

## Cancer Chemotherapy

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- Summary

Cancer cells are everything we would like healthy cells to be: They quickly adapt to toxic environments, they readily alter themselves to assure their continued survival, and they utilize biologic mechanisms to promote cellular immortality. All of these factors make cancer an extremely difficult disease to treat.

Chemotherapy drugs have a high rate of failure because they usually kill only specific types of cancer cells within a tumor or the cancer cells mutate and become resistant to the chemotherapy. Cancer chemotherapy could save more lives if the latest scientific findings were incorporated into clinical medicine.

What concerns us is that respected cancer journals are publishing articles that identify safer and more effective treatment regimens, yet few oncologists are incorporating these synergistic methods into their clinical practice. Cancer patients often suffer through chemotherapy sessions that do not integrate the latest scientific findings. Our objective is to provide the patient with more options to discuss with their oncologist and to bring about multimodality approaches to improve the probability of a successful outcome.

It is impossible to design a single chemotherapy protocol that is effective against all types of cancer. The oncologist might need to administer several chemotherapy drugs at varying doses because tumor cells express survival factors with a wide degree of individual cell variability. This protocol conveys the findings from published scientific studies so that a cancer patient will have a logical basis to augment the effects of chemotherapy and also reduce the potential for side effects.

### How Does Chemotherapy Work?

According to the National Cancer Institute, almost all normal cells grow and die in a controlled way through a process called apoptosis. Cancer cells, on the other hand, keep dividing and forming more cells without a control mechanism to induce normal apoptosis.

Anticancer drugs destroy cancer cells by stopping them from growing or dividing at one or more points in their growth cycle. Chemotherapy may consist of one or several cytotoxic drugs that kill cells by one or more mechanisms. The chemotherapy regimen chosen by most conventional oncologists is based on the type of cancer being treated. As you will read later in this protocol, there are factors other than the type of cancer that can be used to determine the ideal chemotherapy drugs that should be used to treat an individual patient.

The goal of chemotherapy is to shrink primary tumors, slow the tumor growth, and kill cancer cells that may have spread (metastasized) to other parts of the body from the original, primary tumor. However, chemotherapy kills both cancer cells and healthy normal cells. Oncologists try to minimize damage to normal cells and to enhance the cell killing (cytotoxic) effect on cancer cells. Too often, unfortunately, this delicate balance is not achieved.

Clinical studies show that for certain types of cancer chemotherapy prolongs survival and increases the percentage of patients achieving a remission. A partial remission is defined as 50% or greater reduction in the measurable parameters of tumor growth as may be found on physical examination, radiologic study, or by biomarker levels from a blood or urine test. A complete remission is defined as complete disappearance of all such manifestations of disease. The goal of all oncologists is to strive for a complete remission that lasts a long time--a durable complete remission, or CR. Unfortunately, the vast majority of remissions that are achieved are partial remissions. Too often, these are measured in weeks to months and not in years. Some types of cancer do not show any meaningful response to chemotherapy.

- Protecting Against Anemia
- Inhibiting the COX-2 Enzyme
- Controlling Cancer Cell Growth
- Combining a COX-2 Inhibitor with a Statin Drug and Chemotherapy
- Should Antioxidants Be Taken at the Same Time as Chemotherapy

It is highly desirable to know what drugs are effective against your particular cancer cells before these toxic agents are systemically administered to your body. A company called Rational Therapeutics, Inc., performs chemosensitivity tests on living specimens of your cancer cells to determine the optimal combination of chemotherapy drugs.

Dr. Robert Nagourney, a prominent hematologist/oncologist, founded Rational Therapeutics, Inc., in 1993. Rational Therapeutics pioneers cancer therapies that are specifically tailored for each individual patient. They are a leader in individualized cancer strategies. With no economic ties to outside healthcare organizations, recommendations are made without financial or scientific prejudice.

Rational Therapeutics develops and provides cancer therapy recommendations that 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). This will determine exactly which drug(s) will be most effective for you. They then make a treatment recommendation. The treatment program developed through this approach is known as assay-directed therapy.

At present, medical oncologists, according to fixed schedules, prescribe chemotherapy. These schedules are standardized drug regimens that correspond to specific cancers by type or diagnosis. These schedules, developed over many 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 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' EVA assay uses your living tumor cells to determine which drug or drug combination induces apoptosis in the laboratory. Each patient is highly individualized with regard to sensitivity to chemotherapy drugs. A patient's responsiveness to chemotherapy is as unique as their fingerprints.

Rational Therapeutics, leading the way in custom-tailored, assay-directed therapy, provides personal cancer strategies based on the tumor response in the laboratory. This eliminates much of the guesswork prior to the patient undergoing the potentially toxic side effects of chemotherapy regimens that could prove to be of little value against their cancer. Rational Therapeutics may be contacted at:

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 750 East 29th Street  
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 Web site: [www.rationaltherapeutics.com](http://www.rationaltherapeutics.com)

In addition to the EVA chemosensitivity testing, we advocate immunohistochemistry testing of your tumor to provide additional data that will assist in making treatment decisions. The importance of the immunohistochemistry test is described in the Cancer Treatment: The Critical Factors protocol. The immunohistochemistry test can be done if your physician sends a specimen of your tumor to a specialty laboratory called Impath ([www.impath.com](http://www.impath.com)). Impath can be reached by calling (800) 447-5816. Impath also performs chemosensitivity testing of living tumors (fresh specimens). Because many chemotherapy patients' primary tumors were previously removed or irradiated, Impath can perform the immunohistochemistry test with a frozen or paraffin-preserved tissue sample that is accessible through the pathology laboratory that examined your previous tumor(s).

### **Protecting Against Anemia**

The importance of maintaining or enhancing the oxygen-carrying capacity of blood cannot be overemphasized. Blood oxygen-carrying capacity may be the single most important factor in determining whether chemotherapy is successful.

In response to a low-oxygen environment, cancer cells send out growth signals that result in increased angiogenesis (blood vessel growth into the tumor). Oxygen deprivation not only induces angiogenesis, but also causes cancer cells to express additional survival factors that make them highly resistant to the toxic effects of chemotherapy.

It is an established fact that a low-oxygen environment (hypoxia) promotes tumor growth. If nothing else in this protocol is followed, correcting a hypoxic state could vastly enhance the odds of long-term survival.

The first step in correcting hypoxia is to guard against anemia. Anemia is common in cancer patients, and the result is that less oxygen is delivered to the tumor, that is, hypoxia occurs. The importance of avoiding anemia is well established in scientific literature. A study was conducted to systematically review and obtain an estimate of the effect of anemia on the survival of cancer patients. This study found that the increased risk of mortality in cancer patients who were anemic was an astounding 65% (Caro et al. 2001)!

Chemotherapy often induces anemia that then exacerbates hypoxia in the tumor. The best way of evaluating blood oxygen-carrying capacity is to measure hematocrit and hemoglobin levels. These are standard components of the complete blood count (CBC) test that should be routinely performed in all cancer patients.

Since cancer cells thrive in a hypoxic environment, the cancer patient's hematocrit and hemoglobin should be maintained in the upper one-third of normal range prior to the initiation of chemotherapy. Table 1 describes the optimal ranges of hematocrit and hemoglobin for cancer patients.

**Table 1: Optimal Ranges of Cancer Patients' Hematocrit and Hemoglobin Levels**

Based on findings from survival studies, cancer patients should fall within the optimal ranges of the following two blood tests that measure the oxygen-carrying capacity of blood:

<b>Blood measure</b>		<b>Normal Laboratory Reference Range</b>	<b>Optimal Range For Cancer Patients</b>
Hemoglobin	(men)	12.5-17 grams/dL	15.5-17 grams/dL
	(women)	11.5-15 grams/dL	13.83-15 grams/dL
Hematocrit	(men)	36-50%	45-50%
	(women)	34-44%	41-44%

*Normal reference ranges based on Labcorp's standards as of May 14, 2002.*

Hypoxia (low oxygen) promotes tumor growth by inducing angiogenesis and causing cancer cells to express survival factors that interfere with the ability of chemotherapy to kill them. Chemotherapy drugs are supposed to promote apoptosis. In a hypoxic environment, however, cancer cells develop survival mechanisms that protect them against apoptosis.

There are nutrients that help improve anemic states, but any cancer patient who does not have his or her hematocrit and hemoglobin in the upper one-third of the normal range (as described in Table 1) should consider the drug Procrit (or Epogen) to achieve such levels. Procrit is a natural erythropoietin that stimulates the production of red blood cells. There is also a new long-acting erythropoietin agent approved by the FDA called Aranesp, which allows dosing every 2 weeks instead of weekly injections.

If an oncologist fails to address anemia, the patients should assume the role of advocate, demanding that attention be paid to the quality of his blood counts.

A problem that cancer patients will encounter is that oncologists normally view low blood counts as normal in cancer patients and are reluctant to prescribe Procrit unless anemia is demonstrated. Because Procrit is an expensive drug, most insurance companies refuse to pay for it unless a cancer patient is severely anemic (<10g/dL). Remember, anemia means hematocrit and hemoglobin are below the low-normal laboratory reference ranges. A cancer patient, on the other hand, should aim to have levels in the high upper-third range of normal for hematocrit and hemoglobin. Some insurance companies will not pay for Procrit until hematocrit levels are at least 20% below the lowest normal range. Is it any wonder that chemotherapy fails for so many cancer patients?

Since most insurance companies will not pay for Procrit for the purpose of boosting hematocrit and hemoglobin to the upper ranges of normal, patients may have to pay for this drug as an out-of-pocket expense. The first hurdle is convincing the oncologist to prescribe Procrit. The good news is that most cancer patients may only need Procrit for a few months, so the high cost does not have to be borne indefinitely.

The Life Extension Foundation has located pharmacies that will sell Procrit at lower prices. If your insurance company will not reimburse for this costly drug, call (800) 544-4440 for referrals to pharmacies that may charge less than conventional retail prices.

### **Inhibiting the COX-2 Enzyme**

Some progressive oncologists are prescribing cyclooxygenase-2 (COX-2) inhibitor drugs along with chemotherapy to improve the

odds of successful treatment. COX-2 is an enzyme that many types of cancers use in order to propagate. COX-2 and its byproducts such as prostaglandin E2 (PGE2) have been shown to help fuel the growth of cancers such as colon, pancreas, estrogen-negative breast, prostate, bladder, and lung cancer.

Drugs that inhibit the cyclooxygenase enzyme are known as COX-2 inhibitors. Celebrex and Vioxx are two popular COX-2 inhibitors. Both Celebrex and Vioxx are nonsteroidal anti-inflammatory drugs (NSAIDs) that are usually prescribed to treat the symptoms of rheumatoid arthritis and osteoarthritis. There appears to be more research about Celebrex in the treatment of cancer than Vioxx.

Since chemotherapy can cause gastrointestinal bleeding, careful physician monitoring is needed when using a COX-2 inhibiting drug such as Celebrex. Caution is urged for those with known kidney disease, poor heart-lung function, liver disease, or susceptibility to stress-induced ulcers. The protocol entitled Cancer Treatment: The Critical Factors has a detailed description of the connection between COX-2 and cancer and why inhibiting the COX-2 enzyme is so important in treating many cancers.

In 1996, Life Extension recommended that most cancer patients take a COX-2 inhibiting drug because of solid evidence that cancer cells use the COX-2 enzyme to sustain their rapid division. In 1996, Americans had to import a COX-2 inhibitor named nimesulid from other countries because this class of drug was not widely available in the United States.

Experiments in laboratory animals suggest that drugs such as Celebrex could help cure cancer, especially if combined with chemotherapy or radiation (Hsueh et al. 1999; Pyo et al. 2001; Swamy et al. 2002). There are 100 separate cancer studies involving COX-2 inhibitors going on worldwide at this time.

Doctors are predicting that COX-2 inhibiting drugs may become standard therapy in 5-10 years. There was adequate evidence in 1996, however, to recommend COX-2 inhibiting drugs available to cancer patients. There are three potent COX-2 inhibiting drugs on the American marketplace. You may ask your physician to prescribe one of the following COX-2 inhibitors:

Lodine XL, 1000 mg once a day or  
Celebrex, 200-400 mg every 12 hours or  
Vioxx, 12.5-25 mg once a day

[continue ▶](#)

# Cancer Chemotherapy

## Controlling Cancer Cell Growth

A family of proteins known as ras oncogenes often governs the regulation of cancer cell growth. The Ras family is responsible for modulating the regulatory signals that direct the cancer cell cycle and rate of proliferation. Mutations in genes encoding Ras proteins have been intimately associated with unregulated cell proliferation, that is, cancer.

There is a class of cholesterol-lowering drugs known as statins that has been shown to inhibit the activity of Ras oncogenes. Some of these cholesterol-lowering drugs are lovastatin, simvastatin, and pravastatin (Ura et al. 1994; Narisawa et al. 1996; Tatsuta et al. 1998; Wang et al. 2000; Furst et al. 2002; van de Donk et al. 2002).

In advanced primary liver cancer (hepatoma or hepatocellular carcinoma), patients who received 40 mg of pravastatin survived twice as long compared to those who did not receive this statin drug (Kawata et al. 2001). Interestingly, statins are also associated with the preservation of bone structure and improvement in bone density (Edwards et al. 2000; 2001; Pasco et al. 2002).

Some types of cancer (breast and prostate) have a proclivity to metastasize to the bone (Waltregny et al. 2000; Pavlakis et al. 2002). This results in bone pain that also may be associated with weakening of the bone and an increased risk of fractures (Papapoulos et al. 2000; Plunkett et al. 2000). Patients with prostate cancer, for example, are found to have a very high incidence of osteoporosis even before the use of therapies that lower the male hormone testosterone (Berruti et al. 2001; Smith et al. 2001).

In prostate cancer, when excessive bone loss is occurring, there is a release of bone-derived growth factors, for example, TGF- $\beta$ 1 (transforming growth factor-beta 1), that stimulate the prostate cancer cells to grow further (Reyes-Moreno et al. 1998; Shariat et al. 2001). In turn, prostate cancer cells elaborate substances such as interleukin-6 (IL-6) that facilitates the further breakdown of bone (Paule 2001; Garcia-Moreno et al. 2002). Thus, a vicious cycle results: bone breakdown-stimulation of prostate cancer cell growth that results in production of IL-6 and other cell products, which leads to further bone breakdown. When there is a breakdown of bone, the growth factors released can fuel cancer cell growth. (All cancer patients should refer to the Osteoporosis protocol in order to optimally maintain bone integrity and prevent the release of these cancer cell growth factors. The Prostate Cancer protocol has an extensive discussion about the importance of maintaining bone integrity.)

As far as statin drug dosing, higher amounts than are required to lower cholesterol are suggested for a period of several months. Cancer patients, for instance, have used 80 mg a day of lovastatin (Mevacor). This should be considered during chemotherapy in some cases. A monthly SMAC/CBC blood test is also recommended while taking a statin drug to monitor liver function. A rare potential side effect that can occur with the use of statin drugs is a condition known as rhabdomyolysis in which muscle cells are destroyed and released into the bloodstream. If muscle weakness should occur, alert your doctor so you can have a creatine kinase (CK) test to determine if muscle damage has occurred.

## Combining a COX-2 Inhibitor with a Statin Drug and Chemotherapy

Depending on the type of cancer, a logical approach would be to combine a statin (such as Mevacor) with a COX-2 inhibitor and the appropriate dosing of chemotherapy.

Mevacor augmented up to five-fold the cancer-killing effect of the COX-2 inhibitor Sulindac (Agarwal et al. 1999). In this study, three different colon cancer cell lines were induced to undergo apoptosis by depriving them of COX-2. When Mevacor was added to the COX-2 inhibitor, the kill rate increased five-fold.

Physician involvement is essential to mitigate potential side effects of these drugs. Those who are concerned about potential toxicity should take into account the fact that the types of cancers that these drugs might be effective against have extremely high mortality rates. Please note that the use of statin drugs and COX-2 inhibitors for cancer is considered an off-label use of these drugs. You may ask your doctor to prescribe one of the following statin drugs to inhibit the activity of Ras oncogenes:

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

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

Fish Oil Capsules: 2400 mg of EPA and 1800 mg of DHA a day. (Six Mega EPA fish oil capsules provide this potency.)

Green Tea Extract: 1500 mg of tea polyphenols a day. (Five Super Green Tea Extract Caps provide this potency.)

Aged Garlic Extract: 2000 mg a day. (Two Kyolic One Per Day caplets provide this potency.)

## Should Antioxidants Be Taken at the Same Time as Chemotherapy?

- Option One
- Option Two

There is a controversy as to whether cancer patients should take antioxidant supplements at the same time that cytotoxic chemotherapy drugs are being administered.

Proponents of antioxidants point to human studies showing that antioxidant supplements protect healthy cells from the damaging effects of chemotherapy drugs. Chemotherapy drugs can cause lethal heart muscle damage in a small percentage of cancer patients. Antioxidants such as vitamin E, coenzyme Q10 (CoQ10), N-acetyl-cysteine (NAC), glutathione, retinoids, ginkgo biloba, and vitamin C have been shown to specifically protect against chemotherapy-induced heart muscle damage (Tajima 1984; Mortensen et al. 1986; Iarussi et al. 1994; De Flora et al. 1996; D'Agostini et al. 1998; Schmidinger et al. 2000; Agha et al. 2001; Prasad et al. 2001; Blasiak et al. 2002). Other antioxidants have been shown to protect kidneys, bone marrow, and the immune system against chemotherapy toxicity.

Those who argue against antioxidant supplementation during chemotherapy are concerned that antioxidants will protect cancer cells against free-radical-induced destruction. Chemotherapy drugs work by varying mechanisms to induce cellular death. Some chemotherapy drugs kill cells by inflicting massive free-radical damage, while other chemotherapy drugs interfere with different cellular metabolic processes in order to eradicate cancer cells (and healthy cells as well). Depending on the type of cytotoxic drug used, however, antioxidants may confer protection to cancer cells during active chemotherapy.

The difficulty in reaching a consensus is that there are no controlled human or animal studies comparing the effects of various chemotherapy drugs, with and without antioxidants, against different cancers. The issue is complicated by studies showing that certain nutrients are associated with improved survival in cancer patients.

One problem is that there is little data to indicate whether supplements that have been shown to benefit the cancer patient should be taken during active chemotherapy. In other words, we know that anti-oxidants protect against chemotherapy side effects and may improve long-term survival in cancer patients, but do they lower the odds of achieving a long-term remission when administered during active chemotherapy?

Cancer patients contemplating cytotoxic chemotherapy are thus faced with a dilemma. They can take antioxidant nutrients to protect their healthy cells against the toxic effects of chemotherapy, or they can avoid all antioxidants during chemotherapy to possibly improve the chances that the chemotherapy drugs will kill enough cancer cells to induce a complete response or cure.

To further complicate matters, certain supplements have proven mechanisms that could augment the cytotoxic efficacy of chemotherapy. For instance, curcumin has been shown to suppress growth factors that cancer cells use to escape eradication by chemotherapy drugs. (A complete description of curcumin's potential synergistic benefits with chemotherapy drugs appears later in this protocol.) The problem is that curcumin is also a potent antioxidant, and one recent animal study shows that curcumin could interfere with the cancer cell-killing effect of certain chemotherapy drugs. The scientists who authored this study pointed out that while curcumin has demonstrated potent effects in preventing cancer, its use during active chemotherapy is questionable because of its ability to protect cells against the type of molecular damage inflicted by these chemotherapy drugs (Somasundaram et al. 2002).

Critics of this study point out that the low dose of curcumin used in this animal study was adequate to provide antioxidant protection to the cancer cells but not high enough to suppress growth factors that enable cancer cells to escape regulatory control by the chemotherapy drugs. It was also pointed out that not all chemotherapy drugs kill cancer cells by generating free radicals. This means that curcumin may not hinder other chemotherapy drugs, as evidenced by remarkable tumor regressions found in other animal studies and human case histories.

Due to the multiple molecular complexities of this issue and the lack of specific in vivo studies, cancer chemotherapy patients are faced with choosing one of the following options:

**Option One:** Two weeks prior to the initiation of a chemotherapy regimen, discontinue all antioxidant supplements until 2-3 weeks after the last chemotherapy session. Most chemotherapy sessions are scheduled to last for 6-8 weeks.

The risk in depleting your body of antioxidants is that healthy cells will not be as well protected against the toxic effects of chemotherapy. This means that depending on the chemotherapy drug used, you could experience organ damage. You may also have increased immune impairment that could weaken your ability to fight the cancer. The toxic side effects of chemotherapy drugs can be the direct cause of death in some patients. Those who choose to deplete their bodies of certain antioxidants will also lose the potential benefit that these nutrients may have on cancer cells. These nutrients help prevent cancer cells from developing escape mechanisms that enable them to develop resistance to chemotherapy and other anticancer drug(s). The potential benefit is that the chemotherapy drug(s) might work better if these antioxidants are not present.

**Option Two:** Continue taking antioxidant supplements recommended in this and the Cancer Adjuvant Treatment protocol before, during, and after the chemotherapy is administered.

The risk is that these antioxidants could interfere with the cell-killing effects of the chemotherapy drugs. This is no small risk because cancer patients who need chemotherapy usually have only one opportunity to eradicate enough cancer cells to experience a long-term remission or cure. Cancer cells not killed by the first round of chemotherapy may become highly resistant to future.

As stated earlier, it is important to note that not all chemotherapy drugs function by inducing free-radical damage to the cancer cells. In fact, many cytotoxic chemotherapy drugs function by alternative toxic actions such as interfering with DNA/RNA synthesis (the antimetabolites), disrupting the microtubular network (microtubule inhibitors), and inhibiting chromatin function (topoisomerase inhibitors). To help a cancer patient understand the mechanism of action of common cytotoxic chemotherapy drugs, we have provided Table 2.

**Table 2: How Different Chemotherapy Drugs Kill Cancer Cells**

<b>Drug</b>	<b>Trade Name</b>	<b>Mechanism of Action</b>
Chemotherapy drugs that kill cancer cells by inflicting free-radical damage:		
<b>Alkylating agents</b>		<b>Free-radical damage</b>
Busulfan	Myleran	
Carboplatin	Paraplatin	
Carmustine	BiCNU	
Chlorambucil	Leukeran	
Cisplatin	Platinol	
Cyclophosphamide	Cytoxan	
Ifosfamide	Ifex	
Procarbazine	Matulane	
<b>Anthracyclines</b>		<b>Free-radical damage</b>
Bleomycin	Blenoxane	
Doxorubicin	Adriamycin	
Daunorubicin	Cerubidine	
Epirubicin	Ellence	
Mitomycin C	Mutamycin	
<b>Plant alkaloids</b>		<b>Free-radical damage</b>
Teniposide	Vumon	
VP-16	Etoposide	
Chemotherapy drugs that kill cancer cells by other mechanisms:		
<b>Antimetabolites</b>		<b>Inhibition of DNA/RNA synthesis</b>
Asparaginase	Elspar	
Azacitidine	Mylosar	
Cladribine	Leustatin	
Cytarabine	Cytosar	
Fludarabine	Fludara	
Fluorouracil	Adrucil	
Hydroxyurea	Hydrea	(Analog of the vitamin folic acid)
Mercaptopurine	Purinethol	
Methotrexate	Abitrexate	
Pentostatin	Nipent	
Ralitrexed	Tomudex	
Thioguanine	Lanvis	

**Topoisomerase inhibitors** **Inhibition of chromatin function**

Bleomycin	Blenoxane	Inhibition of topoisomerase II
Dactinomycin	Cosmegen	Inhibition of topoisomerase II
Daunorubicin	Cerubidine	Inhibition of topoisomerase II
Doxorubicin	Adriamycin	Inhibition of topoisomerase II
Epirubicin	Ellence	Inhibition of topoisomerase II
Etoposide	Vepesid	Inhibition of topoisomerase II
Gemcitabine	Gemzar	Inhibition of topoisomerase I
Idarubicin	Idamycin	Inhibition of topoisomerase II
Irinotecan	Camptosar	Inhibition of topoisomerase I
Mitoxantrone	Novantrone	Inhibition of topoisomerase II
Plicamycin	Mithramycin	Inhibition of topoisomerase II
Teniposide	Vumon	Inhibition of topoisomerase II
Topotecan	Hycamtin	Inhibition of topoisomerase I

**Microtubule inhibitors****Inhibition of chromatin function**

Docetaxel	Taxotere	
Paclitaxel	Taxol	
Teniposide	Vumon	
Vinblastine	Velban	Mitotic arrest through binding of microtubules and spindle precursors
Vincristine	Oncovin	
Vinorelbine	Navelbine	Mitotic arrest through binding of microtubules and spindle precursors
VP-16	Etoposide	

Table 2 provides some understanding of the mechanisms of action of chemotherapy drugs. Based on this information, it might appear that one could make a determination as to whether to take antioxidants based on the type of chemotherapy drug(s) used. Regrettably, there are other pathways (in addition to those listed) by which chemotherapy drugs induce cancer cell apoptosis that could be interfered with by taking the wrong dose of antioxidants. As already indicated, it is not possible to reach a scientific consensus as to which option to choose, that is, antioxidants or no antioxidants during active chemotherapy. There are too many variables such as the type of cancer, category of chemotherapy drug(s), molecular makeup of the cancer cells, individual variability, etc., to provide a conclusive recommendation for or against antioxidant supplementation during chemotherapy.

Cancer patients often take antioxidant supplements based on published studies showing that antioxidants help prevent cancer. Although some nutrients have been shown to reverse precancerous lesions, antioxidants alone are not a cure once cancer develops. There is persuasive evidence, however, that certain antioxidant supplements are effective in the adjuvant treatment of cancer. In other words, these supplements may help conventional therapies work better. What is missing is evidence of the effects of antioxidants in cancer patients undergoing aggressive chemotherapy.

For further guidance on the issue of whether chemotherapy patients should take antioxidant supplements, there is an extensive discussion among experts about the pros and cons of this topic in the protocol entitled Cancer: Should Patients Take Dietary Supplements?



# Cancer Chemotherapy

## MAKING CHEMOTHERAPY DRUGS WORK MORE EFFECTIVELY

The dose-delivery schedule of chemotherapy drugs can determinate their efficacy in killing cancer cells and the degree of toxicity to the patient. Conventional chemotherapy treatment often uses a maximum tolerated dose (MTD) of chemotherapeutic drugs, typically administered on a schedule that varies from once a week to every 21 days, allowing a period of rest so that healthy tissue has a chance to recover. Unfortunately, while the MTD schedule is convenient for oncologists, allowing them to squeeze more patients each month into their chemotherapy unit, the rest period enables cancer cells to recover and develop survival mechanisms such as new blood vessel growth into the tumor. This means that when the next high dose of chemotherapy is given 7-21 days later, the cancer cells have become more resistant. The administration of the MTD also exposes healthy tissues to more damage.

Some studies indicate that a better approach would be to lower the dose of conventional cytotoxic agents, reschedule their application, and combine chemotherapy drugs with antiangiogenesis agents to effectively interfere with cancer's various growth pathways and inhibit the production of blood vessels (Holland et al. 2000) (<http://www.cancer.gov/clinicaltrials/developments/anti-angio-table>).

This lower-dose approach, known as metronomic dosing, uses a dosing schedule as often as every day or alternates different chemotherapy drugs every other day instead of administering them all together the same day. An amount as low as 25% of the MTD, sometimes given on alternative days in combination with various signal transduction pathway inhibitors, targets the endothelial cells making up the vessels and microvessels feeding the tumor. Tumor endothelial cells then die with much less chemotherapy than cancer cells and the side effects to healthy tissue and the patient in general are dramatically reduced (Hanahan et al. 2000).

During standard chemotherapy, the typical 21-day rest period is enough to allow the tumor endothelial cells a chance to recover. However, with tighter chemotherapy dose scheduling, the slowly proliferating endothelial cells are unable to recover. In one study, mice were given the chemotherapeutic drug vinblastine at doses far below the MTD. This dose had little effect on tumor growth in the mice. A second group of mice was given the drug DC101 that inhibits the formation of new blood vessels into tumors (by blocking the induction of vascular endothelial growth factor). In the DC101 group of mice, tumor growth was slowed, as it was with the vinblastine, but then tumor growth resumed. However, in a third group of mice, a combination of the two drugs, at the low dose, resulted in full regression of the tumors with no recurrence for 6 months (Klement et al. 2000).

The administration of low doses of conventional chemotherapy drugs on a frequent basis with no breaks enables these drugs to invoke an antiangiogenesis effect, particularly when combined with a tumor endothelial cell-specific antiangiogenic drug (Gately et al. 2001; Man et al. 2002). There are clinical studies using antiangiogenic drugs (<http://www.cancer.gov/clinicaltrials/developments/anti-angio-table>). As will be described later in this protocol, certain dietary supplements have also been shown to interfere with angiogenesis.

At the time of this writing, a number of animal studies suggested that chemotherapy drugs could work better if the dosing schedule were changed. Human studies are ongoing, meaning it will be difficult to convince an oncologist to incorporate metronomic dosing instead of the standard MTD. While we cannot definitively recommend metronomic (lower dose/more frequent administration) chemotherapy at this time, the results of new human studies on this subject will be posted at [www.lefcancer.org](http://www.lefcancer.org).

## GOING BEYOND CHEMOTHERAPY

- Inhibiting Signal Transduction Pathways
- Natural Signal Transduction Inhibitors
- Agents That Inhibit Angiogenesis and Block Signal Transduction Are Failing
- Inhibiting Angiogenesis

Conventional chemotherapy drugs too often show limited efficacy. Yet there is evidence indicating that the cancer cell-killing effects of these drugs can be enhanced if additional compounds are administered to the patient.

One approach is to inhibit the overexpression of receptor sites on cancer cells, which enables these cells to bind to growth factors that allow them to become resistant to the cell-killing effects of the chemotherapy drugs. Cancer cells use these signal transduction pathways as growth vehicles to escape natural regulatory control and also to protect themselves against the cytotoxic effects of cancer drugs. The utilization of these signal transduction inhibitors enhances the potential effect of low(er) dosing of chemotherapeutic drugs.

Another therapeutic target is the endothelial cells that form new blood vessels. The process by which new blood vessels are formed is called angiogenesis, and cancer cells initiate blood vessel proliferation in order to fuel rapid growth (Hanahan et al. 2000). Agents that interfere with the formation of new blood vessels are an important part of a comprehensive treatment strategy.

Because cancer cells are stimulated to produce new blood vessels in response to a low-oxygen environment (hypoxia), the critical importance of boosting the oxygen-carrying capacity of blood was discussed earlier in this protocol.

### **Inhibiting Signal Transduction Pathways**

All cells, both normal and cancerous, have molecular receptor sites on their surface. These sites are much like locks that may be opened or activated only by the correct molecular key. Once opened or activated, a chain of biochemical events occurs specific to that receptor. Cytokine growth factors are a class of substances that stimulate cell growth by a variety of mechanisms.

An example of such a pathway is the binding of transforming growth factor-alpha (TGF-alpha) to the epidermal growth factor receptor (EGFR) site. Such a binding is a growth pathway for many cancers, causing rapid cell proliferation. The overexpression of this pathway is also implicated in tumor cells that are resistant to cytotoxic drugs (including the interferons).

Interference with this pathway at the EGFR receptor site can effectively shut down overexpression and the subsequent cell proliferation, making the cancer much more vulnerable to therapy. Blocking the EGFR has been shown to inhibit tumor growth by interfering with cancer cell repair, tumor invasion, metastasis, and angiogenesis (Arteaga 2002; Wakeling et al. 2002).

Drugs that inhibit the EGFR showed promise in early studies but have failed in recent clinical trials when combined with cytotoxic chemotherapy drugs. One of these EGFR inhibiting drugs is Iressa. One reason that Iressa and a similar-acting drug named Erbitux failed in human clinical studies is that an inadequate combination and dosing schedule of chemotherapy drugs may have been used to kill the cancer cells. Drugs such as Iressa will not cure cancer by themselves, but they could be of benefit if metronomic-dosing chemotherapy were used and/or during immune-augmentation therapy if they were used with drugs such as alpha interferon.

The objective of blocking the signal transduction pathway is to prevent cancer cells from mutating in a way that enables them to avoid destruction.

### **Natural Signal Transduction Inhibitors**

As noted, molecular evidence and animal studies suggest that agents that inhibit certain growth signals used by cancer cells might work synergistically with metronomic cycled chemotherapy or be useful as post chemotherapy agents along with immune-augmentation therapy.

There are natural signal transduction inhibitors available, but because most of them are potent antioxidants, some cancer patients may choose to wait 2-3 weeks after chemotherapy ends to start using them.

Soy (genistein) extract is known to inhibit the epidermal growth factor (EGF) receptor via an interference with the TGF-alpha pathway (Bhatia et al. 2001).

Genistein is also known to block the induction of the basic fibroblast growth factor (bFGF), a potent growth and angiogenic factor in cancers such as renal cell carcinoma and malignant melanoma (Hurley et al. 1996). Additionally, genistein is known to block induction of the vascular endothelial growth factor (VEGF) considered essential for angiogenesis and tumor endothelial cell survival (Mukhopadhyay et al. 1995).

The blockade of the overexpression of the EGF receptor and the inhibition of the signaling pathways, bFGF and VEGF, is dose-dependent response. Soy genistein may be an effective adjuvant to conventional or metronomic chemotherapy, but human clinical studies are lacking, which is unfortunately the case with most nonpatented natural therapies. There is a controversy about the use of soy as a cancer treatment. A complete description of the pros and cons of high-dose genistein therapy can be found in the Cancer Adjuvant Therapy protocol.

Curcumin, an extract of the spice turmeric, is synergistic with genistein and inhibits angiogenic growth signals emitted by tumor cells. Curcumin acts via a different mechanism than genistein to inhibit the EGF receptor but is up to 90% effective in a dose-dependent manner. It is important to note that while curcumin has been shown to be up to 90% effective in inhibiting the expression of the EGF receptor on cancer cell membranes, this does not mean that it will be effective in 90% of cancer patients or reduce tumor volume by 90%. Because two-thirds of all cancers, however, over-express the EGR receptor and such overexpression frequently fuels the metastatic spread of cancer throughout the body, the suppression of this receptor is desirable.

Curcumin has a number of other antiangiogenic properties that appear to be synergistic with metronomic dosing chemotherapy. These potential synergistic and/or additive mechanisms include:

- Inhibition of the induction of basic fibroblast growth factor (bFGF). bFGF is both a potent mitogen (growth signal) for many cancers and an important signaling factor in angiogenesis (Arbiser et al. 1998).
- Inhibition of the induction of hepatocyte growth factor (HGF), overexpression is involved in hepatocellular (liver cell-related) carcinoma (Seol et al. 2000).
- Inhibition of the expression of COX-2, the enzyme involved in the production of PGE-2, a tumor-promoting prostaglandin (Zhang et al. 1999).
- Inhibition of a transcription factor in cancer cells known as nuclear factor-kappa B (NF-KB). Many cancers overexpress NF-KB and use this as a growth vehicle to escape regulatory control (Plummer et al. 1999).
- Increased expression of nuclear p53 protein in human basal cell carcinomas, hepatomas, and leukemia cell lines, which increases apoptosis (Jee et al. 1998).

### ***Why Agents That Inhibit Angiogenesis and Block Signal Transduction Are Failing***

Based on the multiple favorable mechanisms listed, higher-dose curcumin would appear to be useful for cancer patients. There are contradictions in scientific literature concerning curcumin intake at the same time as chemotherapy drugs. Some studies indicate enhanced benefit, whereas other studies hint at reduced benefit and even potential toxicity. The anticancer drug cisplatin is strongly enhanced with curcumin, (Navis et al. 1999), yet cisplatin kills cancer cells by generating free radicals, and curcumin is an antioxidant. Another study showed that low-dose curcumin inhibited camptothecin-, mechlorethamine-, and doxorubicin-induced apoptosis of several different human breast cancer cells. This same study showed that curcumin inhibited cyclophosphamide-induced breast tumor regression in an in vivo animal model (Somasundaram et al. 2002). Another in vitro study involving curcumin's concomitant use with the chemotherapy drug Irinotecan indicated potential toxicity (Michaels et al. 2001), yet in and of themselves chemotherapy drugs are inherently toxic.

Whether high-dose curcumin is beneficial or detrimental depends on the type and dose of the chemotherapeutic drug used, the kind of cancer cell, and the dose of the curcumin. Until more definitive information is published, we prefer to err on the side of caution and recommend that chemotherapy patients wait 3 weeks after their last dose of chemotherapy before taking high-doses of curcumin.

Pharmaceutical companies are investing billions of dollars to develop drugs proven to interfere with cancer cell growth. Unfortunately, these drugs have failed to extend survival in late-stage cancer patients. In some of these clinical studies, tumor shrinkage is observed, but the patients still die. Experts remain convinced, however, that these drugs will eventually play a significant role in the treatment of cancer.

One reason these drugs are not working is that they usually suppress only one of the growth factors that cancer cells use to escape regulatory control. Scientists know of more than 20 growth factors used by tumors. Late-stage breast cancer cells, for example, may express as many as six different growth factors that induce angiogenesis. Cancer cells emit these growth factors to draw new blood vessels into tumors and/or overexpress the EGF receptor.

Human studies have tested angiogenesis inhibitors or EGF receptor blockers on late-stage patients whose cancer cells have mutated to become highly resistant. If these drugs were tested earlier in the disease process, some physicians believe they would work better. One problem is that the FDA restricts the testing of new cancer drugs to only patients who have failed all other proven therapies. Regrettably, we know that cancer cells mutate each time they are exposed to a new therapy. By testing new cancer drugs only on patients who have failed previous therapy, a tremendous burden of efficacy is being placed on these new compounds, that is, these drugs are expected to kill cancer cells in their most aggressive stages.

Some experts note that ultimately successful treatment using antiangiogenesis and signal transduction blockers may depend on the use of a multidrug cocktail, one that would block all known growth factors used by cancer cells. That would parallel the success in treating AIDS, in which several antiviral drugs that work by different mechanisms are combined into cocktails that have turned the condition into a manageable disease for some people.

Based on current knowledge, it would appear logical to simultaneously test a wide range of angiogenesis inhibitors and signal transduction pathway blockers on early-stage cancer patients. Such testing might be considered at the time that other cytotoxic therapies are administered or shortly thereafter.

The potential advantage of combining high potency genistein, curcumin, and green tea extracts is that they have been shown to suppress a wide variety of growth factors used by cancer cells. Considering the enormous cost of testing drugs that work in similar ways to genistein, curcumin, and green tea, it is doubtful that these nonpatented natural agents will be tested on cancer patients in the near future. The cancer patient is thus faced with deciding whether or not to incorporate these natural agents into their overall

treatment program based on the data currently available.

### **Inhibiting Angiogenesis**

Angiogenesis provides nourishment for the tumor's rapid propagation. Antiangiogenesis agents inhibit this new tumor blood vessel growth and are being studied as potential cancer therapies. As noted, genistein and curcumin have demonstrated molecular effects involved in the inhibition of new blood vessel growth into tumors. An extract from green tea may also be an effective antiangiogenesis agent.

The primary action of green tea is through its catechin, epigallocatechin gallate (EGCG), which blocks the induction of vascular endothelial growth factor (VEGF), considered essential in angiogenesis and tumor endothelial cell survival. In vivo studies have shown green tea extracts to have the following actions on human colon cancer cells:

Inhibition of tumor growth 58%  
Inhibition of microvessel density 30%  
Inhibition of tumor cell proliferation 27%  
Increased tumor cell apoptosis 1.9-fold  
Increased tumor endothelial cell apoptosis three-fold  
(Jung et al. 2001b.)

The optimal dose of green tea, soy, and curcumin and when they should be taken will be discussed later in this protocol. Please note that EGCG is a powerful antioxidant, as are other polyphenols found in green tea. Some chemotherapy patients may choose to wait 3 weeks after chemotherapy has ended to initiate green tea (EGCG) supplementation.

As indicated near the beginning of this protocol, the most effective way of inhibiting tumor angiogenesis may be by guarding against hypoxia. It is crucial for cancer patients to maintain their blood oxygen-carrying capacity (as measured by hematocrit and hemoglobin) in the upper range of normal.



# Cancer Chemotherapy

## MITIGATION OF CHEMOTHERAPY SIDE EFFECTS

- Vitamins E and C and N-Acetyl-Cysteine
- CoQ10
- Selenium
- Whey Protein
- Shark Liver Oil
- Melatonin
- Melatonin Precautions
- Protecting Immune Function
- Enhancing Immune Function

Cancer chemotherapy is known to produce severe side effects such as heart muscle damage, gastrointestinal damage, anemia, nausea, and lethal suppression of immune function.

Nutrients and hormone therapies can be used to mitigate the toxicity of chemotherapy. Bolstering the immune system may help alleviate or reduce the severity of the complications associated with chemotherapy. As discussed earlier in this protocol, however, using natural antioxidants to protect against chemotherapy side effects could possibly reduce the cancer cell-killing efficacy of the cytotoxic drug(s). Regrettably, there are no survival studies to verify the long-term effects of using natural therapies to mitigate the toxic effects that chemotherapy inflicts on healthy normal cells. In other words, we know that certain nutrients can protect normal cells against the immediate toxic effects of chemotherapy, but we do not know if this protection extends to cancer cells in such a way as to diminish cancer cell death.

For those who choose to use antioxidants to protect against chemotherapy side effects, supplementation with these nutrients should be initiated several days or even weeks before any planned chemotherapy is begun and should be continued well after the chemotherapy has been completed.

### **Vitamins E and C and N-Acetyl-Cysteine**

Vitamins E and C and N-acetyl-cysteine (NAC) can protect against heart muscle toxicity for cancer patients undergoing high doses of chemotherapy. A controlled study examined the effects of these nutrients on cardiac function on a group of chemotherapy and radiation patients. One group was given supplements of vitamins C and E and NAC, while the other group was not supplemented. In the group not supplemented, left ventricle function was reduced in 46% of the chemotherapy patients compared to those who took the supplements. Furthermore, none of the patients from the supplement group showed a significant fall in overall ejection fraction, but 29% of the nonsupplement group showed reduced ejection fraction (Wagdi et al. 1996).

Vitamin C improved the antineoplastic activity of the chemotherapeutic drugs doxorubicin, cisplatin, and paclitaxel in human breast carcinoma cells. Patients reported improved appetite while taking vitamin C, as well as a reduced need for painkillers.

Vitamin E has been shown to protect against cardio-myopathies induced by chemotherapy. Vitamin E has also been used in combination with vitamin A and CoQ10 to reduce the side effects of the chemotherapy drug Adriamycin (doxorubicin). Vitamin E is complementary to chemotherapy in that it boosts the effectiveness of these drugs. One study showed enhanced efficacy of both 5-FU and doxorubicin against human colon cancer cells, with vitamin E supplementation (Chinery et al. 1997).

**Note:** *Fluorouracil, or 5-FU, is an antineoplastic agent used in the palliative management of certain cancers.*

The mechanism of action of vitamin E appears to be the induction of the tumor suppressor protein p21. The dry powder succinate form of vitamin E appears to be most beneficial to cancer patients. The more common acetate form has proven ineffective in slowing cancer cell growth in some test tube studies, whereas natural dry powder vitamin E succinate has shown efficacy (You et al. 2001).

Still another study specifically suggested that cancer patients treated with Adriamycin should supplement with vitamins A and E and selenium to reduce its toxic side effects (Faure et al. 1996).

### **CoQ10**

CoQ10 is used with vitamin E to protect patients from chemotherapy-induced cardiomyopathies. CoQ10 is nontoxic even at high dosages and has been shown to prevent liver damage from the drugs Mitomycin C and 5-FU. Adriamycin-induced cardiomyopathies have been prevented by concomitant supplementation with CoQ10.

**Caution:** Some studies indicate that CoQ10 should not be taken at the same time as chemotherapy. If this were true, it would be disappointing because CoQ10 is so effective in protecting against Adriamycin-induced cardiomyopathy. Adriamycin is sometimes used as part of a chemotherapy cocktail. Until more research is known, it is not possible to make a definitive recommendation of whether to take CoQ10 during chemotherapy.

## Selenium

Selenium has been used in combination with vitamin A and vitamin E to reduce the toxicity of chemotherapy drugs, particularly Adriamycin (Faure et al. 1996; Vanella et al. 1997). The synergistic effect of vitamin E and selenium together to enhance the immune system is greater than either alone. A new form of selenium is Se-methylselenocysteine (SeMSC), a naturally occurring selenium compound found to be an effective chemopreventive agent. SeMSC is a selenoamino acid that is synthesized by plants such as garlic and broccoli. SeMSC has been shown to induce apoptosis in certain ovarian cancer cells (Yeo et al. 2002) and to be effective against breast cancer cell growth both in vivo and in vitro (Sinha et al. 1999). SeMSC has also demonstrated significant anticarcinogenic activity against mammary tumorigenesis (Sinha et al. 1997).

Moreover, SeMSC is one of the most effective chemopreventive compounds, inducing apoptosis in leukemia HL-60 cell lines (Jung et al. 2001a). Some of the most impressive data suggest that exposure to SeMSC blocks clonal expansion of premalignant lesions at an early stage. This is achieved by simultaneously modulating certain molecular pathways that are responsible for inhibiting cell proliferation and enhancing apoptosis (Ip et al. 2001).

Unlike selenomethionine, which is incorporated into protein in place of methionine, SeMSC is not incorporated into any protein, thereby offering a completely bioavailable compound for preventing cancer. Therefore, 200-400 mcg of SeMSC a day is suggested for cancer patients. Please note that selenium also possesses antioxidant properties, so its use before, during, or immediately after chemotherapy could theoretically inhibit the actions of certain chemotherapy drugs.

## Whey Protein

Glutathione balance is very important for the cancer patient. Glutathione is an antioxidant that protects normal cells from toxic chemotherapy drugs. Glutathione levels in cancer cells are very high and act to protect against the destructive actions of chemotherapy and radiation. Whey actually lowers the cancer cell glutathione levels, allowing the chemotherapy and radiation to be more effective at destroying cancer cells but not normal cells.

Tumor cell glutathione concentration may be among the determinants of the cytotoxicity of many chemotherapeutic agents and radiation. An increase in glutathione concentration in cancer cells appears to be at least one of the mechanisms of acquired drug resistance to chemotherapy. Whey proteins used in combination with glutathione appear to reduce the concentrations of glutathione in cancer cells, thereby making them more vulnerable to chemotherapy while maintaining or even increasing glutathione levels in normal healthy cells.

Cancer cells had reduced glutathione levels in the presence of whey protein while at the same time normal cells had increased levels of glutathione levels with increased cellular growth of healthy cells. Selective depletion of tumor GSH may render malignant cells more vulnerable to the action of chemotherapeutic agents (Kennedy et al. 1995).

Glutathione production in cancer and healthy cells is negatively inhibited by its own synthesis. Because glutathione levels are higher in cancer cells, it is believed that cancer cells would reach a level of negative-feedback inhibition for glutathione production more easily than normal cells.

Chemotherapy patients should consider taking 30-60 grams a day of whey protein concentrate (in divided doses) 10 days before initiation of chemotherapy, during chemotherapy, and at least 10 days after the chemotherapy session is completed.

**Note:** *If blood testing shows that chemotherapy has suppressed the immune system, patients should insist that their oncologists use the appropriate immune restoration drug(s) as outlined later in this protocol.*

Whey protein concentrate selectively depletes cancer cells of their glutathione, making them more susceptible to cancer treatments such as radiation and chemotherapy (Bounous 2000; Tsai et al. 2000).

## Shark Liver Oil (Not Shark Cartilage)

Chemotherapy causes a reduction in blood cell production. A natural therapy to restore healthy platelet production is 5 capsules a day of standardized shark liver oil, containing 200 mg of alkylglycerols per capsule. Shark liver oil can boost the production of

blood platelets. Studies have shown the immune-enhancing capabilities of shark liver oil (Pugliese et al. 1998).

**Caution:** Shark liver oil capsules should be taken at a dose of 5 capsules containing 200 mg of active alkylglycerols for a maximum duration of 30 days. A complete blood count (CBC) and platelet count should be obtained weekly to monitor the effectiveness of shark liver oil and to prevent against excessive platelet production, that is, values greater than 400,000. Platelet counts exceeding 400,000 have been associated with increased risks of both thrombosis and hemorrhage.

## Melatonin

Melatonin has been shown to protect against chemotherapy-induced immunosuppression. Melatonin mediates the toxicity of chemotherapy and inhibits free-radical production (Lissoni et al. 1999). In a randomized study to evaluate the effect of melatonin on the toxicity of chemotherapy drugs, patients receiving melatonin with chemotherapy had lower incidences of neuropathies, thrombocytopenia, stomatitis, alopecia, malaise, and vomiting. The appropriate dose of melatonin was between 30-50 mg at bedtime (Lissoni et al. 1997a; Lissoni et al. 1997b). Adding melatonin to a chemotherapy regimen may prevent some toxic effects of the chemotherapy drugs, especially myelosuppression (suppression of blood cells production in bone marrow) and neuropathies (abnormality of nerve functioning both within and outside the central nervous system).

It is important to understand that melatonin protects against thrombocytopenia. If melatonin is considered, it should be started before chemotherapy is initiated. Melatonin may also be an especially effective and safe therapy to correct thrombocytopenia, a condition characterized by a decrease in the number of blood platelets. In patients who randomly received chemotherapy alone or chemotherapy plus melatonin (20 mg each evening), thrombocytopenia was significantly less frequent in patients treated with melatonin (Lissoni 2002).

Malaise and lack of strength were also significantly less frequent in patients receiving melatonin. Finally, stomatitis (inflammation of the mouth area) and neuropathy were less frequent in the melatonin group. Alopecia and vomiting were not influenced (Lissoni et al. 1997b). Administration of melatonin during chemotherapy may prevent some chemotherapy-induced side effects, particularly myelosuppression and neuropathy.

Oncologists often prescribe drugs (Leukine) that work in a similar way as melatonin to protect the immune system. Leukine, for instance, is a granulocyte/macrophage colony-stimulating factor drug that can restore immune function debilitated by toxic cancer chemotherapy drugs. If you are on chemotherapy and your blood tests show white blood cell immune suppression, you should request the appropriate immune restoration drug (such as Leukine or Neupogen) from your medical oncologist.

Studies have shown that melatonin specifically exerts colony-stimulating activity and rescues bone marrow cells from apoptosis induced by cancer chemotherapy compounds. The number of granulocyte/macrophage colony-forming units has been shown to be higher in the presence of melatonin; the dose used was between 30-50 mg nightly (Maestroni et al. 1994a; 1994b; 1998).

Melatonin enhances the anticancer action of interleukin-2 (IL-2) and reduces IL-2 toxicity when used in combination. Melatonin used in association with IL-2 cancer immunotherapy has been shown to have the following actions:

1. Amplification of IL-2 biological activity by enhancing lymphocyte response and by antagonizing macrophage-mediated suppressive events
2. Inhibition of production of tumor growth factors that stimulate cancer cell proliferation by counteracting lymphocyte-mediated tumor cell destruction
3. Maintenance of a circadian rhythm of melatonin, which is often altered in human neoplasms and influenced by cytokine injection

The subcutaneous administration of 3 million IU a day of IL-2 and high doses of melatonin (40 mg each evening orally) has appeared to be effective in tumors resistant either to IL-2 alone or to chemotherapy. The dose of 3 million IU a day of IL-2 is a low dose, while serious toxicity normally begins at 15 million IU a day.

European oncologists have treated numerous end-stage solid tumor patients with the melatonin/IL-2 combination. The conclusion drawn from clinical studies is that melatonin protects against IL-2 toxicity and synergizes with the anticancer action of IL-2 (Conti et al. 1995). The combination strategy was shown to be a well-tolerated therapy to control tumor growth.

In the largest clinical study to date, the effects of melatonin were evaluated in 1440 patients with untreatable advanced solid tumors. One group received supportive care alone, while the other group received supportive care plus melatonin. In a second study, the influence of melatonin on the efficacy and toxicity of chemotherapy was evaluated in 200 metastatic patients with chemotherapy-resistant tumors. These patients were randomized to receive chemotherapy alone or chemotherapy plus melatonin. In both studies, 20 mg of melatonin were given orally at night. The frequency of cachexia, asthenia, thrombocytopenia, and lymphocytopenia was significantly lower in patients treated with melatonin compared to those who received supportive care alone.

Moreover, the percentage of patients with disease stabilization and the percentage one-year survival rate were both significantly higher in patients concomitantly treated with melatonin than in those treated with supportive care alone. The objective tumor response rate was significantly higher in patients treated with chemotherapy plus melatonin than in those treated with chemotherapy alone. In addition, melatonin induced a significant decline in the frequency of chemotherapy-induced asthenia, thrombocytopenia, stomatitis, cardiotoxicity, and neurotoxicity. These clinical results demonstrate that melatonin may be successfully administered in the supportive care of untreatable advanced cancer patients and for the prevention of chemotherapy-induced toxicity (Lissoni 2002).

**Table 3: Summary of Studies Using Melatonin**

**Lissoni's Phase II Randomized Clinical Trial Results**

Tumor Type	Patient Number	Basic Therapy	Melatonin Dose	1-Year Survival	
				Melatonin	Placebo
Metastatic Nonsmall Cell Lung	63	Supportive Care Only	10 mg	26%	Under 1%
Glioblastoma	30	Conventional Radiotherapy	10 mg	43%	Under 1%
Metastatic Breast	40	Tamoxifen	20 mg	63%	24%
Brain Metastases	50	Conventional Radiotherapy	20 mg	38%	12%
Metastatic Colorectal	50	IL-2	40 mg	36%	12%
Metastatic Nonsmall Cell Lung	60	IL-2	40 mg	45%	19%

*Compiled by Cancer Treatment Centers of America and published in the March 2002 issue of Life Extension magazine.*

**Melatonin Precautions**

The Life Extension Foundation introduced the world to melatonin in 1992, and it was the Life Extension Foundation that issued the original warnings about who should not take melatonin. These warnings were based on preliminary findings, and in two instances, the Foundation was overly cautious.

First, we suggested that prostate cancer patients might want to avoid high doses of melatonin. However, subsequent studies indicated that prostate cancer patients could benefit from moderate doses of melatonin, although the Foundation still advises prostate cancer patients to have their blood tested for prolactin. Prolactin is a hormone secreted by the pituitary gland. Its role in the male has not been demonstrated, but in females, prolactin promotes lactation after childbirth.

Melatonin could possibly elevate prolactin secretion, and if this were to happen in a prostate-cancer patient, the drug Dostinex (0.5 mg twice a week) could be used to suppress prolactin so that the melatonin could continue to be taken (in moderate doses of 1-6 mg each night). Please note that the starting dose of Dostinex is 0.125 mg twice a week. If well tolerated, increase to 0.25 mg twice a week. If again well tolerated after 2 weeks, then increase to 0.5 mg twice a week while checking morning fasting prolactin levels.

Some physicians initially thought that ovarian cancer patients should not take melatonin, but a study in *Oncology Reports* indicated that high doses of melatonin may be beneficial in treating ovarian cancer. In this study, 40 mg of melatonin were given nightly, along with low doses of IL-2, to 12 advanced ovarian cancer patients who had failed chemotherapy. While no complete response was seen, a partial response was achieved in 16% of patients, and a stable disease was obtained in 41% of the cases (Lissoni et al. 1996). This preliminary study suggested that melatonin is not contraindicated in advanced ovarian cancer patients. It is still not known what the effects of melatonin are in leukemia; therefore, leukemia patients should use melatonin with caution.

**Protecting Immune Function**

Cancer patients using cytotoxic chemotherapy drugs should ask their oncologist to place them on FDA-approved immune-protective medications concurrently with chemotherapy. Leukine in particular partially restores immune cell production lost due to the toxic effects of chemotherapy. The primary benefit of Leukine is to stimulate macrophage production to prevent bacterial infection in the chemotherapy patient. Macrophages also engulf cancer cells and assist in their destruction by the immune system (Kobrinisky et al. 1999). In one study, patients with refractory (resistant to treatment) solid tumors treated with standard chemotherapy and Leukine had a 33.3% objective response rate versus 15% with chemotherapy alone (Baxevanis et al. 1997).

The timing of administration of colony-stimulating drugs such as Leukine is crucial. The oncologist should not wait until there are toxic bone marrow effects to prescribe leukine. The administration of Leukine should be timed to be initiated 24-48 hours after the last round of chemotherapy in order to prevent a dangerous nadir (precipitous decline) in immune cells (granulocytes). The proper administration of Leukine can dramatically reduce the immune damage that chemotherapy inflicts on the body and increase the cancer cell-killing efficacy of conventional chemotherapy drugs.

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# Cancer Chemotherapy

## ***Enhancing Immune Function***

Alpha-interferon and/or IL-2 are immune cytokines (regulators) that should be considered by some cancer patients. Interferon directly inhibits cancer cell proliferation and has been used in the therapy of hairy cell leukemia, Kaposi's sarcoma, malignant melanoma and squamous cell carcinoma. IL-2 allows for an increase in the cytotoxic activity of natural killer (NK) cells. An oncologist must carefully administer these drugs because they can produce temporary side effects. A significant side effect of interferon is that it can leave some patients temporarily debilitated. One reason why interferon has not become popular.

A cancer patient has to weigh the benefit of achieving complete tumor eradication in relation to the debilitation occurring during the time of active therapy. A typical dose of alpha-interferon is 3 million IU administered by self-injection daily for 2 weeks. To mitigate the debilitating effects, most patients take interferon for 2 weeks and then skip 2 weeks. IL-2 has been self-administered by subcutaneous injection in the dose of 3-6 million IU a day for 5-6 days each week.

**Note:** *Interferon has been shown to work on squamous cell carcinomas but not on common adenocarcinomas.*

Retinoic acid (vitamin A) analog drugs enhance the efficacy of some chemotherapy regimens and reduce the risk of secondary cancers. These vitamin A analog drugs have been shown to work well when taken in conjunction with alpha-interferon. Ask your oncologist to consider prescribing vitamin A analog drugs such as Accutane (13-cis-retinoic acid) or Vesanoid (all-trans retinoic acid). The use of a retinoid drug therapy depends on your type of cancer. Some cancers have historically responded well to retinoid drug therapy while others have not. The tumor cell testing recommendations in the protocol Cancer Therapy: The Critical Factors can help determine whether retinoid drug therapy is appropriate. Your oncologist must carefully prescribe the use and dosage of potentially toxic retinoid drugs such as Accutane.

Some cancer patients produce too many T-suppressor cells that shut down optimal immune function. The administration of drugs such as cimetidine helps to prevent cancer cells from prematurely shutting down the immune system. Cimetidine, also known as Tagamet, is an over-the-counter medication that blocks the action of histamine on stomach cells and reduces stomach acid production. An immune cell blood test will reveal the status of your T-helper cells, T-suppressor cells, and natural killer (NK) cell count and activity. A suggested cimetidine-dosing regimen is 800 mg each night. Cimetidine also interferes with metastasis by blocking the expression of an adhesion molecule known as E-selectin that enables cancer cells to bind to blood vessel walls and start metastatic colonies.

**Caution:** Cimetidine may increase the toxicity of certain chemotherapy drugs. Cimetidine increased blood concentrations of the drug epirubicin used to treat breast cancer (Murray et al. 1998), while cimetidine combined with 5-fluorouracil dramatically improved survival in certain types of colon cancer (Matsumoto et al. 2002). If you are taking cimetidine, tell your oncologist so that the dose of your chemotherapy drug can be adjusted if necessary.

## **ANTI-NAUSEA DRUGS FOR CHEMOTHERAPY PATIENTS**

- Aprepitant (Emend®) for Chemotherapy-Induced Nausea and Vomiting

Nausea is one of the most common and most difficult aspects of chemotherapy for cancer patients. Nausea can have secondary effects on cancer patients by interfering with their eating habits during and immediately after chemotherapy.

Drugs to mitigate chemotherapy-induced nausea include Kytril, Megace, and Zofran. The high cost of some of these drugs has kept many cancer patients not covered by insurance from obtaining one of these potentially beneficial drugs. If you are receiving chemotherapy and are experiencing nausea, you should be able to demand that any HMO, PPO, or insurance carrier pay for this class of drug. These drugs may enable a cancer patient to tolerate chemotherapy long enough for it to be effective.

An interesting study evaluated glutathione and vitamins C and E for their anti-nausea properties. Glutathione and vitamins C and E significantly reduced cisplatin-induced vomiting in dogs. The anti-nausea activity of antioxidants was attributed to their ability to react with free radicals generated by cisplatin. Ginger extract has also been shown effective in reducing nausea symptoms (Keating et al. 2002).

### **Aprepitant (Emend®) for Chemotherapy-Induced Nausea and Vomiting**

Chemotherapy-induced acute and delayed nausea and vomiting (CINV) can occur with either an initial chemotherapy cycle or with repeated chemotherapy cycles. Cisplatin is a commonly used chemotherapy drug known to cause CINV in most patients who

receive it. Cisplatin is used to slow or stop cancer cell growth in patients with metastasized testicular and ovarian tumors who have already had surgical and/or radiotherapy procedures. It is used in patients with metastasized ovarian tumors who are unresponsive to standard chemotherapy, but have not yet received cisplatin.

Patients with advanced transitional-cell bladder cancer that is no longer controlled by surgery and/or radiotherapy also receive cisplatin. The drug is given intravenously in cycles, often in combination with other chemotherapy drugs. Severe CINV usually occurs within 1 to 4 hours after administration and symptoms can continue for 24 hours or persist for up to a week. A delayed form can occur in patients who had no nausea when cisplatin was initially administered. This form begins 24 hours or more following cisplatin chemotherapy. The symptoms of cisplatin CINV are so debilitating that some patients refuse further chemotherapy treatment.

On March 26, 2003, aprepitant (Emend®) received FDA approval. Aprepitant is a drug to be used in combination with other anti-nausea/anti-vomiting drugs to prevent CINV. Standard anti-nausea therapy for CINV is dexamethasone (Decadron®, a corticosteroid) and ondansetron (Zofran®, a 5-HT<sub>3</sub> or serotonin receptor antagonist). However, aprepitant works in combination with these anti-nausea drugs by targeting a different family of receptors in the brain associated with nausea called the NK1 receptors (neurokinin 1). A typical combination treatment regimen directed by a treating physician is:

- Day 1: 125 mg of aprepitant orally 1 hour before chemotherapy; 32 mg of ondansetron intravenously before chemotherapy; and 12 mg of dexamethasone orally.
- Days 2 through 4: 80 mg of aprepitant orally on days 2 and 3 only; and 8 mg of dexamethasone orally in the morning on days 2 to 4.

Aprepitant (Emend) is the first NK1 blocking drug to be approved by the FDA. FDA approval was based on the results of studies including over 1000 cancer patients who received chemotherapy that caused CINV (de Wit et al. 2003; Heskith et al. 2003; Poli-Bigelli et al. 2003). In these studies, when compared to symptoms in patients who received standard CINV medicines, the symptoms of CINV were reduced significantly when aprepitant was included with the standard medicines.

In a Phase III study (520 patients; multicenter, randomized, double-blind, placebo-controlled; endpoint of complete response) that evaluated patients for 5 days after chemotherapy, 72.7% of the patients using aprepitant had complete response on days 1 to 5 (no nausea and vomiting; no rescue therapy). This response was significantly higher than the 52.3% response in the standard therapy group (Heskith et al. 2003). A similar Phase III study evaluated 523 patients for efficacy and 568 patients for safety for 5 days following high-dose cisplatin chemotherapy. During the 5 days after chemotherapy, patients in the aprepitant group had a complete response of 62.7% vs. 43.3% in the standard therapy group. Incidence of adverse events was similar in both groups (72.8% vs. 72.6%). In the aprepitant group, complete response ranged from 82.8% on day 1 to 62.7% on days 2 to 5 vs. 68.4% on day 1 and 46.8% on days 2 to 5 for the standard therapy group (Poli-Bigelli et al. 2003).

Another Phase III double-blind study (endpoint of complete response) enrolled 202 patients and observed them for 6 chemotherapy cycles. The group receiving aprepitant (125 mg before cisplatin and 80 mg on days 2 to 5 vs. 375 mg/250 mg) reported a complete response of 64% vs. 49% for the group receiving standard ondansetron/dexamethasone treatment. After cycle 6, the aprepitant group still had a complete response of 59% compared to 35% in the standard therapy group (de Wit et al. 2003). Researchers conducting these three studies concluded that aprepitant plus a standard regimen of ondansetron and dexamethasone consistently provided superior protection from CINV compared to standard therapy alone (de Wit et al. 2003; Heskith et al. 2003; Poli-Bigelli et al. 2003). Additionally, de Wit et al. (2003) concluded that aprepitant provided sustained protection against CINV over multiple cycles of chemotherapy when existing drugs often become less effective.

A multi-center, randomized, double-blind, placebo-controlled study seeking to define the most appropriate dose regimen of oral aprepitant (375 mg/250 mg vs. 125 mg/80 mg vs. 40 mg/25 mg vs. standard therapy) was conducted in 376 patients with cancer who were receiving initial cisplatin. (While the study was ongoing, aprepitant 375 mg/250 mg was discontinued resulting from pharmacokinetic data obtained that indicated an apparent interaction with dexamethasone.) The authors concluded that an aprepitant 125-mg/80-mg regimen added to a standard regimen of intravenous ondansetron and oral dexamethasone had the most favorable benefit to risk profile (Chawla et al. 2003). Possible drug interactions with aprepitant include some chemotherapies, birth control pills (reduces effectiveness), blood thinners (Coumadin), and other drugs (e.g., Orap®, Seldane®, Hismanal®, and Propulsid®) as well as non-prescription and herbal products (Merck 2003).

## **NATURAL APPROACHES TO ENHANCING CHEMOTHERAPY EFFICACY**

- Fish Oil
- Caffeine
- Theanine

## **Fish Oil and Chemotherapy**

Fish oil may enhance the effectiveness of cancer chemotherapy drugs. A study compared different fatty acids on colon cancer cells to see if they could enhance Mitomycin C, a chemotherapy drug efficacy. Eicosapentaenoic acid (EPA) concentrated from fish oil was shown to sensitize colon cancer cells to Mitomycin C (Tsai et al. 1997). It should be noted that fish oil also suppresses the formation of prostaglandin E2, an inflammatory hormone-like substance involved in cancer cell propagation.

In another study, a group of dogs with lymphoma were randomized to receive either a diet supplemented with arginine and fish oil or just soybean oil. Dogs on the fish oil and arginine diet had a significantly longer disease-free survival time than dogs on the soybean oil (Ogilvie et al. 2000).

## **Caffeine and Chemotherapy**

The use of caffeine in combination with chemotherapy has been shown to enhance the cytotoxicity of chemotherapy drugs. Caffeine occurs naturally in green tea and has been shown to potentiate the anticancer effects of tea polyphenols. In SKH-1 mice at high risk of developing malignant and nonmalignant tumors, oral administration of caffeine (as sole source of drinking fluid for 18-23 weeks) inhibited the formation and decreased the size of both nonmalignant tumors and malignant tumors (Lou et al. 1999).

In cancer, p53 gene mutations are the most common genetic alterations observed, occurring in 50-60% of patients, including those with carcinomas and sarcomas. Caffeine has been shown to potentiate the destruction of p53 defective cells by inhibiting growth in the G2 phase. This ability of caffeine is important because the basis of many anticancer therapies is to damage tumor DNA and destroy the replicating cancer cells. Caffeine uncouples tumor cell-cycle progression by interfering with the replication and repair of DNA (Blasina et al. 1999; Ribeiro et al. 1999; Jiang et al. 2000; Valenzuela et al. 2000).

## **Theanine and Chemotherapy**

### ■ Theanine Makes Chemotherapy Work

L-theanine is a unique amino acid, naturally occurring in green tea, shown in one study to enhance Adriamycin concentration in tumors 2.7-fold and reduce tumor weight 62% over controls, whereas Adriamycin by itself did not reduce tumor weight (Sugiyama et al. 1998). Adriamycin is an anthracycline antibiotic having a wide spectrum of antitumor activity. Additionally, L-theanine was shown to reverse tumor resistance to certain chemotherapeutic drugs by forcing more of the drug to stay inside the tumor. It does not, however, increase the amount of drug in normal tissue, which sets it apart from other drugs designed to overcome multidrug resistance (Sadzuka et al. 2000a).

### ***Theanine Makes Chemotherapy Work***

In 1999 researchers performed a study testing the use of theanine in conjunction with a drug similar to doxorubicin known as idarubicin. The use of idarubicin has been tried in drug-resistant leukemia cells, but it caused toxic bone marrow suppression.

Researchers wanted to see if theanine would cause the drug idarubicin to work. In the first experiment, about one-fourth of the standard dose of idarubicin was used. At this dose, the drug usually does not work, and it also does not cause toxicity. When combined with theanine, however, idarubicin worked but still without toxicity. Tumor weight was reduced 49%, and the amount of drug in the tumors doubled. In the next experiment, theanine was added to the usual therapeutic dose of idarubicin. Theanine increased the effectiveness of idarubicin and significantly lessened usual bone marrow suppression. Leukocyte loss was reduced from 57% to 37% (Sadzuka et al. 2000c).

Part of theanine's activity can be attributed to its mimicking of glutamate, an amino acid that potentiates glutathione. Theanine crowds out glutamate transport into tumor cells. Cancer cells (in confusion) erringly take in theanine, and theanine-created glutathione results. Glutathione (created by theanine) does not detoxify like natural glutathione, and instead blocks the ability of cancer cells to neutralize cancer-killing agents. Deprived of glutathione, cancer cells cannot remove chemotherapeutic agents, and the cell dies as a result of chemical poisoning (Sadzuka et al. 2001b).

## **SUMMARY**

Chemotherapy drugs have a high rate of treatment failure. Twenty years of clinical trials using chemotherapy on advanced lung cancer patients yielded survival improvement of only 2 months. While new chemotherapy regimens appear to be improving survival, when these same regimens are tested on a wider range of cancer patients, the results have been disappointing. Oncologists at a single institution may obtain a 40-50% response rate in a tightly controlled study, but when these same chemotherapy drugs are administered in a real world setting, the response rates decline to only 17-27%.

New approaches beyond chemotherapy are required. There have been few clinical trials however, to determine if adjuvant approaches actually improve survival in cancer patients. In fairness, it should be pointed out that lymphomas (Hodgkin's, non-Hodgkin's, and Burkitt's), myeloma, hairy cell leukemia, and chronic lymphocytic and certain other types of leukemia are all responding better to chemotherapy than 30 years ago. Also, depending on the timing of treatment, certain institutions are achieving better results with breast and early-stage lung cancers.

Our objective in conveying this large body of data is to provide chemotherapy patients with a better opportunity to beat cancer and minimize toxic side effects. We advocate that you follow a protocol based on a wide range of individual considerations, including the results of chemosensitivity and immunohistochemistry testing recommended at the beginning of this protocol. Information on your tumor cells obtained by these tests will help determine therapies most likely to work for you. In addition to these tumor cell tests, and based on your particular medical situation, you and your healthcare team will need to design a program specific to your needs and tolerances. The following is an outline of the steps described in this protocol:

1. Decide on an appropriate chemotherapy regimen. Chemosensitivity and immunohistochemistry tumor cell tests can help you and your physician make a more informed decision.
2. Be certain your physician understands the importance of guarding against hypoxia. This means keeping your hematocrit and hemoglobin in the upper ranges of normal. Since chemotherapy often induces anemia, the drug Procrit along with supplemental iron is often required.
3. Based on tumor type, consider asking your physician to prescribe a COX-2 inhibiting drug, such as Lodine.
4. Based on findings from the immunohistochemistry test, if your tumor expresses the K-Ras oncogene, consider high-dose statin drug therapy such as lovastatin (80 mg a day).
5. The following supplements might help block growth signals used by cancer cells to escape eradication by chemotherapy. These supplements have also displayed antiangiogenesis properties. Some of these supplements may be best initiated 3 weeks after cessation of chemotherapy if one believes that antioxidants will protect cancer cells from the effects of chemotherapy drug(s):
  - Soy Extract (40% isoflavones), five 675-mg capsules taken 4 times a day. The only soy extract providing this high potency of soy isoflavones is a product called Ultra Soy. Note that isoflavones from soy have antioxidant properties.
  - Curcumin, 900 mg, with 5 mg of Bioperine (an alkaloid from Piper nigrum), 3 capsules 2-4 times a day taken two hours away from medications. Super Curcumin with Bioperine is a formulated product that contains this recommended dosage.  
**Warning:** Use caution when combining curcumin with other chemotherapy drugs. Do not take curcumin with the chemotherapy drugs Irinotecan, Camptosar, or CPT-11. Watch for NSAID-like side effects such as gastric ulceration because curcumin is a COX-2 inhibitor. Do not take curcumin if you have a biliary tract obstruction. Also note that curcumin is a potent antioxidant.
  - Green tea extract, two-three 725-mg capsules with meals. Each capsule should be standardized to provide a minimum of 200 mg of epigallocatechin gallate (EGCG). It is the EGCG fraction of green tea that has shown the most active anticancer effects. These are available in a decaffeinated form for persons who are sensitive to caffeine or who want to take the less stimulating decaffeinated green tea extract capsules in the evening dose. Note that green tea is a potent antioxidant.
6. To possibly enhance the efficacy of certain chemotherapy drugs:
  - Fish oil, 8-12 capsules of Mega EPA/DHA w/Sesame Lignans throughout the day.
  - L-theanine, five 100 mg capsules twice a day.
7. The following natural supplements may reduce side effects and healthy tissue damage caused by chemotherapy. All of these supplements except shark liver oil are potent antioxidants:
  - Vitamin E, 400 IU a day of vitamin E succinate (dry powder natural vitamin E).
  - Vitamin C, 4000-12,000 mg throughout the day.
  - Coenzyme Q10, 200-300 mg daily in a softgel capsule for maximum absorption. (Refer to cautions about CoQ10 and chemotherapy.)
  - Melatonin, 3-50 mg at bedtime. Dose may be reduced after chemotherapy ends if too much morning drowsiness occurs. After several months, most cancer patients take 3-20 mg of melatonin at bedtime.
  - Se-methylselenocysteine (SeMSC), 200-400 mcg daily.
  - Whey protein concentrate isolate, 30-60 grams, in divided doses, daily.  
**Note:** Cancer patients undergoing chemotherapy should consider taking whey protein concentrate at least 10 days before beginning therapy and during therapy and then continuing with the whey protein for at least 30 days after completion of the therapy.
  - Shark liver oil, 200 mg alkylglycerols, 5 capsules daily for 30 days.
  - Digestive enzyme capsules may reduce the gas and bloating associated with high soy intake. Taking a 125-mg chewable tablet of Gas-X with each dose of soy might also be helpful.
8. Ask your oncologist to consider prescribing immune-enhancing drugs suggested in this protocol, such as Leukine and alpha interferon or IL-2 (along with a retinoid drug).

For more information on specific types of cancer, see the following protocols: Breast Cancer, Cancer Radiation Therapy, Cancer Surgery, Colorectal Cancer, Leukemia/Lymphoma/Non-Hodgkin's Lymphoma, Pancreatic Cancer, and Prostate Cancer. We suggest you check [www.lefcancer.org](http://www.lefcancer.org) regularly for the latest updates regarding cancer chemotherapy and related subjects.

**Caution:** There is continuing controversy concerning the use of antioxidant nutrients during conventional cancer therapy. Refer to the protocol entitled Cancer: Should Patients Take Dietary Supplements? for a discussion about whether cancer patients should take high doses of free-radical-suppressing nutrients during active therapy.

### **ADDITIONAL INFORMATION ON CANCER TREATMENT**

After reading this protocol, please refer to Cancer Treatment: The Critical Factors. It contains important additional information for the chemotherapy patient that we do not want to duplicate in this protocol section. Cancer patients may want to refer to the other protocols in this edition or visit our website at [www.lef.org](http://www.lef.org) or [www.lefcancer.org](http://www.lefcancer.org).

### **FOR MORE INFORMATION**

U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health National Cancer Institute, Bethesda, MD 20892 and NIH Publication No. 94-1136.

### **PRODUCT AVAILABILITY**

Ultra Soy Extract; Super Curcumin with Bioperine; Mega Green Tea Extract; L-theanine; Super Absorbable CoQ10; melatonin; whey protein concentrate; vitamins A, C, D, and E succinate; Se-methylselenocysteine (SeMSC); Mega EP/DHA w/Sesame Lignans, and Super Digestive Enzymes can be obtained by calling (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](http://www.lefcancer.org).

Before utilizing this cancer protocol, we suggest that you check [www.lefcancer.org](http://www.lefcancer.org) to see if any substantive changes have been made to the recommendations described herein. Based on the sheer number of newly published findings, there could be significant alterations to the information you have just read.



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