

Cancer Treatment: The Critical Factors

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- Summary

Determining the best way of treating cancer remains highly controversial, even among mainstream oncologists. What may surprise the reader is the large number of documented therapies that have been overlooked by establishment medicine.

The fundamental objective of this book is to encourage the expedient transfer of published scientific findings from the research bench to the clinical setting where the patient may benefit. This is the concept of *translational medicine*, which means translating knowledge from the laboratory side of medicine to the front lines of patient care.

Physicians who practice translational medicine react uniquely when informed about a novel therapy. Their curiosity first motivates them to evaluate the new approach in order to reaffirm safety and efficacy in the context of treatment that is appropriate to the patient's condition. The dedicated translational physician uses novel therapeutics based on:

- That which has been established to be effective,
- That which has a good chance of being effective, and
- That which will do no harm or, in the context of the patient's condition, that which is worth taking an appropriate risk.

Once satisfied that a novel therapy has merit, enlightened physicians then integrate this new finding into individual treatment regimens. These physicians, in essence, are translating the results from promising studies directly into life-saving treatments.

As simple as this approach may seem, few physicians practice translational medicine. For instance, the scientific literature documents that if a cancer patient is anemic, the odds of survival are greatly reduced. Regrettably, few oncologists are aggressive in their evaluation and treatment of anemia in everyday practice even though anemia directly correlates with increased mortality.

Oncologists learn about new discoveries at scientific conferences, in medical journals, and on the Internet. Only a fraction of these doctors, however, translate this knowledge into enhanced treatments that would benefit their patients. In fact, many of the outstanding established medical advances are not utilized routinely by large numbers of physicians treating cancer patients.

The lay public is often surprised to learn how seldom breakthrough discoveries are used to save human lives. The facts are that managed care and bureaucratic overregulation have relegated most oncologists to the practice of assembly line medicine. Sadly, in the most advanced medical system in the world today, we have seen a move away from translational medicine and into "fast-food medicine" or, as some would call it, "McMedicine." In this book, we emphasize the need for physicians to return to real medicine and apply what they have learned, making translational medicine a cornerstone of their treatment philosophy so that medical care can evolve.

It is difficult for most cancer patients to locate an oncologist who routinely translates new findings into clinical practice. This protocol reveals overlooked conventional research findings in order to provide the patient and their oncologist with the latest scientific information.

Cancer patients should become educated about the treatment options discussed in this protocol, so they can better discuss them with their oncologist. The objective is to include as many different therapies as is practical and affordable. Cancer is an extremely difficult disease to treat, and a multimodality therapy is therefore highly recommended.

Once you understand how many therapy options already exist in the conventional setting, you should feel more confident of a

positive long-term outcome.

In this protocol, we discuss the following *eight critical steps* that may significantly improve a successful outcome when considered in the treatment of most cancers:

- Evaluating the molecular biology of the tumor cell population
- Analyzing the patient's living tumor cells to determine sensitivity or resistance to chemotherapy
- Protecting against anemia
- Inhibiting the cyclooxygenase-2 (COX-2) enzyme
- Suppressing r R as oncogene expression
- Correcting coagulation abnormalities
- Maintaining bone integrity
- Inhibiting angiogenesis

STEP ONE: EVALUATING THE MOLECULAR BIOLOGY OF THE TUMOR CELL POPULATION

- How To Implement Step One

Throughout this protocol, you will see terminology relating to the molecular aspects of the cancer cell. When we use the term *molecular*, we are referring to specific characteristics of cancer cells such as

- Tumor-promoting genes (oncogenes)
- Tumor suppressor genes
- Receptors or docking sites on the cell membrane where communication with proteins occur
- Cellular differentiation, that is, the degree of maturity, and probability of response of the cancer cell to certain therapies

These individual variations--the unique biology of the cancer cell--help to explain why a particular therapy may be highly effective for some cancer patients but fail others.

People typically think of their disease based on the organ it affects (i.e., adenocarcinoma of the lung, colon cancer, etc.). The problem is that not all adenocarcinomas of the lung are the same. With the advent of advanced molecular diagnostic profiling, it is possible to identify the specific strengths and vulnerabilities of each patient's cancer cell line in order to design a comprehensive, yet tailored, treatment program. We will describe the most important molecular cancer cell tests, along with potentially effective therapies to consider. Most of the suggested therapies will require that your physician be involved in this process.

It is critical to obtain a description of the type of cells that populate your tumor. Not only does this assist the oncologist in recommending the most effective conventional therapy, but it also helps determine what adjuvant nutritional and off-label drug therapies to consider. The human eye alone can serve to provide the most basic information about a cancer cell through the microscopic examination of the cell's *morphology* or general characteristics. Taking this one step further is evaluation by an *immunohistochemistry* test. This test detects markers of diagnostic value on and within the cell surface, through the application of colored dye or stains. In order to perform this and other tests, it is necessary for a sample of your tumor to be sent to a specialized laboratory. The contact information for one of these laboratories (GENZYNE, Inc.) is listed at the end of this section.

GENZYNE provides a comprehensive range of customized analyses to help cancer specialists correctly diagnose difficult tumors, establish prognosis in many cancers (including breast, prostate, and colon), and determine optimal treatment. By providing this information, GENZYNE starts treatment on the right course and helps avoid unnecessary therapies. The findings from an GENZYNE tumor cell test enable patients to benefit from both more effective and more cost-effective cancer management. A typical GENZYNE analysis provides information that can prevent ineffective and potentially debilitating treatments costing many thousands of dollars. GENZYNE performs more specialized analyses for cancer than any other laboratory in the world. Through their review of over 960,000 patient profiles to date, GENZYNE has developed one of the world's largest, most comprehensive cancer databases.

GENZYNE serves more than 8300 physicians, over 2000 hospitals, and over 570 oncology practices. Their expert medical consultation and advanced technologies (immunohistochemistry, flow cytometry and image analysis, cytogenetics, molecular pathology, and chemotherapeutic resistance testing) allow community hospitals and small practices to provide the same sophisticated services as major academic medical centers.

When a patient might have cancer, physicians confront a chain of pressing questions. What type of cancer is it? Where did it originate? Where has it spread? Which treatments are most likely to work? Finding the answers quickly and accurately is vital.

GENZYNE helps clinicians pose the right questions and get the answers they need.

As far as simple diagnosis is concerned, 15-20% of all cancers defy classification by visual examination. In fact, the diagnosis of "metastatic cancer of unknown primary site" is the eighth most common cancer diagnosis. In a majority of these difficult cases, GENZYNE's medical expertise and advanced technologies lead to an accurate diagnosis.

Visual examination of tumors provides very little information about their growth rate or the type of treatment to which they will respond. GENZYNE's prognostic expertise can accurately establish whether the cancer has spread, evaluate its aggressiveness, and predict the effects of therapy. The results are greater predictability of outcome, increased survival, and decreased overall costs.

Difficult cancers have traditionally been treated as follows: if one therapy proves ineffective, then try another until a successful therapy is found or all options are exhausted. GENZYNE eliminates the need for this trial-and-error method by providing individualized information to determine the optimal therapy before initiating treatment.

GENZYNE provides highly sensitive patient monitoring for the follow-up care of many cancers. For example, GENZYNE can determine whether certain types of lymphomas have recurred before they can be detected by any other method. The earlier tumor recurrence is detected, the greater the likelihood of therapeutic success.

GENZYNE not only offers a full range of diagnostic and prognostic cancer analyses, but also emphasizes client service. Typically within 48 hours after receiving a specimen, GENZYNE returns the stained slides along with a thorough and detailed case report to a physician. If your oncologist wants to consult with a member of the GENZYNE staff, telephone lines are open. In *Appendix A* at the end of this protocol are examples of typical GENZYNE laboratory reports that your oncologist receives.

Contact information for GENZYNE is as follows:

New York

521 West 57th Street, Sixth Floor
New York, NY 10019

Los Angeles

5300 McConnell Avenue
Los Angeles, CA 90066

Phoenix

810 East Hammond Lane
Phoenix, AZ 85034
Telephone: (800) 447-5816
Website: www.genzyme.com

HOW TO IMPLEMENT STEP ONE

Make certain your surgeon sends a specimen of your tumor to GENZYNE for immunohistochemistry testing, using the contact information just provided. You may have to pay out of pocket for this test because not all insurance plans reimburse for it. Please note that this test may not be of benefit to all cancer patients. While it provides a basis for improved treatment, not all cancers are effectively treatable with today's technologies.

STEP TWO: ANALYZING THE PATIENT'S LIVING TUMOR CELLS TO DETERMINE SENSITIVITY OR RESISTANCE TO CHEMOTHERAPY

■ How to Implement Step Two

If chemotherapy is being considered, it is desirable to know which of the chemotherapy drugs will have a high probability of being effective against your particular cancer before any toxic agents are administered into your body. It is equally as important, if not more important, to know if your particular cancer cells exhibit extreme drug resistance (EDR) to specific chemotherapy drugs. EDR implies a probability of 95% that the chemotherapy drugs exhibiting EDR will be *ineffective* in killing the cancer cells. A company called Rational Therapeutics, Inc. performs chemo-sensitivity tests on the living specimens of your cancer cells to determine the optimal combination of chemotherapy drugs, as well as determining EDR.

Rational Therapeutics, Inc., was founded in 1993 by Dr. Robert Nagourney, a prominent hematologist and oncologist. Rational

Therapeutics pioneers cancer therapies that are specifically tailored for each individual patient and is a leader in individualized cancer strategies. With no financial ties to outside healthcare organizations, recommendations are made without financial or scientific prejudice.

Rational Therapeutics develops and provides cancer therapy recommendations which have been designed scientifically for each patient. Following the collection of living cancer cells obtained at the time of biopsy or surgery, Rational Therapeutics performs an *Ex-Vivo* Apoptotic (EVA) assay on your tumor sample to measure drug activity (sensitivity and resistance). *Ex-vivo apoptotic* means that your tumor cells are grown outside of your body for the purpose of determining which drug or drug combination most effectively induces cell death (apoptosis) in the laboratory. Each patient is highly individualized with regard to his or her sensitivity to chemotherapy drugs. Your responsiveness to chemotherapy is as unique as your fingerprints. Therefore, this test will help to exactly determine which drug(s) will be most effective for you. Dr. Nagourney will then make a treatment recommendation based on these findings.

The treatment program developed through this approach is known as *assay-directed therapy*. In 1999, there were more than 1.2 million newly diagnosed cases of cancer in the United States, with 563,000 deaths attributed to this disease. Unfortunately, 50% of newly diagnosed cancer patients have advanced disease that is beyond the hope of a surgical or radiation cure. Patients with advanced disease and those with recurrent disease are candidates for systemic therapy, which is administered usually in the form of chemotherapy. Despite the enormity of the cancer problem, in the last 45 years, there has been virtually no major change in the outcome for the common advanced solid tumors such as those of the lung, prostate, colon, and breast. While there have been improvements in treating lymphomas, certain types of leukemia, and some earlier-stage cancers, the grim facts indicate more aggressive tumor diagnostic tests are needed to provide the medical oncologist with better prognostic information about your individual tumor.

At present, cancer chemotherapies are prescribed by medical oncologists, according to fixed schedules. These schedules are standardized drug regimens that correspond to specific cancers by type or diagnosis. These schedules, developed over years of clinical trials, assign patients to the drugs for which they have the greatest statistical probability of response.

Patients with cancers that exhibit multidrug resistance are on the wrong side of the probability curve, that is, they will likely receive treatments that are wrong for them. A failed attempt at chemotherapy is detrimental to the physical and emotional well-being of patients, is financially burdensome, and may preclude further effective therapies.

Rational Therapeutics provides custom-tailored, assay-directed therapy based on your tumor response in the laboratory. This eliminates much of the guess work prior to your undergoing the potentially toxic side effects of chemotherapy regimens that could prove to be of little value against your cancer. In *Appendix B* at the end of this protocol are typical laboratory reports your oncologist receives from Rational Therapeutics.

Here is the contact information for Rational Therapeutics:

Rational Therapeutics, Inc.
750 East 29th Street
Long Beach, CA 90806
Telephone: (562) 989-6455 ; Fax: (562) 989-8160
Email: www.rationaltherapeutics.com

HOW TO IMPLEMENT STEP TWO

Get in touch with Rational Therapeutics using the contact information provided so that your surgeon can follow the precise instructions required to send a living specimen of your tumor for chemo sensitivity testing. It is important that your surgeon carefully coordinate with Rational Therapeutics in order to ensure your cells arrive in a viable condition. You may have to pay for this test yourself because your insurance may not reimburse for it. Please note that this test may not be of benefit to all cancer patients. While it provides a basis for improved treatment, not all cancers are effectively treatable with today's technologies.

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Cancer Treatment: The Critical Factors

STEP THREE: PROTECTING AGAINST ANEMIA

■ How To Implement Step Three

Anemia diminishes the chances that a cancer patient will survive. Since red blood cells carry oxygen, fewer numbers of red blood cells result in less oxygen transport. When normal cells are oxygen deprived, they lack the vigor to overcome cancer. Cancer cells, on the other hand, thrive in a low oxygen environment. The journal *Cancer* reported that anemia increased the risk of mortality in cancer patients by about 65% (Caro et al. 2001).

Anemia is defined functionally as lack of sufficient red blood cells to maintain tissue oxygenation. Anemia develops when the demand for new red blood cells exceeds the capacity of the bone marrow to produce them. This may be due to inadequate red blood cell production, as occurs when cancer or cancer therapies inhibit the production of erythropoietin, a glycoprotein hormone secreted by the kidney, which acts on stem cells of the bone marrow to stimulate red blood cell production (Spivak 1994).

Cancer-related anemia also results from activation of the immune and inflammatory systems (responses orchestrated by the tumor), leading to an increased release of *tumor necrosis factor-alpha* (TNF-alpha) and interleukin-1 (IL-1). Such cytokines circumvent the ability of the bone marrow to respond to available circulating erythropoietin, resulting in lesser numbers of oxygen-carrying red blood cells being produced (Cazzola 2000). In addition, the lifespan of red blood cells (normally 120 days in men and about 110 days in women) is shortened in cancer-related anemia; thus, production cannot compensate sufficiently for the shorter survival time. The energy-depleting cycle of abnormal metabolism (leading to malnutrition and wasting disease) also is a contributing factor to the progression of anemia.

Weakness, fatigue or faintness, shortness of breath and increased heart rate, headaches, confusion, dementia, depression, cold extremities, dizziness, pallor, and sore mouth are complaints of anemia that complicate recovery. Severe anemia may also result in heart failure.

Too many oncologists wait for anemia to develop before prescribing drugs like Procrit® and Aranesp® to boost red blood cell production. Other oncologists have prescribed high doses of drugs like Procrit® in an attempt to push levels of hemoglobin (the protein in blood that binds with oxygen) to the upper end of the normal reference range. This was done based on research indicating benefits to cancer patients with higher hemoglobin measurements.

Based on new research findings, the FDA is mandating a black box warning on drugs like Procrit®, Aranesp® and Epogen® that warns oncologists to not over-dose these drugs for the purpose of pushing hemoglobin up beyond 12 g/dL (grams per deciliter of blood). The reason for this new black box warning are increased risks of death reported in certain cancer patients who were prescribed higher doses of these red blood cell stimulating drugs.

Based on the conflicting findings that exist today, cancer patients should continue to aggressively protect against anemia, but should not take higher-than-recommended doses of Procrit and other red blood cell boosting drugs.

One problem that cancer patients encounter is that some insurance companies will not pay for expensive drugs like Procrit unless severe anemia is demonstrated. Patients should advocate for immediate access to these red blood cell boosting drugs if indications of anemia manifest, such as low hemoglobin. Anemia appears to contribute to angiogenesis--the vascular network supplying life to the tumor. Vascular endothelial growth factor (VEGF) is an endothelial cell specific mitogen, an agent that induces cell division. The expression of VEGF appears to be an indicator of the angiogenic potential and correlates with the biological aggressiveness of a tumor.

HOW TO IMPLEMENT STEP THREE

- If your hemoglobin or hematocrit levels indicate you are anemic or that you are not in optimal ranges, ask your physician to prescribe an individualized dose of Procrit.
- In order for Procrit to effectively boost red blood cell production, it is essential that your body have adequate iron stores. Even if you have adequate iron stores prior to Procrit therapy, the rapid production of red blood cells induced by Procrit may eventually deplete total body iron stores. Therefore, it is important to obtain baseline studies to exclude the presence of iron deficiency.

Note: *Iron deficiency is best diagnosed by checking the serum ferritin to see if the values are low. Many physicians obtain a serum iron and serum iron binding capacity and divide the former by the latter to obtain the transferrin saturation. If this*

result is < 10%, there is a probability of iron deficiency anemia (IDA). A more modern approach to a diagnosis of iron deficiency anemia, however, is to check the serum ferritin; if it is greater than 220, IDA is essentially ruled out. However, if the serum ferritin level is lower than 220, a blood test called the soluble transferrin receptor (sTfR) assay should be obtained. This measures the receptors for transferrin--receptors that bind to the available iron. If this value is 28 or higher, there is a significant chance of IDA. Regular blood tests to assess ferritin and, when indicated, sTfR will assist your doctor in determining whether or not you need iron supplementation.

- Dietary supplements that can help protect against anemia include folic acid (800 mcg/day), vitamin B12 (500 mcg/day), and melatonin (3-10 mg/day, taken at night) (Vaziri et al. 1996; Herrera et al. 2001).

STEP FOUR: INHIBITING THE CYCLOOXYGENASE-2 (COX-2) ENZYME

- How To Implement Step Four

Our diet, the amount of saturated and polyunsaturated fat we eat, and the unfavorable fats that we create in our bodies play a crucial role in the development and progression of malignancy. A critical pathway that represents a "Rosetta Stone" to all aspects of our health is that involving the metabolism of omega-6 fatty acids leading to either di-homo gamma-linolenic acid (DGLA) or to arachidonic acid.

These "roads" are called the eicosanoid pathways. The metabolism of DGLA leads to the production of fats that are actually beneficial to our health, that is, good eicosanoids. Unfortunately, in today's world, this is the "road less traveled" for most people. The metabolism of arachidonic acid, the bad eicosanoid pathway, leads to most of the health maladies currently faced by our society. A key enzyme in the bad eicosanoid pathway is cyclooxygenase (cyclooxygenase or COX). It is the COX-2 enzyme that results in the production of prostaglandin E2 or PGE2.

Initially, scientists believed COX-2 was merely an inducible response to inflammation. It is now speculated that COX-2 performs biological functions in the body, particularly in the brain and kidneys as well as the immune system. COX-2 becomes troublesome when up - regulated (sometimes 10- to 80-fold) by pro - inflammatory stimuli (interleukin-1, growth factors, tumor necrosis factor, and endotoxin). When over - expressed, COX-2 participates in various pathways that could promote cancer, that is, angiogenesis, cell proliferation, and the production of inflammatory prostaglandins (Sears 1995; Newmark et al. 2000).

A number of researchers have established the COX-2 cancer connection:

- The *Wall Street Journal* (September 7, 1999) reported the results of a trial involving a group of rats given a potent carcinogen along with a COX-2 inhibitor. Rats treated with the COX-2 inhibitor experienced a 90% reduction in cancer compared to a group of rats not given a COX-2 inhibitor. Also, the tumors that appeared were 80% smaller and less numerous than in the control group.
- An article in the journal *Cancer Research* showed that COX-2 levels in pancreatic cancer cells are 60 times greater than in adjacent normal tissue (Tucker et al. 1999).
- Solid tumors contain oxygen-deficient or hypoxic areas, that is, a reduction of oxygen supply to a tissue below physiological levels. Cells low in oxygen cloud prognosis, promoting up - regulation of COX-2 and angiogenesis, as well as establishing a resistance to ionizing radiation (Gately 2000).
- Greater microvessel density was observed in cancers over - expressing COX-2, compared to those with less COX-2 activity (Uefuji et al. 2000).

Within the nonsteroidal anti-inflammatory drug (NSAIDs) class (NSAIDs) is a subclass referred to as COX-2 inhibitors (cyclooxygenase inhibitors). COX-2 inhibitors are popularly prescribed to relieve pain but now have found a place in oncology. It began when scientists recognized that people who regularly take NSAIDs lowered their risk of colon cancer by as much as 50% (Reddy et al. 2000).

COX-2 inhibitors also significantly reduced colon polyps (considered precursors to cancer) in individuals with a propensity to polyp formation. Laboratory animals showed a similar benefit, that is, about 52% fewer polyps among mice treated with COX-2 inhibitors (Nakatsugi et al. 1997; Moran 2002). JAMA reported that a 9.4-year epidemiological study showed that COX-2 upregulation was related to more advanced tumor stage, tumor size, and lymph node metastasis as well as diminished survival rates among colorectal cancer patients (Sheehan et al. 1999). With more regular use of aspirin (a COX-2 inhibitor), the risk of dying from the disease decreased (Brody 1991; Knorr 2000). The journal *Gastroenterology* reported additional encouragement, showing that three different colon cell lines underwent apoptosis (cell death) when deprived of COX-2; when lovastatin was added to the COX-2 inhibitor, the kill rate increased another fivefold (Agarwal et al. 1999). The benefits, however, observed with COX-2 inhibitors extend beyond colon protection (Tsujii et al. 1998).

The COX-2 enzyme is increased in neoplastic epithelium in a number of other types of cancers (breast, bladder, lung, prostate,

and head and neck cancers) as well as the blood vessel network surrounding the cancerous mass. Tumors expressing COX-2 are considered more treacherous than tumors that lack COX-2 (in part) because of the angiogenic (blood vessel-promoting) nature of cyclooxygenase. It appears cancer cells use COX-2 as a biological mechanism to fuel rapid cell division, growing larger tumor cells than those that lack COX-2 stimulation (Tsuji et al. 1998).

The Life Extension Foundation predicts that COX-2 inhibitors will eventually be approved to treat cancer. Progressive oncologists already have COX-2 inhibitors in their anticancer protocols, but the numbers are few. Unfortunately, the risks associated with traditional NSAIDs include gastrointestinal perforation, ulceration and bleeding and less frequently, renal and liver disease.

Blood tests to assess liver and kidney function are essential, along with serum tumor markers and imagery testing to determine gains or losses during COX-2 inhibiting therapy.

While there are potential side effects to COX-2 inhibiting drugs, some cancer patients accept this small risk in exchange for the anticancer benefit. Since the COX-2 enzyme appears an excellent target for pharmacological intervention, a number of natural COX-2 inhibitors, safe and with diverse anticancer properties, are detailed in the protocol entitled *Cancer Adjuvant Therapy*.

HOW TO IMPLEMENT STEP FOUR

Ask your physician to prescribe one of the following COX-2 inhibiting drugs:

- Lodine XL, 1000 mg once daily, or
- Celebrex, 100-200 mg every 12 hours

STEP FIVE: SUPPRESSING RAS ONCOGENE EXPRESSION

- How To Implement Step Five

The family of proteins known as Ras plays a central role in the regulation of cell growth. It fulfills this fundamental role by integrating the regulatory signals that govern the cell cycle and proliferation.

Defects in the Ras-Raf pathway can result in cancerous growth. Mutant Ras genes were among the first oncogenes identified for their ability to transform cells to a cancerous phenotype, that is, a cell observably altered because of distorted gene expression. Mutations in one of three genes (H, N, or K-Ras) encoding Ras proteins are associated with upregulated cell proliferation and are found in an estimated 30-40% of all human cancers. The highest incidences of Ras mutations are found in cancers of the pancreas (80%), colon (50%), thyroid (50%), lung (40%), liver (30%), melanoma (30%), and myeloid leukemia (30%) (Duursma et al. 2003; Minamoto et al. 2000 ; Vachtenheim 1997; Bartram 1988 ; Bos 1989; Minamoto et al. 2000).

According to information in *Scientific American*, the differences between oncogenes and normal genes are slight. The mutant protein that an oncogene ultimately creates may differ from the healthy version by only a single amino acid, but this subtle variation can radically alter the protein's functionality.

The Ras-Raf pathway is used by human cells to transmit signals from the cell surface to the nucleus. Such signals direct cells to divide, differentiate, or even undergo programmed cell death (apoptosis).

A Ras protein gene usually behaves as a relay switch within the signal pathway that tells the cell to divide. In response to stimuli transmitted to the cell from outside, cell-signaling pathways are activated; in the absence of stimulus, the Ras protein remains in the "off" position. A *mutated Ras* protein gene behaves like a switch stuck on the "on" position, continuously misinforming the cell, instructing it to divide when the cycle should be turned off (Gibbs et al. 1996; Oliff et al. 1996). Researchers have known for some time that injecting anti-Ras antibodies, specific for amino acid 12, cause a reversal of excessive proliferation and a transient alteration of the mutated cell to one of a normal phenotype (Feramisco et al. 1985).

To establish new methods for diagnosing pancreatic cancer, K-Ras mutations were examined in the pancreatic juice of pancreatic cancer patients. Pancreatic juice was positive for K-Ras in 87.8% (36/41) of patients. When combined with p53 mutations in the stool and CA 19-9 (a blood marker for pancreatic cancer), it may be possible to identify the disease in its earliest stage. Thus, a program can be implemented that includes addressing mutant K-Ras and p53 to achieve a more favorable outcome (Lu et al. 2001).

Greater understanding regarding the activity of mutant Ras genes opens exciting avenues of treatment. Researchers found that newly formed Ras molecules are functionally immature. Precursor Ras genes must undergo several biochemical modifications to

become mature, active versions. After such maturation, the Ras proteins attach to the inner surface of the cells outer membrane where they can interact with other cellular proteins and stimulate cell growth.

The events resulting in mature Ras genes take place in three steps, the most critical being the first, referred to as the farnesylation step. A specific enzyme, farnesyl-protein transferase (FPTase), speeds up the reaction. One strategy for blocking Ras protein activity has been to inhibit FPTase. Inhibitors of this enzyme block the maturation of Ras protein and reverse the cancerous transformation induced by mutant Ras genes (Oliff et al. 1996).

A number of natural substances impact the activity of Ras oncogenes. For example, a historic body of literature indicates individuals consuming large quantities of citrus products have a lower incidence of cancer. One of the essential oils within citrus products is limonene, a monoterpene that has been shown to act as a farnesyl transferase inhibitor. Administering high doses of limonene to cancer-bearing animals blocks the farnesylation of Ras, thus inhibiting cell replication (Bland 2001; Asamoto et al. 2002). A study conducted at Mercy Hospital of Pittsburgh also showed that diallyl disulfide, a naturally occurring organosulfide from garlic, inhibits p21 H-Ras oncogenes, displaying a significant restraining effect on tumor growth (Singh et al. 2000).

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Researchers at Rutgers University investigated the ability of different green and black tea polyphenols to inhibit H-Ras oncogenes. The Rutgers team found that all the major polyphenols contained in green and black tea except epicatechin showed strong inhibition of cell growth (Chung et al. 1999). Texas A&M University also found that fish oil decreased colonic Ras membrane localization and reduced tumor formation in rats. In view of the central role of oncogenic Ras in the development of colon cancer, the finding that omega-3 fatty acids modulate Ras activation likely explains why dietary fish oil protects against colon cancer (Collett et al. 2001).

Statins are a class of popular cholesterol-lowering drugs. Mevacor (lovastatin), Zocor (simvastatin), and Pravachol (pravastatin) are statin drugs shown to inhibit the activity of Ras oncogenes (Wang et al. 2000). Statin drugs block the hydroxymethylglutaryl - coenzyme A (HMG-COA) reductase enzyme, which depletes cells of farnesyl pyrophosphate. Levels of total Ras do not decrease but rather shifts in when Ras protein occurs, that is, farnesylated Ras decreases and unmodified, non un farnesylated Ras increases (Hohl et al. 1995).

Illustrative of the potential of statin therapy, patients with primary liver cancer were treated with either the chemotherapeutic drug 5-FU or a combination of 5-FU and 40 mg/day of pravastatin. Median survival increased from 9 months, among patients treated with only 5-FU, to 18 months when using 5-FU combined with the statin drug pravastatin (Pravachol®). Increased survival was attributed to decreased cellular proliferation and incidence of metastasis (Wang et al. 2000).

If a statin drug is planned to be co - administered with chemotherapy, some patients are medicated cyclically, that is, 3 weeks of a statin drug such as lovastatin (80 mg/day) followed by a 2-week break before restarting the statin. Other regimens involve using the statin drug for 6 continuous months or until signs of toxicity develop.

Note: *Some cancer patients may benefit from coenzyme Q10 supplementation when taking statin therapy. For a detailed explanation, please consult the Coenzyme Q10 section in the Cancer Adjuvant Therapy protocol.*

Individuals with cancer should consider an immunohistochemistry test of their cancer tissue for mutated ras genes at GENZYME Laboratories (*see the beginning of this protocol*), a recommendation the Life Extension Foundation first made in 1997. The Life Extension Foundation strongly believes all cancer patients should undergo immunohistochemical testing to determine p53 and Ras status. As mentioned previously, the following laboratory can perform the test:

GENZYME Laboratories,
Telephone: (800) 447-5816

HOW TO IMPLEMENT STEP FIVE

Ask your physician to prescribe one of the following statin drugs to inhibit the activity of Ras oncogenes:

Mevacor (lovastatin), 40 mg twice each day, or
Zocor (simvastatin), 40 mg twice each day, or
Pravachol (pravastatin), 40 mg once a day

Note: *These statin drugs can produce toxic effects in patients. Physician oversight and careful surveillance with monthly blood tests (at least initially) to evaluate liver function, muscle enzymes, and lipid levels are suggested.*

In addition to statin drug therapy, consider supplementing with the following nutrients to further suppress the expression of Ras oncogenes:

- Fish Oil Capsules: 2100 mg of EPA and 1500 mg of DHA day (Six Super Omega-3 fish oil capsules provide this potency)
- Green Tea Extract: 1400 mg of tea polyphenols a day (Two Mega Green Tea Extract Caps provide this potency)
- Aged Garlic Extract: 2400 mg (Four Kyolic® Reserve capsules provides this potency)

STEP SIX: CORRECTING COAGULATION ABNORMALITIES

- How to Implement Step Six

Both experimental and clinical data have shown that coagulation disorders are common in patients with cancer, although clinical symptoms occur less often. Many cancer patients reportedly have a hypercoagulable state, with recurrent thrombosis due to the impact of cancer cells and chemotherapy on the coagulation cascade (Samuels et al. 1975). Pulmonary embolism is a particular problem for patients with pancreatic and gastric cancer, cancer of the large bowel, and women with ovarian cancer (Cafagna et al. 1997). Thus, momentum is building for anticoagulant therapy through reports, the vast majority of which are derived from secondary analyses of clinical trials on the treatment of thromboembolism.

Research on low-molecular-weight heparin (LMWH), an anticoagulant, shows promise in regard to increasing cancer survival rates. Data comparing unfractionated heparin to LMWH indicate that LMWH is equally beneficial if not more beneficial to cancer patients in terms of survival. The improved life expectancy gathered from anticoagulant therapy is not solely a result of the reduced complications from thromboembolism, but also from enzyme interactions, cellular growth modifications, and anti - angiogenic factors (Cosgrove et al. 2002). It appears heparin inhibits the formation of cancer's vascular network by binding to angiogenic promoters, that is, basic fibroblast growth factor and VEGF (Mousa 2002).

Another important aspect of anticoagulant therapy involves breaking down fibrin, a coagulation protein found in blood. Fibrin has various strategies it employs to accommodate the tumor. For example, fibrin covers maverick cells with a protective coat, hindering recognition by the immune system. In addition, fibrin relays a signal to the cancer cell to start angiogenesis, the growth of new blood vessels. As fibrin encourages a healthy vascular network and tumor growth increases, it sets the stage for metastasis.

German scientists evaluated whether cancer fatalities in women with previously untreated breast cancer were reduced using LMWH therapy. The study showed that breast cancer patients receiving LMWH, compared to women receiving unfractionated heparin, had a lower rate of mortality during the first 650 days following surgery. The survival advantage was evidenced after even a short course of therapy (von Tempelhoff et al. 2000). In another study of 300 breast cancer patients, none of the trial participants developed metastasis while receiving anticoagulant therapy although 37 (12.3%) died from the disease (Wellness Directory of Minnesota 2002).

Similar advantages were evidenced among small cell lung cancer patients undergoing anticoagulant therapy in union with conventional treatments. When anticoagulants were a part of the program, subjects enjoyed a better prognosis, that is, greater numbers of complete responses, longer median survival, as well as better survival rates at 1, 2, and 3 years compared to patients denied treatment (Lebeau et al. 1994 ;). See the following references, however (however, see also Zacharski et al. 1984, 1987; Chahinian et al. 1989).

HOW TO IMPLEMENT STEP SIX

Ascertain if you are in a hypercoagulable state by having your blood tested for prothrombin time (PT), partial thromboplastin time (PTT), and D-dimers. A hypercoagulable state is suggested if the shortening of the PT and PTT are seen in conjunction with elevation of D-dimers (see *table on laboratory tests for hypercoagulability*).

If there is any evidence of a hypercoagulable (prethrombotic) state, ask your physician to prescribe the appropriate individualized dose of low-molecular-weight heparin (LMWH). Repeat the prothrombin blood test every 2 weeks to guard against overcoagulation. If you cannot afford LMWH, ask that lower-cost Coumadin be prescribed instead.

Lab Tests for Hypercoagulability

Tests routinely available	Results if hypercoagulable	Tests requiring dedicated coagulation laboratory	Results if hypercoagulable
Protime (PT)	Less than normal	Alpha-1 antitrypsin (A1AT)	Elevated
Partial thromboplastin time (PTT)	Less than normal	Euglobulin clot lysis time (ECLT)	Prolonged
Platelet count (part of CBC)	Elevated	Factor VIII levels	Elevated
Fibrin split products (FSP)	Elevated	D-dimers (DD)	Elevated
Fibrinogen	Elevated		

STEP SEVEN: MAINTAINING BONE INTEGRITY

- How to Implement Step Seven

Some types of cancer (breast and prostate) have a proclivity to metastasize to the bone (Hohl et al. 1995; Wang et al. 2000). The

result may be bone pain, which also may be associated with weakening of the bone and an increased risk of fractures (Spivak 1994; Caro et al. 2001).

Patients with prostate cancer have been found to have a very high incidence of osteoporosis or osteopenia even before the use of therapies that lower the male hormone testosterone (Cazzola 2000). In settings such as prostate cancer, when excessive bone loss is occurring, there is a release of bone-derived growth factors, such as TGF-beta - 1, which stimulate the prostate cancer cells to grow further (Samuels et al. 1975; Dunst et al. 1999). In turn, prostate cancer cells elaborate substances such as interleukin-6 (IL-6), which has as one of its main effects the further breakdown of bone (Cafagna et al. 1997; Mousa 2002). Thus, a vicious cycle results: bone breakdown, the stimulation of prostate cancer cell growth, and the production of interleukin IL -6 and other cell products, which leads to further bone breakdown (see *Figure 3*).

The intravenous (IV) or oral administration of any of the drugs called bisphosphonates, such as Aredia (IV), Zometa (IV), and Fosamax or Actonel (oral), can be used to stop this vicious cycle. Such agents stop excessive bone breakdown (resorption) and favor bone formation (Zacharski et al. 1984; Zacharski 1987; Chahinian et al. 1989; von Templehoff et al. 2000). Administration of bisphosphonates should be accompanied by an adequate intake of a bone supplement that supplies all raw materials to make healthy bone. These include calcium, magnesium, boron, silica, and vitamin D.

The problem that prostate and breast cancer patients face is that bisphosphonate therapy is approved for treatment only after cancer cells have metastasized to the bone and become clinically apparent by a nuclear medicine bone scan. If bisphosphonates were administered to those with certain types of cancers, the risk of bone metastasis could be significantly reduced (Zurborn et al. 1982; Kohli et al. 2002). The Life Extension Foundation recommended bisphosphonate drugs (similar to those mentioned above) for certain types of cancer patients more than a decade ago. For many cancer patients, it would be ideal to continue bisphosphonate drug therapy a year or longer. Insurance companies, however, do not pay for bisphosphonates until after the cancer has metastasized to the bone.

Maintaining bone integrity may inhibit the growth of a wide range of cancers. Even when bone is broken down as a result of normal aging, the release of growth factors, such as interleukin IL -6 and transforming growth factor, can fuel tumor cell propagation.

Bisphosphonate class drugs, along with the appropriate mineral supplements and exercise to stimulate bone formation, can help to maintain bone integrity and, thus, save the lives of cancer patients.

The Life Extension Foundation strongly advises that the status of bone integrity should be evaluated periodically by means of a quantitative computerized tomography bone mineral density study called QCT. At the very least, this should be done annually. We prefer to use the QCT scan over the D E XA since the QCT is not falsely affected by arthritis or calcifications in blood vessels that are commonly seen in men and women in their 50s and over. It is fairly common to see patients with a normal D E XA scan and yet the QCT will be blatantly abnormal.

QCT sites possibly near you can be found via Mindways, Inc. at (877) 646-3929 or Image Analysis at (800) 548-4849.

Tests that assess bone breakdown are inexpensive and involve a random urine collection obtained in the morning at the time of the second voided specimen. One such highly accurate test of bone resorption is called DPD (deoxy pyridinoline). This test provides information on excessive bone breakdown (resorption).

The deoxy pyridinoline (DPD) cross links urine test can be ordered through the Life Extension Foundation by calling 1-800-208-3444.

HOW TO IMPLEMENT STEP SEVEN

- If you have a type of cancer with a proclivity to metastasize to the bone (breast or prostate), ask your physician for a bisphosphonate drug before evidence of bone metastasis occurs. An oral bisphosphonate drug to consider is Actonel in the high dose of 30 mg twice a week. Alternatively, Fosamax can be used at a dose of 70 mg once a week. These agents should be taken on an empty stomach at least 1 hour and optimally 2 hours before breakfast. Some people experience gastroesophageal side effects from oral bisphosphonate drug therapy and prefer administration directly into the vein. An IV-administered bisphosphonate drug such as Aredia may be administered monthly beginning at 30 mg the first month, 60 mg the second month, and working up to 90 mg for subsequent months. Alternatively, Zometa can be given at a dose of 4 mg intravenously over 15 minutes every 3-4 weeks. When taking a bisphosphonate drug, it is important to take a wide array of bone-protecting supplements such as calcium, magnesium, zinc, manganese, and vitamin D3. Six capsules a day of a product called Bone Assure provides optimal potencies of bone-protecting nutrients.
- Because excessive bone breakdown releases growth factors into the bloodstream that can fuel cancer cell growth, the DPD urine test should be done every 60-90 days to detect bone loss. A QCT bone density scan should be done annually. If either of

these tests reveals bone loss, ask your physician to initiate bisphosphonate drug therapy. Every cancer patient should take a bone-protecting supplement such as Bone Assure to protect against excess bone deterioration.

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Cancer Treatment: The Critical Factors

STEP EIGHT: INHIBITING ANGIOGENESIS

■ How To Implement Step Eight

Angiogenesis, the growth of new vessels from preexisting blood vessels, is critical during fetal development but occurs minimally in healthy adults. Exceptions occur during wound healing, in inflammation, following a myocardial infarction, in female reproductive organs, and in pathologic conditions such as cancer (Shammas et al. 1993; Suh 2000).

Angiogenesis is a strictly controlled process in the healthy, adult human body, a process regulated by endogenous angiogenic promoters and inhibitors. Dr. Judah Folkman, the father of the angiogenesis theory of cancer, explains: "Blood vessel growth is controlled by a balancing of opposing factors. A tilt in favor of stimulators over inhibitors might be what trips the lever and begins the process of tumor angiogenesis."

According to the National Cancer Institute, solid tumors cannot grow beyond the size of a pinhead, that is, 1-2 cubic mm, without inducing the formation of new blood vessels to supply the nutritional needs of the tumor. Since rapid vascularization and tumor growth appear to occur concurrently, interrupting the vascular growth cycle is paramount to overcoming the malignancy.

Tumor angiogenesis results from a cascade of molecular and cellular events, usually initiated by the release of angiogenic growth factors. At a critical phase in the growth of a tumor, the tumor sends out signals to nearby endothelial cells to activate new blood vessel growth. The pro - angiogenic growth factors diffuse in the direction of preexisting blood vessels, encouraging development (Folkman 1992 b ; Folkman et al. 1992 a).

Various agents are known to activate endothelial cell growth, including angiogenin, estrogen, interleukin-8, fibroblast growth factors (both acidic and basic), prostaglandin E2, tumor necrosis factor, granulocyte colony-stimulating factor, and VEGF. VEGF and basic fibroblast growth factors are expressed by many tumors and appear particularly important to tumor development and angiogenesis (NIH/NCI 1998)

A number of substances from orthodox and natural pharmacology (angiostatin, endostatin, interferons, interleukin-2, curcumin, green tea, lactoferrin, N-acetyl-cysteine (NAC), resveratrol, grape seed-skin extract, retinoic acid (vitamin A), and vitamin D) are anti - angiogenic in nature (*to read more about natural products with an anti - angiogenesis profile, please turn to the Cancer Adjuvant Therapy protocol*). Endostatin, a fragment of collagen XVIII, and angiostatin, a fragment of plasminogen involved in the coagulation process, have produced remarkable results in animal models.

Anti-angiogenesis drugs approved by the FDA to consider include Avastatin® and thalidomide.

HOW TO IMPLEMENT STEP EIGHT

- There are clinical trials using other anti-angiogenesis agents. Call (800) 422-6237 or log on to www.cancer.gov/clinicaltrials to find out if you are eligible to participate.
- In the *Cancer Adjuvant Therapy protocol* of this book, there are nutrients that have demonstrated potential antiangiogenesis effects such as green tea extract and curcumin. Refer to the *Cancer Adjuvant Therapy protocol* for information and dosing recommendations.

SUMMARY

- Step One
- Step Two
- Step Three
- Step Four
- Step Five
- Step Six
- Step Seven
- Step Eight
- Implementing The Eight Steps

This protocol has described therapies that a leading-edge oncologist can prescribe to improve the odds of long-term survival and possible cure.

The fundamental message is to have your oncologist thoroughly assess the individual characteristics of your tumor, your blood system, and available treatments. Based on this evaluation, patients can interact with their oncologists to determine what therapies may work synergistically with standard conventional treatments.

The objective of this multimodality approach is to attack tumor cells where they are most vulnerable. The primary determining factor in choosing the specific drugs is finding the various tumor cell and blood tests recommended in this protocol, along with historical statistical data that can help ascertain how your tumor will respond to specific therapies.

The following summary is a succinct reiteration of the eight approaches discussed in this protocol:

Step One: Evaluating the Molecular Biology of the Tumor Cell Population

How to implement: Make certain your surgeon sends a specimen of your tumor to IMPATH (Telephone: (800) 447-5816, website: www.impath.com) for immunohistochemistry testing, using the contact information just provided. You may have to pay out-of-pocket for this test.

Step Two: Analyzing the Patient's Living Tumor Cells to Determine Sensitivity or Resistance to Chemotherapy

How to implement: Get in touch with Rational Therapeutics (Telephone: (562) 989-6455, website: www.rationaltherapeutics.com) using the contact information provided so that your surgeon can follow the precise instructions required to send a living specimen of your tumor for chemosensitivity testing. It is important that your surgeon carefully coordinate with Rational Therapeutics in order to ensure your cells arrive in a viable condition. You may have to pay for this test yourself because insurance may not reimburse you for it.

Step Three: Protecting Against Anemia

How to implement: If your hemoglobin or hematocrit levels are not in the optimal ranges, ask your physician to prescribe an individualized dose of Procrit.

In order for Procrit to effectively boost red blood cell production, it is essential that your body have adequate iron stores. Even if you have adequate iron stores prior to Procrit therapy, the rapid production of red blood cells induced by Procrit may deplete iron stores. Anyone using Procrit should have periodic assessment of their iron stores by means of a serum ferritin level. If less than 200, a soluble transferrin receptor (sTfR) level should be obtained. If evidence of iron deficiency is found, your physician will consider iron supplementation after ruling out excessive blood loss due to a variety of causes.

Dietary supplements that can help protect against anemia due to other causes include folic acid (800 mcg/day), vitamin B12 (500 mcg/day), and melatonin (3-10 mg/day, at night) (Vaziri et al. 1996; Herrera et al 2001).

Step Four: Inhibiting the COX-2 Enzyme

How to implement: Ask your physician to prescribe one of the following COX-2 inhibiting drugs:

- Lodine XL, 1000 mg once daily, or
- Celebrex, 100-200 mg every 12 hours, or

Step Five: Suppressing Ras Oncogene Expression

How to implement: Ask your physician to prescribe one of the following statin drugs to inhibit the activity of Ras oncogenes:

Lovastatin, 40 mg twice daily, or
Zocor, 40 mg twice daily, or
Pravachol, 40 mg once daily

Note: These statin drugs can produce toxic effects in a minority of patients. Physician oversight and monthly blood tests to evaluate liver function are suggested.

In addition to statin drug therapy, consider supplementing with the following nutrients to further suppress the expression of Ras oncogenes:

Fish Oil Capsules: 8-12 capsules of Mega EPA/DHA w/Sesame Lignans per day.

Green Tea Extract: two-three 725 mg capsules daily.

Garlic Extract: 3 tablets daily with meals.

Step Six: Correcting Coagulation Abnormalities

How to implement: Ascertain if you are in a hypercoagulable (prethrombotic) state by having your blood tested for prothrombin (PT), partial thromboplastin time (PTT), and D-dimers. A prethrombotic state is indicated by a shortening of PT and/or PTT and an increase in D-dimers.

If there is any evidence of a prethrombotic state, ask your physician to prescribe the appropriate individualized dose of LMWH. If you cannot afford LMWH, ask that lower-cost Coumadin be prescribed instead. Anticoagulation requires significant patient education and monitoring of laboratory tests to minimize the risks of hemorrhage due to overanticoagulation. As in all biological systems, a balance must be established if health is to be restored.

Step Seven: Maintaining Bone Integrity

How to implement: If you have a type of cancer with a proclivity to metastasize to the bone (breast or prostate), ask your physician for a bisphosphonate drug before evidence of bony metastasis occurs. An oral bisphosphonate drug to consider is Actonel at a dose of 30 mg twice a week or Fosamax at a dose of 70 mg once a week. Either drug must be taken at least 1 hour before breakfast and with water only. Some people experience gastroesophageal side effects from oral bisphosphonate drug therapy and prefer administration directly into the vein. An IV-administered bisphosphonate drug such as Aredia may be administered monthly beginning at 30 mg the first month, 60 mg the second month, and working up to 90 mg for subsequent months.

A newer, more potent IV bisphosphonate, Zometa, can be used at a starting dose of 1-2 mg for the first dose and then 4 mg every 3-4 weeks thereafter. Zometa is routinely given as a 15-minute infusion. When taking a bisphosphonate drug, it is important to take a wide array of bone-protecting supplements such as calcium, magnesium, zinc, manganese, and vitamin D3. Six capsules a day of a product called Bone Restore provide optimal potencies of bone protecting nutrients. Some physicians also prescribe a synthetic vitamin D such as Calcitriol (Rocaltrol) or Hecetrol.

Since excessive bone breakdown releases growth factors into the bloodstream that can fuel cancer cell growth, the DPD urine test (which can be ordered through the Life Extension Foundation (800)-208-3444) should be done every 60-90 days to detect bone loss. A QCT bone density scan should be done annually. If either of these tests reveals bone loss, ask your physician to initiate bisphosphonate drug therapy. Every cancer patient should take a bone-protecting supplement like Bone Restore to protect against excess bone deterioration.

Step Eight: Inhibiting Angiogenesis

How to implement: There are a number of clinical trials using anti-angiogenesis agents such as angiostatin. Call (800) 422-6237 or log on to www.cancer.gov/clinicaltrials to find out if you are eligible to participate. In the *Cancer Adjuvant Therapy protocol* of this book, there are nutrients that have demonstrated potential antiangiogenesis effects such as green tea extract and curcumin. Refer to the *Cancer Adjuvant Therapy protocol* for information and dosing recommendations. The drug Avastatin® is now approved, and may be considered as an anti-angiogenesis therapy against a variety of cancers.

Implementing the Eight Steps

As can be seen from the eight-step list, a patient might be prescribed several treatments in addition to standard therapy for the purposes of inhibiting the COX-2 enzyme, suppressing the Ras oncogene, protecting against anemia/hypercoagulation, inhibiting blood vessel growth in the tumor (angiogenesis), maintaining bone integrity, and so forth.

While these therapies are substantiated in the published scientific literature and most are part of mainstream medicine, few cancer patients are benefiting from this knowledge.

If you are determined to wage modern medicine against your tumor, some or all of these therapies should be considered, depending on your individual situation. The reader is advised to refer to the *Cancer Adjuvant Therapy protocol* for additional guidance. If standard therapies such as radiation or chemotherapy are being contemplated, please refer to the *Cancer Surgery, Cancer Radiation and/or Cancer Chemotherapy protocols*.

PRODUCT AVAILABILITY

Super EPA/DHA w/Sesame Lignans, Mega Green Tea Extract, Kyolic® Reserve Garlic Extract and melatonin, folic acid, vitamin B12, and Bone Restore are available by telephoning (800) 544-4440 or by ordering online.

STAYING INFORMED

The information published in this protocol is only as current as the day the manuscript was sent to the printer. This protocol raises many issues that are subject to change as new data emerge. Furthermore, cancer is still a disease with unacceptably high mortality rates, and none of our suggested regimens can guarantee a cure.

The Life Extension Foundation is constantly uncovering information to provide to cancer patients. A special website has been established for the purpose of updating patients on new findings that directly pertain to the published cancer protocols. Whenever Life Extension discovers information that may benefit cancer patients it will be posted on the website www.lefcancer.org.

Before utilizing the cancer protocols in this book, we suggest that you check www.lefcancer.org to see if any substantive changes have been made to the recommendations described in this protocol. Based on the sheer number of newly published findings, there could be significant alterations to the information you have just read.

Alternatively, call 1-800-226-2370 and ask a Health Advisor if your topic of interest has been updated on the website - www.lefcancer.org.



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