



Compassionate
Oncology Medical Group

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"PCAAC"

PROSTATE CANCER ANTIANGIOGENIC COCKTAIL

I attended the chemotherapy symposium, "Innovative Cancer Therapies for Tomorrow," in New York in November 2001. At that conference, I concluded that the future of most cancer therapy will be to try to control cancer, rather than trying to cure it. When cancer has metastasized, it is almost always incurable, even if the metastases are microscopic and cannot be detected by our current technology. Our limits of resolution cannot pick up micrometastases.

I believe that we will be treating metastatic and probably recurrent prostate cancer with what I am calling "PCAAC" or "prostate cancer antiangiogenic cocktail." Other drugs that block certain growth factors or that can help cells mature into more normal-appearing cells may also be utilized. The good news is that we have a number of currently available antiangiogenic products to help in our treatment of prostate cancer. Proscar is thought to have antiangiogenic properties and is one of the drugs in our cocktail. Thalidomide is probably the most potent antiangiogenic drug that is commercially available. The National Cancer Institute today is sponsoring a study utilizing thalidomide in prostate cancer patients to help prevent or postpone the need to go back on hormone blockade in men who have already received hormone blockade for prostate cancer. A prior NCI prostate cancer study demonstrated that thalidomide helped from 58 to 68 percent of men with metastatic hormone refractory prostate cancer. Their current study uses 200 milligrams per day. I believe that is far too high a dose.

Our experience with thalidomide suggests that much lower doses are effective, and are obviously much less toxic. At the New York Cancer Symposium in November 2001, I concluded that our goal should be to have men remain on thalidomide

indefinitely. The dose that I recommend is 50 milligrams per day. The goal of antiangiogenic therapy is merely to control prostate cancer, and cut off the blood supply to it. Antiangiogenic products are not thought to be able to kill cancer cells, but they can arrest them and keep them under control for prolonged, and possibly indefinite periods of time. This goal means we are trying to induce a permanent state of dormancy for prostate cancer cells.

There are very few cancers that require only one antiangiogenic product to control them. Hence, the need for an antiangiogenic cocktail. Almost all cancers produce several to many different pro-angiogenic products (substances that bring blood supply to them). Besides Proscar and thalidomide, I recommend a COX-2 inhibitor, usually Celebrex, 200 to 400 milligrams twice a day. Celebrex clearly has antiangiogenic activities, as well as promoting apoptosis (programmed cell death of the cancer cell).

Another prominent drug in my "PCAAC cocktail" is Zometa (or Aredia, if Zometa is not covered by insurance). Zometa has been shown to have antiangiogenic properties, in addition to other beneficial properties for men with prostate cancer. It is also active in some other types of cancers. Aredia may have similar properties. Medicare has approved Zometa for treating metastatic prostate cancer and other cancers metastatic to bone. Zometa and Aredia are also the most potent drugs available to treat osteoporosis.

An interesting over-the-counter drug that may be useful is a specific form of shark cartilage made by Aeterna Laboratories in Canada. It is a frozen liquid extract of shark cartilage. This is the product that is being studied by the National Cancer Institute in Canada. A report in the *Annals of Oncology*, Volume 13, pages 1259-1263, 2002, reported on Aeterna's liquid shark extract, Neovastat. The survival in patients with metastatic kidney cancer who were treated with 240 milliliters of Neovastat per day was more than twice as long as the survival of patients treated with 60 milliliters per day. This same product has shown intriguing activity in non-small cell lung cancer. It has also been used in prostate cancer, but I am not yet aware of publication of any result in prostate cancer. For those of you interested in utilizing complementary therapies, this is one form that I can recommend. It definitely has antiangiogenic properties. The powdered shark cartilage

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available from health food stores is worthless, in my opinion.

On page 1685 of the November 21, 2001 issue of the *Journal of the National Cancer Institute*, there is a page of information, "Natural Compounds Show Antiangiogenic Activity." This *JNCI* editorial mentioned Aeterna Laboratories' shark cartilage product, Neovastat. Unfortunately, it is not commercially available. The product that is commercially available from Aeterna Labs is CarTcel. The Aeterna sales representative is Michael Stern (866-628-2355/310-739-1706).

For men with metastatic disease, I also add GM-CSF and pegylated interferon. Dr. Eric Small reported in the *Clinical Cancer Research* journal in July 1999 that GM-CSF treatment for patients with hormone refractory prostate cancer worked rather well as a single agent. The median decline in PSA was 32 percent, and there was one patient who had over a 99 percent decline, with an improvement in bone scan, and this lasted for 14+ months. There is another abstract reporting results of GM-CSF in patients with advanced prostate cancer, in which nine of 14 patients had an initial PSA decline, with a median decline of 27 percent. GM-CSF probably works by activating some of the cells in your immune system, perhaps dendritic cells. I don't know whether it is also antiangiogenic or not.

We utilize GM-CSF five nights in a row each week. Our usual dose is approximately 200 micrograms per night, although our dose can vary from 150 to 250 micrograms, five nights in a row per week.

Interferon has been shown to be able to cure one or two types of tumors that behave like cancers. This activity has been reported by Dr. Judah Folkman. Dr. Folkman, as we remember, is considered the Father of Angiogenesis, having discovered angiostatin. In my opinion, Dr. Folkman will very soon receive the Nobel Prize in Medicine for his work in angiogenesis and antiangiogenesis. I had the privilege of speaking to him in November 2001 at a cancer conference. He is the one who gave me the idea about using PEG (pegylated) interferon. PEG stands for polyethylene glycol. Interferon has both antiproliferative effects, meaning it inhibits the growth of cancer cells, but especially in this

slow-release form, has antiangiogenic effects. Pegylated interferon is the same type of interferon that has been commercially available for 20 years, but by adding the PEG part to the molecule, interferon is very slowly released over the course of a week. We utilize a very low dose of interferon. If we are giving regular interferon, our usual dose is approximately 1,000,000 units per night, seven nights a week. On occasion, we have had to cut the dose to as low as 300,000 units per night. The highest dose I have utilized is 2,000,000 units per night. The dosage of PEG-Intron varies.

Chemotherapy is one of the most potent antiangiogenic categories of drugs available. However, when chemotherapy is used in the standard fashion, that is once every three weeks, you only get antiangiogenic benefits for a few days. Even when we use our low-dose, weekly chemotherapy for metastatic prostate cancer, we are only getting antiangiogenic benefits for perhaps six or seven days a month. For my antiangiogenic cocktail therefore, I am adding in low-dose oral continuous Cytoxan. This is truly low-dose chemotherapy in the form of Cytoxan (cyclophosphamide). I have used as high a dose as 17,000 milligrams of Cytoxan administered over two days to a patient with malignant lymphoma. The dose of Cytoxan that I have chosen in our PCAAC protocol is 25 milligrams twice a day. We are using this mini-dose Cytoxan for its antiangiogenic effect, rather than any antitumor effect.

When you give chemotherapy in this low continuous dose regimen, it is called metronomic dosing or scheduling of chemotherapy. An article in *The Lancet Oncology*, Volume II, December 2001, pages 733-739, describes this. The article is entitled, "Metronomic Scheduling: The Future of Chemotherapy?" Metronomic chemotherapy minimizes the toxic effects of drugs, allowing more combinations of "potentially synergistic selective inhibitors of angiogenesis." The article credits an author, Hanahan, for proposing the term, "metronomic dosing of cytotoxic drugs" to describe schedules based on low doses of chemotherapy given regularly, targeting angiogenesis. I started my first patient on this type of program on November 6, 2001. This article mentions COX-2 inhibitors as being antiangiogenic, another ingredient in our PCAAC. It also discusses using low-dose Cytoxan (cyclophosphamide) for its antiangiogenic properties. They go on to mention interferon having antiangiogenic effects,

independent of its well-documented antiproliferative activity. However, when given alone, metronomic dosing of chemotherapy did **not** produce long-term anticancer effects. Hence, the need for this cocktail.

Essentially all of our patients are taking a COX-2 inhibitor, usually Celebrex, 200 milligrams twice a day. We have utilized doses as high as 400 milligrams twice a day. For patients who are intolerant of Celebrex, we either utilize Vioxx, 25 milligrams per day or Bextra, 20 milligrams per day. My discussion from the *Journal of Urology* regarding abstract #1199 from the American Urologic Association, May 2002, reports on the use of Celebrex and its effect on PSA in men with recurrent prostate cancer. The abstract describes 13 patients with rising PSA's after prior treatment with radiation therapy or radical prostatectomy. The men were treated with Celebrex, 200 milligrams twice a day. At three months, 92% of the patients had a downward effect on the rate of their PSA rise; 38% had an actual decrease in the PSA value, and an additional 24% had stabilization in PSA's. Of the remaining five patients, four had slowing in their PSA doubling time, with the average doubling time slowing threefold. This means that if their PSA doubling time was eight months before Celebrex, the doubling time on Celebrex lengthened to 24 months. Most importantly, there was no change in the serum testosterone levels in these patients. These results suggest that COX-2 inhibitors may help delay disease progression, and can help avoid the need to start or resume hormone blockade. We have been recommending COX-2 inhibitors for our patients with prostate cancer since 1999. Close to 100% of the men in our practice are being treated with a COX-2 inhibitor. Remember, if there is abnormal kidney function, COX-2 inhibitors should not be given, since they can worsen kidney function. There are other possible side effects, and you are urged to discuss and consider the risk/benefit ratio before deciding to be treated with a COX-2 inhibitor. Celebrex can cause a skin rash; Vioxx can cause fluid retention and/or raise the blood pressure. Liver and kidney blood tests must be monitored while on COX-2 inhibitors. We have seen three patients develop mouth sores while on COX-2 inhibitors; one was on Celebrex; one on Bextra, and one on Vioxx. This is not a reported side effect, but if you get mouth sores, stop the medicine and see what happens.

Since the mid-1990's, there have been sporadic reports that an antibiotic, Biaxin, could reverse resistance to certain types of chemotherapy for certain malignancies. The first tumor type described was multiple myeloma. It seemed that patients who previously had progressed on a particular chemotherapy went into remission when Biaxin was added to the same chemotherapy. One possible mechanism of action is that Biaxin might interact with *bcl-2*. *Bcl-2* prevents a cell from entering apoptosis or programmed cell death (cell suicide). It is thought that Biaxin works as "an assistant" to other medications and makes them more effective. A second antibiotic that is also thought to possibly be beneficial is doxycycline. Either antibiotic is used in lower doses than are utilized to treat infection. The benefit of these two antibiotics is not related to fighting bacteria. Instead, it seems to enhance the effectiveness of other medicines. Antibiotics by themselves are not effective against cancer. Beginning in August 2002, I have added either doxycycline or Biaxin to a number of patients' antiangiogenic cocktails. After one week, one patient has had a decline in PSA. It is obviously too early to determine whether this strategy will work.

The *Lancet Oncology* article also mentioned trastuzumab or what is commercially called Herceptin. This antiepidermal growth factor receptor agent also inhibits angiogenesis. Its effect is potentiated by some cytotoxic drugs. This article points out that thalidomide is another worthy drug in their theoretical treatment cocktail. They then mention that long-term treatment with daily low doses of interferon resulted in a high cure rate of infants with life-threatening hemangiomas, without evidence of acquired resistance. This is what else is unique about antiangiogenic drugs, because you are targeting a normal cell, that is the cells that line the blood vessels or vascular endothelial cells. Therefore, the risk of acquiring drug resistance is much reduced. Cancer cells that are exposed to chemotherapy are constantly trying to mutate, and acquire drug resistance. This article talks about how these various antiangiogenic drugs might represent the future way to treat cancer. In our practice, the future is now.

Intriguing data beginning in the 1970's has suggested that anticoagulants may have some type of anticancer effect. For patients with metastatic cancer, some studies have shown chemotherapy plus anticoagulants to have superior survival compared to the same chemotherapy alone. Coumadin, or its

generic version warfarin, in my opinion, is not as effective as the injectable anticoagulants. In the past, the only injectable anticoagulant was heparin. In the 1990's, however, safer and longer-acting forms of heparin became available; the so-called low-molecular weight heparins. An example of this is Lovenox. Lovenox is given once every 24 hours. There have been many more studies suggesting that these injectable anticoagulants have antitumor activity. Simplistically, one can picture that in order for a cancer cell to successfully metastasize, it must travel through the blood stream and settle in bone, for example. Anticoagulants can make it much more difficult for these cancer cells to "stick" to the bone. It turns out that the antitumor qualities of anticoagulants are much more complicated than this. In addition, anticoagulants block multiple different processes, all of which result in antitumor benefit. A *Wall Street Journal* article from January 22, 2002 referenced an article appearing in the *National Academy of Science* describing this antitumor property of heparan-type products. They specifically reference the fact that anticoagulants inhibit the growth of prostate cancer cells in mice.

Although it is controversial, I am confident that anticoagulants do exert some type of anticancer effect. How much of an effect, I cannot say; which cancers most benefit from anticoagulant use is not yet known; and the relative benefit from using anticoagulants as anticancer agents compared to the possible risk of bleeding is also not known. Once again, in my opinion, Lovenox is probably safer to use than Coumadin, and in patients with metastatic cancer, I favor Lovenox. One additional benefit of anticoagulants in patients with metastatic cancer is the fact that they also obviously prevent blood clots. Up to 25 percent of patients with metastatic cancer do develop blood clots. Anticoagulants are only indicated to treat or prevent blood clots, but off-label use of drugs and pharmaceuticals is permitted if the patient is well-informed of the risks and benefits. Whether any of the anticancer properties of anticoagulants are related to an antiangiogenic effect is not known to me. I believe Lovenox adds substantial benefit to this treatment regimen, and most of the time I recommend that patients be treated with Lovenox unless they have a pre-existing bleeding condition or some other contraindication to receiving anticoagulants.

The use of multi-target therapeutic strategies, in

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particular inhibitors of angiogenesis with metronomic schedules of cytotoxic agents, is to achieve long-term control of cancer, or induce a dormant state in residual areas of tumor, without unacceptable toxic effects. It appears that survival time depends more on merely containing cancer than on actually shrinking it. The goal of chemotherapy has always been to shrink cancer. We must realistically appreciate that we are not going to be able to cure metastatic prostate cancer. We can, however, achieve very long-term control. I continue to be tremendously impressed with the response to this antiangiogenic cocktail. A number of men with metastatic, hormone refractory prostate cancer whose PSA's were not controlled in spite of hormone blockade and chemotherapy have continued to respond to this antiangiogenic cocktail. The first patient was treated beginning in November 2001. Briefly, in men with metastatic, hormone refractory prostate cancer, I utilize chemotherapy plus hormone blockade to debulk the body of as much metastatic cancer as possible. After that, I switch men to the antiangiogenic cocktail and continue with hormone blockade. In those men whose PSA's remain controlled for an additional two or three months, I often stop hormone blockade completely, and actually add high-dose testosterone to their antiangiogenic cocktail. That is a discussion for another paper.

There is also a patient in our practice who has a condition called "metastatic cancer of unknown origin." He has been on the antiangiogenic cocktail since December 2001. Every three months, CT scans are obtained to assess his response to treatment. He started out with a massive amount of disease in his abdomen and pelvis. You could literally feel a cantaloupe-sized, rock-hard mass in his pelvis prior to AAC. After a few months treatment, the mass has completely disappeared by exam. It does persist on CT scans, but each CT scan shows further reduction in size.

Another patient with metastatic ovarian cancer continues to respond to her antiangiogenic cocktail, and has avoided the need to go back on chemotherapy for the past year.

These patients are being treated with GM-CSF, interferon, Proscar, Celebrex, Herceptin, thalidomide, low-dose Cytoxan and Lovenox (or Coumadin).

If these results are sustainable, and I emphatically

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emphasize, if the results are sustainable, then this will be one of the few true miracles in medicine that I have been privileged to observe. A response after all known chemotherapies failed would be a clinical triumph, but until it is a sustained remission, it cannot be labeled anything more than that. Let us all hope and pray that we are witness to a miracle. (In oncology, a miraculous remission is something that lasts more than nine to 12 months in someone who has previously progressed after all known effective treatments.) Perhaps if I were a patient, I would save the word miracle for a cure, but an oncologist welcomes any major advance since they occur far too infrequently.

This paper was originally written on January 25, 2002, my birthday. I additionally announced in that paper that my daughter-in-law gave birth to my first ever granddaughter, Rachel. Both grandsons, Samuel and Max, continue to do superbly well.

Be happy,

Be well,

Live long and prosper,

DR. BOB

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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.