COX-2 INHIBITORS

Evolving literature has shown that COX-2 inhibitors are playing an ever more important role in helping to prevent, treat and/or help inhibit the spread of various types of cancers, including prostate cancer. In experimental animals injected with prostate cancer cells until there is an established tumor, treatment with a COX-2 inhibitor results in reduction in number and size of metastases. COX-2 inhibitors have been shown to have an antiangiogenic effect, and a pro-apoptotic effect. Emerging data suggests COX-2 inhibitors may be useful in helping to prevent cognitive dysfunction (like Alzheimer’s). They are known to help prevent colon polyp formation in patients with familial adenosis polyposis syndrome (multiple colon polyp syndrome), and seem to reduce the risk of colon cancer developing in these types of patients. There is evidence that they help with many types of cancers, since COX-2 is overexpressed in at least a dozen different cancers and hematologic (malignant blood) disorders.

As of the end of 2001, the National Cancer Institute initiated studies comparing radical prostatectomy, with and without Celebrex 200 mg twice a day, in order to see if COX-2 inhibitors can improve survival. Colon cancer patients are randomized to surgery, with and without Celebrex 200 mg twice a day. However, Celebrex, 400 mg twice a day is approved in helping to prevent recurrence of colon polyps in patients with familial colon polyp syndrome. This higher dose has also been approved for at least one other indication. Some of our patients take this higher dose of Celebrex. It is our prediction that in the relatively near future, almost everyone with almost any type of cancer will be treated with a COX-2 inhibitor.

For all of our patients on COX-2 inhibitors, we also recommend taking an Ecotrin-type baby aspirin, one a day. This should be taken with food to decrease the risk of upset stomach, heartburn, indigestion and/or ulcers. If any upper
GI symptoms develop, aspirin and your COX-2 inhibitor should be discontinued, and the symptoms should be discussed and evaluated by your local physician as soon as you develop any of these symptoms.

COX-2 inhibitors do not have an anti-platelet effect. Therefore, they do not increase the risk of bleeding when you are cut. They do not increase the risk of bruising. In fact, they are not associated with increased risk of bleeding from anywhere other than the stomach. There is a small increase in gastroduodenal abnormalities, which could cause upper GI bleeding. This is entirely different from the situation regarding standard nonsteroidal anti-inflammatory products. These products, such as Advil, Motrin, Aleve, ibuprofen, etc., do affect platelets, and therefore increase the risk of bleeding anywhere in the body. You can take COX-2 inhibitors up to 36 hours before surgery without any increased risk of bleeding, and can restart them 36 hours after surgery. COX-2 inhibitors do not cause bleeding from the colon or rectum.

In the November 12, 2001 edition of the “Medical Letter,” the cardiovascular safety of COX-2 inhibitors was discussed. This publication is considered to offer the most objective information regarding pharmacologic agents. It does not have any ties to any pharmaceutical company whatsoever, and accepts no advertising. The conclusion is that one study of Vioxx revealed a 1.11 percent incidence of thrombotic cardiovascular events in Vioxx-treated patients compared to 0.45 percent of patients treated with a regular nonsteroidal anti-inflammatory. Taking baby aspirin with a COX-2 inhibitor could protect against any possible cardiovascular effect. Until more prospective studies, with and without low-dose aspirin are available, it would be premature to conclude that Vioxx or Celebrex increased the risk of thrombotic cardiovascular disease. This is the written conclusion from the “Medical Letter.”

In March 2002, the first of the second generation COX-2 inhibitors became commercially available. The trade name is Bextra; the generic name is valdecoxib. As of October 2002, we are only advising patients to use Bextra if they have gastrointestinal intolerance or other side effects from Celebrex or Vioxx. Bextra is supposed to be less nephrotoxic (that means less risk of damage to the kidneys),
and according to studies involving almost 2,000 patients, Bextra was not associated with any increased incidence of gastroduodenal ulcers in Bextra-treated patients compared to placebo-treated controls. The first generation COX-2 inhibitors, Vioxx and Celebrex, are associated with increased risk of gastroduodenal ulcers, compared to placebo. However, the risk of bleeding with COX-2 inhibitors (Celebrex and Vioxx) is much lower than with Advil, Motrin, Aleve, ibuprofen or the other nonsteroidal anti-inflammatory drugs (NSAID’s) which block both COX-1 and COX-2 receptors. Because Bextra is an even more selective COX-2 inhibitor than the first generation products, Vioxx and Celebrex, this may help to explain the reduced gastrointestinal toxicity. However, it is now apparent that some of the anticancer benefit from Celebrex is not entirely related to COX-2 inhibition. There seems to be more than one mechanism for the anticancer benefit. Celebrex is antiangiogenic and blocks pro cancer growth factors. We are so impressed with the reports regarding Celebrex that it is now difficult for us to recommend Bextra or Vioxx in lieu of Celebrex.

Earlier, we had recommended that some patients switch from Vioxx or Celebrex to Bextra. However, the field of prostate cancer is constantly evolving, and our opinions regarding the best treatment for it are also constantly evolving. We feel that Celebrex is our COX-2 inhibitor of choice regarding anticancer benefit. Many patients report Vioxx relieves pain better than Celebrex, but we are concerned primarily with the anticancer benefit of COX-2 inhibitors. Vioxx should only be used at a 25 mg dose per day, although you can use 50 mg per day for up to five days to help control pain.

An abstract 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. After a radical prostatectomy you do not have any normal prostate tissue. Therefore, a rising PSA must be coming from prostate cancer cells. The 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 in 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 their PSA doubling time was eight months before Celebrex, the doubling time on Celebrex lengthened to 24 months. Importantly, there was no change in the serum testosterone levels in these patients, so the benefit was not related to hormone blockade. These results suggest that Celebrex may help delay disease progression, and can help avoid or delay the need to restart 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 a patient has abnormal kidney blood tests, 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 with your doctor 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. Occasionally diarrhea may develop. 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.

We believe that COX-2 inhibitors, especially Celebrex, play an important role in helping to treat and control prostate cancer.

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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