

Leukemia

Leukemia refers to cancers that begin in the blood-forming cells of the body. These abnormal cells grow and multiply in an uncontrolled way. As the disease progresses, leukemic cells move through the blood stream and invade other organs, such as the spleen, lymph nodes, liver, and central nervous system. In the US, more than 30,000 new cases of leukemia are diagnosed every year, and adult onset accounts for 90 percent of the new cases (Xie Y et al 2003).

Risk factors for leukemia include advanced age, poor nutrition, previous chemotherapy and radiation treatment for other cancers, and smoking. Medical treatment for leukemia primarily revolves around chemotherapy and radiation therapy. Nutritional supplements help support the healthy function of the immune system, and in particular, the white blood cells in leukemia patients. In addition, some nutritional supplements are able to kill leukemia cells. Key examples include vitamin A, genistein from soy extract, and curcumin from turmeric.

TYPES OF LEUKEMIA

Leukemia can be classified into four major types based on whether the disease is acute or chronic and according to the type of white blood cell affected:

- Acute myelogenous leukemia (AML)
- Chronic myelogenous leukemia (CML)
- Acute lymphocytic leukemia (ALL)
- Chronic lymphocytic leukemia (CLL)

Myelogenous leukemia involves myeloid cells, granulocytes (neutrophils, basophils, and eosinophils) and monocytes (macrophages). Lymphocytic leukemia involves T and B cells (lymphocytes).

Leukemia cases in USA

In the US, leukemia occurs more frequently in males than females (Call TG et al 1994; Cartwright RA et al 2002; McNeil DE et al 2002b). In addition, Caucasians are more likely to develop leukemia than African-Americans and Hispanics (McNeil DE et al 2002a; Xie Y et al 2003)

Table 1

Type of Leukemia	Number of New Cases/Year	Average Age at Diagnosis (years)
AML	10,000	65
CLL	7,800	Over 50
CML	4,500	67
ALL	4,000	Under 10

With the exception of ALL, leukemia is generally associated with aging. Furthermore, the behavior of leukemia in older individuals differs from that seen in younger people. For example, AML occurring in older individuals is more resistant to chemotherapy than AML in younger patients (Schoch C et al 2001).

HOW DOES LEUKEMIA DEVELOP?

All cancers begin with damage to the cells' deoxyribonucleic acid (DNA). Within a cell, DNA is found in structures called chromosomes, which are themselves made up of segments called genes. Leukemia begins with DNA damage in the white blood cells, which protect the body from infections. In leukemia, DNA damage can occur through chromosome translocations (shifting and re-arrangement of chromosome segments) or mutations. Any one type of leukemia can have several genetic abnormalities at its core — this further complicates the interaction with other healthy genes, as well as the individual's nutritional status in the development of leukemia (Greaves MF 2004; Irons RD et al 1996).

RISK FACTORS

Inherited, abnormal genes account for a small proportion of leukemia cases (Alter BP 2003; Bischof O et al 2001; Fong CT et al

1987). However, in most cases, the DNA damage that eventually results in the onset of leukemia is brought about by interactions between genes, age, and a variety of environmental or lifestyle factors such as nutrition and exposure to chemicals (Greaves MF 2004; Irons RD et al 1996).

Age. Since up to 70 percent of leukemia cases are in those over 50, age can be considered the biggest risk factor for developing leukemia (Fenech MF et al 1997; Russell RM 2000a). The chromosomes of white blood cells in older people are more fragile than those in young adults and are more vulnerable to the types of DNA damage (e.g., free radical damage) known to cause leukemia (Esposito D et al 1989; Mendoza-Nunez VM et al 1999).

A diet rich in fruits and vegetables and other antioxidants can help guard against DNA damage caused by free radicals (Ames BN et al 1993). However, the ability of the elderly to repair DNA damage is poor and is associated with suboptimal micronutrient status (Ames BN 1998; Fenech MF et al 1997). The metabolism of elderly people is altered in such a way that while they continue to efficiently absorb macronutrients such as fats and proteins, absorption of micronutrients such as vitamin B12 and vitamin D is compromised, leading to malnutrition (Russell RM 2000a). Suboptimal levels of micronutrients can cause DNA damage associated with leukemia and limit the ability to repair this damage (Ames BN 1998; Ames BN 1999).

Nutrition. Diets lacking in essential micronutrients are as detrimental as cigarette smoking in the cause of cancer and can cause the same kind of DNA damage as exposure to radiation (Ames BN 1998). Micronutrients shown to contribute to leukemia include folic acid and vitamins B12 and B6 (Ames BN 1999).

Folic acid deficiency causes chromosome breaks (Fenech MF et al 1997) and is a risk factor in the development of ALL. In folic acid deficiency, efforts to repair damaged DNA are compromised and lead to breakages in genes (chromosome breaks) (Ames BN 1999; Skibola CF et al 2002; Wickramasinghe SN et al 1994). Deficiencies in vitamins B12 and B6 are thought to act in the same way as folic acid deficiency in increasing the risk for both adult and childhood ALL (Ames BN 1999).

There is a possible relationship between the restricted nutrient intake of slimming diets and the development of acute leukemia (Visani G et al 1997). Another theory is that phenol and hydroquinone, chemicals mainly ingested from meat and protein-rich diets, known to produce DNA damage, and antibiotics, may cause leukemia (McDonald TA et al 2001).

Chemotherapy. Chemotherapy, used for the treatment of other cancers, can cause DNA damage and make increase the risk of developing some form of leukemia. For example, chemotherapy for the treatment of other cancers is the major recognized cause of AML in the young, referred to by clinicians as secondary or treatment-related AML (Felix CA 1998). Treatment-related AML is associated with therapy for breast cancer, ovarian cancer, Hodgkin's disease and non-Hodgkin's lymphoma, and accounts for up to 20 percent of AML cases (Kaldor JM et al 1990; Smith MA et al 1996). Treatment with epipodophyllotoxins (etoposide and teniposide) is associated with development of secondary AML (Hawkins MM 1991; Pedersen-Bjergaard J et al 1991). Cyclosporine A, used to treat suppressed red blood cell production, is associated with the development of secondary leukemia (Yamauchi T et al 2002).

Radiation. Exposure to high doses of radiation causes leukemia by inducing DNA damage through translocations (Kamada N et al 1987). Population studies show a link between radiation exposure from nuclear testing between 1951 and 1962 in the United States and the onset of leukemia (Archer VE 1987; Johnson CJ 1984). The incidence of leukemia was high in the United States in the years during and immediately after the nuclear testing. Utah showed high increases (up to five times the norm) in leukemia rates, which persisted as late as the 1980s (Archer VE 1987; Johnson CJ 1984). Exposure to radiation is linked to acute and myeloid leukemia in children (Archer VE 1987). The association between radiation exposure and leukemia was noted in survivors of the atomic bomb in Japan (Ichimaru M et al 1991) and in people who lived near the nuclear reactors in the Chernobyl disaster of 1986 (Noshchenko AG et al 2002). Leukemia caused by radiation typically appears 10 years after exposure (Tilyou SM 1990).

Chemicals. Long-term or occupational exposure to benzene is a cause of acute leukemia (Austin H et al 1988; Rinsky RA et al 1981). Long-term exposure to herbicides, pesticides, and other agricultural chemicals is linked to an increased risk of developing leukemia (Meinert R et al 2000). Hair dyes contain chemicals that cause cancer and are associated with leukemia (Sandler DP 1995), particularly the long-term use of permanent dyes (Rauscher GH et al 2004).

Smoking. Cigarette smoke contains leukemia-causing chemicals like benzene (Korte JE et al 2000). Although smoking in the young is associated with modest increases in the risk of developing leukemia, in those over 60 smoking is associated with a twofold increase in risk for AML and a threefold increase in the risk for ALL (Sandler DP et al 1993).

Genetics. Children with Down's syndrome have a 10 to 20 times higher risk of developing leukemia than the general population (Fong CT et al 1987). This risk is not confined to childhood years and extends through adulthood. There are also inherited disorders, such as Fanconi's anemia and Bloom's syndrome, that are characterized by genetic instability and inability to repair DNA damage and are associated with an increased risk of leukemia (Alter BP 2003; Bischof O et al 2001).

Viruses. Acute T cell leukemia is associated with infection by the human T cell leukemia virus (HTLV); human lymphotropic virus-1

causes leukemia in humans. In infected individuals, HTLV proteins attach themselves to proteins in the lymphocytes responsible for regulating cell growth and corrupt their functions resulting in the uncontrolled cell growth of leukemia (Uchiyama T 1997). This type of leukemia is rare in the United States and is generally found in Asia and parts of the Caribbean.

DIAGNOSIS

Symptoms associated with leukemia include weakness, fatigue, unexplained weight loss, pain, (abdominal, bone, and joint), abnormal bleeding, infection, fever, excessive bruising, and enlarged spleen, lymph nodes, and liver.

The first step in diagnosing leukemia is a complete blood count (CBC). With a diagnosis of leukemia, further testing of cell samples obtained by bone marrow aspiration or lumbar puncture determines the specific type of leukemia. Specific treatment is then targeted for leukemia based upon a number of factors, including results of genetic tests and leukemic cell sub-type.

What You Have Learned So Far

- Leukemia is a collective name for cancers of the white blood cells that grow, multiply, and change uncontrollably
- It occurs through damage to the genes, such as chromosome translocations or mutations
- Leukemia can be chronic or acute and occur in myeloid or lymphocytic white blood cells
- Risk factors for leukemia include environmental or lifestyle factors such as nutrition, smoking, exposure to chemicals, viruses, radiation, and previous chemotherapy or radiotherapy treatment for other cancers
- Diagnosis is made from results of blood and bone marrow tests
- Leukemia is more prevalent in the aged who have altered metabolism causing micronutrient deficiencies and reduced bone marrow function (Chatta GS et al 1996)
- Vitamin D3, curcumin, green tea, and soy extracts help support healthy cell growth, function, and maturation in patients with leukemia

CONVENTIONAL MEDICAL THERAPY

Chemotherapy and radiotherapy. Leukemia generally responds well to chemotherapy and radiation therapy, and these are often used in combination. Chemotherapy agents attack rapidly dividing cells; however, they do not distinguish leukemia cells from other rapidly dividing but non-cancerous cells. As a result, chemotherapy harms healthy red and white blood cells, blood-clotting platelets, hair follicles, and cells lining the gastrointestinal tract, thus creating unpleasant side effects.

The damage to white blood cells increases the risk of infection. Medications known as colony-stimulating factors (CSFs) increase white blood cell counts and are often given in combination with chemotherapy (Dale DC 2002; Lyman GH et al 2003). The use of CSFs in leukemia is discussed in the Immunomodulators and Enhancers section.

Successful treatment with chemotherapy and severity of associated side effects in leukemia may be positively influenced by nutritional status. Antioxidant levels are reduced in leukemia patients undergoing chemotherapy (Kennedy DD et al 2004). Low levels of antioxidant intake are associated with increases in adverse effects of chemotherapy in children with ALL (Kennedy DD et al 2004). Vitamins C, E, and beta-carotene are associated with reduced toxicity from chemotherapy and lower frequencies of infections (Gajate C et al 2003; Kennedy DD et al 2004). A discussion on chemotherapy, nutritional support, and natural strategies to counteract the associated side effects can be found in the Cancer Chemotherapy chapter.

Radiotherapy kills leukemia cells by exposing them to ionizing radiation that damages cell DNA. In clinical practice, radiotherapy is typically used in 4 percent of leukemia cases (Featherstone C et al 2005). This is partly due to chemotherapy alternatives (Peiffert D et al 1999). Irradiation of the spleen is sometimes used in the treatment of leukemia patients with enlarged spleens (McFarland JT et al 2003; Peiffert D et al 1999).

Interferon therapy. Interferons (IFN) are a group of naturally occurring substances sometimes used in the treatment of chronic leukemia (Guilhot F et al 2004; Zinzani PL et al 1994). Interferon reduces the growth and reproduction of leukemia cells and enhances the immune system's response to cancer (see Immunomodulators and Enhancers section). Interferon is particularly useful when used as a maintenance therapy in patients after partial or complete remission. Use of interferon in combination with all-trans retinoic acid (a synthetic vitamin A analog) may prolong the lives of patients with promyelocytic and other forms of leukemia (Sacchi S et al 1997; Zheng A et al 1996).

Stem cell therapy. As the chemotherapy required to kill leukemia cells also damages the rapidly dividing blood-forming cells, stem-cell therapy replenishes bone marrow. Stem-cell therapy is the transplantation of stem cells into the patient's bone marrow following chemotherapy and/or radiation therapy to kill the leukemia cells (Isidori A et al 2005; Linker CA 2003; Reiffers J et al 1996). Stem cells may be obtained from the patient (autologous) or from a donor (allogeneic) who is a close tissue match to the

patient (Isidori A et al 2005; Linker CA 2003; Reiffers J et al 1996). Autologous stem-cell therapy is a rare procedure due to the challenge of ensuring that the removed stem cells are not contaminated with leukemia cells. Stem cells can be obtained either by bone marrow aspiration or by a procedure called apheresis (also called peripheral blood stem-cell (PBSC) transplant), through which the cells are removed from the peripheral blood system. This type of therapy is still in the experimental stages.

Inhibiting cell-signaling pathways. Early in disease progression, many types of leukemia produce certain inflammatory and immunosuppressive cytokines (chemical messengers) and use cell-signaling pathways.

For example:

- Vascular endothelial growth factor (VEGF) is considered essential for leukemia cell growth, survival and spread (Podar K et al 2004). Expression of high VEGF levels is associated with shortened survival in chronic lymphocytic leukemia patients (Ferrajoli A et al 2001).
- Basic fibroblast growth factor (bFGF) is a potent mitogen (growth signal) and is essential for blood vessel growth and spread of cancer cells (Bieker R et al 2003).
- Hepatocyte growth factor (HGF) stimulates the growth and spread of leukemia cells (Aguayo A et al 2000). HGF is particularly over-expressed in AML, CML, CLL, and chronic myelomonocytic leukemia (Aguayo A et al 2000).
- Tumor necrosis factor-alpha (TNF-alpha) is a pro-inflammatory cytokine significantly elevated in all leukemias except for AML and myelodysplastic syndromes (Aguayo A et al 2000).
- Interleukin-6 (IL-6) is a pro-inflammatory and immunosuppressive cytokine. Elevated serum IL-6 is associated with a poor prognosis and shortened survival in CLL (Fayad L et al 2001).

Types of leukemia that over-express these cytokines are (Aguayo A et al 2000; Bieker R et al 2003; Fayad L et al 2001; Podar K et al 2004):

Disease	Cytokines Over-expressed
Chronic myeloid leukemia	VEGF, bFGF, HGF, TNF-alpha, IL-6
Acute myeloid leukemia	VEGF, bFGF, HGF
Chronic myelomonocytic leukemia	VEGF, bFGF, HGF, TNF-alpha
Acute lymphoblastic leukemia	bFGF, HGF, TNF-alpha
Chronic lymphocytic leukemia	VEGF, bFGF, HGF, TNF alpha, IL-6
Myelodysplastic syndromes	VEGF, bFGF, HGF

Regulating normal cell growth. The drug Gleevec® (formerly STI571) slows proliferation and causes apoptosis in Bcr-Abl cell lines and fresh leukemic cells from "Philadelphia chromosome positive" (Ph+) CML. Gleevec® (imatinib mesylate) is indicated for the treatment of patients with Ph+ CML in blast crisis, accelerated phase, or chronic phase after failure of interferon-alpha therapy. Although Gleevec® is an FDA-approved drug its effectiveness is continuously evaluated. The latest findings can be found on the website www.gleevec.com. It is interesting that a drug that functions through a mechanism similar to certain dietary supplements (e.g. curcumin and genistein) was put on the FDA's "fast-track" for approval.

Immunomodulators and immune enhancers. Substances that enhance the function of the immune system are used to support the conventional treatment of leukemia with chemotherapy and radiotherapy. These substances fall into three main categories:

- Hematopoietic growth factors
- Cytokines (glycoprotein messengers)
- Immunotoxins

The use of growth factors such as granulocyte-colony stimulating factor (G-CSF) during chemotherapy elevates the number of normal white blood cells, thus enabling patients to tolerate high chemotherapeutic doses and reducing infections (Dale DC 2002; Lyman GH et al 2003). G CSF (filgrastim, Neupogen®) treats low neutrophil counts (neutropenia) during CML therapy (Quintas-Cardama A et al 2004). Another growth factor, granulocyte-macrophage-colony stimulating factor (GM-CSF, sargramostim, Leukine™), blocks the migration of myeloid cells and leukemia spread (Eubank TD et al 2004).

Cytokines are glycoprotein messengers that enhance the function of immune cells. The use of interferon in the treatment of chronic leukemia is common (Guilhot F et al 2004; Zinzani PL et al 1994). The use of the cytokine IL-2 in AML and CML patients reportedly improves immune responses (Morecki S et al 1992).

Antibodies, specifically targeted to molecules present on the surface of AML cells, exhibit anti-leukemic responses in clinical studies (Balaian L et al 2004; Feldman EJ 2003; Ritz J et al 1982). The binding of an antibody to a leukemia cell marks the cell as a target for destruction. Antibodies can be attached to cytotoxic agents that can be selectively delivered to leukemia cells (Feldman EJ 2003; Ritz J et al 1982). Antibody therapy is beneficial in treating CLL (Lin TS et al 2004) and hairy cell leukemia (Cervetti G et al

2004).

Cancer vaccines present an opportunity to manipulate the immune system into attacking leukemia cells (Lee JJ et al 2004). Research on this therapeutic option is still in the experimental stage and has focused on solid tumors.

Drugs to Reduce the Side Effects of Chemotherapy

Neulasta® and GM-CSF. The frequency and duration of low white blood cell counts (low neutrophil counts) that is caused by chemotherapy can be reduced by the use of medications such as Neulasta® (G-CSF, also known as pegfilgrastim) and GM-CSF (Biganzoli L et al 2004b; Itala M et al 1998; Komrokji RS et al 2004; Quintas-Cardama A et al 2004). In clinical trials, Neulasta® reduced the frequency of infections, hospitalizations, and enabled continuing use of chemotherapy doses that normally would be reduced as a result of chemotherapy-associated neutropenia (Biganzoli L et al 2004a).

Procrit® and Epogen®. Anemia (low red blood cells) associated with both the leukemia and chemotherapy can be treated using Procrit® and Epogen® (epoetin alfa, also known as recombinant human erythropoietin) (Maisnar V et al 2004; Quirt I et al 2001a). In clinical assessments, epoetin alpha improved anemia in 77% of CLL patients (Maisnar V et al 2004).

HORMONES AND METABOLISM

The development of acute leukemia is accompanied by abnormalities in levels of cholesterol and some lipids (Baroni S et al 1994; Baroni S et al 1996; Moschovi M et al 2004). In particular, AML and ALL patients have low levels of high-density-lipoprotein cholesterol (Baroni S et al 1994; Baroni S et al 1996; Moschovi M et al 2004). Upon treatment, cholesterol levels return to normal in patients that respond to treatment, suggesting that cholesterol could be used as a marker to monitor chemotherapy (Baroni S et al 1994; Baroni S et al 1996; Moschovi M et al 2004). Research using specific types of leukemia cells (HL-60 cells) and showing that cholesterol is required for cells to progress through cell division (Fernandez C et al 2004) may explain the link between low cholesterol levels and acute leukemia that is characterized by the failure of cells to reach maturity.

Levels of the anti-inflammatory hormone cortisol are elevated in AML, CML,(Everaus H et al 1997; Singh JN et al 1989) and CLL (Everaus H 1992) patients. These high levels of cortisol, a powerful immunosuppressive agent, are associated with impaired immune cell responses (Everaus H 1992; Everaus H et al 1997) and may be partially responsible for the immune dysfunction seen in these patients.

DHEA. The hormone dehydroepiandrosterone (DHEA) has been shown to favorably alter inflammatory cytokines such as interleukin-2 in leukemic mice (raghi-Niknam M et al 1997). DHEA favorably modulated the immune dysfunction that occurred during leukemia retrovirus infection in old mice (Inserra P et al 1998) and prevented leukemia growth (Catalina F et al 2003).

DHEA might be effective in supporting healthy immune function in leukemia patients with a DHEA deficiency, which can be determined by a blood test (Uozumi K et al 1996). DHEA is contraindicated in both men and women with certain hormone-related cancers.

NUTRITIONAL THERAPY

Vitamins D3, E, K2, and B12. Vitamin D3 and its analogs may help certain leukemia cells (AML) to become, or differentiate into, normal cells (Srivastava MD et al 2004). However, a monthly complete blood count (CBC) to monitor serum calcium, and kidney and liver function, is necessary to prevent vitamin D3 toxicity.

Vitamin E levels are lower in CML patients compared to healthy individuals (Singh V et al 2000). Vitamin E (as the succinate salt), in combination with vitamin D3, promotes cell maturation in HL-60 leukemia cells (Sokoloski JA et al 1997).

Vitamin K2 analogs help normalize leukemia cells (Miyazawa K et al 2001). Vitamin K2 supplementation taken alone or with all-trans retinoic acid (ATRA) therapy may benefit myelogenous leukemia (Yaguchi M et al 1997).

Deficiency of vitamin B12 causes chromosome breaks and is a risk factor for ALL (Ames BN 1999; Skibola CF et al 2002). Vitamin B12 supplementation is thought to reduce chromosome damage that leads to ALL (Ames BN 1999).

Soy extract. Soy extracts contain high levels of genistein, an inhibitor of protein tyrosine kinase, an enzyme that becomes dysfunctional in cancer cells. Protein tyrosine kinase activity is reduced by genistein, subsequently impeding the growth of cancer cells (Carlo-Stella C et al 1996b; Carlo-Stella C et al 1996a).

Studies have shown that genistein increased the potency of the chemotherapeutic agent bleomycin against the leukemia cell line HL-60, and reduced the damage this agent normally causes to normal lymphocytes, thus it may reduce normal tissue toxicity associated with chemotherapy (Lee R et al 2004).

The benefits of soy extract may be more significant in leukemia cases with a mutant p53 gene, making the leukemia cells more sensitive to chemotherapy. For example, genistein derived from soy extracts has been shown to increase expression of the gene that helps to suppress cancer cell growth (i.e. normal p53 tumor suppressor gene) in solid tumors that acts to protect the body from cancer development (Lian F et al 1999).

The presence of mutant p53 genes is determined by a pathologist's examination of the leukemia cells. Consult your physician to determine if the pathologist performing an immunohistochemistry test for mutant or functional p53 discovered mutant p53; alternatively ask your physician to perform this test via Genzyme Genetics (formerly IMPATH Laboratories): http://www.genzymeimpath.com/lymphoma_leukemia.html.

Curcumin. An extract of the spice turmeric, curcumin acts in combination with the soy isoflavone genistein to reduce the number of leukemia-promoting properties, such as growth signals and pro-inflammatory cytokines that are over-produced in leukemia (Arbiser JL et al 1998).

Curcumin has been shown to:

- Inhibit production of bFGF, a potent growth signal for cancer cells that is known to be over-produced in AML, CML, and ALL (Arbiser JL et al 1998).
- Increase expression of the cancer-protective p53 gene in leukemia cell lines, thus making them more susceptible to cell death (Jee SH et al 1998).
- Reduce the production of the inflammatory cytokine, TNF-alpha, that is over-produced in CML and ALL (Xu YX et al 1997).

Green and black tea. Epigallocatechin gallate (EGCG) in green tea blocks the production of vascular endothelial growth factor (VEGF), considered essential for leukemia growth and spread (Lee YK et al 2004). EGCG may be particularly useful in CLL, a leukemia type that relies heavily on VEGF for its survival. EGCG significantly increased the rate of cell death in 8 out of 10 CLL samples (Lee YK et al 2004). Green tea blocks the proliferation of lymphocytes from adult T cell leukemia patients (Li HC et al 2000). Theaflavins found in black tea have also been shown to be as potent as EGCG from green tea in blocking proliferation of leukemia cell lines (Lung HL et al 2004).

Essential fatty acids (EPA, DHA, and GLA). Several leukemias are associated with abnormally high levels of the inflammatory cytokines TNF alpha and IL-6 (Aguayo A et al 2000; Fayad L et al 2001). Docosahexaenoic acid (DHA) and gamma-linolenic acid (GLA) are essential fatty acids that suppress these dangerous inflammatory cytokines (De CR et al 2000; Purasiri P et al 1997). The use of GLA and DHA has been shown to improve the response of leukemia to chemotherapy (Liu QY et al 2000). GLA and eicosapentaenoic acid (EPA) have been shown to cause death in HL-60 leukemia cells (Gillis RC et al 2002). Furthermore, a recent Phase I/II clinical study in humans with solid cancer also showed that DHA may improve responses to paclitaxel and carboplatin chemotherapy (Harries M et al 2004).

Essential fatty acids DHA and EPA are derived from fish, primrose, and borage oils.

Antioxidants (lipoic acid and L-ascorbic acid). Lipoic acid is a powerful antioxidant with anti-aging effects (Hagen TM et al 1999; Lykkesfeldt J et al 1998). Exposure of the Jurkat leukemia cell line to lipoic acid increased cell death (apoptosis) of the cancer cells but did not affect lymphocytes from normal healthy individuals (Sen CK et al 1999). Lipoic acid activates the enzyme caspase that drives a particular type of apoptotic cell death (Sen CK et al 1999). Lipoic acid helps crippled, damaged immune cells (such as those of cancer patients) to function more normally (Sen CK et al 1997).

Research shows that lipoic acid, used in combination with vitamin D3, helps to support normal (versus cancerous) growth and maturation of leukemia cells (Sokoloski JA et al 1997).

Laboratory tests show L-ascorbic acid inhibits proliferation of HL-60 leukemia cells and supports their normal (versus cancerous) growth and maturation (Kang HK et al 2003). In fact, L-ascorbic acid is being assessed for the treatment of AML because laboratory tests showed that it blocked growth of three AML cell lines and fresh leukemic cells from three AML patients (Kennedy DD et al 2004; Park S et al 2004).

Whether or not use of antioxidants antagonizes or supports chemotherapy agents may depend on the type of leukemia, the drug used, and the dose of antioxidant. People undergoing chemotherapy should discuss the use of antioxidants with an oncologist and refer to the Cancer Chemotherapy chapter.

Nutritional supplementation for specific forms of leukemia

Promyelocytic Leukemia: The use of retinoic acid (derived from vitamin A) and its synthetic derivatives, often in combination with vitamin D3, is well established in promyelocytic leukemia. This strategy takes into account the underlying genetic problems in this type of leukemia (Huang ME et al 1988; Mann G et al 2001).

Chronic Myeloid Leukemia: Several dietary supplements share similarities with Gleevec®, (Manley PW et al 2002; Nakajima M et al 2003) the FDA approved drug for CML. These include curcumin, (Aggarwal BB et al 2003) genistein from soy extracts, (Carlo-Stella C et al 1996b) catechin from green tea, and alkylglycerols from shark liver oil (Lee YK et al 2004; Pugliese PT et al 1998), all of which inhibit the activity of protein tyrosine kinase, an enzyme that is abnormal in CML cells. In addition, curcumin inhibits the production of growth factors and chemical messengers that are abnormal in CML, therefore reducing the leukemic cell's ability to multiply and grow (Arbiser JL et al 1998; Xu YX et al 1997). Ajoene, a garlic extract, has been shown in some studies to have activity against CML cells (Hassan HT 2004).

Acute Myeloid Leukemia: Some studies have suggested that curcumin and genistein can block growth of AML cells by interfering with growth factors that are over-produced in AML cells (Arbiser JL et al 1998; Bhatia N et al 2001; Hurley MM et al 1996). L-Ascorbic acid is being clinically tested for AML after encouraging laboratory tests (Park S et al 2004). Studies have shown that resveratrol and ajoene are capable of killing AML cells (Asou H et al 2002; Estrov Z et al 2003; Hassan HT 2004; Xu B et al 2004).

Moreover, ajoene has been shown to kill chemotherapy resistant AML cells that present particular difficulties in the older patients (Ahmed N et al 2001).

Acute Lymphocytic Leukemia: Curcumin and genistein have been shown to possess the ability to block inflammatory substances, such as TNF-alpha, that are observed in high levels in ALL (Arbiser JL et al 1998; Bhatia N et al 2001; Hurley MM et al 1996; Xu YX et al 1997).

Chronic Lymphocytic Leukemia: Epigallocatechin from green tea, curcumin from turmeric, and genistein from soy extracts have all been shown to block the production of growth factors such as VEGF (Arbiser JL et al 1998; Carlo-Stella C et al 1996b; Lee YK et al 2004) typically seen in high levels in CLL (Ferrajoli A et al 2001). Essential fatty acids have been shown to suppress other inflammatory factors, such as IL-6 and TNF-alpha that are seen in high levels in CLL (De CR et al 2000; Purasiri P et al 1997).

Shark liver oil. Alkylglycerols are naturally occurring ester-lipids that were first isolated from shark liver oil and used in the treatment of children with leukemia (BROHULT A 1958). Treatment of cancer cells with alkylglycerols lowered the cancer cell's ability to reproduce and invade healthy cells (Wang H et al 1999). Animal studies show that alkylglycerols curtail tumor growth by blocking cancer cell blood vessel growth (Pedrono F et al 2004). Alkylglycerols also inhibit protein kinase C, a protein critical in cell proliferation that is often deregulated in malignancy (Pugliese PT et al 1998). Shark liver oil is the main source of alkylglycerols and could be taken up to 100 mg, three times per day, for three months without side effects (Pugliese PT et al 1998). Shark liver oil should not be consumed without first consulting with your physician.

Garlic extract (Ajoene). Ajoene, a natural sulfur-containing compound extracted from garlic, has anti-leukemia properties (Ahmed N et al 2001; Hassan HT 2004; Xu B et al 2004). Ajoene has anti-thrombotic and cholesterol-lowering properties but has not been tested clinically. Laboratory tests show ajoene blocks division and growth of leukemia cell lines, lowers cholesterol biosynthesis through HMG-CoA-reductase inhibition, and causes death of CML cells (Hassan HT 2004).

Ajoene enhances the ability of two chemotherapeutic agents (cytarabine and fludarabine) to kill human AML cells that were previously resistant to chemotherapy (Ahmed N et al 2001; Hassan HT 2004). Ajoene is a promising new therapy for relapsed AML and AML in the elderly, which are more resistant to chemotherapy. Pure garlic supplements contain ajoene.

Vitamin A. Oral administration of vitamin A analogs as well as synthetic vitamin A derivatives helps to support normal growth and maturation of cells and is associated with remission rates as high as 90 percent when used to treat certain types of leukemia (Huang ME et al 1988; Mann G et al 2001; Okuno M et al 2004). Fat-soluble vitamin A (Retinyl palmitate) has been used to maintain long-term survival of children with AML (Skrede B et al 1994). Vesanoid (Tretinoin®), a vitamin A analog that inhibits cell division and allows myeloid cells to reach maturity and attain normal function, is approved for treatment of certain leukemias (Kerr PE et al 2001).

Studies have shown that chemotherapy drug resistance may be overcome using vitamin A derivatives in combination with vitamin D3 and its analogs (Defacque H et al 1996; Elstner E et al 1996; Miyauchi J et al 1997; Nakajima H et al 1996).

Vitamin A is available as the prescription drug Retinol (which is a vitamin A alcohol). Oral administration of water-soluble vitamin A may inhibit deficiency in those with malabsorption, a low protein intake, active infection, or undergoing antibiotic therapy. A monthly blood test to measure serum concentration of vitamin A is necessary to monitor for vitamin A-induced liver toxicity. Animal studies show that vitamin E protects against vitamin A toxicity and increases assimilation and storage of vitamin A (Jenkins MY et al 1999; St CM et al 2004).

Supplementation with vitamin A in patients being treated with synthetic retinoids or vitamin A analogs (mimics) for cancer should be avoided because of the potential toxicity with the combination. Supplementing with vitamin A to support healthy cell growth and maturation may be considered ONLY after consultation with your physician if you are also being treated for leukemia with synthetic vitamin A derivatives.

Resveratrol. Resveratrol, a plant polyphenol found in grapes and red wine, has been shown in scientific studies to inhibit the growth of leukemia cell lines. Resveratrol reduces the growth of AML cell lines and causes death in HL-60 leukemia cells (Su JL et al 2005). Resveratrol has been shown to block the proliferation of fresh AML cells taken from the bone marrow of five newly diagnosed patients (Asou H et al 2002; Estrov Z et al 2003). Exposure of the leukemia cell line U937 to concentrations of resveratrol similar to those found in red wine blocked cell proliferation but, in this case, did not increase cell death of these abnormal cells (Castello L et al 2005).

Studies of resveratrol in humans suggest it is safe, (Aggarwal BB et al 2004) but appropriate human doses for leukemia therapy have not been determined. However, a study in mice showed resveratrol, taken orally, only showed potential anti-leukemic activity at high doses of 80 mg/kg body weight (Gao X et al 2002). Supplementation with resveratrol to support healthy cell growth and maturation should be done ONLY after consulting with your physician if you are also being treated for leukemia.

Folic Acid. Studies have suggested that folate supplementation of a mother's diet during pregnancy protects the child from childhood ALL (Thompson JR et al 2001) and that abnormalities in the genes responsible for folate metabolism are a known risk factor for adult and childhood ALL (Skibola CF et al 2002). However, folic acid supplementation during leukemia treatment should be approached with caution because it may interfere with the chemotherapy drugs being used to treat the leukemia.

The best example of this is the drug methotrexate. Methotrexate, a chemotherapy drug used to treat many different types of cancers including certain types of leukemias, works by competing with folic acid for a key enzyme used in cell growth. Since cancer cells grow much faster than normal cells, methotrexate works by interfering with the cancer cells' ability to grow quickly. For example, methotrexate is used to treat childhood ALL (Cohen IJ 2004; Kisliuk RL 2003). However, supplementing with folic acid may interfere with methotrexate's ability to limit cancer cell growth.

If a patient with leukemia or other cancer is being treated with methotrexate, or another anti-folic acid drug that is actually a folate analog, then folic acid supplementation should be avoided because it may interfere with methotrexate's anti-cancer effect.

Melatonin. Melatonin, a hormone produced by the pineal gland during nighttime hours, regulates sleep and waking cycles in humans (Haimov I et al 1997). Additionally, it helps support the immune system by stimulating lymphocyte activity (El-Sokary GH et al 2003).

The use of melatonin supplements in leukemia treatment was initially approached with caution (Conti A et al 1992). However, recent studies show that melatonin may augment the efficiency of leukemia treatment (Granzotto M et al 2001; Lissoni P et al 2000). A study in animals showed that melatonin sensitized a chemotherapy resistant leukemia cell line (P388) to treatment (Granzotto M et al 2001). Furthermore, a clinical study showed that melatonin supplementation supported the treatment of leukemia with the cytokine interleukin-2 (Lissoni P et al 2000). Melatonin supplementation and co-treatment with autologous or allogeneic cells has been proposed as a model for control of malignant beta-cell leukemia (Nir I et al 1999). The use of melatonin to support a healthy neuroendocrine system should be used with caution and ONLY after consultation with your physician if you are being treated for leukemia.

TRACKING YOUR PROGRESS

Because all leukemia therapies produce individual responses based on factors such as the type of leukemia, patient's age, nutritional status, and the presence of other diseases, monthly blood testing to monitor progress is recommended. Patients treated for leukemia should work closely with their physician to follow the results of blood and other tests to determine the best treatment course.

The following tests are valuable:

- **Cholesterol levels:** low cholesterol return to normal physiological levels with response to treatment in AML and CML (Baroni S et al 1994; Baroni S et al 1996; Moschovi M et al 2004).
- **Total lipid profiles:** monitoring of lipids such as serum albumin and body mass index can play a role in assessing response to treatment as these lipids are low at leukemia diagnosis (Fiorenza AM et al 2000; Moschovi M et al 2004).
- **Cortisol levels:** increased levels in AML, CML, and CLL are associated with immune dysfunction (Everaus H 1992; Everaus H et al 1997; Singh JN et al 1989). Monitoring cortisol levels in cancer patients may be useful in observing the psychological impact of the disease and associated treatment on the individual (Cohen L et al 2001).
- **DHEA levels:** abnormal levels may be associated with immune cell dysfunction (Uozumi K et al 1996). Baseline levels can be determined by radioimmunoassay before DHEA supplementation, shown to correct impaired immune function in animal models (Catalina F et al 2003; Inserra P et al 1998).
- **Coagulation profile:** blood-clotting parameters are usually abnormal in leukemia. Tests may show low levels of platelets, increased prothrombin time (PT), partial thromboplastin time (PTT), and/or decreased fibrinogen (Barton JC et al 1986). Response to therapy is often accompanied by normalization of these blood tests with increased fibrinogen and decreased PTT (Anders O et al 1988; Higuchi T et al 1997).
- **Hemoglobin levels:** anemia is common in patients with leukemia, and this can be monitored by periodically measuring hemoglobin status. Hemoglobin levels less than 11g/dL are typically seen with leukemia (Quirt I et al 2001b).
- **Cytokine panel:** tests in patients with leukemia typically reveal that blood levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-1 beta (IL-1 β), and tumor necrosis factor-alpha (TNF-a) are elevated.
- **Genetic profile:** p53 (Lian F et al 1999; Melo MB et al 2002; Nakano Y et al 2000) and Bcr-Abl tyrosine kinase (Patlak M 2002).
- **Blood smears:** assessments of blood cell shape and size show the presence of leukemia cells by highlighting irregularities in cell shape and structure.
- **Bone marrow tests:** samples taken by aspiration can detect leukemic cells in bone marrow and monitor treatment effectiveness.
- **X-rays:** leukemia progression can be monitored by X-rays to detect disease spread to the lymph nodes, lungs, bone, and joints. Magnetic resonance imaging (MRI) can detect brain metastases (Vera P et al 1999).
- **Abdominal sonography:** this is a diagnostic imaging method used to monitor the effect of treatment through detection of enlarged spleen (splenomegaly) and abdominal lymph nodes (Bessmel'tsev SS et al 1991).
- **Physical examinations** play a very important role in monitoring the response to treatment and checking for relapse following leukemia remission, including the presence of enlarged lymph nodes or an enlarged spleen (Saven A et al 1998).

For More Information...

Leukemia patients may wish to read these chapters and design a program that will address the full range of their cancer problems:

- Cancer Chemotherapy
- Cancer Radiation
- Complementary Adjuvant Cancer Therapies
- Blood Disorders

For general information on all aspects of leukemia:

The American Cancer Society, (800) ACS-2345

The Leukemia & Lymphoma Society, (800) 955-4572 http://www.leukemia-lymphoma.org/hm_lls

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Leukemia patients should consult their physicians before starting to use any nutritional supplements while receiving conventional medical treatment. In addition, leukemia patients using nutritional supplements should enlist the assistance of their physicians to ensure the implementation of blood tests and diagnostic procedures that are essential for monitoring the effectiveness of any

The Life Extension Foundation suggests:

- **Vitamin A**— 40,000 to 50,000 IU daily (Kakizoe T 2003; Meyskens FL, Jr. et al 1995)
- **Vitamin D3**— 16,000 IU three times per week (Mellibovsky L et al 1993)
- **Curcumin**— three 800 mg capsules up to three times daily, 2 hours apart from all medications (Gescher A 2004)
- **Green tea**— 725 mg of green tea extract (containing 93% polyphenols, 34% epigallocatechin gallate) three times daily, or 10 cups of Japanese green tea (Laurie SA et al 2005; Pisters KM et al 2001)
- **Soy extract**— containing 50 mg of isoflavones twice daily (Anderson GD et al 2003b)
- **Lipoic acid**— 600 mg orally three times daily (Rock E et al 2003)
- **Vitamin E**— 400 IU daily (Kakizoe T 2003)
- **Vitamin B12**— 1 mg daily (Gonin JM et al 2003)
- **L-Ascorbic acid**— 2000 mg daily (Kakizoe T 2003)
- **Shark liver oil**— 1500-3000mg [containing 20% alkylglycerols (300-600mg)] a day in divided dosages (Pugliese PT et al 1998)
- **Essential fatty acids**— 700 mg GLA daily; 4.8 grams EPA daily; 4.9 grams DHA daily (Buckley R et al 2004; Johnson CD et al 2001)
- **DHEA**— 50 mg daily for men; 25 mg daily for women (Huppert FA et al 2001)
- **Resveratrol**— 25 mg daily (Walle T et al 2004)
- **Folic acid**— up to 1 mg daily (Scagliotti GV et al 2003)
- **Melatonin**— 20 mg before bedtime (Lissoni P et al 2000)
- **Panax ginseng**— 100 mg standardized to contain 4% ginsenosides twice daily (Anderson GD et al 2003a)
- **Garlic**— 600 mg of aged garlic extract twice daily (Hassan HT 2004)

LEUKEMIA SAFETY CAVEATS

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

Curcumin

- Do not take curcumin if you have a bile duct obstruction or a history of gallstones. Taking curcumin can stimulate bile production.
- Consult your doctor before taking curcumin if you have gastroesophageal reflux disease (GERD) or a history of peptic ulcer disease.
- Consult your doctor before taking curcumin if you take warfarin or antiplatelet drugs. Curcumin can have antithrombotic activity.
- Always take curcumin with food. Curcumin may cause gastric irritation, ulceration, gastritis, and peptic ulcer disease if taken on an empty stomach.
- Curcumin can cause gastrointestinal symptoms such as nausea and diarrhea.

DHEA

- Do not take DHEA if you could be pregnant, are breastfeeding, or could have prostate, breast, uterine, or ovarian cancer.
- DHEA can cause androgenic effects in woman such as acne, deepening of the voice, facial hair growth and hair loss

EPA/DHA

- Consult your doctor before taking EPA/DHA if you take warfarin (Coumadin). Taking EPA/DHA with warfarin may increase the risk of bleeding.
- Discontinue using EPA/DHA 2 weeks before any surgical procedure.

Folic acid

- Consult your doctor before taking folic acid if you have a vitamin B12 deficiency.
- Daily doses of more than 1 milligram of folic acid can precipitate or exacerbate the neurological damage caused by a vitamin

Garlic

- Garlic has blood-thinning, anticlotting properties.
- Discontinue using garlic before any surgical procedure.
- Garlic can cause headache, muscle pain, fatigue, vertigo, watery eyes, asthma, and gastrointestinal symptoms such as nausea and diarrhea.
- Ingesting large amounts of garlic can cause bad breath and body odor.

Genistein

- Consult your doctor before taking genistein/genistin if you have prostate cancer.
- Do not take genistein/genistin if you have estrogen receptor–positive tumors.
- Genistein/genistin can cause hypothyroidism in some people.

Ginseng

- Consult your doctor before taking ginseng if you have high blood pressure. Overuse of ginseng can increase blood pressure.
- Consult your doctor before taking ginseng if you take nonsteroidal anti-inflammatory drugs (NSAIDs) and/or warfarin (Coumadin). Taking NSAIDs or warfarin with ginseng can increase the risk of bleeding.
- Consult your doctor before taking ginseng if you have diabetes. Taking ginseng can cause an extreme drop in your blood glucose level.
- Ginseng can cause breast pain, vaginal bleeding after menopause, insomnia, headaches, and nosebleeds.

GLA

- Consult your doctor before taking GLA if you take warfarin (Coumadin). Taking GLA with warfarin may increase the risk of bleeding.
- Discontinue using GLA 2 weeks before any surgical procedure.
- GLA can cause gastrointestinal symptoms such as nausea and diarrhea.

Green Tea

- Consult your doctor before taking green tea extract if you take aspirin or warfarin (Coumadin). Taking green tea extract and aspirin or warfarin can increase the risk of bleeding.
- Discontinue using green tea extract 2 weeks before any surgical procedure. Green tea extract may decrease platelet aggregation.
- Green tea extract contains caffeine, which may produce a variety of symptoms including restlessness, nausea, headache, muscle tension, sleep disturbances, and rapid heartbeat.

Melatonin

- Do not take melatonin if you are depressed.
- Do not take high doses of melatonin if you are trying to conceive. High doses of melatonin have been shown to inhibit ovulation.
- Melatonin can cause morning grogginess, a feeling of having a hangover or a “heavy head,” or gastrointestinal symptoms such as nausea

Shark Liver Oil

- Do not exceed the maximum recommended dose.
- Prolonged use (more than 30 days in a row) causes a rare side effect known as thrombocythemia (excess platelets), which can cause the blood to clot.
- Shark liver oil can cause rash, breath that smells like garlic, fatigue, irritability, and gastrointestinal symptoms such as nausea and diarrhea.

Vitamin A

- Do not take vitamin A if you have hypervitaminosis A.
- Do not take vitamin A if you take retinoids or retinoid analogues (such as acitretin, all-trans-retinoic acid, bexarotene, etretinate, and isotretinoin). Vitamin A can add to the toxicity of these drugs.
- Do not take large amounts of vitamin A. Taking large amounts of vitamin A may cause acute or chronic toxicity. Early signs and symptoms of chronic toxicity include dry, rough skin; cracked lips; sparse, coarse hair; and loss of hair from the eyebrows. Later signs and symptoms of toxicity include irritability, headache, pseudotumor cerebri (benign intracranial hypertension), elevated serum liver enzymes, reversible noncirrhotic portal high blood pressure, fibrosis and cirrhosis of the liver, and death from liver failure.

Vitamin B12 (cyanocobalamin)

- Do not take cyanocobalamin if you have Leber's optic atrophy.

Vitamin C

- Do not take vitamin C if you have a history of kidney stones or of kidney insufficiency (defined as having a serum creatine level greater than 2 milligrams per deciliter and/or a creatinine clearance less than 30 milliliters per minute).
- Consult your doctor before taking large amounts of vitamin C if you have hemochromatosis, thalassemia, sideroblastic anemia, sickle cell anemia, or erythrocyte glucose-6-phosphate dehydrogenase (G6PD) deficiency. You can experience iron overload if you have one of these conditions and use large amounts of vitamin C.

Vitamin D

- Do not take vitamin D if you have hypercalcemia.
- Consult your doctor before taking vitamin D if you are taking digoxin or any cardiac glycoside.
- Only take large doses of vitamin D (2000 international units or 50 micrograms or more daily) if prescribed by your doctor.
- See your doctor frequently if you take vitamin D and thiazides or if you take large doses of vitamin D. You may develop hypercalcemia.
- Chronic large doses (95 micrograms or 3800 international units or more daily) of vitamin D can cause hypercalcemia.
- Chronic large dosages of 95 micrograms or 3,800 IU/day or greater may cause hypercalcemia in healthy individuals.

Vitamin E

- Individuals taking warfarin/coumadin should be cautious in using high doses of vitamin E and should do so only under a physician's supervision.
- Individuals with vitamin K deficiencies, such as those with liver failure, should be cautious in using high doses of vitamin E.
- Individuals with any lesions that have a propensity to bleed (e.g., bleeding peptic ulcers), those with a history of hemorrhagic stroke and those with inherited bleeding disorders (e.g., hemophilia) should use Vitamin E with extreme caution.
- Vitamin E supplementation should be discontinued one month prior to any surgical procedure.

For more information see the Safety Appendix

A genetic profile (e.g. expression of p53 and Bcr-Abl tyrosine kinase) can be determined via Genzyme Genetics http://www.genzymeimpath.com/lymphoma_leukemia.html and may be ordered by a physician telephoning (800) 966-4440.

All Contents Copyright © 1995-2009 Life Extension Foundation All rights reserved.

LifeExtension[®]

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.