



**TAXOTERE PLUS AVASTIN**  
**Antiangiogenic Proof of Principle**

In the early 1970's, Dr. Judah Folkman, recognized as the Pioneer and Father of Angiogenesis and Antiangiogenesis, first postulated that there were substances that were produced in all cancer patient that could enhance the growth of cancer cells while other factors inhibited the growth of cancer by turning on or turning off the blood supply to cancer. He believed and was later proven 100% correct that islands of cancer cells are unable to grow larger than 2 mm in size without attracting their own blood supply.

I first began utilizing antiangiogenic agents as soon as thalidomide became FDA approved, shortly after a November 1998 conference that I attended, "Innovative Cancer Therapies of Tomorrow." By 2001, I had shown that a "cocktail" of antiangiogenic agents was more effective than single agents used sequentially. I called this my prostate cancer antiangiogenic cocktail (AAC), although I have used these same medications to treat breast, ovarian, kidney, lung, and other types of malignancies.

Recently there has literally been an explosion in medical literature describing the use of antiangiogenic agents for treating cancer. Some of these articles report on various phase I, II, III or IV clinical trials while other articles are preclinical or basic research.

Bevacizumab (Avastin), a Genentech product, is a monoclonal antibody that specifically inhibits VEGF (which is known as vascular endothelial growth factor). VEGF is a proangiogenic factor that stimulates endothelial cell growth which means it helps to bring blood supply to cancer cells. Avastin first received FDA approval to treat metastatic colorectal cancer after prospective randomized studies comparing chemotherapy alone to the same chemotherapy plus bevacizumab found that patients treated with Avastin had improved overall survival compared with chemotherapy alone. Avastin was the first antiangiogenic agent (A/A/A) to receive FDA approval and is probably one of the most effective A/A/A(s) discovered to date.

Prospective randomized studies were done and led to the approval of Avastin to treat patients with metastatic lung cancer, and more recently metastatic breast cancer. In all of

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these studies Avastin was administered with and without chemotherapy. When the Avastin plus chemotherapy arm showed benefit over chemotherapy alone, Avastin received FDA approval to treat these other cancers. Avastin will probably soon receive approval to treat the most common type of metastatic kidney cancer, and many believe approval for prostate cancer and certain types of brain cancer is not far off.

There are very few (actually none) chemotherapeutic agents that are active against so many different types of cancer suggesting that Avastin may well be found to be active in many additional other types of malignancies. Preclinical studies, in fact, found that VEGF protects endothelial cells against the antiangiogenic effects of Taxotere, and that Avastin inhibits this effect, thereby enhancing the benefits of Taxotere. We had anecdotally noted that a number of our patients with metastatic prostate cancer who had progressed on Taxotere responded to Taxotere plus Avastin.

Previously, the results of a phase II study comparing Taxotere plus Avastin were reported to have higher response rates and longer duration of response compared to prior studies utilizing Taxotere alone.

An article that will be published later in 2008 in the journal, *European Association of Urology*, was published online ahead of print on February 5, 2008. The criteria for inclusion in this study are men with metastatic HRPC who had previously been treated with Taxotere as first-line chemotherapy whose disease progressed on their prior Taxotere-based chemotherapy. All patients had received at least two prior chemotherapy regimens for metastatic HRPC. All patients had progressed on prior Taxotere treatment 70 mg/M<sup>2</sup> (mg per square meter of body surface area; most men have about 1.8 to 2.5 mg/M<sup>2</sup>) every three weeks plus prednisone 10 mg per day. In addition, all patients had previously been treated with mitoxantrone chemotherapy; two-thirds had received vinorelbine chemotherapy; one-third had received platinum compounds, and a number of patients had received, in addition, other agents. Regarding prior hormone blockade, all patients had received LH-RH agonist, Casodex, flutamide, and Emcyt; one-third had been treated with estrogen, and 60% with cyproterone acetate. A major PSA response was defined as at least a 50% reduction in PSA on two consecutive measurements, taken at least two weeks apart, and a minor response was defined as between 25% and 49% PSA decrease,

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whereas stable disease was less than a 25% PSA decrease up to less than a 25% PSA increase, and progressive disease was defined as PSA rising at least 25% on two consecutive measurements taken at least two weeks apart. Overall, 55% of patients had a major response; 10% a minor response; 10% had stable disease, and only 25% had progressed. The overall average PSA decline was 65%. These results are spectacular since these men had previously progressed on so many different types of chemotherapy and hormone blockade.

When these patients received Taxotere as first-line therapy, approximately 70% had a major PSA response. Even though these patients then progressed in spite of Taxotere, 50% of them responded to a lower dose of Taxotere, but with the addition of Avastin. Twenty percent of patients had stable disease when first treated with Taxotere, but with the addition of Avastin, half of these patients had a major PSA response. Ten percent of the patients had progressed on prior Taxotere, but all of them responded to Taxotere plus Avastin, although there were only two patients in this latter category.

The authors pointed out that bevacizumab was able to restore sensitivity to Taxotere in spite of the fact that patients had previously progressed while on Taxotere. This reversal of prior resistance is almost unheard of in oncology; if confirmed in larger studies, it would represent a type of "Holy Grail."

This same article references other reports utilizing antiangiogenic agents in prostate cancer patients who had were chemotherapy naive. The combination of Taxotere, Avastin, and Emcyt had a PSA response rate of 77%. Another study utilizing thalidomide, Avastin, and Taxotere showed an 87% PSA response rate (PSA declines of greater than or equal to 50%). At this time as I am writing this article, there is an ongoing national cooperative study (CALGB) Cancer And Leukemia Group B study 90401 which randomizes men to Taxotere plus/minus Avastin. This study will hopefully confirm the benefit of adding Avastin to Taxotere in men with metastatic HRPC.

I am certain that we are only at the very beginning frontier discovering the potential benefits using A/A/A to help control various types of cancer. It has already been shown that A/A/A work best when administered with other effective treatments like chemotherapy, hormone blockade, and (probably) radiation therapy compared to using an antiangiogenic drug alone.

We are all indebted to the pioneering efforts of Dr. Judah Folkman who, in my opinion, clearly deserved and deserves the honor of being awarded the Nobel Prize in Medicine for his work in antiangiogenic research that has led to discoveries that are improving the overall survival of patients with numerous types of malignancies. Unfortunately, Dr. Folkman died earlier in 2008 of a heart attack at the Denver airport where he was en route to a lecture on his favorite subject, antiangiogenesis. I have known Dr. Folkman since I first spent some time working with him in 1974 while rotating through Harvard Children's Hospital as part of my hematology/oncology fellowship. All of us are saddened by his sudden and premature death. He left behind an unfillable void reminiscent of a "Black Hole" in space.

As always -

Be happy,

Be well,

Live long and prosper,

*DR. BOB*

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. 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.