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-b1 (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. (Seven Super Omega-3 EPA/DHA fish oil capsules provide this potency.)

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

Aged Garlic Extract: 2000 mg a day. (Four Kyolic® Reserve Aged Garlic Extract™ capsules provide this potency.)

Should Antioxidants Be Taken at the Same Time as Chemotherapy?

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 calls. 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 inihibitors). 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

Drug	**Trade Name**	**Mechanism of Action**
Chemotherapy drugs that kill cancer cells by inflicting free-radical damage:		
Alkylating agents		***Free-radical damage***
Busulfan	Myleran	
Carboplatin	Paraplatin	
Carmustine	BiCNU	
Chlorambucil	Leukeran	
Cisplatin	Platinol	
Cyclophosphamide	Cytoxan	
Ifosfamide	Ifex	
Procarbazine	Matulane	
Anthracyclines		***Free-radical damage***
Bleomycin	Blenoxane	
Doxorubicin	Adriamycin	
Daunorubicin	Cerubidine	
Epirubicin	Ellence	
Mitomycin C	Mutamycin	
Plant alkaloids		***Free-radical damage***
Teniposide	Vumon	
VP-16	Etoposide	
Chemotherapy drugs that kill cancer cells by other mechanisms:		
Antimetabolites		***Inhibition of DNA/RNA synthesis***
Asparaginase	Elspar	
Azacitidine	Mylosar	
Cladribine	Leustatin	

Cytarabine	Cytosar	
Fludarabine	Fludara	
Fluorouracil	Adrucil	
Hydroxyurea	Hydrea	
Mercaptopurine	Purinethol	(Analog of the vitamin folic acid)
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
Vincristine	Oncovin	microtubules and spindle precursors
Vinorelbine	Navelbine	Mitotic arrest through binding of
VP-16	Etoposide	microtubules and spindle precursors

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?