



Compassionate

Oncology Medical Group

Bob Leibowitz, M.D.

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

ANTIANGIOGENIC COCKTAIL (AAC)

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) .

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 survive. 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.

ANTIANGIOGENIC COCKTAIL (AAC)

Page 2

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 our 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 are clearly Leukine (GM-CSF) and the combination of thalidomide/Revlimid. For most patients, insurance coverage permitting, we use thalidomide 50 mg, alternating with Revlimid 5 mg. 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. Thalidomide/Revlimid can be found in semen; therefore, birth

ANTIANGIOGENIC COCKTAIL (AAC)

Page 3

control precautions are mandatory. 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.

As of August 2008, I believe (opinion) that 95% of the beneficial results from AAC are due to Leukine and thalidomide/Revlimid. 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), and statins (like Crestor) to lower cholesterol and reduce the risk of dying from cardiovascular events. A number of studies 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 anticoagulation with low-molecular weight heparin (not warfarin/Coumadin), mini-mini-dose alpha interferon, and perhaps vitamin D. Avastin is also possibly a major significant player and we try to use it in certain settings, but I do not believe it is anywhere near as effective as Leukine and thalidomide/Revlimid. We also may use a metronomic schedule of oral cyclophosphamide (Cytosan) in 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, and Gleevec.

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 D, vitamin C (including extremely high-dose intravenous vitamin C); pomegranate juice, Lyc-O-Mato, Rapamune (m-TOR inhibitor), Herceptin, Erbitux, Sandostatin, pegylated interferon, oral low-dose methotrexate, Biaxin, Atacand, and Hytrin. I apologize if I have left off any products from this list.

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

ANTIANGIOGENIC COCKTAIL (AAC)

Page 4

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.

ANTIANGIOGENIC COCKTAIL (AAC)

Page 5

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

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 smoldering 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

ANTIANGIOGENIC COCKTAIL (AAC)

Page 6

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, however. Revlimid is a small molecule derivative of Thalomid. As of Labor Day 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 September 2008, I am not convinced that there is a significant difference between Revlimid/thalidomide regarding their clinical anti-cancer efficacy in patients. At times, our patients might take thalidomide two nights in a row, Revlimid the next, or vice versa.

Earlier in this paper, I pointed out that a significant percent of patients treated with Leukine as a single agent have enjoyed

ANTIANGIOGENIC COCKTAIL (AAC)

Page 7

prolonged remissions beyond five years, and at the time of publication of this article, some patients were still in remission more than five and one-half years after their Leukine treatment was started. In fact, I am not aware of any other single agent form of systemic therapy (systemic therapy refers to something that treats the whole body...e.g., chemotherapy, hormone blockade, immunotherapy, vaccines, etc.) that has been able to control prostate cancer for this long a period of time that was not a form of hormone blockade and/or chemotherapy. Effective systemic therapy can kill prostate cancer cells anywhere in the body, even if those cells have spread to your bones, lymph nodes, etc. Local treatment like radical prostatectomy or radiation therapy can only kill prostate cancer cells in the prostate and the few nearby lymph nodes that are removed with most radical prostatectomies. 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 (see my paper, "Potpourri of Prostate Pearls and Insights," as well as the PAACT Newsletter, December 2007). You can download all of my papers for free at compassionateoncology.org.

In the June 2006 *Journal of Urology*, Volume 175, pages 2,087-2,091, is the article by Rini, Brian; Small, Eric, et al., which reported the GM-CSF results referenced above. This article describes 30 hormone sensitive patients who had rising PSA's following either surgery or radiation therapy. At the time treatment with Leukine was started, their baseline PSA's ranged from 0.4 to 6. None of them had evidence of metastatic disease by scans. Amongst this cohort of patients, seven of them have remained on Leukine as a single agent "long-term." The authors defined long-term as longer than four years. At the time this article was published, this group of patients had remained on Leukine for a median of 5.1 years, with a range of 53 to 67 months; were still being treated, and were still in remission! The authors emphasized the fact that therapy was extremely well tolerated. "No long-term toxicity from Leukine was observed in this 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 also found that these patients had measurable improvements in several different functions of their immune system, consistent with the known beneficial effects of Leukine

ANTIANGIOGENIC COCKTAIL (AAC)

Page 8

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.

At the Prostate Cancer Symposium in February 2007 in Orlando, Florida, Abstract #229 reports a study that used Revlimid and Leukine to treat men with progressive hormone refractory 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 Labor Day 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 while being treated with our various treatment protocols. They are available to help explain their treatment experiences to patients wishing to learn more about their 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, it

ANTIANGIOGENIC COCKTAIL (AAC)

Page 9

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 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 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

ANTIANGIOGENIC COCKTAIL (AAC)

Page 10

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, you can reduce one of the two other medicines that you still are taking two of 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 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 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 (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.

ANTIANGIOGENIC COCKTAIL (AAC)

Page 11

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 patients on Leukine, and are not an illness, and should be ignored. Most 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 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 Compassionate Oncology Medical Group, 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. Rather than waiting three to six years for the results of such a study, our patients are currently being treated with what will probably not become a standard of practice for at least five more years. Taxotere did not become FDA approved to treat prostate cancer until May 2004. I started treating my prostate cancer patients with Taxotere beginning in the summer of 1997. If I had waited for the FDA to approve Taxotere to treat prostate cancer patients, many of my patients who are today alive, well, and in remission, would not be able to be described by any of those three adjectives. Doing prospective, randomized double-blind, placebo-controlled studies helps us further medical advances that help the "many," rather than the one. I have always tried to treat patients the way I would want to be treated if I were a layperson and had their illness. This means treating each patient with whatever treatment protocol seems to be 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

ANTIANGIOGENIC COCKTAIL (AAC)

Page 12

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 can never be a scientist....I believe that the needs of the one (you, each individual patient) outweigh the needs of the many. The many may require you to treat many patients with treatment A even though you are virtually certain treatment B is better. This is another example explaining how, in our practice, the needs of the one outweigh the needs of the many. By individualizing dosage adjustments from week-to-week on each patient, I believe is another major explanation for the reduced toxicities we see in our patients, as well as the far superior response rates and survival statistics that patients of Compassionate Oncology Medical Group continue to enjoy.

As always -

Be happy,

Be well,

Live long and prosper,



BOB LEIBOWITZ, M.D.

P.S. On Thursday, June 22, 2006, I was blessed yet again. My daughter, Kimberly, gave birth to her first child, a daughter, Sophia, my seventh grandchild. My son-in-law, Stephen, played a vital role, as well.

P.P.S. Since June of 2006 (the time of the original writing of this paper), Dr. Bob has been blessed with two more grandchildren, numbers 8 and 9, Ariella and Ezra.

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

** 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.

Revised 8/25/08