

**Life Extension Foundation**

TO: The physician treating \_\_\_\_\_(Type in your name here)

**RE: Adjuvant drug therapy for cancer patients**

Dear Doctor:

Our non-profit organization has uncovered evidence that suggests two prescription drugs may be of *significant* value in treating cancer **in addition** to other therapies. Here is an excerpt from a research report we published in 1999:

Cancer cells often produce large amounts of the enzyme **cyclooxygenase-2**, abbreviated COX-2. This enzyme acts as a biological fuel by causing rapid cell division. An article in the journal *Cancer Research* (1999 Mar 1; 59 (5) showed that COX-2 levels in **pancreatic cancer cells** are 60 times greater than in the adjacent normal tissue.

According to a study in the *British Journal of Cancer* (1997;75 (8), **human prostate cancer cells** sustain their growth by stimulating themselves to up-regulate their production of COX-2, which facilitates cell proliferation via several mechanisms. However, COX-2 inhibition results in a decrease in cell replication and a reduction in the synthesis of COX-2 and its metabolites, such as the dangerous prostaglandin E2. The authors of this study concluded that COX-2 is involved in the maintenance of growth and homeostasis of human prostate cancer cells.

In the Sept 7, 1999 issue of the *Wall Street Journal*, an investigative report revealed that scientists are actively investigating COX-2 inhibitors as drugs that would be effective in the prevention and treatment of many cancers. COX-2 inhibiting drugs, given to small numbers of patients with **colon polyps** (pre-cancerous lesions), caused the complete disappearance of the lesions. When a group of rats were given a potent carcinogen, there was a 90% reduction in those who developed cancer if they were on COX-2 inhibition therapy. In the few rats that did develop the tumors while taking COX-2 inhibition therapy, the tumors were 80% smaller and less numerous than the group not on COX-2 inhibition therapy. The *Wall Street Journal* revealed that a handful of physicians, knowledgeable about COX-2 and cancer, are prescribing COX-2 inhibitors to their patients.

In a report published in *JAMA* (1999 Oct 6;282(13), a nearly 10 year epidemiological study showed that COX-2 expression in **colorectal cancer** was significantly related to survival. The doctors concluded that the data add to the growing epidemiological and experimental evidence that COX-2 may play a role in colorectal tumorigenesis".

The Life Extension Foundation predicts that COX-2 inhibiting drugs will eventually be approved to treat cancer, but in the meantime, we are requesting physicians to look into the matter and consider prescribing a COX-2 inhibiting drug as an adjuvant cancer therapy. The COX-2 inhibitory drug of choice will be described later in this article. But first we want to briefly discuss another prescription drug that may also benefit cancer patients:

The protein products of *res genes* normally participate in the signal

transduction cascade of sending messages from the cell surface to the nucleus. In addition, the Ras family of oncoproteins can modulate the transduction of signals of cancer cell growth, proliferation and metastasis. Mutations in genes encoding Ras proteins have been intimately associated with unregulated cell proliferation in a number of different kinds of cancers, e.g., leukemia, brain tumors, breast and pancreatic cancers.

The "statin" class of cholesterol-lowering drugs has been shown to inhibit the activity of RAS oncogenes. Some of the "statin" drugs that have shown efficacy are lovastatin, simvastatin, and pravastatin.

There are mechanisms other than inhibition of RAS oncogene activity that make the "statin" drugs attractive as adjuvant anti-cancer agents. According to a study in *The Journal of Biological Chemistry* (1998, Vo. 273, No.17), **prostate cancer cells** are very sensitive to the induction of growth arrest and cell death by lovastatin. This study showed that lovastatin was particularly effective to induce prostate cancer cell G1 DNA replicative phase arrest and cell death in human androgen-independent (hormone-refractory) lines. This study is confirmed by other studies, which showed that "statin" drugs interfere with critical growth pathways that enable cancer cells to proliferate out of control.

A suggested combination therapy to inhibit COX-2 and provide "statin" regulatory control of cell hyperproliferation is as follows:

*Lodine XL*, an FDA approved arthritis drug, interferes with COX-2 metabolic processes. The maximum dosage for Lodine is 1,000 mg daily. The most convenient dosing schedule for the patient involves the prescribing of two Lodine XL 500 mg tablets in a single daily dose. As with any nonsteroidal anti-inflammatory drug (NSAID), extreme caution and physician supervision is required. The most common complaints associated with Lodine XL use is related to the gastrointestinal tract. Serious GI toxicity such as perforation, ulceration, and bleeding can occur in patients treated chronically with NSAID therapy. Occasionally serious renal and hepatic reactions have been reported. Lodine XL should not be given to patients, who have previously shown hypersensitivity to it, or in whom aspirin or other NSAID's induce asthma, rhinitis, urticaria, or other allergic reactions. In such cases, even fatal reactions may be the consequence of NSAID administration.

Nimesulide is a safer COX-2 inhibitor, however, it is not approved by the FDA. It is available from Mexican pharmacies, or can be ordered by mail from European pharmacies. The suggested dose for nimesulide is two 100 mg tablets a day. The Life Extension Foundation recommended nimesulide as an adjuvant cancer therapy in 1997. Unfortunately, only a few members could obtain it because the FDA's seizure of personal use unapproved drug importation.

The two newest COX-2 inhibitors are Celebrex and Vioxx, but we suggest that cancer patients consider other drugs that have a more predictable safety history. Suppression of COX-1 is associated with the severe gastrointestinal complications induced by NSAIDs in humans, whereas selective inhibition of COX-2 reduces this side effect risk. It seems that it is the COX-2 enzyme that fuels cancer cell proliferation, so the objective of choosing the proper NSAID in the treatment of cancer is to find one that suppresses the minimum percentage of COX-1 and maximum COX-2. Said differently, it is critical to not overly suppress COX-1 because the digestive tract needs it to maintain its structure, whereas it is important to suppress COX-2 because it is, amongst the other factors, an enzyme that cancer cells use to multiply.

In a meticulous study published in the *Proceedings of the National Academy of Sciences* (1999;Vol 96), Lodine (etodolac) was compared with other nonsteroidal antiinflammatory (NSAID) drugs, including Celebrex and Vioxx, to assess its effect on suppressing COX-1 and COX-2. This study showed that Lodine caused an 80% suppression of dangerous COX-2, while only inhibiting 25% of the important COX-1. This study showed that Lodine was slightly more effective than Celebrex in suppressing COX-2, and slightly less effective than Vioxx.

A novel treatment approach would be to combine a COX-2 inhibitor with a "statin" drug such as Lovastatin. A study published in the journal, *Gastroenterology* (1999, Vol.116, No. 4, Supp A369) showed that Lovastatin augmented by up to five-fold, the cancer cell killing effect of a drug with COX-2 inhibiting properties (Sulindac). In this study, three different **colon cancer** cell lines were killed (made to undergo programmed cell death) by depriving them of COX-2. When Lovastatin was added to the COX-2 inhibitor, the kill rate increased by up to five fold.

We thus suggest that physicians consider prescribing a COX-2 inhibitor and a "statin" drug to cancer patients, in addition to other conventional and integrative therapies, for a period of three months. Here is a suggested doing schedule:

- 80 mg a day of Mevacor (lovastatin) and
- 1000 mg a day of Lodine XL

Blood tests to assess liver and kidney function are critical in protecting against potential side effects. To ascertain efficacy, regular serum tumor marker testing (such as the CEA, PSA, CA 19.9 depending on the typr of cancer) and imagery scanning is suggested.

Scientific abstracts substantiating this aggressive adjuvant approach to treating cancer can be found at the Foundation's Website ([www.lef.org](http://www.lef.org)). cancer update abstracts

Sincerely,

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