

Lymphoma

More than 60,000 Americans were diagnosed with some form of lymphoma in 2004, and more than 20,000 died from their disease. Lymphomas are linked to a variety of risk factors, including diet, medical history, environmental exposure to chemicals, and infections. To date, conventional medical treatment for lymphoma has been based on combinations of chemotherapy, radiotherapy, and stem cell therapy. However, new treatments for lymphoma now add to these traditional therapies the use of substances that can specifically target the delivery of radiotherapy to lymphoma cells (radioimmunotherapy) or activate the immune system to kill lymphoma cells (chemoimmunotherapy).

Nutritional supplements with demonstrated activity against lymphoma cells include curcumin, genistein from soy extract, vitamins A, C, D, and E, green tea, resveratrol, ginger, fish oil, and garlic. These supplements can be used to complement conventional drugs, and they can be closely monitored for effectiveness with a range of blood tests and diagnostic procedures described in this protocol.

WHAT IS LYMPHOMA?

The lymphatic system consists of organs such as the lymph nodes, the thymus gland, the spleen, and bone marrow, which participate in the production and storage of infection-fighting white blood cells (lymphocytes), as well as in the network of vessels that carry these white blood cells around the body. Lymphomas are cancers of the white blood cells (lymphocytes) within the lymphatic system.

There are two types of lymphoma (Hansmann ML et al 1996):

- Hodgkin's lymphoma, also known as Hodgkin's disease (HD)
- Non-Hodgkin's lymphoma (NHL).

The diagnosis, staging (Lister TA et al 1989), and general symptoms (Jose BO et al 2005) of lymphoma are summarized in Table 1.

Table 1. Lymphoma: symptoms, diagnosis, and staging

	Hodgkin's Lymphoma (HD)	Non-Hodgkin's Lymphoma (NHL)
Symptoms	Swollen lymph nodes Fever Night sweats Weight loss	Swollen lymph nodes Excessive sweating Severe itching Weight loss
Diagnosis	Magnetic resonance imaging (MRI) Computed tomography (CT) Tissue biopsy	Similar to that of HD
Staging	Ann Arbor Staging Classification system: 4 stages (I, II, III, and IV) Stage 1: Least serious Stage IV: Most serious or HD is also classified as type A (no symptoms) and B (with fever, sweats, and weight loss)	The Working Formulation: Low grade (slow growing) Intermediate grade High grade (fast growing) or The Revised European American Lymphoma (REAL) system: Indolent (slow growing) Aggressive (fast growing) Highly aggressive

Hodgkin's lymphoma begins in the lymph nodes and is characterized by the presence of Reed-Sternberg cells, which are large, cancerous cells that increase in number with disease progression (Harris NL 1999; Kuppers R et al 2002). Evidence suggests that B lymphocytes (B-cells), the infection- and tumor-fighting cells that produce antibodies, produce Reed-Sternberg cells (Brauninger A et al 1999; Harris NL 1999; Kuppers R et al 2002). However, T lymphocytes (T-cells) have also been implicated in rare cases (Kuppers R et al 2002).

Although it can affect any lymph tissue, HD most commonly affects the supraclavicular, high-cervical, or mediastinal lymph nodes (Jose BO et al 2005). There are five different types of Hodgkin's lymphoma.

Non-Hodgkin's lymphoma describes all lymphoma types without Reed-Sternberg cells (Coffey J et al 2003; Jimenez-Zepeda VH et al 1998). NHL develops as a result of malignant B and T lymphocytes (white blood cells). B-cell lymphomas are more common and account for over 85 percent of NHL cases (Coffey J et al 2003). There are at least 29 different types of NHL; the main types, which can be further classified into subtypes, are summarized in Table 2.

Table 2. Different types of Non-Hodgkin's lymphoma and MALT (mucosa-associated lymphoid tissue) lymphoma

NHL types	Characteristics
B-cell lymphoma	Lymphoma cells have characteristics similar to B-cells
Burkitt's lymphoma	Associated with a viral infection; common in Africa
Cutaneous T-cell lymphoma	Initially involves the skin and lymph nodes
Diffuse lymphoma	Lymphoma cells are evenly spread throughout the lymph nodes
Follicular lymphoma	Lymphoma cells are concentrated in clusters/follicles in the lymph node
High-grade lymphoma	Progresses rapidly if left untreated
Low-grade lymphoma	Progresses slowly if left untreated
MALT lymphoma	Originates in the intestinal lining
Mantle cell lymphoma	Originates in the mantle zone of the lymph node
T-cell lymphoma	Lymphoma cells have characteristics similar to T-cells

LYMPHOMA OCCURRENCE

New cases of Hodgkin's lymphoma represent less than 1 percent of all cancer cases in the United States. By contrast, non-Hodgkin's lymphoma is the fifth most common cancer after lung, breast, colorectal, and prostate cancers (Groves FD et al 2000). Moreover, NHL is among the top five causes of cancer-related death (Fisher SG et al 2004; Hauke RJ et al 2000) and is the leading cause of cancer death in males aged 15-54 (Mohammad RM et al 2003). US cases of lymphoma for 2004 are summarized in Table 3 (Baris D et al 2000).

Table 3. Lymphoma cases in the US in 2004 (US National Cancer Institute SEER data)

Lymphoma Type	New Cases in 2004	Deaths in 2004
Hodgkin's Lymphoma (HD)	7,880 (4,330 males; 3,550 females)	1,320
Non-Hodgkin's lymphoma (NHL)	53,370 (28,850 males; 25,520 females)	19,410

Lymphoma is generally more common in men than in women (Cartwright RA et al 2002; Groves FD et al 2000). The incidence of lymphoma also varies by race. Statistics indicate that African-Americans are less likely to develop lymphoma than Caucasians (Glaser SL 1991; Groves FD et al 2000).

GENETIC ABNORMALITIES IN LYMPHOMA

Like all cancers, lymphoma begins with damage to the cell's deoxyribonucleic acid (DNA), the molecules containing all the information that determines the structure and function of cells. Within each cell, DNA is housed in structures known as chromosomes, which are made up of sections called genes.

The development of lymphoma begins with damage to the DNA of T-cells and B-cells (lymphocytes), immune cells that protect the body from infections (Coffey J et al 2003; Kuppers R et al 2002). DNA damage that can start cancer development occurs in genes called oncogenes or tumor-suppressor genes, which play important roles in maintaining a balance between cell death and cell growth.

Excessive cell growth occurs in lymphoma as a result of malfunction of the proteins that control cell growth (leading to permanent cell division) and cell death (making the cell insensitive to normal signals to die). Numerous genetic abnormalities have been implicated in the malfunction of cell controls. Two critical proteins involved in lymphoma development are bcl-2 and bcl-6.

The identification of these genetic irregularities has important implications for treating lymphoma, as it indicates potential targets for manipulation with pharmaceutical drugs or nutritional supplements. For example, pharmacological agents capable of inactivating bcl-6 can cause increased cell death (apoptosis) in lymphoma cells (Pasqualucci L et al 2003). Furthermore, in clinical studies, an agent that targets bcl-2 has also been shown to have efficacy in non-Hodgkin's lymphoma patients (Chanan-Khan A 2004).

WHAT CAUSES LYMPHOMA?

The cause of lymphoma is still a subject of much debate, and many lymphoma patients do not have obvious risk factors.

Hodgkin's Lymphoma

Epstein Barr and Herpes Viruses. The Epstein Barr virus is thought to cause one third of all HD cases (Jarrett RF 2003). In addition, HD patients often show high numbers of herpes-infected cells (Krueger GR et al 1994). These viruses are thought to contribute to the development of lymphoma (Krueger GR et al 1994), and are also linked to the development of NHL (Danese C et al 2004; Muller AM et al 2005).

Weakened Immune System. Individuals with suppressed immune systems associated with HIV infection appear to be at higher risk of developing HD (Lim ST et al 2005; Thompson LD et al 2004).

Non-Hodgkin's Lymphoma

Factors that play a role in susceptibility to non-Hodgkin's lymphoma include nutrition, medical history, environment, and use of medications.

Diet/Nutrition. NHL is more common in individuals with weakened immune systems (Zhang S et al 1999; Zhang SM et al 2000). Clinical studies have now shown that diets rich in animal protein and fats, which are thought to diminish immune function (Calder PC et al 2002; Jones DE 2005; Plat J et al 2005), are associated with an increased risk of developing NHL (Chang ET et al 2005; Chiu BC et al 1996; De SE et al 1998; Zhang S et al 1999). Clinical studies have also shown that diets rich in fruits and vegetables, which are thought to enhance immune cell function (Gaisbauer M et al 1990; Rossing N 1988; Loghem JJ 1951), are associated with a reduced risk of developing NHL (Zhang SM et al 2000; Zheng T et al 2004).

Medical History. Evidence suggests that some medical conditions or procedures, especially those that reduce immune system activity, increase the risk of developing non-Hodgkin's lymphoma. These include:

- Blood transfusions and organ transplantation
- Diabetes
- Celiac disease
- Hepatitis C
- Epstein Barr virus
- Gastric ulcers (*Helicobacter pylori*)
- HIV
- HTLV (human T-lymphotropic virus)
- Herpes.

Numerous studies have examined the link between blood transfusions and the development of NHL. However, the data are conflicting, with some studies showing that allogeneic blood transfusions (i.e., from other people/donors) are associated with a twofold increase in the risk of developing NHL (Cerhan JR 1997a; Vamvakas EC 2000). Similarly, the risk of NHL is thought to increase in organ transplant patients (Vamvakas EC 2000), most likely as a result of post-transplant immunosuppression.

In older women, adult-onset (type II) diabetes of long duration has also been shown to increase the risk of developing NHL (Cerhan JR et al 1997b). Other clinical studies have also shown that diabetes sufferers are at greater risk of developing NHL (Natazuka T et al 1994), presumably because diabetes impairs the efficiency of the immune system (Jackson RM et al 1987; Kohn LD et al 2005).

Celiac disease, a condition characterized by inflammation of the intestinal lining due to sensitivity to a protein called gluten (found in wheat and rye), is also associated with increased risk of developing NHL, particularly localized in the gut (Catassi C et al 2002; Smedby KE et al 2005; Sonet A et al 2004).

Hepatitis C virus, a common infection in the US, is linked to the development of B-cell NHL (Fiorilli M et al 2003; Vallisa D et al 2005), MALT lymphoma (Seve P et al 2004), and a rare type of NHL known as primary hepatic lymphoma (Noronha V et al 2005). Interestingly, this association appears to have some geographical variations, although some studies do not support it (Giannoulis E et al 2004; Morgensztern D et al 2004).

Helicobacter pylori infection, normally associated with peptic ulcers, is also linked to the development of gastric MALT lymphomas (Franco M et al 2005; Wotherspoon AC 1998).

The immunosuppression caused by infection with the human immunodeficiency virus (HIV) is associated with a greater risk of developing NHL (Irwin D et al 1993; Kaplan LD 1990; Tulpule A et al 1999). The incidence of NHL in HIV-positive individuals is 60 times greater than that observed in the general population (Tulpule A et al 1999).

The human T-lymphotropic virus, a close relative of HIV, is also known to cause T-cell lymphomas (Nicot C 2005).

Environment. Exposure to pesticides and herbicides is associated with an increased risk of developing non-Hodgkin's lymphoma, particularly in rural farming communities where these substances are used routinely (Quintana PJ et al 2004; Waddell BL et al 2001; Weisenburger DD 1990). Asthmatics exposed to pesticides have a higher risk of developing NHL compared to non-asthmatics (Lee WJ et al 2004). Chemicals known as dioxins, which are emitted from solid waste incinerators, are thought to increase the risk of non-Hodgkin's lymphoma (Floret N et al 2003). Contamination of drinking water with nitrates is also thought to increase the risk of developing NHL (Ward MH et al 1996), though other studies show that contamination levels would have to be very high to pose this risk (Freedman DM et al 2000).

Medications. Long-term use of medications such as conventional hormone replacement therapy (primarily unopposed estrogens with synthetic, equine-derived estrogens), certain antibiotics, and pain relievers is associated with an increased risk of certain types of NHL (Cerhan JR et al 2002; Kato I et al 2002; Kato I et al 2003). In particular, individuals with rheumatoid arthritis who are long-term users of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) have a greater risk of developing NHL (Cerhan JR et al 2003).

What You Have Learned So Far

- Lymphomas are cancers of the lymphatic tissues that are involved in storage and distribution of infection- and tumor-fighting white blood cells.
- Because lymph tissue is found throughout the body, lymphoma can begin in almost any part of the body and spread to almost any tissue or organ.
- Risk factors linked to the development of lymphoma include diet, medical history, certain viruses, chemical exposure, and conditions that weaken the immune system.
- Swollen lymph nodes and weight loss are possible signs of lymphoma.
- Tests that examine the lymph nodes are used to detect and diagnose lymphoma.
- Medical treatment for lymphoma traditionally has been based on combinations of chemotherapy, radiotherapy, and stem cell therapy.
- Innovative treatments include radioimmunotherapy and chemoimmunotherapy.
- Nutritional supplements that can be used to complement conventional treatments include curcumin, genistein in soy extract, vitamins A, C, D, and E, green tea, resveratrol, ginger, fish oil, and garlic.

CONVENTIONAL THERAPY

Currently, medical treatment for lymphoma revolves around the following therapies:

- Chemotherapy
- Radiotherapy
- Stem cell therapy.

A discussion of how chemotherapy and radiotherapy agents kill blood cancers, and the use of stem cell therapy, is available in the Leukemia protocol.

The standard chemotherapy regimen for NHL, known as CHOP, combines four agents: cyclophosphamide, doxorubicin, vincristine, and prednisone (Canellos GP 2004; Escalon MP et al 2005; Younes A 2004). Although CHOP has been the accepted "gold standard" for NHL chemotherapy treatment for the past 30 years, its delivery was recently optimized with a change to a 14-day dose-dense schedule, which increased clinical responses compared to the traditional 21-day schedule (Younes A 2004). A recent study showed the effectiveness of another chemotherapy combination (carmustine, doxorubicin, etoposide, vincristine, and cyclophosphamide, plus mitoxantrone, cytarabine and methotrexate with a factor known as BAVEC-MiMA) for NHL treatment (Rigacci L et al 2005).

The standard chemotherapy combination for HD is known as ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) (Canellos GP 2004).

The use of these chemotherapy agents is often combined with radiotherapy (Mukai HY et al 2003) and stem cell therapy (Lavoie JC et al 2005).

SIDE EFFECTS OF CONVENTIONAL THERAPY

Chemotherapy often has a side effect of reducing white blood cell count to very low levels, thereby leaving the patient vulnerable to infections (Lyman GH 2000). As with other cancers, the risk of developing lymphoma increases sharply with increasing age (Holmes FF et al 1991). Changes in the aging body reduce the patient's ability to tolerate standard chemotherapy and radiotherapy regimens that are often better suited to the relatively more robust immune systems of young adults.

In particular, the aging body experiences a decline in its ability to make new white blood cells (Chatta GS et al 1996). The use of chemotherapy in elderly patients therefore aggravates this problem because it destroys patients' normal white blood cells, leaving them prone to infections. Readers should refer to the Cancer Chemotherapy protocol for a range of prescription drugs that can be taken to reduce this negative side effect of chemotherapy. Readers should also refer to the protocol on Blood Disorders: Anemia, Leukopenia, and Thrombocytopenia for other practical guidelines on dealing with reduced white and red blood cells.

Heart disease (cardiomyopathy) is the most important long-term toxicity of Adriamycin® (doxorubicin) administration, which is used to treat both NHL and HD. Several clinical studies suggest that some changes in the heart's electrical activity caused by Adriamycin® may be prevented by coenzyme Q10 supplementation (Tajima M 1984; Tsubaki K et al 1984). Coenzyme Q10 supplementation has a protective effect on cardiac function during therapy with Adriamycin® in lymphoma patients (Iarussi D et al 1994; Wang SQ 1991). Some investigators believe that simultaneous coenzyme Q10 and vitamin E supplementation is indicated during Adriamycin® therapy in order to reduce its toxicity and prevent fatal congestive heart failure (Wang SQ 1991).

NEW AND UPCOMING THERAPIES FOR LYMPHOMA

New treatments for lymphomas largely involve the use of established chemotherapy and radiotherapy agents in combination with methods that capitalize on innate features of the immune system. Successful treatment of lymphoma must take into account the patient's age and the role of nutrition in helping the body tolerate and recover from cytotoxic treatments.

Immunotherapy (e.g., Rituxan® [Rituximab]). B-cells, and therefore all lymphomas of B-cell origin, have a molecule on their surface known as CD20 (Maloney DG 2005). Rituxan® is an antibody designed to bind to CD20 on lymphoma cells (Plosker GL et al 2003). Upon the binding of Rituxan®, a process known as antibody-dependent cell cytotoxicity (ADCC) is initiated; this causes the immune system to destroy the lymphoma cell. Because normal B-cells also have CD20 on their cell surface, use of Rituxan® also leads to their destruction, and patients suffer from low B-cell numbers for approximately six months; however, these numbers return to normal 9 to 12 months after treatment (Plosker GL et al 2003).

In the US, Rituxan® is already available for the treatment of low-grade or follicular, relapsed NHL (Plosker GL et al 2003). Recent studies suggest that Rituxan® is also effective against diffuse large B-cell lymphoma (Nakai S et al 2005).

Chemoimmunotherapy (e.g., Rituxan® and CHOP). Recent studies have shown the use of Rituxan® in combination with CHOP chemotherapy to be more effective than CHOP chemotherapy alone in elderly patients with diffuse large B-cell lymphoma (Feugier P et al 2005). This therapy is also effective in previously untreated mantle cell lymphoma and aggressive recurrent pediatric B-cell large-cell NHL (Jetsrisuparb A et al 2005; Lenz G et al 2005). Although Rituxan® in combination with CHOP is approved in Europe for the treatment of diffuse large B-cell lymphoma (the most common aggressive form of NHL), it is yet to be approved for this use in the US (Plosker GL et al 2003).

Radioimmunotherapy. Radioimmunotherapy is the use of antibodies that target the CD20 molecule on lymphoma cells to specifically deliver the radiation required to destroy the cancer cell (DeNardo GL 2005). Two such radio-labeled antibodies to CD20 (iodine-131 tositumomab and yttrium-90 [90Y] ibritumomab tiuxetan) have been tested against NHL (Dillman RO 2003). In 2002, 90Y ibritumomab tiuxetan was approved in the US for the treatment of relapsed or refractory low-grade, follicular, or transformed lymphoma; it is commercially available as Zevalin® (Dillman RO 2003; Forero A et al 2003; Grillo-Lopez AJ 2005; Lewington V 2005; Wiseman GA et al 2005). The second radioimmunotherapy agent, I-131 tositumomab, has also been approved in the US and is commercially available as Bexxar® (Lewington V 2005).

(Additional information to Radioimmunotherapy section - added 7/24/2007) According to a recent New York Times report, two potentially lifesaving drugs are languishing in obscurity, largely due to market forces. The drugs, Zevalin and Bexxar, have been approved by the Food and Drug Administration for the treatment of lymphoma, including non-Hodgkins lymphoma; the fifth most common cancer in the United States. But only about 10 percent of eligible patients are receiving the drugs, despite some remarkable results among those few who have been treated with them. Although patients are more likely to respond to Zevalin or Bexxar than to older, more commonly-used lymphoma treatments -- and the newer drugs are better tolerated, with fewer side effects (Riley MB 2004) -- oncologists have been slow to embrace them.

Part of the problem stems from the fact that the drugs are the first members of a promising new class of treatments, known as radioimmunotherapies. These drugs utilize cutting-edge monoclonal antibody technology to deliver radioactive particles directly to tumor cells. But, while radioactivity is the key to their effectiveness, it is also a stumbling block that has rendered many oncologists reluctant to prescribe them. Due to their radioactivity, they must be administered in a hospital setting. As a result, oncologists must abandon financial incentives they might otherwise reap for prescribing older chemotherapy drugs, and they must coordinate their efforts with additional clinicians. Patients taking the new drugs must also be monitored for changes in blood cell counts.

A single treatment may cost about \$25,000. But one treatment is often all that is required to effect remission. The more common alternative -- treatment with months of chemotherapy, followed by a commonly prescribed drug, Rituxan -- costs about the same.

But Bexxar or Zevalin are often more effective at stopping the deadly disease. A recent study found the drugs offer “ .impressive clinical outcomes (approximately 20%-40% complete response rates and 60%-80% overall response rates for patients with [non-Hodgkins lymphoma].” (Macklis RM 2007) Another study reported similar results. (Witzig TE et al 2007) An older study compared the newer drugs to Rituxan and found an overall response rate of “ .80% for the [Zevalin] group versus 56% for the [Rituxan] group.” The same study found that 30% of Zevalin patients experienced complete remission, as opposed to 16% of patients receiving Rituxan (Witzig TE et al 2002).

Advocates worry the drugs' makers may abandon production if physicians don't overcome their reluctance to use them soon. They hope the as-yet-unreleased results of ongoing clinical trials, designed to assess the efficacy of the drugs among large groups of patients, may finally convince oncologists to embrace their use. According to the New York Times, some lymphoma patients have been forced to take matters into their own

hands, demanding access to the drugs, often with remarkable results.

Vaccine Therapy. The use of vaccination as a treatment for lymphoma is also being investigated. Further details on vaccine therapy for lymphoma can be found in the Experimental & Investigational Therapies protocol.

NUTRITIONAL THERAPY

Nutritional supplements with demonstrated activity against lymphoma cells include:

- Curcumin
- Soy extract
- Vitamins A, C, D, and E
- Green tea
- Resveratrol
- Ginger
- Fish oils
- Garlic.

Curcumin. Curcumin, an extract from the spice turmeric, blocks the growth of various types of lymphoma cells, including Burkitt's lymphoma and EBV B-cell lymphomas (Han SS et al 1999; Ranjan D et al 1999; Wu Y et al 2002b). In addition to arresting the growth of lymphoma cells, curcumin also causes lymphoma cell death by reducing the levels of some genes (*c-myc*, *bcl-2*) and mutant p53 proteins (Han SS et al 1999; Ranjan D et al 1999; Wu Y et al 2002c). Curcumin has an additional benefit in that it blocks the production of growth factors that cancer cells require to invade other organs (Dulak J 2005). Clinical studies have shown curcumin supplements to be safe in doses of up to 3.6 grams a day (Gescher A 2004).

Soy Extract. Genistein, found in soy extracts, induces cell death in lymphoma cells (Baxa DM et al 2003; Buckley AR et al 1993). It increases the effectiveness of chemotherapy for lymphoma by making cells more susceptible to agents that cause lymphoma cell death (Mohammad RM et al 2003). Genistein also reduces the ability of cancer cell spread (angiogenesis) by blocking the production of proteins (angiogenesis growth factors) that cancer cells need to form new blood vessels (Dulak J 2005).

Vitamins A and D3. Natural and synthetic vitamin A (also known as retinoids) promote normal cell differentiation and have been used to treat T-cell lymphomas (Kempf W et al 2003; Mahrle G et al 1987; Zhang C et al 2003). Vitamin D3 blocks the growth of lymphoma cells (Mathiasen IS et al 1993).

Green Tea. Green tea, which contains epigallocatechin gallate (EGCG), triggers lymphoma cell death (Bertolini F et al 2000; Katsuno Y et al 2001). In addition, EGCG from green tea reduces the ability of lymphoma cells to invade other organs by blocking the production of growth factors, such as vascular endothelial growth factor (VEGF) and the glycoprotein messenger interleukin-8 (IL-8), which lymphoma cells need to spread (Dulak J 2005).

Vitamins C and E. In experimental studies, vitamin C has improved the effectiveness of chemotherapy in inducing lymphoma cell death (Chen Q et al 2005; Nagy B et al 2003; Prasad SB et al 1992). Vitamin E supplements boost the function of immune cells capable of killing lymphoma cells (Ashfaq MK et al 2000; Dalen H et al 2003b; Dasgupta J et al 1993). Alpha-tocopheryl succinate, a semisynthetic analogue of vitamin E, is a potential adjuvant in cancer treatment (Dalen H et al 2003a).

Resveratrol. Resveratrol, a naturally occurring substance found in grapes, blocks the growth of lymphoma cells and also increases their rate of cell death (Bruno R et al 2003; Park JW et al 2001). Resveratrol sensitizes chemotherapy-resistant lymphoma cells to treatment with paclitaxel-based chemotherapy (Jazirehi AR et al 2004). Resveratrol also reduces the production of growth factors such as VEGF and IL-8, and theoretically should be beneficial in reducing the ability of lymphoma cells to spread to other organs (Dulak J 2005).

Ginger. Extracts from ginger, known as galanals A and B, induce cell death in human lymphoma cells (Miyoshi N et al 2003).

Fish Oil. Eicosapentaenoic acid (EPA) found in fish oil induces cell death in lymphoma cells (Heimli H et al 2001, 2002, 2003). Omega-3 fatty acids in fish oil normalized elevated blood lactic acid in a dose-dependent manner, increasing disease-free survival and survival time for dogs with Stage III lymphoma (Ogilvie GK et al 2000).

Garlic. Garlic extracts can induce death in lymphoma cells (Arditti FD et al 2005; Scharfenberg K et al 1990). Indeed, in a recent study, conjugation of a garlic extract to the antibody rituximab (which targets lymphoma cells) led to the death of these cells (Arditti FD et al 2005).

BLOOD TESTS

Patients are advised to consult their physicians about the following blood tests that can be used to monitor the effectiveness of conventional medical treatment and nutritional supplements for lymphoma.

- **Cancer cell markers:** Several nutritional supplements, including curcumin and ginger extracts, work by reducing the production of proteins such as p53 and bcl-2. Production of these proteins could be monitored to assess the continued effectiveness of therapy (Han SS et al 1999; Miyoshi N et al 2003; Ranjan D et al 1999; Wu Y et al 2002d; Wu Y et al 2002a).
- **Angiogenesis markers:** Supplements of green tea, curcumin, resveratrol, and genistein work in part by blocking the production of growth factors, such as VEGF and interleukin-8 (IL-8), that cancer cells need to spread to other organs (Dulak J 2005). Patients using these nutritional supplements could routinely monitor these growth factors in their blood samples to assess the effectiveness of their therapy and check for disease progression. Reductions in VEGF levels have been linked to treatment response in lymphoma patients (Pedersen LM et al 2005).
- **IL-6:** Patients could also monitor levels of the cytokine (messenger) IL-6, as reductions in its levels have been linked with treatment response and can be used to forecast survival (Pedersen LM et al 2005).
- **Beta-2-microglobulin:** Levels of this protein are elevated in lymphoma patients, and monitoring it can be used to assess treatment response and disease progression; levels less than 3.0 mg/L are associated with remission (Escalon MP et al 2005; Litam P et al 1991).
- **Lactate dehydrogenase (LDH):** Levels of this enzyme are elevated in lymphoma patients before treatment, and monitoring it can be used to assess response to treatment and to forecast survival (Escalon MP et al 2005; Schneider RJ et al 1980).
- **Molecular monitoring:** Lymphoma cells can be detected in samples of blood and bone marrow. However, when these cells are present in very low numbers, molecular monitoring using a technique known as polymerase chain reaction (PCR) is recommended to determine response to treatment and check for remission (Martin S et al 2005).
- **Calcium levels:** Patients using vitamin D supplements should be monitored for vitamin D toxicity, which can result in abnormally high calcium levels in the blood (Lagman R et al 2003).

Physical examination and X-ray scans can detect disease progression by monitoring the body, body weight, and size of lymph nodes.

For More Information

Lymphoma patients may wish to consult the following protocols and design a program that addresses the full range of their cancer problems:

- Leukemia
- Cancer Radiation
- Cancer Chemotherapy
- Anemia, Leukopenia, and Thrombocytopenia
- Experimental & Investigational Therapies.

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Lymphoma patients should consult their physicians before using any nutritional supplements while receiving conventional medical treatment. In addition, lymphoma patients using nutritional supplements should enlist their physicians in ensuring the use of blood tests and diagnostic procedures that are essential in monitoring the effectiveness of any adjuvant therapy for lymphoma.

The Life Extension Foundation suggests:

- **Curcumin**—up to 3.2 grams (g) daily (Gescher A 2004)
- **Soy extract** (containing up to 60 milligrams (mg) of isoflavones): twice daily (Anderson GD et al 2003)
- **Vitamin A**—40,000 to 50,000 international units (IU) daily (Kakizoe T 2003; Meyskens FL, Jr. et al 1995)
- **Vitamin D3**—16,000 IU three times weekly (Mellibovsky L et al 1993)
- **Green tea**—725 mg three times daily, or 10 cups of Japanese green tea (Laurie SA et al 2005; Pisters KM et al 2001)
- **Vitamin C**—2000 mg daily (Kakizoe T 2003)
- **Vitamin E**—400 IU daily (Kakizoe T 2003)
- **Resveratrol**—20 to 40 mg daily (Walle T et al 2004)
- **Ginger**—up to 6 g daily (Betz O et al 2005)

- **Fish oil**—4.8 g of EPA/DHA daily (Buckley R et al 2004)
- **Garlic**—600 mg of aged garlic extract twice daily.

LYMPHOMA 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.

Daidzein

- Consult your doctor before taking daidzein/daidzin if you have prostate cancer.
- Do not use daidzein/daidzin if you have estrogen receptor–positive tumors.
- Daidzein/daidzin can cause hypothyroidism in some people.

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.

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.

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.

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 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.

Vitamin E

- Consult your doctor before taking vitamin E if you take warfarin (Coumadin).
- Consult your doctor before taking high doses of vitamin E if you have a vitamin K deficiency or a history of liver failure.
- Consult your doctor before taking vitamin E if you have a history of any bleeding disorder such as peptic ulcers, hemorrhagic stroke, or hemophilia.
- Discontinue using vitamin E 1 month before any surgical procedure.

For more information see the Safety Appendix

BLOOD TEST AVAILABILITY

Cancer cell markers (tumor antigen profile) can be determined via Genzyme Genetics (http://www.genzymeimpath.com/lymphoma_leukemia.html) and may be ordered by a physician by calling 1-800-966-4440.

Tests for angiogenesis markers (e.g., VEGF) and chemical messengers (IL-6 and IL-8) are available at UCLA's Jonsson Comprehensive Cancer Center (<http://www.cancer.mednet.ucla.edu/>).

Lactate dehydrogenase (LDH), calcium levels (part of a Chemistry Panel/Complete Blood Count), and IL-6 blood tests are available via Life Extension/National Diagnostics, Inc., and may be ordered by calling 1-800-544-4440 or ordering online at <http://www.lef.org/bloodtest/>.

X-rays, scans, and physical examinations can be arranged through your physician.

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