Health Concerns

Health Concerns Quick Link

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

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 antinausea 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-HT3 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 (Hesketh 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 odansetron 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).

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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, 7-11 capsules of Super Omega-3 EPA/DHA w/Sesame Lignans & Olive Fruit Extract 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 alkyglycerols, 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 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 or 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); Super Omega-3 EPA/DHA w/Sesame Lignans & Olive Fruit Extract, 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.

Before utilizing this cancer protocol, we suggest that you check 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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