



Compassionate

Oncology Medical Group

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

**LEUKINE (GM-CSF) and REVLIMID, the Second
Generation THALIDOMIDE Product**

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?

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). By early 2007, this prediction, in my opinion and experience, became fact.

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.

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.

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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, Dr. Bob 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 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

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100% of men who were hormone sensitive responded 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 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.

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 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. Later it 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. 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.

Unlike thalidomide, use of Revlimid is not 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 a blood thinner; either Coumadin (warfarin), which is a pill; or much more often, with a low-molecular weight heparin (LMWH). We believe that low-molecular weight heparin may have direct anticancer benefits, in addition to being a superior blood thinner, especially in cancer patients.

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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, but perhaps on an every other day basis. We have not had to give any patient a platelet transfusion, however. Revlimid is a small molecule derivative of Thalomid; a second-generation Thalomid derivative, and to be on the safe side, the same precautions regarding the risk of fetal abnormalities are appropriately FDA mandated for Revlimid.

After treating approximately 150-200 patients with Revlimid, I can confirm that patients taking Revlimid do not report developing symptoms of either peripheral neuropathy nor 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 to Revlimid. In some patients who have low platelet counts from Revlimid, and do not have symptoms of peripheral neuropathy, we will alternate and have them take Revlimid one night, thalidomide the next night, etc. At times, patients might take thalidomide two nights in a row, Revlimid the next, or vice versa.

In January 2006, Revlimid received FDA approval to treat one type of "smouldering leukemia" or preleukemia. That same month, Compassionate Oncology Medical Group began evaluating the effectiveness of Revlimid (prescribing it "off-label") alone, in combination with Leukine, and as part of our other various treatment protocols. We have combined Revlimid with hormone blockade, chemotherapy, antiangiogenic agents and/or targeted therapies. We have confirmed that Revlimid is active in helping to control prostate cancer, but as yet, we are unable to determine whether it is more, less, or equally as effective, as thalidomide. In the lab, Revlimid shows anti-cancer cell killing effects that are up to 1,000 times more

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potent than thalidomide. However, since such a high percentage of patients treated with thalidomide develop significant symptoms of peripheral neuropathy (a type of nerve damage that may be irreversible), while Revlimid does not cause either peripheral neuropathy or sedation, we advise patients to consider changing to Revlimid, if their insurance permits. Most of our patients take Revlimid and thalidomide each week, but never both on the same day. Thus, the total maximum number of Revlimid and thalidomide capsules is seven per week; not seven of each; seven total between thalidomide and Revlimid each week. For patients who had to discontinue thalidomide because of symptoms of peripheral neuropathy, you should talk to your physician about the possibility of taking Revlimid since we have not had any patient on Revlimid develop peripheral neuropathy symptoms.

Earlier in this paper (my original version of this paper was written prior to the publication of the June 2006 article described below), I pointed out that Leukine has been found to control prostate cancer for extremely long periods of time. In fact, I am not aware of any other form of systemic therapy 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. 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 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 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 that paper, and all of Dr. Bob's papers for free at compassionateoncology.org.

In the June 2006 *Journal of Urology*, Volume 175, pages 2,087-2,091, is an article by Rini, Brian; Small, Eric, et al., reporting long-term results using GM-CSF (Leukine) as a single agent to control prostate cancer. This article describes the results of a study involving 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

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

This article reports that approximately 25% of the patients treated only with Leukine were able to have their prostate cancer controlled for more than five years. In the entire cohort of patients, the median PSA doubling time (PSADT) increased from 8.4 to 15 months, while the PSADT was approximately 32 months for the patients in the long-term group. This group had their average PSA decline by about 70% from baseline to nadir (lowest PSA while on treatment). 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 or thalidomide/Revlimid 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 the treatment did not include chemotherapy, represents a major advance.

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At the 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 the response rate improved compared to their earlier report.

Before taking your first dose of Leukine, it is necessary for you to please call one of our physician assistants. 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.

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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. 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. 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.

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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 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.

On January 10, 2006, the manufacturer of Leukine announced that they had reformulated their product to deliver extended shelf life for additional convenience for patients. The new formulation included the preservative EDTA (edetate disodium). This formulation was launched around February 1, 2006. The powder formulation Leukine was not changed and does not contain EDTA.

On January 23, 2008, Bayer Health Care announced that they were immediately withdrawing the current liquid formulation of Leukine (a product withdrawal) from the supply system. The powder formulation was not withdrawn. Bayer requested that any unused vials of Leukine be returned to them for credit. You may call Bayer at 1-888-842-2937 for further information.

The decision to withdraw Leukine was made because of an upward trend in spontaneous reports of syncope (fainting) with or without documented hypotension (low blood pressure). The timing of the increased reporting of these adverse events coincided with the change in formulation of liquid Leukine when EDTA was added.

I spoke with the Leukine pharmacist specialist at Bayer on February 4, 2008 to try to get the most recent information. He

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told me that the risk of these adverse events seems to occur almost exclusively with the first dose of Leukine. Serious allergic or anaphylactic reactions (shock) have been reported only rarely with the old or new formulations. I am waiting to hear from another Bayer expert for additional details.

COMG has been using Leukine since 2001, and most of our patients take Leukine five to seven times a week. I am certain that we have treated many hundreds of patients with Leukine and we are not aware of any patient experiencing these adverse events.

What should you do? If you have access to the powder form of Leukine, it may be safest to switch to it. The liquid form is stable for 20 days after a vial has been entered if it has been shipped and stored refrigerated. Unopened vials are stable until the expiration date if shipped and kept refrigerated.

The powder form should be stored and shipped refrigerated and is safe at room temperature for about 96 hours, but upon delivery, it must immediately be refrigerated. Unopened vials are good until expiration date. The powder form may be reconstituted with sterile water for injection (SWFI) which does not contain any preservative, but if SWFI is used, the solution must be used within six hours or discarded. If mixed with bacteriostatic (0.9% benzyl alcohol) water for injection (BWFI), the solution is stable for about 20 days if refrigerated.

Bayer is in discussions with the FDA to see if they can switch back to the non EDTA formulation. However, Bayer has informed us that there is not enough powder form available to supply everyone who is currently being treated with liquid Leukine, and Bayer is allocating the powder version for patients being treated with Leukine for a bone marrow transplant or following aggressive chemotherapy being used to treat acute leukemia.

Using Leukine to treat CaP is an off-label use, and Bayer is clearly informing us that there will be a major shortage that will last at least through the summer, and depending on the FDA requirements, the shortage may continue much longer.

According to Bayer, there have not been any deaths from Leukine and almost all of the adverse events occurred with the first one or two doses.

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If you have any remaining vials of liquid Leukine, and if you send them to Bayer for a refund, you will not be able to find any pharmacy anywhere that can fill a prescription for liquid Leukine, and you will have an extremely difficult time trying to get any powder Leukine. If you have prostate cancer and wish to remain on Leukine, it is not against the law. A doctor's responsibility is to explain all the treatment options available including risks, benefits, and alternatives, and then each patient decides which path to pursue.

Please weigh all of your options and good luck!!

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 not become a standard of practice for at least five years. Taxotere did not become FDA approved to treat prostate cancer until May 2004. I started treating my 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 individualized, as new information becomes available, we adjust and modify our protocols to take advantage of this 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 know treatment B is better. But, the chairman of your

department wants to complete his research protocol comparing treatment A to treatment B, and your academic institution needs the research funds that accompany the study. This is another example explaining why, in our practice, the needs of the one outweigh the needs of the many (Star Trek fans should recognize these words).

As always -

Be happy,

Be well,

Live long and prosper,

DR. Bob

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.

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