MITIGATION OF CHEMOTHERAPY SIDE EFFECTS

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 (Kobrinsky 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.