are flying in a plane at 32,000 feet and look down, you cannot see the high school, the basketball courts, and you certainly cannot see anyone playing basketball. Trying to rely on a bone scan, CT scan, MRI or PET scan to exclude the presence of clinically significant populations of cancer cells is like looking out the window of a plane and believing that no one is playing basketball because you cannot see anyone. Carrying our analogy forward, if you fly over the Rose Bowl on New Year's Day (or whenever their bowl game is held) and look out the airplane window, you can tell that **something** is going on. But it takes a Rose Bowl full of cancer cells before you get an abnormal scan.

At the Prostate Cancer Symposium in February 2007 in Orlando, Florida, Abstract #229 reported a study that used Revlimid and Leukine to treat men with progressive hormone refractory

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prostate cancer (HRPC). The authors are Garcia, J.R.; Rini, B.; Dreicer, R., et. al. Seventy-five percent of the patients had metastatic HRPC; the other 25% had rising PSAs without known metastases. Overall, 56% of men have had a decline in their PSA. It is important to point out that the Revlimid and Leukine doses and schedule used in this study are very different from the protocol I have found most effective for our patients. However, a 56% response rate for men with HRPC, and whose treatment did not include chemotherapy, represents a major advance in the ability to help treat prostate cancer.

At the May 2007 ASCO meeting, Abstract #15515, further follow-up on this study was reported by Dreicer, R., et al. Overall 76% of patients experienced a decline in their PSA level. It is wonderful to see that their response rate improved compared to their earlier report. As of November 2008, I am pleased and proud to report that at Compassionate Oncology Medical Group, our response rate to PCAAC in men with hormone sensitive disease is still close to (if not exactly) 100%. You can call our office and request a copy of our Patient Volunteer List which has 80+ names and phone numbers of patients who have volunteered to discuss their experiences when treated with our various treatment protocols. They are available to help explain their treatment experiences to patients wishing to learn more about their own treatment options.

Before taking your first dose of Leukine, it is necessary for you to please call one of our physician assistants, Mary or Carla. 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, this will almost certainly cause nasty side effects. Do not take more than what 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 shot 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 three regular-strength Tylenol every four hours, but only as needed. Do not take aspirin or anti-inflammatory drugs if you are on anticoagulation. If not on anticoagulants, we advise taking three Advil (200 mg), or any similar ibuprofen product, along with each Tylenol dose. Patients on anticoagulants may use Celebrex, 200 mg twice a day, or pain medicines that do not contain aspirin or a nonsteroidal anti-inflammatory. Only use Celebrex if you do not have a medical reason that prevents the use of Celebrex. Examples of safe medicines to use even if you are taking an anticoagulant include Darvocet-N 100, Trilisate 750 mg, Vicodin-type tabs, and/or Percocet. Rarely, Leukine can cause bone pain, particularly if it raises your white count too high. Ibuprofen is quite effective to relieve this type of bone pain, but is an NSAID, so you cannot take it if you are on anticoagulation. 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 (or sooner), you can reduce one of the two other medicines that you still are taking two of

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each night (if you first cut Tylenol). After this, you can next reduce Zantac or Benadryl pills from two to one. One week later (or sooner), reduce to just three pills per night (one of each). Continue to reduce one pill at a time. If side effects return, you can increase your premedications up to two of each (six total), and taper more slowly.

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 regarding the mechanics of how and where your injection should be given. 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 or Carla will explain the procedures that we find work 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 (WBC) 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, is admitted to the hospital and/or is seen by another doctor, and a CBC (complete blood count) is ordered, 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. Leukine also often raises a type of white blood cell named eosinophils or EO's. This type of white blood cell may be increased in patients with allergic histories and/or certain parasitic infections. EO's are increased in at least one-third of our patients on Leukine, and are not an illness, and should be ignored. Almost all doctors are not familiar with the effects Leukine has on your different white blood cell counts. It is important for you to inform the doctor that Leukine raises the total white cell count, **and** also the polys, and often eosinophils, too. Polys suggest bacterial infection to a doctor. If you do not inform your doctor about being on

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Leukine and how it affects your white blood cells, and specifically your polys and EO's, 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. Please carry a copy of this paper with you to show to any doctor.

At COMG, our patient responses to date have already proven to us that combining Leukine with Revlimid and/or thalidomide is clearly more effective than using either agent alone, based on our observations rather than waiting for the double-blind prospective randomized trials that scientists require to reach their conclusions.

As discussed earlier, I treat each patient with whatever treatment protocol or protocols that seem to me, after intensive review, to be the most effective and promising, based on evolving, current state-of-the-art knowledge, insight, wisdom, and at times, a touch of intuition. Since each patient's treatment protocol is individualized, as new information becomes available, we adjust and modify our protocols to take advantage of any new knowledge, rather than be chained to an inflexible institutional protocol. This is one of the major reasons that I am unable to be a scientist....I believe that the needs of each individual patient outweigh the needs of society.

Individualizing dosage adjustments from week-to-week on each patient helps to explain the reduced toxicities we see in our patients, as well as the far superior response rates and survival statistics that our patients at Compassionate Oncology Medical Group continue to enjoy. Unlike Colonel Saunders with his secret blend of herbs and spices for Kentucky Fried Chicken, I gladly and freely share my knowledge and experiences with any interested person. This is why this paper's title starts with "Dr. Bob's (not so) Secret Recipe...".

The antiangiogenic cocktail continues throughout the chemotherapy and hormone blockade treatments. After the nine (or 13) months of hormone blockade ends, we continue the AAC as maintenance therapy, and at that time, we can discuss the **possibility** of adding in high-dose testosterone replacement therapy (TRT), if a patient is interested, and if their

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specific clinical condition might permit consideration of a discussion regarding the risks, benefits, and treatment options regarding high-dose TRT.

The 3-pronged approach that I have described in this paper using alternative hormone blockade, T/E/C chemotherapy, and antiangiogenic cocktail works so much better and with less toxicity than anything ever reported. About ten years ago, I used the following words to describe my Triple Hormone Blockade® results. Why am I the only one that you are afraid to believe?

As always -

Be happy,

Be well,

Live long and prosper.


DR. BOB

P.S. I am blessed again to report that my ninth grandchild Ezra, just turned 1. My daughter, Kimberly, recently told us that Ezra and his 2-year-old "Big Sister," Sophia, will have, with G-d's blessing, a new sibling next Spring.

®Triple Hormone Blockade, Triple Androgen Blockade, and Finasteride Maintenance are the registered trademarks of Robert L. Leibowitz, M.D.

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** 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. 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.