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CELEBREX, A COX-2 INHIBITOR

**CELEBREX - Off Label Use for Treating Prostate and Other Cancers:**

**CELEBREX UPDATE ADDENDUM - 12/22/06**

In the August 2005 Mayo Clinic Proceeding (8:1100-1101), there is a letter to the editor by Guru Sonpavde that should convince all of my readers about the potential benefit for using Celebrex to treat prostate cancer. This case report describes a 53-year-old man, who presented with urinary discomfort, low back pain, and a bone scan showing widespread metastatic disease. His PSA was 522, and Gleason score 9. He was started on Lupron and Casodex, and after six months of therapy, PSA dropped to 4. However, three months later, PSA rose to 22, and then to 37. His Casodex was discontinued. Twelve months after initiating treatment, his PSA was 55, and he was started on ketoconazole/hydrocortisone. In spite of this, his PSA rose to 80 one month later, with the addition of worsening low back pain. He refused to be treated with chemotherapy. Because of his bone pain, he was started on Celebrex, 200 mg per day. Within days, he had clinical improvement, with resolution of his back pain. Two months after starting Celebrex, his PSA dropped to 5.48. That represented his nadir PSA value. Four months after starting Celebrex, his PSA was 11.5, and his dose was increased to 200 mg twice each day. His PSA dropped to 10.4. Six months after starting Celebrex, his PSA was 22; it was almost 80 when he started Celebrex.

This is certainly the most dramatic response to Celebrex as a single agent that I have ever heard about or seen. Remember that Celebrex is just one of the ingredients in my antiangiogenic cocktail. I believe that when you treat prostate cancer with only a single agent, it is fairly easy for the cancer cells to mutate and become resistant. Using the various ingredients in my antiangiogenic cocktail is a way to help avoid the development of resistance.

At the American Urologic Association Meeting, May 21, 2005, Abstract Number 828 reports on use of Celebrex and its effect on prostate cancer. The authors are Derksen, J. Eric, et al. Forty patients who had rising PSA's following radiation therapy (#8), or radical prostatectomy (#32), were treated with

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Celebrex, 200 mg twice per day (12 patients), or 400 mg twice per day (28 patients). Most patients have an 18 month follow-up. Thirty-six of 40 patients (90%) had an inhibitory effect on PSA after three months. Eleven out of 40 had an actual decline in PSA; eight out of 40 had stabilization. Of the remaining 21 patients, 17 of them showed a slowing of their PSA doubling time (DT) after starting Celebrex by an average of 4.5-fold, compared to pre-Celebrex. Only four patients failed to demonstrate a slowing of the PSA doubling time at three months follow-up, but three of these four eventually did show a slowing of PSA doubling time from .2-fold to 4.0-fold at the 12 month follow-up. This suggested that they needed a longer period of treatment before benefitting from Celebrex.

The short-term responses seen initially at three months continued at six, 12, and 18 months, which were the study mandated PSA follow-up measurement points. The improved, slower PSA doubling times persisted at all time points measured. Only two of the initial 40 patients failed to improve their PSA. These new results represent an expanded study previously reported and described in prior versions of my COX-2 paper.

Abstract No. 4593, by Pruthi, R., et al., in the Proceedings of the American Society of Clinical Oncology, Volume 23; 2004, reports on 24 patients who had serially rising PSA levels following radical prostatectomy (20 patients) or radiation therapy (four patients). Patients were treated with Celebrex, either 200 mg twice each day or 400 mg twice each day. Twenty-two of 24 (92%) had a favorable PSA response. Eight out of 24 had an absolute decline in PSA; three additional patients with rising PSA's before Celebrex had their levels stabilize after starting Celebrex. Of the remaining 13 patients, 11 had slowing of their PSA doubling time, with the average doubling time slowing 4.5-fold compared to pretreatment, e.g., if prior to Celebrex the PSA doubling time was 3-1/2 months, then on Celebrex, the doubling time lengthened to 14 months. Responses at three months continued at six and 12 months. There was a significant shift for patients with rapid baseline PSA doubling times to slower or stable doubling times after starting Celebrex. This benefit persisted at each time point measured. Testosterone levels did not change.

The authors concluded that COX-2 inhibitors help control rising PSA's in patients with biochemical progression after radiation therapy or radical prostatectomy. These results suggest COX-2

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inhibitors may delay prostate cancer disease progression. Following radical prostatectomy, your PSA is expected to be less than 0.02 within one month of surgery. If your PSA is higher and rising, it means that surgery failed to cure you. Unfortunately, each year, more than 60,000 men have rising PSA's following radical prostatectomy or radiation therapy; 60,000 men each year who are not cured in spite of radical local therapy, and 60,000 men have exposed themselves to the life-altering side effects of impotence, incontinence, gastrointestinal, and other unpleasant side effects.

Radical prostatectomy removes all prostate tissue, malignant and benign. We believe that a rising PSA after radical prostatectomy is almost always coming from occult, metastatic prostate cancer cells somewhere in the body (almost always from bones). Other sites such as lymph nodes may also harbor occult prostate cancer metastases. Compassionate Oncology believes that isolated local recurrences are extremely uncommon. We feel that men with a local recurrence invariably also have metastatic prostate cancer cells in sites distant from the prostate, especially in bones. Since Celebrex had a beneficial effect for patients with rising PSA's after radical prostatectomy or radiation therapy, and since radical prostatectomy removes all prostate tissue, it seems obvious that Celebrex is exhibiting a beneficial effect against prostate cancer cells. We believe Celebrex can help to control prostate cancer cells that are local and/or systemic.

An earlier abstract in the Proceedings of the American Urologic Association, May 2002, reported on the effect of Celebrex for men with rising PSA's after radical prostatectomy or radiation therapy. The abstract reports on 13 such patients. The men described here are **not** the same population of men reported in the first abstract discussed above. Rising PSA means that local therapy failed to cure these men. Again we feel that although some men may have a local recurrence, we believe local recurrence without systemic disease is not common. In this particular study, all men were treated with Celebrex, 200 mg 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 their PSA levels, and an additional 24% had stabilization of PSA's (whereas before Celebrex their PSA's were rising). Of the remaining five patients, four had slowing in their PSA doubling time, with the average doubling time slowing threefold. This means that if the PSA doubling time was eight months before Celebrex, the

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doubling time on Celebrex lengthened to 24 months. Importantly, there were no changes in the serum testosterone levels in these patients, so the benefit of Celebrex was not due to hormone blockade. These results reinforce our belief that Celebrex can control disease progression, and may help avoid or delay the need to start hormone blockade.

### **COX-2 Side Effects:**

All medicines have side effects. COX-2 inhibitors may adversely affect kidney function. Celebrex contains a type of sulfa and can cause skin rashes, especially for those who are allergic to sulfa, although the form of sulfa in Celebrex is the type found in Lasix (furosemide), and most patients allergic to sulfa do not develop a rash from Celebrex. An occasional patient reports diarrhea; some may develop fluid retention or mildly elevated blood pressure. Liver and kidney blood tests must be monitored while on Celebrex. It is generally agreed that the risk of gastrointestinal bleeding is lower for patients treated with a COX-2 inhibitor compared to patients treated with aspirin or traditional NSAID's, e.g., Motrin, Aleve, ibuprofen, Advil, and all of the medicines in the NSAID drug class. COX-2 inhibitors may have other side effects, and you should discuss this subject with your primary care physician. Each patient must consider the risk/benefit ratio for taking any medication.

In all of our prior versions of this paper, dating back to 2001, we warned of the possibility that COX-2 inhibitors could cause increased cardiovascular toxicity. In 2001, we stated that "taking one baby aspirin with food per day while on a COX-2 inhibitor **might** be able to protect against possible cardiovascular side effects." We advise all our patients treated with Celebrex to take one baby-strength Ecotrin per day (with food).

Celebrex remains commercially available. In the prostate cancer studies I described at the beginning of this section, Celebrex resulted in improved PSA control for men with serially rising PSA's, following radical prostatectomy or radiation therapy. If you do not have an increased cardiovascular risk profile, Compassionate Oncology feels that you might consider using Celebrex. Doses of less than 200 mg **twice** daily may not have any anticancer benefits. Patients on an anticoagulant should check with us so we can review your individual

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situation to determine whether it is safe to take any aspirin while you are also taking an anticoagulant.

Celebrex is known to be antiangiogenic and is able to lower PSA's in men with a rising PSA following prior radical prostatectomy or radiation therapy. Since Celebrex helps this stage of prostate cancer, it seems logical that Celebrex may also benefit patients with all other stages of prostate cancer, whether or not they previously had local therapy. We recommend that each patient assess the risk-benefit ratio for using Celebrex, and then make an informed decision. We cannot advise a patient to take Celebrex; we can only present all of the available relevant information to them, but the final decision must be made by each person. To date, Celebrex is the only nonsteroidal anti-inflammatory drug that has been shown to have a beneficial effect for controlling PSA's in patients previously treated for prostate cancer.

On a draft of this paper that I wrote on December 20, 2004, I stated, "We know that additional information will become available in the future, and may provide us with enough information to **know** what to do. The one thing we know we are certain of today is that we do not know exactly what to do." When I wrote that, I did not realize how prescient this statement would be. On December 21<sup>st</sup>, The National Institutes of Health reported interim results from a trial involving approximately 2,400 patients. These patients had been randomized to receive Celebrex, 200 mg twice each day, naproxen (Aleve is an over-the-counter version of naproxen), at a dosage of 220 mg twice each day, or placebo. Neither the doctor nor the patient knew which drug they were taking. All three medications appeared identical. Naproxen first became commercially available in the United States in 1976. It is a nonselective COX-1 and COX-2 inhibitor. The startling results from this study found that patients taking Naproxen had a 50% **higher** risk for cardiovascular events **compared** to patients taking either Celebrex or placebo. Patients randomized to Celebrex had essentially the same number of cardiovascular events as those patients treated with placebo.

Prior to the results of the Naprosyn/Celebrex/placebo study, physicians believed that all of the nonselective NSAID's were cardioprotective. It was thought that the same mechanism that increased the risk for bleeding also reduced the risks of developing clots in the coronary arteries and/or carotid arteries. That belief was disproved with the findings showing

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Naprosyn (naproxen) use was associated with a statistically significant increased risk of cardiovascular complications compared to Celebrex or placebo. Yet another new wrinkle was reported in the December 13, 2004, *Archives of Internal Medicine*. There was a 50% increased risk of cardiovascular complications for the first 29 days following abrupt discontinuation of traditional NSAID's such as ibuprofen, Advil, Motrin, Aleve and/or Naprosyn. Thus, there is an increased risk of cardiovascular complications taking naproxen, and a 50% increased risk of myocardial infarction if you suddenly discontinue taking Naprosyn.

Additional studies confirm that the use of most NSAID's is associated with an increased risk of cardiovascular complications. Therefore, this problem is not limited to Celebrex or selective COX-2 inhibitors.

We believe that the ongoing Celebrex studies will show that Celebrex reduces the risk for developing colon polyps and cancer. In the Vioxx colon polyp prevention study (now terminated), at least according to one report, the use of Vioxx was associated with a reduced risk for developing new colon polyps.

The only thing we know for certain is that the final recommendations for the use of COX-2 inhibitors are confusing and in evolution.

If you are perplexed, it may be comforting to learn that you are not alone; we are, too. Stay tuned -- Compassionate Oncology will continue to update you. Use our website, [compassionateoncology.org](http://compassionateoncology.org) to download for free all of our past, current, and revised papers.

I had to revise the "facts" regarding selective and nonselective COX-2 inhibitors at least ten different times in the month of February 2005 alone. It sure would be nice if our "experts" could agree on the facts, and not keep changing them.

### **CELEBREX ADDENDUM - 4/26/05**

One of the areas of research that will now be explored will be to try to use a lower dose of Celebrex, perhaps 200 mg once each day, but adding another agent such as one of the antiangiogenic drugs, or one of the targeted drugs (like Nexavar or Sutent). In mouse models of colon cancer, "the

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combination was very effective. The mice haven't developed any polyps in five or six months, and that had never been seen before in any prior animal study."

At the 2005 American Association of Cancer Research, it was reported that increased cardiovascular complications were not limited to the selective COX-2 inhibitors, Vioxx, Bextra, and Celebrex. Instead, there appears to be a class effect, since over-the-counter products including all the ibuprofen competitors (Motrin, Advil, Nuprin, etc.); Naprosyn, and Aleve were found to have increased cardiovascular complications as well. An interesting study mentioned that adding Lipitor to lower dose Celebrex seemed to enhance the anticancer beneficial effects without the increased cardiovascular problems. In addition, Lipitor would be expected to reduce cardiovascular complications.

As always --

Be happy,

Be well,

Live long and prosper,

DR. BOB

**\*\*** 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.

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