

LIFE EXTENSION FOUNDATION  
1100 West Commercial Blvd  
Ft. Lauderdale FL 33309

January 2, 2000

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 value in treating cancer in addition to other therapies. Here is an excerpt from our latest research report:

Cancer cells often produce large amounts of COX-2 and use it as a biological fuel to cause rapid proliferation of cell division. An article in the journal *Cancer Research* (1999 Mar 1; 59 (5) shows that COX-2 levels in pancreatic cancer cells are 60 times greater than adjacent normal tissue.

According 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. 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. When COX-2 drugs are given to patients with colon polyps (pre-cancerous lesions), the lesions completely disappear. 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. 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 study published in *JAMA* (1999 Oct 6;282(13), a 9.4 year epidemiological study showed that COX-2 expression in colorectal cancer was significantly related to survival. The doctors concluded that "these data add to the growing epidemiological and experimental evidence that COX-2 may play a role in colorectal tumorigenesis".

The December 1999 issue of the *British Journal of Cancer* showed that a COX-2 inhibiting drug significantly reduced the metastasis of colon cancer cells to the lungs of mice. The scientists concluded that COX-2 inhibitors may be a novel class of therapeutic agents to prevent colon cancer metastasis.

In the January 1, 2000 issue of the *Journal of Immunology*, COX-2 inhibition in human lung cancer cells led to marked lymphocytic infiltration of the tumor and reduced tumor growth. COX-2 inhibition was accompanied by a significant decrease in immunosuppressive cytokine IL-10 and a restoration of the more beneficial IL-12. The doctors conducting this study concluded that COX-2 inhibition suppresses tumor activity by restoring the balance of IL-10 and IL-12 in vivo.

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

The regulation of cancer cell growth is often governed by a family of proteins known as RAS oncogenes.

The RAS family is responsible for modulating the regulatory signals that govern the cancer cell cycle and proliferation. Mutations in genes encoding RAS proteins have been intimately associated with unregulated cell proliferation (i.e., cancer).

The "statin" class of cholesterol-lowering drugs have 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, Vol. 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 in inducing prostate cancer cell G1 arrest and cell death in human androgen-independent (hormone-refractory) lines. This study is confirmed by other studies showing 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 is an arthritis drug approved by the FDA that 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 a must. The most common complaints associated with Lodine XL use relate to the gastrointestinal tract. Serious GI toxicity such as perforation, ulceration, and bleeding can occur in patients treated chronically with NSAID therapy. Serious renal and hepatic reactions have been reported rarely. Lodine XL should not be given to patients who have previously shown hypersensitivity to it or in whom aspirin or other NSAIDs induce asthma, rhinitis, urticaria, or other allergic reactions. Fatal asthmatic reactions have been reported in such patients receiving NSAIDs.

Nimesulide is a safer COX-2 inhibitor, but 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, but few members could obtain it because the FDA was seizing personal use importations of unapproved drugs like nimesulide back then.

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. A study published in *Nature Medicine* (1999;5:1348-1349, 1418-1423) showed that suppression of COX-2 blocks angiogenesis, a desirable effect for cancer patients. However, this same study cautions that COX-2-inhibitors may limit the ability of the stomach and intestinal lining to heal itself. Physicians should therefore watch out for gastrointestinal complications for some cancer patients undergoing cytotoxic chemotherapy regimens.

The COX-2 enzyme is involved via several different mechanisms in propagation and metastasis of cancer cells. It therefore appears highly desirable to suppress excess levels of COX-2. 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 the maximum percentage of COX-2. Avoiding excess suppression of COX-1 is critical because the digestive tract requires COX-1 to maintain its structure, whereas COX-2 is the enzyme that causes cancer cells use to proliferate via several different mechanisms.

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 induced 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 in suppressing COX-2.

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 PSA, CEA, CA 19.9) and imagery testing is suggested. Especial care to guard against gastrointestinal toxicity should be taken in the patient taking a COX-2-inhibitor and cytotoxic chemotherapy.

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)).

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